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NOVEL INSIGHTS IN REHABILITATION OF NEGLECT, 2nd EDITION

Topic Editors
Tanja Nijboer and Stefan Van der Stigchel

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NOVEL INSIGHTS IN REHABILITATION OF NEGLECT, 2nd EDITION

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Hemispatial neglect is the failure to report, respond to, or orient to novel or meaningful stimuli presented in the contralesional visual field. It constitutes one of the most invalidating neurological disorders that can occur after stroke. It is therefore important to treat neglect as adequate as possible and much of the research dedicated to neglect therefore focuses on rehabilitation. In this special topic, you will find 29 articles on the rehabilitation of neglect. This Research Topic has opened new perspectives, and has given us an indication of where the field is going. Although some of the current rehabilitation techniques have proven to be beneficial, there is limited agreement on the most valuable technique or the mechanisms underlying the ameliorating effects.

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Introduction to the Research Topic Novel Insights in Rehabilitation of Neglect

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Hemispatial neglect is the failure to report, respond to, or orient to novel or meaningful stimuli presented in the contralesional visual field. This failure cannot be attributed to motor or sensory defects (Heilman and Valenstein, 1979). It constitutes one of the most invalidating neurological disorders that can occur after stroke. As discussed in this Research Topic, patients with neglect are less independent in various activities of daily living compared to patients without neglect (Nijboer et al., 2013). It is therefore important to treat neglect as adequately as possible and much of the research dedicated to neglect therefore focuses on rehabilitation. Here we provide a brief overview of the 29 articles featured in this Research Topic.

This Research Topic points to a number of promising technological innovations. For instance, it is argued that computer-based testing allows more sensitive quantification of attentional disorders and recovery than paper-and-pencil tests (Bonato and Deouell, 2013). These innovations are likely to result in improved diagnosis and more tailor-made rehabilitation trajectories. Furthermore, future studies will hopefully take into account improved statistical approaches, like mixed linear modeling, which are more appropriate than ANOVAs to assess change over time when measuring recovery patterns (Goedert et al., 2013). Also innovations are proposed with respect to treatment of neglect. Prism adaptation (PA) is currently the most profoundly studied rehabilitation technique for neglect. New insights are reported in this Research Topic. First, the effect of PA extends to walking trajectories: PA when applied to the upper right limb improved the walking trajectory of a neglect patient, and this effect remained up to 15 months after treatment (Rabuffetti et al., 2013). Second, in line with the technological innovations mentioned above, computer-based PA is shown to be feasible, yet no improvement of neglect has been found on neuropsychological neglect tests (Smit et al., 2013). Third, two studies aimed to unravel the specific conditions in which the beneficial effects of PA are optimal. One of the articles discusses an effective novel adaptation procedure, which is more ecologically valid and regarded as more pleasant by patients (Fortis et al., 2013). The success of this new procedure is also highlighted in a review on different PA procedures, which revealed that the different available PA procedures are equally effective (Facchin et al., 2013). The results of these studies indicate that one can choose the best fitting or most suitable procedure for a given patient, without lowering the efficacy of the PA adaptation itself.

The underlying mechanism of PA is currently unclear. In this Research Topic, there was a debate on which aspect of neglect is part of the successful PA treatment: the perceptual or visual aspect or the motor aspect (Saevarsson and Kristjansson, 2013; Striemer and Danckert, 2013), whereas another research proposes that a distortion of visual space explains neglect performance while adapting to prisms (Scriven and Newport, 2013). This debate is still ongoing and will hopefully be resolved in the coming years, perhaps by using relatively novel measures like visually evoked magnetic fields (Mizuno et al., 2013).

Besides PA, a wide range of rehabilitation techniques tapping into various domains underlying hemispatial neglect, such as galvanic vestibular stimulation (Schmidt et al., 2013), transcutaneous electrical nerve stimulation (Pitzalis et al., 2013), motivational manipulations (Russell et al., 2013), visual scanning training (Van Kessel et al., 2013), space- and alertness-related training (Sturm et al., 2013), limb activation training (Pitteri et al., 2013), pro-cholinergic treatments (Lucas et al., 2013), and optokinetic stimulation (Daini et al., 2013), are described. From this list, it becomes clear that there is a wealth of different techniques, although effectiveness was shown to be quite diverse. One study directly compares the beneficial effects of visual scanning training, PA, and limb activation and reveals that all three treatments can be considered as comparably effective rehabilitation interventions (Priftis et al., 2013). There are also newly proposed techniques, such as noradrenergic stimulation to improve motor neglect (Sampanis and Riddoch, 2013) and videogame based neglect rehabilitation due to their high flexibility (Borghese et al., 2013).

Systematic reviews of the different techniques point to major shortcomings of the current literature on rehabilitation methods of neglect. The effectiveness of almost all techniques has not been investigated thoroughly enough to allow firm conclusions (Fasotti and van Kessel, 2013). For instance, when looking at the studies that used the behavioral inattention test as the primary outcome, the conclusion was drawn that all these studies had low power and suffered from limitations in the blinding of the design (Yang et al., 2013). With respect to upcoming non-invasive brain stimulations, such as TMS and tDCS, only few studies are reported, which are too heterogenous in methodology and outcome measures to draw firm conclusions on effectiveness from them (Muri et al., 2013). The same conclusion holds for eye patching, for which there is a great need for randomized controlled trials (Smania et al., 2013).

One of the factors that might contribute to the lack of consistent findings on the different rehabilitation techniques is the heterogeneity of the neglect syndrome. One of the proposals in this Research Topic is that a deficit in spatial working memory is one of the possible components of neglect. With respect to treatment, it is known that for example PA has no influence on spatial working memory deficits, which might explain why some patients benefit from PA whereas others do not (Striemer et al., 2013). Others characterize neglect as a disorder in representational updating, which reflects our ability to build mental models and adapt those models to changing experience (Shaqiri et al., 2013). Furthermore, neglect might be related to the motor system as reflected by a case description of a patient with motor extinction (Punt et al., 2013).

CONCLUSION

This Research Topic has opened new perspectives, and has given us an indication of where the field is going. Although some of the current rehabilitation techniques have proven to be beneficial, there is limited agreement on the most valuable technique or the mechanisms underlying the ameliorating effects. Future studies should focus on the heterogeneous nature of the neglect syndrome. There is a need for a better link between the various primary components of neglect and a more sensitive diagnosis (e.g., using computer-based testing) in future rehabilitation studies.

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Predicting functional outcome after stroke: the influence of neglect on basic activities in daily living

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One prominent deficit resulting from stroke is visuo-spatial neglect, which has been associated with slower and more attenuated recovery patterns of sensory-motor impairment as well as limitations in activities of daily living (ADL). The aim of the current study was to further specify the relationship between neglect and recovery of different domains of ADL. One hundred eighty four patients were assessed with the Functional Independence Measure in the first week of inpatient rehabilitation, and again at 6, 12, and 36 months post-stroke. On average, neglect patients scored significantly lower on Self-care, Transfers, and Locomotion compared to non-neglect patients, but these differences became smaller with progress of time. Overall, no differences between groups were found for Sphincter control and Cognition. Patients with more severe neglect scored significantly lower on Self-care and Transfers compared to patients with mild neglect. During rehabilitation, it would be of importance to test for independence in ADL domains in neglect in order to define realistic treatment goals. The current findings could be taken into account in early multidisciplinary intervention planning in the sub-acute phase, to optimize regaining ADL.

Keywords: stroke, neglect, recovery, ADL

INTRODUCTION

One prominent deficit resulting from stroke is visuo-spatial neglect, commonly referred to as neglect; about 25–30% of all stroke patients show impaired or lost awareness for events and (visual, auditory, and/or tactile) stimuli located at the side opposite of the brain lesion (Appelros et al., 2002; Buxbaum et al., 2004). Neglect can result from a lesion to either hemisphere, but is more severe and enduring after right hemisphere damage (Stone et al., 1993). The time course of spontaneous neurological recovery of neglect shows a natural logistic curve up to the first 12–14 weeks post-stroke, after which neglect severity becomes invariant (Nijboer et al., 2012). Neglect has been associated with slower and more attenuated recovery patterns of sensory-motor impairment (Katz et al., 1999) as well as limitations in activities of daily living (ADL) (Katz et al., 1999; Cherney et al., 2001; Di Monaco et al., 2011; Verhoeven et al., 2011) compared to non-neglect patients. None of the previous studies, however, differentiated between the different domains of ADL, whereas there is general consensus that some of these domains are more complex (e.g., Self-care, Transfers, Locomotion) than others (e.g., bowel management) (Granger et al., 1993; Grimby et al., 1996). Additionally, skills that easily allow for compensation strategies (e.g., grooming), improve earlier compared to more complex skills (e.g., dressing and climbing stairs) (Kwakkel and Kollen, 2013).

The aim of the current study was to further specify the relationship between neglect and recovery of different domains of ADL. Knowledge about factors that determine the final outcome in terms of post-stroke activities is important for early stroke management, in order to set suitable rehabilitation goals, enable early discharge planning, and psycho-education (Kwakkel and Kollen, 2013). One of the most widely used functional outcomes measures in rehabilitation facilities is the Functional Independence Measure (FIM), which measures degree of disability. Performance on the five domains of the FIM (i.e., Self-care, Sphincter control, Transfers, Locomotion, and Cognition) were compared between neglect and non-neglect patients in a repeated measures design up to 3 years post-stroke. Additionally, the relation between neglect severity and functional independence was investigated, as strong associations between severity of neurological deficits and final basic ADL outcomes have been described (Kwakkel and Kollen, 2013).

MATERIALS AND METHODS

PARTICIPANTS

The "Functional Prognostication and disability study on stroke" (FuPro-stroke) database was used for the current study. The aim of FuPro-stroke was twofold: first, to determine which functional outcome measures are most effective in a stroke population; and second, to investigate prognostic factors of functional outcome and recovery up to 3 years post-stroke onset. In FuPro-stroke, 318 patients were selected from stroke patients consecutively admitted to four Dutch rehabilitation centers for an inpatient rehabilitation program in the period April 2000–July 2002. The inclusion criteria were: (1) first-ever stroke, as revealed by CT or MRI; (2) a one-sided supratentorial lesion; (3) age above 18; and (4) written or verbal informed consent. Exclusion criteria for the FuPro-stroke were: (1) disabling comorbidity [pre-stroke Barthel Index (BI) below 18 (range 0–20)]; (2) premorbid inability to speak Dutch. Exclusion criteria for the present study were: (1) subarachnoid hemorrhage ($n = 34$); (2) no letter cancelation at start of the study ($n = 100$).

PROCEDURE

Patients were included at the start of rehabilitation. Informed consent was obtained. Personal and stroke characteristics were recorded at the first assessment. The scoring of ADL independency and neglect was assessed in the first week of inpatient rehabilitation, and again at 6, 12, and 36 months post-stroke. The study was approved by the Ethics Review Boards of the University Medical Center Utrecht and all participating rehabilitation centers.

OUTCOME MEASURES

The FIM (Linacre et al., 1994; Marshall et al., 1999; Schepers et al., 2006) consists of 18 items assessing level of independence at 5 domains: Self-care [i.e., eating, grooming, bathing, dressing (upper and lower body), toileting], Sphincter control (i.e., bladder and bowel management), Transfers (i.e., bed/chair/wheelchair, toilet, tub/shower), Locomotion (i.e., walk/wheelchair, stairs), and Cognition (i.e., comprehension, expression, social interaction, problem solving, and memory). Each item is scored on a seven-point Likert scale, and the score indicates the amount of observed assistance required to perform each item (1, total assistance, 7, total independence), resulting in a final summed score ranging from 18 up to 126.

Additionally, the patient's medical record was reviewed. The following *admission* to rehabilitation data were captured: age, gender, time post-stroke, hemisphere and subtype of stroke, BI, Motricity Index (MI), Center of Epidemiologic Studies Depression Scale (CES-D), Mini Mental State Examination (MMSE), and sensory deficit in the arm as determined by the Thumb Finding Test (TFT).

The BI (Collin et al., 1988) measures the extent to which stroke patients can function independently in their ADL (i.e., feeding, bathing, grooming, dressing, bowel and bladder control, toileting, chair transfer, ambulation, and stair climbing). Scores range from 0 (completely dependent) up to 20 (completely independent).

The MI (Collin and Wade, 1990) was used to determine the motor functions. There are three items for the arms (i.e., pinch grip, elbow flexion, shoulder abduction) as well as three items for the legs (i.e., ankle dorsiflexion, knee extension, hip flexion). Scores range from 0 (no activity, paralysis) up to 33 [maximum (normal) muscle force] for each dimension, with a maximum total score of 100.

The CES-D (Shinar et al., 1986; Parikh et al., 1988) was used to determine the magnitude of depressive symptomatology. Scores range from 0 (no depressive symptoms) up to 60 (many depressive symptoms). It investigates mood over the past 7 days.

Cognitive status was measured with the MMSE (Folstein et al., 1975). It is a 30-point questionnaire used for screening orientation, memory, attention, calculation, language, and construction functions. Scores vary from 0 (severe cognitive impairments) up to 30 (no cognitive impairments). A score of less than 24 is considered as cognitive impairment.

In the TFT (Kalra and Crome, 1993; Rieck and Moreland, 2005), the patient is asked to find his thumb with his unaffected hand, while the affected arm supported in front and eyes are closed. Scores vary from 0 (unable) up to 3 (no deficit).

The Letter Cancelation Test (LCT, Lezak, 1995) was used to categorize patients as neglect or non-neglect. In the LCT, patients need to cancel O's among other letters to demonstrate presence and severity of neglect. Patients were requested to cross all O's on a sheet of A4 paper containing 20 O's on the left side and 20 O's on the right, among 425 distractor letters in total. Both target and distractor letters were arranged in random order throughout the page. The difference in number of crossed letters on the contralesional and ipsilesional side was used to indicate neglect [i.e., an asymmetry of at least two omissions[1] between contralesional and ipsilesional sides (Kelley and Kovacs, 1986)] and hence, categorize patients as neglect or non-neglect. Severity of neglect was indicated by the magnitude of this asymmetry.

STATISTICAL ANALYSES

Demographics and stroke characteristics of the neglect and no-neglect patients were compared using Mann–Whitney *U* tests.

The extent of recovery of dependency for functional activities explained by time was estimated using random coefficient analysis with MLWin (Rasbash et al., 2009a,b,c). The advantages of using random coefficient analysis in this case are, first, the explicit "time" variable and second, the efficiency when number of time-dependent measures across individuals varies. As such, information about change within an individual as well as across individuals will be taken into account. Observed differences in change across individuals can be associated with individual characteristics (i.e., important predictors of change over time) (Singer and Willet, 2003).

The iterative generalized least-squares (IGLS) was used to estimate the regression coefficient (Singer and Willet, 2003). Regression coefficients were calculated for the association between outcome (FIM domains: Self-care, Sphincter control, Transfers, Locomotion, and Cognition) and neglect at admission and time, corrected for motor impairment (MI), sensory deficits (TFT), dependence (BI), and magnitude of depressive symptomatology (CES-D) at admission, to certify that potential differences between groups are attributable to neglect and not to other group differences. In addition, interaction terms (neglect × time) were fitted to determine if the post-stroke relationship between neglect at admission (with non-neglect as reference) and outcome was dependent upon the time of measurement.

Additionally, regression coefficients were calculated (neglect patients only) for the association between outcome (FIM domains: Self-care, Sphincter control, Transfers, Locomotion, and Cognition) and neglect severity (i.e., magnitude of asymmetry in left versus right sided omissions on the LCT).

The Wald-test was used to obtain *p*-values for the regression coefficients (Twisk, 2006). For all tests, a two-tailed significance level of 0.05 was used.

[1] One might argue that this cut-off value is rather liberal. Therefore we also grouped patients with a less liberal asymmetry (4); this did not change the results. Therefore, we chose to keep the asymmetry of 2 as criterion for neglect, in line with the norms of the test.

RESULTS

DEMOGRAPHIC AND STROKE CHARACTERISTICS

In the present aim, 184 patients (mean age: 57.42, SD: 11.09) were included from the original FuPro-stroke database. In general, patients were relatively young and infarctions were more frequent than hemorrhages. Neglect was present at admission in 28.80%. An overview of all demographics and stroke characteristics of the neglect and no-neglect patients is given in **Table 1**. The groups did not differ with respect to age, gender, time post-stroke, and cognitive impairment. In line with literature, the brain lesion was located in the right hemisphere in most of the neglect patients, whereas this was more equally distributed in the non-neglect patients. Overall, neglect patients showed more sensory deficits, were more impaired in motor functions for both upper and lower extremities and more dependent in ADL at start of the study compared to non-neglect patients, as measured with the TFT, MI, and BI respectively. Furthermore, neglect patients showed more depressive symptoms compared to non-neglect patients.

RANDOM COEFFICIENT ANALYSIS

For Self-care, neglect patients scored approximately four points lower at start compared to non-neglect patients, and with each subsequent measurement, this difference decreased with approximately one point (**Table 2**). For Transfers, neglect patients scored approximately three points lower compared to non-neglect patients, and with each subsequent measurement this difference decreased with approximately one point. Finally, for Locomotion, neglect patients scored approximately two points lower compared to non-neglect patients, and with each subsequent measurement this difference decreased with approximately one point. No differences in time-dependent patterns of recovery were found for Sphincter control and Cognition.

RELATION BETWEEN SEVERITY OF NEGLECT AND ADL

This analysis was performed with neglect patients only. On average, neglect patients showed an asymmetry of 7.62 (SD = 4.16; asymmetry range: 3–19 omissions) omissions on the left versus right side. Patients with more severe neglect scored significantly lower on Self-care and Transfers. No relation between neglect severity and Sphincter Control, Locomotion, and Cognition was found (see **Table 3**). There was a positive relation between time and all levels of the FIM; with each subsequent measurement, independence on all levels increased (see **Table 3**). There were no significant interactions between neglect severity and time for any of the levels of the FIM (no modification of the effects; overall, $p > 0.172$), hence, the interaction term was removed from the model.

DISCUSSION

The aim of the current study was to investigate the relation between neglect and recovery patterns of Self-care, Sphincter control, Transfers, Locomotion, and Cognition up to 3 years post-stroke. Results indicated markedly lower scores for patients with neglect on the Self-care, Transfers, and Locomotion scales of the FIM, compared to non-neglect patients at start of the study. These differences decreased with progress of time. For Sphincter control and Cognition, similar scores and time-dependent recovery patterns were found for both groups. Additionally, patients with more severe neglect were more dependent for Self-care and Transfers, but no relation between neglect severity and Sphincter control, Locomotion, and Cognition was found. There was also no relation between neglect severity and time-dependent recovery for any of the levels of the FIM.

Earlier studies also compared ADL performance between neglect and non-neglect patients, yet did not differentiate between

Table 1 | Demographical and stroke characteristics per group (neglect versus non-neglect) at admission.

Clinical variables	Neglect (SD)	Non-neglect (SD)	Statistics
Group size	53	131	
Age in years	55.5 (10.29)	58.1 (11.33)	$U = 3846$, $Z = -1.362$, $p = 0.173$
Gender (female)	47.2%	35.1%	$U = 3053$, $Z = -1.517$, $p = 0.129$
Time post-stroke in days	56.1 (29.84)	47.6 (20.31)	$U = 4530$, $Z = -1.247$, $p = 0.212$
Hemisphere of stroke (*R*)	88.7%	51.9%	$U = 2195$, $Z = -4.65$, $p < 0.001$
Subtype of stroke			$U = 2503$, $Z = -3.21$, $p = 0.001$
Cortical ischemic (%)	73.6	51.0	
Subcortical ischemic (%)	18.9	28.2	
Intracerebral hemorrhage (%)	7.5	19.8	
BI (0–20)	10.5 (4.2)	13.2 (4.3)	$U = 1174$, $Z = -2.97$, $p = 0.003$
MI UE (0–100)	32.6 (31.1)	58.8 (28.2)	$U = 1842$, $Z = -4.94$, $p < 0.001$
MI LE (0–100)	47.4 (29.9)	58.7 (23.3)	$U = 2689$, $Z = -2.33$, $p = 0.020$
MI total (0–100)	40.0 (28.6)	58.7 (23.3)	$U = 2150$, $Z = -3.99$, $p < 0.001$
CES-D (0–41)	17.3 (9.4)	12.2 (9.3)	$U = 2218$, $Z = -3.46$, $p = 0.001$
MMSE (0–30)	25.6 (2.8)	26.3 (2.6)	$U = 2883$, $Z = -1.63$, $p = 0.103$
Sensory deficit (TFT)			$U = 2276$, $Z = -3.838$, $p < 0.001$
Problem (%)	63.5	36.3	

BI, Barthel Index; MI, Motricity Index; UE, upper extremities; LE, lower extremities; CES-D, Center of Epidemiologic Studies Depression Scale; MMSE, Mini Mental State Examination; TFT, Thumb Finding Test.

Table 2 | Regression coefficients, confidence intervals (CI), and level of significance for the analysis of time-dependency of recovery between the neglect and non-neglect of the dimensions of the Functional Independence Measure (Self-care, Sphincter control, Transfers, Locomotion, and Cognition), corrected for motor impairment (Motricity Index), sensory deficits (Thumb Finding Test), dependence (Barthel Index), and magnitude of depressive symptomatology (CES-D) at admission.

Task	β value	CI	*P*-value
Self-care			
Neglect	3.79	1.79 to 5.79	<0.001
Time	1.73	1.18 to 2.28	<0.001
Neglect × time	−0.92	−1.57 to −0.28	0.005
Sphincter control			
Neglect	0.11	−0.59 to 0.81	0.764
Time	0.37	0.17 to 0.56	<0.001
Neglect × time	−0.15	−0.38 to 0.08	0.198
Transfer			
Neglect	3.11	1.85 to 4.36	<0.001
Time	1.83	1.46 to 2.21	<0.001
Neglect × time	−1.01	−1.46 to −0.58	<0.001
Locomotion			
Neglect	2.16	1.00 to 3.33	<0.001
Time	1.71	1.36 to 2.06	<0.001
Neglect × time	−0.70	−1.11 to −0.30	0.001
Cognition			
Neglect	0.03	−0.95 to 1.01	0.947
Time	−0.62	−0.88 to −0.37	<0.001
Neglect × time	0.02	−0.28 to 0.32	0.912

Table 3 | Bivariate regression coefficients, confidence intervals (CI), and level of significance for the analysis of time-dependency of recovery of the dimensions of the Functional Independence Measure (Self-care, Sphincter control, Transfers, Locomotion, and Cognition) as a function of neglect severity (for neglect patients only).

Task	β value	CI	*P*-value
Self-care			
Severity	−0.506	−0.748 to −0.271	<0.001
Time	1.59	0.70 to 2.48	<0.001
Sphincter control			
Severity	−0.060	−0.127 to 0.007	0.078
Time	0.327	0.07 to 0.58	0.012
Transfer			
Severity	−0.181	−0.344 to −0.018	0.029
Time	1.83	1.25 to 2.41	<0.001
Locomotion			
Severity	−0.104	−0.245 to 0.037	0.149
Time	1.59	1.09 to 2.10	<0.001
Cognition			
Severity	0.017	−0.071 to 0.105	0.706
Time	−0.67	−1.00 to −0.34	<0.001

different domains of ADL. For example, Cherney et al. (2001) and Katz et al. (1999) found that FIM Motor total scores were significantly lower for neglect patients compared to non-neglect patients. In these studies, patients were tested three times: at admission to a rehabilitation facility, at discharge, and either 3 (Cherney et al., 2001) or 6 months after discharge (Katz et al., 1999). Even though, in both these studies, the initial performance of neglect patients was lower for the Motor items, the results are largely in line with our results; neglect patients scored significantly lower compared to non-neglect patients up to 6 months after discharge. A major strength of the current study compared to the other two studies is that measurements were fixed in times, rather than using a relative moment (i.e., discharge), minimizing variation due to differences in the time elapsed since stroke. Additionally, the current results specified that the patterns of recovery differed for the functional domains of the FIM.

In both the current study as well as the study of Cherney et al. (2001), no differences were found for FIM Cognition scores. Katz et al. (1999), however, did find significant differences between neglect and non-neglect patients with respect to Cognition scores. Katz et al. (1999) showed that patients with severe neglect had lower scores on Cognition items of the FIM compared to patients with less severe neglect. We did not find such a relation between neglect severity and cognition. This discrepancy between studies might be explained by the level of cognitive function at start of study. Here, patients were only included when performance on the LCT was available at start of the study. As such, patients with other cognitive impairments (e.g., language problems) restricting performance on the LCT were excluded. MMSE scores for both neglect and non-neglect groups in the current study were fairly high and might explain the confined influence of neglect on cognitive functions. It is important to note, that the MMSE is a short and broad screening list and the Cognition part of the FIM is an observation scale and as such do not give a full and detailed measure of cognitive performance like when using neuropsychological or experimental tests. It might be that differences between groups would have appeared when using tests with a strong time component, either in duration (e.g., sustained attention versus "rapid" changes) or *ad hoc* decision making in a dynamic environment.

Further examination of demographical and stroke characteristics indicates that, at admission, neglect patients showed more depressive symptoms compared to non-neglect patients. This is in line with the results of Nys et al. (2006) who found that among all cognitive disorders, neglect was the greatest risk for depressive symptoms in the long term. Additionally, neglect has been negatively associated with life satisfaction 1 year post-stroke (Verhoeven et al., 2011).

For skill acquisition, it is important to make a distinction between *restitution* of function (i.e., regaining the ability to perform a given task through the same pre-stroke pattern of activation, Levin et al., 2009) and *substitution* of function (i.e., regaining the ability to perform a given task, but not necessarily through the same pre-stroke pattern of activation, Levin et al., 2009). The former is related to neurological recovery (Krakauer et al., 2012) within the first months post-stroke (Kwakkel et al., 2004; Nijboer et al., 2012), whereas the latter is related to compensatory responses (Krakauer et al., 2012), which are likely to account for recovery after 3 months post-stroke (Kwakkel et al., 2004; Nijboer et al., 2012). As the first follow-up measurement was done 6 months post-stroke, no distinction can be made between restitution and substitution of function in the first few months post-stroke. The question therefore remains whether neglect has a negative influence on spontaneous recovery of functions in the first months post-stroke.

A second possible limitation is ceiling effects, which may be responsible for a relatively long period of stability in recovery (Kwakkel and Kollen, 2013). As such it may be that a difference between groups in magnitude or pattern of recovery may exist, yet the scale will be unable to capture it. With for example the Frenchay Activities Index (Pedersen et al., 1997; Schepers et al., 2006), extended ADL, which require initiative from the patients, are measured. The limitation is that this index cannot be used during the admission to a rehabilitation center, but might be of value during follow-up.

Finally, it is important to note that all patients included in this study received inpatient rehabilitation after hospitalization, which might impede the generalizability. In general, patients referred to inpatient rehabilitation are relatively young and moderately disabled. We did not, however, find a relationship between age and neglect, suggesting that the relatively young age of our sample age does not limit the generalizability of our results.

In conclusion, neglect has a negative influence on functional independence in Self-care, Transfers, and Locomotion, especially in the sub-acute phase. During rehabilitation, it would be of importance to test for *independence in ADL* in neglect in order to define realistic treatment goals. The current findings could be taken into account in early multidisciplinary intervention planning in the sub-acute phase, to optimize regaining ADL.

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Hemispatial neglect: computer-based testing allows more sensitive quantification of attentional disorders and recovery and might lead to better evaluation of rehabilitation

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Past studies aiming to test the effectiveness of rehabilitation techniques for hemispatial neglect have been often criticized for a number of methodological limitations, from non-random assignment to the groups, to absence of blind scoring (Cicerone et al., 2000; Cappa et al., 2005; Bowen and Lincoln, 2007; Paci et al., 2010; Teasell et al., 2011). While it seems that these shortcomings are being addressed by more recent studies, we here maintain that a major methodological improvement in studies of neglect rehabilitation might derive from the adoption of computer-based assessment, which has several advantages over the commonly used bed-side clinical or paper-and-pencil (PnP) tests. These more sensitive measures of neglect may provide a more accurate assessment of the effect of rehabilitation procedures, which may be missed with the currently employed classical measures of neglect, and may provide an indication for rehabilitation in patients who are currently not treated because of their normal performance on PnP tests.

Unfortunately, to our knowledge, there are very few rehabilitation studies utilizing such diagnostic tasks and they are mostly focused on rehabilitation of sustained attention (DeGutis and Van Vleet, 2010; Van Vleet and Degutis, 2013; see also Finke et al., 2012).

Paper-and-pencil tests are routinely adopted to measure patients' performance after stroke. They are used in the acute phase to select the patients which will undergo rehabilitation, and in the chronic phase to monitor patients' performance before, during, and after rehabilitation. PnP tests suffer however from various limitations which are particularly evident when the tests are repeatedly administered during recovery (see Deouell et al., 2005 for discussion). First, PnP tests typically do not change from one examination to the next, allowing for significant learning and compensatory strategies. Second, they are static, further allowing the implementation of compensatory strategies while not reflecting the dynamic character of the natural environment. These characteristics, coupled with the fact that only accuracy is measured, lead to early "normalization" of PnP scores, or a ceiling effect, when the patient may still demonstrate significant behavioral abnormalities in everyday life situations. Furthermore, in cancellation tests, a common type of PnP test, the tests are typically summarized into a single score, with no indication of performance variance which may be in itself a sensitive marker of the deficit (Anderson et al., 2000).

The sensitivity of some PnP tests may be increased by scoring measures that are sensitive to specific deficits. However, most of finer-grained approaches to PnP test scoring cannot be applied *a posteriori*, even when the raw tests are available [with the exception of the Center of Cancellation (Rorden and Karnath, 2010) for cancellation tasks]. For instance, execution time or start- and end-point require additional information to be registered by a trained examiner while performing the test (Manly et al., 2009; Buxbaum et al., 2012), which is not always feasible. Moreover, they provide only gross measures of performance with respect to the wealth of information potentially available through computer-based tests. The quantitative assessment of drawing tests is also problematic given the heterogeneity of potential errors (Seki and Ishiai, 1996), and paucity of normative data. Overall the sensitivity of the PnP tests in the post-acute and chronic phases cannot be considered satisfactory (Azouvi et al., 2002; Deouell et al., 2005; Hasegawa et al., 2011; Bonato, 2012). Thus, whereas PnP tests may be acceptable to assess neglect at the bed-side in the acute phase (Nijboer et al., in press), at later stages computer-based tasks provide more sensitive and informative assessment, allowing to detect contralesional impairments in performance even in patients who perform normally at PnP tests (Schendel and Robertson, 2002; Deouell et al., 2005; Erez et al., 2009; Bonato, 2012; van Kessel et al., 2013).

Compared to PnP tests, more sensitivity and flexibility is offered by computerized tests (Schendel and Robertson, 2002; List et al., 2008), which typically record much more information (e.g., accuracy and reaction time measures simultaneously). Stimuli may be presented in varying locations and times across trials, sessions, and sensory modalities, and repeated many times (Deouell et al., 2005; Bonato et al., 2010; Buxbaum et al., 2012; Van Vleet and Degutis, 2013). Various difficulty levels can be easily implemented and eventually combined with concurrent tasks to manipulate the load, and may be combined with other measures (e.g., eye movements, Van der Stigchel and Nijboer, 2010; touch screen recording, Rabuffetti et al., 2012). These features, along with the addition of RT measures, reduce the chances for ceiling effects and allow for quantitative, continuous measures, and even significance levels in single patients, including sensitive individual monitoring of performance changes through repeated assessments. Because of their unpredictable nature (presenting stimuli in random places, shapes, and times), the computerized tests are harder to learn, and to develop compensatory strategies for. They are thus more suitable for test-retest designs, which are a *sine qua non* in rehabilitation studies. Moreover, since computerized tests are hard-coded, their administration is less sensitive to the identity of the experimenter and environmental variability.

The sensitivity of computer-based approaches was evident in recent studies (Bonato et al., 2010, 2012, 2013) in which the presentation of brief lateralized stimuli was combined with resource-demanding tasks, two methodological characteristics which maximize the possibility to detect contralesional omissions. Post-acute (1–3 months from stroke) right-hemisphere damaged patients were tested in three conditions. In the single-task condition only the position of the target(s) had to be verbally reported. In the two dual-tasks, while monitoring for target(s) appearance, patients also had to perform a concurrent task. In the visual dual-task they had to report a centrally presented letter, while in the auditory dual-task they had to count at steps of two from an auditorily presented number. Both extinction rate for bilateral targets and omission rate for unilateral contralesional targets dramatically increased under dual-task conditions, even in patients who were normal according to clinical standards for neglect such as the Behavioral Inattention Test (BIT, Wilson et al., 1987). A patient who was followed-up for several months after discharge and showed deficits during the dual-task conditions, similarly showed severe deficits in attention-demanding everyday life contexts (Bonato et al., 2012) despite normal performance at the BIT. Another sensitive approach has been proposed by Deouell et al. (2005) using the Starry Night Test (SNT). In the SNT, relatively brief targets can appear in many spatial positions on a computer screen. Spatial uncertainty plausibly deploys attentional monitoring resources and hampers the implementation of compensatory strategies. Moreover, in the SNT, the presence of flickering distracters across the display does not allow patients to respond as soon as something appears on the screen (pop-out) but forces them to identify the target before responding. Deouell et al. demonstrated a higher sensitivity in the SNT compared to the BIT at the individual level, and described in detail the deficits shown in everyday life by a patient whose neglect was only evident in the SNT (see also Erez et al., 2009). Moreover, some patients with normal behavior by the BIT at the early stage, who showed slow reaction times on the left in the SNT, achieved more symmetric RTs after a period of recovery (Sacher et al., 2004).

The Dual-Task, and the SNT paradigms were described in some detail above to illustrate the principle based on our own experience, and not in order to endorse those specific tests over others. Several other computerized tests were shown to unveil unilateral neglect (see Bonato, 2012 for review). These tests include variants of visual perimetry (Müller-Oehring et al., 2003; Nijboer et al., 2011), variants of the classic Posner-like detection tasks which can provide RTs measures for contralesional vs. ipsilesional hemispace (Bartolomeo, 1997; Nijboer et al., 2008; Rengachary et al., 2009), feature and conjunction search tasks (Erez et al., 2009), as well as tasks manipulating load (e.g., Russell et al., 2004, in press; Buxbaum et al., 2008, 2012; Dawson et al., 2008; Bellgrove et al., 2013; van Kessel, et al., 2010, 2013). These computer-based tasks are typically well tolerated by patients in the post-acute and chronic phases after a stroke, when tasks' differential sensitivity with respect to PnP tests is maximal. Dealing with a computer is, typically, relatively easier for those patients without neglect at PnP tests.

Although no study to date compared the sensitivity of these heterogeneous computer-based tests, most if not all demonstrated improved sensitivity to residual deficits with respect to standard clinical tests. Moreover, these tasks can be more easily tailored to recruit cognitive resources close to those adopted in everyday life, reducing the gap between everyday life and neuropsychological testing. Given that the average performance in PnP tests is frequently dissociated from performance in everyday life (Hasegawa et al., 2011), it has been considered mandatory to resort to independent measures to quantify impairments in ADL (Azouvi et al., 2002). While the final aim of rehabilitation is to increase the independence of the patients, the scales adopted to measure everyday performance such as FIM, Barthel, and Bergego only allow quantifying disability in "easy" tasks such as eating or dressing, but do not appear to be sensitive enough to detect either subtle neglect in complex settings or small differential improvements in everyday life activities. Additionally, they do not discern whether performance is impaired due to contralesional motor, intentional, or attentional problems or to a combination of those deficits (but see Eschenbeck et al., 2010 for neglect-specific ADL assessment). It seems that, somewhat paradoxically, in computer-based tasks allowing less compensatory strategies, the dissociation between daily life and testing performance which often characterizes the chronic phase is reduced relative to the PnP tests. By virtue of their added level of complexity and flexibility, computerized tasks have the potential to simulate the performance of patients in everyday life by reproducing the cognitive demands everyday life requires. After their discharge from the hospital, some patients performing normally at PnP tests but showing impairments in computer-based tasks also show severe impairments in everyday life (Deouell et al., 2005; Bonato et al., 2012). Furthermore, performance at computer-based tasks may correlate with ADL performance (Erez et al., 2009) and with a real world task (Buxbaum et al., 2012). Notably, the performance of older drivers in a computer-based visual dual-task (UFOV) is highly predictive of car crash problems (Ball et al., 1993, see also the case report in Deouell et al., 2005). Thus, computer-based approaches may eventually help clinicians in evaluating and predicting individual performance in everyday demanding situations. A first step for future research would be to further establish the ecological validity of these new tests and their correlation with the level of disability and handicap.

Despite the advantages of the computerized tests, we do not suggest that time honored PnP should be completely discarded. Over the years, many such tests have been developed, likely capturing non-overlapping aspects of neglect. Although patients' individual performance often dissociates according to the task and spatial domain under investigation (Halligan and Marshall, 1991; Azouvi et al., 2002; Buxbaum et al., 2004; Sacher et al., 2004; Sarri et al., 2009) computerized tests tapping all the multiple components of neglect are still missing. Computerized tests also have practical limitations, as normative data are not present for all tests and they require dedicated hardware and software not always available at the clinical setting, although this is likely to become less of a problem in the (near) future.

To conclude, we argue that the inclusion of quantitative, standardized, computerized tests, recording a continuous measure like RT, as well as accuracy, and allowing to increase task difficulty to reduce the effect of compensatory strategies, have major advantages over traditional PnP tests in the context of evaluating spontaneous recovery and the effects of rehabilitation interventions. The sensitivity of these methods have the potential of detecting ecologically meaningful improvements in patients' performance, which are missed using traditional PnP tests. More effort needs to be done in devising such tests that will tap into various aspects of UN, correlated with the patients' handicap. Like jewelers weighing precious stones, neuropsychologists need to adopt sensitive scales before and after the implementation of a valuable technique for neglect rehabilitation.

AUTHOR NOTE

To obtain copies of the dual-task or of the SNT task, contact mariobonato@hotmail.com or msleon@mscc.huji.ac.il.

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Advancing the science of spatial neglect rehabilitation: an improved statistical approach with mixed linear modeling

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Valid research on neglect rehabilitation demands a statistical approach commensurate with the characteristics of neglect rehabilitation data: neglect arises from impairment in distinct brain networks leading to large between-subject variability in baseline symptoms and recovery trajectories. Studies enrolling medically ill, disabled patients, may suffer from missing, unbalanced data, and small sample sizes. Finally, assessment of *rehabilitation* requires a description of continuous recovery trajectories. Unfortunately, the statistical method currently employed in most studies of neglect treatment [repeated measures analysis of variance (ANOVA), rANOVA] does not well-address these issues. Here we review an alternative, mixed linear modeling (MLM), that is more appropriate for assessing change over time. MLM better accounts for between-subject heterogeneity in baseline neglect severity and in recovery trajectory. MLM does not require complete or balanced data, nor does it make strict assumptions regarding the data structure. Furthermore, because MLM better models between-subject heterogeneity it often results in increased power to observe treatment effects with smaller samples. After reviewing current practices in the field, and the assumptions of rANOVA, we provide an introduction to MLM. We review its assumptions, uses, advantages, and disadvantages. Using real and simulated data, we illustrate how MLM may improve the ability to detect effects of treatment over ANOVA, particularly with the small samples typical of neglect research. Furthermore, our simulation analyses result in recommendations for the design of future rehabilitation studies. Because between-subject heterogeneity is one important reason why studies of neglect treatments often yield conflicting results, employing statistical procedures that model this heterogeneity more accurately will increase the efficiency of our efforts to find treatments to improve the lives of individuals with neglect.

Keywords: spatial neglect, rehabilitation, mixed linear modeling, statistical methods, power simulation, type I error simulation

INTRODUCTION

Spatial neglect, a deficit in perceiving, orienting, or initiating action toward stimuli in contralesional space (Heilman et al., 2003), affects an estimated one half of right hemisphere stroke survivors annually (Paolucci et al., 2001; Buxbaum et al., 2004; American Heart Association, 2011; Nijboer et al., 2013). Individuals with spatial neglect experience greater disability than do other stroke survivors (Buxbaum et al., 2004; Jehkonen et al., 2006): they have longer hospitalizations (Kalra et al., 1997), poorer rehabilitation outcomes (Gillen et al., 2005), and greater incidence of chronic functional disability (Paolucci et al., 2001). Thus, there is an urgent need to identify therapies that successfully induce recovery of neglect-related cognitive and motor impairment. Our ability to identify these therapies, however, is constrained by the methods we use to assess them.

We argue that the statistical approach typically employed in studies of neglect rehabilitation – repeated measures ANOVA (rANOVA) – is inappropriate given the characteristics of the neglect syndrome and the nature of neglect rehabilitation research. In this research, typically two or more patient groups are assessed prior to the administration of an experimental or control treatment and assessed again one or more times after the treatment. The critical question is whether the amount of change across the assessments is different for the different treatment[1] groups. Thus, in assessing change across time, rehabilitation research studies are longitudinal studies. We argue that it is time for neglect rehabilitation scientists to join many other psychological scientists in using mixed linear modeling (MLM) for longitudinal data analysis.

Here we first review techniques currently employed in rehabilitation studies of neglect. We then review key characteristics

[1]In the current paper, the terms *treatment* and *rehabilitation* are used interchangeably, given that the goal of most neglect treatment studies is rehabilitation. However, these two terms can have distinct meanings: treatment sometimes refers to interventions designed to address only symptoms of a disorder, while rehabilitation consistently refers to interventions designed to ameliorate the underlying cause of symptoms.

of neglect that critically impact the kind of data rehabilitation researchers encounter, discussing how current techniques fail to adequately address these issues. Finally, we introduce MLM and show how it more appropriately accounts for the inherent variability in the neglect syndrome, allowing for more accurate estimation of treatment-related parameters. Using both real and simulated data, we demonstrate the superior ability of MLM to discriminate recovery trajectories of patient groups relative to rANOVA. Although authors in several fields have deemed MLM superior to rANOVA for most longitudinal and repeated measures data (e.g., Tate and Pituch, 2007; Kwok et al., 2008; Pietrzak et al., 2010; Bernal-Rusiel et al., 2013), neglect rehabilitation researchers have yet to embrace this approach. Our goal in the current paper is to contrast MLM with rANOVA, the analysis technique most frequently used in neglect rehabilitation. Furthermore, in an effort to guide nascent MLM users in the field of neglect rehabilitation, we provide power and Type I error analyses for data structures like those encountered in neglect research. These analyses result in recommendations for the design of future neglect rehabilitation studies.

Table 1 | Status of current data analysis in neglect rehabilitation.

Statistical technique	Number of studies	Mean sample size (min, max)	Mean measurement waves (min, max)
t Test	14	17.1 (4, 39)	2.6 (2, 4)
rANOVA	45	17.9 (4, 40)	2.7 (2, 6)
MANOVA	1	20 (20, 20)	6 (6, 6)
Non-parametric	15	16.5 (10, 30)	2.5 (2, 4)
One-way ANOVA	1	60 (60, 60)	3 (3, 3)
MLM	1	21 (21, 21)	6 (6, 6)
None	1	15 (15, 15)	3 (3, 3)
Total	78	18.1 (4, 60)	2.8 (2, 6)

rANOVA, repeated measures ANOVA.

Variance-Covariance Matrix

	1	2	3	4	5
1	σ^2	COV	COV	COV	COV
2	COV	σ^2	COV	COV	COV
3	COV	COV	σ^2	COV	COV
4	COV	COV	COV	σ^2	COV
5	COV	COV	COV	COV	σ^2

FIGURE 1 | Variance-covariance matrix depicting homogeneity of variance and compound symmetry assumptions of a repeated measures ANOVA with six repeated assessments.

CURRENT ANALYSIS TECHNIQUES AND THEIR ASSUMPTIONS

The assessment of individuals at multiple points over time leads to nested and correlated data structures: assessments over time are nested within each subject. These measurements taken from the same subject are likely to be more similar to one another than those taken from different subjects (Raudenbush, 2009). Thus, neglect rehabilitation data involves dependent, rather than independent, observations. This dependence among observations renders the use of some statistical procedures such as linear regression or analysis of variance (ANOVA) inappropriate, while other statistical methods such as the dependent samples *t* test, rANOVA, and multivariate ANOVA (MANOVA) may be appropriate under certain circumstances.

We performed a review to assess the current use of statistics in neglect rehabilitation studies: we identified studies for the review via a PubMed literature search using three sets of search terms: "neglect" and "rehabilitation"; "spatial neglect" and "treatment"; and "visual neglect" and "treatment." We included in our review neglect treatment studies that performed statistical group comparisons of two different neglect treatments, or of a treatment to a control group, or of a group to themselves (e.g., crossover design), with a minimum of two assessment time-points (minimum pre-post). We included only human rehabilitation studies.

Our review identified 78 studies meeting the above criteria, published between January, 1990, and December, 2012. **Table 1** depicts key characteristics of these studies' design and analyses. As can be seen in the Table, the majority of neglect rehabilitation studies employed rANOVA. The average sample size was 18.11 (SD = 10.58, median = 14.5), but 25% of the studies had total sample sizes of 11 or fewer. Of the 78 studies, 34 studies employed only pre-post measurement (i.e., two measurement waves); 33 employed three measurement waves; 8 employed four waves and three studies employed six waves. Thus, most studies employed rANOVA, had two assessment sessions/measurement waves, and had sample sizes of 15 or less.

Repeated measures ANOVA, the most frequently employed statistical technique, makes three primary assumptions: (1) normality; (2) homogeneity of variance; and (3) either compound symmetry or sphericity (Twisk, 2003). Normality is the assumption that residual variance is normally distributed. Homogeneity of variance is the assumption that variances at all assessment points (and in all groups) are equal. Compound symmetry is the assumption that covariances between all measurement points are equal. **Figure 1** represents these latter two assumptions in a variance-covariance matrix for a study with six repeated assessments. The variances at each assessment point are equal (main diagonal) and the covariances between all assessment points are equal (tip: read the Figure like a correlation table, with covariances as squared correlations). A less stringent way of approximating the compound symmetry requirement is the sphericity assumption, which is the assumption that all possible pairs of difference scores between the repeated measures have the same variance (see Rabe-Hesketh and Skrondal, 2012, p. 264, for a more detailed description of compound symmetry vs. sphericity). Data meeting the compound symmetry assumption meets sphericity, but not vice versa. In addition to these assumptions, ANOVA requires complete data, as well as relatively equal samples sizes to ensure homogeneity of variance (Fitzmaurice and Molenberghs, 2009).

Among the other statistical techniques employed in neglect rehabilitation research, MANOVA does not require sphericity or compound symmetry, but it does require normality. Dependent samples *t* tests also require both normality and homogeneity of variance. While non-parametric tests do not entail strict assumptions about the data structure, these are less powerful to detect effects, particularly with violations of homogeneity of variance, and are more limited in their use (e.g., inability to directly test interactions; Siegel and Castellan, 1988; Zimmerman, 1998). Furthermore, similar to ANOVA, the MANOVA, *t* test, and non-parametric test all require complete data, with MANOVA and *t* tests also requiring relatively equal cell sizes (Twisk, 2003; Fitzmaurice and Molenberghs, 2009).

THE NEGLECT SYNDROME AND NEGLECT REHABILITATION DATA

Here we review characteristics of the neglect syndrome that affect the structure of neglect rehabilitation data. Some of these characteristics create particular issues for the neglect rehabilitation researcher, while other characteristics create issues that are common amongst longitudinal patient-based research studies. As we discuss in detail below, rANOVA falls short in handling each of these issues.

Between-subject heterogeneity

Working in the area of neglect rehabilitation presents a special challenge: neglect is not a homogeneous disorder. Rather, spatial neglect is a syndrome resulting from disruption in potentially distinct brain networks, leading to diverse impairments, such as object-centered neglect, perceptual-attentional "where" spatial dysfunction, and motor-intentional "aiming" spatial dysfunction, any one of which may or may not be present in a given patient (Na et al., 1998; Barrett and Burkholder, 2006; Hillis, 2006; Verdon et al., 2010; Corbetta and Shulman, 2011). As a result, there is variability across patients both in the type and severity of symptoms prior to treatment, as well as in how those symptoms change over time either with or without treatment (e.g., Hamilton et al., 2008; Manly et al., 2009; Rengachary et al., 2011; Goedert et al., 2012; Nijboer et al., 2013). Thus, neglect rehabilitation demands a statistical approach that accounts for potentially large between-subject heterogeneity among patients both at baseline and in their recovery trajectories.

In rANOVA, variability due to between-subject differences is modeled with the "subjects" term. As a main effect of subjects, it portrays the total variability in the data due to subjects, averaged over the repeated assessments. Thus, while rANOVA models between-subject variability, it does not distinguish between-subject differences in baseline performance from between-subject differences in recovery trajectories (i.e., slope of the change over the repeated assessments). More accurate modeling of these two separate contributions of subjects to the overall variability in the data has the potential to decrease the amount of error variability, thereby improving power to detect treatment effects. However, the ability to do this eludes the researcher who employs rANOVA.

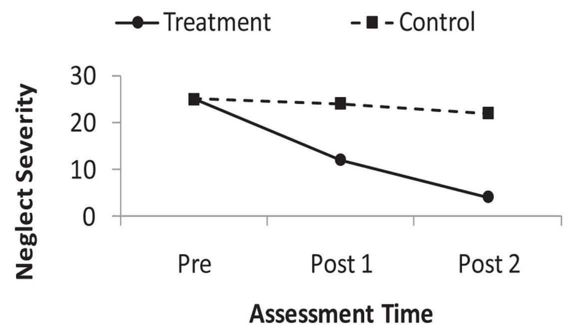

FIGURE 2 | Depiction of fictional, idealized recovery trajectories in the control, and treatment groups of a neglect rehabilitation study. Larger values on the *y*-axis indicate more severe neglect.

Change over time

Although the use of only pre- and post-treatment assessments is very common, evaluating the success of rehabilitation necessitates an interest in change over time – that is, an interest in patients' recovery *trajectories*. Whether a treatment changes the nature of neglect patients' recovery trajectories is a question regarding *continuous* development. **Figure 2** represents the fictional results of an idealized neglect treatment study in which the severity of neglect in both a control and treatment group have been assessed three times. A key question for neglect rehabilitation is whether the slope of the recovery trajectory in the treatment group differs from that of the control group – that is, whether there is a time by group interaction. **Figure 2** represents idealized data as both groups have a similar starting neglect severity and the control group changes little after the treatment (i.e., a very shallow slope on the recovery trajectory), while the treatment group has a steep slope on its recovery over the repeated assessments.

Repeated measures ANOVA does not provide a description of continuous change over time in this situation. In the ANOVA, time is a discrete factor variable, rather than a continuous variable. Thus, were we to analyze the fictional data in **Figure 2** and find a significant group by time interaction, we would know that somewhere among the six means (three assessments for each of the two groups) there were significant differences not accounted for by either the main effect of session or the main effect of group. *Post hoc* tests would be needed to determine where those significant differences were (Twisk, 2003; Keppel and Wickens, 2004). Thus, ANOVA does not provide a descriptive value of the magnitude of the change over time, such as the slope value that is produced in linear regression.

Violations of compound symmetry and sphericity

Although distinct in a number of respects, neglect rehabilitation research also faces problems common amongst studies of change over time (for a review, see Gibbons et al., 2010). Repeated measures taken from the same subjects are likely to be correlated (Twisk, 2003; Raudenbush, 2009). Furthermore, they are likely to have an auto-regressive covariance structure, such that data-points closer together in time tend to be more correlated with one another than data-points farther away in time. That is, the strength of autocorrelation in the data decreases as time between the assessments increases (e.g., Littell et al., 2000; Fitzmaurice and Molenberghs, 2009). For example, referring to **Figure 1**, an auto-regressive structure would be apparent if the correlation (or covariance) between measurements taken at time 1 and 2 were higher than that observed between time 1 and 3.

Given that repeated measures taken from the same individuals often have an auto-regressive covariance structure, the assumptions of compound symmetry and sphericity required for rANOVA may be violated in neglect rehabilitation data. Although one can test for violations of sphericity, these tests are sensitive to sample size and are likely to be significant with small violations of sphericity in large samples and, conversely, fail to reach significance with large violations of sphericity in small samples (Twisk, 2003). When the assumption of sphericity is violated, some researchers have turned to employing corrections on the degrees of freedom from the rANOVA (e.g., Greenhouse and Geisser, 1959), or to non-parametric methods. Both options, however, suffer from reduced power to detect treatment effects. Other researchers choose to employ repeated measures MANOVA, which does not entail the compound symmetry or sphericity assumption, but it does require complete data with relatively equal cell sizes (Twisk, 2003; Fitzmaurice and Molenberghs, 2009).

Correlations between baseline performance and recovery trajectories

In addition to the likelihood of having an auto-regressive covariance structure, there may be a distinct relationship between neglect patients' baseline severity and the slope of their recovery trajectories. Although one might expect that the better-off a patient is at baseline, the less room that patient would have for improvement (e.g., Wang et al., 2009), recent studies of spatial neglect demonstrated the opposite: patients better-off at baseline improved more with a prism adaptation treatment than did more severe patients (e.g., Mizuno et al., 2011; Chen et al., 2012; Goedert et al., 2012). Thus, there is an expectation that subjects' starting point and the slope of their recovery trajectory will be correlated. This correlation is theoretically interesting as it can reveal information about the nature of the neglect treatment (e.g., may only work for less severely impaired patients). Furthermore, this correlation represents systematic variability in the data that can potentially be modeled in an analysis, thereby potentially reducing error variability increasing power. However, it is not possible to model this correlation when using rANOVA.

Small sample sizes, missing data, and unequal cell sizes

Similar to other patient-based longitudinal work, neglect rehabilitation researchers face missing data, unequal cell sizes, and small samples. These issues, however, may be particularly exacerbated when studying neglect: stroke survivors with spatial neglect usually have multiple medical conditions and are, as a group, more disabled than other stroke survivors (Buxbaum et al., 2004; Jehkonen et al., 2006; Paolucci et al., 2010). This makes data collection at rigidly fixed intervals very challenging. When subjects miss an assessment due to circumstances outside the researcher's control (Fitzmaurice et al., 2011), this leads to missing data. Furthermore, neglect is also associated with higher caregiver burden and reduced self-awareness (Buxbaum et al., 2004), which may lead to increased attrition, resulting in unbalanced sample sizes among treatment groups or overall small sample sizes.

AN ALTERNATIVE TO ANOVA: MIXED LINEAR MODELING

Given that as rehabilitation researchers we are interested in change over time, it would be beneficial to adopt a statistical tool developed for the purpose of analyzing change over time. One such tool, MLM or multilevel modeling (also referred to as hierarchical linear modeling, mixed-effects modeling, and random effects analysis), has emerged as a clear alternative to ANOVA for analysis of longitudinal and repeated measures data (see West et al., 2007, for a review). The MLM approach is a regression-based approach that differs from rANOVA in two key respects critical to neglect rehabilitation and other longitudinal research studies: (1) While ANOVA accounts for the correlated structure of repeated measures by modeling a main effect of subjects (i.e., the effect of subjects averaged over the repeated assessments), in MLM one can model subject-level differences in both intercepts (i.e., starting neglect severity) and in slopes (i.e., neglect recovery over time), as well as the correlation between subjects' intercepts and slopes. (2) With ANOVA, one asks whether any of the repeated measurement points differs from any of the others, but with MLM, one obtains a slope of the recovery trajectory that describes how a patient's symptoms change over time.

To introduce MLM, let's take as a starting point the equation for simple linear regression and assume we want to predict neglect severity (Y_i) with assessment time-point as the sole predictor:

$$Y_i = b_0 + b_1(\text{assessment}) + \varepsilon_i \tag{1}$$

Here, Y_i is the predicted Y value at time-point i, b_0 is the group-level intercept and b_1 is the group-level slope on assessment (it describes the average recovery trajectory across all subjects), and ε_i is the residual error variability at time-point i. Because this is a regression analysis, assessment time in Eq. 1 is treated as a continuous predictor. Standard regression, however, assumes independence of observations. It is therefore not appropriate for repeated measures data, such as the repeated assessment of neglect over time. In contrast, MLM is appropriate for repeated measures data.

Although it is a regression-based model, MLM accounts for the dependencies in repeated measures data by separately modeling variability due to subjects, with the option to do so for both between-subject differences in intercepts and between-subject differences in slopes. These subject effects are termed *random effects.* In the case of repeated assessments within subjects, this separate modeling of subject effects occurs via the creation of two levels of regression equations. At the highest level is a regression equation that describes the group-level intercept and slope, as depicted in Eq. 1. This group-averaged intercept and slope are the *fixed effects* in the MLM analysis. At the lowest level in the MLM analysis are subject-specific regression equations representing the random effect of subjects[2]. At this level, the predicted Y differs for each subject j such that:

$$Y_{ij} = (b_0 + b_{0j}) + (b_1 + b_{1j})(\text{assessment}) + e_{ij} \quad (2)$$

Here, Y_{ij} is the predicted Y value at time-point i for subject j, b_0 is the group-level intercept, b_{0j} is the *difference* between subject j's intercept and the group-average intercept, b_1 is the group-level slope, and b_{1j} is the *difference* between-subject j's slope and the group-average slope. Thus, taking Eqs 1 and 2 together, MLM models variability in the intercept and slope as averaged over the group (fixed effects), and it models variability due to individual differences around the group intercept (random intercept), as well as variability due to individual differences around the group slope (random slope). The MLM model can also be constructed so as to estimate the observed correlation between subjects' intercepts and slopes. Although computationally the MLM analysis builds an individual regression equation for each subject, the typical output from statistical packages running MLM analyses provides summary terms for the random intercept and slope, reporting the amount of variance in the data due to these effects. Additional analysis commands can be used to extract the subject-level regressions.

What is the purpose of modeling these random effects? A researcher may desire to model these subject-level random effects because of an interest in the individual variability in its own right. For example, as stated earlier, in the case of prism adaptation treatment for neglect, there appears to be a negative correlation between patients' starting severity (i.e., their intercept) and their response to treatment (i.e., the slope of their recovery trajectory over time; Chen et al., 2012; Goedert et al., 2012). Conversely – or additionally – a researcher may be interested in modeling subject-level random effects as a means of potentially reducing error variability in the statistical analysis, with the possibility of improving power to detect group-level treatment effects (Gueorguieva and Krystal, 2004; Brown and Prescott, 2006; Fitzmaurice et al., 2011). For the neglect rehabilitation researcher, finding a treatment that works at the group-level is the likely goal of this analysis. Thus, the main focus of interpretation in neglect rehabilitation would likely be on the fixed effects (i.e., group-level effects).

Assumptions and decisions when using MLM

Mixed linear modeling is not without its own assumptions. Standard MLM assumes normality in residuals of the fixed and random effects. It assumes homogeneity of variance at all levels of the model, and, like simple linear regression, it assumes a linear relation between the predictor and outcome (Singer and Willett, 2003). While a number of these assumptions are similar to those of rANOVA and MANOVA, with MLM it is possible to modify the standard analysis to accommodate violations of these assumptions.

Indeed, unlike rANOVA, when performing an MLM, the researcher *must* make a number of decisions for how to structure the analysis. One such decision is with regards to the structure of the residual covariance matrix: the residual variability represented by the terms ε and e in Eqs 1 and 2 refer to residual covariance structures (i.e., structures similar to that depicted in **Figure 1**). When performing an MLM, the researcher must decide *whether* to impose assumptions on the covariance structure and what assumptions to impose. For example, one could assume an auto-regressive covariance structure (as described in Violations of Compound Symmetry and Sphericity). A number of different covariance structure choices are available in statistical packages. Alternatively, the researcher could decide to make no assumptions about the residual covariance structure, estimating the covariance directly from the data, thereby rendering homogeneity of variance and other assumptions about the variance-covariance structure unnecessary (e.g., Littell et al., 2000).

Although basic MLM makes assumptions of linearity and normality, like other regression models, the researcher has the option to build non-linear relations into the MLM (e.g., polynomial trends, linear splines; Littell et al., 2000; Singer and Willett, 2003; Twisk, 2003; Davidian, 2009). With MLM (as with regression) non-normality may be accommodated via bootstrapping the standard errors of the intercept and slope parameters (Guan, 2003). Thus, MLM models allow for a better match between the model assumptions and the actual data typically observed in neglect rehabilitation and other longitudinal studies.

However, in MLM one must decide how to evaluate significance of the parameter estimates – i.e., how to assess significance of the fixed intercept and slope. Although assessing the significance of terms in the rANOVA is typically straightforward, the researcher deciding to use a degrees of freedom correction for violations of sphericity (e.g., Greenhouse–Geisser or Huynh–Feldt) is making a decision about how to assess significance. In MLM the primary issue is with regards to estimating degrees of freedom, and different statistical packages provide different options and defaults. For example, in STATA and Mplus, Wald's z is the method for assessing significance, which assumes infinite degrees of freedom. Thus, it is only appropriate for large samples. SPSS and SAS assess significance of fixed effects using an F distribution. They offer different options for computing degrees of freedom for the F test, all of which take into account the size of the sample and number of repeated observations in the analysis. Finally, one must decide whether to use a maximum likelihood estimation procedure or restricted maximum likelihood for the MLM analysis. (A complete discussion of these latter two issues is beyond the scope of the current paper; for a thorough discussion of both, the reader is directed to West et al., 2007, pp. 25–29, 36–38, and 110–113).

[2]Note, in MLM terminology, the random effects of subjects, as described here, would be considered level-1 effects and the group-level fixed effects would be considered level-2 effects. Whether "subjects" are the level-1 or level-2 effects depends, however, on the study design. In a study of patients nested within hospitals, patients would be the lowest level (i.e., level-1) and hospitals would be the higher level (i.e., level-2; see Chapter 1 of West et al., 2007, for a comparison of study designs appropriate for MLM and a description of what constitutes the levels in those designs). One could also create a 3-level model with multiple measurement points (level-1) nested within patients (level-2), which themselves are nested within hospitals (level-3).

Advantages of MLM and a longitudinal modeling approach

Greater power with smaller samples. Because of the immediate, urgent need to move new therapies forward into widely available clinical practice guidelines, neglect rehabilitation research requires an approach that can make use of smaller sample sizes than those required for typical parametric analysis. Because MLM considers the correlated and nested data structure inherent in measuring the same subjects repeatedly, it results in a much more accurate estimation of variance to calculate between-subject treatment effects (Fitzmaurice et al., 2011). Modeling random intercepts and slopes can result in reduced standard errors for the estimates of the fixed effects (Littell et al., 2000; Gueorguieva and Krystal, 2004; Brown and Prescott, 2006)[3]. Thus, MLM can result in greater power to detect group-level differences, as well as in more narrow confidence intervals around the group-level parameter estimates.

Description of the recovery trajectory. A second benefit of the MLM analysis is that it allows us to describe recovery trajectories of treatment and control groups. Again, referring to the fictional data depicted in **Figure 2**, using MLM we could assess the group by time interaction and if we determine it is significant, produce separate group-level slopes for our treatment and control groups. Thus, MLM, like linear regression, yields a metric that describes the magnitude of change over time in our two groups.

Flexible model-building and analysis. An additional benefit of the MLM analysis is that one can readily examine the effects of controlling for additional nuisance variables that may happen to be continuous rather than categorical (e.g., differences in baseline status) or that may be time-varying as opposed to constant across the assessment time-points (Rabe-Hesketh and Skrondal, 2012). Furthermore, these analyses can be conducted while controlling for potential interactions between the continuous predictors and the recovery trajectories (e.g., Cnaan et al., 1997). For example, one could ask whether there were differences in the group-level recovery trajectories while controlling for any improvements across the sessions that may be attributable to baseline status (i.e., while controlling for a baseline status by assessment-session interaction). Although rANOVA and MANOVA can accommodate continuous covariates, one cannot use ANOVA and MANOVA to examine complicated interactions among continuous and factor predictors or among two or more continuous predictors (Twisk, 2003).

Good tolerance for missing data and unequal cell sizes. Mixed linear modeling is tolerant of both unequal cell sizes (i.e., unbalanced data) and data that are missing at random (Laird and Ware, 1982; Quene and van den Bergh, 2004; Kwok et al., 2008; Skrondal and Rabe-Hesketh, 2008; Molenberghs and Fitzmaurice, 2009; Gibbons et al., 2010). This relative robustness in the face of missing and unbalanced data results from characteristics of the MLM analysis: (1) treating time as a continuous rather than a factor variable (Kwok et al., 2008) and (2) using maximum likelihood estimation, which entails finding the set of parameter estimates that maximizes the likelihood of the data, rather than least squares estimation, as employed in ANOVA.

In sum, MLM meets the demands of neglect rehabilitation research: it accounts for the between-subject heterogeneity in baseline and recovery that is expected given the distinct brain networks potentially contributing to the neglect syndrome. It affords greater power and it is tolerant of missing and unbalanced data.

DEMONSTRATION AND SIMULATION ANALYSES USING MLM vs. REPEATED MEASURES ANOVA

In this section we compare the performance of MLM and rANOVA. We start with a re-analysis of a set of our own published data (Chen et al., 2012), comparing the results using an MLM analysis to those using rANOVA. Next, we use simulation methods to compare the power and Type I error rates of MLM and ANOVA under a variety of conditions facing researchers in the field of neglect rehabilitation (i.e., varying sample sizes, varying effect sizes, different number of assessment sessions). Although other simulation studies have compared the power and Type I error rates of MLM and rANOVA (e.g., Gueorguieva and Krystal, 2004; Maas and Hox, 2005), these studies have simulated minimum sample sizes of 20, 30, or even 50, all of which are larger than the average study of neglect patients, whose median sample size is 14.5 (**Table 1**). Furthermore, previous simulation studies have assumed a zero correlation between subjects' intercepts and slopes – a situation uncharacteristic of neglect rehabilitation data (Mizuno et al., 2011; Chen et al., 2012; Goedert et al., 2012). Thus, to confirm that MLM is indeed more powerful than rANOVA for neglect rehabilitation data, without a concomitant increase in Type I error rates, we performed a set of simulations generating power and Type I error rates for conditions likely to be encountered by the neglect rehabilitation researcher.

For both the real and simulated data, we assume a study in which we have two groups, each measured over time. Thus the full-factorial analysis includes the main effects of group and assessment time-point as well as their interaction. Here, we focus on the power of the analyses to detect the treatment group by assessment-session interaction, because the key focus of neglect rehabilitation studies would be to detect group *differences* in change over time. All analyses and data simulation were performed using STATA/IC 12.1.

[3]This is not a necessary effect of modeling the random effects (Rabe-Hesketh and Skrondal, 2012), but frequently results when modeling the random effects for data with large between-subject variation relative to within-subject variation (discussed by Brown and Prescott, 2006; Fitzmaurice et al., 2011; Gueorguieva and Krystal, 2004). It is a result we have observed in our own MLM analyses of neglect rehabilitation data, likely due to large between-subject variation. That is, adding random effects to an MLM model that first contained fixed effects typically does not change the fixed effect coefficients, but it reduces the standard error on those coefficients. However, as discussed by Rabe-Hesketh and Skrondal (2012, pp. 167–168), the exact result of introducing random effects into the MLM also depends on whether the fixed effect factor is completely within-cluster (i.e., within-subjects), as time is when assessing change over time, or whether the fixed effect factor is completely between-cluster. For within-cluster fixed effects, adding specification of the random effects can reduce the standard errors of the fixed effect parameter estimates (relative to ordinary least squares regression). The opposite can occur for completely between-cluster fixed effect factors. Furthermore, the magnitude of these changes varies with sample size (Snijders and Bosker, 1993, p. 253). Other factors affect the fixed effects standard errors, such that when the sample size is small, the data are not balanced, and between-subject variability is small relative to within-subject variability, the estimated standard errors may be too small (i.e., a biased estimate of the variance) and corrections may be necessary when significance testing (Brown and Prescott, 2006, pp. 75–76; Kenward and Roger, 1997).

RE-ANALYSIS OF PUBLISHED CHEN ET AL. (2012) DATA

We first turn to a set of data described in a recent study published by members of our research group (Chen et al., 2012). Capitalizing on work demonstrating an association between motor-intentional neglect symptoms and the frontal cortex (e.g., Ghacibeh et al., 2007), as well as work demonstrating that prism adaptation improves motor-intentional, but not perceptual-attentional, neglect (Striemer and Danckert, 2010; Fortis et al., 2011) we expected that patients with frontal lesions might experience more improvement with prism adaptation treatment than those without frontal lesions. Twenty-one right brain-damaged subjects with left spatial neglect underwent 2 weeks of prism adaptation treatment (once daily for 5 days per week). We assessed subjects' neglect with the Catherine Bergego Scale (CBS) just prior to the start of prism adaptation treatment and weekly thereafter for 5 weeks. We used subjects' clinical CT or MRI scans to map their lesions and categorized subjects as having the presence ($n = 13$) or absence ($n = 8$) of a frontal lesion. Although the original study reported a more complicated MLM analysis, here we focus on a simple analysis including the predictors of frontal lesion (present, absent), assessment session (one through six), and the frontal lesion by assessment-session interaction.

Analyses and results

For the MLM we modeled the frontal lesion by assessment-session factorial as fixed effects (with assessment session as a continuous variable) and we modeled subjects' intercepts and slopes as random effects. Because we were primarily interested in the fixed effects, we used maximum likelihood estimation, which provides more accurate estimates of the fixed effects than does restricted maximum likelihood, which may better-model random effects (West et al., 2007). We used an unstructured covariance matrix for the random effects, which meant our analysis could estimate a correlation between the random intercepts and slopes. And, we used a residual covariance matrix that assumed homogeneity of variance across the assessment sessions. Although STATA reports Wald's z for evaluating the significance of the fixed effects, we report the results of F tests, calculated using between-within degrees of freedom (West et al., 2007). As mentioned previously, use of z assumes a large sample, and may overestimate the significance of fixed effects. Therefore, we assessed their significance using the same *df* and F distribution that would be used in the comparable mixed between-within ANOVA. Results of this MLM analysis are depicted in **Table 2**.

For the rANOVA we modeled the full factorial of frontal lesion (presence, absence) and assessment session (one through six), with assessment session as a discrete, factor variable. The test of sphericity was significant, $p < 0.001$, indicating neither the compound symmetry nor sphericity assumption was met in this set of data. **Table 3** depicts the results of the rANOVA and, given the violation of sphericity, Greenhouse–Geisser corrected p-values.

Comparing across analyses, we see that the MLM detected a significant lesion by session interaction, while the ANOVA did not. Inspection of the group-level slopes from the MLM revealed that the group without frontal lesions had a slope on their recovery trajectory that did not differ significantly from zero, $b = -0.63$, SE = 0.13, 95% CI [−1.46, 0.19], while the group with frontal lesions showed significant improvement across the assessment sessions, $b = -1.80$, SE = 0.32, 95% CI [−2.42, −1.18]. Conversely, the ANOVA indicated significant main effects of session and presence of frontal lesion, while the MLM did not. Note that for the ANOVA, the effect of session indicates that at least one of the six assessment sessions significantly differs from another. In contrast, for the MLM, the non-significant effect of session signifies that, controlling for the group by session interaction, the group-average linear slope on session was not significantly different than zero.

The significant main effect of presence vs. absence of frontal lesions for the ANOVA, but not the MLM, suggests that this effect might be an artifact of the random effects structure of the data that is accounted for by the MLM but not by the ANOVA. In particular, note that with the MLM we have estimated the variability due to individual differences in subjects' slopes from the group slope (SD for slope on session) as well as the variability due to individual differences in subjects' intercepts from the group intercept (SD on intercept). Finally, the MLM estimates the correlation between the subjects' intercepts and slopes. Because lower scores on the CBS indicate less severe neglect, this negative correlation of −0.93 indicates that subjects with less severe neglect at baseline demonstrated greater improvement across the assessment sessions.

We see from this re-analysis of the Chen et al. (2012) data that MLM was better-able to detect a difference between the recovery trajectories of the groups with and without frontal lesions. Additionally, the MLM analysis described the continuous change in the data with the slope values: across the six assessments, the group

Table 2 | Results of MLM analysis of Chen et al. (2012) data.

	b	SE	95% CI	*F* test
Fixed effects				
Session	−0.63	0.42	−1.46, 0.19	$F(1, 86) = 2.25$, $p = 0.137$
Frontal lesion	−2.39	4.06	−10.34, 5.56	$F(1, 19) = 0.35$, $p = 0.562$
Session × lesion	−1.17	0.53	−2.21, −0.13	$F(1, 86) = 4.88$, $p = 0.030$
Random effects				
SD (slope on session)	0.927	0.24	0.56, 1.53	NA
SD (intercept)	8.423	1.51	5.93, 11.96	NA
Corr (int, slope)	−0.933	0.05	−0.99, −0.71	NA
Residual SD	2.56	0.22	2.16, 3.03	NA

Table 3 | Results of repeated measures ANOVA of Chen et al. (2012) data.

Source	Partial SS	*df*	*F* test	G–G corrected *p*
Frontal lesion	1142.59	1	$F(1, 19) = 8.44$, $p = 0.009$	
Subjects	2572.08	19		
Session	451.20	5	$F(5, 78) = 9.68$, $p < 0.001$	$p < 0.001$
Session × lesion	89.74	5	$F(5, 78) = 1.92$, $p = 0.099$	$p = 0.185$
Residual	727.77	78		

with frontal lesions improved an average of 1.80 points on the CBS per week, while the group without frontal lesions improved an average of 0.63 points per week.

SIMULATION STUDY

In order to compare the power and Type I error rates of MLM and rANOVA under varying circumstances likely to be encountered by neglect rehabilitation researchers, we performed a Monte Carlo simulation study: we repeatedly generated data sets and performed MLM and rANOVA analyses on each of the generated datasets. In total, we performed 24 simulations in which we generated data sets that varied in sample size ($N = 6$, 20, or 30), the number of assessment sessions/measurement waves (3 or 6), and effect size. Here we chose to present the simulation of 3 and 6 measurement waves because a minimum of three assessment points is considered critical for the assessment of change over time (see Discussion). Furthermore, the focus of our simulation was on the ability to detect a group by assessment-session interaction, because this would indicate a difference in response to treatment in the two groups. Because we were interested in the interaction, we measured effect size as the standardized difference between the slopes of the two groups ($d = 0.20$, 0.50, 0.80, or 1.00; assuming a SD on the group-level slopes of 2.00). Finally, we assessed Type I error rates with simulations in which the standardized difference between the group slopes was zero. **Table 4** summarizes the group-level fixed effect slopes used in the data-generation process at each effect size. The simulation yielded estimates of power and Type I error. These estimates indicate the proportion of samples we would expect to achieve significance at a significance level of 0.05. We provide these estimates for the repeated measures ANOVA (rANOVA), the Greenhouse–Geisser corrected rANOVA (GG-ANOVA), the Wald's z test of the MLM fixed effects (MLM-z), and the F test of the MLM fixed effects (MLM-F). A complete description of the simulation method appears in the Appendix.

Simulation results and discussion

Three assessments/measurement waves. **Figure 3** depicts the power to detect the group by session interaction with three measurement waves. Looking across effect sizes, it is clear that the MLM (for both z and F) has superior power to the ANOVA, particularly at smaller sample and smaller effect sizes. The rANOVA with the Greenhouse–Geisser correction has the poorest power, except at large effect and large sample sizes. For example, for an effect size of $d = 0.20$, the GG-rANOVA would reach significance less than 4% of the time for samples of size 6 and only 6% of the time for samples of size 20. Conversely, the MLM using Wald's z (MLM-z) has greater power than the other estimates, except where there is convergence among all the measures for the effect size of $d = 1.00$ with at least 20 subjects.

Table 4 | Summary of group-level fixed slopes for putative "control" and "treatment" groups at each simulated effect size.

	Group	
Effect size (*d*)	**Control**	**Treatment**
0.20	0.00	−0.40
0.50	0.00	−1.00
0.80	0.00	−1.60
1.00	0.00	−2.00
0.00	0.00	0.00

But a complete picture of these measures' performance requires an inspection of their concomitant Type I error rates, which are depicted in **Figure 4A**. Given the choice of 0.05 as the significance level, the extent to which any of the estimates shows a Type I error rate greater than or less than 0.05 suggests bias in the statistical test. As can be seen in **Figure 4A**, the MLM using Wald's z shows unacceptable levels of Type I error at a sample size of six. Although this rate of Type I error reduces at larger sample sizes, it still hovers just below 0.06, likely due to the large sample assumption of the z distribution. Thus, our results confirm the inappropriateness of Wald's z for smaller sample sizes.

The MLM-F has a Type I error rate that is just below 0.05 for the smallest sample size and right at 0.05 for samples of size 20 and 30. Thus, for three measurement waves, the MLM-F does not show bias. The rANOVA, however, remains below 0.05 across sample sizes, and thus, shows a slight conservative bias, which would lead to Type II errors (i.e., failure to detect a real effect). The GG-rANOVA is even more conservatively biased than is the rANOVA: it too would lead to Type II errors.

In sum, with three measurement waves, the MLM using the F distribution with between-within degrees of freedom (West et al., 2007) shows good power, while also showing no bias in Type I error rates. This result is consistent with other simulation work showing that MLM performs well in estimating fixed effects with few repeated measurements (Bell et al., 2010). We extend this previous work by showing the superiority of the MLM even for very small sample sizes ($N = 6$), as long as one uses the F distribution for assessing significance.

Six assessments/measurement waves. **Figure 5** depicts the power to detect the group by session interaction with six measurement waves. Looking in particular at the small effect sizes, we see a pattern that is very different from that observed with three measurement waves. With sample sizes of 20 and 30, the rANOVA demonstrates superior power to the other three statistics. Consistent with the pattern observed with three measurement waves, the Greenhouse–Geisser corrected ANOVA shows poor power except with larger samples and large effect sizes. Similar to what was observed with three measurement waves, the estimates of all the analyses converge with samples of at least 20 at the largest effect size ($d = 1.00$).

Again, for a complete picture of the analyses' performance we must inspect their Type I error rates, which are depicted in **Figure 4B**. **Figure 4B** depicts not only the simulations described above, but an additional simulation of the Type I error rates in a sample size of 100. In the Figure, we can see that both MLM-z and MLM-F are biased at smaller sample sizes, with Type I error rates well above 0.05 at a sample size of six. However, this bias reduces as the sample size increases, with the Type I error rate converging on 0.05 at larger sample sizes. Conversely, for the rANOVA, Type I error rates remain unacceptably large even at the largest sample

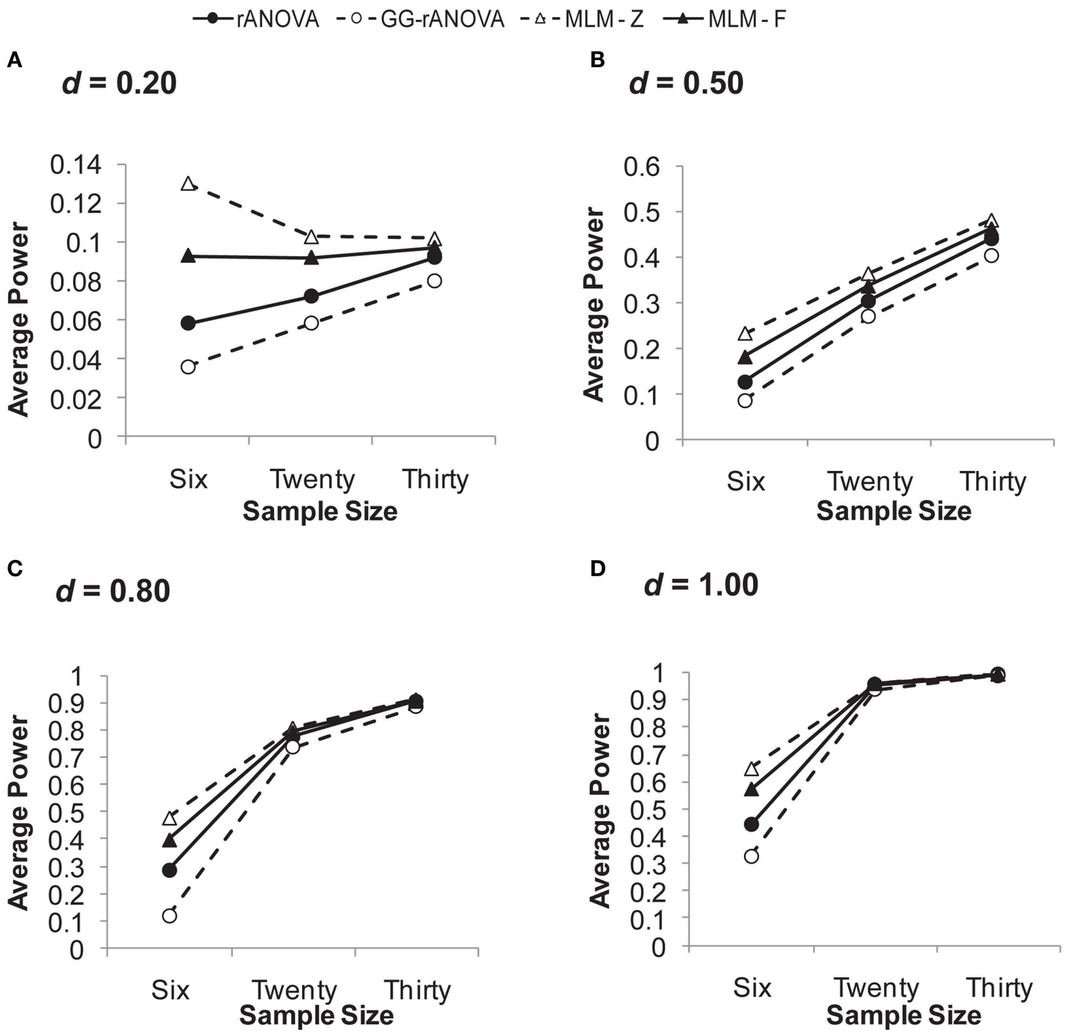

FIGURE 3 | Average power on the session by group interaction with three measurement waves. **(A)** for $d = 0.20$; **(B)** for $d = 0.50$; **(C)** for $d = 0.80$; **(D)** for $d = 1.00$. d, standardized difference between group slopes. rANOVA = repeated measures ANOVA, GG-rANOVA is Greenhouse–Geisser corrected repeated measures ANOVA, MLM-Z is Wald's Z from the MLM, MLM-F is the between-within df for F from the MLM.

size of 100. The Greenhouse–Geisser corrected rANOVA shows conservative bias at the smaller sample sizes, but like the MLM estimates, its Type I error rates converge on 0.05 at the larger sample sizes.

Simulation summary. The Monte Carlo simulation allows us to compare the performance of MLM and rANOVA with different sample and effect sizes. In sum, the simulation study demonstrates that overall, MLM using Wald's z creates too much Type I error, while the rANOVA using the Greenhouse–Geisser correction is too conservative, sacrificing too much power. The simulation study further demonstrates that with three measurement waves, the MLM-F has superior power and is unbiased, while the rANOVA has poorer power and is conservatively biased (i.e., Type I error rates less than 0.05). Thus, with three repeated assessments, the MLM-F is better-able to detect treatment effects without an increase in Type I error rates. With six measurement waves, the ANOVA has more power at smaller sample sizes, but also has an unacceptably high rate of Type I error at *all* samples sizes (i.e., even at $N = 100$ the Type I error rate of rANOVA is at 0.08). Conversely, the Type I error rates of the MLM converge on 0.05 at larger sample sizes. Thus, it appears that with six repeated assessments, the MLM more accurately estimates the fixed effects with increases in sample size; whereas the accuracy of the rANOVA does not systematically increase with increases in sample size.

GENERAL DISCUSSION

We argued that neglect rehabilitation demands a statistical approach commensurate with characteristics of the neglect syndrome. In the re-analysis of our previously published data we demonstrated how MLM provides a description of the recovery trajectory and how it was better-able to detect the difference in the recovery trajectories of the groups with and without frontal lesions. Furthermore, the difference between the MLM and

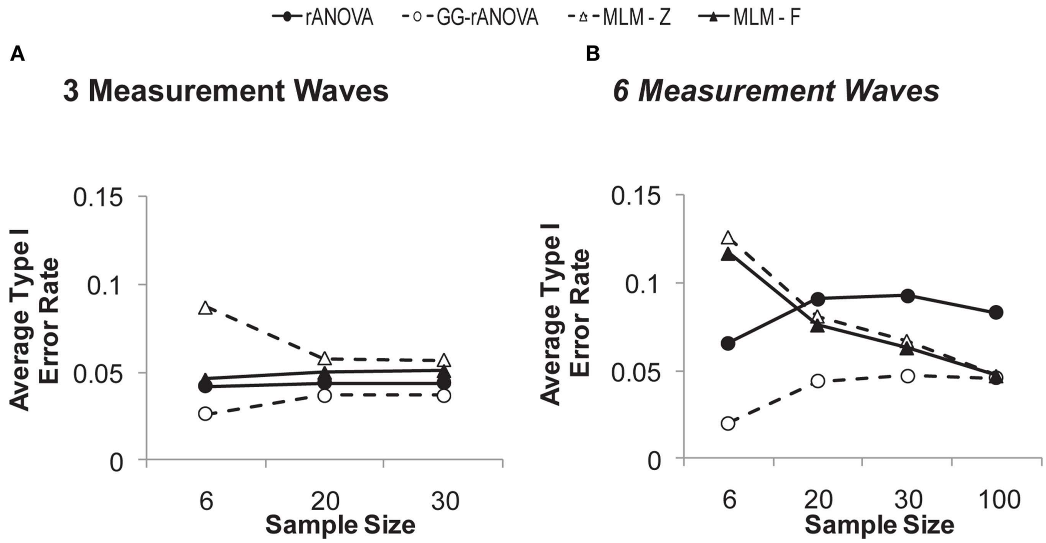

FIGURE 4 | Type I error rates on the session by group interaction with (A) three and (B) six measurement waves.

rANOVA analyses suggest that the ANOVA may have inappropriately modeled variability arising from individual differences in recovery trajectories.

The results of our simulation suggest that MLM does indeed have superior power at smaller sample sizes, and that it can be confidently used with the small samples often employed in neglect rehabilitation research if analyzing a small number of measurement waves. With many measurement waves (in this case six), larger sample sizes may be needed for MLM to accurately estimate the fixed effects. This result is consistent with the observations of others (Snijders, 2005), that accuracy of estimation of the fixed effects is primarily driven by the size of the sample at that level of estimation. Furthermore, our results likely overestimate the ability of ANOVA relative to MLM, given that we simulated complete and balanced data structures. Relative to ANOVA, MLM has the added advantage of continuing to perform well even when data are missing at random (Gueorguieva and Krystal, 2004; Quene and van den Bergh, 2004), a situation likely encountered by researchers of neglect rehabilitation.

MORE THAN ANALYSIS TOOL: LONGITUDINAL MODELING AS A RESEARCH APPROACH

Perhaps more than just the benefits afforded by a potentially more powerful and more appropriate statistical tool, a look at using MLM could help neglect rehabilitation researchers better-conceptualize their research problem. As researchers interested in the rehabilitation of patients with neglect, we must be interested in how individuals change over time and how we can alter those recovery trajectories with rehabilitative treatment. Thus, we need a statistical tool that allows us to describe those trajectories.

However, the ability to describe recovery trajectories is related not just to the statistical approach, but also to the study design: the majority of the treatment studies that we reviewed measured patients' performance at only two time-points: once before treatment and once immediately after treatment. However, use of only two assessment points pre- and post-treatment confounds true change and measurement error (Rogosa et al., 1982; Singer and Willett, 2003). Furthermore, a simple pre-post difference does not provide a picture of how patients' change over time because it tells us nothing of subjects' individual recovery trajectories (Singer and Willett, 2003). For example, are recovery trajectories linear or quadratic? Are the benefits of a treatment experienced immediately and then level off, or do benefits of the treatment continue as time post-treatment increases? Assessing neglect patients at a minimum of three measurement waves will help answer these important questions about neglect recovery and its relation to rehabilitation.

LIMITATIONS AND BARRIERS IN THE USE OF MLM

Despite the potential advantages of MLM, it is not without its own limitations. First, although bootstrapping procedures may be used to overcome violations of normality in the distribution of the residuals, the use of bootstrapped standard error estimates may restrict the researcher to less complicated forms of MLM analysis (e.g., modeling only random intercepts, without modeling of random slopes). Second, MLM models do not always resolve. That is, the maximum likelihood estimation process may not converge on a set of parameter estimates or may be unable to estimate standard errors. This is more likely to happen with smaller sample sizes and with more complex models. Thus, under certain circumstances, the researcher may be restricted to using a simpler MLM model (e.g., may have to assume homogeneity of variance rather than modeling an auto-regressive residual covariance structure).

Finally, MLM procedures are statistically more complex than is rANOVA. However, MLM procedures are now integrated into major statistical packages including SPSS, SAS, STATA, and R. It must be recognized that some of the statistical complexity comes with the added benefit of greater flexibility in the analyses, such as the ability to model alternate residual structures so as to avoid violations of assumptions like homogeneity of variance (Cnaan et al., 1997).

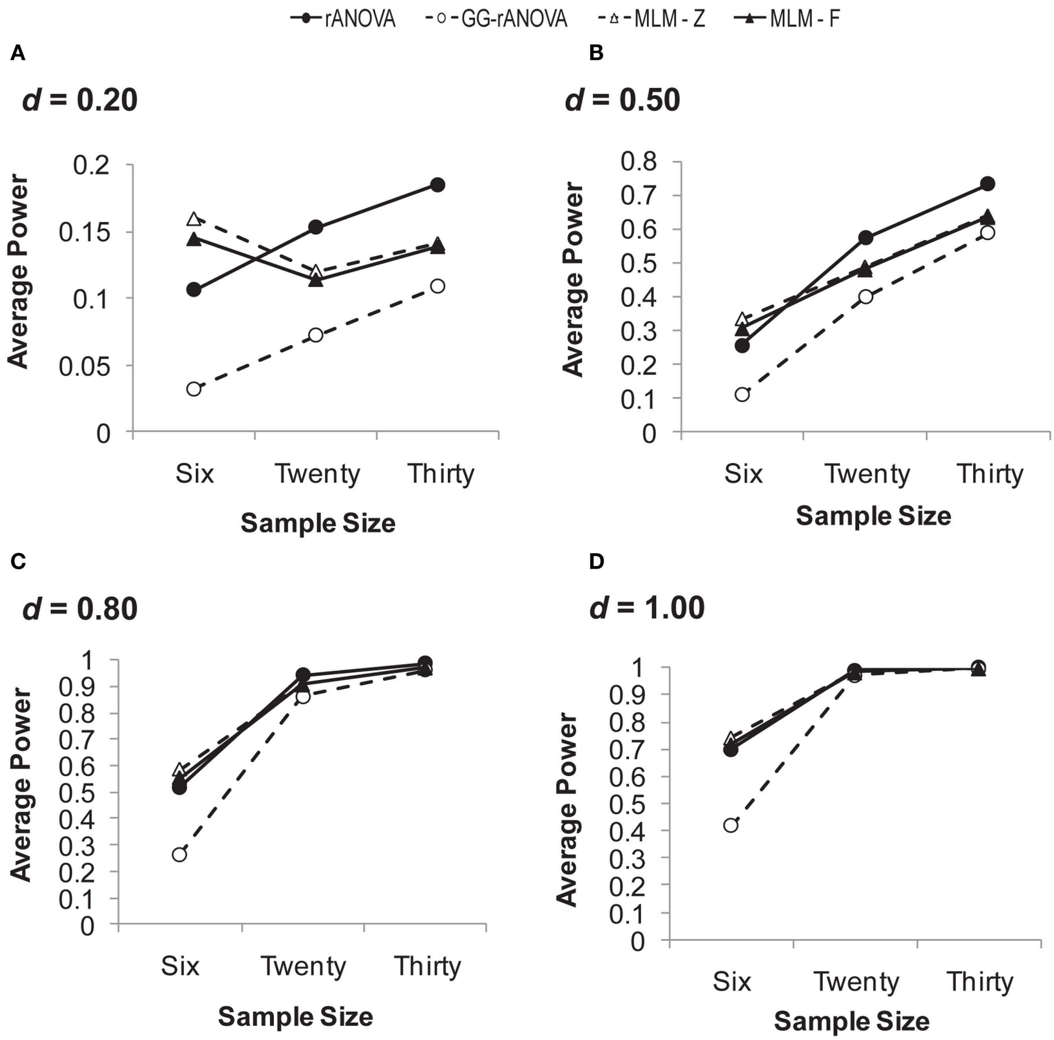

FIGURE 5 | Average power on the session by group interaction with six measurement waves. **(A)** for $d = 0.20$; **(B)** for $d = 0.50$; **(C)** for $d = 0.80$; **(D)** for $d = 1.00$. d = standardized difference between group slopes, rANOVA = repeated measures ANOVA, GG-rANOVA is Greenhouse–Geisser corrected repeated measures ANOVA, MLM-*Z*, Wald's *Z* from the MLM, MLM-*F* is the between-within *df* for *F* from the MLM.

LIMITATIONS IN THE CURRENT TREATMENT OF MLM

Our discussion of MLM in the current paper is necessarily limited by our desire to present a simple introduction to MLM for the neglect rehabilitation researcher who is likely to be currently using rANOVA. As a result, there are several issues of importance in using MLM to analyze longitudinal data from treatment (and other) studies that were beyond the scope of this paper.

First, it is standard when performing MLM to quantifying the amount of nested dependency in a dataset by calculating the intraclass correlation coefficient (ICC). In the case of repeated assessments nested within subjects, the ICC is the proportion of total variance in the data that is accounted for by between-participant differences (Singer and Willett, 2003). ICCs at or close to zero suggest that the data are actually independent rather than dependent, and that modeling of subjects' random effects is unnecessary.

Second, the models we presented, both for the fictional data (**Figure 2**) and for the re-analysis of the Chen et al. (2012) data, were necessarily simplified. In a neglect treatment study, MLM would allow the researcher to control for and assess additional factors affecting neglect recovery, such as baseline severity. Indeed, in the previously published Chen et al. (2012) analysis, we controlled for patients' spontaneous recovery rates as estimated by the slope of their recovery trajectories prior to initiating a prism treatment.

Third, in this paper, we focused primarily on the performance of MLM on fixed effects estimation – that is, the group-level intercepts and slopes – and in particular, on the group by session interaction. This focus does not do justice to the full potential of the MLM analysis, particularly for modeling individual change over time. As we saw in the re-analysis of our previously published data, MLM provides estimates not just of fixed effects, but also of the variability due to the random effects, and the correlation between the random intercept and slope. Additionally, one can also model cross-level interactions, as well as examine individual-level trajectories (e.g., Cnaan et al., 1997; Rabe-Hesketh and Everitt, 2003). None of the power and Type I error simulations we performed here may be generalized to the subject-level random effects. Power and precision of the random effects estimation is largely driven by the sample size at that level (Snijders, 2005).

Indeed, MLM may be appropriate for many study designs involving dependencies among measures (e.g., longitudinal, repeated measures, and clustered data) with outcomes that are either continuous, binary, or ordinal (Rabe-Hesketh and Skrondal, 2012). A full discussion of its uses, however, is beyond the scope of the current paper. West et al. (2007) provide a good treatment of the use of MLM in different study designs. Furthermore, Liu et al., 2012 provide a comprehensive discussion of how to decide among analyses for use with longitudinal data. They argue that rANOVA might be more appropriate when the researcher wishes to treat time as a factor variable. However, in an MLM time can be treated as a factor variable. Indeed, rANOVA may be thought of as a special case of MLM – one in which the residual variance-covariance matrix assumes both homogeneity of variance and sphericity and in which the only random effect modeled is the random intercept (i.e., the subjects term in the ANOVA is analogous to the random intercept of the MLM).

RECOMMENDATIONS FOR NEGLECT RESEARCHERS STARTING IN MLM

Our simulation results lead us to make several recommendations for neglect rehabilitation researchers:

(1) If using three assessment sessions, MLM offers more power than rANOVA, particularly at the small samples sizes typical of neglect rehabilitation research.
(2) If using six assessment sessions, rANOVA has high Type I error rates even at large sample sizes, while MLM performs well as sample size increases. Thus, if using many repeated assessment sessions, rANOVA should not be used and the use of MLM will require a larger sample size (e.g., 30 or more) for valid statistical inference on the fixed effects.
(3) The default means of assessing significance of the MLM fixed effects parameters in STATA and Mplus (Wald's z) should not be used with the small samples typical of neglect rehabilitation studies. Rather, the F distribution should be used for assessing the significance of these effects.

Several resources are particularly useful for researchers getting started in using MLM. Andy Field provides a very accessible first-introduction to performing MLM analyses, with chapters dedicated to MLM in his books on SPSS and R (Field, 2010; Field et al., 2012). West et al. (2007) is an excellent introduction to performing various types of MLM analyses, illustrating the analyses in R, SPSS, SAS, and STATA. Rabe-Hesketh and Skrondal (2012) is an authoritative and thorough examination of MLM for longitudinal data structures in STATA. Finally, both Fitzmaurice et al. (2011) and Singer and Willett (2003), provide comprehensive conceptual treatments of using MLM for longitudinal data analysis.

CONCLUSION

Neglect rehabilitation research demands a statistical approach commensurate with the characteristics of the neglect syndrome. Given that neglect arises from disruptions to potentially distinct brain networks and results in disparate patterns of behavioral symptoms, the field requires a statistical technique designed to adequately account for between-subject variability in baseline status and recovery trajectory. Further, the study of neglect rehabilitation requires a technique that allows the researcher to describe patients' change over time. MLM meets both these demands of neglect rehabilitation data. MLM offers the additional advantage of superior power at small sample sizes, and it does not require complete data.

Given its power and Type I error rate, and given its robustness in the face of missing data, we think MLM the ideal tool for analyzing data from neglect rehabilitation studies. We look forward to the future of neglect rehabilitation research when, hopefully, it will be more common to find 3+ measurement waves and when multilevel modeling to investigate patient change over time is the new standard.

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APPENDIX

DATA-GENERATION PROCESS FOR SIMULATION

We used the random effects model depicted in Eq. 2 as the underlying data-generating model, creating different equations for the "control" and "treatment" groups. We derived parameters from which to generate the random effects and residual variability by averaging the variability due to subjects' intercepts, their slopes, and their residuals over the Chen et al. (2012) data and other data from our lab (Goedert et al., 2012).

To generate each data set, we first set the group-level slopes for the control and treatment groups per **Table 4**. We introduced slightly variability in the group-level intercept, as we had observed in our own data, setting that of the control to 19.07 and that of the treatment group to 21.12. We then generated each subjects' deviation around the mean intercept and slope (i.e., b_{0j} and b_{1j} of Eq. 2) by randomly drawing values from a normal distribution with means of 0 and a standard deviation of 8.5 for the intercept and 0.99 for the slope, with the constraint that b_{0j} and b_{1j} would have a negative correlation of −0.67 (SDs and correlation estimated from Chen et al., 2012 and Goedert et al., 2012). This step produced a negative correlation between slopes and intercepts, as observed in our own data and that of others (Mizuno et al., 2011; Chen et al., 2012). We estimated e_{ij} of Eq. 2 by randomly drawing from a normal distribution with a mean of 0 and SD of 2.56 (residual variance estimated from Chen et al., 2012 and Goedert et al., 2012).

Thus far, we have described all the components necessary to generate Y_{ij} based on Eq. 2. However, we added one additional step in the data-generation process. Because slopes observed in our real data had a slight negative skew rather than a normal distribution, we first estimated each subject's slope as $b_1 + b_{1j}$, but then transformed this slope value (Feiveson, 2002) using the method suggested by Fleishman (1978)[1] to produce slopes that better-resembled the real data. This new, slightly negatively skewed slope was substituted for $b_1 + b_{1j}$ in Eq. 2. We repeated this data-generation process a minimum of 1000 times for each of the simulation conditions and ran separate MLM and repeated measures ANOVA analyses on each of the generated datasets.

ANALYSES AND CALCULATIONS OF SIMULATED POWER AND TYPE I ERROR

As with the real data, in the MLM analyses on the generated data, we used maximum likelihood estimation, modeling both random intercepts and random slopes, with an unstructured covariance structure on the random effects. We assumed homogeneity of variance in the residuals. We were as generous as possible to the repeated measures ANOVA, modeling only complete and balanced datasets (equal numbers of subjects in control and treatment groups). For the MLM, we modeled the full-factorial of session and group as the fixed effects, with session as a continuous variable. For the ANOVA, we modeled the full-factorial of session and group, with session as a factor variable, the practice that is common in the field.

For each of the repeated measures ANOVAs and MLMs, we estimated observed p-values on the group by session interaction. We estimated p-values associated with the uncorrected repeated measures ANOVA (rANOVA) and those using the Greenhouse and Geisser (1959) correction (GG-rANOVA). For the MLM, we estimated p-values both using Wald's z and the F distribution with between-within df (West et al., 2007). As stated earlier, because z assumes a large sample, it is assumed that F would be a more appropriate distribution to use when testing significance in a relatively small sample. Thus, by estimating and presenting both, we directly tested that assumption here.

It is possible to estimate power and Type I error directly from the proportion of p-values below 0.05 on the 1000 datasets generated for each of the simulations described above (e.g., Gueorguieva and Krystal, 2004; Rotello et al., 2008). However, such estimates still demonstrate variability (i.e., the estimates may vary slightly in a different set of 1000 datasets). Therefore, we estimated power and Type I error rates in a second step in which we bootstrapped estimates of power and Type I error: we randomly sampled with replacement samples of size 800 from the 1000 p-values and calculated the proportion of p-values below 0.05. For effect sizes greater than zero, this proportion is an estimate of power. For effect sizes of zero, this proportion is an estimate of Type I error. We repeated this random sampling process 100 times and present the mean of these 100 bootstrapped samples as the estimates of power and Type 1 error.

[1] Fleishman introduced the following transformation to produce simulated data with a non-normal distribution:

$$Y = a + bX + cX^2 + dX^3,$$

where a, b, c, and d, are the mean, standard deviation, skewness, and kurtosis, respectively. For our purposes here, we set the mean and standard deviation equal to the mean and standard deviation of the slopes generated via the random normal procedure, but then set $c = -0.90$ and $d = -0.04$, to produce a slight skew in the slopes that mirrored the slight negative skew observed in the individual regression slopes of our real datasets (Chen et al., 2012; Goedert et al., 2012).

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Long-lasting amelioration of walking trajectory in neglect after prismatic adaptation

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In the present study we explored the effect of prismatic adaptation (PA) applied to the upper right limb on the walking trajectory of a neglect patient with more severe neglect in far than in near space. The patient was asked to bisect a line fixed to the floor by walking across it before and after four sessions of PA distributed over a time frame of 67 days. Gait path was analyzed by means of an optoelectronic motion analysis system. The walking trajectory improved following PA and the result was maintained at follow-up, 15 months after treatment. The improvement was greater for the predicted bisection error (estimated on the basis of the trajectory extrapolated from the first walking step) than for the observed bisection error (measured at line bisection). These results show that PA may act on high level spatial representation of gait trajectory rather than on lower level sensory-motor gait components and suggest that PA may have a long-lasting rehabilitative effect on neglect patients showing a deviated walking trajectory.

Keywords: neglect, rehabilitation, gait, prismatic adaptation, near space, far space, space representation

INTRODUCTION

Neglect patients behave as if the left part of the world had ceased to exist. As a consequence, both in clinical tasks and in many daily life activities, the patient's behavior is usually biased toward the right side of space. It has also been demonstrated that neglect for proximal space (i.e., space within reaching distance) can be dissociated from neglect for distal space (space beyond reaching distance) (Halligan and Marshall, 1991; Cowey et al., 1994, 1999; Vuilleumier et al., 1998). In addition, near and far space representations were found to be dynamic, rather than static. Neurophysiological (Iriki et al., 1996) and neuropsychological studies (Berti and Frassinetti, 2000; Berti et al., 2002; Neppi-Mòdona et al., 2007) have shown that far space can me remapped as near, and near space as far, depending on the tool/action used by the patient to reach objects located in near and far space, respectively. Furthermore, among the functions that can be impaired in neglect there is walking, with patients showing a lateral deviation of the walking trajectory. Published research is contradictory regarding the direction of the lateral deviation, reporting both leftward and rightward deviations (Robertson et al., 1994; Tromp et al., 1995; Berti et al., 2002; Huitema et al., 2006; Turton et al., 2009). Leftward deviations have been found to be related to milder neglect (Tromp et al., 1995) or to a better preserved walking ability (Huitema et al., 2006).

Berti et al. (2002) have shown that neglect patients with more severe neglect in far than in near space produce a bisection error to the right (in the case of left neglect) of the true center of the line, when explicitly asked to walk across lines fixed to the floor in far space (3 m away). On the contrary, when the line was located in near space (1 m), the bisection error was less severe or even absent. This error pattern paralleled the bisection error made by the same patients in a line bisection task in near and far space using a projection light pen. Interestingly, patients' walking trajectories were rectilinear when the line was located in far space. This suggested that the spatial representation activated at the beginning of the walking path (a far space representation, more severely impaired) was not updated during walking. Indeed, if this had been the case, a near (less impaired) space representation should have been activated while approaching the line: as a consequence, the trajectory would have been corrected resulting in a curvilinear path and the final error would have been reduced. The absence of spatial remapping during walking may be responsible for the collisions with objects and people occurring to neglect patients in their everyday life.

Although many different rehabilitative techniques have been effective in transitorily improving neglect, they often failed to produce a long-lasting beneficial effect. Some years ago, however, Rossetti et al. (1998) observed for the first time that wearing goggles fitted with prismatic lenses that shift the visual field 10°to the right may improve neglect in conventional neuropsychological tests performed in the patient's peripersonal space. The positive result was already evident 5 min after prismatic adaptation (PA), lasting up to 2 h. Subsequent studies have shown that the effect of PA can be relatively long-lasting, being still effective up to 6 months post treatment (Frassinetti et al., 2002; Serino et al., 2006, 2007; Rusconi and Carelli, 2012).

In the present study we explored the effect of PA on the walking trajectory of a neglect patient with more severe neglect in far than in near space who was asked to repeatedly bisect a fixed line on the floor by walking across it. When neglect is more severe in far than in near space, two predictions can be made (Berti et al., 2002): (1) *space is not remapped*: the walking trajectory is rectilinear and the severity of neglect in far space determines the final bisection error; (2) *space is remapped:* the walking trajectory is curvilinear and the final bisection error is smaller because it is influenced by the near space representation (less compromised) activated while approaching the target. In both instances, if prism adaptation has a rehabilitative effect on the walking trajectory, it should produce a reduction of the final bisection error, either by improving the far space representation *at the beginning* of walking [in both cases 1 and 2), or by refining the remapping of far space into near space *during* walking (in case 2) only].

MATERIALS AND METHODS

PATIENT'S CLINICAL DATA

MR is a 56-year-old right-handed lady with 12 years of formal education. She worked as a teacher of primary school until her retirement at the age of 50. At the age of 55 she suffered from a subarachnoid hemorrhage, secondary to the rupture of a right posterior communicating artery aneurysm. She underwent a neurosurgical operation to evacuate the cerebral hematoma and the aneurysm was successfully clipped. However, after surgery she showed left hemianestesia, left hemiparesis, left hemianopia, and left visuospatial neglect. MR was severely impaired in daily life activities such as dressing, washing, and housekeeping. She obtained a low global score in the Activities of Daily Living (ADL score 10/20) (Wade, 1992).

Ten months after the stroke MR was considered for the present study while she was following both motor and cognitive rehabilitation training. Her walking ability had considerably improved, although she still reported difficulties in everyday life because of frequent collisions with obstacles located in her left space. She was still affected by left homonymous hemianopia, left hemianestesia, and chronic left neglect. Motor deficits were no longer detectable at the time of testing. We did not test MR for motor neglect. However, it may be inferred from the results of neuropsychological testing and from direct observation of her motor behavior that she did not suffer from motor neglect or directional hypokinesia (Bisiach et al., 1998): e.g., she bisected lines to the left of true center, a behavior opposite to that expected in case of directional hypokinesia, and had no problems and showed no reluctance in using her left arm for reaching objects, a behavior not compatible with motor neglect (see Saevarsson, 2013 for a critical review on diagnostic, clinical and anatomical issues related to premotor and motor neglect).

Lesion reconstruction from MRI scans showed a large lesion affecting the right temporal pole and extending, superiorly, to the Sylvian fissure and, posteriorly, to the more anterior temporomedial structures, including the fusiform gyrus, the uncus, and probably, the amygdala (Broadman areas 38, anterior parts of areas 22, 21, 20, 36, 37) (see **Figure 1**). The patient gave her informed consent to participate in the study.

NEUROPSYCHOLOGICAL ASSESSMENT

When we evaluated MR, 10 months after the stroke, she was motivated and co-operative. Her performances in the Italian version of the Mini Mental State Examination (Measso et al., 1993) and in the Verbal Intelligence Judgment were normal (Spinnler and Tognoni, 1987). Her non-verbal intelligence performance (Carlesimo et al., 1995) was also normal. MR presented with severe *left* visual neglect as diagnosed on the basis of the performance on cancelation tests (Albert, 1973; Wilson et al., 1987) and drawing tests (Gainotti et al., 1972; Marshall and Halligan, 1993). Despite showing left neglect in these tasks (see **Table 1** for details and **Figure 2**), she bisected line segments to the *left* of the objective midpoint (right neglect) both in conventional line bisection and in the walking bisection tasks. This behavior cannot be accounted for by hemianopia. In patients with neglect and hemianopia (such as MR), bisection errors are to the right of the objective midline (Doricchi and Angelelli, 1999; Doricchi et al., 2002). This kind of behavioral dissociation has been previously described in the literature (Berti et al., 2002) and will be further discussed in the Section "Discussion" (p. 14). The patient did not show personal neglect (Bisiach et al., 1986) or neglect dyslexia (Pizzamiglio et al., 1990).

EXPERIMENTAL PROCEDURE

The experimental procedure for the detection and characterization of bisection errors included several manual and walking bisection tests and was applied before and after each of four sessions of PA (see Prismatic Adaptation below). Moreover, bisection errors were also measured in two follow-up sessions.

Manual line bisection

In order to assess the presence of dissociations between neglect in near and far space (Halligan and Marshall, 1991; Cowey et al., 1994, 1999) patient MR was asked to bisect line segments made of 30 mm large white tape fixed to the floor. In *near space* the target line was located at a distance of 0.75 m from the patient's feet and she had to bisect the line by reaching it with a carbon fiber stick. In *far space* the target line was located 3 m from the patient's feet and the patient bisected the line by means of a laser pointer. The two conditions *reaching in near space* and *pointing in far space* were considered the "baseline" conditions to reveal the presence of dissociations between neglect in near and in far space (see Berti and Frassinetti, 2000; Pegna et al., 2001; Neppi-Mòdona et al., 2007). When using a stick to bisect a segment located in near space or a laser pointer to bisect a segment located in far space, patients do not remap near space into far space or far space into near space, respectively; instead, when using a laser pointer to bisect a segment located in near space, an object-dependent far space representation can be activated (a laser pointer is often associated to actions

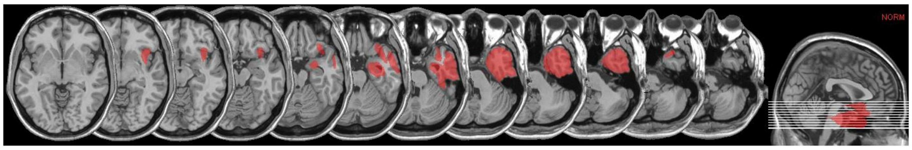

FIGURE 1 | Patient's lesion reconstruction. See text for details.

Table 1 | General neuropsychological assessment.

	Range	Cut-off	Score	Left omiss.	Right omiss.
GENERAL COGNITIVE LEVEL					
MMSE[1]	0–30	<23.8	25.99		
Verbal Judgment[2]	0–60	<32	60		
Raven's Colored Progressive Matrices 47[3]	0–36	<18.96	21	8/12	0/12
NEGLECT (CONVENTIONAL TESTS)					
Albert's test[4]	0–50	>1 omission	45*	4/25	1/25
Star cancelation[5]	0–54	>3 omission	22*	27/27	5/27
Word reading[6]	0–40	1	40		
Sentence reading[7]	0–9	1	9		
Personal neglect[8]	0–3	≤1	0		

*Pathological Score; [1]Measso et al. (1993); [2]Spinnler and Tognoni (1987); [3]Carlesimo et al. (1995); [4]Albert (1973); [5]Wilson et al. (1987); [6]Caramazza and Hillis (1990); [7]Pizzamiglio et al. (1990); [8]Bisiach et al. (1986).

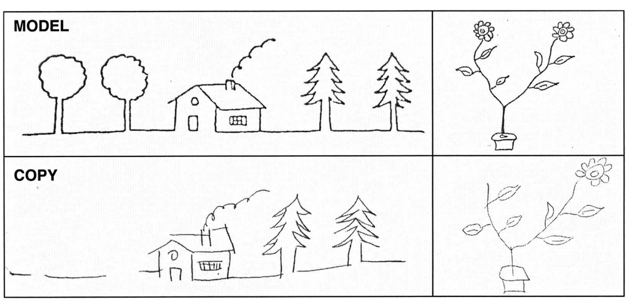

FIGURE 2 | Examples of patient's copy of drawings. Upper part of the figure: original; lower part: patient's copy. Note that some details are missing on the left side of the copy.

carried out in far space); similarly, when using a stick to bisect a segment located in fare space, a near space representation can be activated (the stick activates a near space representation because the far object, once reached with the stick, is automatically recoded as being located in proximal space as a consequence of tool use). A patient is considered to have a dissociation if the bisection errors in near and far space are significantly different.

The target lines were centered on the patient's body midline. MR executed a total of 20 bisections (10 in near and 10 in far space). The length of the line was varied in near and far space so as to keep the visual angle subtended by each line constant (24.5°). Lines in near space were 0.71 m long whereas lines in far space were 1.45 m long. Bisection errors were measured as deviation in mm from the objective midpoint of the line and expressed as percentage of target line half-length (NBE, Near space Bisection Error; FBE, Far space Bisection Error). Positive values indicate deviations to the right of the objective midpoint, whereas negative values indicate deviations to the left.

Line bisection by walking

The patient was also asked to bisect lines in near and far space by walking across them. This allowed us to assess whether a possible dissociation between near and far space neglect was consistent across different output modalities (manual/walking bisection). The lines were identical to those used in the bisection by reaching/pointing and were placed at a distance of 0.75 m (near space) and 3 m (far space) from the patient's starting location. She was instructed to cross the line in the middle, taking her body midline as reference point. We did not advise the patient to walk as straight as possible because this instruction could interfere with the task and influence the results of the experiment (for example it could interfere with spatial remapping during gait execution by driving the patients attention to her walking rather than to the bisection task itself). As for bisection by reaching/pointing, she was given a sequence of 10 trials for each spatial sector, for a total of 20 trials (10 in near and 10 in far space). No environmental cues were available to the patient to guide her walking trajectory (a large uniform light green carpet completely covered the floor and a 5-m wide uniform cyan curtain was hanged about 2 m behind the target line).

The measurement of the trajectories was performed by means of an ELITE optoelectronic motion analysis system (BTS, Milan, Italy) whose sensors consisted in four TV cameras working in the infrared range and focused on a calibrated volume (length: 5.0 m; height: 1.7 m; width: 1.2 m) intended to include the subject, the starting point and the target line. Three passive hemispherical reflective markers (diameter: 15 mm) were placed on the patient's body in correspondence of specific anatomical landmarks: the sacrum and the posterior aspect of the calcaneus on both feet, while two markers were placed at both line extremities and one on the starting point. The patient was dressed normally and wore her regular walking shoes. The TV cameras recorded the marker trajectories at a sampling frequency of 100 Hz. Specific stereophotogrammetric algorithms made it possible to compute the 3D instant position of any marker detected by at least two TV cameras. Such setup and related algorithms provide an accuracy that is approximately 1/3000 of the calibrated volume's largest dimension, therefore the experimental accuracy of the measurements was about 2 mm. Raw coordinates data were low pass filtered (cut-off frequency 2 Hz). The sacrum was assumed as the body reference point, being strongly correlated with the body center of mass during walking (Thirunarayan et al., 1996). The sacrum trajectory actually consists of different components:

- a major rectilinear progression component;
- a possible curvilinear component which accounts for possible walking steering;
- small cyclic lateral and vertical oscillations due to the particular mechanics of bipedal walking (Inman et al., 1981).

The latter component is not relevant for the current study. A geometrical model of the first two components, the "progression curve," was defined in order to identify a second-order polynomial curve ($Y = aX^2 + bX + c$), where the instant lateral displacement is a function of the longitudinal component (see example in

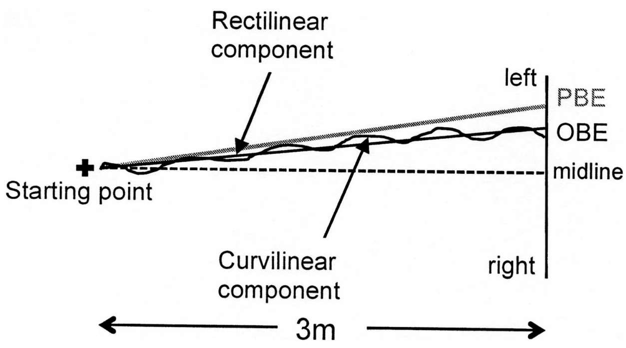

FIGURE 3 | Graphic representation of a typical walking trajectory of patient MR and its components: (1) a major rectilinear component and (2) a curvilinear component forming a second-order polynomial curve (the progression curve) whose intersection point with the target line corresponds to the observed bisection error (OBE). The point of intersection with the target line of the tangent to the "progression curve" at the starting point identifies the bisection error predicted by the first walking step (PBE).

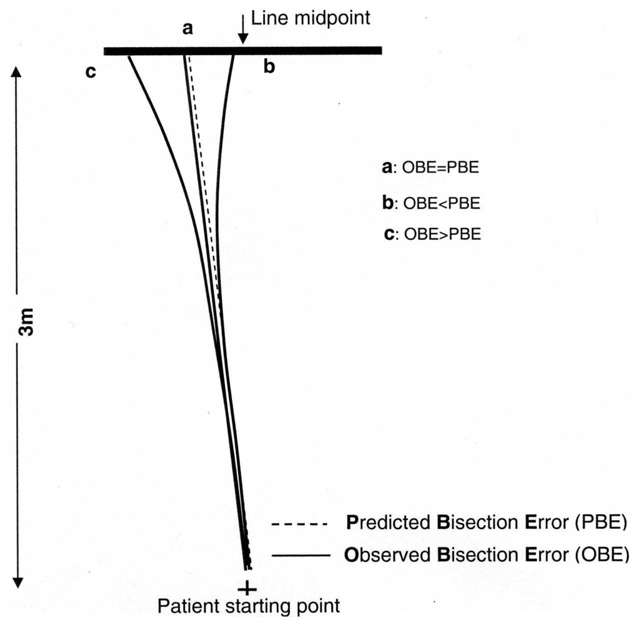

FIGURE 4 | Graphic representation of different possible walking trajectories of the patient and observed (OBE) or predicted (PBE) bisection errors: if OBE = PBE (a) **the trajectory is rectilinear and space remapping is absent**. The far space representation (more compromised) activated at the beginning of walking is maintained throughout the entire path, resulting in a leftward error; if OBE < PBE (b) the trajectory is curvilinear because the patient corrects the trajectory while approaching the target remapping the initial far space representation (more compromised) into a near space representation (less compromised). This results in an error reduction relative to (a); if OBE > PBE (c) it is indicative of a tendency to veer in the direction of neglect during walking not related to space remapping but consequent to an error in heading control resulting from the patient attempt to correct the ipsilesional deviation of the subjective midline which is typically associated to neglect (Huitema et al., 2006).

Figure 3). The elements of this second-order polynomial curve include the major rectilinear direction (first order component) and the possible veering (second order component).

Two bisection error parameters were computed from all identified progression curves (see **Figure 3**). The first error was Observed Bisection Error (OBE): the actual bisection error measured at the end of the walking trajectory (intersection of the progression curve with the target line). The second error was Predicted Bisection Error (PBE): the bisection error predicted on the basis of the initial walking direction (point of intersection with the target line of the tangent to the "progression curve" at the starting point). Both OBE and PBE are expressed as percentages of the target line half-length and can be preceded by a positive or a negative sign indicating errors to the right and to the left of the target line midpoint, respectively.

If OBE = PBE, the walking trajectory is rectilinear, indicating that the patient did not change gait direction while walking (**Figure 4**, case a). Conversely, if OBE ≠ PBE, gait direction has changed according to a curvilinear trajectory, indicating that spatial remapping has occurred. If the absolute value of OBE is lower than the absolute value of PBE (|OBE| < |PBE|) and both errors are toward the same side of the target line, the patient has corrected the initial trajectory progressively reducing the bisection error while approaching the line (**Figure 4**, case b). Therefore, the difference (|PBE| − |OBE|) can be considered an index related to the curvature of the walking trajectory and to the occurrence of remapping.

We could also consider the unexpected, but nonetheless theoretically possible, condition that |OBE| > |PBE|. In this case the correction of the patient's trajectory would not be the consequence of spatial remapping, but would be the result of a defective heading control while walking (**Figure 4**, case c). Huitema et al. (2006) suggested that neglect patients with a preserved walking ability – as is the case for patient MR – when asked to walk toward a target might veer toward the left as a consequence of an attempt to compensate for the rightward deviation of their subjective midline.

Prismatic adaptation

In order to improve neglect for left space, patients can be treated with wedge prisms shifting the visual field to the ipsilesional *right* side while performing pointing movements with the ipsilesional hand toward a visual target located in near space. The rightward optical deviation initially causes an ipsilesional pointing error, i.e., patients misreach the targets to the right of their actual position (pre-adaptation error). After a variable number of trials, they spontaneously correct the visual shift induced by the prisms by directing their pointing movements to the contralesional (left) side until they aim correctly for the target (adaptation effect). Once prisms are removed, patients show a directional pointing error toward the contralesional *left* side (after-effect).

Patient MR, despite having suffered a lesion to the right hemisphere, bisected lines to the *left* of the objective midpoint and veered to the left while walking. The presence of this leftward bias made us consider the opportunity to orient the wedge prisms so as to deviate the visual field to the *left* in order to obtain a realignment of visuo-motor coordinates to the right (after-effect).

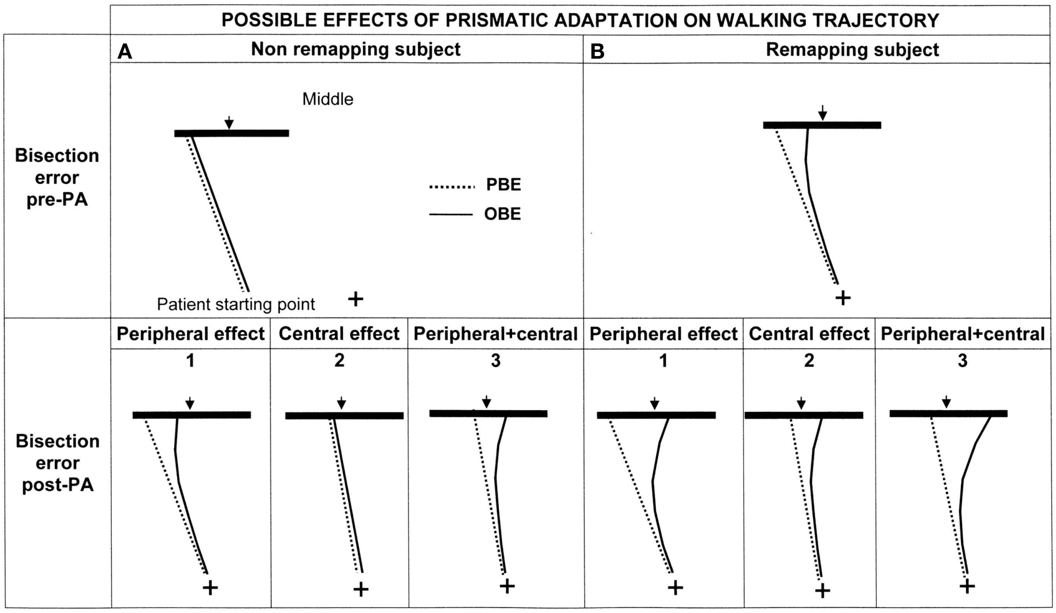

FIGURE 5 | Graphic representation of the possible effects of PA on the walking trajectory of patient MR depending on the presence (B: upper right panel) or absence (A: upper left panel) of spatial remapping and on the level at which PA is effective (lower panels: 1 = peripheral effect; 2 = central effect; 3 = peripheral + central effect). See text for details.

However, given that MR's left neglect was still apparent in copying and cancelation tasks, we decided to apply the adaptation procedure normally employed with left neglect patients using prismatic lenses deviating the visual field to the *right*. Therefore, MR wore a pair of prismatic goggles fitted with wide-field point-to-point 20 diopters lenses that induced a 10° *rightward* optical deviation. During the PA procedure, she was asked to repeatedly point with her right index finger, with a one shot movement, to four small black filled circles (1 cm in diameter and numbered 1–4), horizontally aligned, and centered on the vertical axis of an a A3 sheet of paper. The A3 sheet of paper was centered on the patient's midsagittal plane and was located at a distance of 50 cm. PA involved a total of 120 randomized pointing movements grouped in three sequences of 40 movements each, and required approximately 20 min to be completed. Upon verbal command of the examiner, the patient pointed at one of the four numbered circles while wearing a lattice glove. Her right index finger was inked so as to leave a visible mark on the sheet. For each pointing movement, a pointing error was measured to the nearest mm (i.e., the lateral displacement of the center of the mark from the target).

The patient received four sessions of PA, distributed over a time span of 67 days: the second session was administered 1 week after the first session, while there was a 1 month interval between the second and third and the third and fourth session. In order to evaluate the presence of long-lasting effects of PA on bisection performance, two follow-up sessions were conducted 3 months and 15 months after the last training session (session 4).

PREDICTIONS

Predictions need to take into account two factors: presence/absence of space remapping and the nature (peripheral/central) of the effect of PA (see **Figure 5**). Indeed, normal human behavior implies a rectilinear walking direction with null PBE and OBE. This instance is not included in the figure, where it is only considered the pathological behavior showing a deviated walking trajectory (|PBE| > 0).

Space remapping

Considering that patient MR showed more severe neglect in far rather than in near space – see Section "Results" – we may advance two hypotheses (Berti et al., 2002) in relation to space remapping that make different predictions regarding the bisection performance in the walking modality: (1) *space is not remapped* during walking (**Figure 5A**, upper section). In this case, because space representation is not updated during walking, the trajectory is assumed to be rectilinear and the *first representation* that is activated (the representation of far space, in our patient the most impaired one) should be the one responsible for the bisection performance. In this case OBE = PBE or, alternatively, OBE is not significantly different from PBE; (2) *space is remapped* during walking. In this case, patient MR should activate the most impaired representation at the beginning of each walking path and the less impaired, or even unimpaired, representation toward the end. Her walking trajectories should, therefore, be deviated at the beginning of each walking path, when the starting point is at 3 m, and then, gradually, as she approaches the line, with the activation of the more preserved representation, they should be corrected. According to this hypothesis the *last representation* that is activated should be the one responsible for the line bisection performance. Because this prediction implies a correction of the trajectory during walking, OBE should differ from PBE, in particular |OBE| < |PBE| (**Figure 5B**, upper section).

Effect of prismatic adaptation

If PA is effective in improving the patient's walking trajectory, we expect to see a reduction of bisection errors. Three hypotheses may be advanced, for both remapping or not remapping subjects, in relation to the processing level at which PA is effective (see **Figure 5**, lower panel):

1. PA mainly acts at a peripheral level by realigning the visuomotor coordinates *during walking*. In this case the effect should be evident on OBE and not on PBE, because trajectory correction should manifest during walking rather than from the first step (pre-treatment PBE will be equal to post-treatment PBE, whereas post-treatment OBE will diminish: hence, the curvature of the trajectory post treatment will increase if already occurring before PA (**Figure 5B1**) or be newly introduced if absent before PA (**Figure 5A1**).
2. PA acts at a higher level (at the level of space representation). In this case the correction should be evident at the beginning of walking and affect PBE, because it would be due to a restoring of the functioning of far space representation *before* the initiation of walking. Post-treatment PBE will be smaller, i.e., less deviated, than pre-treatment PBE: as a consequence, also OBE will decrease of a substantially equivalent amount and the curvature of the trajectories pre and post treatment will be substantially the same, depending on the presence (**Figure 5B2**) or absence of remapping (**Figure 5A2**).
3. PA acts at both levels. In this case its effect is a combination of the effects previously predicted and, therefore, PBE and OBE should change at the beginning of walking (effect on space representation) and during walking (effect on space remapping) (see **Figures 5A3,B3**).

RESULTS

In the following analyses, the dependent variables (bisection errors in reaching/pointing tasks and in walking tasks computed prior to each PA session) are expressed as % deviation with respect to half line length – positive values indicate a rightward error, negative values indicate a leftward error. In order to investigate the presence of dissociations between near and far space neglect, we evaluated bisection errors both in near and in far space. The effect of PA, instead, was evaluated in far space only. The reason is twofold: (1) neglect was absent in the manual bisection task in near space (the bisection error (−3.0%) was not significantly different from the null value in a One Sample t test: $t_9 = -1.30$; $p = 0.23$); (2) in the walking bisection task it is possible to investigate the occurrence of spatial remapping of gait trajectory only when the line is located in far space. A summary of the results is reported in the subsequent **Tables 2** and **3**.

Table 2 | Bisection by pointing in far space (FBE).

FBE	S1	S2	S3	S4	Follow-up 1
Pre PA	−13.1 (7.7)	−15.4 (6.6)	−10.5 (9.7)	−0.8 (11.0)	−21.6 (8.8)
Post PA	−3.0 (11.4)	−16.1 (11.3)	4.2 (5.8)	−8.6 (5.2)	

Table 3 | Bisection by walking in far space.

	S1	S2	S3	S4	Follow-up 1	Follow-up 2
PBE						
Pre PA	−54.3 (15.8)	−37.8 (39.0)	−43.7 (39.0)	−24.4 (26.0)	−28.5 (20.1)	−29.3 (15.6)
Post PA	−51.8 (10.3)	−24.0 (25.5)	−20.5 (23.3)	−11.0 (36.2)		
OBE						
Pre PA	−8.2 (13.3)	−9.1 (9.0)	−2.1 (10.6)	−2.7 (9.3)	−4.1 (9.6)	0.5 (4.4)
Post PA	1.8 (7.3)	−6.6 (15.9)	5.9 (6.1)	3.8 (6.6)		

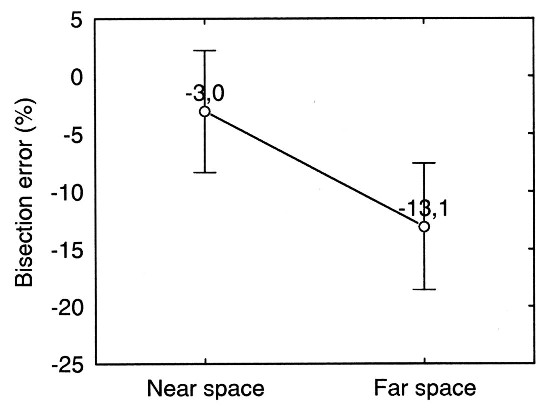

FIGURE 6 | Near and far space bisection errors of patient MR in the manual bisection task. Error bars represent standard errors. Bisection error is expressed as % deviation with respect to half line length. Negative and positive values indicate errors to the left and to the right of the objective midline, respectively. The error is to the left of the true center of the line and is significantly larger in far space than in near space.

DISSOCIATION BETWEEN FAR AND NEAR SPACE NEGLECT IN THE MANUAL BISECTION TASK

Mean errors in bisection tests performed with a stick in near space and with a laser pointer in far space (baseline conditions), are presented in **Figure 6**.

Each point represents average data from the first pre-treatment session. As evident from **Figure 6**, MR bisected lines to the left of the objective midpoint. This behavior is usually associated to right-sided neglect. However, MR had a right brain lesion and left sided neglect in copying and cancelation tasks. (See section Discussion for a discussion of this point). Moreover, a strong dissociation between near and far space neglect was present. There was significantly more bisection error in far space (−13.1%) than in near space (−3.0%) (Paired Samples t test: $t_9 = 2.63$; $p = 0.03$) and the latter was not significantly different from 0 (One Sample t test: $t_9 = 1.30$; $p = 0.23$).

DISSOCIATION BETWEEN FAR AND NEAR SPACE NEGLECT IN THE BISECTION BY WALKING TASKS

Similarly to the manual bisection condition, a (weak) dissociation between far and near space neglect was found in the bisection by walking condition. Indeed, in far space, neglect was significantly worse than in near space when we compare PBE in far space with OBE in near space [PBE_{far} (−54.3%) vs. OBE_{near} (−18.4%): $p = 0.0002$ on Newman–Keuls *post hoc* test] (see **Figure 7**). These two error parameters can be considered the baseline conditions to assess the presence of dissociations between neglect in near and in far space because both are free from any effect related to spatial remapping during walking. A repeated measures ANOVA with ERROR PARAMETER (PBE/OBE) and SPACE (Near/Far) as two levels within subjects factors and % bisection error as dependent variable showed a significant main effect of ERROR PARAMETER ($F_1 = 24.68$, $p < 0.001$) and of the interaction between the two factors [$F_{(1,9)} = 36.04$, $p < 0.001$]. The main effect of ERROR PARAMETER indicates that the patient corrected her trajectories during walking, as evidenced by the fact that average OBE was smaller (−13.3%) than average PBE (−43.17%). OBE, however, remained significantly >0% on a One sample *t* test ($t_9 = -3.93$; $p = 0.003$). The significant effect of the interaction ERROR PARAMETER *SPACE apparently suggests that PBE and OBE dissociate in far and near space (PBE appears more severe in far space whilst OBE appears more severe in near space). However, this interpretation is incorrect and should be reconsidered taking into account the fact that the reduction of OBE from a near to a far starting location is determined by spatial remapping of far space (more compromised) into near space (less compromised) while approaching the target from a far starting location. The error reduction is smaller when the starting location is in near space (0.75 m from target) probably because the near space representation activated at the beginning of the walking path needs more than a single footstep to induce a reduction of the bisection error comparable to that observed when the starting location is in far space.

PRISMATIC ADAPTATION

In order to assess the occurrence of PA we compared the average error at the beginning of the adaptation phase (initial sequence of eight pointing movements: no. 1–8) with the average error at the end of the adaptation phase (final sequence of 8 pointing movements: no. 113–120) of each treatment session (four sessions) (see **Figure 8**). A repeated measures ANOVA was performed on the pointing error on the horizontal plane measured in mm (dependent variable) as a function of PA phase (initial sequence of pointing movements/final sequence of pointing movements) and of PA session (1–4) as within subjects factors. Both factors resulted statistically significant [PA phase: $F_{(1,7)} = 15.73$; $p < 0.005$; PA session: $F_{(3,21)} = 11.41$; $p < 0.001$]. In all the sessions, except the second one, the pointing error reduction at the end of the adaptation phase was significant ($p < 0.05$ for all comparisons at paired samples *t* tests, two tailed; Error reduction: session 1 = 14 mm; session 2 = 4 mm; session 3 = 9 mm; session 4 = 13 mm). This indicates that the patient consistently adapted to the optical shift induced by prisms. The main effect of the variable session, it has to be ascribed to the significantly greater pre-adaptation mean error in the first PA session than in all of the following sessions. In fact the mean pre-adaptation error in the first PA session (16 mm) was significantly greater than the pre-adaptation error measured in session 2 (0 mm), session 3 (6 mm), and session 4 (4 mm) (all comparisons are significant at paired samples *t* tests, one tailed, $p < 0.01$). The pre-adaptation error reduction in sessions 2 through 4 is due to the fact that the massive adaptation obtained in the first session is substantially maintained in the subsequent sessions: indeed, the mean post-adaptation error in session 1 was comparable to the pre-adaptation error in sessions 2, 3, and 4 (all comparisons $p > 0.3$ at paired samples *t* test, two tailed) (See **Figure 8**).

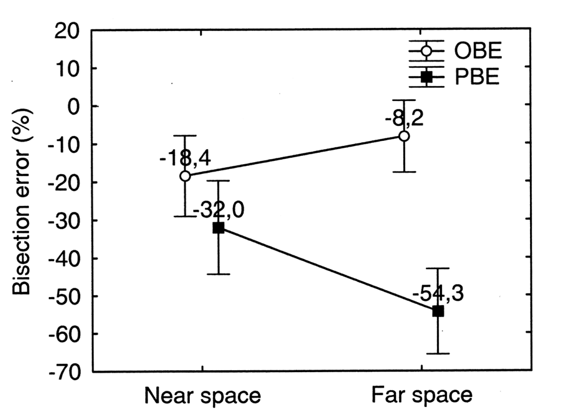

FIGURE 7 | Far and near space bisection errors of patient MR in the walking bisection task. Error bars represent standard errors. Bisection error is expressed as % deviation with respect to half line length. OBE, observed bisection error; PBE, predicted bisection error. Negative and positive values indicate errors to the left and to the right of the objective midline, respectively. Neglect is more severe in far space than in near space: PBE in far space is significantly greater than OBE in near space. See text for details.

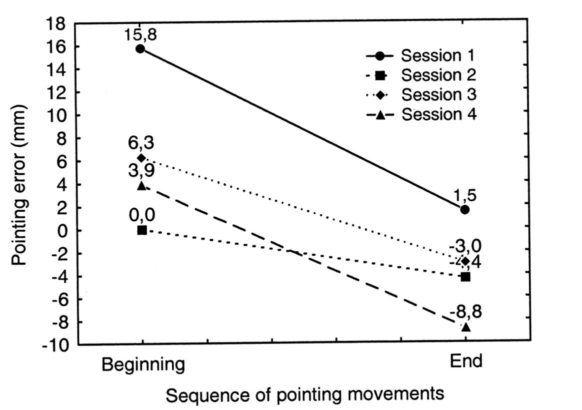

FIGURE 8 | Graphic representation of the occurrence of prismatic adaptation (PA) in patient MR during each treatment session (session 1–4). Positive and negative values indicate deviations to the right and to the left of the target, respectively. Adaptation occurs if the rightward pointing error measured at the end of the adaptation procedure (End: pointing movements no. 113–120) is significantly smaller than the error measured at the beginning of the adaptation procedure (Beginning: pointing movements no. 1–8). Error reduction is significant in every treatment session except in session no. 2. See text for details.

EFFECT OF PRISMATIC ADAPTATION IN THE BISECTION BY POINTING TASK

Figure 9 shows the trend of the bisection error in far space prior to each PA session (1–4) and at the follow-up 3 months after session 4. It is to be noted that, starting from session 2, the pre-adaptation bisection error incorporates the effect (if any) of PA of the preceding session.

In order to test statistically the effect of PA sessions on neglect, we ran a repeated measures ANOVA on bisection error prior to PA (dependent variable) as a function of PA sessions (within subject factor, four levels: PA session 1–4). PA session resulted significant [$F_{3,27}$=5.83; $p = 0.003$]. Neglect significantly improved in session 4, where bisection error was close to 0% and was significantly less severe than in sessions 1–3 ($p \leq 0.01$ at Newman–Keuls *post hoc* for all comparisons). However, neglect reappeared in the follow-up session, which occurred 3 months after session 4, and was significantly worse than in session 1, 3 and 4 ($p = 0.01$, $p = 0.03$, and $p < 0.01$, respectively, at Paired samples *t* tests). For this reason we did not run a second follow-up.

In summary, the bisection error in far space not only was significantly reduced by PA, but disappeared after three sessions of treatment carried out over a period of 37 days; this improvement was still evident a month later (session 4). However, at the follow-up 90 days after session 4, neglect reappeared and was comparable to neglect prior to treatment.

EFFECT OF PA IN THE BISECTION BY WALKING TASKS

The overall effect of PA on bisection error in the walking tasks is shown in **Figure 10**, where each point represents the average bisection error of four PA sessions collapsed together. Consistently with **Figure 10** the direction of the bisection error already observed in the preliminary bisection test (see **Figure 7**), the patient crossed the line to the left of its true center, showing apparent right-sided neglect.

In order to test statistically the overall effect of PA on walking tasks, we performed a repeated measures ANOVA on bisection error (dependent variable) as a function of PA (two levels: Pre PA/Post PA) and Error Parameter (two levels: PBE/OBE) as within subjects factors. Both factors significantly influenced bisection performance [PA: $F_{(1,9)} = 12.29$; $p < 0.001$; Error Parameter: $F_{(1,9)} = 115.67$; $p < 0.0001$], while the interaction PA* Error Parameter was not significant. The main effect of Error Parameter showed that the bisection error predicted at the beginning of the walking trajectory (PBE = −40.0%) was more severe than the bisection error observed at the end of the walking trajectory (OBE = −5.5%), indicating that the patient remapped the representation of far space – more compromised – into near space – more preserved – while approaching the target (see also **Figure 11**). Moreover, the significant effect of PA shows that it was effective in reducing neglect.

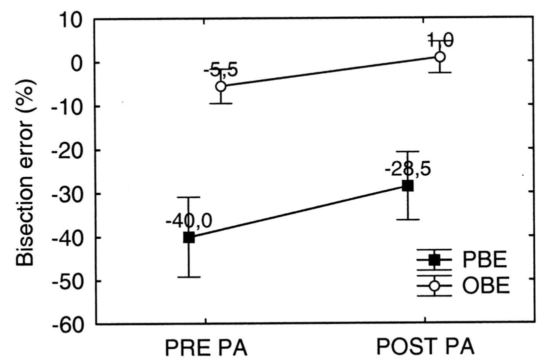

FIGURE 10 | Graphic representation of the overall effect of prismatic adaptation (PA) on MR's bisection by walking error in far space. PA is effective in significantly reducing both the observed (OBE) and the predicted (PBE) bisection error. PBE is significantly larger than OBE, but error reduction due to PA is comparable. Error bars represent standard errors. Bisection error is expressed as % deviation with respect to half line length. Negative and positive values indicate errors to the left and to the right of the objective midline, respectively. See text for details.

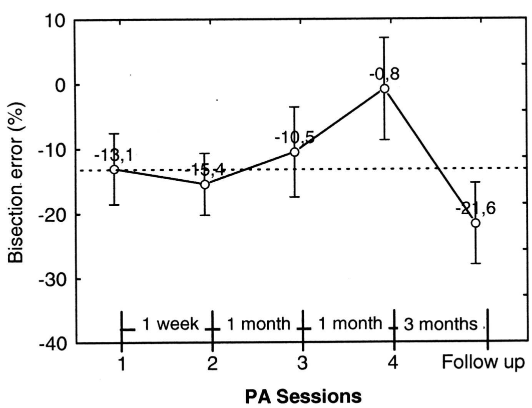

FIGURE 9 | Graphic representation of the effect of prismatic adaptation (PA) on the patient's bisection by pointing errors in far space. Each data point represents the bisection error prior to PA. The error is significantly reduced in session 4. However, at follow-up (3 months after session 4) the effect of PA is no longer present and neglect is as severe as prior to PA. Error bars represent standard errors. Bisection error is expressed as% deviation with respect to half line length. Negative and positive values indicate errors to the left and to the right of the objective midline, respectively.

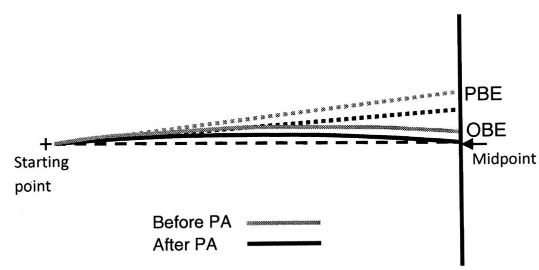

FIGURE 11 | Graphic representation of the shape of MR's predicted (dotted lines) and observed (continuous lines) walking trajectories prior (black lines) and after (gray lines) prismatic adaptation (PA). Note that PA reduces both the predicted (PBE) and the observed (OBE) bisection error but does not modify the shape of the trajectories (continuous lines), showing that spatial remapping in patient MR is independent of PA.

Interestingly, PA significantly reduced both PBE ($PBE_{post\ PA}$ - $PBE_{pre\ PA} = -11.5\%$: $p < 0.001$ on Newmann Keuls *post hoc*) and OBE ($OBE_{post\ PA} - OBE_{pre\ PA} = -6.5\%$: $p = 0.037$ on Newmann Keuls *post hoc*) (see **Figure 10**). Despite the effect of PA on OBE was (non-significantly) smaller ($p = 0.21$ on Paired samples t test), the difference between PBE and OBE prior and after treatment was comparable [$(PBE\text{-}OBE)_{Pre} = -34.5\%$; $(PBE\text{-}OBE)_{Post} = -29.4\%$; $t_9 = -1.33$: $p = 0.21$ on paired samples t test]. Since the difference (PBE-OBE) quantifies the effect of gait direction changes due to spatial remapping, this result indicates that PA had no significant effect on the shape of the trajectories, which already showed the effect of spatial remapping before PA (see also **Figure 11** for a graphical representation).

In order to analyze the effect of each PA session on bisection error, we performed an additional repeated measures ANOVA on pre-adaptation bisection error as a function of PA session (four levels: sessions 1–4) and Error parameter (two levels: PBE and OBE) as within subjects factors (see **Figure 12**). Consider that the pre-adaptation bisection error measured on session 1 is free from any effect of treatment and it can be considered as the baseline condition. Starting from session 2, instead, the pre-adaptation bisection error incorporates the effect (if any) of PA of the preceding session.

The analysis showed that the factor Error Parameter was, indeed, significant [$F_{1,9} = 8.43$; $p < 0.0001$], with the overall error predicted at the beginning of the walking trajectories resulting more severe than the error observed at the end of the walking trajectories. The factor PA Session, instead, resulted non-significant. However, PBE measured in session 4 resulted significantly smaller than PBE in session 1 ($p = 0.02$ on paired samples t test). Furthermore, PBE measured at follow-up 3 and 15 months after session 4 remained significantly smaller than in session 1 ($p = 0.016$ and $p = 0.007$, respectively, on paired samples t tests) and was comparable to the error measured in session 4. Considering OBE, the effect of PA session was of smaller entity. We compared OBE of session 1 and 2 collapsed together (mean error $= -8.65\%$) with OBE of follow-up sessions 1 and 2 collapsed together (mean error $= -1.83\%$) (we collapsed session 1 with session 2 and follow-up 1 with follow-up 2 because they did not differ significantly). The results show that OBE at follow-up resulted significantly smaller than OBE prior to treatment ($t = -2.19$, $p < 0.05$, on a paired samples t test) and comparable to OBE in session 4.

In summary, PA was effective in reducing the bisection by walking error of patient MR. The reduction was higher for PBE than for OBE, suggesting that PA was more effective in ameliorating the initial spatial representation of the trajectory than spatial remapping during gait execution. In addition, the amelioration of neglect persisted up to 15 months post treatment.

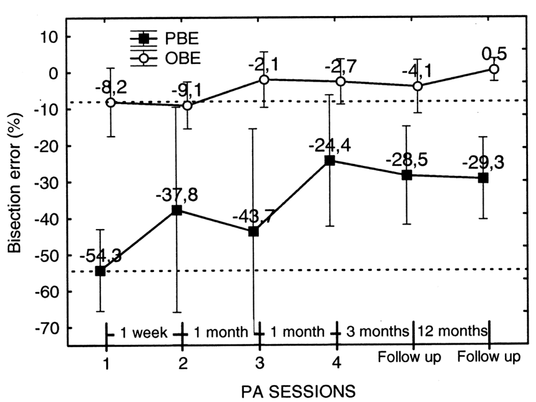

FIGURE 12 | Graphic representation of the effect on the walking bisection error of individual PA sessions (1–4) and of the duration of the effect (follow-up). Each point represents the pre-adaptation bisection error, i.e., the error measured prior to each PA. The pre-adaptation error measured in session 1 serves as baseline (upper and lower dashed lines). Note that the effect of PA in terms of error reduction a) is greater for the predicted (PBE) than for the observed (OBE) bisection error and b) it is maintained at follow-up 3 and 15 months after the last PA session (no. 4). Error bars represent standard errors. Bisection error is expressed as % deviation with respect to half line length. Negative and positive values indicate errors to the left and to the right of the target objective midline, respectively. See text for details.

DISCUSSION

As a premise, we must point out that this is a single case experimental report, and can be considered a pilot study preceding a possible larger group study. We used this design because, to our knowledge, no study exists that has addressed the issue of the prevalence of neglect patients with a dissociation between near and far space neglect in walking. Since we cannot exclude that these patients have a low incidence, we wanted to assess whether PA would work on this specific patient. When single case research designs are employed, the patient undergoes different treatments in a pseudo-randomized order, and thus acts as his/her own control (Brossart et al., 2008; Bulté and Onghena, 2008).

The aim of the present study was to investigate the effect of PA on two different bisection tasks (bisection by reaching/pointing and bisection by walking) in a right brain-damaged patient (MR) with a dissociation between near and far space neglect. In particular, MR presented with more severe neglect in far than in near space in both bisection tasks. The dissociation was stronger in the bisection by reaching/pointing than in the bisection by walking task. It is worth noting that patient MR had *left* neglect in conventional cancelation and drawing tasks, but bisected line segments to the *left* of the objective midpoint (right neglect) both in conventional line bisection and in bisection by walking tasks.

Greater severity of far space neglect was especially evident if we consider the PBE, that is the error computed on the basis of the initial direction of the walking path (see **Figure 7**). However, MR partially corrected her initial walking error as she approached near space, as evidenced by the significant reduction of the bisection errors when she reached the line (OBE). This walking pattern shows that patient MR updated space representation during walking according to the degree of severity of her neglect in far vs. near space. It is very likely that MR activated the most impaired representation at the beginning of each walking path in far space and the less impaired representation while approaching the target in near space. According to our hypotheses, this indicates that the representation guiding MR's line bisection is the last representation activated during walking, i.e., near space representation.

In patient MR we also evaluated the effect of PA in bisection by pointing and in bisection by walking tasks. In the *pointing task* the effect of PA was significant starting from session no. 4, where bisection error reduced to a value close to 0%. However, neglect reappeared in the follow-up session, which occurred 3 months after session 4. This indicates that, in the case of bisection by pointing, the positive effect of PA was not long-lasting. Conversely, in the *bisection by walking task* the effect of PA was maintained for a longer time. In particular the effect was still present 15 months after the last PA session. It is worth noting that PA primarily influenced the PBE parameter, that is the walking direction estimated at the beginning of the walking path, while the trajectory curvature *per se* did not change (see **Figure 11**): this is evidenced by the fact that the difference between PBE and OBE prior and after PA did not significantly change. According to our hypothesis, the reduction of PBE by PA strongly suggests the restoring of the more compromised representation, i.e., far space representation, *before* gait execution. This indicates that PA has a central effect on spatial representation, directly affecting higher level components of space representation rather than influencing lower level on-line recalibration factors. Importantly, this conclusion is confirmed by the fact that PA was carried out with prismatic lenses oriented so as to deviate MR's visual field toward the *right* space (as it is normally done in order to reduce neglect for the left side of space), despite the fact that MR showed apparent neglect for the *right side* of space in line bisection tasks (MR misbisected segments to the left of the objective midpoint in both bisection by reaching/pointing and in bisection by walking). Because in conventional copying and cancelation tests patient MR showed left side neglect, we reasoned that MR's leftward deviation was likely to be the consequence of compensatory strategies, a sort of leftward motor hyper correction, rather than a genuine right side neglect. Indeed, a similar behavior is known to be displayed by neglect patients that might compensate for their exogenous orienting deficit and ipsilesional deviation of the subjective midline by means of relatively intact endogenous searching processes (Bartolomeo and Chokron, 2002; Huitema et al., 2006). Therefore, we used right deviating prism to be sure that we did not change the usual rehabilitation procedure employed for left side neglect patients. The rationale was that if prism adaptation acted on on-line recalibration factors, we should have found a further deviation toward the left of the patient's walking trajectory (i.e., a worsening of bisection performance). Instead, we observed a rightward deviation that showed an improvement of neglect. This means that the effect of PA intervenes before actual walking initiation, presumably on the higher spatial representation levels preceding movement execution and known to be affected in neglect.

It is unlikely that the observed results are influenced by fatigue effects. Despite the long duration of each experimental session (approximately 2 h), the patient's performance did not decrease with time. Indeed, if this was the case, a worse performance should be expected toward the end of the experiment. This did not happen: immediately after PA-applied during the second half of the experimental session – neglect ameliorated, as shown by the reduction of bisection errors.

A novel finding of our research is that PA obtained through manual pointing (requiring visuo-motor coordination of the upper limb) transfers to gait (requiring motor coordination of the lower limbs). In line with our results, Tilikete et al. (2001) showed that PA can extend to body regions different from the one which has been adapted and that a brief adaptation to rightward shifting prisms in a reaching task generalizes to the postural system and improves neglect patient's postural imbalance. More recently, Savin and Morton (2008) showed that arm pointing adaptation generalizes to leg pointing (see also Morton and Bastian, 2003, for somehow different results: the authors found that PA during walking generalized to reaching, but adaptation during reaching did not generalize to walking. It is worth noting that one factor that could account for the difference between these findings and ours is that Morton and Bastian tested normal subjects: it is well known that the effect of PA on normal subjects is limited if compared with the effect on neglect patients (Colent et al., 2000; Michel et al., 2003a,b). Furthermore, direct comparison of our single case experimental results with those from small group studies should be considered with caution given the difference in the two experimental designs.

Our findings may have important implications for the rehabilitation of neglect patients. Neglect symptoms may, at least partially, spontaneously recover in the acute phase post stroke (see Farnè et al., 2004), but only a very small percentage of patients (9% in the study by Farné et al.) show a complete remission of all symptoms (Hier et al., 1983; Samuelsson et al., 1997; Katz et al., 1999). Among the symptoms that may become chronic are gait deficits that prevent neglect patients to navigate safely through the environment. Symptomatology can vary from frequent falls (Webster et al., 1995) and bumping into objects located in left space (Grossi et al., 2001) to generic locomotion problems in daily living transfer activities (Nijboer et al., 2013) and a deviated walking trajectory (Brain, 1941; Berti et al., 2002; Huitema et al., 2006).

The efforts to rehabilitate unilateral neglect are further complicated by the presence of anosognosia (Halligan and Marshall, 1998), leading to a scarce cooperation of the patient in the rehabilitation programs. As a result, the presence of neglect after stroke remains one of the major factors associated with a poor functional outcome (Denes et al., 1982; Edmans et al., 1991; Jehkonen et al., 2000). Not surprisingly, a large variety of different rehabilitation techniques have been developed in order to treat neglect (see Luauté et al., 2006 for a review). PA has demonstrated to be one of the most effective. Among the symptoms showing improvement following PA are the following: the deficit of exploration of contralesional visual-space (Ferber et al., 2003), contralesional somatosensory perception (McIntosh et al., 2002; Maravita et al., 2003; Dijkerman et al., 2004), wheel-chair navigation (Jacquin-Courtois et al., 2008), and postural imbalance (Tilikete et al., 2001; Michel et al., 2003b). To the best of our knowledge PA has never been used to correct the deviated walking trajectories of neglect patients, except for a study by Keane et al. (2006) in which two ambulatory patients were shown to improve their walking abilities after PA. However, patients in this study were simply required to walk through a hallway and the authors only reported that their walking path, directed toward the right half of the hallway prior to PA, occupied the middle of it following PA. It is therefore unclear to what extent walking profited from PA and if prisms acted at the level of gait representation, gait execution, or both. Our results show that PA acts more upon the spatial representation activated at the beginning of the walking path (when the direction of the walking trajectory is first computed) than on the modulation of spatial representation during gait execution. This result may be specific for our patient, in which the far space representation – activated at the beginning of walking – was significantly more compromised than the near space representation – activated only successively, at some point during the patient's approach to the target. Therefore, it is not surprising that the effect of PA, in this case, is stronger on the far than on the near space representation.

A further interesting and promising characteristic of PA is the long-lasting duration of its beneficial effect upon spatial representation of gait trajectory. In our case, four sessions of PA were sufficient to produce a positive outcome which lasted up to 15 months after treatment (the duration of the effect of PA on the bisection error by reaching was smaller: 3 months after treatment the bisection error reappeared). Indeed, long-lasting effects of PA after *repeated* and *prolonged* sessions of treatment have been demonstrated in previous works. In a study by Frassinetti et al. (2002) seven neglect patients were treated with two sessions of PA per day for 2 weeks and six out of seven showed an improvement of the symptomatology, in a standardized battery of visuo-spatial tests, that was maintained up to 5 weeks after treatment. In a more recent study by Serino et al. (2007), 16 neglect patients were submitted to a PA treatment for 10 daily sessions over a period of 2 weeks and showed ameliorated visuo-spatial abilities up to 3 months after treatment. Rusconi and Carelli (2012) have shown an amelioration of neglect in seven patients after 2 weeks of treatment with PA that was maintained up to 30 months after the end of treatment. In our study, four sessions of PA distanced in time one from the other, have determined a long-lasting amelioration in MR's neglect walking trajectory. One could argue that her improvement could alternatively be attributed to spontaneous recovery. However, as we assessed MR's neglect 10 months after stroke, this is unlikely to be the case: it has been demonstrated that neglect symptoms tend to improve up to 6–9 months from lesion, and stabilize or get worse after such time interval (Cherney and Halper, 2001).

An interesting aspect of PA in our patient is that its positive effects increase over time: both in manual and in walking bisection tasks, pre-adaptation bisection errors in the last PA session (session 4: 67 days apart from session 1) are significantly smaller than pre-adaptation errors in the preceding PA sessions (see **Figures 9** and **12**) (see Fortis et al., 2010, for a similar result). Additionally, the improvement in the walking trajectory is maintained 15 month after treatment, longer than the improvement in the bisection by pointing task (McIntosh et al., 2002; Pisella et al., 2002). These results should not surprise us if we consider the important role of the cerebellum in walking and in PA. On the one hand, it is well known that cerebellar lesions can produce a gait deficit known as cerebellar gait ataxia and that the cerebellum participates in postural balance (Tilikete et al., 2001), locomotion balance and, to a lesser degree, in leg coordination (Morton and Bastian, 2003); on the other hand, lesions of the right cerebellum impair adaptation to right-shifting prisms (Pisella et al., 2005) and cerebellar activation during PA in neglect patients covariates positively with the left spatial neglect improvement (Luauté et al., 2006). Hence, the cerebellum is a good candidate to play an important role in mediating the long term improvement of walking trajectory induced by PA in our patient (indeed, MR's lesion spared the cerebellum). To investigate this possibility, fMRI research should examine the long-term plastic changes in the cerebellum in response to PA in neglect patients with gait deficits.

An alternative (or additional) explanation of the difference in the duration of the improvement induced by PA in the two bisection tasks calls into play the role of the dorsal stream in visuo-spatial processes. Specifically, according to recent anatomical and functional animal and human data (Kravitz et al., 2011), the dorsal stream gives rise to three distinct pathways: a parieto-prefrontal pathway, a parieto-premotor pathway and a parieto-medial temporal pathway, each supporting different visuo-spatial functions. The parieto-medial temporal pathway, the retrosplenial cortex in particular, seems to be implicated in spatial-navigation. Interestingly, the retrosplenial cortex and the medial occipital-parietal cortex, which sends feedback signals to the former, are spared by the lesion in our patient; instead, the involvement of the temporal pole may have more severely affected spatial representation processes not specifically related to spatial-navigation ability, such as those implicated in the bisection by pointing task. This may be one reason why the effect of PA was more durable in the bisection by walking than in the bisection by pointing task.

In conclusion, our results show, for the first time, a long-lasting rehabilitative effect of PA on walking trajectory in a patient with chronic neglect: as few as four sessions of PA ameliorated neglect during walking for as long as 15 months post treatment. Following PA, far space neglect was reduced in our patient, allowing a better representation of gait trajectory right from the first step. Instead, the curvature of the walking trajectory did not change following PA, suggesting that PA did not influence the low level processes subserving gait execution. These results show that PA acts on high level spatial cognition rather than on peripheral sensory-motor processing and is responsible for the realignment of the egocentric frame of reference guiding our patient's gait trajectory following treatment (Fortis et al., 2010). The results of our single case experiment support a future group study on neglect patients aimed at verifying whether PA can be employed as a long-lasting rehabilitative tool in neglect patients in which gait trajectory is deviated and are prone to the adaptation effect with prismatic goggles. Finally, we hypothesize that the cerebellum and/or the retrosplenial cortex could play a crucial role in mediating the long-lasting rehabilitative effects of PA on gait trajectory in our patient.

ACKNOWLEDGMENTS

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The feasibility of computer-based prism adaptation to ameliorate neglect in sub-acute stroke patients admitted to a rehabilitation center

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Introduction: There is wide interest in transferring paper-and-pencil tests to a computer-based setting, resulting in more precise recording of performance. Here, we investigated the feasibility of computer-based testing and computer-based prism adaptation (PA) to ameliorate neglect in sub-acute stroke patients admitted to a rehabilitation center.

Methods: Thirty-three neglect patients were included. PA was performed with a pair of goggles with wide-field point-to-point prismatic lenses inducing an ipsilesional optical shift of 10°. A variety of digitalized neuropsychological tests were performed using an interactive tablet immediately before and after PA.

Results: All 33 patients [mean age 60.36 (SD 13.30)], [mean days post-stroke 63.73 (SD 37.74)] were able to work with the tablet and to understand, perform, and complete the digitalized tests within the proposed time-frame, indicating that there is feasibility of computer-based assessment in this stage post-stroke. Analyses of the efficacy of PA indicated no significant change on any of the outcome measures, except time.

Discussion: In conclusion, there is feasibility of computer-based testing in such an early stage, which makes the computer-based setting a promising technique for evaluating more ecologically valid tasks. Secondly, the computer-based PA can be considered as a reliable procedure. We can conclude from our analysis, addressing the efficacy of PA, that the effectiveness of single session PA may not be sufficient to produce short-term effects on our static tasks. Further studies, however, need to be done to evaluate the computer-based efficacy with more ecologically valid assessments in an intensive double-blind, sham-controlled multiple PA treatment design.

Keywords: neglect, stroke, feasibility, efficacy, computer-based assessment, computer-based prism adaptation

INTRODUCTION

One of the major recent advances in neuropsychology is the use of computers during both screening and rehabilitation. There is wide interest in transferring paper-and-pencil tests to a computer-based setting (Schatz and Browndyke, 2002), resulting in a more detailed and precise recording of performance during screening and training (Rabuffetti et al., 2002; Chiba et al., 2006; Tsirlin et al., 2009) as well as enhanced consistency in testing across settings, making comparisons across patients more valid. Consequently, as the prism adaptation (PA) procedure has a fairly easy and repetitive design (see below), it is a good candidate for computer-based rehabilitation. Here, we investigate the feasibility of computer-based assessment and PA to ameliorate neglect in sub-acute stroke patients admitted to a rehabilitation center.

Neglect is a disabling disorder that frequently occurs after right hemisphere stroke (Bowen et al., 1999; Ringman et al., 2004). It refers to the failure to report, respond, or orient to stimuli on the contralesional side of space or body that cannot be accounted for by primary sensory or motor deficits (Halligan and Marshall, 1991; Robertson, 1999). Neglect is associated with poor functional recovery (Cherney et al., 2001; Jehkonen et al., 2006). Farne et al. (2004) found that whereas 43% of neglect patients demonstrated spontaneous recovery in the first 2 weeks, only 9% recovers completely. These findings concur with a recent study where patients were assessed several times during 1 year post-stroke (Nijboer et al., in press). In this study, spontaneous recovery of neglect appears to occur mainly during the first 12–14 weeks after stroke (Nijboer et al., in press) even though approximately 40% of the neglect patients do not fully recover and still show neglect on neuropsychological tests a year after stroke (Karnath et al., 2011; Rengachary et al., 2011; Nijboer et al., in press). Development of effective treatment techniques is therefore an important aim in neglect research, especially in the sub-acute phase, as the brain is primed to neurological recovery in the first 3 months post-stroke (Kwakkel et al., 2004; Murphy and Corbett, 2009).

One of the most widely investigated techniques to ameliorate neglect is PA (Rossetti et al., 1998; for overview, see Newport and Schenk, 2012). PA, originally proposed by Rossetti et al. (1998), is a promising experimental technique with strong therapeutic potential (Kerkhoff and Schenk, 2012). PA induces a proprioceptive shift in space by repetitive pointing to visual targets, resulting in a recalibration of the egocentric coordinate system. In other words, it creates a pointing bias in the opposite direction after prism removal and a contralesional shift in subjective body midline (Heilman et al., 1983; Saj and Vuilleumier, 2007). Positive effects of PA have been reported across many visuo-manual tasks in patients in the chronic phase, such as bisecting lines, line crossing, copy drawing (Saevarsson et al., 2010; Striemer and Danckert, 2010; Sarri et al., 2011), but also in more non-manual tasks, such as picture scanning, object-naming tasks and reading tasks (words and non-words) (Farne et al., 2002), and daily situations, such as wheelchair navigation (Rossetti et al., 1999; Watanabe and Amimoto, 2010) and postural control (Tilikete et al., 2001). The beneficial effects of PA have been reported to last 2 h (Rossetti et al., 1998) up to 1 week (Pisella et al., 2002; Dijkerman et al., 2004), and even up to 2 years (Nijboer et al., 2011).

Notwithstanding these promising results, evidence on feasibility and secondarily the efficacy of PA in the sub-acute stroke stage in a rehabilitation setting is relatively scarce. Nonetheless, it is important to identify an optimal or "critical period" for the optimal treatment response, keeping in mind that neurological recovery takes place in the first 3 months post-stroke (Kwakkel et al., 2004; Murphy and Corbett, 2009; Nijboer et al., in press). There are only a few randomized control trials that assessed the efficacy of PA exclusively in sub-acute (range 2–86 days) stroke patients (Nys et al., 2008; Turton et al., 2010; Mizuno et al., 2011). The effectiveness of PA in this stage remains equivocal, however. Whereas Mizuno et al. (2011) performed an intensive 2-week PA treatment and found improvement on the conventional Behavioral Inattention Test (BIT) and on a functional independence measure, Turton et al. (2010) did not find such an effect. The lack of efficacy in the latter study might be attributable to the use of 6° goggles, which is a lesser degree of lateral displacement than that used in other studies (Barrett et al., 2012). Nys et al. (2008) only found short-term superiority in performance on the BIT, compared to placebo treatment. Clearly, the effectiveness of PA in the sub-acute stage post stroke needs further research.

To date, we do not know whether testing in general and computer-based assessment is too difficult or too time-consuming in this stage of syndrome since many previous studies were performed in the chronic stage. Therefore, our aim is to investigate the feasibility of computer-based assessment in a sub-acute stage post-stroke. Secondly, we combined the widely used PA procedure with a computer-based setting in order to investigate the feasibility of computer-based treatment (PA). Importantly, it is unknown whether a prismatic after-effect can be obtained with computer-based treatment. Furthermore, we gain insight in the adaptation procedure by means of more detailed and precise recordings of the pointing movements during the adaptation procedure as well as the magnitude of the after-effect. Lastly, we want to investigate the efficacy of a single session of computer-based PA on neuropsychological digitalized tests.

METHODS

PARTICIPANTS

In this study 33 stroke patients [mean age 60.36 (SD 13.30); mean days post-stroke 63.73 (SD 37.74)] with neglect (31 left visuospatial neglect) were included (see **Table 1** for patient characteristics). All patients were admitted to rehabilitation center de Hoogstraat. Patients were included when they met the following criteria: (1) a brain lesion as revealed by CT or MRI; (2) presence of spatial neglect as assessed with a short screening including the Object Cancelation and Letter Cancelation (see Inclusion Based on Short Neuropsychological Screening below in this paragraph); (3) aged between 18 and 80 years; (4) able to understand and carry out the test instructions; (5) written or verbal informed consent and sufficient motivation to participate.

All patients received multidisciplinary standard stroke care and treatment and participating in the study did not interfere with daily routines. Additionally, all patients received visual scan training, which was the current intervention used for rehabilitation of neglect in this rehabilitation center.

Inclusion based on short neuropsychological screening

The short screening that took place prior to the inclusion of the present study was part of the standard stroke care. At this level, severity of neglect was evaluated on the bases of the standard outcome measures of the Object Cancelation and the Letter Cancelation (number of omissions). The average number of omissions was 7.21 (SD = 8.39) for the Object Cancelation and 7.11

Table 1 | Demographical and stroke characteristics of the included patients.

Clinical variables	Included patients (SD)
Group size	33
Age (years)	60 (13.30)
Gender (male)	57.58%
Stroke characteristics	
Days post-stroke	63.73 (37.74)
Hemisphere of stroke (*R*)	90.91%
Unilateral	96.97%
Type of stroke	
Cortical ischemia	63.64%
Subcortical ischemia	3.03%
Intracerebral hemorrhage	30.30%
Other*	3.03%
Barthel index ($n = 28$)	12.07 (5.77)
Motricity index arm ($n = 23$)	57.43 (41.38)
Motricity index leg ($n = 23$)	67.43 (36.75)
MMSE ($n = 25$)	25.54 (4.29)
Hemianopia	39.39%

*MMSE, mini mental state exam; *ischemia due to acute disseminated encephalomyelitis.*

(SD = 5.80) for the Letter Cancelation. It should be noted that only 15 patients of our total sample performed the Letter Cancelation in the screening. When evaluating the level of lateralized impairment, we calculated the asymmetry in the number of omitted items. For the Object Cancelation, 27 patients (out of 33) showed an asymmetry in omitted items in the range from 0 to 10 ($M = 2.44$; SD = 2.39) and 6 patients had an asymmetry score between 15 and 30 ($M = 19.33$; SD 3.78). For the Letter Cancelation test (LC), 16 (out of 18) patients displayed an lateralized deficit between 0 and 10 ($M = 3.63$; SD 3.07) and 2 patients had an asymmetry score between 10 and 15 ($M = 14.00$; SD 1.41).

APPARATUS

Both the PA procedure and the neuropsychological tests were done using a 22-inch interactive WACOM (PL2200) tablet screen (1920 × 1080), with a screen size of 477.64 mm × 268.11 mm. The tablet includes a widescreen display (luminance: 200 cd/m^2) and full HD resolution (0.01 mm/point) and has a screen refresh rate of 5 ms. The display offers a large working area and provides good spatial (±0.01 mm/point) and temporal resolution (133 points/s, max).

Patients had to respond to stimuli by drawing on or pointing at the screen with a digital stylus. We used an electromagnetic resonance method to record patients' performance of the stylus. DiagnoseIS (developed by Metrisquare, Netherlands) was used to program the neglect screening tests (e.g., Cancelation tests). The tablet was driven by a laptop in order to monitor stimuli and patients performance on the experimenter's laptop. During performance the tablet screen was oriented horizontally and slightly tilted (18°) with an adjustable stand.

DIGITALIZED PRISM ADAPTATION PROCEDURE

The PA procedure was adapted from Rossetti et al. (1998) and was performed with a pair of goggles fitted with wide-field point-to-point prismatic lenses, inducing a rightward optical shift of 10°.

The distance between the visual stimuli and the body midline was approximately 65 cm. Patients were presented with three visual targets (red, yellow, blue) on a horizontal axis. The left and right visual targets were both 11.5 cm away from a central visual stimulus. Exposure consisted of 100 fast repetitive pointing movements. Half of the pointing movements were made to the left visual target, the other half were made to the right visual target. Patients were occasionally instructed to point to the central visual stimulus when pointing appeared to become a routine. These additional pointing movements prevented automatic pointing in a sequence of motor acts to either the left or the right target. When patients experienced difficulties in distinguishing between left and right, the color of the visual stimulus was used. Whenever the patient touched the tablet screen with the digital stylus, x and y coordinates and timing data were recorded. Error reduction was achieved when patients hit the target. Patients pointing performance was only and immediately presented at the laptop of the experimenter, allowing the experimenter to monitor the accuracy of the pointing movements online.

After the adaptation phase (e.g., repetitive pointing), prisms were withdrawn and the after-effect was measured. Conventionally, the strength of the adaptation can be obtained by measuring the spatial deviation from a target stimulus. During the repetitive pointing movements (the adaptation phase), visuomotor corrections toward the contralateral side in order to point to the target as accurate as possible, are executed. Thus, when prisms are removed, the spatial deviation will be in the opposite direction of the visual displacement imposed by the prism glasses, a phenomenon known as the after-effect. In our sample we used the central target to measure the after-effect. Here, after prism removal, patients were instructed to look carefully at the central visual target. After a few seconds they were instructed to point with the digital stylus at the central target, with eyes closed to prevent online adjustments. Again, patients did not get feedback about the landing position of the digital stylus, which was only shown at the experimenter's laptop. For after-effects, the mean error displacement from the central stimulus was calculated and should have been at least 3 cm, otherwise the PA procedure was continued.

STIMULI, TESTS, AND PROCEDURE

All measurements were conducted in a sound-attenuated room. Patients were seated as comfortable as possible, in upright position in front of the tablet. All tests were done using the tablet. These tests were done prior and immediately after PA in the same order if possible. The whole test procedure lasted for an hour and patients were allowed to have a small break when needed prior or after the PA procedure.

In an *Object Cancelation* test (OC), patients were presented with 54 targets, and 75 distractors. Patients had to cross out all the targets. Patients were given feedback; they could see their own performance; e.g., see the stripe of the digital stylus through the canceled items. Outcome measurements were the total number of omissions, total time for test completion, search time in the ipsilesional and contralesional field and the horizontal and vertical Center of Cancelation (CoC). The CoC is an indicative measure of severity of neglect, since it obtains information of both the number of omissions and the location of canceled items. Generally, a positive CoC-score (+) indicates that the mean horizontal location of the canceled items is at the right side of the stimulus sheet, e.g., indicating lateralized deficits on the far left and vice versa. A CoC-score toward zero means a more symmetrical spatial error distribution. Calculations for the CoC were adapted from Rorden and Karnath (2010). Additionally, the same method was applied for the number and spatial distribution of perseverations.

The *Letter Cancelation* test (LC) consisted of 5 rows of 34 random letters (170 letters in total). Patients were instructed to cancel the target letters, which were randomly placed between the distractor letters. Outcome measures were the total number of omissions, total time for test completion, search time in the ipsilesional and contralesional field and the horizontal CoC (Rorden and Karnath, 2010).

In a *Line bisection* test (LB), patients were presented with three horizontal lines (31 cm in length and 1 mm in width). The lines were outlined in a staircase fashion and patients had to indicate (upper to low) the true center of each line. This test was performed twice. Outcome measurement was the total deviation of the true midpoint for each line and total time for test completion.

ANALYSES

In the first part of the result section qualitative information about the feasibility of computer-based testing and computer-based treatment will be addressed. Moreover, reasons of exclusion will be specified.

In the second part, analyses of the efficacy of PA will be discussed. Regarding the cancelation tests; 27 and 26 patients were included in the OC and LC, respectively (see below for reason of exclusion). For both tasks paired sample t-tests were performed between pre- and post-test for total number of omissions, total time for test completion, and the search-times on both the ipsilesional and contralesional side. Moreover, the mean CoC were calculated for both the cancelation tasks. The mean Center of Perseveration was only calculated for the OC, due to a small amount of perseverations in the LC. Paired samples t-tests were performed between the pre-horizontal and vertical CoC/CoP and the post-horizontal and vertical CoC/CoP.

For the LB, 27 patients were included (see below for reason of exclusion). Paired samples t-tests were performed between pre-session and post-session for the mean deviation of the true center (i.e., mean line 1^a pre-test and line 1^b pre-test versus mean line 1^a post-test and line 1^b post-test, likewise for line 2 and 3) and total time for test completion. For all tests, since we had both left and right neglect patients in our sample, we made "contralesional" and "ipsilesional" classifications in order to consider them as one group. A two-tailed significance level of 0.05 was used. Results of the efficacy of PA on the digitalized tests are outlined in **Table 2**.

RESULTS

FEASIBILITY OF COMPUTER-BASED TESTING

First, all 33 patients were capable to respond to stimuli by drawing, canceling on, or pointing at the screen with a digital stylus, indicating that computer-based testing was feasible. Second, considering the overall feasibility of performing tests in such an early stage post-stroke we observed that, all but one patient, performed the pre- and post OC and LB; that particular patient did not complete the post-test (as well for the LC) due to emotional factors. For the LC, 31 patients performed the pre- and post-test. One patient did not perform the pre- and post LC due to a language barrier and illiteracy. Third, patients were able to complete test performance within the proposed time-frame. The total duration of performing all digitalized tests, pre and post, was approximately 6.7 min, which indicates that after the verbal instruction was given, patients worked continuously on the digitalized tasks, meaning that test instructions were understood quickly. The total duration of the PA (first pointing movement till after-effect) was, on average, 8.4 min.

FEASIBILITY OF COMPUTER-BASED PA IN SUB-ACUTE STROKE PATIENTS

Generally, patients were able to perform the PA procedure, e.g., pointing at the screen with a digital stylus, on a computer. However, for some patients the PA procedure (repetitive pointing movements) was sometimes strenuous. Four patients experienced difficulties distinguishing left from right. Two out of four of these patients preferred color naming over left-right responses. Additionally, one patient experienced a headache while pointing. This became less when the adaptation procedure proceeded. Due to repetitive pointing one patient experienced exhaustion of the right arm. For another patient, working with the digital stylus became difficult as a result of rheumatic problems.

Additionally, a Pearson correlation coefficient was performed in order to assess whether a relationship existed between neglect severity at baseline and the magnitude of the error displacement. Neglect severity was assessed with the "asymmetry score" of the OC from the neuropsychological screening, see participant section. However, Pearson correlation coefficient revealed no significant relationship between the magnitude of the error displacement and the asymmetry score in the OC, $r = 0.132$, $n = 33$, $p = 0.463$. This indicates that neglect severity was not associated with the level of adaptation.

To recall, the strength of the adaptation was obtained by measuring the spatial deviation (in cm) from the central stimulus, which is called the after-effect phenomenon (see Digitalized Prism Adaptation Procedure in Methods section). Regarding the magnitude of the after-effect, the mean error displacement from the center target of all the 33 patients was 4.12 cm (SD 2.00) with a minimum displacement of 0.38 and a maximum displacement of 7.24, indicating that most, but not all patients, adapted well to the prism procedure (see **Figure 1**). For five patients the adaptation procedure was continued, and after a second adaptation phase, these patients still showed a minor error displacement ($M = 1.26$; $SD = 0.81$). These patients were not included in the analyses on the efficacy of the digitalized neuropsychological tests (see below). One patient whom had also a small after-effect was not secondly adapted due to emotional factors (see above).

EXCLUDED PATIENTS

In sum, six patients were excluded from the overall analyses in the LB and OC. For the LC, seven patients were excluded.

RECORDINGS OF THE POINTING MOVEMENTS DURING THE ADAPTATION PROCEDURE

Recordings of the pointing movements revealed that the error displacement was the largest at the first five pointing movements

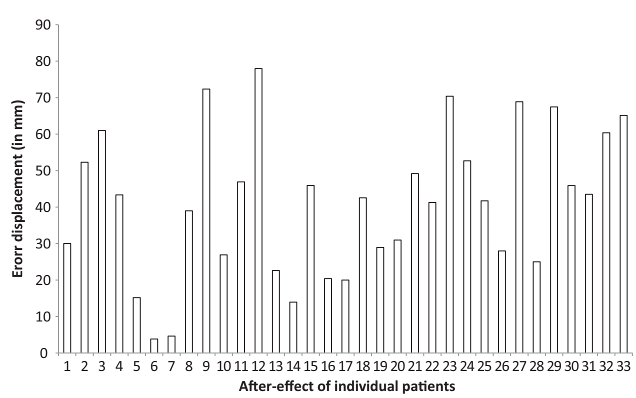

FIGURE 1 | The error displacement (after-effect after the adaptation phase) in millimeters from the central target for each individual patient.

(see **Figures 2** and **3**). Thereafter the error displacement became relatively stable and patients become fairly accurate in pointing to either the left, right, or central target. This indicates that the process of recalibrating the new egocentric coordinate system sets in rapidly. Note that the absolute center of each target was used as a referent and not the whole target. In this regard, patients could have hit the target (i.e., error reduction was achieved), but not the true center (*x*, *y* coordinate) of that target.

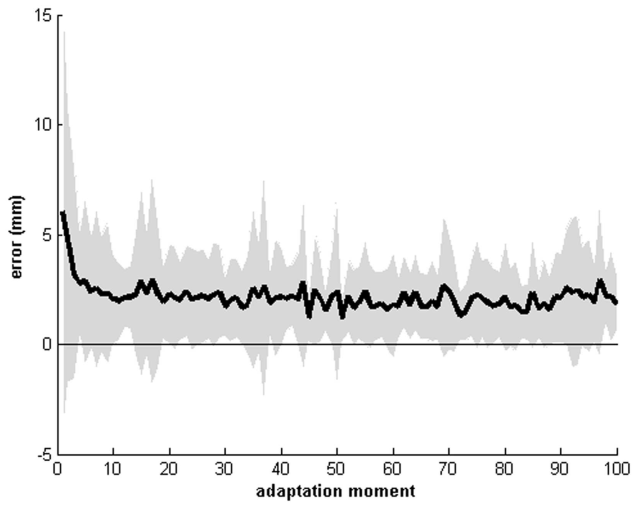

FIGURE 2 | Mean recordings of the pointing movements of all 33 patients for the first 100 pointing movements. The horizontal axis displays the moment of pointing (0 till 100), the vertical axis displays the error displacement of either the right, left, or central target. Shaded area indicates the mean standard deviation. Note that the absolute center of each target (*x*, *y* coordinate) was used as the referent.

EFFICACY OF A SINGLE SESSION OF COMPUTER-BASED PA

Analyses of the efficacy of PA did not reveal significant changes in deviation from the actual center on the line bisection nor in number of omissions on the cancelation tests. Additionally, no significant shift in the location of the omissions and perseverations was found (CoC and CoP outcome measures). The total time taken to complete the test improved significantly after PA for the OC, LC, as well as the LB. Results of the digitalized tests are outlined in **Table 2**.

Regarding time for test completion, all tests were performed significantly faster (total time) after PA, see **Table 2**. Additionally, when addressing the search-times (**Table 2**) on either the ipsilesional as well as the contralesional side of the stimulus-sheets presented on the tablet, patients performed significantly faster post PA in the OC. For the LC this was only faster on the contralesional side post PA. Search-times were based on the search-times within one field, and could reflect either searching a target but also recursively exploring one side due to perseveratory behavior.

GENERAL DISCUSSION

The aim of the current study was to (1) investigate the feasibility of computer-based testing (2) and computer-based treatment in sub-acute stroke patients; (3) gain insight in the adaptation procedure by means of more detailed and precise recordings of pointing movements; and (4) investigate efficacy of a single session of computer-based PA on neuropsychological digitalized tests. Regarding the feasibility of computer-based neuropsychological assessment, all of the included patients were able to work with the tablet and to understand and perform the digitalized tests within the proposed time-frame. This indicates that there is feasibility of computer-based testing in an early stage post-stroke. Although, using this type of tablet and stylus was indeed feasible in our sample, it should be noted that

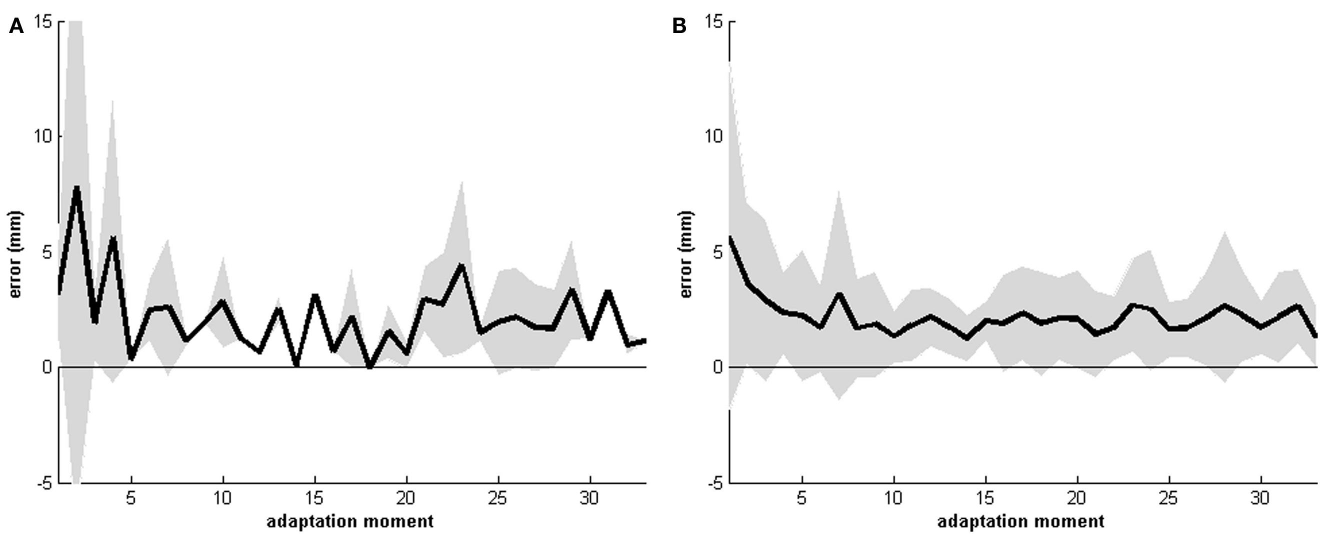

FIGURE 3 | Mean recordings of the pointing movements of all 33 patients for 30 pointing movements for either the "right" (A) and the "left" (B) target. The horizontal axis displays the moment of pointing (0 till 30), the vertical axis displays the error displacement from the right **(A)** or the left **(B)** target. Shaded area indicates the mean standard deviation. Note that the absolute center of the target (*x*, *y* coordinate) was used as the referent.

Table 2 | Mean results of the digitalized pre-test and post-test.

Test	N	Outcome measure	Mean pre-test	Mean post-test	Statistics
OC	27	Omissions total	4.48 (6.44)	5.37 (6.80)	$t(26) = -1.464$, $p = 0.155$
	27	CoC-*x*	0.04 (0.13)	0.05 (0.13)	$t(26) = -0.417$, $p = 0.680$
		CoC-*y*	0.00 (0.02)	0.00 (0.03)	$t(26) = -0.910$, $p = 0.371$
	27	Perseverations total	7.04 (10.87)	6.52 (11.83)	$t(26) = 0.517$, $p = 0.610$
	27	CoP-*x*	0.08 (0.30)	0.06 (0.41)	$t(26) = 0.265$, $p = 0.793$
		CoP-*y*	0.08 (0.29)	0.06 (0.36)	$t(26) = 0.232$, $p = 0.818$
	25[1]	Total time in sec	99.16 (40.85)	84.00 (37.21)	$t(24) = 3.318$, $p = 0.003^{**}$
		Time contralesional	32.40 (18.38)	25.80 (16.05)	$t(24) = 3.234$, $p = 0.004^{**}$
		Time ipsilesional	33.70 (16.02)	26.80 (12.23)	$t(24) = 4.082$, $p < 0.0001^{***}$
LC	26	Omissions total	6.23 (7.00)	5.00 (5.69)	$t(25) = 1.786$, $p = 0.086$
	26	CoC-*x*	0.06 (0.16)	0.04 (0.14)	$t(25) = 1.126$, $p = 0.271$
		CoC-*y*	0.00 (0.04)	0.00 (0.03)	$t(25) = 0.088$, $p = 0.931$
	25[1]	Total time in sec	106.14 (49.63)	93.09 (31.73)	$t(24) = 2.394$, $p = 0.025^{*}$
		Time contralesional	25.52 (11.78)	22.85 (11.28)	$t(24) = 2.357$, $p = 0.027^{*}$
		Time ipsilesional	28.54 (10.03)	27.93 (9.89)	$t(24) = 0.422$, $p = 0.677$
LB (mm)	27	Deviation line 1^a1^b	−1.97 (18.30)	−1.81 (12.82)	$t(26) = -0.061$, $p = 0.952$
		Deviation line 2^a2^b	−9.30 (21.68)	−8.77 (19.34)	$t(26) = -0.268$, $p = 0.791$
		Deviation line 3^a3^b	−17.75 (28.13)	−23.78 (29.61)	$t(26) = 1.672$, $p = 0.106$
		Total time	10.19 (6.42)	7.94 (4.34)	$t(26) = 2.458$, $p = 0.021^{*}$

*Standard deviations are given in parenthesis. OC, Object Cancelation; LC, Letter Cancelation; CoC, Center of Cancelation; CoP, center of perseveration; LB, Line Bisection, deviation score in millimeters, − deviation to the right, + deviation to the left; *significant <0.05, **<0.005, ***<0.0001. [1]Specific timing data was due to a synchronization error not stored for two patients in the OC, and one patient in the LC.*

our sample was relatively young and suffered from relatively mild neglect on neuropsychological neglect screening tests. Moreover, our sample rehabilitated with the intention to reintegrate in society as soon as possible. One might assume that these patients display fewer problems (both physically and mentally) than long stay stroke patients whom live in nursing homes. Our sample may thus not be representative for the overall stroke population. In this regard, a finger activated tablet might be a more appropriate solution in chronic patients or during bedside testing.

Not only can computer-based testing improve the traditional paper-and-pencil assessment of neglect by means of more precise and detailed recordings (Rabuffetti et al., 2002; Chiba et al., 2006; Tsirlin et al., 2009), it also holds opportunities in developing more ecologically valid tests. For instance, daily situations are far more dynamic and require fast responses in order to avoid obstacles in complex environments. We suggest that dynamic tests (e.g., ecologically based) increases the attentional load similar to daily life and will be more sensitive in detecting the "real level of neglect" (Tsirlin et al., 2009). This is impossible with the traditional paper-and-pencil tests.

In addition, the computer-based treatment can be considered as a reliable tool in performing PA, since most patients adapted well to the procedure, as quantified with the magnitude of the after-effects. These after-effects were comparable with our traditional (paper and pencil) PA after-effects (Nijboer et al., 2008, 2010, 2011; Bultitude et al., 2013). Moreover, detailed recordings of the pointing movements revealed that, on average, the error displacement was the largest for the first five pointing movements. Thereafter the error displacement was relatively stable and patients became fairly accurate in pointing to either the left, right, or central target. This implies that the process of recalibrating a new egocentric coordinate system sets in rapidly. Combining computer-based treatment with computer-based ecologically valid assessments in the sub-acute stage seems like a promising thought in identifying a "critical period" for the optimal treatment response with more detailed measures, especially when neurological recovery takes place in the first 3 months post-stroke (Kwakkel et al., 2004; Murphy and Corbett, 2009; Nijboer et al., in press).

Analyses of the efficacy of PA indicated no significant change on any of the outcome measures, except time. However, our sample as a group showed only mild visual neglect at baseline in especially the cancelation tasks. In this regard, there was less room for further improvement. Second, it is likely that concurrent compensation training already changed the scanning strategy in these neglect patients and that one session of PA does not further enhance attentional processing. In addition, since our tests were statically presented at the tablet till task-completion, patients could apply their in-hospital learned cognitive strategy (top-down scanning strategies toward contralesional stimuli), which could have masked their real level of neglect. It would have been interesting to investigate differences in feasibility (pointing movements) and efficacy in both left- and right-sided neglect. The sample size of especially the group of right-sided neglect patients (2) was too small, however, to statistically compare the efficacy of single session PA between those two groups.

Moreover, our design was not fit to fully evaluate effects of PA. We did not use a control-group to counteract learning- and/or motivational-effects. Although we lacked an effect of PA on the digitalized tasks, we do not know whether PA had no effect at all. Subtle treatment effects could be overruled by fatigue at the end of the test-session, since post-stroke fatigue is common (De Groot et al., 2003; Lerdal et al., 2009). Furthermore, one session may be insufficient to produce long-term and even short-term effects, which is in line with the conclusion in a recent review (Schenk and Karnath, 2012). However, generalizable and stable improvement of PA was found when using an intensive treatment program with multiple sessions (10 or more) of PA (Frassinetti et al., 2002; Serino et al., 2009; Mizuno et al., 2011). In addition, we do not know whether a computer-based setting influenced test performance either positively or negatively. It is possible that patients were more alert at the start of the novel test-situation (with a tablet) and became less alert when the computer-based setting became more familiar. In order to disentangle treatment effects from motivational effects and to control for a computer-based setting, a sham-controlled design is necessary.

In conclusion, there is feasibility of computer-based testing in such an early stage, which makes the computer-based setting a promising technique for evaluating more ecologically valid tasks. Secondly, the computer-based PA can be considered as a reliable procedure. We can conclude from our analysis, addressing the efficacy of PA, that the effectiveness of single session PA may not be sufficient to produce short-term effects on our static tasks. Further studies need to be done to evaluate the computer-based efficacy with more ecologically valid assessments in an intensive double-blind, sham-controlled multiple PA treatment design.

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Exploring the effects of ecological activities during exposure to optical prisms in healthy individuals

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Prism adaptation improves a wide range of manifestations of left spatial neglect in right-brain-damaged patients. The typical paradigm consists in repeated pointing movements to visual targets, while patients wear prism goggles that displace the visual scene rightwards. Recently, we demonstrated the efficacy of a novel adaptation procedure, involving a variety of every-day visuo-motor activities. This "ecological" procedure proved to be as effective as the repetitive pointing adaptation task in ameliorating symptoms of spatial neglect, and was better tolerated by patients. However, the absence of adaptation and aftereffects measures for the ecological treatment did not allow for a full comparison of the two procedures. This is important in the light of recent findings showing that the magnitude of prism-induced aftereffects may predict recovery from spatial neglect. Here, we investigated prism-induced adaptation and aftereffects after ecological and pointing adaptation procedures. Forty-eight neurologically healthy participants (young and aged groups) were exposed to rightward shifting prisms while they performed the ecological or the pointing procedures, in separate days. Before and after prism exposure, participants performed proprioceptive, visual, and visual-proprioceptive tasks to assess prism-induced aftereffects. Participants adapted to the prisms during both procedures. Importantly, the ecological procedure induced greater aftereffects in the proprioceptive task (for both the young and the aged groups) and in the visual-proprioceptive task (young group). A similar trend was found for the visual task in both groups. Finally, participants rated the ecological procedure as more pleasant, less monotonous, and more sustainable than the pointing procedure. These results qualify ecological visuo-motor activities as an effective prism-adaptation procedure, suitable for the rehabilitation of spatial neglect.

Keywords: prism adaptation, aftereffects, spatial neglect, right brain damage, rehabilitation, ecological, pointing

INTRODUCTION

Unilateral spatial neglect is a neuropsychological disorder that typically results from damage to the right cerebral hemisphere. Neglect is characterized by a failure to orient toward, respond to, and report stimuli that occur in the side of space contralateral to the side of the lesion (left, contralesional, in right-brain-damaged patients), and cannot be traced back to primary sensory-motor impairments. Patients with left neglect exhibit a large spectrum of symptoms involving different sensory modalities, internally generated images, and the contralesional side of the body. Spatial neglect may be qualified in terms of defective perceptual awareness, and impairment of the planning and execution of movements directed contralesionally (Bisiach and Vallar, 2000; Halligan et al., 2003; Husain, 2008; Heilman and Valenstein, 2011; Vallar and Bolognini, in press). In the past decades a number of rehabilitation procedures have been set up in order to ameliorate neglect symptoms (Parton et al., 2004; Luauté et al., 2006; Pizzamiglio et al., 2006; Arene and Hillis, 2007; Bowen and Lincoln, 2007; Adair and Barrett, 2008).

Adaptation to prisms displacing laterally the visual scene is a particularly promising technique: non-invasive, and easy to administer, it improves a wide range of neglect-related deficits (Rossetti et al., 1998, for a seminal study; see reviews in Redding and Wallace, 2006; Striemer and Danckert, 2010; Barrett et al., 2012). The standard procedure employed in prism interventions in neglect patients consists in the repetition of pointing movements toward visual targets. The same procedure has been typically used in healthy participants (Redding et al., 2005; Michel, 2006). Participants pointing to targets during prism exposure initially make a pointing error in the direction of the optical deviation (i.e., a rightward deviation for rightward shifting prisms, which are used for rehabilitating right-brain-damaged patients with left neglect). *Adaptation* to prisms is demonstrated by a progressive reduction of the pointing error throughout the exposure phase. Once prisms are removed, participants exhibit *aftereffects*, namely deviations in pointing and visual judgments (Redding and Wallace, 2006). Aftereffects have been mainly assessed through a *proprioceptive* test, in which blindfolded participants point to the subjective straight ahead, and a *visual-proprioceptive* test, in which they point toward visual targets, without viewing their arm. In these two tests participants make pointing errors in a direction opposite to that of the optical shift (i.e., leftwards for rightward deviating prisms). An additional measure of aftereffects is a *visual* test, in which participants verbally estimate the position of a visual target. Contrary to the shift induced in the pointing movements, the prism aftereffects observed in the visual test occur in the same direction of the optical displacement (i.e., rightward deviation for rightward shifting prisms, see Redding and Wallace, 2006, 2010).

Although repeated pointing movements have been the most widely used prism adaptation procedure for the rehabilitation of neglect patients, this method may be not optimal for long-term interventions, due to the repetitive and tedious nature of the pointings. The use of engaging and diverse visuo-motor tasks may be preferable for rehabilitation programs that require consecutive sessions for at least 2 weeks (Frassinetti et al., 2002; Fortis et al., 2010; Vangkilde and Habekost, 2010; Mizuno et al., 2011). A more varied procedure may provide a useful alternative if these can be shown to have similar beneficial effects.

In an early seminal study Stratton (1896, 1897) reported his own experience with prismatic lenses reversing upside down the visual scene; for 8 days he wore prismatic goggles during the day for several hours, while performing activities of daily life, such as walking indoor or outdoor (for reviews of early work see Day and Singer, 1967; Kornheiser, 1976). More recently, different tasks have been used in experiments performed in unimpaired participants and in patients with different types of brain-damage. These visuo-motor activities include movements for line bisection (Goedert et al., 2010; Fortis et al., 2011), locomotion/walking (Lackner, 1973; Morton and Bastian, 2004; Michel et al., 2008), and ball throwing (Martin et al., 1996; Fernández-Ruiz and Díaz, 1999). In a rehabilitation study, chronic neglect patients were exposed to prisms for 8 consecutive weeks, while tossing rings and performing a pegboard exercise; after prism adaptation the magnitude of leftward eye movements increased, and the center of gravity moved leftwards, indicating a reduction of left neglect (Shiraishi et al., 2008). In a recent study, we investigated whether a new *ecological* prism adaptation procedure could be effective in improving left neglect in a series of 10 right-brain-damaged patients (Fortis et al., 2010). The procedure consisted of a series of visuo-motor activities performed with daily life objects. In that study, patients underwent 20 sessions of prism adaptation during a period of 2 weeks, in which they performed the pointing task of Frassinetti et al. (2002) during 1 week and the ecological procedure during the other week, with the order of the two prism adaptation procedures being balanced across participants. Neglect signs improved after the first week and continued in the second week of treatment, with no differences between the two procedures (ecological vs. pointing). The main result is that the ecological prism adaptation procedure may provide a viable alternative to the traditional prism adaptation by repeated pointings. However, the study of Fortis et al. (2010) did not measure adaptation or aftereffects for the ecological task. Such measures are considered to be key indicators of the effectiveness of prism adaptation (Welch, 1978; Redding and Wallace, 1993). Thus, in the present study, we investigated whether the ecological procedure resulted in adaptation and aftereffects comparable to those previously demonstrated in the pointing task. Forty-eight healthy participants underwent 2 consecutive days of exposure to rightward shifting prism, performing the ecological task and the pointing task in separate days. The presence of aftereffects on each day was assessed by the proprioceptive, visual and visual-proprioceptive tests (Redding et al., 2005).

Both young and elderly participants entered the study. Age-dependent differences in sensorimotor adaptation have been reported, with elderly participants showing reduced rates of learning in visuomotor adaptation tasks (McNay and Willingham, 1998; Fernández-Ruiz et al., 2000; Bock, 2005; Bock and Girgenrath, 2006; Seidler, 2006), which are associated with a higher computational load (Bock and Schneider, 2002). Other studies show that sensorimotor adaptation is largely preserved in the elderly (Bock and Schneider, 2002; Roller et al., 2002). Particularly, in a sensorimotor (throwing) task, adaptation to laterally displacing visual prisms has been reported to be either preserved (Roller et al., 2002) or defective (Fernández-Ruiz et al., 2000). Conversely, aftereffects are preserved, or even larger, in elderly people (McNay and Willingham, 1998; Fernández-Ruiz et al., 2000; Roller et al., 2002; Bock, 2005). Experiments in healthy participants, using the paradigm of prism adaptation through repeated pointings, have been typically performed in young individuals (Berberovic and Mattingley, 2003; Michel et al., 2003, 2008; Loftus et al., 2009, 2008; Bultitude et al., 2012). In the present study the elderly group aimed at providing results suitable to be discussed with reference to the prism adaptation studies in the typically older brain-damaged patients. Finally, we administered a questionnaire at the end of each adaptation task, in order to assess the participants' level of satisfaction in performing the adaptation procedures, and the possible difficulties they had encountered in executing them.

MATERIALS AND METHODS

Two groups of healthy participants (young and aged) were tested. The young group included 24 undergraduate students (12 females; age $M = 24$ years, $SD = \pm 2.67$, range 19–30; education $M = 15$ years, $SD = \pm 1.37$, range 13–17), enrolled in the Department of Psychology of the University of Milano–Bicocca, Italy. The aged group included 24 elderly participants (12 females; age $M = 68$ years, $SD = \pm 5.74$, range 57–79; education $M = 13$ years, $SD = \pm 5.60$, range 5–18), recruited from the inpatient population of the Neurorehabilitation Unit of the IRCCS Istituto Auxologico Italiano, Milan, Italy, with no history or evidence of neurological or psychiatric disorders. All participants had normal or corrected-to-normal vision, were right handed for writing, and were naïve to the purpose of the study. Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). The questionnaire included 10 items assessing hand preference, and two items assessing foot and eye preference, with scores 10 and 2 indicating complete right-handedness. The handedness scores were: $M = 9.53$ ($SD = \pm 0.65$, range 9–10) and $M = 1.82$ ($SD = \pm 0.51$, range 1–2) in the young group; $M = 9.39$ ($SD = \pm 0.78$, range 8–10) and $M = 1.67$ ($SD = \pm 0.69$, range 0–2), in the aged group. All participants gave informed consent prior to participating in the study. Students received course credits for their participation, which had been approved by the local Ethical Committees.

PRISM ADAPTATION PROCEDURE

Participants underwent two prism adaptation sessions in 2 consecutive days, in which they completed a paradigm including: (1) a pre-exposure evaluation; (2) an exposure condition to base-left wedge prisms (Optique Peter, Lyon, France) displacing the visual field horizontally by 10° to the right; (3) a post-exposure evaluation, identical to the pre-exposure one.

During the exposure condition, participants performed the pointing adaptation task on 1 day and the ecological adaptation tasks on the other day. The order of the two prism adaptation procedures was counterbalanced: 24 participants (12 young and 12 aged) underwent the pointing adaptation task in the first day, and the ecological task in the following day; the other 24 participants (12 young and 12 aged) performed the adaptation tasks in the reverse order. Each adaptation task was carried out with the right arm.

POINTING ADAPTATION TASK

Participants sat at a table and positioned their right upper limb inside a 2-layer wooden box (32 cm high, 74 cm wide). The lower and upper surface of the box had a pentagonal shape with the base facing the participants' side. The pentagon's depth at the center (distance between the base and the vertex of the box) was 32 cm, and 19 cm at the lateral sides. Participants were asked to point with their right index finger to a target (the top of a red pen) presented by the examiner at the distal side of the box. They were instructed to perform one quick out-and-back movement. After each pointing, participants returned their hand to the starting position on the mid-line of the body, on the sternum, above the navel. A black cloth attached from the participant's neck to the upper surface of the box occluded the vision of the starting position of the arm. The pentagonal shape of the box occluded the view of the arm's movement up to the terminal part, so that only the right index finger emerging from the distal side of the box was visible. Ninety pointing movements were made. Target was presented in a pseudorandom fixed order 10° to the right or to the left of the participants' mid-sagittal plane of the trunk. The same number of trials was presented for each of the two target positions. The initial and last four pointing trials included two instances of the right and left target positions. The distal edge of the box was marked with angular gradations (degrees, °), attached on the upper side of the box on the examiner's side, which was not visible to participants. The distance between the target and the participants' finger was measured. A positive score denoted a rightward displacement with respect to the position of the target, a negative score a leftward displacement. The pointing adaptation task lasted 20 min, as in the study by Frassinetti et al. (2002), and was timed by stopwatch.

ECOLOGICAL ADAPTATION TASK

During the ecological adaptation task participants performed 10 visuo-motor activities based on the manipulation of common daily life objects, selected from those employed by Fortis et al. (2010). The activities were presented in the following order: (1) collecting coins on the table and putting them in a money box, (2) selecting rings and bracelets from a box and wearing them on the left hand and fingers, (3) closing jars with the corresponding lids, (4) assembling jigsaw puzzles, (5) moving blocks from one compartment of a box to another compartment, as described in the Box and Block Test (Desrosiers et al., 1994), (6) sorting cards, (7) threading a necklace with 12 spools and rope, (8) copying a chessboard pattern on an empty chessboard, (9) serving a cup of tea, (10) composing a dictated word using letters printed on a square. Standardized instructions as to how to do each task were read to each participant before performing the experiment. During the ecological procedure the vision of the arm was available for the entire movement path. Immediately prior to and after the execution of the ecological activities, participants performed four pointing movements that were administered with an identical procedure as the one employed during the pointing adaptation task. The ecological adaptation task lasted 20 min, as the pointing task in the study by Frassinetti et al. (2002), and was timed by stopwatch.

PRE- AND POST-EXPOSURE EVALUATION: AFTEREFFECT MEASURES

Participants sat at a table with their head aligned with the mid-sagittal plane of their body, and stabilized by a chin-rest attached to the table. A transparent square panel (50 cm side) marked with a goniometry with lines radiating from −90° to +90° was placed on the table, centered on the participants' mid-sagittal plane. During the pre- and post-exposure evaluation, three aftereffects measures were assessed: proprioceptive, visual, and visual-proprioceptive. The three tasks were presented in counterbalanced order across participants. For the proprioceptive and the visual-proprioceptive tests participants were asked to perform fast and accurate pointing movements with their right upper limb. The participant's arm was positioned at the center of the panel, with the right hand resting on the starting location near their body and aligned with the mid-sagittal plane of the body. This served as a starting point for all movements.

Proprioceptive test

Participants were blindfolded and instructed to indicate the subjectively estimated position of their body midline on the panel surface. They performed 10 straight-ahead pointing movements. On each trial, the experimenter recorded the deviation of the finger position from the true objective body midline (°, degrees of visual angle).

Visual test

A red LED was mounted on a pulley (120 cm long, 1.5 cm wide) placed horizontally at the top of a black wooden box (35 cm high, 75 cm long, and 20 cm wide). The box was positioned in a darkened room at the distance of 85 cm from the participants' mid-sagittal plane. Two strings, placed on the two sides of the LED, were used to move it on the pulley. The speed of the LED movement was varied between trials in order to avoid counting strategies (Ronchi et al., 2011).

The visual test did not involve arm movements: participants were instructed to verbally stop the movement of the LED, when its position corresponded to their subjective mid-sagittal plane. The LED was moved 10 times: five times from right to left and five times in the opposite direction, starting with the right-to-left movement first, with respect to the participants' view. A centimeter attached to the pulley on the experimenter's side allowed for the recording of the deviation of the LED position from the center of the pulley corresponding to the participants' physical mid-sagittal plane (cm). Each measurement was then transformed in degrees of visual angle (°).

Visual-proprioceptive test

The same pulley-mounted LED box of the visual test was used. Participants performed 10 pointing movements on the panel surface to indicate the downward projected position of the LED. On each trial, the LED was placed in front of the participants' mid-sagittal plane, but participants were unaware of its position. The movement of the arm was occluded from vision by a 2-layer wooden box (30 cm high, 75 cm wide, and 50 cm deep) and by a black cloth attached from the participant's neck to the upper surface of the box. Participants were instructed to close their eyes between each trial to allow the experimenter to re-position the light.

QUESTIONNAIRE

A Likert-scale questionnaire was administered at the end of each day of the experiment, in order to assess the participants' experience of the adaptation tasks. Participants were required to indicate their level of agreement with each of 13 questionnaire statements. The scale ranged from 1 ("totally disagree") to 7 ("totally agree"). The 13 items of the questionnaire (see Appendix) were then grouped into five general topics, referring to the pleasantness and feasibility (items 1–3), and monotony (4–5) of the task, to the motor discomfort caused by the activities (6–7), to prism-related discomfort (items 8–11), and to the willingness to repeat or extend the adaptation procedure over time (items 12–13).

STATISTICAL ANALYSIS

To evaluate to what extent participants adapted to prism exposure, by correcting the lateral deviation induced by the prismatic displacement (adaptation effect, see Redding et al., 2005; Redding and Wallace, 2006), the mean errors in the beginning (1–4) and end (87–90) four pointing trials of the prism exposure condition were computed during the pointing procedure. For the ecological task, the mean errors in the four pointing trials performed immediately before and after the visuo-motor adaptation activities were computed. A mixed-design analysis of variance (ANOVA) was performed with Time (Beginning/End four pointing trials) and Task (Ecological/Pointing) as the within-subjects factors, and Order of adaptation task (Pointing-Ecological/Ecological-Pointing) and Age (Young/Aged) as the between-subjects factors. Subsequent analyses were performed in order to quantify the presence and magnitude of aftereffects. The difference between the post- and the pre- exposure measures was computed, hereinafter referred to as *shift*. To compare the magnitude of aftereffects, an initial analysis was performed on the shifts induced in the proprioceptive, visual, and visual-proprioceptive tests. Since the prism aftereffects observed in the visual test occur in the direction opposite to those induced in the proprioceptive and visual-proprioceptive tests (Redding and Wallace, 2010), the sign of the shift of the visual test was inverted in the present analysis. A mixed-design ANOVA was performed on the shift, with Test (Proprioceptive, Visual and Visual-proprioceptive) and Task (Ecological/Pointing) as the within-subjects factors, and Order of adaptation task (Pointing-Ecological/Ecological-Pointing) and Age (Young/Aged) as the between-subjects factors. Secondly, to investigate the magnitude of the lateral shifts induced in the 2 days of prism exposure in the young and aged groups, three subsequent separate analyses, one for each test (Proprioceptive, Visual and Visual-proprioceptive), were performed on the shift, with Task (Ecological/Pointing) as the within-subjects factor, and Order of adaptation task (Pointing-Ecological/Ecological-Pointing), and Age (Young/Aged) as the between-subjects factors. In these analyses the visual shift was computed on the data, without sign inversion, as shown in **Figure 1**. Finally, the participants' mean responses for each topic of the questionnaire were analyzed by mixed-design ANOVAs with Task (Ecological/Pointing) as the within-subjects factor, and Order of adaptation task (Pointing-Ecological/Ecological-Pointing), and Age (Young/Aged) as the between-subjects factors. Significant differences were explored by Student-Newman–Keuls' *post-hoc* multiple comparisons.

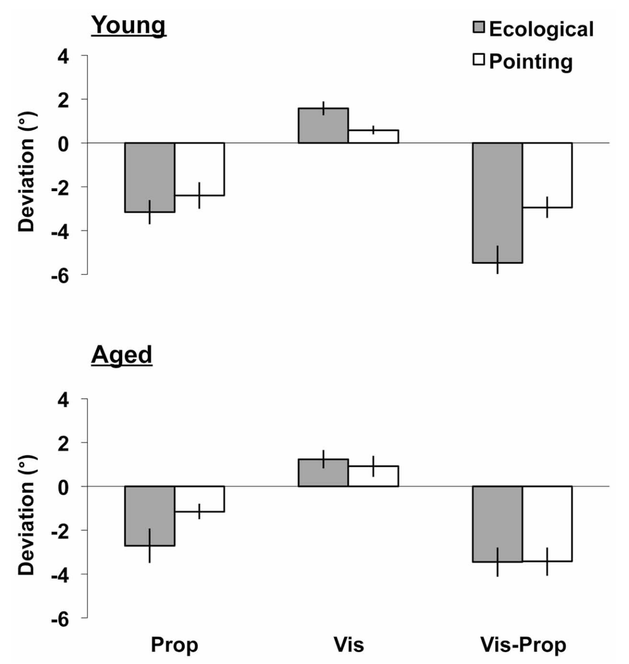

FIGURE 1 | Aftereffects. Upper/lower panels: young/aged groups. Shifts (post-prism exposure *minus* pre-prism exposure mean pointing errors °, *SEM*; ±: rightward/leftward errors) induced by prism adaptation in the three aftereffects tests (proprioceptive, Prop: left bars; visual, Vis: middle bars; visual-proprioceptive, Vis-Prop: right bars), during the ecological (gray column) and the pointing (white column) adaptation procedures.

RESULTS

ADAPTATION AS ERROR CORRECTION EFFECT

The main effect of Time [$F_{(1, 44)} = 584.12$, $p < 0.001$] was significant, showing that adaptation occurred so that the prism-induced rightward deviation in the initial four trials ($M = 3.54°$, $SD = \pm 1.15$) of prism exposure was corrected in the last four trials ($M = 0.12°$, $SD = \pm 0.53$). The main effect of Task [$F_{(1, 44)} = 4.72$, $p = 0.035$] was also significant, indicating overall more deviation in the pointing task ($M = 1.95°$, $SD = \pm 0.77$) than in the ecological task ($M = 1.71°$, $SD = \pm 0.91$). Importantly, the interaction between Time and Task was not significant [$F_{(1, 44)} = 0.07$, $p = 0.79$], indicating that the ecological (initial trials $M = 3.34°$ $SD = \pm 1.40$; last trials $M = -0.02°$, $SD = \pm 0.89$) and the pointing (initial trials: $M = 3.65°$, $SD = \pm 1.53$; last trials: $M = 0.26°$, $SD = \pm 0.52$) tasks induced the same magnitude of adaptation effect. Furthermore, this interaction did not depend on Age [Time by Task by Age: $F_{(1, 44)} = 0.44$, $p = 0.509$], indicating that the ecological and the pointing tasks were equally effective in the young and in the aged groups. No interaction was found between Time and Age [$F_{(1, 44)} = 0.60$, $p = 0.445$], indicating equally strong adaptation in the young and aged groups, when averaging across tasks. The Task by Order of adaptation task interaction [$F_{(1, 44)} = 46.79$, $p < 0.001$], and the Task by Time by Order of adaptation task interaction [$F_{(1, 44)} = 7.34$, $p = 0.010$] were significant. Because the two tasks (ecological, pointing) were performed in different days, with the order specified in the Order of adaptation task factor, the interaction between Task and Order of adaptation task effectively reflected differences in the overall deviation between the 2 days in which adaptation was measured. The deviation on the beginning and the end trials (adaptation effect) was greater in the first day than in the second day. Inspection of the means revealed that this effect was driven by less rightward mean deviation in the beginning pointing errors of the second day ($M = 3.00°$, $SD = \pm 1.34$) compared to the first day ($M = 4.09°$, $SD = \pm 1.39$, $p < 0.001$). Similarly, the last mean pointing errors of the second day ($M = -0.11°$, $SD = \pm 0.68$) were less rightward deviated than the last mean pointing errors of the first day of prism exposure ($M = 0.34°$, $SD = \pm 0.74$, $p < 0.001$). The Age by Order of adaptation task interaction [$F_{(1, 44)} = 5.25$, $p = 0.027$] was also significant. *Post-hoc* comparisons revealed a trend toward significance for a greater overall mean deviation in the old group, who performed the task in the order ecological-pointing ($M = 2.31°$, $SD = \pm 0.75$), than in the order pointing-ecological ($M = 1.55°$, $SD = \pm 0.22$, $p = 0.073$). A similar trend of a greater overall deviation in the old group, who performed the task in the order ecological-pointing ($M = 2.31°$, $SD = \pm 0.75$), compared to the young group with the same order ($M = 1.61°$, $SD = \pm 0.75$), was found. No other significant main effects or interactions were found in the analysis ($p > 0.054$, for all tests).

PRE-POST TEST DIFFERENCES: AFTEREFFECTS MEASURES

The initial analysis compared the shift (the difference between the post- and the pre- exposure measures) induced in the proprioceptive, visual, and visual-proprioceptive tests following the ecological and the pointing adaptation tasks in the young and aged participants (see **Figure 1**). The main effect of Test [$F_{(2, 88)} = 21.63$, $p < 0.001$] was significant. *Post-hoc* comparisons showed that prism exposure induced a greater lateral deviation in the visual-proprioceptive test, followed by the proprioceptive, and the visual tests ($p < 0.003$, for all tests). Importantly, the main effect of Task was significant [$F_{(1, 44)} = 8.75$, $p = 0.005$] revealing that the magnitude of aftereffects varied according to the task performed during the adaptation phase. Inspection of the means showed a greater deviation after the ecological than the pointing adaptation task (see **Figure 1**). Furthermore, the Task by Test by Age interaction was significant [$F_{(2, 88)} = 3.26$, $p = 0.043$], indicating that the ecological and the pointing tasks differently affected the aftereffects in the young and aged groups, as further assessed in the following three ANOVAs, one for each test. No other significant main effects or interactions were found in the analysis ($p > 0.124$, for all tests).

PROPRIOCEPTIVE TEST

The shift after prism exposure was significant (comparison of mean shift against zero; i.e., intercept of the ANOVA, [$F_{(1, 46)} = 50.29$, $p < 0.001$]), showing that exposure to rightward shifting prisms induced a significant leftward deviation in the proprioceptive measures. The main effect of Task was significant [$F_{(1, 44)} = 4.85$, $p = 0.033$], revealing that the magnitude of the aftereffects varied according to the task performed during the adaptation phase. As shown in **Figure 1** (left bars), the ecological adaptation task brought about a greater leftward deviation than the pointing task in both the young and the aged groups. No other significant main effects or interactions were found in the analysis ($p > 0.209$, for all tests).

VISUAL TEST

The shift after prism exposure was significant (comparison of mean shift against zero; i.e., intercept of the ANOVA [$F_{(1, 44)} = 30.82$, $p < 0.001$]), showing that exposure to rightward shifting prisms induced a significant rightward deviation in the visual measures. The main effect of Task showed a trend toward significance [$F_{(1, 44)} = 3.79$, $p = 0.058$] revealing that the magnitude of the aftereffects varied according to the task performed during the adaptation phase. As can be seen in **Figure 2** (central bars), there was a trend toward a greater rightward deviation after the ecological adaptation task than after the pointing adaptation task in both the young and the aged groups. The Age by Order of adaptation interaction [$F_{(1, 44)} = 3.90$, $p = 0.055$] showed a trend toward significance. Inspection of the means revealed a greater mean deviation in the old group who performed the task in the order pointing-ecological ($M = 1.72°$, $SD = \pm 1.35$) than in the order ecological-pointing ($M = 0.43°$, $SD = \pm 1.35$). No other main effects or interactions were significant (all $p > 0.173$).

VISUAL-PROPRIOCEPTIVE TEST

The shift after prism exposure was significant (comparison of mean shift against zero; i.e., the intercept of the ANOVA [$F_{(1, 44)} = 124.26$, $p < 0.001$]), showing that exposure to rightward shifting prisms induced a significant leftward deviation in the visual-proprioceptive measures. The main effect of Task was significant [$F_{(1, 44)} = 4.17$, $p = 0.047$], and the interaction of

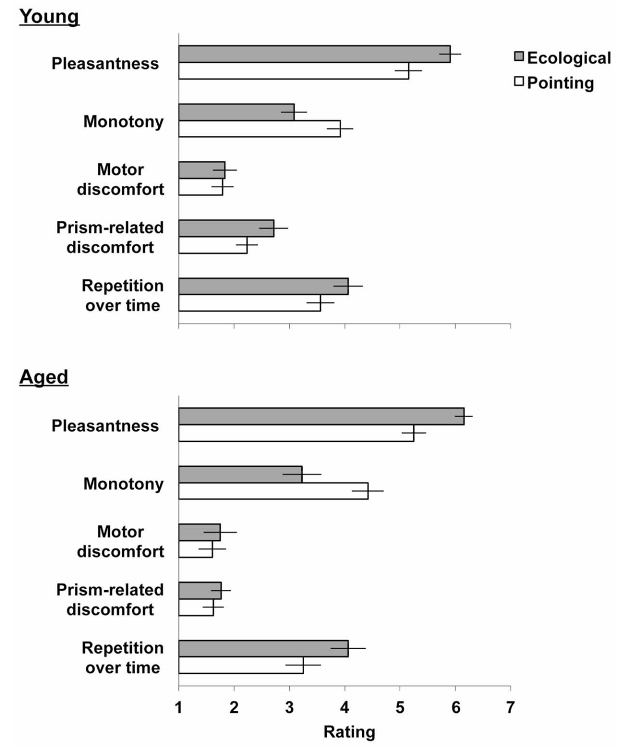

FIGURE 2 | Mean level of agreement scores (*SEM*) of the ecological (gray bars) and the pointing (white bars) prism adaptation procedures by the five questionnaire topics. Scale range: 1 ("totally disagree") –7 ("totally agree").

Task by Age was close to significance [$F_{(1, 44)} = 4.01$, $p = 0.051$]. As shown in **Figure 1** (right bars), inspection of the means revealed that the ecological task brought about a greater leftward deviation in the young group (ecological: $M = -5.48°$, $SD = \pm 3.88$; pointing: $M = -2.93°$, $SD = \pm 2.39$), whereas a much smaller difference between the two tasks was found in the group of aged participants (ecological: $M = -3.45°$, $SD = \pm 3.28$; pointing: $M = -3.43°$, $SD = \pm 3.18$). In addition, the ecological task brought about a greater shift in the young group than in the elderly group (young: $M = -5.48°$, $SD = \pm 3.88$; elderly: $M = -3.45°$, $SD = \pm 3.28$). No other significant main effects or interactions were found in the analysis ($p > 0.140$, for all tests).

QUESTIONNAIRE

Figure 2 shows that both the young and the elderly groups of participants preferred performing the ecological adaptation task, as they found it more pleasant, less monotonous and more desirable to repeat for prolonged periods. Adaptation to prisms was well tolerated by both groups, with a slightly increased prism-related discomfort after the ecological procedure for the young group only.

For the pleasantness of the task, the main effect of Task was significant [$F_{(1, 44)} = 33.26$ $p < 0.001$], showing that the ecological task was considered more pleasant than the pointing adaptation task. No other significant main effects or interactions were found in the analysis ($p > 0.314$, for all tests).

As for the monotony of the task, the main effect of Task was significant [$F_{(1, 44)} = 19.95$, $p < 0.001$]. The Task by Order of adaptation task [$F_{(1, 44)} = 4.68$, $p = 0.036$] was also significant. *Post-hoc* comparisons revealed that the ecological task performed by the pointing-ecological group in the second day (level of agreement $M = 2.63$, $SD = \pm 1.34$) was considered less monotonous than the pointing task performed in the first day ($M = 4.13$, $SD = \pm 1.31$); similarly it was considered less monotonous than the ecological task ($M = 3.69$, $SD = \pm 1.34$) and the pointing task ($M = 4.20$, $SD = \pm 1.31$) performed by the ecological-pointing group ($p < 0.01$, for all tests). Thus, when the ecological task was performed after the pointing task it was considered less monotonous. No other significant main effects or interactions were found in the analysis ($p > 0.071$, for all tests).

As for the discomfort related to the motor activities, no significant main effects or interactions were found in the analysis ($p > 0.494$, for all tests) suggesting that young and elderly participants experienced pain in the arm or in the body neither after the ecological nor after the pointing adaptation task.

As for the prism-related discomfort, the main effects of Task [$F_{(1, 44)} = 16.07$, $p < 0.001$] and of Age [$F_{(1, 44)} = 7.00$, $p = 0.012$] were significant, and the interaction of Task by Age showed a trend toward significance [$F_{(1, 44)} = 3.68$, $p = 0.062$]. Inspection of the means revealed that young participants experienced greater side effects of prisms after the ecological adaptation task ($M = 2.91$, $SD = \pm 1.31$) than after the pointing adaptation task ($M = 2.38$, $SD = \pm 1.01$). This difference was smaller in the aged group of participants (ecological task $M = 1.92$, $SD = \pm 1.08$; pointing task $M = 1.73$, $SD = \pm 0.97$). Nevertheless, responses remained at the disagreement level, suggesting that the execution of both adaptation procedures was overall well tolerated by either group of participants. No other significant main effects or interactions were found in the analysis ($p > 0.454$, for all tests).

Lastly, for the items that assessed the willingness to extend the adaptation procedure over time, the main effect of Task [$F_{(1, 44)} = 10.14$, $p < 0.001$] was significant, showing that participants preferred to perform the ecological task for a longer period of time. No other significant main effects or interactions were found in the analysis ($p > 0.157$, for all tests).

DISCUSSION

In the present study we assessed whether a new ecological procedure, performed during exposure to rightward shifting prisms, could generate adaptation and aftereffects, in two groups of young and elderly healthy participants. To this end, we compared the effects induced by the ecological procedure with those induced by the pointing task, a standard procedure employed in prism adaptation studies (Redding et al., 2005; Redding and Wallace, 2010).

ADAPTATION EFFECT

Performing ecological or pointing adaptation tasks induces comparable corrections of the pointing movements during prism exposure, resulting in spatially accurate performance at the end of the exposure phase (adaptation effect), with no age differences. Indeed, in the beginning trials of the exposure condition, participants make pointing errors that are rightward deviated from target location as a consequence of the optical displacement. Errors are similarly reduced at the end of the exposure phase following either adaptation tasks. These results are in line with the evidence that elderly healthy participants exhibit adaptation effects (achieved through a throwing task) to prisms displacing the visual scene laterally, comparable to those of young participants (Roller et al., 2002). In another study (Fernández-Ruiz et al., 2000), using a similar paradigm, the aged group adapted more slowly than the young group, but both achieved the same adaptation levels. The present results extend to the ecological and pointing tasks that there are no-age-related differences in healthy participants as for adaptation effects.

AFTEREFFECTS MEASURES

The ecological and the pointing procedures bring about significant deviations in the three aftereffects measures in both the young and the aged groups of participants. Specifically, the visually-guided movements performed by participants during the ecological tasks cause deviations in the three aftereffects measures in the same direction as those previously reported after exposure to rightward shifting prisms, with adaptation having been achieved through repeated pointings (Redding et al., 2005). Strikingly, we found greater aftereffects following the ecological task: particularly, in the proprioceptive task in both the young and the aged groups of participants, and in the visual-proprioceptive task in the young group. For the visual task a similar trend was found in both age groups.

The increased magnitude of the three aftereffects following the ecological procedure is of interest, since it provides some hints as to the factors modulating the building up of aftereffects. Several differences between the ecological and the pointing tasks may underlie this result.

The pointing task is based on timed and interrupted movements; it requires to point and return to the rest position and to wait for a signal by the experimenter, to execute the next trial. Conversely, during the ecological task, participants perform free and more varied patterns of movements, in which they manipulate several everyday objects. This more varied manipulation may have required the allocation of attentional resources more than in the pointing task. There is evidence that a task such as mental arithmetic during adaptation brings about a reduction of visual aftereffects, putatively due to the allocation of attentional resources to the secondary task (Redding et al., 1985). In the present study, the more varied ecological task may have required the allocation of more attentional resources than the repetitive pointing task, resulting in enhanced aftereffects.

Additionally, participants may have been more engaged and motivated during the ecological than during the pointing procedure. The results of the questionnaire are by and large in line with these conclusions. The role of all these factors was not addressed in the present study, which aimed at assessing the aftereffects brought about by the two prism adaptation activities. These issues may be investigated in future specific studies.

Some differences in the magnitude of the aftereffects in the young and in the aged groups of participants were also found. The visual-proprioceptive shift in the ecological task was greater in the young than in the aged group. The available literature provides conflicting evidence. One prism adaptation study found larger aftereffects in the elderly group (Fernández-Ruiz et al., 2000 throwing a ball, and testing a visuo-proprioceptive shift), while another, using the same prism adaptation method, found no age-related differences (Roller et al., 2002). Overall, our results in the pointing task agree by and large with the conclusion that aftereffects are comparable in young and elderly participants (see Roller et al., 2002, who used the task of ball throwing, broadly similar to the present pointing task). The greater visuo-proprioceptive aftereffects exhibited by young participants after ecological adaptation might tentatively indicate a more effective visuo-motor integration in the young group, possibly supported by relatively more efficient cognitive abilities (Redding et al., 1985; Bock and Schneider, 2002), involved in the more varied ecological procedure, that is open to strategic effects (e.g., choosing how to perform the task).

Another factor that may modulate age-related differences in prism adaptation involves pre-existing biases of spatial attentional systems. Young healthy participants show a leftward bias in bisection tasks (*pseudoneglect*), which diminishes in aged participants, with a relative rightward deviation (Jewell and McCourt, 2000, for review; Schmitz and Peigneux, 2011), although there is also evidence for a stability of left pseudoneglect in the life span (see Beste et al., 2006, for visual line bisection; Brooks et al., 2011, for tactile rod bisection). This age-related difference may reflect a minor hemispheric asymmetry of spatial functions in elderly participants (Cabeza, 2002; Dolcos et al., 2002), which results in a reduction of the leftward deviation. Goedert et al. (2010), using a line bisection task, found rightward and leftward aftereffects in elderly participants, after exposure to leftward and rightward deviating prisms respectively, and no left pseudoneglect. Conversely, young participants, who showed left pseudoneglect, exhibited (rightward) aftereffects only after exposure to leftward deviating prisms, although a trend with rightward deviating prisms was found. In the present study, only rightward deviating prisms were used, and we found aftereffects in both age groups, in line with previous evidence (Fernández-Ruiz et al., 2000; Roller et al., 2002). It should be noted, however, that the tasks were different [line bisection (Goedert et al., 2010) vs. pointing and ecological activities in the present study, more similar in this respect to those of Roller et al. (2002), and of Fernández-Ruiz et al. (2000)], preventing a direct comparison.

IMPLICATION FOR STUDIES IN PATIENTS WITH LEFT NEGLECT

The finding of consistent aftereffects following the ecological procedure has potentially relevant implications for the rehabilitation of neglect patients. The suggestion has been made that the recovery of spatial neglect after a prism adaptation treatment is related to the magnitude and the duration of the aftereffects. In a group study (Fortis et al., 2010) of 10 right-brain-damaged patients with left neglect, who underwent 10 sessions of prism adaptation performed with a pointing task over a period of 1 week, the size and the duration of the visual-proprioceptive aftereffects were related to the improvement of neglect, as assessed by cancellation tasks; the persistence and magnitude of the long-term aftereffects even mediated the improvement of functional abilities of neglect patients, as assessed by the Functional Independence Measure (FIM™) scale (Tesio et al., 2002). In a single session study performed in 13 right-brain-damaged patients, those participants who showed prism adaptation-induced improvement in target cancellation exhibited larger proprioceptive aftereffects than those patients whose cancellation performance did not improve; conversely, the visual-proprioceptive aftereffects were minor in size, and unrelated to recovery from neglect (Sarri et al., 2008). Other reports appear to relate the improvement of neglect after prism exposure to the adaptation effect (i.e., error correction during the exposure phase), rather than to the aftereffects. In two studies (Frassinetti et al., 2002; Serino et al., 2007) patients who show no or little adaptation effects exhibit less improvement of the neglect deficit; in one study (Serino et al., 2006) the improvement of neglect is related to the development of prism adaptation during 1 week of treatment, rather than to the magnitude of aftereffects. In functional models of prism adaptation (Redding and Wallace, 2006), the improvement of left spatial neglect is related to the aftereffects (leftward visuo-proprioceptive, and proprioceptive; rightward visual) induced by exposure and adaptation to rightward displacing visual prisms. The rightward "visual shift would bring the neglected left-hemispace into the narrowed task-work space, thereby ameliorating neglect," and the "leftward shift in origin of proprioceptive reference frame would produce more responses in the neglected hemispace" (*loc. cit.*, pp. 14–15). The present findings of greater aftereffects following the ecological tasks raise the possibility that the ecological procedure for prism adaptation may even improve the rehabilitation outcome of neglect patients, as compared with prism adaptation through pointings (Frassinetti et al., 2002). Future studies should test whether the present findings in healthy participants generalize to neglect patients.

Importantly, there are differences in the magnitude of the aftereffects found in right-brain-damaged patients with left spatial neglect and in healthy participants. After adaptation to rightward displacing prisms through repeated pointings patients with left neglect show disproportionately large leftward aftereffects (as assessed by the proprioceptive straight ahead task), and appear unaware of the optical effects of prisms (Michel et al., 2007, for related evidence in healthy participants; Rossetti et al., 1998; Rode et al., 2003). The possibility may be considered that the larger leftward aftereffects (i.e., the reduction of a disproportionate rightward proprioceptive shift) found in right-brain-damaged patients with left neglect represent a reduction of a manifestation of neglect itself, namely a rightward bias in the subjective straight ahead, as assessed by the proprioceptive task (Heilman et al., 1983). In line with this view, Sarri et al. (2008) found in right-brain-damaged patients with left spatial neglect, as compared with neurologically unimpaired control participants, disproportionate leftward aftereffects of prism adaptation on the disproportionately rightward deviated proprioceptive straight ahead, but not on a task requiring pointing to visual targets located on the mid-sagittal plane. These findings comport with the view that a basic deficit of neglect is an ipsilesional deviation of the egocentric reference frame, originally proposed by Ventre et al. (1984), and subsequently revived by Karnath (1994, with a rightward visual shift). Other studies in right-brain-damaged patients with left neglect, however, have questioned these findings and interpretations, showing that the subjective straight ahead is largely preserved (Farnè et al., 1998), and its shifts (found to occur both rightwards and leftwards) unrelated to the main clinical manifestations of left spatial neglect, such as defective target cancellation or drawing, and line bisection performance (Chokron and Bartolomeo, 1997; Hasselbach and Butter, 1997; Perenin, 1997; Bartolomeo and Chokron, 1999). Furthermore, patients with parietal damage and optic ataxia without unilateral spatial neglect show an ipsilesional deviation of the egocentric reference (Perenin, 1997). In sum, while right-brain-damaged patients with left neglect show disproportionate leftward aftereffects in the proprioceptive task after prism adaptation, it is dubious that this shift is a cardinal manifestation of spatial neglect. Future studies in brain-damaged patients may explore the magnitude of aftereffects after pointing and ecological adaptation procedures.

Results from the questionnaire show that the ecological procedure is considered more pleasant and interesting to perform than the pointing task. Participants evaluate the ecological visuomotor activities less repetitive, more enjoyable, and easier to perform. They are also more willing to repeat them over time. Increasing the patients' compliance to the therapy may allow a higher number of brain-damaged patients to go through the whole training, as a result of a greater and active participation in the activities aimed at inducing adaptation and aftereffects. Previous studies have indeed shown that, in general, the patients' compliance with the treatment can improve the rehabilitation outcome, including measures of functional independence, and can even result in a shorter hospitalization time (Maclean and Pound, 2000; Lenze et al., 2004).

A number of studies have shown that multiple sessions are effective for rehabilitating spatial neglect. In the study by Fortis et al. (2010) 2 weeks of treatment were more effective than 1 week, which nevertheless brought about some improvement. A treatment of at least 2-weeks (10 sessions) appears to be an effective standard (Frassinetti et al., 2002; Humphreys et al., 2006, one patient, 5 weeks of treatment, with two sessions weekly; Serino et al., 2006, 2007; Shiraishi et al., 2008, 8 weeks of treatment, with about four sessions weekly; Vangkilde and Habekost, 2010; Làdavas et al., 2011; Nijboer et al., 2011, one patient, 3 months with daily sessions). Rehabilitation studies reporting negative findings in neglect patients employed treatments with shorter duration (Nys et al., 2008, 4 days), or weaker displacing lenses (Turton et al., 2010, 6° lenses). Importantly, long-term training has shown positive impact on functional abilities of everyday life, as assessed by Activities of Daily Living (ADL) Scales: the FIM™ (Tesio et al., 2002) scale (Fortis et al., 2010; Mizuno et al., 2011); the Barthel Index (Mahoney and Barthel, 1965), and Lawton's IADL scale (Shiraishi et al., 2008, 2010). In sum, it is preferable to use an adaptation procedure more appreciated by patients, given the length (at least 2 weeks) of the treatment.

Finally, the ecological adaptation procedure opens up new possibilities for extending the prism adaptation-based rehabilitation of neglect patients for longer time periods. Indeed, ecological visuo-motor activities may be easily designed for home-based rehabilitation programs, customized to the domestic environment. This appears to be an especially important development, considering that it may allow for long-term programs that are not feasible in inpatient rehabilitation facilities, due to the increasing trends (Taylor et al., 2010) toward shorter hospitalization periods.

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APPENDIX

Questionnaires performed after the ecological procedure (version A) and after the pointing procedure (version B).

A: *How did you experience wearing the goggles while you were manipulating the objects?*

B: *How did you experience wearing the goggles while you were pointing to the pen?*

1. It was enjoyable
2. It was interesting
3. It was easy to perform
4. It was boring
5. It was repetitive
6. It was painful for my arm
7. It was tiring to maintain the posture
8. My eyes were getting tired
9. It made me dizzy
10. It made me sick
11. I visually perceived objects distorted
12. I would have liked to continue the activity
13. I would like to participate in future experiments with the same procedure

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Prismatic adaptation in the rehabilitation of neglect patients: does the specific procedure matter?

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In rehabilitation studies, adaptation to lateral displacing prisms (rightward optical deviation) has been shown to reduce many manifestations of unilateral spatial neglect (USN) (Rossetti et al., 1998; Striemer and Danckert, 2010) and, when compared to other bottom-up techniques, has been proved to be effective for a longer time (Luaute et al., 2006a; Pisella et al., 2006; Newport and Schenk, 2012).

Prism adaptation (PA) itself is not a new technique; it has been used as a tool to investigate perceptual and motor control and adaptation for over a century (Helmholtz, 1910/1924; Held and Hein, 1958), but it has been used in neuropsychological rehabilitation only recently (Rossetti et al., 1998). PA is particularly suited to both theoretical and applied research because it produces observable effects in a short time (Redding and Wallace, 1997; Michel et al., 2003; Michel, 2006; Bultitude and Woods, 2010).

According to a standard procedure (Redding and Wallace, 1997, 2002) when a subject performs a pointing task through displacing prism lenses, his/her initial movements typically show an error in the direction of the prismatic shift. After a few trials such an error disappears and adaptation occurs. After this adaptation process, when prism goggles are removed, a pointing error appears in the opposite direction. This phenomenon is called aftereffect (AE), and is the hallmark of PA. In order to minimize the decay of the AE, an Open loop pointing (OLP) procedure, without visual feedback from the hand, can be used both before and after PA. The difference between these two sessions is considered to be the best measure of AE.

The most widespread PA procedure is the following. The subject is seated in front of a table, with his/her chin on a chinrest to prevent head movements. The subject has to perform fast hand movements starting from a fixed position on the table, near the body midline, to one or more targets that also lie on the table, within reaching distance. The starting position of the hand is usually occluded, so subjects can only see their own hand during the final part of the movement (Redding et al., 2005). This procedure, called terminal exposure, cannot be used as a rehabilitation technique with most neglect patients, because they frequently have left hemiplegia that reduces their global mobility. Hence different PA procedures were proposed specifically for rehabilitating neglect patients. In one popular procedure patients are required to perform simple pointing movements from the sternum to two or more landmarks placed on a table or on a tilted board, within reaching distance. Since the whole of the arm is visible during the movement, this procedure has been called concurrent exposure (Cohen, 1967). It is easy to perform for most neglect patients, but it does not allow one to assess the adaptation process directly because online corrections of the movement make pointing errors disappear. Moreover AE assessment is difficult; the first study of PA in neglect (Rossetti et al., 1998) used pointing to the subjective "straight ahead" (SSA) as a measure of AE.

Open loop pointing estimates of AE can be obtained with terminal exposure procedures in neglect patients using a wooden box to prevent visual feedback. The box is open on both the side facing the patient and the opposite side facing the experimenter who presents stimuli in different positions (Frassinetti et al., 2002). The box allows the patient to see only the final part of the movement, the gap between the box and the patient's trunk being covered with a black curtain; this apparatus allows one to obtain both online adaptation and final AE measures directly and precisely with a single setup. Usually, patients are required to point with their (right) index finger from the sternum to one of three targets placed at −20 or +20° from the midline. Some variations of this procedure have been proposed (Fortis et al., 2010; Wilms and Mala, 2010). The procedure with the PA Box tends to be rather long because both PA and AE measures are taken with the same apparatus, and movements are perceived as unnatural. Hence, overall, the technique is perceived as boring by the patients.

Recently a more patient friendly task has been proposed: PA was applied with ecological visuo-motor (VM) activities (Shiraishi et al., 2008; Fortis et al., 2010). Patients performed different VM activities consisting of manipulating common objects while wearing prismatic goggles. To estimate AE, OLP was administered before and after PA, using a PA box (Fortis et al., 2010). Since there are no restrictions on the visual input coming from the arm, this PA procedure can be classified as a concurrent exposure technique.

Concurrent and terminal exposure procedures are very different in terms of the patient's experience, but are they equally effective in neglect rehabilitation? Two studies tackled this issue, with opposite results (Fortis et al., 2010; Ladavas et al., 2011). The aim of the present work is to discuss the two methods and the aforementioned studies in the wider context of a general model of PA (Redding and Wallace, 1997, 2002, 2006).

Fortis et al. (2010) compared PA obtained with a terminal exposure procedure, and PA obtained using a VM task. They found that both procedures had similar rehabilitative efficacy. Not surprisingly, patients preferred to perform their rehabilitation by means of VM tasks. Ladavas et al. (2011) compared concurrent and terminal exposure by using a PA box with different amplitudes of visual feedback (terminal exposure: the last 12 cm of the movement were visible; concurrent exposure: the second half of the movement was visible). Terminal exposure produced larger rehabilitative effects than concurrent exposure. In both studies (Fortis et al., 2010; Ladavas et al., 2011) rehabilitative effects were measured by means of neuropsychological tests or batteries assessing neglect, which were administered before and after treatment (10 sessions of PA of about 20–30 min each). Clearly, the results of the two aforementioned researches are in contrast to each other. Indeed, VM tasks and pointing with concurrent exposure have in common a free-view of the arm and both allow the use of visual feedback from the movement. So we consider both VM tasks and concurrent exposure pointing as two procedures of concurrent exposure.

Both studies focused on the final rehabilitative effects – the impact on neglect measures – and failed to take into account the main factor that causes such effects, i.e., the adaptation process. Clearly if adaptation has been induced by using a PA box, one can derive a direct measure of adaptation – error reduction. Such a direct assessment is impossible if PA has been obtained by a VM task. So in the latter case, the only possibility of measuring the level of adaptation is an indirect one: by looking at the AE (Harris, 1963; Redding et al., 2005). Indeed AE magnitude is the same in patients and controls (Sarri et al., 2008; Facchin et al., in press). If different methods induce a comparable level of adaptation, an identical AE should be found. Previous studies comparing concurrent and terminal exposure procedures in healthy subjects found no significant difference in AE (Uhlarik and Canon, 1971; Choe and Welch, 1974; Redding and Wallace, 1988). Redding and Wallace (1993) measured AE several times during the PA process, and could detect some difference only at the beginning of the procedure, with an advantage of concurrent over terminal exposure. Such a difference later disappeared.

So, did the AE differ according to the procedure used in the two aforementioned studies? Both papers report a similar AE for both concurrent and terminal exposure. Both studies compared the two types of exposure within patients – thus providing a safer test of the hypothesis that they both produce the same AE. So, given that a similar AE was found with concurrent and terminal exposure in both studies, the inference can be made that the stimulation given by PA and the mechanism involved were the same in both cases. Why, then, did Ladavas et al. (2011) find a difference in neglect recovery? The question becomes, what is the relationship between AE (as assessed by OLP) and neglect recovery? Many studies did not find any clear relationship between AE and neglect recovery (Serino et al., 2007; Sarri et al., 2008; Ladavas et al., 2011), while others found a relationship only after having partialed out the effect of other explanatory variables (Fortis et al., 2010). The time scale discrepancy between the AE, which typically lasts for seconds or minutes, and neglect recovery, which can last for hours, days, or even weeks, has been well known since the beginning of research on PA in neglect rehabilitation (Frassinetti et al., 2002). AE confirms only that adaptation has occurred, but its size does not predict the improvement of neglect.

The dissociation between AE and rehabilitation efficacy has also been confirmed in anatomo-functional studies. The structures underlying PA seem to be intact in most neglect patients (left posterior parietal cortex, left superior temporal gyrus, right cerebellum) (Luaute et al., 2006b, 2009; Shiraishi et al., 2008) and this explains the occurrence of a normal adaptation process in this population. Other structures responsible for the mechanism of recovery induced by PA could be either injured (explaining cases where no improvement was found) or intact (significant improvement), independent of the areas involved in PA listed above.

We are left with the question of why different exposure procedures induce equal AE. This fact is a natural consequence of the mechanisms which have been assumed to underlie PA in an influential model. According to Redding and Wallace (Redding and Wallace, 1997, 2002; Redding et al., 2005), PA is due to two main processes: recalibration and realignment. The former is essentially a strategic cognitive process yielding a direct reduction of the error given by prisms; recalibration appears early in the procedure, as it requires a few trials to be triggered. The latter is a fully automatic reorganization of specific spatial maps (based on different frames of reference), and occurs later (and more slowly) in time. Realignment is defined as a kind of implicit perceptual learning (Redding and Wallace, 1997, 2002; Redding et al., 2005) and seems to be crucial in neglect rehabilitation (Redding and Wallace, 2006, 2009). To observe PA, recalibration (beginning after just a few trials) is not sufficient; a realignment of spatial maps is necessary, which can only be developed after several trials.

One crucial difference between concurrent and terminal exposure is in the amount of direct visual feedback from the pointing errors. In the terminal exposure condition, a large error is visible in the first trials, and the reduction of such an error in the following trials demonstrates that recalibration is indeed occurring. In the concurrent exposure condition, little or no error is visible from the first trials (because full visual feedback is available to correct the movement), so little recalibration takes place. By contrast, realignment, which is an automatic process, would develop across trials in both conditions in exactly the same way. More generally, Redding and Wallace (1997) assume that all methods of adaptation that use a visuo-manual task requiring precise movements toward a target, present an identical AE, exactly because PA in all of them depends on the same, automatic process of realignment.

According to this claim, the PA procedure should be selected on the basis of considerations other than its alleged "efficacy" (AE) – which, as we have shown, is expected to be identical in all procedures. Namely, it should be chosen taking into account the skills of the patient, his/her clinical conditions and needs. In the acute phase, or when patients have limited sustained attention, PA could be more easily performed via VM tasks or free-view pointing, perhaps toward center or right (if neglect prevents the patient from pointing leftwards). Terminal exposure might be an option only if a patient is able to perform it. With some patients the standard procedure involving AE estimates both before and after PA could be too long and demanding. Adaptation occurs in almost all patients, hence AE assessment could be given up, or, in the case of repeated sessions, could be administered only on the first session. If VM tasks are used, the optical aberration of prisms, i.e., chromatic aberration, distortion, and field curvature (Cotter, 2002; Facchin et al., in press) should be considered, as it can be more disturbing than with simple pointing. Whatever the choice, PA should consist of at least 90–100 trials (Frassinetti et al., 2002; Dijkerman et al., 2003), to be sure that realignment take place (see for negative results with less than 90 trials (Dijkerman et al., 2004; Keller et al., 2008).

In conclusion, the application of terminal exposure (pointing task) or concurrent exposure (pointing task or VM task) adaptation should be selected according to the patient's needs, because, from the point of view of adaptation "efficacy" they are likely to be equivalent. If neglect is moderate or severe, a PA box is very difficult to use and pointing in free-view is preferable. VM tasks, which are less boring, make it easier for the clinician to motivate patients to join the rehabilitation program. Furthermore, performing a set of easy daily activities would help the patient not only in terms of neglect improvement, but also as a form of general rehabilitation therapy.

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A note on Striemer and Danckert's theory of prism adaptation in unilateral neglect

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The nature of the therapeutic effects of prism adaptation (PA; see Striemer and Danckert, 2010a for a description) is a major point of controversy in clinical and neurocognitive psychology (e.g., Saevarsson et al., 2009, 2010). A detailed understanding of these effects could greatly advance the treatment and assessment of unilateral neglect. Many authors have concluded that perceptual aspects of neglect, such as visual perception and higher-order visuospatial cognition, improve following PA (e.g., Pisella et al., 2006; Redding and Wallace, 2006; Serino et al., 2006; Saevarsson et al., 2009, 2011; Nijboer et al., 2010, 2011). In contrast to this mainstream view, Striemer and Danckert (2010a) recently proposed that PA produces beneficial effects on spatial and premotor neglect (PMN; defined as the bias of movement from the ipsilesional to the contralesional side, most commonly reported for hand movements; Watson et al., 1978; Bisiach et al., 1990). For example, patients may have difficulties with initiating contralesional directional movements (directional hypokinesia; see Saevarsson, in press for an overview). Striemer and Danckert (2010b) argued that PA has little or no effect on perceptual biases and that only a few PA studies do, in fact, address perceptual neglect directly. Those that do, they claim, show only limited improvement following PA, especially in tasks requiring more explicit perceptual judgments than standard clinical neglect tests. Striemer and Danckert (2010a) also support their view by referring to plasticity changes in areas in the dorsal visual stream that are sometimes spared in neglect, such as the superior parietal lobule and the intraparietal sulcus. These areas are responsible for visuomotor behavior and attention, but are not involved in "more explicit perceptual judgments" (Striemer and Danckert, 2010a, p. 308), and are believed to play a major role in PA. In line with this, they also refer to studies where PA has been found to improve pointing and eye movements (Dijkerman et al., 2003; Ferber et al., 2003; Angeli et al., 2004; Serino et al., 2006).

We argue, however, that the evidence (Striemer and Danckert, 2010a,b) base their conclusions on can be interpreted differently. Visual neglect is in many cases accompanied by PMN although the motor response deficits of neglect may appear on their own (Goodale et al., 1990; Làdavas et al., 1993; Saevarsson, in press). It has proven to be more difficult to differentiate between the two than is often claimed because of various methodological problems (e.g., Mattingley and Driver, 1997). For example, a recent PA study by Striemer and Danckert (2010b) is based on the logic that motor and sensory components can be differentiated with standard neglect tests (see also Fortis et al., 2011). They measured motor components in three neglect patients with the landmark and line bisection tests. Their main finding was a reduced ipsilesional bias online bisection but not on the landmark task. This conclusion was based on the assumption that by requiring manual as well as verbal responses, visual, and premotor components of neglect could be isolated. We argue, however, that this is not as straightforward as claimed since these tests involve both contralesional visual input and eye movements even when responses are made verbally. Difficulties of many patients with shifting their gaze to the contralesional side (straight-ahead viewing bias; Ebersbach et al., 1996; Kim et al., 1997; see Beis et al., 1999 for evidence for improved gaze in neglect following hemifield eye-patching) is an important factor in this context. The two types of neglect, in other words, are conflated in the tasks. We note that performance on standard neglect tests can be interpreted in various ways and has been found to be inconsistent within the same PMN patient group (e.g., Harvey et al., 2002). For instance, an item on the contralesional side may be neglected because of difficulties with reaching to the contralesional side, eye movements to the affected side (less contralesional stimuli are foveated), or simply due to a lack of visual awareness of the contralesional side (e.g., Mattingley and Driver, 1997). The bisection and landmark tests do not distinguish between these sources of performance deficits. We argue, in other words, that standard neglect tests are as much tied to motor behavior as they are to visual processes. Uncoupling the two with standard tests may be impossible because of assessment issues such as whether visual neglect is accurately controlled for or not, related sensory and motor deficits and the role of cognitive load (see Saevarsson, in press). Importantly, Mattingley and Driver (1997) concluded that improved PMN may directly lessen symptoms of perceptual neglect because of more efficient feedback from eye movements, and that intact visual input may reduce PMN. In the four PA studies on motor function in neglect that Striemer and Danckert cite in support of their argument (Dijkerman et al., 2003; Ferber et al., 2003; Angeli et al., 2004; Serino et al., 2006), movements and visual input were not independently controlled for, and their independent roles (passive or active) in improved motor behavior are therefore unclear. For example, Dijkerman et al. (2003) argues that their patients suffered from visual neglect based on their performance on standard tests that are also sensitive to PMN components as discussed earlier.

Striemer and Danckert (2010a, p. 311) argue that there is little evidence for any effect of PA on "real-world" function, noting that "previous work has failed to observe significant effects of PA upon serial visual search tasks that measure attention in what could be considered a more 'real-world' scenario." But this claim is directly contradicted by a recent study by Vangkilde and Habekost (2010) who tested visual search performance following PA in a complex scene (the "where's Waldo" task) in addition to a task where patients were placed in front of a cupboard containing a number of items and were asked to find particular ones. PA resulted in robust and consistent long-term improvements in the performance of both tasks (see Saevarsson et al., 2009, 2010; Saj et al., 2013).

Despite considerable progress, many unanswered questions remain regarding the neuroanatomy of motor and sensory components of neglect. For instance, Saevarsson (in press) analyzed 30 PMN studies and found that PMN is connected to various right-hemisphere and right-subcortical lesions that are commonly damaged in this affliction, such as frontal, parietal, and thalamus, among other structures. It is therefore not known whether PA improves PMN in patients where areas of the dorsal stream are spared, since these areas might not play an important role in the proposed interaction between PA and the motor response components of neglect. It is not clear whether it can be determined from lesion location whether patients suffer from PMN or not, and whether modulations of certain dorsal areas or the existence of certain lesions can explain corrected motor function in neglect following PA.

Although the effects of PA on neglect have been heavily studied over the last 15 years, the underlying mechanisms are still not fully understood. The evidence reviewed by Striemer and Danckert (2010a) seem to support their motor PA theory to some extent, although other interpretations are possible and further extensions are needed. Motor components of neglect and their relation to PA need to be investigated systematically, with controls for vision or other types of perception, along with careful study of the underlying neuroanatomy. In other words, PA experiments based on advanced assessment of motor and sensory components and statistical voxel-by-voxel lesion mapping are likely to provide more detailed information about the exact nature of any therapeutic effects of PA therapy on neglect. While in many ways we agree with Striemer and Danckert (2010a), our proposal is that PA corrects spatial premotor components (e.g., reaching from the ipsilesional to the contralesional side) in neglect, while visual neglect plays a passive role in preventing or reducing de-adaptation effects when neglect patients are confronted with their environment. This means that improved motor actions such as eye and hand movements are likely to last longer if the patient suffers from visual neglect as well as PMN. In other words, the better the visual awareness, the faster the de-adaptation will be and the fewer errors will occur, and vice versa (e.g., Michel et al., 2003, 2007; Goedert et al., 2010; Aimola et al., 2012). The lack of significant visual neglect or PMN might therefore explain the lack of consistent clinical effects. A number of other findings support this proposal. For example, Cubelli et al. (1991) found reduced directional hand deficits of visual neglect patients when blindfolded; the performance of many patients when pointing straight ahead when blindfolded improved compared to when they made similar pointing movements without a blindfold (see Làdavas et al., 1993 for discussion). This finding underlines the need to control for visual components when PA is used as an assessment tool. Evidence indicating considerable high comorbidity of visual neglect with PMN and a likely lack of isolated PMN cases may support the role of visual neglect in PA (Saevarsson, in press). Lee and Donkelaar (2006) found slowed PA in healthy subjects when subjects' pointing movements were completely visible and their premotor cortex was stimulated with TMS; but when only the endpoint of the movement was visible, PA occurred faster. This highlights the important role of passive on-line movement corrections of intact visual awareness in healthy observers and the potential importance of parietal lesions in PMN and premotor areas for PA. Furthermore, Saevarsson et al. (2008) found that right hemifield patching that is applied simultaneously with PA strengthens the effects on neglect compared to combined left hemifield patching and PA. This falls in the line with the proposed role of visual neglect in de-adaptation during PA since a combination of right patching and PA prevents visual feedback from the presumably non-affected visual field and forces adaptation to the affected hemifield. The adaptation may therefore be stronger and faster compared to when it is based on feedback from the "intact" visual field. It is also important to note that most studies report only the general effects on unilateral neglect, which obscures the symptom heterogeneity of subgroups such as PMN patients. For instance, the open-loop paradigm that is based on straight forward pointing while blindfolded is not particularly sensitive to PMN symptoms because it does not require contralesional reaching *per se*. Lack of exact diagnoses, experimental task differences, and neuroanatomical differences (e.g., Saevarsson et al., 2009 for lesion mapping evidences) between experimental groups may explain a considerable number of non-significant or controversial findings (e.g., Morris et al., 2004; Saevarsson, 2009; Saevarsson et al., 2009). Furthermore, using PA on healthy subjects has proved to be problematic since the effects have been found to be small or non-significant on different visuomotor tests, although short-lived adaptation has been found with pointing movements in the open-loop task (e.g., Morris et al., 2004; Michel, 2006; see Saevarsson, 2009 for a series of studies on healthy subjects). Interestingly, these findings have been attributed to intact visual awareness or lack of unilateral neglect.

The conclusion that visual or perceptual aspects of neglect are not part of successful PA treatment, in our opinion, is premature. What Striemer and Danckert's (2010a, p. 311) analysis correctly highlights is how heterogenous symptoms are between individual patients: "Just as the neglect syndrome is heterogenous and highly variable in presentation, the influence of PA on neglect could also be heterogenous and variable across patients." This gets at the heart of the matter and could, in fact, explain why larger controlled trials fail to reveal clear effects at the group level. The heterogeneity in lesions and symptoms and various assessment complications prevent generalization. Striemer and Danckert (2010a) are right in pointing out how motor and visual neuroanatomical aspects of neglect are confounded in PA. It is for this reason that the conclusion that PA improves motor function without major influences of vision is inaccurate, given the current evidence. In conclusion, we feel that the evidence Striemer and Danckert's proposal (2010a) is not compelling enough. Advanced PMN diagnosis and lesion mapping with respect to PA is needed before definitive conclusions can be drawn regarding their hypothesis.

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Spatial compression impairs prism adaptation in healthy individuals

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Neglect patients typically present with gross inattention to one side of space following damage to the contralateral hemisphere. While prism-adaptation (PA) is effective in ameliorating some neglect behaviors, the mechanisms involved and their relationship to neglect remain unclear. Recent studies have shown that conscious strategic control (SC) processes in PA may be impaired in neglect patients, who are also reported to show extraordinarily long aftereffects compared to healthy participants. Determining the underlying cause of these effects may be the key to understanding therapeutic benefits. Alternative accounts suggest that reduced SC might result from a failure to detect prism-induced reaching errors properly either because (a) the size of the error is underestimated in compressed visual space or (b) pathologically increased error-detection thresholds reduce the requirement for error correction. The purpose of this study was to model these two alternatives in healthy participants and to examine whether SC and subsequent aftereffects were abnormal compared to standard PA. Each participant completed three PA procedures within a MIRAGE mediated reality environment with direction errors recorded before, during and after adaptation. During PA, visual feedback of the reach could be compressed, perturbed by noise, or represented veridically. Compressed visual space significantly reduced SC and aftereffects compared to control and noise conditions. These results support recent observations in neglect patients, suggesting that a distortion of spatial representation may successfully model neglect and explain neglect performance while adapting to prisms.

Keywords: neglect, PA, spatial compression, MIRAGE mediated reality, prism aftereffects, strategic motor control, error-detection threshold

INTRODUCTION

Neglect syndrome is typified by an inability to explore, or react to objects and events in, the side of space contralateral to a cerebral lesion (Halligan and Marshall, 1993) and is most commonly associated with right hemisphere strokes (Halligan et al., 1990). Unilateral neglect is far more common on the left, following right hemisphere lesions, than right neglect, following left-hemisphere lesions (Corbetta et al., 2005). It is distinct from primary sensory and motor deficits as demonstrated by behavioral testing. Lesion sites do not necessarily include primary regions (Heilman et al., 2003) and spontaneous recovery is faster than that which follows primary damage (Halligan and Marshall, 1993). It presents as a very heterogeneous disorder, with various subcomponents depending on lesion site and extent of damage (e.g., Buxbaum et al., 2004; Verdon et al., 2010).

Neglect patients present with a range of related behaviors, such as colliding with objects on the left, attending only to the right side of their body, and eating only the left half of a plate of food, losing objects, and failing to respond to people in the neglected space. They often have difficulties reading, writing, and drawing, and even remembering the left half of a familiar memory or scene (Bisiach and Luzzatti, 1978; Wilson, 1999). Patients also commonly lack insight into their condition, which significantly influences rehabilitation progress (Kinsella and Ford, 1985; Appelros et al., 2002). As such neglect has significant clinical implications, with a severe effect on daily function.

While a number of rehabilitation therapies have been developed and tested (Bowen and Lincoln, 2007), PA has been found to be one of the more effective, long-term, and simple strategies. Rossetti et al. (1998) demonstrated that a PA procedure significantly reduced neglect behaviors in classic tests including line bisection, cancelation, drawing, and reading for up to 2 h, significantly longer than 10-min effects in previous methods. Prism goggles cause a shift in visual input relative to the proprioceptively defined position of the limb, resulting in individuals mis-reaching in the direction of the prismatic shift when trying to point to or grasp a target. PA occurs when participants quickly learn to adjust their reach to become accurate again. After a short but sufficient training period, when the prism goggles are removed participants will mis-reach in the direction opposite to prismatic shift. These *aftereffects* reflect the recalibration of reference frames for visuo-motor maps in order to realign them (Redding and Wallace, 2006).

While it is possible that the aftereffects merely neutralize the neglect bias due to a contraversive shift, the fact that PA improves performance in attentional and perceptual tasks, as well as visuomotor tasks, indicates a genuine improvement in neglect behaviors (Newport and Schenk, 2012). Stable effects are shown to generalize across a range of neglect behaviors including postural control, tactile, and auditory extinction, mental imagery (Rode et al., 2001), number line bisection, neglect dyslexia, oculomotor biases, and even wheelchair navigation (Arene and Hillis, 2007). An additional benefit as a rehabilitation technique is that PA is a bottom-up technique and does not require an awareness of the disorder. In a review by Newport and Schenk (2012), more than 90% of studies found a positive effect of PA in reducing neglect so long as the prismatic shift was strong enough and included repeated treatment sessions for long-term effects. Indeed, a recent study reported permanent improvements following long-term daily PA treatment (Nijboer et al., 2011).

It is likely that PA may not affect all neglect component behaviors (e.g., Striemer and Danckert, 2010; Fortis et al., 2011a,b), but may be valuable in identifying a meaningful subcomponent of neglect and its underlying pathology. The unique relationship between PA mechanisms and neglect syndrome is both important and unclear, and further investigation may provide a novel theoretical framework on which to focus new lines of research. Two primary mechanisms, "SC" and "spatial realignment" (SR), have been identified during the realignment of visuo-motor systems in PA. These processes dissociate (Pisella et al., 2004; Newport and Jackson, 2006; Aimola et al., 2012) and are comprehensively addressed by Redding and Wallace (2006), but will be briefly detailed here. Initial corrections for prism-induced errors can be made on-line during the reaching movement, or in subsequent movements by deliberately mis-reaching in the direction opposite to the prismatic deviation. This "SC" is a rapid and conscious process, and is useful for remapping spatially coded movement commands in a dynamic environment in order to reduce performance error (Redding and Wallace, 2006). However, SC is not sufficient for aftereffects to occur and a greater number of trials are required for the second, slower process of "SR." SR is an unconscious recalibration of visual and motor co-ordinate systems used to plan goal-directed actions, as a result of which, when the prisms are removed after sufficient trials participants now miss in the direction opposite to the prismatic shift. After prism removal, with continued pointing to visual targets, healthy participants are typically very fast to deadapt and return to baseline accuracy (see Redding and Wallace, 2006; Newport and Schenk, 2012 for more detailed explanations of these processes).

These mechanisms do not simply counter the neglect bias since they do not account for the remarkably long-term effects of PA specifically found in neglect patients, which are significantly longer than comparable stimulation techniques (Rossetti et al., 1998). It has been suggested that abnormally long-lasting aftereffects may be due to a reduced awareness of prism-induced errors. Redding and Wallace (2006) proposed that in healthy individuals SC may limit the need for SR, and consequently, a dysfunctional SC may remove this limit leading to extraordinarily larger aftereffects. Michel et al. (2007) supported this idea, citing anecdotal evidence for neglect patients having reduced awareness of visual perturbations caused by prism goggles from studies by Rode et al. (2003) as well as their own investigations of unaware PA in healthy controls. If error awareness is a precondition for SC, this "hypernosognosia" – over-self-attribution of movement error – may lead to an increased dependency on SR processes. They found evidence to support this by incrementally increasing the prism shift in healthy individuals, with reduced error awareness of PA resulting in larger aftereffects. Aimola et al. (2012) tested this idea in neglect patients and confirmed reduced SC in neglect, with patients showing significantly less adaptation than right-brain damaged controls and healthy controls, failing to eliminate prism-induced error even after 72 reaches. However, they also found that aftereffects were not pathologically increased, contradictory to predictions. While proprioceptive aftereffects are often considered key to neglect recovery following PA (e.g., Sarri et al., 2008; Fortis et al., 2010, 2013), others argue that they dissociate from the persistence of neglect amelioration and that it is the adaptive processes involving SC which are predictive of recovery (e.g., Serino et al., 2006; Ladavas et al., 2011).

Aimola et al. (2012) suggested that poor SC in neglect might be caused by dysfunctional error-detection, either due to a pathological failure to detect errors for which the error signal falls in neglected space or, alternatively, that there is an increased tendency to treat reaches with errors as being under the patient's own control (hypernosognosia). In both cases, deliberate intertrial error correction would be unnecessary: in the former, there are no errors to correct and in the latter the strategic correction of sub-threshold errors would not be required. On the one hand errors are simply not detected, while on the other errors may be detected, but are treated as being within normal limits. In order to investigate this further, the current experiment was designed to measure the effects of introducing environments that encouraged each of these potential causes for dysfunctional error correction in healthy controls during a PA task. A failure to detect errors was modeled by compressing visual space such that errors were perceived as much smaller than in reality and hyponosognosia was modeled by introducing small visual perturbations, or noise, to the motor output in order to blur the boundaries between reaches that were self-generated and those that were as a result of the prism displacement and therefore requiring strategic correction. Both of these ideas will be expanded upon in the next sections.

Typically, error-detection and correction involves neural comparator mechanisms which detect discrepancies, such as between the intended outcome of a movement and the predicted or (estimated) actual outcome of that movement (Wolpert, 1997). Small errors result in largely unconscious movement correction while larger errors can lead to the attribution of movement control to an external agent or influence. In the case of prism-induced errors, this would lead to the deliberate and strategic correction of movement parameters in subsequent reaches. Dysfunctional processes in neglect might lead to impaired error-detection either by damage to neural comparators or by interrupting or distorting input to the comparator system. The failure of movement discrepancies to reach conscious thresholds would remove the requirement to correct movement errors on subsequent trials and also to an over-attribution of erroneous movements as being judged as self-generated (i.e., not as a consequence of wearing prisms).

Hypernosognosia, the over-self-attribution of movement agency, was observed in a small group of neglect patients by Preston et al. (2010) who found that they exhibited an over-attribution of self-generated movement in line with that suggested by Michel et al. (2007). In that study, patients gripped a mechanical arm with their unaffected hand while making goal-directed reaches, but the computer-generated visual feedback of the movement was perturbed to the left or right to varying degrees on a trial-by-trial basis. Neglect patients were poorer at detecting modifications to their own movements, tending to self-attribute reaches at larger perturbations than controls, while being better at the task than a patient with anosognosia for hemiplegia. The authors postulated that the comparators typically responsible for detecting errors may be damaged or have raised thresholds in neglect patients, and so do not consciously register an error. If this is the case then it could be modeled in healthy controls by introducing "noise" to their movements by giving visual feedback with perturbations at close-to-threshold limits so that reaches consistently miss slightly to the left or right. The introduction of noise would potentially raise intact comparator error-thresholds, resulting in greater self-attribution of errors and reduced SC.

The alternative mechanism, one in which errors are not detected, is less straightforward. Aimola et al.'s (2012) proposal was that the failure to detect errors was specific to rightward errors; that is, those in which the target falls to the left of the hand as it does during the early stages of rightward PA. Their proposal was that the target error, being to the left of the hand, falls in neglected space (or, at least, space that is more compressed than the space to the right of the hand). However, with targets in PA often being spread across the workspace, it is not certain whether the error would necessarily fall in neglected space or even whether patients look toward the target or the hand (or both) when the hand becomes visible toward the end of the reach. A potential answer to this problem might be to create a workspace that is modeled on the spatial compression theory of neglect. By using this model, it would not matter whether the patient fixates the hand or the target because the separation between the two would be perceived to be smaller (compressed) compared to reality.

Halligan and Marshall (1991) proposed a left-to-right compression of space based on a neglect patient's systematic deflection in judgments of target position. Keller et al. (2000), who also found evidence in accordance with neglect patients' distorted egocentric representation, proposed that this results from the dynamic remapping of space based on imbalanced input. An attentional distribution may cause such an imbalance, leading to a compression of the affected hemi-space relative to ipsilesional space. Kerkhoff (2000) found distortions of perceived space between objects and both Kerkhoff (2000) and Harvey et al. (2007) observed misrepresentations of object size in the horizontal plane in accordance with theories of anisotropic representation of space in which only the horizontal dimension of visuo-spatial representations might be relaxed toward contralesional and compressed toward ipsilesional space in accordance with Bisiach et al. (1998). It has been argued that such compression has also been observed during reaching tasks: Jackson et al. (2000) found evidence for a distorted topography of representation in neglect, revealed by abnormally curved hand paths to visually defined targets compared to proprioceptively defined targets, indicative of an impairment in the visual space used to guide movements, without a general failure of the spatial representation of target position.

In a hypothetical representation of space in which the dynamic workspace to the left of the hand is compressed, both the hand and target would be visible at the end of the prism-displaced reach, but the distance between the two would be perceived to be smaller than in reality preventing the efficient detection of reach errors. Such compression would also allow for the direction-specific effects described by Aimola et al. (2012) in which hand-target errors to the right of the hand are detected normally whereas errors to the left are not. The hypothesis here is that compressed space would prevent the detection of errors that are specifically to the left of the hand, hindering SC during adaptation, but not during deadaptation when the error would fall to the right.

The present study aimed to investigate these two competing theories in relation to PA by modeling them in healthy individuals. A typical PA procedure was employed in which participants completed reaching movement toward visual targets before, during, and after PA in the two modeled neglect conditions and a control condition. By comparing the pattern of PA between these conditions, it can be examined whether they successfully impair SC as suggested by Aimola et al. (2012) and also any consequent dissociation of SC and SR in these conditions.

MATERIALS AND METHODS

PARTICIPANTS

Twelve participants (11 female; mean age 21 years, range 18–25) took part in the study as volunteers. All were healthy, right-handed undergraduate students with normal or corrected-to-normal vision. All participants gave informed consent and the experiment was conducted in accordance with the Ethics Committee at the University of Nottingham.

APPARATUS AND STIMULI

The entire experiment was conducted using a MIRAGE mediated reality device (Newport et al., 2010) in order to create the various visual feedback conditions. MIRAGE uses cameras and mirrors to display a live (delay ∼20 ms) video image of the participant's own hand in the same physical location as their real hand (see **Figure 1**). Although the real hand is never seen directly, participants treat the representation as their own hand without a noticeable delay (e.g., Newport and Preston, 2010). Perturbations to the visual feedback presented to the participant were calculated on-line and involved displacement-dependent lateral shifts of the viewed image of the hand based on the moment-to-moment location of the real hand. The location of the real hand and the targets were recorded and monitored on-line using a Polhemus Liberty electromagnetic motion tracker sampling at 60 Hz. Single Polhemus sensors were attached to the nail of the right index finger and to both targets. For conditions which required the location of the hand to be hidden from the participant for some or all of the movement, this was achieved by replacing the relevant pixels in the image with a zero value, creating the illusion of a virtual bar across the workspace.

The two targets (physical objects seen within the MIRAGE environment) were placed 20 cm forward and 2.5 cm to the left and right of a tactile start point placed close to the leading edge of the workspace and 7.5 cm to the right of the midline. For each trial only one target was visible, displayed in a pseudorandom order such that no target appeared three times in succession, with the other being removed from the image digitally. For the adaptation phases of the experiment, participants wore base-left 10-diopter

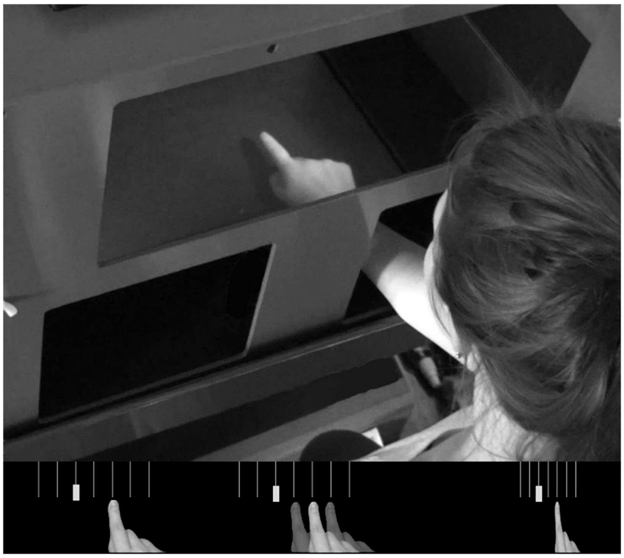

FIGURE 1 | Top panel; the MIRAGE mediated reality device used throughout the experiment. MIRAGE modifies real-time video capture of the real limb and displays it in the same plane as the actual limb. Bottom panel: a schematic representation of each condition. Left – Control; middle – Noise; right – Compression. Semi-opaque hands represent the addition of left and right noise perturbations. Vertical lines represent 3° separations in real space (not visible to participants). In each panel, the solid hand represents a real space reaching error of 6°.

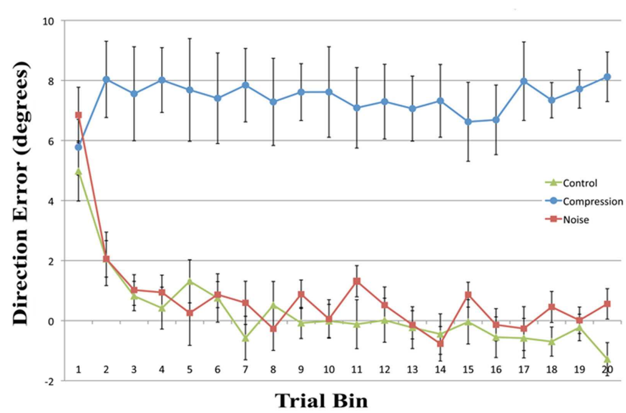

FIGURE 2 | Mean directional pointing error (with SE bars) for each two-trial bin in the prism-adaptation phase for all three conditions. Positive values indicate a rightwars error in the direction of the prism displacement.

Table 1 | Phase order and number of trials per phase with visual feedback conditions.

Phase	Trials	Visual feedback
Pre-open loop (PreOL)	4	No visual feedback of the hand
Pre-visual feedback (PreVF)	4	Terminal visual feedback
Prism-adaptation (PA)	40	Terminal feedback
Post-open loop (PosOL)	4	No visual feedback of the hand
Post-visual feedback (PosVF)	4	Terminal visual feedback
Deadaptation	26	Terminal visual feedback

wedge prisms, deviating vision by ∼6° to the right. While 10-diopter prisms are relatively weak in terms of neglect research (see Newport and Schenk, 2012), their use here was both necessary and appropriate due to a combination of the close confines of the MIRAGE apparatus and the magnitude of the deviation applied in the Noise condition to which the other conditions were compared.

PROCEDURE

For each condition there were six phases completed in a set order (see **Table 1**) involving two pre- and post-test measurements either side of the experimental adaptation condition and a final deadaptation phase. Pre-Adaptation Open Loop (PreOL) involved pointing to each target twice without visual feedback of the hand. This was taken as the baseline against which Post-Adaptation Open Loop (PosOL) pointing was compared in order to assess the magnitude of prism-induced aftereffects. The procedure for PosOL was identical to that for PreOL. Pre-Adaptation Visual Feedback (PreVF) involved pointing twice to each target with terminal visual feedback of the limb (terminal visual feedback refers to the hand only being visible toward the end of the reach – on this occasion, the last 20% of movement distance). PreVF was the baseline against which post-adaptation accuracy (PosVF) was measured with the procedure for PosVF being identical to PreVF. To avoid open loop measures being tainted by exposure to vision of the hand, PreOL, and PosOL always preceded PreVF and PosVF respectively. Between the pre- and post-accuracy measures, participants wore 10-diopter prism goggles and pointed 40 times (20 to each target) in one of three PA conditions. In the Control condition (standard PA), visual feedback was an accurate representation of the actual reach. In the Noise condition visual feedback was perturbed such that reaches were shifted by 3° to the left or right of the actual hand path in a pseudorandom order such that no particular perturbation could be presented three times in succession. Three degrees was chosen as a recent experiment using similar equipment, but investigating attribution of movement agency, revealed that participants were below chance when judging whether movements with 3–4° perturbations were self-generated (that is, more often erroneously rating them as self-generated when they were not) (Preston and Newport, 2010). For the Compression condition a simple spatial compression was applied to the visual workspace such that everything was compressed to the right. This was achieved by removing every alternate vertical line of pixels from the displayed image of the workspace. Thus, objects (such as the targets) to the left of the workspace were compressed rightwards by a greater degree than those toward the right of the workspace. For example: in a hypothetical workspace 20 cm wide, an object on the left hand edge, 20 cm from the right edge, would be compressed to appear 10 cm (20/2 cm) to the right of its real location; an object in the center, 10 cm from the right edge, would be compressed 5 cm rightwards (10/2 cm) and an object 5 cm from the right hand edge would be compressed 2.5 cm (5/2 cm) rightwards. The functional effect of the compression was that of halving the apparent magnitude of any directional reaching error. Finally, a further 26 deadaptation reaches were made, with full visual feedback, in order to return the participant to normal levels of pointing accuracy in preparation for the next condition. Participants carried out all three PA conditions in a counterbalanced order between participants.

RESULTS

Reach errors were calculated as the difference in degrees between straight lines from the start point to the target and the start point to the index finger at the end of the reach. In order to remove late movement corrections based on visual feedback of the hand, movement end-point was determined by the movement frame in which the finger would have become visible (i.e., breaching an imaginary line 4 cm short of the target distance). Thus, any reduction in reach end-point errors would have been the result of both adaptation and inter-trial strategic correction, but would have excluded on-line within-trial conscious error reduction. For analysis, trials were binned into target pairs so that each data point represented the mean of a reach to both a left and a right target.

ADAPTATION PHASE

Mean end-point error for the first four bins and the final bin were entered in a two-way repeated measures ANOVA with the factors CONDITION (Noise, Control, and Compression) and BIN (One, Two, Three, and Four). The analyses revealed a significant main effect for CONDITION [$F(2, 22) = 128.1$, $p < 0.001$] and BIN [$F(4, 44) = 13.6$, $p < 0.001$] as well as a significant interaction [$F(8, 88) = 5.0$, $p < 0.01$]. In order to assess the rate and ultimate success of error correction, planned pair-wise comparisons were conducted between each condition pair for the first four bins and the last bin with the alpha level corrected to 0.0033 for multiple comparisons. While there were no differences in accuracy between any of the conditions for the first bin [Max: $F(2, 22) = 2.33$, $p = 0.13$], the Compression condition was significantly less accurate than either the Control or Noise condition for bins 2–4 and bin 20 [Min: $F(2, 22) = 26.10$, $p < 0.001$] while the latter two conditions were not different from each other in any bin [Max: $F(2, 22) = 2.26$, $p = 0.14$]. In short, while both Noise and Control showed normal PA error reduction, reducing rapidly to baseline accuracy, participants failed to adapt in the Compression condition, even after 40 trials (see **Figure 2**).

AFTEREFFECT

Mean end-point errors for the first bin in the open loop trials were also entered in a two-way repeated measures ANOVA with the factors CONDITION (Noise, Control, and Compression) and

Table 2 | Mean (with SD) directional pointing error in degrees for the first four trials in each phase in the Control, Compression, and Noise conditions.

	Pre-open loop	Pre-visual feedback	Prism-adaptation	Post-open loop	Post-visual feedback
Control	−1.74 (4.36)	−0.59 (4.06)	2.06 (3.02)	−7.83 (4.74)	−3.68 (2.81)
Compression	−1.95 (5.31)	−2.32 (3.61)	8.66 (4.29)	−2.27 (4.51)	−1.56 (1.89)
Noise	−0.21 (4.07)	−0.35 (3.60)	2.71 (3.50)	−8.34 (4.82)	−3.41 (3.04)

Negative values indicate a leftward error in the direction opposite to the prism displacement.

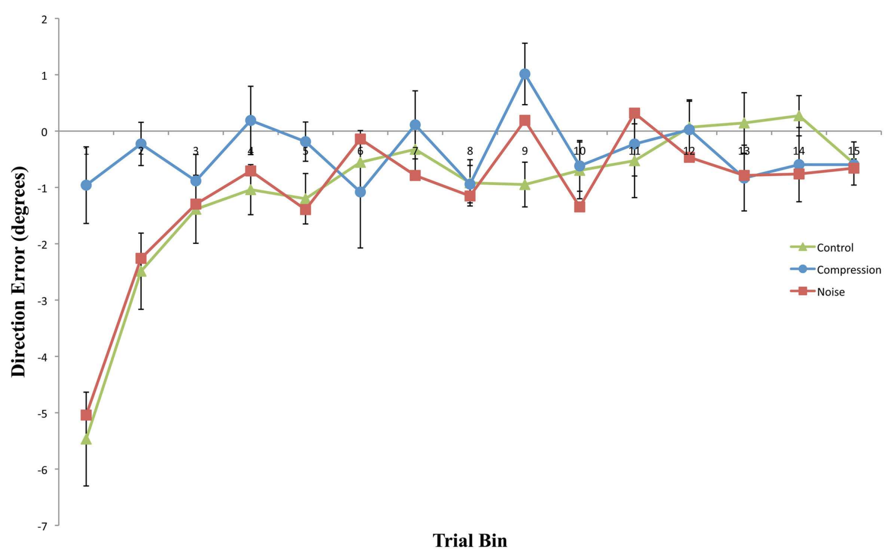

FIGURE 3 | Mean directional pointing error (with SE bars) for each two-trial bin in the Post-Adaptation phase for all three conditions. Negative values indicate a leftward error in the direction opposite to the prism displacement.

PHASE (Pre-adaptation, post-adaptation). The analyses revealed a significant main effect for PHASE [$F(1, 11) = 24.0$, $p < 0.001$], but not CONDITION [$F(2, 22) = 2.2$, $p > 0.05$] although there was a significant interaction [$F(2, 22) = 17.2$, $p < 0.001$]. Planned pair-wise comparisons were run between "preOL" and "posOL" trial bins to determine whether adaptation had occurred for each condition (see **Table 2**). There was a significant difference between "PreOL" and "PosOL" in the Control [$F(1, 11) = 23.1$, $p < 0.001$] and Noise conditions [$F(1, 11) = 53.7$, $p < 0.001$] with "PosOL" having a greater leftward error in both conditions, but there was no significant difference between "PreOL" and "PosOL" for the Compression condition [$F(1, 11) = 0.59$, $p = 0.45$] indicating an absence of aftereffects following the adaptation phase.

DEADAPTATION

As with Adaptation measures, mean end-point error for the first four bins and the final bin were entered in a two-way repeated measures ANOVA with the factors CONDITION (Noise, Control, and Compression) and BIN (One, Two, Three, and Four). The analyses revealed a significant main effect for CONDITION [$F(2, 22) = 8.9$, $p < 0.05$] and BIN [$F(4, 44) = 20.0$, $p < 0.001$] as well as a significant interaction [$F(8, 88) = 4.9$, $p < 0.01$]. Pair-wise comparisons (with corrected alpha level = 0.0033) for bins one to four and the final bin (15) in the PosVF/Deadaptation phase revealed that both Noise and Control were significantly different to Compression for the first two Bins [Min: $F(2, 22) = 10.32$, $p < 0.001$] with both having greater aftereffects. There were no differences between either Noise or Control compared to Compression for the remaining Bins [Max: $F(2, 22) = 2.01$, $p = 0.16$] and no difference between Noise and Control for any Bin [Max: $F(2, 22) = 0.46$, $p = 0.50$]. In summary, Noise and Control showed typical aftereffects, rapidly decaying to baseline whereas Compression exhibited no aftereffects, being at baseline throughout.

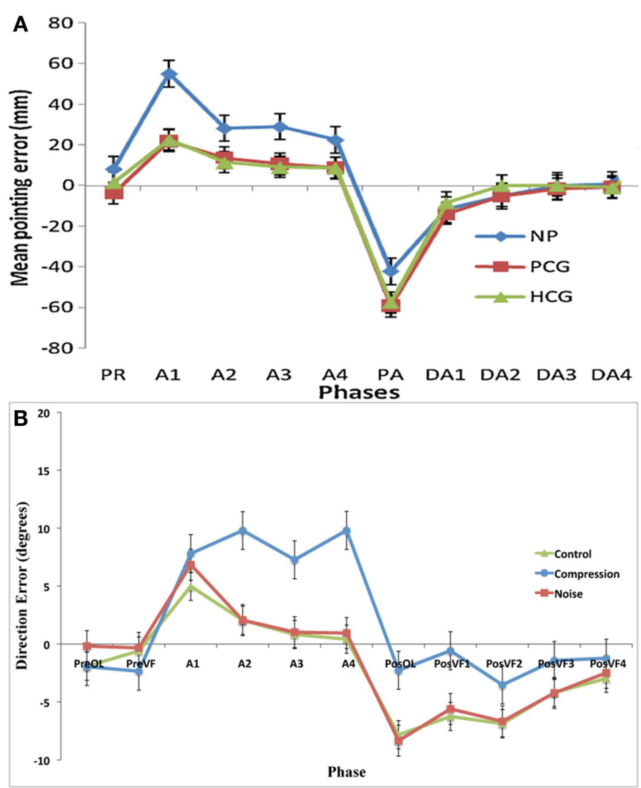

FIGURE 4 | (A) Data adapted from Aimola et al. (2012) showing the mean pointing error in millimeter (with SE bars) in each group across five phases: PR, Pre-adapt; A, adaptation; DA, Deadaptation or aftereffect; NP, neglect patients; PCG, patient control group; HCG, healthy control group; **(B)** Current data showing the mean pointing error (with SE) in degrees for the first trials in each phase: PreOL, pre-open loop; PreVF, pre-visual feedback; A (Prism-Adaptation), PosOL; post-open loop; PosVF, Post-visual feedback/deadaptation. Data from Aimola et al. show the means of no visual feedback trials from each block of adaptation.

DISCUSSION

This experiment was designed to assess whether noisy or compressed visuo-motor environments were able to model the pattern of prism adaption effects observed in neglect patients. With the introduction of noise, both adaptation and aftereffects were indistinguishable from standard PA in healthy controls with both conditions showing an initial rightward shift before returning to baseline accuracy followed by an aftereffect that rapidly decayed (**Figures 2** and **3**). The introduction of spatial compression, on the other hand, impaired adaptation, and reduced aftereffects in a manner similar to that observed by Aimola et al. (2012) (see **Figure 4**).

In the compression condition, participants failed to adapt to the prismatic displacement even after 40 trials. Although the actual reaching error was similar to that observed during early trials in the noise and control conditions, the perceived error would have been half that. That is, an error of 6°, large enough to stimulate strategic correction under normal adaptation conditions, would only have been perceived as being an error of 3°, equivalent to a distance of about 1 cm, and potentially below the threshold for detection as an externally generated error. This evidence supports the idea that without conscious registration of the prism-induced perturbations, SC cannot occur.

It should be noted that reducing the perceived 6° error by half is not quite the same as wearing half-strength (3°) prism goggles. Six degree prisms would have perturbed the target by 6°, required a 6° rotation of the eyes (although, see Newport et al., 2009, for a discussion of why this might not be important) and induced a concomitant actual and perceived directional error. In contrast, with 3° prisms target displacement, eye rotation, and directional error would all have been smaller. In the compression condition, compared to 3° displacing prisms, only the perceived error was smaller.

Compression-modeled neglect did not significantly increase the magnitude or longevity of aftereffects relative to the control condition. Indeed, aftereffects were entirely absent both with and without visual feedback of the reaching limb following removal of the prism goggles. In contrast, both Noise and Control post-adaptation reaches displayed similar immediate, but short-lived, aftereffects. As would be expected, these aftereffects were larger in the PosOL phase than in the equivalent visual feedback phase, demonstrating the rapid and normal use of visual feedback in the reduction of prism-induced aftereffects.

It is evident that incomplete SC in compression-modeled neglect does not necessarily lead to larger or longer-term spatial recalibration as reflected by aftereffects. These results closely mimic those of Aimola et al. (2012) (**Figure 4**), and are contradictory to predictions made by Redding and Wallace (2006) and Michel et al. (2007) that impaired SC in neglect leads to a greater dependency on SR mechanisms and subsequently greater aftereffects. It should be noted, however, that in the current experiment aftereffects were not merely reduced; they were completely absent. This result was unexpected and it would appear that the failure to detect an error at a conscious level (as evidenced by the lack of strategic correction) was mirrored by a failure to detect an error at a lower level. While it is thought that strategic correction helps to promote SR (Redding and Wallace, 1996), a failure of strategic correction can lead to excessive realignment and abnormally large aftereffects (Newport and Jackson, 2006). In this case, however, there was neither correction nor realignment. It is possible that the error in the current study was too small to require the motor system to correct or that, given the size of the error, not enough trials were completed in order to produce noticeable aftereffects.

Regardless of whether the spatial compression applied here is an accurate representation of the visuo-motor experience in neglect, dynamically altering multisensory interactions using virtual reality could provide a promising avenue for rehabilitative research. Spatial representations are the result of dynamic remapping processes determined by multisensory input. PA creates an additional rightward bias to that already present in neglect, and patient's recalibration for this seems to trigger subsequent recalibration of their task-work space position. Redding and Wallace (2006), however, speculate that PA is ineffective in recalibrating *size* of the work space, and that this may result from a compressed spatial representation. Thus, manipulation of the visual workspace and the subsequent compensatory visuo-motor adjustment to this may theoretically enable neglect patients to correct the size of the task-work space as well as the spatial recalibration. Indeed, with the current system it would be possible to create a visual workspace based upon the Oppel–Kundt illusion which has been shown to modulate both neglect and healthy control performance on visuo-spatial tasks (Savazzi et al., 2007, 2012; Pia et al., 2012). Future research could therefore focus on determining the characteristics of compressed distortion in individual patients and assess whether dynamically resizing the visual workspace in accordance with that distortion could be more beneficial in rehabilitating neglect than standard, rigid, prism goggles.

In summary, compression-modeled neglect successfully impairs SC in PA, replicating the results found by Aimola et al. (2012) in neglect patients. Alongside previous research and theories for neglect syndrome, these results suggest that spatial representations primarily involved in visuo-spatial behavior is compressed in neglect and that investigations that manipulate anisotropic distortions of the visual workspace may be a fruitful avenue of research for rehabilitation.

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Early visual processing is affected by clinical subtype in patients with unilateral spatial neglect: a magnetoencephalography study

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Objective: To determine whether visual evoked magnetic fields (VEFs) elicited by right and left hemifield stimulation differ in patients with unilateral spatial neglect (USN) that results from cerebrovascular accident.

Methods: Pattern-reversal stimulation of the right and left hemifield was performed in three patients with left USN. Magnetoencephalography (MEG) was recorded using a 160-channel system, and VEFs were quantified in the 400 ms after each stimulus. The presence or absence of VEF components at around 100 ms (P100m component) and 145 ms (N145m component) after stimulus onset was determined. The source of the VEF was determined using a single equivalent current dipole model for spherical volume conduction. All patients were evaluated using the behavioral inattention test (BIT).

Results: In response to right hemifield stimulation, the P100m and N145m components of the VEF were evident in all three patients. In response to left hemifield stimulation, both components were evident in Patient 3, whereas only the P100m component was evident in Patient 1 and only the N145m component was evident in Patient 2. Patient 1 exhibited impairments on the line bisection and cancelation tasks of the BIT, Patient 2 exhibited impairments on the copying, drawing and cancelation tasks of the BIT, and Patient 3 exhibited impairments on the cancelation task of the BIT.

Conclusion: These results demonstrate that early VEFs are disrupted in patients with USN and support the concept that deficits in visual processing differ according to the clinical subtype of USN and the lesion location. This study also demonstrates the feasibility of using MEG to explore subtypes of neglect.

Keywords: visual evoked magnetic field, pattern-reversal stimulation, attention network, diagnosis of unilateral spatial neglect, neglect subtypes, visual attention networks, viewer-centered neglect, stimulus-centered neglect

INTRODUCTION

Unilateral spatial neglect (USN) is a characteristic failure to explore the contralateral space of a brain lesion (Heilman et al., 1993). Although there have been many studies of the affected brain regions and pathological mechanisms of USN, general consensus is still lacking. This is largely because USN is a heterogeneous disorder with various subtypes that involve deficits in a variety of different spatial and representational cognitive processes, including personal or extrapersonal neglect and viewer-centered or stimulus-centered neglect, among others (Arene and Hillis, 2007). Most USN patients have a combination of the different subtypes. Therefore, it is difficult to find one common mechanism that underlies symptoms in all patients.

From a neuroanatomical perspective, brain lesions in a variety of regions have been emphasized as critical for USN, and there is controversy as to the one critical brain region. In particular, although several studies have suggested that lesions to the right inferior parietal lobe might be critical for USN (Vallar and Perani, 1986; Mesulam, 1999), another study found that lesions to the right superior temporal lobe were most common in USN patients (Karnath et al., 2001). Previous studies have also emphasized the role of fronto-parietal white matter disconnection in USN. Doricchi and Tomaiuolo (2003) found that damage to the fronto-parietal pathway caused chronic neglect, and Thiebaut de Schotten et al. (2005) found that inactivation of the right fronto-parietal connecting fibers during brain surgery caused stronger rightward deviation on the line bisection test. These findings suggest that fronto-parietal communication is essential for symmetrical visual processing, and indicate that spatial neglect is caused not by the dysfunction of a single cortical region, but by the disruption of large attention networks that include many discrete cortical regions.

In a recent study, Verdon et al. (2010) reported a relation between the clinical features of USN and the location of the brain lesion, highlighting the need to consider the different subtypes of USN when investigating the relation between lesion location and clinical characteristics of USN. However, prism adaptation and sensory stimulation ameliorate various symptoms of neglect (Luauté et al., 2006), suggesting that there may be a common mechanism underlying all subtypes of USN. Therefore, it is not clear if the clinical subtypes of USN share a common mechanism, or are mechanistically distinct.

It is largely accepted that USN is a high-order deficit and that sensory processing of contralesional stimuli remains intact (Heilman and Valenstein, 1979). Studies examining early (<200 ms) visual evoked potentials (VEPs) or event-related potentials reported that cortical activities are evoked by stimuli presented on the neglected side, thus supporting this view (Lhermitte et al., 1985; Vallar et al., 1991). However, recent studies have suggested that the early visual processing of contralesional stimuli is not normal in USN patients. The latency of steady-state VEPs was longer for contralesional than ipsilesional stimuli (Pitzalis et al., 1997), and early components of VEPs were delayed and of lower amplitude for left-side than for right-side stimuli in left USN patients (Di Russo et al., 2008). In addition, functional magnetic resonance imaging (fMRI) studies have reported that the right visual cortex of acute left USN patients was activated less by left hemifield stimulation than by right hemifield stimulation (Corbetta et al., 2005), and the response of the right primary visual cortex to left hemifield stimulation was reduced with high attentional load at fixation in left USN patients (Vuilleumier et al., 2008). These studies suggest that high-order attentional deficit can affect lower-order (early) sensory processing.

Visual processing of USN patients has been investigated using VEPs (Vallar et al., 1991; Di Russo et al., 2008), and fMRI (Corbetta et al., 2005; Vuilleumier et al., 2008). Although VEPs have higher temporal resolution than fMRI, they have a lower spatial resolution. Magnetoencephalography (MEG) is a non-invasive method of investigating human brain function that has been applied to the study of human visual processing (Cohen, 1968; Brenner et al., 1975). It can be used to measure changes in magnetic fields around the head that represent the electrical activities of neurons in the cortex, and has good potential for estimating source localization and temporal resolution of sensory processing. Therefore, using MEG to measure visual evoked magnetic fields (VEFs) can be a suitable method for elucidating the temporal and topographical process of early visual processing of USN patients. However, MEG has not yet been used to investigate visual processing in USN patients.

Visual pattern-reversal stimulation is a basic paradigm for the study of early visual processing (Halliday et al., 1972; Barnikol et al., 2006). Visual pattern-reversal stimuli evoke changes in the VEF (Nakamura et al., 1997; Hashimoto et al., 1999), and VEFs that are elicited by pattern-reversal stimulation have been well investigated (Nakamura et al., 1997; Hashimoto et al., 1999; Barnikol et al., 2006). In healthy subjects, VEFs have three components with latencies of 75–90, 100–120, and 145–160 ms, which are termed N75m, P100m, and N145m respectively (Nakamura et al., 1997; Hashimoto et al., 1999). Nakamura et al. (1997) reported that the N75m component was weaker than the P100m and N145m components. In addition, with dipole source analysis, reliable equivalent current dipoles (ECDs) of N75m elicited by hemifield stimulation were estimated in only 7 out of 12 sessions, even in healthy subjects (Nakamura et al., 1997). Therefore, N75m is not suitable for diagnostic evaluation of USN patients. Previous studies have suggested that the ECDs of P100m and N145m are located in or near the primary visual cortex (Nakamura et al., 1997; Hashimoto et al., 1999; Barnikol et al., 2006), but are in opposing directions, i.e., the ECD of P100m is directed medially and that of N145m is directed laterally (Nakamura et al., 1997; Hashimoto et al., 1999). Therefore, the direction and location of ECDs can be used to confirm the component under study.

It has been suggested that early visual processing in USN is affected by higher cortical dysfunction (Vallar et al., 1991; Corbetta et al., 2005; Di Russo et al., 2008; Vuilleumier et al., 2008). However, there are no studies that have compared visual processing across USN patients with different lesion locations or different neglect subtypes. The purpose of this study was to compare visual processing of USN patients between right and left hemifield stimulation, and to investigate whether lesion location or neglect subtype modulates visual processing.

MATERIALS AND METHODS

SUBJECTS

Three patients with left USN were studied. This research was conducted in accordance with Declaration of Helsinki, and informed consent was obtained from each patient after the nature of the study was explained. Basic demographic characteristics of all patients are shown in **Table 1**. Magnetic resonance imaging (MRI) was performed with a GE Signa 1.5-T system (GE Yokogawa Medical Systems, Japan) and lesion locations were determined using T1-weighted images. The lesion of Patient 1 included the posterior parietal lobe and the posterior frontal lobe. The lesion of Patient 2 was in the posterior frontal lobe, temporal lobe, and extended to the temporo-parietal junction (TPJ). The lesion of Patient 3 was in the inferior frontal lobe and the temporal lobe (**Figure 1**).

EVALUATION OF USN

The behavioral inattention test (BIT) is a battery that is commonly used to assess spatial neglect (Wilson et al., 1987). It consists of a six-item conventional test and a nine-item behavioral test. The cut-off values for spatial neglect are determined for each item and for the total score of the conventional and behavioral tests, and are determined as the average minus two standard deviations of the score of controls (Ishiai, 1999). Scores below the cut-off value indicate the presence of spatial neglect.

VISUAL STIMULATION AND MEG RECORDING

Visual stimulation consisted of a reversal of a black-and-white checkerboard pattern. The luminance of the white squares was 200 cd/m^2 and that of the black squares was 20 cd/m^2, resulting in a contrast of 81.8%. The stimulus was back-projected onto a screen through a cylindrical duct (diameter 105 mm, length 600 mm) using a data projector (VPL FX-51, Sony, Tokyo, Japan) with a stable delay time (8.3 ms). The viewing distance was 15 cm. Patients lay comfortably in a supine position on a bed in a magnetically

Table 1 | Demographic characteristics of all patients.

Subjects	Age	Sex	Disease	Time from onset (months)	BIT-C	BIT-B
Patient 1	54	Male	Rt. MCA infarction	4	108/146	64/81
Patient 2	70	Male	Rt. MCA infarction	4	82/146	45/81
Patient 3	57	Male	Rt. MCA infarction	1.5	99/146	68/81

All subjects are right-handed.
BIT-C, conventional test of BIT; BIT-B, behavioral test of BIT; MCA, middle cerebral artery.

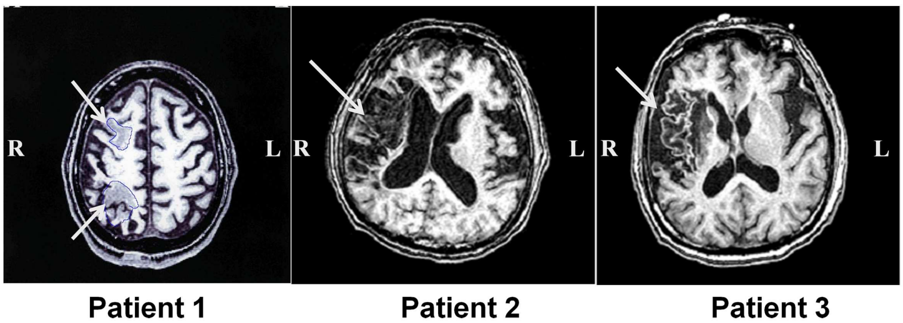

FIGURE 1 | Lesion location in patients with unilateral spatial neglect. T1-weighted magnetic resonance images for all three patients with unilateral spatial neglect. White arrows indicate lesions.

shielded room and watched the screen monocularly with the right eye. They were instructed to focus on a small red fixation point located in the center of the pattern. The background luminance of the shielded room was approximately 50 cd/m^2. The pattern-reversal stimulation had 64 squares arranged in a matrix. The size of the stimulation was 20° × 20° and the inner edge was 1° lateral to the fixation point. The check size was 2.5° × 2.5°. The frequency of checkerboard reversal was 1 Hz. During each recording session, the stimulation was presented in the right or left hemifield, and an experimenter was sitting close to the patient to confirm eye focus. MEG was recorded using a whole-head 160-channel MEG system (MEGvison: Yokogawa Elec. Co., Japan). Five marker coils (Yokogawa Elec. Co., Japan) were placed on the skull for subsequent analysis of VEF source using MRI. MRI was performed within a week before or after MEG recording. T1-weighted images with 1.5-mm-thick contiguous slices were used for overlays, with the ECD sources determined from MEG data.

ANALYSIS

Visual evoked magnetic fields were quantified using MEG data from 100 ms before to 400 ms after each stimulus. Around 200 responses were averaged for each patient. In healthy subjects, VEFs have three components: N75m, P100m, and N145m (Nakamura et al., 1997; Hashimoto et al., 1999). However, the N75m component is weak, and does not have reliable ECDs, even in healthy subjects (Nakamura et al., 1997). Thus, only the P100m and N145m components of the VEF were evaluated. The local responses from all 160 channels were superimposed, and we determined the times of the VEF peaks that occurred at around 100 and 145 ms visually. And then, the distribution of the magnetic field potential was represented in an isofield contour map according to the amplitude at each recording point at the determined time peak (**Figures 2** and **3**). In a contour map, green lines represent outward-going flux, and red lines represented inward-going flux. A source–sink pair indicated existence of a single-ECD source. Sixteen channels that covered the expected ECD location on the isofield contour map were selected at each time point for dipole source analysis. The root mean square (RMS) amplitude of the signal was calculated from the selected 16 channels, and a component was considered present if the peak RMS amplitude was above 40 ft.

To estimate location, intensity, and direction of each component, source analysis was based on a single-ECD model for spherical volume conduction. Using single-dipole theory, the ECDs were estimated at each time peak from the 16 channels that covered the occipital region and were localized on the MRI (**Figures 2** and **3**). Goodness-of-fit values greater than 90% were considered to indicate a good dipole model.

RESULTS

VEF COMPONENTS

In response to right hemifield stimulation, P100m and N145m were evident in all three patients (**Figure 2**). The ECD of P100m was located in the primary visual cortex and directed medially, and the ECD of N145m was located near that of P100m and directed laterally (**Figure 2**). In response to left hemifield stimulation, P100m and N145m were evident in Patient 3, whereas only P100m was evident in Patient 1 and only N145m was evident in Patient 2 (**Figure 3**). In Patient 1 the ECD of the observed VEF was directed medially and in Patient 2 it was directed laterally,

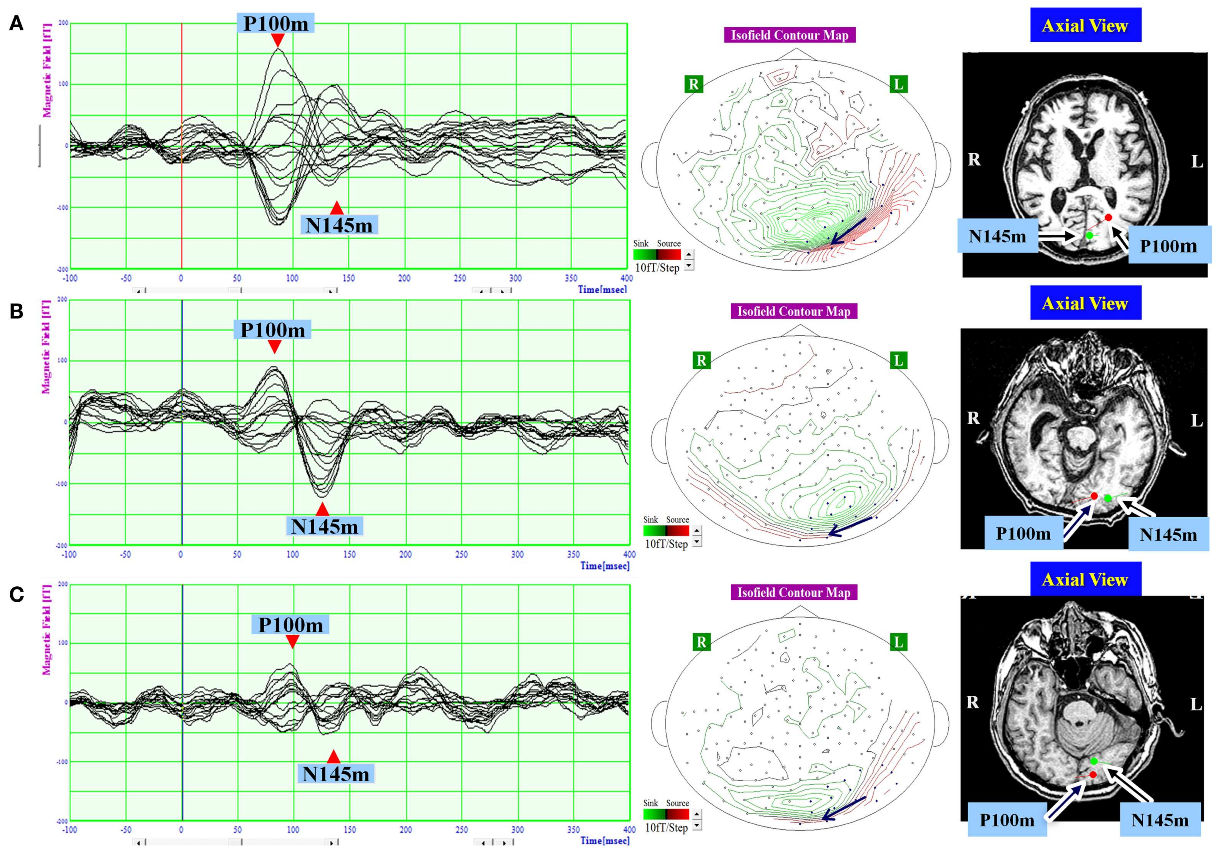

FIGURE 2 | The waveform and equivalent current dipole sources of visual evoked magnetic fields elicited by right hemifield stimulation in patients with unilateral spatial neglect. Left: the waveforms of visual evoked magnetic fields (VEFs) in response to pattern-reversal stimulation of the right hemifield in Patient 1 **(A)**, Patient 2 **(B)**, and Patient 3 **(C)**. Waves detected by selected 16 magnetoencephalography recording channels are superimposed. Around 200 responses were averaged for each patient. Middle: the location of the 16 channels used to estimate ECD on the isofield contour map at peak time of P100m. In a contour map, green lines represent outward-going flux, and red lines represented inward-going flux. A black arrow indicates an expected location and direction of ECD. Small circles indicate distribution of recording sensors. Blue circles indicate selected 16 channels. Right: the equivalent current dipoles (ECDs) superimposed on axial magnetic resonance images. Red represents the P100m component of the VEF; Green represents the N145m component of the VEF. The dot represents dipole location, and the bar represents dipole direction. Both components were evident and were located in occipital lobe in all patients. The P100m component was directed medially, and the N145m component was directed laterally.

confirming that these were not the same components. The ECD of all detected components was located in the right occipital lobe around the primary visual cortex (**Figure 3**).

USN SYMPTOMS

Behavioral inattention test scores are shown in **Table 1**. All patients obtained full marks on the line cancelation test, and all patients exhibited impairments (score below the cut-off value) on the letter and the star cancelation tests. Patient 1 also exhibited impairments on the line bisection test, and Patient 2 exhibited impairments on the copying and drawing tests (**Table 2**). The absent VEF component and abnormal components of the BIT are summarized for each patient in **Table 3**.

DISCUSSION

Although many studies have investigated the cortical mechanisms of USN, the early visual processing of contralesional stimuli in USN patients is not well understood. To investigate early visual processing in USN, we compared the early components of VEFs elicited by right and left hemifield stimulation. Previous studies have suggested that the P100m and N145m components of the VEF are primarily generated in V1/V2 (Nakamura et al., 1997; Hashimoto et al., 1999; Barnikol et al., 2006). In this study, we determined criteria for evaluating the presence or absence of VEF components (RMS amplitude >40 ft and dipole source analysis goodness-of-fit >90%), and a response that did not satisfy these criteria was regarded as "absent." Therefore, absence of a component does not necessarily mean "no response." According to these criteria, the P100m and N145m components were both evident in response to pattern-reversal stimulation of the right hemifield in all three patients. However, the components of the VEF that were evident in response to left hemifield stimulation differed in the three patients. The three patients also had different neglect symptoms and different brain lesion locations (**Table 3**).

Early studies reported that early visual processing was intact in patients with USN. The early components of the VEP (<200 ms

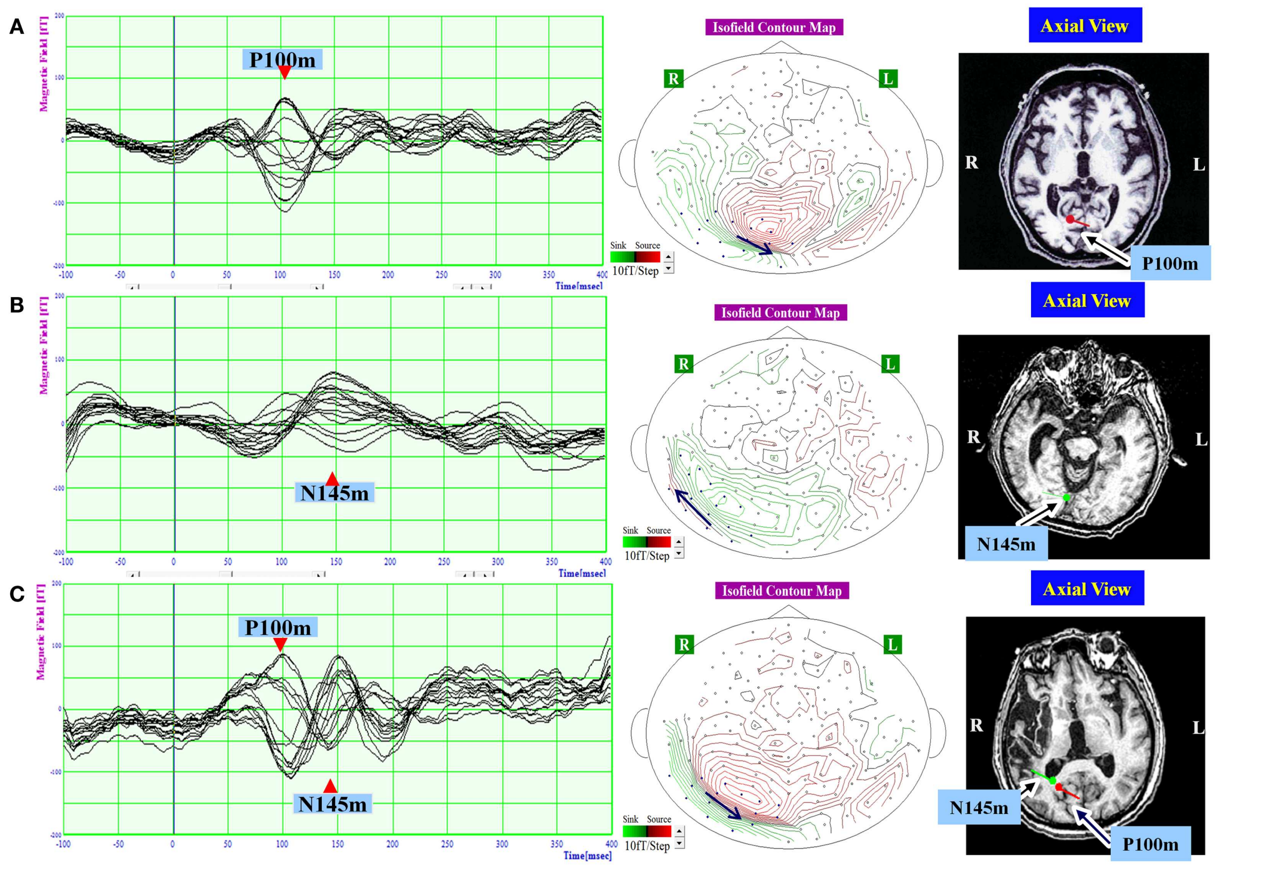

FIGURE 3 | The waveform and equivalent current dipole sources of and visual evoked magnetic fields elicited by left hemifield stimulation in patients with unilateral spatial neglect. Left: the waveforms of visual evoked magnetic fields (VEFs) in response to pattern-reversal stimulation of the left hemifield in Patient 1 **(A)**, Patient 2 **(B)**, and Patient 3 **(C)**. Waves detected by selected 16 magnetoencephalography recording channels are superimposed. Around 200 responses were averaged for each patient. Middle: the location of the 16 channels used to estimate ECD on the isofield contour map at peak time of P100m **(A,C)** or N145m **(B)**. In a contour map, green lines represent outward-going flux, and red lines represented inward-going flux. A black arrow indicates an expected location and direction of ECD. Small circles indicate distribution of recording sensors. Blue circles indicate selected 16 channels. Middle: the equivalent current dipoles (ECDs) superimposed on axial magnetic resonance images. Red represents the P100m component of the VEF; green represents the N145m component of the VEF. The dot represents dipole location, and the bar represents dipole direction. The P100m component was evident in Patient 1 **(A)** and Patient 3 **(C)**. The N145m component was evident in Patient 2 **(B)** and Patient 3 **(C)**. All observed components were located in the occipital lobe. The P100m components were directed medially, and the N145m components were directed laterally.

Table 2 | The profile of the conventional behavioral inattention test in all patients.

Patient	Line cancelation	Letter cancelation	Star cancelation	Line bisection	Copying	Drawing
Patient 1	36	30*	34*	3*	3	2
Patient 2	36	8*	29*	7	1*	1*
Patient 3	36	14*	33*	9	4	3

BIT, behavioral inattention test.
**Scores under cut-off value.*

latency) were normal (Vallar et al., 1991), but the P300 component, which is related to attention, was abnormal for left-side information in left USN patients (Lhermitte et al., 1985). However, in the study of Vallar et al. (1991), USN patients were primarily diagnosed using cancelation and reading tests, rather than a using a standardized battery such as the BIT, and only two patients were evaluated by VEP. Therefore, they could not divide the patients into clinical subtypes. In addition, high-resolution recording system was not used in this study, there is no assurance that VEP components detected in response to left hemifield stimuli were really

Table 3 | The absent visual evoked magnetic field component, behavioral inattention test deficits, neglect components, and brain lesion location in all patients.

Patient	VEF component	Deficit of BIT-C	Neglect component	Brain lesion
Patient 1	N145	Bisection cancelation	Perceptual/visuo-spatial Exploratory/oculo-motor	PPC, PFL
Patient 2	P100	Copying, drawing cancelation	Allocentric/object-based Exploratory/oculo-motor	TPJ, TL, PFL
Patient 3	not related	Cancelation only	Exploratory/oculo-motor	TL, IFL

PPC, posterior parietal cortex; PFL, posterior frontal lobe; TPJ, temporo-parietal junction; TL, temporal lobe; IFL, inferior frontal lobe.

evoked in the right visual cortex. More recent studies performed using higher resolution recording systems suggest that early visual processing is affected in USN patients. Di Russo et al. (2008) found abnormalities in components of the VEP that occurred more than 130 ms after stimulus onset for stimuli located in the neglected side, whereas components of the VEP that occurred within 130 ms of stimulus onset were intact. Using fMRI, Corbetta et al. (2005) showed that the anatomically intact right striate cortex was less activated by visual stimulation than the intact left striate cortex in acute left USN patients. In USN patients with visual extinction, the P1 (80–120 ms latency) and N1 (140–180 ms latency) components of the event-related potential were absent or reduced for an extinguished stimulus with respect to a perceived stimulus located in the left visual field (Marzi et al., 2000; Driver et al., 2001). However, these studies did not consider the association between the subtype of neglect and the cortical activation observed in response to visual stimuli.

Attention and concentration increased the amplitude of VEPs elicited by pattern-reversal stimulation (Hoshiyama and Kakigi, 2001), and attentional load modulated the first (80 ms latency) and the second (108–120 ms latency) components of the event-related potential in early visual processing (Fu et al., 2009). These results suggest that higher cognitive function may affect early visual processing in the primary visual cortex. Furthermore, it has been suggested that the P100m and N145m components of the VEF are generated by independent and/or parallel activities of visual processing (Hashimoto et al., 1999; Barnikol et al., 2006), and the frequency and location of visual stimulation differentially affect early (equivalent to N75–P100) and late (equivalent to N145–P200) components of VEPs in healthy subjects (Parker and Salzen, 1977; Plant et al., 1983). These results suggest that attentional deficits may independently affect P100m and N145m. There is also evidence that higher cortical function may modulate early perceptual processing in USN patients. Valenza et al. (2004) reported that left primary somatosensory cortex responses to tactile stimuli on the "intact" right hand decreased when the hand was in the neglected left space, and Vuilleumier et al. (2008) reported that attentional load at fixation reduced right visual cortex responses to left hemifield stimuli in USN patients. These results suggest that early visual processing may be affected by higher cortical dysfunctions and by lesions in functionally related regions (Corbetta et al., 2005).

In this study, we found that the components of the VEF that were evident in response to left hemifield stimulation differed across the three USN patients. The three patients also had different symptoms, and different lesion locations. Although based on a small number of subjects, this is consistent with the recent suggestion that different subtypes of neglect are related to different cortical networks and/or regions (Hillis et al., 2005; Committeri et al., 2006). A recent neuroanatomical study supports this idea. Verdon et al. (2010) evaluated lesion location using voxel-based lesion-symptom mapping and revealed neural correlates for each component of neglect, namely the right inferior parietal lobule for the perceptive/visuo-spatial component related to the line bisection test, the right dorsolateral prefrontal cortex for the exploratory/visuo-motor component related to cancelation tests, and the deep temporal lobe region for the allocentric/object-centered component related to allocentric error in the Ota search test (Ota et al., 2001), which characterizes the object-based component of neglect. Although we did not use the Ota search test, the copying and drawing tasks of the BIT primarily evaluate the symmetry of figures that patients copy and draw, and may therefore be considered to represent the object-based component of neglect.

In a previous study, Di Russo et al. (2008) investigated early visual processing in USN patients, the majority of whom had lesions that included the parietal lobe. The results showed that visual processing 130 ms after stimulus onset was abnormal in the parietal lobe of USN patients, suggesting that low amplitude of N145m is related to parietal lesions. Combined with the finding of Verdon et al. (2010) that parietal lesions were associated with deviation in the line bisection test, these results suggest that a lack of N145m is related to parietal lesions and the perceptual component of neglect. Consistent with this proposal, we found that Patient 1 had a lesion of the posterior parietal lobe, no N145m VEF component in response to left hemifield stimulation, and exhibited strong deviation in the line bisection test.

In Patient 2, only one VEF component, at around 145 ms, was evident in response to left hemifield stimulation. This could be either a delayed P100m component or an N145m component. In previous studies, the ECD of P100m is always directed medially (Nakamura et al., 1997; Hashimoto et al., 1999); however, the ECD of the VEF component observed in Patient 2 was directed laterally. Therefore, we consider this to be N145m. Previous studies suggested that the frequency and location of visual stimulation differentially affected early (equivalent to N75–P100) and late (equivalent to N145–P200) components of VEPs in healthy subjects (Parker and Salzen, 1977; Plant et al., 1983). Therefore, P100m and N145m can be affected independently by higher cortical dysfunction. On the other hand, both P100m and N145m were present in Patient 3. This is compatible with previous reports that the early components of VEP were intact in USN patients (Lhermitte et al., 1985; Vallar et al., 1991). The lesions of Patient 2 and Patient 3 widely overlapped, making it difficult to discuss associations between lesion location and VEFs. However, only the lesion of Patient 2 extended to the TPJ; therefore, it is suggested that the absence of P100m is related to TPJ lesion and allocentric neglect. In addition, because all three patients exhibited impairments on the cancelation task, we suggest that the oculo-motor exploration necessary for the cancelation task was not related to the early VEF components.

Albeit from results of a single case, one possible hypothesis can be proposed to explain the VEF pattern of Patient 2. The check size of 2.5° × 2.5° in this study was larger than those of previous studies (Nakamura et al., 1997; Hashimoto et al., 1999). Previous studies demonstrated that amplitude of P100(m) increased in larger check size up to around 2° × 2° (Kurita-Tashima et al., 1991; Sahinoglu and Erar, 1999; Nakamura et al., 2000; Chen et al., 2005), while N145(m) decreased above 1° × 1° (Kurita-Tashima et al., 1991; Sahinoglu and Erar, 1999). It was also suggested that large checks activated peripheral vision more than central (foveal) vision (Nakamura et al., 2000) and large and small checks may preferentially activate different channels (Holder et al., 2010). Furthermore, the study that used large check size of 10.5° × 10.5° indicated activity in V5 complex area, as well as activity in V1/V2 area, contributed to P100m (Barnikol et al., 2006), while other studies that used smaller checks (<1°) showed that the ECD of P100m located in V1 area (Nakamura et al., 1997; Hashimoto et al., 1999). These findings suggest that dysfunction of TPJ may modulate activity of V5 area for peripheral vision that contributes to generation of P100m. However, N145m was preserved because it might be less sensitive to modulation of TPJ dysfunction than P100m. Further studies are needed to confirm this hypothesis.

A few limitations of this study warrant consideration. First, the number of subjects is small. Second, because there are no normal control subjects in this study, we cannot determine if the latencies and amplitudes of detected VEF components were intact. Third, MRIs were not recorded at the same day as MEG, and we did not use a standard brain image. In addition, because we use the single-ECD model for dipole source analysis, the effects of ECDs that may have existed at the same time as P100m and N145m were not considered, and we could not accurately estimate ECD location. Fourth, the check size of 2.5° × 2.5° is larger than that used in some previous studies (Nakamura et al., 1997; Hashimoto et al., 1999), although smaller than that used by Barnikol et al. (2006), and the signal strength of monocular stimulation may be smaller than that of binocular stimulation. These differences in stimulus condition may affect our results. However, because we stimulated both the right and the left hemifield with the same stimulus, we consider the differences between left and right hemifield stimulation to be reliable. Fifth, because of the MEG system's technical limitations, devices such as electrooculogram could not be used to monitor eye movements and blinks, and we could therefore not remove the responses contaminated by eye movements and blinks.

Despite these limitations, we suggest that VEFs elicited by left hemifield stimulation are disrupted in USN patients. Our results support the concept that deficits in visual processing differ according to the clinical subtype of USN and the lesion location. USN is characterized by large heterogeneity in clinical aspects and neuroanatomical correlates (Arene and Hillis, 2007), and is considered to have multiple clinical components (Vuilleumier et al., 2008). Our study demonstrates the feasibility of exploring subtypes of neglect using VEFs measured by MEG, and this method can now be applied to larger groups.

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Now you feel *both*: galvanic vestibular stimulation induces lasting improvements in the rehabilitation of chronic tactile extinction

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Tactile extinction is frequent, debilitating, and often persistent after brain damage. Currently, there is no treatment available for this disorder. In two previous case studies we showed an influence of galvanic vestibular stimulation (GVS) on tactile extinction. Here, we evaluated in further patients the immediate and lasting effects of GVS on tactile extinction. GVS is known to induce polarity-specific changes in cerebral excitability in the vestibular cortices and adjacent cortical areas. Tactile extinction was examined with the Quality Extinction Test (QET) where subjects have to discriminate six different tactile fabrics in bilateral, double simultaneous stimulations on their dorsum of hands with identical or different tactile fabrics. Twelve patients with stable left-sided tactile extinction after unilateral right-hemisphere lesions were divided into two groups. The GVS group ($N = 6$) performed the QET under six different experimental conditions (two Baselines, Sham-GVS, left-cathodal/right-anodal GVS, right-cathodal/left-anodal GVS, and a Follow-up test). The second group of patients with left-sided extinction ($N = 6$) performed the QET six times repetitively, but without receiving GVS (control group). Both right-cathodal/left-anodal as well as left-cathodal/right-anodal GVS (mean: 0.7 mA) improved tactile identification of identical and different stimuli in the experimental group. These results show a generic effect of GVS on tactile extinction, but not in a polarity-specific way. These observed effects persisted at follow-up. Sham-GVS had no significant effect on extinction. In the control group, no significant improvements were seen in the QET after the six measurements of the QET, thus ruling out test repetition effects. In conclusion, GVS improved bodily awareness permanently for the contralesional body side in patients with tactile extinction and thus offers a novel treatment option for these patients.

Keywords: body, extinction, vestibular, touch, brain recovery, awareness, rehabilitation

INTRODUCTION

In daily life touch is important in many situations, i.e., when we grasp objects, manipulate them, or identify them, e.g., when retrieving a key from our pocket. Brain lesions, due to stroke, head trauma, or other causes impair a variety of somatosensory abilities dramatically in more than 50% of patients (Van Stralen et al., 2011). Among these impairments, tactile or somatosensory extinction is a frequent disorder (Kerkhoff et al., 2011). Extinction of sensory stimuli – in whatever modality – is defined as the inability to process or attend to the more contralesionally located stimulus when two stimuli are simultaneously presented. By definition, the processing of a single stimulus should only be marginally impaired, thereby ruling out gross elementary sensory deficits (i.e., hemianopia, hemianesthesia, unilateral hearing loss). Extinction may occur in the visual (Conci et al., 2009), auditory (Deouell and Soroker, 2000), olfactory (Eskenazi et al., 1983), or tactile modality (Berti et al., 1999; Maravita et al., 2003). Tactile extinction is frequently found after unilateral, mostly right-sided brain lesions (70%, Schwartz et al., 1977, 1979; Heldmann et al., 2000), is a negative predictor for the patient's outcome (Rose et al., 1994), and often persists for years after lesion (Heldmann et al., 2000). Causative lesions are found in the frontal, parietal or temporal cortex (Schwartz et al., 1977; Deouell and Soroker, 2000), and the basal ganglia (Vallar et al., 1994). In addition, anterior callosal lesions may disrupt the processing of the left hand tactile stimulus (Schwartz et al., 1979), which may explain the more frequent occurrence of tactile extinction on the left body side than on the right (Schwartz et al., 1979). Moreover, tactile extinction does not only occur when the patient has to *detect* tactile stimulation (Bender, 1952), but also appears when he/she has to *discriminate* different tactile surfaces (Schwartz et al., 1977), and even occurs

Abbreviations: DSS, double simultaneous stimulation; GVS, galvanic vestibular stimulation; L-GVS, left-cathodal/right-anodal GVS; mA, milliAmpere; R-GVS, right-cathodal/left-anodal GVS; TP, time-point of measurement; QET, quality extinction test.

when a patient simultaneously explores two common household objects actively by touch (Berti et al., 1999). Tactile extinction is modulated by stimulus properties (i.e., additional sensory stimulation of the hand) *and* response factors (verbal vs. non-verbal output; cf. Vaishnavi et al., 2000). The latter indicates that interference between both stimuli can even occur at a post-perceptual level, probably close to the language system.

Two main explanations of extinction have been proposed: sensory (Bender, 1952) and attentional theories (Vallar et al., 1994). While the prior explains extinction as the result of a weakened sensory integration process, the latter holds that elementary sensory abilities may be completely intact, and yet extinction occurs. In favor of the latter account, several studies have shown that early sensory or pre-attentive processes are often reasonably intact in patients with visual extinction (Conci et al., 2009). Various stimulation maneuvers such as caloric vestibular stimulation (Vallar et al., 1993), optokinetic stimulation (Nico, 1999), repetitive peripheral magnetic stimulation (RPMS) (Heldmann et al., 2000), visuomotor prism adaptation (Maravita et al., 2003), or positioning of the "extinguishing" limb in the ipsilesional hemispace (Aglioti et al., 1999; Sambo et al., 2012) significantly modulate tactile extinction. This accords with proposals that somatosensory deficits in right-hemisphere patients may relate, at least partially, to neglect (Vallar, 1997), which can be significantly modulated by sensory stimulation maneuvers (Kerkhoff, 2003). Yet, few studies have so far evaluated to which degree tactile extinction can be *permanently* cured with such methods. A remarkable case study (Dijkerman et al., 2004) reported a long-lasting (for at least 1–3 weeks), beneficial effect of only *two* sessions of prism adaptation on somatosensory functions (pressure sensitivity and proprioception), indicating a considerable capability for the treatment of these disorders. Other sensory stimulation techniques might induce similar beneficial effects on somatosensory deficits after stroke, thus offering a potential treatment choice beyond the classic therapies already available for a longer time (cf. Carey, 1995; Carey and Matyas, 2005).

One such technique is *galvanic* vestibular stimulation (GVS). GVS is a non-invasive vestibular stimulation that is, unlike *caloric* vestibular stimulation, easier to use, lacking adverse side effects (with currents <1.5 mA) and therefore appears more appropriate for *repetitive* treatment without habituation effects (Utz et al., 2010, 2011b). Practically, weak direct currents (DCs) are delivered via two electrodes of different polarity (anode and cathode) attached to the two mastoids behind the ears. On the neural level, GVS induces polarization effects in the vestibular nerves, leading to an activation of the semicircular canals, otolith organs, and the adjacent vestibular nerves (Fitzpatrick and Day, 2004). Cortical activation is seen in the posterior insula and the temporo-parietal region in healthy subjects during GVS. Further activation was found in the middle and superior temporal gyrus, the putamen, the anterior cingulate gyrus, and thalamus (Lobel et al., 1998; Bense et al., 2001). Interestingly, *bilateral* activations of vestibular cortices are obtained by applying left-cathodal/right-anodal GVS (further termed L-GVS), whereas *unilateral*, right-hemispheric activations are induced by right-cathodal/left-anodal GVS (further termed R-GVS) (Dieterich et al., 2003; Fink et al., 2003).

Only a few studies have so far evaluated the potency of GVS in patients with neglect, extinction, and related spatial disorders. Rorsman et al. (1999) showed a transient reduction of visual neglect symptoms in patients with neglect (i.e., line cancelation) during R-GVS. A recent case study found a significant improvement in visuo-constructive deficits (copy of Rey-figure) during GVS (Wilkinson et al., 2010). Recently, we have already been successful in modulating neglect with GVS: one 20 min session of R-GVS temporarily reduced the ipsilesional bias in line bisection (Utz et al., 2011a), whereas 20 min of L-GVS normalized the profound deficits in left arm position sense in patients with left neglect (Schmidt et al., 2013).

As outlined above, GVS can modulate the thalamocortical network of the brain in a polarity-specific way, either by activation (anodal stimulation) or de-activation (cathodal stimulation) (Utz et al., 2010). As tactile extinction is viewed by some theories (Schwartz et al., 1979) as resulting from an imbalance of somatosensory inputs received simultaneously from both hands we hypothesized that GVS may re-balance this disturbed weighting via activations of certain brain areas involved in tactile extinction or inhibition of mirror-symmetric areas in the intact hemisphere. In two recent case studies we could show a lasting influence of a few sessions of GVS on tactile extinction (Kerkhoff et al., 2011), thus serving as an initial proof-of-principle test of the therapeutic efficacy of GVS.

Furthermore, promising effects of GVS in the modulation and/or treatment of other symptoms associated with neglect syndrome (Kerkhoff and Schenk, 2012) initiated to study the effects of GVS on tactile extinction in a larger sample, including a non-treated control group showing the same disorder as the treated, experimental group. From available literature on GVS we expected a *transient* reduction of left-sided (left hand) extinction errors under GVS, but no specific effect on right-sided (right-hand) errors induced by GVS. Regarding polarity we had no directional hypothesis as some of the few available studies on GVS showed improvements during L-GVS, whereas others showed improvements during R-GVS (as mentioned above). In the present study we therefore explored the effects of GVS on tactile extinction in two comparable samples of patients with right-sided stroke (experimental group: $N = 6$, control group: $N = 6$), all showing left-sided tactile extinction. Apart from *online*-stimulation effects (*during* GVS) we were particularly interested in the *after*-effects of GVS and potential enduring treatment effects on tactile extinction in the experimental group. In the control group, the influence of retesting was analyzed by testing the patients six times in an identical study protocol, but without GVS (see below, **Figure 1**).

MATERIALS AND METHODS

PARTICIPANTS

A total of 12 patients with right-hemisphere stroke and left-sided tactile extinction as determined in the Quality Extinction Test (QET; see below) were included in the study. Six patients served as the experimental group (four males, GVS group) and received different protocols of GVS, while the other six patients served as the control group (three males, control group) which was retested six times with the QET in identical schedule to rule out test repetition and other unspecific effects (**Table 1**). Allocation of patients

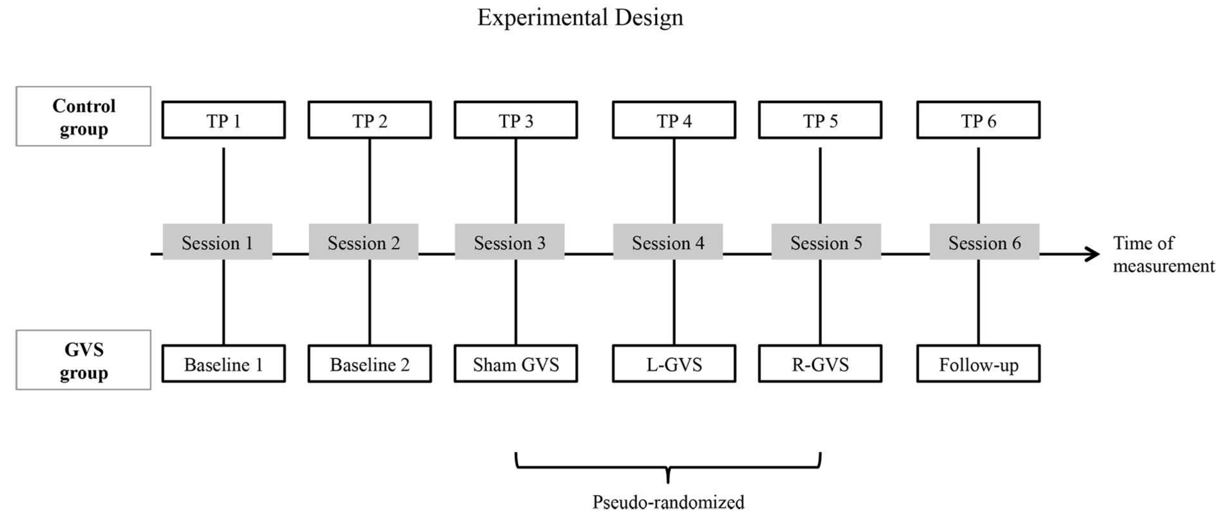

FIGURE 1 | A schematic overview of the experimental design: the galvanic vestibular stimulation (GVS) conditions performed with the six experimental patients with extinction and the different time-points of measurement (TP) performed with the six control patients with extinction, respectively in six different sessions. Abbreviations: L-GVS, left-cathodal/right-anodal GVS; R-GVS, right-cathodal/left-anodal GVS; Sham, Sham stimulation with GVS but without the application of current; Follow-up, mean follow-up 2.8 months (84 days) after GVS.

into the two patient groups was done in the following way: first, six experimental patients with extinction were treated with GVS as described below; second, six control patients with extinction were recruited in order to match the sample of experimental patients in demographic and clinical variables and extinction severity. Time intervals between the six different sessions were identical between the two patient groups. They did not differ with respect to age [$T(10) = 1.526$, $p = 0.236$], sex [$\chi^2(df = 1) = 3.43$, $p = 0.558$], or time since lesion [$T(10) = 1.541$, $p = 0.154$]. They did not differ in their Baseline performances in the QET, neither for their left or right-hand nor for different or identical materials (all ps > 0.05). All subjects except one were right-handed according to the Edinburgh handedness questionnaire (Salmaso and Longoni, 1985) and had no history of psychiatric disorders or dementia. A visual neglect screening including digit cancelation (cancel all digits "5" out of 200 single digits on a 21 cm × 29.7 cm large white paper, 10 targets per hemispace), horizontal line bisection of a 20 cm × 0.5 cm long black line and text reading of a 180 word reading text were conducted in all patients (details of these tests in Schmidt et al., 2013). All investigations were performed in accordance with the Declaration of Helsinki II and all participants gave their informed written consent before examination. A positive, written ethical approval by the local medical ethical committee (Ärztekammer Saarland) was available for the use of subliminal GVS in brain-damaged patients. No patient was enrolled in any other neuropsychological treatment (attention, neglect) or motor therapy (physiotherapy, occupational therapy) during the course of the study.

QUALITY EXTINCTION TEST

The QET (Schwartz et al., 1977) is a sensitive tactile extinction test that requires the subject to identify and name six different tactile surfaces first in unilateral trials on the left and right dorsum of hands and then in double simultaneous stimulation (DSS) trials with the same materials. Previous studies with the QET have shown that patients with right frontal or right parietal lesions consistently show marked left-sided tactile extinction in those trials with *bilateral* different stimuli while showing normal performance in unilateral target presentations (Schwartz et al., 1977, 1979). Subsequent studies with the QET provided evidence that tactile extinction is modulated by somatosensory input delivered via RPMS of the left forearm (Heldmann et al., 2000; Kerkhoff et al., 2001). Moreover, we found that apart from those bilateral trials with *different* fabrics (e.g., left hand: sandpaper, right-hand: silk) those bilateral stimulations using *identical* fabrics (e.g., both hands: silk) also made a useful diagnostic contribution, although they appeared to be easier to solve (cf. Kerkhoff et al., 2011).

The present version of the QET includes six different materials varying in tactile quality (soft sandpaper, silk, fleece, plastic, jute, and rubber gum) that were attached singly to wooden boards (size: 15 cm × 10 cm). Patients placed their hands with palms down and beside each other (hence in the normal "anatomical" position) on the table in front of the experimenter. During all testing sessions patients were blindfolded and wore a closed head-phone in order to prevent visual and auditory cues during the tactile stimulation procedure. Patients were instructed to identify and name the six different tactile materials used throughout the test. To this purpose, single boards were moved slowly by the experimenter with a speed of 2 cm/s from proximal to distal across the dorsum of either the left or right-hand. Each material was presented three times in this way and the patients had to report the material verbally. Twelve unilateral trials were run for each hand separately per patient, for every testing session. After these unilateral trials, which served to assess unilateral tactile performance, bilateral stimulation trials were performed. Here, two boards were presented simultaneously, one to each hand, and the patient had to

Table 1 | Clinical and demographic data of 12 patients with left-sided tactile extinction due to a right-hemisphere brain lesion.

Patient	Group	Age, sex	Handedness	Etiology	Lesion, Lesion age (months)	Motor deficits	Visual field	Digit cancelation omissions L/R max. (10/10)	Line bisection (20 cm, deviation in mm)	Neglect dyslexia	Visual neglect	Tactile extinction
1-LA	GVS	70, Male	Right-hander	ICB	Right fronto-parietal, 60.3	Left hemiparesis	Normal	0/0	−3	No	Yes	Yes
2-RE	GVS	45, Female	Right-hander	ICB	Right frontal, right temporal, 71.2	Left hemiparesis	Left hemianopia, 10°	1/1	+2	No	Yes	Yes
3-KA	GVS	66, Male	Right-hander	ICB	Right parietal, 6	Left hemiparesis	Normal	4/1	+13	Yes	Yes	Yes
4-NI	GVS	51, Female	Right-hander	MCI	Right fronto-parietal, 6	Left hemiparesis	Normal	5/2	−10	No	Yes	Yes
5-SC	GVS	72, Male	Right-hander	PCI	Right occipital, right thalamus, 25	Normal	Left hemianopia	4/1	−12	Yes	Yes	Yes
6-KL	GVS	47, Male	Left hander	Thalamus infarction	Right pulvinar, 2.3	Normal	Left upper quadranopia	2/1	−7	Yes	No	Yes
Mean	*N* = 6	58.3 (SD = 12.4)			28.5 (SD = 30.2)			3/1	−2.8			
7-ME	Control	59, Male	Right-hander	ICB	Right fronto-parietal, 8	Left hemiparesis	Normal	2/2	−4	Yes	No	Yes
8-TA	Control	47, Female	Right-hander	ICB	Right basal ganglia, 12	Left hemiparesis	Normal	2/1	−2	No	Yes	Yes
9-CR	Control	68, Male	Right-hander	PCI	Right thalamus and right occipital, 5	Normal	Left hemianopia	5/2	+11	Yes	Yes	Yes
10-WI	Control	45, Male	Right-hander	MCI	Right parietal, 15	Left hemiparesis	Left lower quadranopia	4/2	+9	Yes	Yes	Yes
11-TU	Control	47, Female	Right-hander	ICB	Right parietal, 5	Left hemiparesis	Left lower quadranopia	4/2	+10	Yes	Yes	Yes
12-HA	Control	25, Female	Right-hander	ICB	Right basal ganglia, 11	Normal	Normal	1/1	+3	No	No	Yes
Mean	*N* = 6	48.5 (SD = 14.6)			9.3 (SD = 4.0)			3/2	+4.5			

ICB, intracerebral bleeding; PCI, posterior cerebral artery infarction; MCI, middle cerebral artery infarction. Visual neglect: diagnosis based on conventional tests of digit cancelation, line bisection, and reading (for details, see Schmidt et al., 2013); tactile extinction: as tested by tactile stimulation of the patient's dorsum of hands by light touch.

name the material(s) he/she recognized on each hand. A total of 36 bilateral trials were performed in each complete test: 18 trials with different and 18 trials with identical materials delivered to both hands. Unilateral trials were not repeated during the experimental sessions as normal or near-to-normal unilateral performance had been established already in the two Baseline sessions before GVS. Moreover, the unilateral trials were of no particular interest in this study after normal unilateral performance had been established in all patients. Patients were unaware of the fact that one half of the trials were performed with identical and the other half with different tactile materials as both were intermingled within every session, but they were instructed that materials can be identical or different for both hands. If patients could not identify correctly one or both of the materials in a trial with bilateral stimulation, an extinction response was scored for the corresponding side. Thereafter, the next bilateral stimulation trial was performed. No attempt was made to force the patients to guess in case they were unable to verbally identify the material. The patients were not forced to guess whether the two stimuli were same or different in case of missing verbal response for one side. No time constraints were imposed and no feedback was given during testing. The percentage and raw score of left- and right-sided extinction during DSS with *different* tactile stimuli (based on 18 trials) as well as during DSS with *identical* tactile stimuli (based on the other 18 trials) were computed for every session. Note that the QET – in contrast to conventional tactile extinction procedures using light touches of the patient's hands – requires *discrimination* of six different tactile materials and finally their verbal identification. Therefore, a higher degree of error rates may be found, including some ipsilesional errors as well (Heldmann et al., 2000). Chance level, i.e., when the patient is guessing, is 16.6% in this task.

GALVANIC VESTIBULAR STIMULATION

Bipolar GVS was delivered by a constant DC stimulator (9-V battery, Type: ED 2011, producer: DKI GmbH, DE-01277 Dresden, Germany). The tap water-soaked sponge-covered electrodes (60 mm × 40 mm) were fastened on the skin over each mastoid (binaural stimulation) in order to activate the vestibular system. For L-GVS the cathode was placed on the left mastoid and the anode on the right, whereas for R-GVS this electrode setup was reversed. In the Sham-GVS condition, the two electrodes were positioned as in the L-GVS condition, except that no electric current was applied in order to rule out potential placebo-stimulation effects. We stimulated below the sensation threshold (subliminal) so that the subject was not aware of any electrical stimulation in any experimental or sham condition (Utz et al., 2010). As there is evidence that even subtle attentional cues can modulate neglect and extinction (Riddoch and Humphreys, 1983), we employed this subliminal stimulation as it elegantly circumvents potential attentional cueing effects that might occur with *supra-threshold* stimulation. A switch on the stimulation device delivered current at an individually adjusted level to the patients. The individual threshold was determined by slowly increasing current intensity in steps of 0.1 mA until the patient indicated a tingling. Current was then reduced until the patient indicated that the sensation had disappeared. This procedure was repeated a second time and the mean of both threshold values was defined as the individual threshold. Individual thresholds of each patient were determined at the beginning of both stimulation sessions (L-GVS, R-GVS) in order to exclude supra-threshold stimulation caused by reduced thresholds for GVS (see results, below). Finally, in all conditions, the GVS stimulator was never visible for the patients.

EXPERIMENTAL DESIGN

Patients in both groups participated in six different sessions (see **Figure 1** for an outline of the design). In the control group, six investigations were performed with the QET at six different time-points of measurement (TP, 1–6) without GVS stimulation. In contrast, patients in the experimental (GVS) group performed two Baseline sessions without GVS. In session three to five, they performed the QET again while receiving either L-GVS, R-GVS, or Sham-GVS, respectively in a pseudo-randomized sequence to control for order effects. Subjects were blind to the type of stimulation received. A follow-up was conducted 84 days [=2.8 months (mean); range: 35–147 days] after the fifth testing session in all subjects (hence after the last GVS session in the experimental group and after TP5 in the control group). A 2-day interval (min. 48 h) was established between sessions to avoid carry-over effects. Importantly, the timing of testing sessions was identical in both samples (see **Figure 1**).

STATISTICS

All analyses were carried out using SPSS, version 19. First, we calculated extinction errors (in %) in the QET, separately for the 18 different and 18 identical bilateral trials, for each hand and each group. Repeated-measures analyses of variance (ANOVAs) with the between factor "group" (GVS group, control group) and the within factor "GVS condition/TP" (Baseline 1/TP1, Baseline 2/TP2, Sham/TP3, L-GVS/TP4, R-GVS/TP5, Follow-up/TP6) were carried out separately for the right and left hand and for different and identical stimuli. Subsequent comparisons [ANOVAs and Bonferroni-adjusted t-tests for multiple comparisons (Holm, 1979)] were computed for a more specific examination of significant results. The alpha-level was set at $p = 0.05$, two-tailed for all analyses.

RESULTS

UNILATERAL TRIALS

In the 24 unilateral trials (12 unilateral trials per measurement × 2 measurements) each of the 12 patients scored >95% correct for the left hand and >98% for the right-hand in the QET, thus showing normal or close-to-normal unilateral tactile identifications for both hands.

ANALYSIS OF BASELINE 1 VS. BASELINE 2

Analyses of variances with the between factor "group" (GVS group, control group) and the within factor "TP" (Baseline 1, Baseline 2), separately for different and identical materials and for each hand, revealed no significant effects of these factors, suggesting that there were no differences between the two first time-points of assessment (Baseline 1, 2) in the two groups (largest $F = 3.88$, smallest $p = 0.077$).

Table 2 | Individual and mean threshold values (milliAmpere, mA) for subliminal GVS conditions for patients in the GVS group and mean number of side effects (%) according to the 34-items-questionnaire, averaged over the GVS group and separately for each GVS condition.

Patient	L-GVS	R-GVS
THRESHOLD VALUES (mA)		
1-LA	0.5	0.6
2-RE	0.5	0.5
3-KA	0.8	0.8
4-NI	0.7	0.7
5-SC	0.8	0.8
6-KL	0.6	0.6
Mean	0.7	0.7
Side effects (%)	0	0

L-GVS, left-cathodal/right-anodal GVS; R-GVS, right-cathodal/left-anodal GVS.

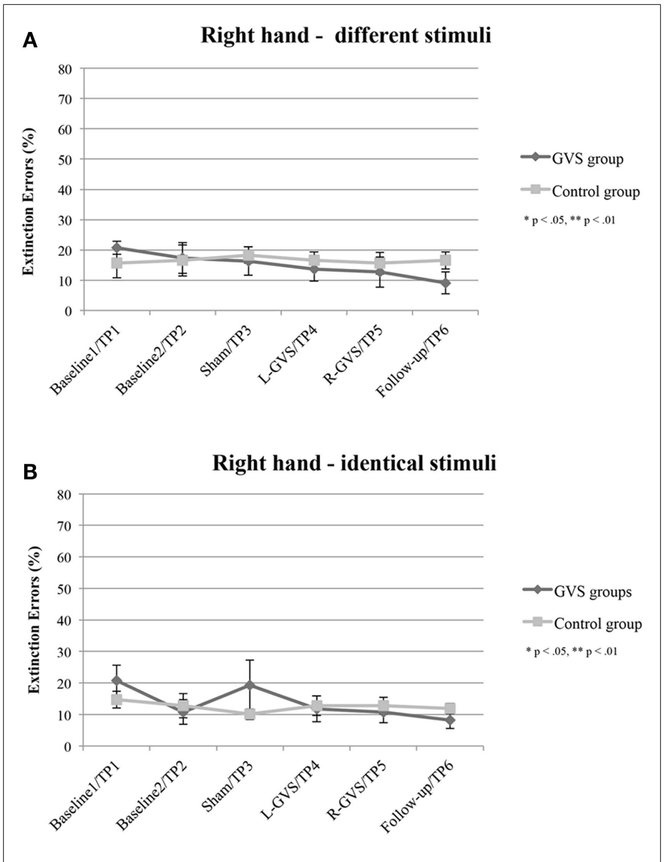

FIGURE 2 | Mean (±standard error of the mean) extinction errors (%) for the right-hand in the Quality Extinction Test (QET) of the GVS group ($N = 6$) and control group ($N = 6$) across the six measurement sessions for application of *different* tactile stimuli (A) and of *identical* tactile stimuli (B). Note that apart from moderate variations in error rates no significant improvement was observed in the control group due to retesting in six subsequent sessions. Abbreviations: L-GVS, left-cathodal/right-anodal GVS; R-GVS, right-cathodal/left-anodal GVS; Sham, Sham stimulation with GVS but without the application of current; Follow-up, follow-up 2.8 months after GVS.

INDIVIDUAL THRESHOLD VALUES AND SIDE EFFECTS OF GVS

The mean current level at GVS threshold in the GVS group was 0.7 mA (range: 0.5–0.8 mA). This averaged threshold did not differ significantly between L-GVS (TP4) and R-GVS (TP5) condition ($Z = -1.0$, $p = 0.317$). A 34-items-questionnaire regarding possible side effects of GVS stimulation, which included items about fatigue, dizziness, vision and sleep disturbances, concentration difficulties, pain, skin disturbances, burning sensations, etc. (cf. Utz et al., 2011b) was read by the examiner to all six patients after every real and sham stimulation. No adverse effects were reported by any of the six experimental patients during or after GVS, except a slight tingling at the beginning of stimulation in the course of the individual threshold determination that was not negatively evaluated, but rather indicated that real current was delivered during GVS stimulation. **Table 2** summarizes the individual and mean threshold values as well as side effects in the experimental group.

BILATERAL DIFFERENT TACTILE STIMULATION

Right-hand

The analysis of extinction errors during bilateral stimulation with *different* tactile stimuli of the right-hand did not show statistically significant main effects of GVS condition/TP [$F(5,50) = 1.01$, $p = 0.424$, $\eta^2 = 0.091$] or group [$F(1,10) = 0.14$, $p = 0.718$, $\eta^2 = 0.014$] or a significant GVS condition/TP × group interaction [$F(5,50) = 1.03$, $p = 0.407$, $\eta^2 = 0.094$] (see **Figure 2A**).

Left hand

In contrast, the analysis of left hand extinction scores during bilateral stimulation with *different* tactile materials yielded a significant main effect of GVS condition/TP [$F(5,50) = 5.99$, $p = 0.003$, $\eta^2 = 0.375$], of group [$F(1,10) = 8.76$, $p = 0.014$, $\eta^2 = 0.467$] as well as a significant interaction between these two factors [$F(5,50) = 4.17$, $p = 0.015$, $\eta^2 = 0.294$]. Subsequent ANOVAs were carried out separately for the two patient groups with the factor GVS condition/TP to examine simple main effects. They yielded a significant main effect of GVS condition/TP only for the GVS group [$F(5,25) = 5.57$, $p = 0.001$, $\eta^2 = 0.527$] but not for the control group [$F(5,125) = 1.23$, $p = 0.326$, $\eta^2 = 0.197$]. Subsequent t-tests analyzing the extinction errors differences between different GVS conditions/TP in the GVS group showed significant improvements in left-sided extinction in the L-GVS [$T(5) = 7.53$, $p = 0.001$], the R-GVS [$T(5) = 3.43$, $p = 0.019$], and the Follow-up [$T(5) = 3.12$, $p = 0.024$] condition as compared to Baseline 1. Likewise, patients in the GVS group showed a less severe extinction in the L-GVS as compared to the Sham condition ($T(5) = 2.91$, $p = 0.034$). The remaining comparisons did not show any significant differences between any of the conditions (largest $T = 2.28$, smallest $p = 0.071$) (see **Figure 3A**). There were no differences between extinction errors in the L-GVS and R-GVS condition for the left hand in different materials [$T(5) = -0.63$, $p = 0.558$]. **Table 3** (below) summarizes the results of the paired comparisons in the GVS group for the left hand, for easier orientation.

BILATERAL IDENTICAL TACTILE STIMULATION

Right-hand

There were no significant effects of GVS condition/TP [$F(5,50) = 1.49$, $p = 0.211$, $\eta^2 = 0.129$], group [$F(1,10) = 0.09$,

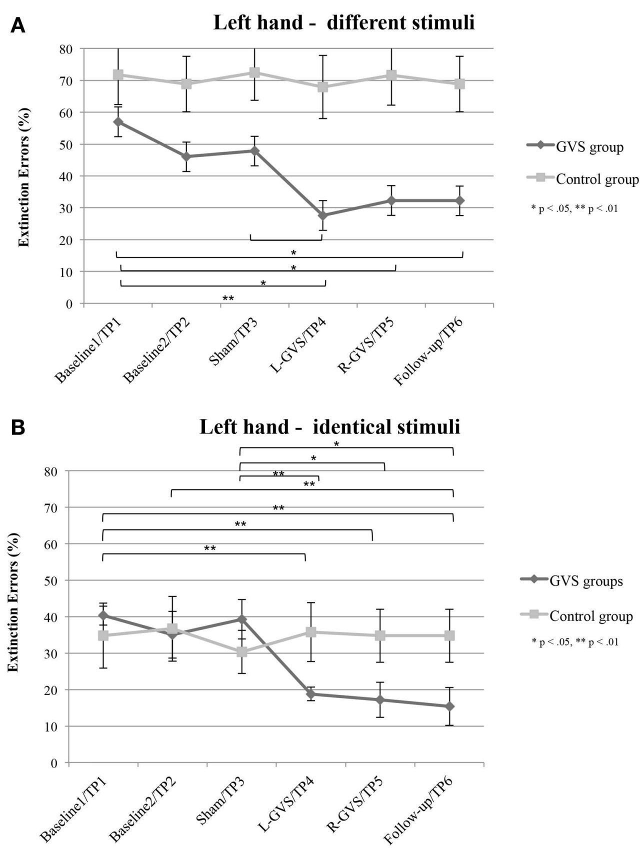

FIGURE 3 | Mean (±standard error of the mean) extinction errors (%) for the left hand in the Quality Extinction Test (QET) of the GVS group ($N = 6$) and control group ($N = 6$) across the six measurement sessions for application of *different* tactile stimuli (A) and of *identical* tactile stimuli (B). Note that apart from moderate variations in error rates no significant improvement was observed in the control group due to retesting in six subsequent sessions. Abbreviations: see legend of **Figure 2**.

$p = 0.770$, $\eta^2 = 0.009$], or of the interaction [$F(5,50) = 1.39$, $p = 0.246$, $\eta^2 = 0.122$], when analyzing error scores in the *identical* stimulation condition (see **Figure 2B**).

Left hand

The analysis of variance of errors during bilateral stimulation with *identical* stimuli revealed a significant effect of GVS condition/TP [$F(5,50) = 5.82$, $p = 0.000$, $\eta^2 = 0.368$] and of the GVS condition/TP × group interaction [$F(5,50) = 7.64$, $p = 0.000$, $\eta^2 = 0.433$] but not of the factor group [$F(1,10) = 0.72$, $p = 0.418$, $\eta^2 = 0.067$]. Further analyses of identical tactile stimuli scores yielded a significant main effect of GVS condition/TP only for the GVS group [$F(5,25) = 8.33$, $p = 0.000$, $\eta^2 = 0.625$], but not for control patients [$F(5,25) = 1.06$, $p = 0.407$, $\eta^2 = 0.175$]. Moreover, subsequent t-tests for left-sided extinction scores showed the following differences between GVS conditions for the GVS group: the initial Baseline 1 score was significantly higher than during L-GVS [$T(5) = 7.39$, $p = 0.001$], R-GVS [$T(5) = 9.49$, $p = 0.000$], and Follow-up [$T(5) = 6.52$, $p = 0.001$] and patients showed a significant improvement in left-sided extinction in the

Table 3 | Summary of paired comparisons between the different GVS conditions for the left hand of the GVS group, separately for different and identical tactile stimuli.

	Baseline 1	Baseline 2	Sham	L-GVS	R-GVS	Follow-up
DIFFERENT STIMULI						
Baseline 1	–	n.s.	n.s.	**	*	*
Baseline 2	–	–	n.s.	n.s.	n.s.	n.s.
Sham	–	–	–	*	n.s.	n.s.
L-GVS	–	–	–	–	n.s.	n.s.
R-GVS	–	–	–	–	–	n.s.
Follow-up	–	–	–	–	–	–
IDENTICAL STIMULI						
Baseline 1	–	n.s.	n.s.	**	**	**
Baseline 2	–	–	n.s.	n.s.	n.s.	n.s.
Sham	–	–	–	**	*	*
L-GVS	–	–	–	–	n.s.	n.s.
R-GVS	–	–	–	–	–	n.s.
Follow-up	–	–	–	–	–	–

L-GVS, left-cathodal/right-anodal GVS; R-GVS, right-cathodal/left-anodal GVS; Sham, Sham stimulation with GVS but without the application of current; Follow-up, follow-up 2.8 months after GVS.
$^*p < 0.05$, $^{**}p < 0.01$.

Follow-up condition as compared to Baseline 2 [$T(5) = 2.63$, $p = 0.047$]. Furthermore, we found a significant improvement in extinction scores under L-GVS [$T(5) = 5.39$, $p = 0.003$], R-GVS [$T(5) = 3.11$, $p = 0.026$], and in the Follow-up [$T(5) = 3.3$, $p = 0.021$] as compared to Sham condition. All other comparisons missed significance (largest $T = 2.54$, smallest $p = 0.054$) (see **Figure 3B**). There were no differences between extinction errors in the L-GVS and R-GVS condition for left hand in identical materials [$T(5) = 0.38$, $p = 0.722$]. **Table 3** gives a summary of the paired comparisons for the left hand in the GVS group.

ADDITIONAL ANALYSES

A closer look at data of Baseline 1 yielded that tactile extinction was significantly more severe (as shown by higher error rates in the QET) for both groups, when *different* tactile stimuli had to be discriminated on the left hand (mean: 64.3%) as compared to the condition with identical tactile stimuli [mean: 37.6%; $T(11) = -4.52$, $p = 0.001$]. No such difference was obtained for the right-hand [mean error rate for different vs. identical stimuli: 18.1 vs. 17.8%, $T(11) = 0.106$, $p = 0.918$].

Moreover, we explored to which extent the improvement of tactile extinction in the experimental group was related to chronicity of the lesions, as this differed widely in the six patients (from 2.3 to 71.2 months). **Figure 4** shows the individual graphs for the left hand extinction errors, respectively for every patient and separately for different and identical trials. All patients showed a reduction in extinction errors for different as well as for identical stimuli, either in the L-GVS or in the R-GVS condition, independently of chronicity. We calculated Pearson correlations between the chronicity of lesions and the improvement in tactile extinction for both GVS polarity conditions as compared to averaged scores of the two Baselines (mean of extinction errors in Baseline 1 and

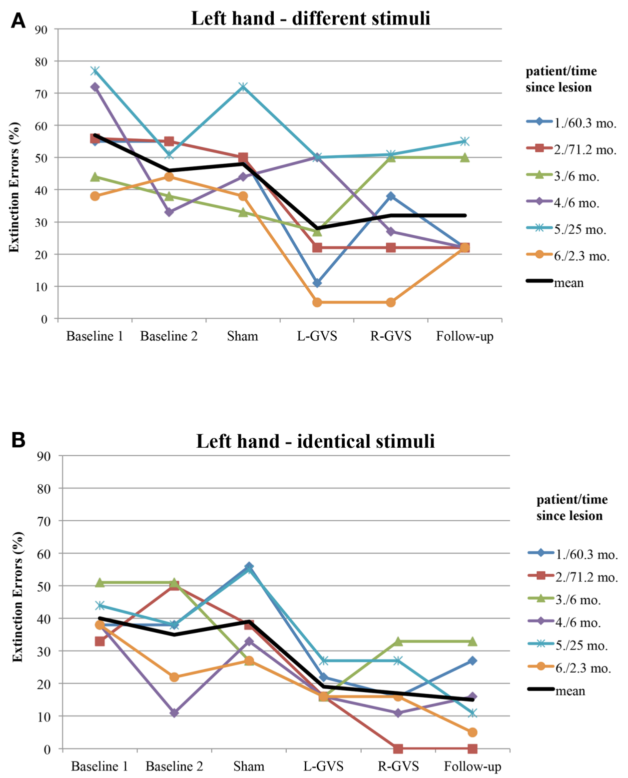

FIGURE 4 | Individual extinction errors (in degrees, averaged over 18 trials) of the six patients with left-sided extinction (GVS group) in the Quality Extinction Test (QET) across the different experimental conditions for the left arm and in relation to lesion chronicity (months), separately for application of different tactile stimuli (A) and of identical tactile stimuli (B). Abbreviations: see legend of **Figure 2**. Mo, months. For patient codes and lesion chronicity, see **Table 1**.

Baseline 2), and did not find any significant coefficients (smallest $p = 0.195$, largest $r_p = 0.61$).

In summary, patients in the GVS and control group did not differ in their right-sided extinction scores for different as well as for identical stimuli in and across any of the GVS conditions, respectively TP. By contrast, concerning left-sided extinction scores, only patients in the GVS group showed differences between experimental conditions, thus ruling out learning, test repetition, or other unspecific effects. When compared against averaged Baseline scores, L-GVS improved transiently the tactile identification of different (improvement of 50%) and of identical materials (47%) and also R-GVS led to a reduction of left-sided extinction rates for different (37%) and identical stimuli (55%). These effects remained stable at the follow-up test 2.8 months later (different: 37% over averaged Baseline scores; identical: 58% over averaged Baseline scores). Sham-GVS had no significant effect.

DISCUSSION

The present study showed the following results: (i) GVS significantly reduced tactile extinction, this effect being independent of the chronicity of lesions. (ii) We did not find polarity-specific effects of GVS on tactile extinction, as L-GVS and R-GVS significantly improved left-sided extinction to a similar extent. (iii) A small number of GVS sessions was sufficient to induce lasting changes in tactile extinction that remained stable for at least 2.8 months post-stimulation. (iv) Sham-GVS or retesting had no effect on tactile extinction, nor was there any reduction of GVS thresholds during the course of the study. (v) Patients showed differences in identification of different and identical stimuli, respectively before treatment as well as during GVS.

EFFECTS OF GVS ON BODILY AWARENESS

Both, L-GVS and R-GVS significantly reduced left-sided tactile extinction in the identification of different and identical tactile fabrics delivered during DSS. Improvements in left hand extinction during and after GVS did not occur at the expense of right-hand errors (which remained completely unchanged throughout the study). Initially, previous studies found an asymmetry of the cortical vestibular system (Dieterich et al., 2003). Therefore, galvanic inhibition of the L-GVS with excitation of the R-GVS results in *right* vestibular cortex activation whereas galvanic inhibition of the R-GVS with excitation of the L-GVS activates vestibular cortices *bilaterally*, at least in healthy subjects (Fink et al., 2003). Thus, L-GVS may lead to a more widespread cerebral activation in *both* hemispheres that could result in a greater effect on tactile extinction as compared to R-GVS. One explanation for the comparable efficiency of R-GVS and L-GVS in reducing left hand tactile extinction could be that even the weaker, unilateral activation induced by R-GVS was sufficient to improve left hand tactile extinction. In contrast, in more severe disorders such as left multimodal neglect, stronger activations may be necessary, so that R-GVS may induce less or even no significant beneficial effects (e.g., on deficits in left arm position sense, cf. Schmidt et al., 2013). Additionally, some theories view extinction as a mild form of neglect (Kaplan et al., 1995), which may be more easily influenced by any type of GVS, regardless of polarity.

In our six experimental patients we found stable improvements in tactile extinction by GVS for at least 2.8 months (Follow-up 1; improvement of 37% over averaged Baselines during different tactile stimulation; improvement of 58% over averaged Baselines during identical tactile stimulation). Furthermore, five out of these patients performed the QET in a second follow-up session 336 days [=11.2 months (mean); range: 90–750 days] after Follow-up 1. We found a persistent effect of GVS on tactile extinction performance even at this later time-point of measurement which confirms the enduring effect of this vestibular stimulation method. The persistence of improvement in tactile extinction after GVS at follow-up assessments could be explained by principles of synaptic plasticity, e.g., long-term potentiation (LTP), a well-known phenomenon of neuroplasticity induced by direct-current-stimulation (Utz et al., 2010) and make in a promising rehabilitation treatment.

Finally, Sham-GVS did not significantly influence tactile extinction, thereby ruling out placebo or unspecific effects of the stimulation procedure. Moreover, the observed modulating effects are unlikely to result from mere attentional cueing because the patients could neither feel the stimulation nor discriminate between different GVS conditions because of subliminal stimulation. This is confirmed by the fact that comparable retesting of extinction *without* GVS in the control group had no effect on extinction. Spontaneous recovery can also be ruled out as an explanation as there was no change in the QET across the two Baselines before treatment and such recovery should have occurred in both patient groups which was not found. The individual threshold was unchanged across stimulation sessions and patients did not report any adverse effects in every GVS sessions, indicating that we stimulated subliminally in each GVS session. This fact rules out potential attentional cueing effects induced by supra-threshold stimulation. Independently of this, future studies might consider whether repetitive GVS may reduce somatosensory thresholds, e.g., in pressure sensitivity, two-point discrimination, or other somatosensory capacities, as this was not the focus of the current study.

DIFFERENT VS. IDENTICAL TACTILE STIMULI

As stated in the description of the QET (see above) and shown by our data it is more difficult to identify (among six different materials) and name two *different* materials than two *identical*. In the latter condition the subject even may adopt an implicit (even unconscious) strategy where he/she decides that if both stimulations were "comparable" both materials must represent the same material. This strategy is not applicable during DSS with different tactile stimuli. We do not know whether such a mechanism was at work since all patients denied having used such a strategy during testing. Nevertheless, a closer look at the data shows a kind of double dissociation: *R-GVS* improved left-sided tactile extinction of *identical* stimuli to a greater extent (+55%) as compared to different stimuli (+37%), whereas *L-GVS* reduced left-sided extinction errors during stimulation with *different* stimuli to a greater extent (+50%) as compared to identical stimuli (+47%), although these differences between the groups and materials were not significant. This trend corresponds to the results in our previous case studies (Kerkhoff et al., 2011), though not to a significant extent. It seems plausible to assume that R-GVS is strong enough to modulate extinction of *identical* trials but only L-GVS leads to such a strong bi-hemispheric activation that it can influence extinction in the more demanding condition with *different* tactile materials in the QET. As discussed in our earlier case studies (Kerkhoff et al., 2011), the greater effect of L-GVS on different stimuli in the QET could be explained by the fact that L-GVS activates perisylvian cortices in *both* hemispheres, hence also in the language-related areas of the left perisylvian cortex of the patients that is needed for the verbal output during extinction testing. In line with this hypothesis, the developers of the QET (Schwartz et al., 1979) proposed that "During the extinction tests a response mechanism in the left (speech) hemisphere bases its perceptual output on the relative strengths of two simultaneous sensory inputs. Damage at any point in the channel from the periphery to the response mechanism weakens one signal in comparison to the other, resulting in a response bias favoring the stronger stimulus" (Schwartz et al., 1979, p. 681f). Thus, GVS may have modulated the different "strengths" of the unimanual tactile inputs during extinction testing at various processing stages in the brain.

IMPLICATIONS FOR REHABILITATION

Apart from the above discussed mechanisms of GVS on tactile extinction, GVS may speed up tactile discrimination learning *during* DSS, which did not occur after mere test repetitions *without* GVS, as shown in **Figures 2** and **3** in the control group. This may reflect another interesting and testable hypothesis for future studies as somatosensory deficits and extinction are frequently encountered after brain damage (Van Stralen et al., 2011). Due to long-lasting effects of GVS, it may be used as an add-on-treatment in combination with other trainings of somatosensory deficits for rehabilitation. Whatever the precise mechanism of improvement induced by GVS, our results are compatible with the hypothesis that GVS permanently changed the relative strengths of the tactile inputs from both hands. This may result either from an enhancement of left hand-input and/or a reduction of right-hand-input, or another kind of re-weighting of both inputs. Importantly, the improved discriminations observed on the left hand did not occur at the expense of a deterioration in right-hand performance. Moreover, as GVS had similar beneficial effects on left-sided tactile extinction in all of our six patients (see **Figure 4**) – despite their different brain lesions and their different lesion chronicity (see **Table 1**) – it appears that treatment effects induced by GVS do not rely on a particular lesion area in order to occur. This makes GVS an interesting candidate for further treatment studies of tactile extinction and related body cognition disorders.

Our study extends earlier findings on the modulation of tactile extinction using the same extinction test but another stimulation technique: RPMS (Heldmann et al., 2000). Following one session of RPMS, left hand tactile extinction was on average reduced by some 28% in seven extinction patients while right-hand scores remained unchanged. In contrast, attentional cueing to the left side in a comparable group with seven other extinction patients had no beneficial effect on left hand extinction scores but increased right-hand errors significantly. Due to clinical limitations no repetitive RPMS sessions could be delivered in these patients so that the authors could not evaluate longer-lasting therapeutic effects of RPMS. As this technique is widely available in many neurology or neurorehabilitation clinics (which is, in fact, technically identical to transcranial magnetic stimulation, TMS), RPMS, and GVS may induce similar therapeutic effects on tactile extinction. Interestingly, both activate – among other brain areas – motor cortex and parietal areas (Struppler et al., 2007; Lopez et al., 2012a), the latter being one cortical projection area of somatosensory pathways and hypoactivation of SII is associated with tactile extinction (Remy et al., 1999). Both RPMS and GVS might thus alleviate tactile extinction – transiently or permanently – by increased activation of this under-activated brain area. This mechanism may occur either by an improved "bottom-up interpretation" of tactile information from both stimulated hands in extinction, or by improved "top-down interpretation" of these signals, or by both mechanisms simultaneously, as suggested recently by Ferrè et al. (2011a). Principles of synaptic plasticity, e.g., LTP, induced by repetitive stimulation may then lead to lasting changes, both on the physiological and behavioral level.

VESTIBULAR CORTEX AND VESTIBULAR STIMULATION

Neurophysiological studies in primates all have indicated the parietal lobe as the main projection area of vestibular input, with other additional subcortical and cortical projection zones (for a review, see Lopez et al., 2012b). Electrical stimulation of the vestibular nerve showed a cortical projection to Brodman area 2 (Schwarz and Fredrickson, 1971) and evoked potentials showed cortical activations in Brodman area 3 (Ödkvist et al., 1974). Functional imaging studies using caloric vestibular stimulation show activations in areas of the perisylvian cortex including the insula and retroinsular cortex, the temporo-parietal cortex, the putamen, somatosensory area II (Bottini et al., 2001), as well as in the intraparietal cortex (Suzuki et al., 2001; Chokron et al., 2007). In accordance with these activations, numerous studies using caloric vestibular stimulation have shown a beneficial influence on neglect and neglect-related disorders such as tactile extinction (Vallar et al., 1993), somatoparaphrenia (Rode et al., 1992), or unawareness of hemiplegia (for a review, see Vallar et al., 2003). Interestingly, caloric vestibular stimulation modifies the body schema (tactile distance estimation and hand-shape judgments; Lopez et al., 2012b) and also enhances somatosensory functions transiently in the *healthy* brain, when very demanding, fine discriminations (detecting a stimulation with a von Frey hair) were required (Ferrè et al., 2011a,b). The authors speculated that vestibular stimulation might have achieved this increase in sensitivity by way of a cross-modal enhancing mechanism. Such mechanisms are well-known for other modalities, e.g., visual and auditory integration (Meredith and Stein, 1986).

CONCLUSION

In conclusion, two sessions of real (verum), subliminal GVS induced a significant and enduring improvement in tactile extinction in six patients with right-hemisphere brain lesions, thus enhancing tactile awareness permanently on their contralesional body side. This beneficial effect ranged up to a level of postsensory processing of bilateral tactile input onto a verbal output level. To our knowledge, this is the first study that reports a long-lasting, therapeutic reduction of tactile extinction in a patient group following a systematic intervention. As subliminal GVS produced no serious side effects in this and other studies (Utz et al., 2011b) it is convenient for *repetitive* stimulations, i.e., in treatment studies. Moreover, subliminal GVS is painless, non-invasive, safe, easily applicable, and elegantly allows the realization of placebo/Sham stimulation without the patient being aware of any stimulation or of the cessation of stimulation. Furthermore, GVS shows other beneficial modulation effects in treatment of neglect, extinction, and related disorders: it reduces, albeit transiently, the ipsilesional bias in line bisection (Utz et al., 2011a), normalizes deficits in left arm position sense in left neglect within one 20-min sessions of GVS for at least 20 min post-stimulation (Schmidt et al., 2013), and multi-session GVS reduces tactile related spatial deficits in a case study of a pusher patient with left neglect (Volkening and Keller, 2012) as well as deficits in target cancelation in two patients with visuo-spatial neglect (Zubko et al., 2013). Therefore, repetitive GVS is a promising treatment approach that could enhance the rehabilitation of body- and space-related disturbances associated with right-hemisphere lesions.

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Transcutaneous electrical nerve stimulation effects on neglect: a visual-evoked potential study

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We studied the effects of transcutaneous electrical nerve stimulation (TENS) in six right-brain-damaged patients with left unilateral spatial neglect (USN), using both standard clinical tests (reading, line, and letter cancelation, and line bisection), and electrophysiological measures (steady-state visual-evoked potentials, SSVEP). TENS was applied on left neck muscles for 15′, and measures were recorded before, immediately after, and 60′ after stimulation. Behavioral results showed that the stimulation temporarily improved the deficit in all patients. In cancelation tasks, omissions and performance asymmetries between the two hand-sides were reduced, as well as the rightward deviation in line bisection. Before TENS, SSVEP average latency to stimuli displayed in the left visual half-field [LVF (160 ms)] was remarkably longer than to stimuli shown in the right visual half-field [RVF (120 ms)]. Immediately after TENS, latency to LVF stimuli was 130 ms; 1 h after stimulation the effect of TENS faded, with latency returning to baseline. TENS similarly affected also the latency SSVEP of 12 healthy participants, and their line bisection performance, with effects smaller in size. The present study, first, replicates evidence concerning the positive behavioral effects of TENS on the manifestations of left USN in right-brain-damaged patients; second, it shows putatively related electrophysiological effects on the SSVEP latency. These behavioral and novel electrophysiological results are discussed in terms of specific directional effects of left somatosensory stimulation on egocentric coordinates, which in USN patients are displaced toward the side of the cerebral lesion. Showing that visual-evoked potentials latency is modulated by proprioceptive stimulation, we provide electrophysiological evidence to the effect that TENS may improve some manifestations of USN, with implications for its rehabilitation.

Keywords: steady-state VEP, TENS, neglect, proprioceptive stimulation, neglect rehabilitation

INTRODUCTION

Transcutaneous electrical nerve stimulation (TENS) is a form of low-voltage stimulation historically used for therapeutic purposes, especially for pain relief (Sedan and Lazorthes, 1978; Dubinsky and Miyasaki, 2010; Rode et al., 2012). In the last decades, TENS was applied also in right-brain-damaged patients with left unilateral spatial neglect (USN), stimulating the contralesional side of the patient's body, typically on the left neck muscles, but also on the left hand. Vallar et al. (1995) assessed the effects of TENS on left USN, using visual-motor exploratory tasks (letter cancelation): left neck stimulation temporarily improved the deficit in 13 out of 14 (93%) patients, while stimulation of the right neck had no positive effects, actually worsening exploratory performance in 9 (64%) patients. The temporary positive effects of left TENS extend to the left somatosensory deficits of right-brain-damaged patients, with and without left visual USN (Vallar et al., 1996). Right-sided TENS had no effects on the right somatosensory deficits of left-brain-damaged patients, with the exception of one left brain-damaged patient with right neglect, in whom the right somatosensory deficit was temporarily improved (Vallar et al., 1996). In sum, TENS may ameliorate both visual USN, and USN-related somatosensory deficits (Vallar, 1997, 1998). These beneficial effects of TENS on various manifestations of left USN have been confirmed by a number of successive studies (Guariglia et al., 1998, drawing by copy and from memory, shape comparison, familiar square description; Guariglia et al., 2000, spatial orientation by shape; Pérennou et al., 2001, neglect-related postural instability; see also Richard et al., 2001, for positive effects in patients with left USN on the rightward deviation of the straight ahead, with TENS delivered to the left sole; Beschin et al., 2012, with effects on both left USN and anosognosia for hemiplegia, although not in all tested patients). There is also evidence that TENS may be effective for rehabilitating left USN (Schröeder et al., 2008). One negative result is on record (Karnath, 1995). TENS, in sum, modulates, with direction-specific effects, a number of manifestations of the USN syndrome, as other side or direction-specific stimulations do (see reviews in Vallar, 1997; Rossetti and Rode, 2002; Kerkhoff, 2003; Rode et al., 2006; Chokron et al., 2007).

The specific mechanisms underlying these effects on a number of manifestations of the USN syndrome may include the restoration of defective representations of the side of space contralateral to the lesion (contralesional), and of the ability to orient spatial attention contralesionally, through complex patterns of activation of both the damaged right hemisphere (RH), and the contralateral left hemisphere, with differences related to the specific stimulation delivered to the patient (Bottini et al., 1995; Luauté et al., 2006; Saj et al., 2013). The directional-specificity of the effects of these stimulations on the different manifestations of the USN syndrome, as well as some evidence for their selectivity (Vallar et al., 1995, 1996), suggests that these effects cannot be considered "placebo" and that general cerebral activation is not the main mechanism supporting it.

In most of the studies showing amelioration of USN after TENS, the deficit was assessed in the visual modality, suggesting that the effects of the stimulation may extend to visual areas. There is electrophysiological (visual-evoked potentials, VEP) evidence from right-brain-damaged patients with left USN that the earliest responses of the RH striate and extra-striate areas to contralesional left-sided visual stimuli may be largely preserved (Vallar et al., 1991; Di Russo et al., 2008). Conversely, later right hemispheric electrophysiological activities in the visual areas (namely, parietal activity and top-down re-activation of extra-striate and striate areas) are reduced in amplitude, and delayed in latency, as compared with the corresponding activity in the left hemisphere (Di Russo et al., 2008, 2012). Such hemispheric differences decrease with recovery from USN following visual-spatial rehabilitation training (Di Russo et al., 2012). Thus, VEP hemispheric asymmetries appear a good marker of the reduction of USN. While Di Russo et al. (2012) focused on the effects of a diversified, multiple-inputs training procedure, lasting about 8 weeks (Pizzamiglio et al., 2006), the present study investigates the effects of a single, brief procedure of peripheral stimulation, namely TENS, at the level of visual cortical responses, to elucidate how the effects of TENS build up, as indexed by VEPs.

We used steady-state visual-evoked potentials (SSVEPs) because this technique is suitable under conditions of limited recording time (as in brain-damaged patients) allowing recording of 100 responses to stimulus repetition in about 1 min (conversely, transient VEPs would require 5–10 min). SSVEPs are the averaged responses to repetitive visual stimulation flickering at high temporal frequency; thus, they provide information about cortical activity patterns related to sustained visual experience. Indeed, the correlation between the SSVEP amplitude and psychophysical contrast threshold is a major indicator of the link between brain electrical activity and visual perception (Campbell and Maffei, 1970). A limitation of the SSVEP method is that, averaging together all different components of the visual response (which are, in contrast, well isolated by transient VEP) does not allow to discriminate between them. fMRI evidence shows that the major sources of SSVEP are V1 and MT/V5 (Di Russo et al., 2007). Nevertheless, as long as visual perception depends on the loop between early and higher-order visual areas, and on the combination of early activation and late re-activation of the same visual areas (e.g., Lamme, 2006), SSVEP, averaging all these activities, is a good candidate to represent an electrophysiological counterpart of visual perception.

Furthermore, previous studies in brain-damaged patients with left spatial neglect, based on SSVEP recording to stimuli located in the left and right visual half-fields (LVF and RVF), have shown that responses to LVF stimulation are delayed as compared with RVF stimulation (e.g., Spinelli et al., 1994). Finally, leftward rotation of the trunk – a maneuver than improves some manifestations of left USN – reduces the disproportionate longer latencies of SSVEP to visual stimuli delivered in the LVF of right-brain-damaged patients with left USN (Spinelli and Di Russo, 1996). In this study, we measured SSVEP asymmetries in right-brain-damaged patients with left USN before, immediately after, and 1 h after TENS.

MATERIALS AND METHODS

PARTICIPANTS

Six right-brain-damaged patients with chronic left USN, and 12 healthy young controls (6 females, age 27.3 ± 2.3 years) participated in the study. Patients were recruited from the Neuropsychological Unit of the Santa Lucia Foundation, Roma, Italy. Demographic and clinical data of the patients are reported in **Table 1**. All patients had intact visual fields, based on standard kinetic perimetry. All patients had unilateral vascular lesions, summarized in **Table 2**. Lesions were large and heterogeneous, generally involving several cortical and sub-cortical areas. Patients with lesions involving the visual areas were not included. Only one patient had occipital damage (**Table 2**, Patient #2), which, however, did not involve early visual areas. As described in **Table 2**, areas V1 (BA17) and V2 (BA18) were totally spared, while extra-striate areas V3 and V3A (BA19) were mostly spared. Moreover, objective functional testing of visual responses to LVF stimuli showed in this patient the same electrophysiological pattern observed in the other patients. For these reasons the patient was included in the study. All participants were right-handed and had normal or corrected-to-normal visual acuity. Informed consent was obtained from each participant, and the study was approved by the local ethics committee of the Santa Lucia Foundation.

Table 1 | Demographic and clinical data for the neglect patients.

Patient #	Sex/age	TFO	Line canc	Lett canc	WJ	Sent read	Line bisect
1	M/69	132	+	+	+	+	+
2	F/77	143	+	+	+	+	+
3	F/68	101	+	+	+	+	+
4	M/81	176	−	+	+	−	+
5	M/68	162	+	+	+	+	+
6	M/60	114	+	+	−	+	+
Mean	70.5	138					

TFO, time from onset (days). Neglect tests: Line canc; line cancelation; Lett canc, letter cancelation; WJ, Wundt–Jastrow; Sent read, sentence reading; Line bisect, line bisection. The sign + identifies pathological performances according to standard normative values, while the sign − indicates performance above the cut-off (Pizzamiglio et al., 1989).

Table 2 | Lesion localization in the six neglect patients (see Materials and Methods for further details).

Patient #	Sites of lesions in the right hemisphere (RH)
1	Middle and posterior superior temporal gyrus, parahippocampal temporal gyrus, posterior half of cingulate gyrus
2	Inferior (supramarginal and angular gyri) and superior parietal lobule, superior temporal gyrus, mesial (supracalcarine) and lateral superior occipital region, occipital paraventricular area (areas 17 and 18 were totally spared, area 19 was mostly spared)
3	Superior temporal gyrus, precentral gyrus, and posterior sector of the frontal gyrus (primary and supplementary motor cortex), anterior cingulate cortex, pars opercularis of the frontal operculum
4	Precentral (primary sensory cortex), and frontal gyrus
5	Precentral and postcentral gyrus and posterior sector of frontal gyrus (primary sensory cortex, primary and supplementary motor cortex), superior temporal gyrus, posterior half of cingulate gyrus, inferior (supramarginal gyrus) parietal lobule, temporal pole, frontal operculum
6	Precentral and postcentral gyrus and posterior sector of the frontal gyrus (primary sensory cortex, primary and supplementary motor cortex), inferior (supramarginal gyrus) and superior parietal lobule, pars opercularis of the frontal operculum, superior temporal gyrus, posterior half of cingulate gyrus

BEHAVIORAL TESTS

Patients performed the following tests:

1. Lines cancelation test (Albert, 1973). Participants were requested to cross 21 line segments randomly arranged on a sheet of white paper (11 on the left and 10 on the right). The score was the number of left and right crossed segments.
2. Letters cancelation test (Diller et al., 1980). Participants were requested to cross 104 letter H randomly arranged on a sheet of white paper (53 on the left- and 51 on the right-hand-side), intermingled with other distracter letters (a total of 208 non-targets). The score was the number of left- and right-sided crossed target letters.
3. Sentence reading test (Pizzamiglio et al., 1989). Six sentences of differing lengths were presented to each patient (e.g., The train goes from one city to another in 8 h) who was requested to read aloud each sentence. The score was the number of sentences correctly read. Hesitations, self-corrections or paralexias were not counted as errors.
4. Wundt–Jastrow area illusion test (Massironi et al., 1988). The stimuli were two semicircular fans of identical shape and size. Ten sizes (ranging from 6 to 58 cm), two orientations (upward-downward convexity), and two directions (leftward-rightward) were used, for a total of 40 stimuli. The participant's task was to indicate which fan was longer. Responses were classified in two categories: "expected responses," those consistent with the illusory effect in healthy participants; "unexpected responses" those not consistent with the illusory effect. The score was the number of "unexpected" responses, when the two fans were oriented toward the left or the right.
5. Line bisection (Albert, 1973). Participants were requested to mark with a soft pen the subjective midpoint of a 15 cm long and 1 mm wide horizontal line drawn on a centimeter paper. The test was repeated for 25 times. In each trial the participant's deviation was measured to the nearest millimeter, scored as a leftward/rightward (−/+) deviation from the objective mid-point of the segment. The score was the average participant's deviation from the objective midpoint.

The presence of USN was assessed using the first four tests, according to the standard neuropsychological battery of Pizzamiglio et al. (1989). Patients who failed on at least two out of four tests were classified as USN patients. For experimental purposes, four tests were administered pre- and post TENS stimulation (Line cancelation, Letter cancelation, Sentence reading, and Line bisection; see Data Analysis for further details). The Wundt–Jastrow Illusion was used for diagnostic purposes only.

ELECTROPHYSIOLOGICAL MEASURES

Stimuli

Stimuli were displayed on a monitor (Barco CDCT 6551) with mean luminance of 16.5 cd/m^2 and frame rate 100 Hz. A cross in the center of the display served as fixation point. The stimulus was a horizontal sinusoidal 0.6 cpd grating of 80% contrast, 20° wide, and 20° high. The grating was displayed in separate runs in LVF and RVF. The edge of the grating was 1.5° to the fixation point. The steady-state VEP was elicited by grating contrast that was reversed sinusoidally at nine temporal frequencies (5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9 Hz).

VEP recordings

Visual-evoked potentials were recorded from scalp electrodes, Oz active with Cz as reference and Pz as ground. Signals were amplified (50,000-fold), band-pass filtered (1–100 Hz) and digitized at 64 points/period. The SSVEP waveform is roughly sinusoidal and is well described by the amplitude and phase of the second harmonic Fourier component. The SSVEP phase changes with temporal frequency; the apparent latency may be derived by measuring the phase as a function of temporal frequency, and estimating the slope of the curve (Spekreijse et al., 1977). The phase of the second harmonic is plotted in p radians as a function of temporal frequency under the assumption that phase advances or retard regularly with temporal frequency. Thus, multiple of 2p radians are added or subtracted to the raw data, in order to produce the maximum orderliness. The technique used in the present study was developed by Burr and Morrone (see Spinelli et al., 1994 for details). The computer performed on-line Fourier analysis to calculate the amplitude and the phase of the second harmonic component. At the same time, the computer averaged the electrical signals at a temporal frequency near that of the stimulus but not synchronously with it. This was taken as an index of noise and artifacts, to assess VEP reliability. For each packet of 20 sums (20 periods of stimulus presentation) the signal-to-noise ratio was calculated. As an independent measure of variability the standard error of the amplitude and phase was calculated from the two-dimensional scatter in amplitude and phase of the individual 20-sum packet. The apparent latency was estimated from the slope of the regression line of phases as a function of temporal frequency. The slope was calculated by least-squares fit, after weighting each data point by its signal-to-noise ratio.

TENS APPLICATION

Transcutaneous electrical nerve stimulation was applied to participants using an AGAR 2000™ stimulator with two disk electrodes (diameter 30 mm) located (15–20 cm apart) on the left superior trapezium muscle. The stimulation frequency was 100 Hz and the pulse duration was 100 μs. The mean intensity was 0.5 μA/mm. We did not include a right-sided TENS condition, since there is evidence that this side of stimulation is ineffective, or may actually worsen the deficit of USN patients, making the procedure unethical (Vallar et al., 1995, 1996).

PROCEDURE

The session started with the VEP recording to LVF and RVF stimuli, followed by the behavioral testing; four tests were administered to the patients, while healthy participants performed only the line bisection test (termed PRE condition). Then, the TENS was administered for 15 min. Immediately after TENS, VEPs to LVF stimuli were recorded, and the behavioral testing were administered again (POST condition). One hour after the termination of TENS, VEPs to LVF and the behavioral testing were administered again (POST60′ condition).

DATA ANALYSIS

Behavioral laterality score

For the line and letter cancelation tests, the laterality score was the difference between the number of canceled items on the left and on the right-hand-sides. Positive scores denoted more omissions in the left-half than in the right-half of the sheet. Reading errors were classified as left-sided or right-sided, depending to their position, with respect to the center of each sentence, which was aligned with the center of the sheet of paper. The laterality score was the difference between the number of errors in the left- and in the right-hand-side of the sentence. Positive scores indicated more reading errors in the left-half than in the right-hand-side of the sentence. Line bisection test directly expressed the value of asymmetry. Positive values indicated a rightward bias of the subjective midpoint. To verify the presence of asymmetry in the PRE condition, preliminary analyses compared the responses to left- and right-sided stimuli in behavioral tests. These scores in the PRE, POST, and POST60′ times were submitted to one-way ANOVAs.

Steady-state visual-evoked potential

It is known that, when comparing the LVF and RVF recordings of USN right-brain-damaged patients, the deficits are usually limited to LVF, while recordings to stimuli in the RVF are within normal limits (e.g., Di Russo et al., 2012). For this reason (as typically done in studies in brain-damaged USN patients) the more appropriate control of the LVF recordings are RVF recordings. Healthy participants were examined in this study just in order to assess the presence of the behavioral and electrophysiological effects of TENS in healthy people, not to compare their data with those of USN patients.

In order to assess the presence of VEP lateral asymmetries in the PRE condition, a preliminary analysis compared electrophysiological responses to LVF- and RVF- stimuli. Apparent latencies were submitted to one-way ANOVAs with Hemifield as factor. VEP amplitudes were submitted to a ANOVA with Hemifield and Temporal Frequency (nine levels 5–9 Hz) as factors. To evaluate the effect of TENS, the LVF amplitude at the peak, and the LVF apparent latency were submitted to one-way ANOVAs with the TENS factor at three levels (PRE, POST, and POST60′). An additional analysis used the values of asymmetry between LVF, tested in PRE, POST, and POST60′ conditions, and RVF baseline (PRE condition). Asymmetry was quantified for peak amplitude and apparent latency. The values of asymmetry were submitted to one-way ANOVAs with the TENS factor at three levels (PRE, POST, and POST60′).

In both behavioral and SSVEP analyses, *post hoc* comparisons were made using Newman–Keuls test. The overall alpha value was fixed at 0.05 after Greenhouse–Geisser correction.

RESULTS

BEHAVIORAL DATA

Figure 1 shows the effects of TENS in the reading and cancelation tests in the six brain-damaged USN patients; the right side of **Figure 2** shows the patients' average error (mm) in line bisection. In all tests we found a significant effect of TENS [$F_{(2, 10)} > 5.53$, $p < 0.05$] on performance asymmetry. *Post hoc* comparisons showed that the asymmetry was reduced after the TENS (PRE > POST, $p < 0.05$), and returned to the PRE

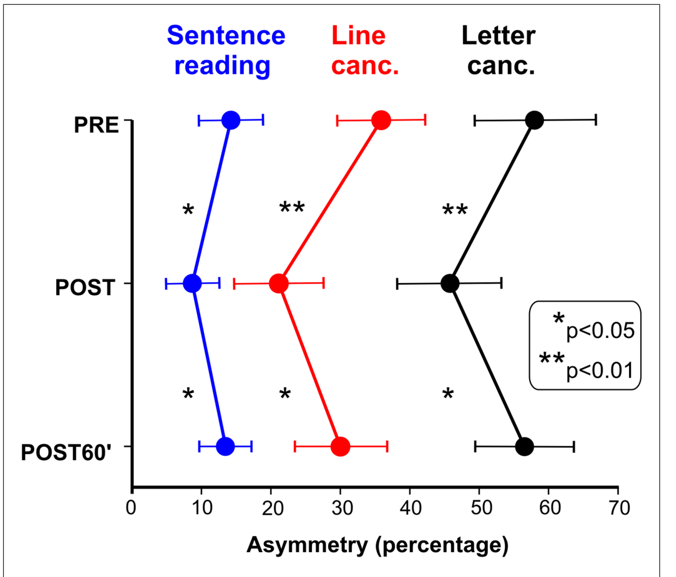

FIGURE 1 | Effect of TENS on neglect patients' performances in sentence reading, line cancelation, and letter cancelation tests. Scores: percent of omitted left minus right targets (positive values indicated more omissions in the left side of space).

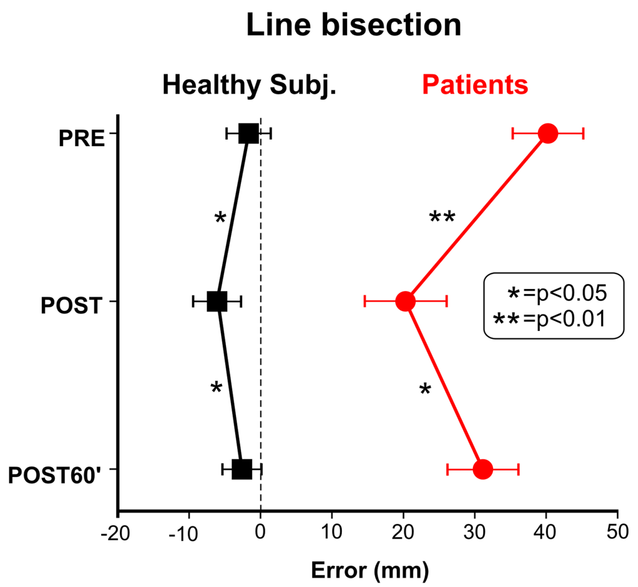

FIGURE 2 | Effect of TENS on line bisection performance of healthy subjects and neglect patients. Positive values indicate a rightward shift of the subjective midline.

stimulation level 1 h after it [POST < POST60′, $p < 0.05$]; PRE and POST60′ conditions did not significantly differ. Also in healthy participants the effect of TENS on the line bisection was significant [$F_{(2, 22)} = 33.1$, $p < 0.0001$]. The bisection error (left hand-side of **Figure 2**) was on average −1.5 mm before the stimulation; after TENS it was about −6 mm [only this latter value was different from the ideal performance (i.e., complete accuracy; t-test against zero, $t_{11} = 3.3$, $p = 0.0034$)]. One hour after TENS the mean deviation was about −2.5 mm. As for patients, the deviation in the POST condition differed from those in the PRE and in the POST60′ conditions ($p = 0.0012$), which did not differ from each other. In sum, the performance of the six right-brain-damaged USN patients improved in Line (44%), and Letter (19%) cancelation, in Sentence Reading (31%), and in Line Bisection (44%), after stimulation (post-treatment interval). On average, we found an improvement of 35% which is somehow comparable to the clinical amelioration found in previous studies using daily vibration TENS therapy (e.g., Johannsen et al., 2003: 25% in the Letter cancelation test and 29% in the Bell Test).

ELECTROPHYSIOLOGICAL DATA

Figure 3 show the average VEP amplitude (left panel) and apparent latency (right panel) superimposing the data of the patients' and control groups, and, for patients, showing the data in the three conditions.

The amplitudes had the typical tuning function, with larger amplitudes around 7–8 Hz, and smaller amplitudes at lower and higher frequencies. The comparison between LVF and RVF amplitudes of the patients' group in the PRE condition indicated that the difference was significant only at the peak of the functions (7.5 Hz), as shown by interaction between Hemifield and Temporal frequency $F_{(8, 40)} = 3.9$, $p = 0.0018$. For this reason only the peak amplitude was considered in the following analyses. The effect of TENS on the amplitude of the LVF responses of patients did not reach the significant level [$F_{(2, 10)} = 2.16$, $p = 0.17$]. Healthy participants, as expected, did not show any difference in the PRE condition between LVF and RVF; moreover, the effect of TENS was not significant (all $ps > 0.54$).

The apparent mean latency (right panel of **Figure 3**) in the PRE condition was 120 ms for the RVF and 160 ms for the LVF in USN patients; this difference was significant [$F_{(1, 5)} = 22.45$, $p = 0.0051$]. The effect of TENS on latencies was significant [$F_{(2, 10)} = 52.9$, $p < 0.0001$]; LVF response latencies in the POST condition (126 ms) were faster ($ps < 0.0019$) than in the PRE (160 ms) and POST60′ (157 ms) conditions. The latter two values did not differ from each other ($p = 0.16$). In healthy participants, LVF and RVF apparent latencies (both about 105 ms) did not differ from each other [$F_{(1, 11)} > 1$, ns]. The effect of TENS was significant [$F_{(2, 20)} = 7.31$, $p = 0.0041$]. The LVF response latency in the POST condition (98 ms) was shorter ($p < 0.0063$) than in the PRE (105 ms), and in the post POST60′ (104 ms) conditions, with the latter latencies being comparable.

Figure 4 shows the VEP data as LVF-RVF asymmetries. Regarding the amplitude (left panel of **Figure 4**), in the patients' group, TENS reduced the asymmetry, pushing the POST values toward the dashed vertical line (zero asymmetry). In healthy participants, the asymmetry tends to increase after TENS (the POST values shift away from the dashed vertical line), although the effect was not significant, both in patients and in healthy participants (all $ps > 0.49$). Regarding the apparent latency, TENS significantly modulated the asymmetry in USN patients [$F_{(2, 10)} > 19.27$, $p = 0.0004$]. The asymmetries of both the PRE and the POST60′ conditions were larger than that of the POST condition ($p < 0.0005$), which did not differ from each other. Also in healthy participants, TENS modulated the hemifield asymmetries [$F_{(2, 22)} = 17.7$, $p = 0.0003$]. The asymmetry in the POST condition (6 ms) was larger ($p < 0.015$) than the other two conditions, which did not differ each other. In summary, patients showed an average improvement of 22% in the VEP latency asymmetry, after stimulation (post-treatment interval).

DISCUSSION

The present results first confirm previous observations (Vallar et al., 1995, 1996; Guariglia et al., 2000), showing that TENS brings about a temporary amelioration of left USN, as measured by standard clinical tests. Notably, the present findings are unlikely to reflect a sort of placebo effect. Contrary to this interpretation, there is evidence that the effects of TENS crucially depend on the side of the input, namely: left, but not right, neck stimulation is effective in temporarily reducing both left USN as assessed by visuo-spatial exploratory tasks (Vallar et al., 1995), and the USN-related component of somatosensory deficits (Vallar et al., 1996).

Second, we report a novel finding, namely an effect of TENS on the electrophysiological cortical activity evoked by stimuli in the left "neglected" half-field. Indeed, in the PRE condition, the apparent latency of VEPs to LVF stimuli was longer than to RVF. After TENS the LVF latency became much shorter (with an average reduction of 22%). A similar, although not significant, trend was

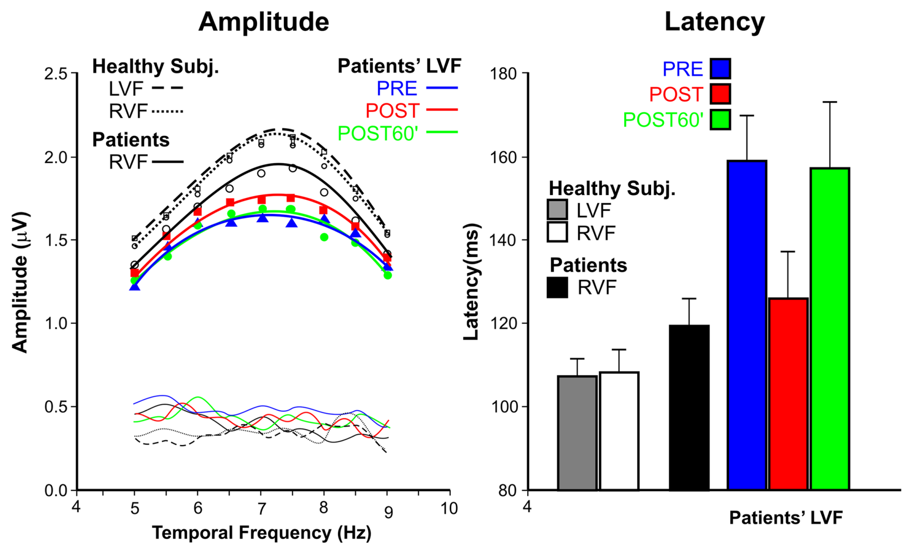

FIGURE 3 | Steady-state visual-evoked potential data. Left panel: amplitudes as function of temporal frequencies for patients with spatial neglect and healthy subjects. For patients, the LVF responses are reported in PRE, POST, and POST60′ conditions. Thin lines without symbols represent the noise levels. Right panel: apparent latencies; as for amplitude, the data are reported in the three tested conditions.

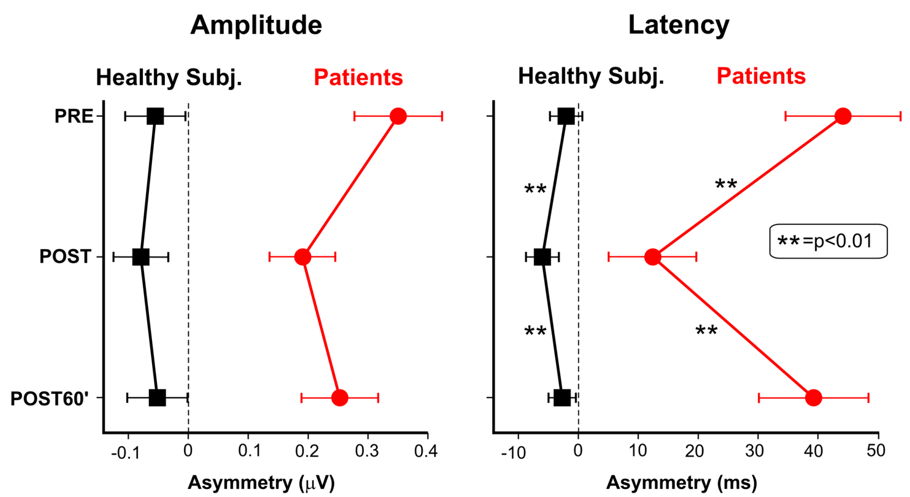

FIGURE 4 | Asymmetry of the cortical responses to stimuli in the two hemifields in healthy subjects and neglect patients. Asymmetry is measured as difference between baseline RVF responses (PRE condition) and LVF responses measured in the three conditions (PRE, POST, and POST60′). The left panel shows the TENS effect on the amplitude at the peak temporal frequency (7.5 Hz). The right panel shows the TENS effect on apparent latency.

present also for signal amplitude, which appears to be a less sensitive index in this respect (see discussion in Di Russo and Spinelli, 2002). Indeed, most of the studies investigating SSVEPs in right-brain-damaged patients with left USN found increased latencies for LVF stimulation, with no effects (Spinelli et al., 1994) or less specific effect (Angelelli et al., 1996) on amplitude.

One may wonder whether such an electrophysiological result reflects a TENS modulation of early or late visual processing. There is evidence from two electrophysiological studies with transient VEPs, using large electrodes array and focal stimuli in the four visual quadrants, which allow a fine discrimination of the VEP components (Di Russo et al., 2008, 2012), that the early components (peaking at 75 and 100 ms) are largely preserved in non-hemianopic USN right-brain-damaged patients. This suggests that visual processing in early striate and extra-striate areas is preserved. In contrast, the visual components peaking at 130, 180, and 250 ms show a definite left-right asymmetry. Furthermore, there is evidence (Di Russo et al., 2012) that early components are not affected by visual-spatial training, which, in turn, reduces the hemispheric asymmetry of the later components. SSVEPs do not allow to isolate different processing levels; indeed, by averaging responses across time, and overlapping bottom-up and top-down activities, they provide a single, overall, value of latency related to the neural processing that takes place in the visual areas (e.g., Störmer et al., 2013). So, at which level the reduction of the lateral spatial asymmetry characterizing USN may occur? The present experiment cannot exclude a direct effect of TENS on the early responses of the visual cortices; however, taking into account the values of response latency to stimuli displayed in the LVF before (160 ms) and after (126 ms) TENS, it seems likely that an important portion of the effect is due to post-sensory components. The bottom-up 130 component (possibly generated in dorsal IPS, and representing a likely candidate in the hemispheric race for priority, Marzi et al., 2000), and the top-down re-entrant feedback on striate and extra-striate areas (components peaking at 180 and 250 ms) might contribute to the effect.

The suggestion has been made (Corbetta et al., 2005) that the dorsal parietal system, anatomically intact in most USN right-brain-damaged patients (Vallar, 2001; Committeri et al., 2007), is dysfunctional as a consequence of damage to the ventral posterior parietal regions (i.e., the inferior parietal lobule). In the present study we observed behavioral and electrophysiological asymmetries in the horizontal meridian space. This was shown in patients without hemianopia and without lesions in early visual areas (see **Table 2**). Therefore, the USN patients' performance cannot be attributed to the inability to compensate for a visual field deficit occurring at an early stage, such as in patients with left USN and left hemianopia (e.g., Doricchi et al., 2003). There is evidence from both monkeys (e.g., Galletti et al., 1996; Page and Duffy, 2003) and humans (e.g., Sereno and Huang, 2006; Bolognini and Maravita, 2007; Smith et al., 2012; Pitzalis et al., 2013), that a number of dorsal parietal areas (VIP, V6A, 2v) are involved in integrating vestibular, somatosensory, and visual inputs. This multimodal dorsal parietal network may receive additional strong and asymmetric inputs by TENS, and would temporarily enhance feedback activity to right-sided visual areas, increasing the saliency of LVF stimuli, and partially and temporarily reducing the pathological unbalance toward the right side. This dorsal network of multimodal parietal areas may constitute a basis for the building up and updating of non-retinal representations of space (e.g., Johannsen et al., 2003). TENS to the left posterior neck muscles can be regarded as a bottom-up activation of these higher-order transformation processes. As shown in **Table 2**, the superior parietal lobule was structurally damaged in two out of six patients (#2 and #2), and largely spared in the remaining four patients. In conclusion, dorsal posterior parietal (typically structurally spared in USN patients) regions may support the effect of TENS measured with SSVEPs; future studies, using high-resolution multi-channels VEP recordings, may assess these hypotheses.

After TENS, healthy participants make a leftward error (TENS effect about 5% of the line length). Thus, they show similar effects, although much minor in size, than those exhibited by USN patients (about 1.4%). In addition, we found that TENS was associated to a reduction of the LVF VEP latency, which was 6 ms earlier than RVF.

It may be noted that, before applying TENS, healthy participants show a leftward (although not significant) deviation in line bisection. This phenomenon has been repeatedly found both when participants see the line, and when they are blind-folded, relying only on tactile and kinesthetic information ("pseudoneglect," see Jewell and McCourt, 2000). The phenomena of neglect and pseudoneglect are considered manifestations of a common underlying attentional asymmetry (Pitzalis et al., 2001). The present data show that both phenomena are affected by TENS, thus supporting view (see Discussion in Jewell and McCourt, 2000) that they share some basic mechanisms.

A final remark concerns the implications for the neuropsychological rehabilitation of USN patients. The different techniques proposed through the years to rehabilitate neglect can be distinguished in two main categories of approaches: top-down and bottom-up. Top-down techniques attempt at actively re-orienting the patients' attention toward the neglected left side of space. Bottom-up techniques, conversely, consist in delivering asymmetrical sensory stimulations, which do not require the patients' active participation in exploring the neglected side of space (see Vallar and Bolognini, 2011; Zoccolotti et al., 2011 for review). TENS, which is a bottom-up technique, may bring about a passive activation of the neglected side of the body, thus potentially compensating for the rightward bias of neglect (e.g., Vallar et al., 1995, 1996; Guariglia et al., 2000). With respect to top-down techniques (which require patients to be aware of their deficits, and to be able to voluntarily maintain attention oriented toward the affected side), treatments based on bottom-up mechanisms are potentially more successful because they are tied to less prerequisites concerning the functional status of USN patients (i.e., they do not necessarily require the patient's cooperation in attending and exploring the left hand-side of space). Furthermore, TENS or neck muscle vibration have the advantage of being suited for stimulus application anywhere and anytime, even at home after discharge from the hospital. Also, these techniques have no side-effects and are easy to apply. It thus seems to be a useful tool to supplement the established methods in the rehabilitation of spatial neglect.

In conclusion, VEP apparent latency and behavioral performance in patients with neglect can be modulated by TENS stimulation which is able to induce a deficit reduction of valuable magnitude; the observed effects regress 1 h after treatment. Also healthy subjects are sensitive to TENS, showing effects similar to patients group, but much less intense. The present study confirms that TENS is a technique potentially useful in the field of neuropsychological rehabilitation.

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Harnessing motivation to alleviate neglect

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The syndrome of spatial neglect results from the combination of a number of deficits in attention, with patients demonstrating both spatially lateralized and non-lateralized impairments. Previous reports have hinted that there may be a motivational component to neglect and that modulating this might alleviate some of the debilitating symptoms. Additionally, recent work on the effects of reward on attention in healthy participants has revealed improvements across a number of paradigms. As the primary deficit in neglect has been associated with attention, this evidence for reward's effects is potentially important. However, until very recently there have been few empirical studies addressing this potential therapeutic avenue. Here we review the growing body of evidence that attentional impairments in neglect can be reduced by motivation, for example in the form of preferred music or anticipated monetary reward, and discuss the implications of this for treatments for these patients. Crucially these effects of positive motivation are not observed in all patients with neglect, suggesting that the consequences of motivation may relate to individual lesion anatomy. Given the key role of dopaminergic systems in motivational processes, we suggest that motivational stimulation might act as a surrogate for dopaminergic stimulation. In addition, we consider the relationship between clinical post stroke apathy and lack of response to motivation.

Keywords: neglect, motivation, reward, attention, extinction, striatum, music

INTRODUCTION

Spatial neglect is widely acknowledged to result from multiple component deficits, which are both spatially lateralized and non-lateralized (Leicester et al., 1969; Corbetta and Shulman, 2011). The majority of these impairments relate to dysfunction of attention (Mesulam, 1981) but it has been suggested that a further potentially influential component could relate to motivation (Mesulam, 1985; Ishiai et al., 1990). There has been a great deal of recent work examining how motivation, particularly in the form of reward, can affect attentional processes in healthy humans, across a diverse range of attention paradigms (Small et al., 2005; Della Libera and Chelazzi, 2006; Kiss et al., 2009; Hubner and Schlosser, 2010). This research has shown, for example, that motivationally salient stimuli are less susceptible to the attentional blink (Raymond and O'Brien, 2009) and that rewarding targets leads to greater priming in visual search (Kristjansson et al., 2010). Here we review studies of how motivational processes can modulate pathologically impaired attention in patients with spatial neglect. We examine the effects of monetary reward, music, task instruction, and emotionally "negative" motivating influences, as well as speculating how these may be incorporated into clinical strategies. Moreover, we examine how these factors may relate to the drug therapies that have been trialed for patients with neglect, and how their effects might inform our understanding of how individual treatments work.

REWARD

There has been a great deal of work examining the effects of reward on selective attention, a process that is profoundly affected in patients with neglect (Bagurdes et al., 2008; Hubner and Schlosser, 2010; Anderson et al., 2011). In one of the earliest of these studies, Della Libera and Chelazzi (2006) examined the effects of associating individual targets during a search task with monetary value, and found that the efficacy of selective attention could be modulated by rewarding feedback. Further studies by these and other authors have consistently demonstrated that associating visual stimuli with monetary incentive can lead to improved task performance. There have been two distinct possibilities proposed for the mechanism by which reward exerts its effect on attention. First, reward might act as a motivation for the top-down strategic control of attention or, alternatively, reward delivery can directly alter the processing of specific stimuli by increasing their attentional priority in a more bottom-up manner (Chelazzi et al., 2012). Furthermore, it is possible that both these mechanisms might simultaneously be activated in some circumstances.

Following on from this research, and anecdotal reports that providing monetary incentive improves neglect (Mesulam, 1985), we went on to systematically evaluate the effects of anticipated monetary reward in a group of 10 patients with spatial neglect secondary to right hemisphere stroke (Malhotra et al., 2013). We adapted a standard cancellation task replacing target stimuli with high value (£1 coins) or no-value (metal buttons) targets on Reward and No-Reward variants of the cancellation search task respectively. Patients were informed that they would receive £1.00 for each target canceled in the Reward task but they were simply instructed to cancel all button targets in the No-Reward task without mention of reward. Patients completed the two variations of cancellation task in a first session and then were given monetary incentive and informed that the amount was based on their performance on the Reward task. After this session, patients returned on a separate day and completed the two tasks again. In this second session performance was significantly improved in the Reward task *only*. This improvement was evident both when examining performance across the entire search array and also when contralesional cancellations were examined separately.

In this paradigm, only being informed that reward would be received was not sufficient for improvement as there was no difference in the two conditions in the first session. However, receipt of incentive and relevant feedback led to improved cancellation. This is in keeping with previous studies where participants either took part in a training session, giving them time to associate stimuli with reward, and/or received online feedback during task performance (Della Libera and Chelazzi, 2006; Engelmann et al., 2009; Kiss et al., 2009; Anderson et al., 2011).

Two patients showed no response to reward, and lesion subtraction showed that the principal brain area damaged in these two patients but intact in those patients that did respond, was the striatum. Although it is possible that attentional response to motivation may be disrupted by secondary or tertiary results of the brain injury itself, such as anosognosia or depression, respectively, this finding is consistent with the known importance of striatal structures in reward processing (O'Doherty et al., 2004), and also potentially sheds light on animal studies showing that experimentally induced neglect is more severe and less likely to recover when cortical damage is accompanied by striatal dysfunction (Van Vleet et al., 2003; Christakou et al., 2005). As we discuss in the next section, it may also increase our understanding of the variable responses to treatment that have been observed in pharmacological studies in neglect.

As neglect is not a unitary disorder, and results from the interaction of a number of deficits (Husain and Rorden, 2003; Hillis, 2006; Bartolomeo, 2007), there are a number of possible avenues for reward's influence on neglect in our study. One explanatory mechanism could be through heightened arousal secondary to administration of financial reward, as increased arousal has been shown to enhance spatial awareness in neglect (Robertson et al., 1998) and the rewarding stimuli employed in this study have been associated with galvanic skin response changes (Pessiglione et al., 2007). This suggests that reward could have led to increased arousal and reduced neglect, but only during the Reward condition in the second session.

Another potential mechanism for the effects of reward could be through increasing target salience and modulated processing of high reward stimuli (Bays et al., 2010). Evidence suggests that association with reward affects stimulus salience, even when detrimental to task performance (Anderson et al., 2011; Della Libera et al., 2011). After Session 1, following incentive gain and performance feedback, the relative salience of all the £1 targets may have been greater, leading to patients finding targets that they were previously unable to mark. As a result it is possible that reward's effects were mediated via arousal, modulation of target salience, or a combination of these mechanisms. Further work is required to evaluate whether reward acts via both, or only one of these routes, but, from the evidence above, it is possible that its incorporation into behavioral therapies for neglect may be of significant benefit (Robertson, 2013), perhaps particularly if it is associated with a functional task goal (Wu et al., 2001).

PLEASANT MUSIC

An alternative means of inducing positive motivation is through the use of enjoyable music. It has been shown by Sarkamo et al. (2008) that listening to music has significant effects on cognition following stroke. These authors found that patients who had suffered middle cerebral artery stroke had better recovery of verbal memory and focused attention if they were regularly listening to their preferred music when compared to patients who were listening to audiobooks or a control group who were receiving standard rehabilitation alone. This result is in keeping with work in healthy subjects showing that listening to enjoyable music can improve cognitive performance in a number of domains (Rauscher et al., 1993; Thompson et al., 2005; Rowe et al., 2007). Preferred music's effect on impaired visual attention has been more directly assessed in a study by Soto et al. (2009), where they examined the effects of pleasant music in three patients on an experimental visual extinction paradigm. They found that when patients listened to music that they preferred, they were better able to identify contralesional targets as compared to when they were listening to unpreferred music, or during a silent condition. In a separate experiment, they examined whether listening to preferred music was associated with increased arousal, which has been shown to improve awareness in neglect patients (Robertson et al., 1998), and found that that this was not the case, suggesting that the improvement was not via an arousal mechanism. This experimental work has been followed by more recent studies looking at the effects of music using standard clinical tasks (Chen et al., 2013; Tsai et al., 2013). In particular, Chen et al. (2013) examined the effects of pleasant music on neglect in a group of 19 patients and found it to improve visual search but to have no effect on line bisection. Moreover, they also observed a significant increase in leftward eye movements in comparison to control conditions. These authors speculated that listening to pleasant music might be more likely to affect performance on tasks requiring global visuospatial attention processing over the whole visual field rather than tasks such as line bisection involving a single object.

In their recent review of the effects of music listening on function after stroke, Sarkamo and Soto (2012) suggest that a possible mechanism for the effects of music on visual awareness is via activation of the mesolimbic dopaminergic reward system, which is in keeping with evidence that emotional arousal whilst listening to music is associated with endogenous dopamine release in striatal structures (Salimpoor et al., 2011). Such an explanation would also be consistent with the effects of monetary reward on neglect, the key role of dopamine in reward processing (Zald et al., 2004), and our own observation that reward did not lead to a reduction of neglect in patients with striatal damage (Malhotra et al., 2013). Together, these findings raise the intriguing possibility that positive motivation, in the form of music and anticipated monetary reward may act via endogenous dopamine release. Dopaminergic stimulation has previously been used as a possible treatment in neglect, but with varying results, and even where positive effects have been found these have not been observed in all treated individuals (Fleet et al., 1987; Geminiani et al., 1998; Grujic et al., 1998; Hurford et al., 1998; Barrett et al., 1999; Mukand et al., 2001; Gorgoraptis et al., 2012). It is possible that positive motivation, as described above, may act as a surrogate for dopaminergic therapy, and help predict good candidates for dopaminergic treatment. Further work is necessary to explore these issues further, and to systematically examine the anatomical substrates that are necessary for attentional responses to positive motivation and effective exogenous dopaminergic [and cholinergic (Rice and Cragg, 2004)] stimulation.

TASK INSTRUCTION AND SEQUENCE COMPLETION

An intriguing slant on improving motivation has been provided by Ishiai et al. (1990), who reported a possible motivational component to impaired search performance in neglect after investigating the effect of numbering targets rather than solely canceling them during a search task. They found that numbering significantly improved search and reduced neglect on such a task, and suggested that the process of numbering increased motivation to find more targets and complete the task. When participants carried out a third cancellation session without numbering, neglect increased again, suggesting that their observation was not due to a practice effect. In another study, addressing neglect during object copying, Ishiai et al. (1997) showed that performance when copying a drawing improved significantly when participants were instructed to arrange items around a central circle rather than to directly copy an example, although both tasks required an identical response. These authors suggested that alteration of the instruction may have led to increased motivation during task performance. These methods of utilizing simple changes in task instruction to improve performance is potentially crucial when considering how harnessing motivation might improve neglect, and highlights the need for careful consideration of task instructions when implementing therapy for patients.

NEGATIVE EMOTIONAL MOTIVATION

The work described so far has attempted to employ positive motivation and the induction of positive mood in order to reduce neglect. However, there is a long research history of the converse – that is the effect of negatively valent emotional stimuli both on attention in healthy individuals, and in studies demonstrating preserved processing of these forms of stimuli in patients with neglect and extinction. This work is highly relevant here as this alternative form of motivation may recruit different mechanisms to those involved with positive motivational stimulation, thereby enabling therapies that are potentially suitable for alternative groups of patients, with different underlying pathological neuroanatomy.

Numerous studies have demonstrated that emotionally valent stimuli, such as faces or emotive words, require less attention to be processed, or under some circumstances, appear to be processed when outside the focus of attention and with consequent effects upon the eventual distribution of attention (Ohman, 1986; Pratto and John, 1991; Stormark et al., 1995; White, 1995; Bradley et al., 1997; Eastwood et al., 2001; Ro et al., 2001; Lavie et al., 2003). This preferential processing of emotive stimuli is particularly strong for negative stimuli such as fearful or unhappy faces (Whalen et al., 1998; Eastwood et al., 2001).

There is now a considerable body of work investigating the effects of emotion-evoking stimuli on attentional deficits in brain-injured patients with visuospatial neglect. A landmark study by Marshall and Halligan (1988) demonstrated the powerful effect of emotionally valent content, such that contralesional information – for which the patient remained entirely unaware – nevertheless influenced explicit decision making. More recently, Vuilleumier and Schwartz (2001b) have shown that contralesional detection on bilateral simultaneous stimulation trials is better for faces rather than shapes, and also better for expressive, whether happy or angry, rather than neutral faces in patients with extinction. In addition, the same authors have shown that fear-related stimuli are more likely to be detected compared to neutral stimuli (Vuilleumier and Schwartz, 2001a), when presented in the contralesional field of patients who exhibited left visual extinction, even when the stimuli are well-matched in low-level visual properties.

These effects have also been observed using versions of standard clinical tasks and during visual search. Tamietto et al. (2005) found that cueing patients with unilateral left cues was significantly better at reducing the rightward bias in line bisection when the cues, although task-irrelevant, were represented by emotional as opposed to neutral faces. Similarly, visual search for emotional left-sided targets amongst distractors has been shown to more efficient, with a greater number detected and with faster reaction times, than for their neutral counterparts (Lucas and Vuilleumier, 2008). Together, these observations suggest that the emotional valence of stimuli in neglected hemispace might be implicitly processed, to a great enough degree that these stimuli can subsequently bias the deployment of spatial attention and encourage motor behaviors into left-sided space. Intriguingly, such findings have not been restricted to the visual modality, and comparable results have been reported for patients with auditory extinction, who demonstrate a reduction in their lateral deficit in the presence of contralesional, emotionally significant, vocal stimuli relative to neutral utterances (Grandjean et al., 2008).

It has been proposed that intact visual pathways to the ventral temporal lobe and amygdala might mediate these distinct mechanisms of emotional attention (Morris et al., 2001; Vuilleumier, 2005). Grabowska et al. (2011) attempted to examine the neural correlates underlying these processes using a variety of emotional and neutral stimuli presented unilaterally in either ipsilesional or neglected contralesional hemifields. In accordance with previous findings, emotional pictures presented in left visual field were reported more frequently than neutral images, thus modulating neglect. This correlated with increased activity in right parahippocampal gyrus and right anterior cingulate cortex. Amygdala activity was not reported even for emotional stimuli detected in right hemispace, which is in contrast to numerous studies that have suggested a crucial role in emotional processes for this structure. Current evidence suggests that a number of brain regions are involved in the capture of attention by emotional stimuli, such as orbitofrontal and anterior cingulate cortex (Vuilleumier et al., 2002; Pessoa and Adolphs, 2010; Schwabe et al., 2011) and further research will help to clarify the exact roles of the amygdala as well as these structures in the mediation of emotional effects upon impaired attention.

This perceptual advantage for emotionally valent stimuli has, very recently, been explored in the context of a rehabilitation tool for patients with neglect. Dominguez-Borras et al. (2013) have reported that following aversive conditioning to a specific visual stimulus, bilateral simultaneous trials involving these stimuli reduced left visual extinction in a patient with right parietal damage, as compared to responses to the same stimuli before conditioning. That is, the patient's contralesional performance improved after a negative emotional significance association was learnt for some stimuli. Although this is a single case study, it introduces a potentially exciting concept for the use of affective strategies in the rehabilitation of neglect.

CONCLUSION

In this review we have considered several mechanisms by which motivational influences might modulate awareness in patients with neglect, and described a number of studies that clearly demonstrate motivation's considerable effects on attention (see **Figure 1**). Until recently, such studies were confined to experimental paradigms exploring this interaction, or anecdotal reports of individual patients improving following positive motivation. However, there have now been studies addressing these issues with more clinical tasks and employing motivational processes in the context of rehabilitation (Chen et al., 2013; Dominguez-Borras et al., 2013). Furthermore, there is very preliminary evidence to suggest that some motivational stimulation may act as a surrogate for pharmacological (in particular dopaminergic) therapy. However, there remains a great deal of work to be done in evaluating the precise mechanisms underlying these interactions and whether they rely on different neuroanatomical substrates. It has been shown that particular lesions appear to blunt motor responses to motivation, especially in the form of reward, and these are closely

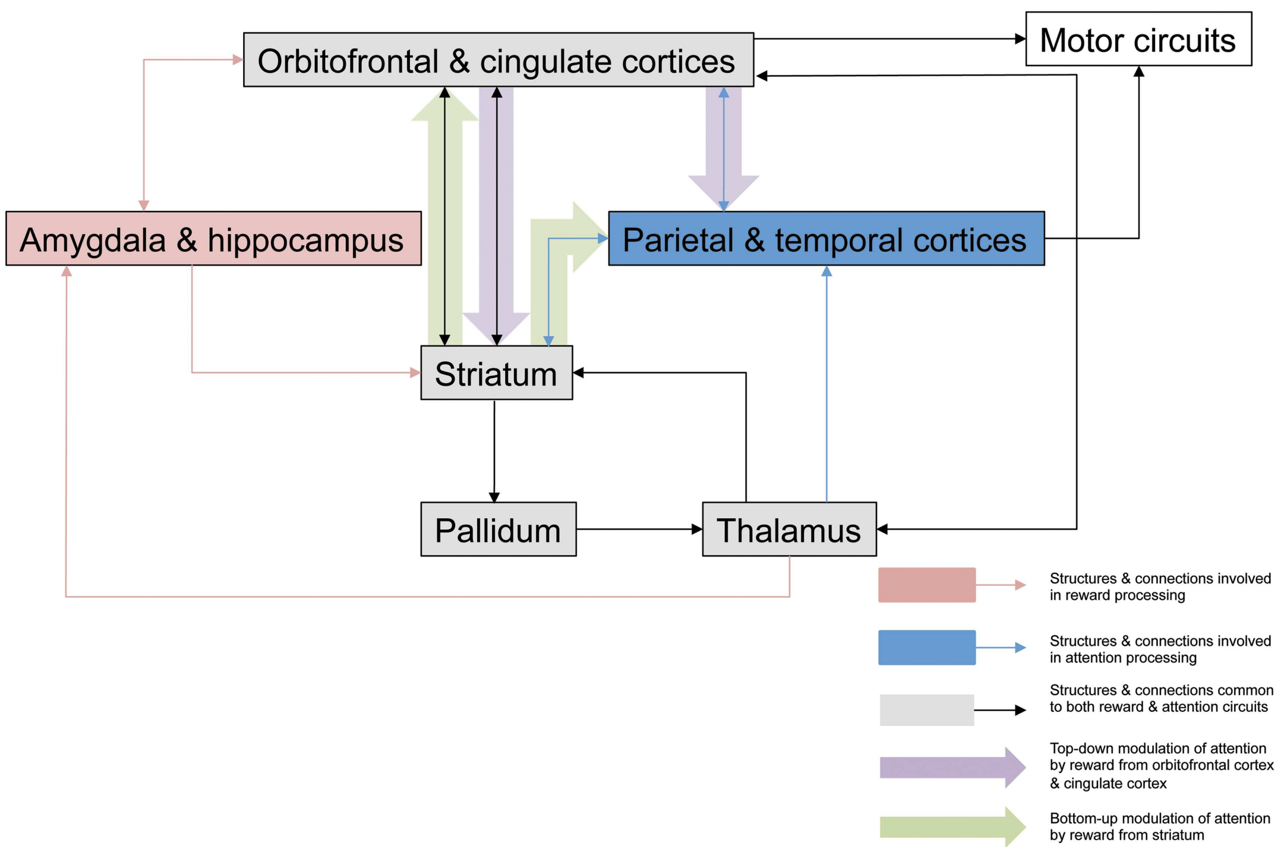

FIGURE 1 | Potential neuroanatomical pathways for motivation-attention interplay. This outlines possible pathways involved in the interaction between motivation and attention that are critical for the actions of reward on spatial neglect. Mesulam (1999) proposed a large scale neurocognitive network with cortical foci in parietal cortex and cingulate cortex that is responsible for attention, and its organization allows very rapid surveys of perceptual representations, multiple coordinate systems, motor strategies, and motivational salience. Striatal neurons have been shown to be critical in reward processing (Haber and Knutson, 2010; Harsay et al., 2011), and striatal dopamine release in response to anticipated reward or amygdala activation secondary to emotionally relevant stimuli may have a direct modulatory effect on attentional signals being relayed to cortical areas for perceptual processing and representation, modulating the salience of such stimuli in a bottom-up manner. Reward may affect top-down control of attentional processes via dopaminergic projections from striatum to cingulate cortex to alter the salience of visual stimuli, with consequent behavioral effects, and there have been several studies demonstrating the role of the ACC in associating action with reward value (Bush et al., 2002; Williams et al., 2004; Small et al., 2005). Additionally this top-down modulation may also take place via orbitofrontal cortex, which appears to be involved in the enhanced processing of attentional information secondary to incentive (Mohanty et al., 2008). It is likely that these mechanisms are engaged to various degrees, according to the type of motivational stimulation, and the specific paradigm being employed.

associated with clinical apathy (Schmidt et al., 2008; Adam et al., 2013), which is characterized by a lack of goal-directed behaviors due to loss of motivation (Marin, 1991). It is common following stroke (Starkstein et al., 1993), and has been found to be associated with disruption of basal ganglia circuits (Onoda et al., 2011). This is supported by the observation that apathy is a common feature of other pathological states associated with dysfunction of the frontal-basal ganglia system (Levy and Czernecki, 2006). Furthermore, in such cases, apathy is associated with a blunted neural response to motivation, especially in the form of reward (Czernecki et al., 2002; Lawrence et al., 2011). Although it has not yet been systematically investigated, this interplay between apathy, motivational response, and attentional impairments may be particularly important in determining outcome for many patients.

From a practical perspective, there remains considerable work to be done before specific therapeutic interventions can be recommended on the basis of well-controlled trials. However, it seems clear that patients with neglect are likely to perform better, if provided with motivational stimulation. This may involve access to music, in addition to the incorporation of a strong motivational component into goal-based therapy and the careful consideration of task instructions. In advance of the development of evidence-based guidelines, such measures could be adapted and applied by clinicians and therapists on an individual basis.

Finally, we have approached neglect as a unitary construct for the purposes of this review but it will be critical to examine experimentally the effects of motivation on the discrete component deficits of the syndrome, including spatial attention, sustained attention, and spatial working memory. After apparent recovery from neglect many patients are left with residual attentional impairments (Driver et al., 2004; Russell et al., 2010, 2012; Bonato, 2012), and it will be of considerable importance to examine whether these individuals also benefit from the exciting potential of motivational enhancement.

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Visual scanning training for neglect after stroke with and without a computerized lane tracking dual task

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Neglect patients typically fail to explore the contralesional half-space. During visual scanning training, these patients learn to consciously pay attention to contralesional target stimuli. It has been suggested that combining scanning training with methods addressing non-spatial attention might enhance training results. In the present study, a dual task training component was added to a visual scanning training (i.e., Training di Scanning Visuospaziale – TSVS; Pizzamiglio et al., 1990). Twenty-nine subacute right hemisphere stroke patients were semi-randomly assigned to an experimental ($N = 14$) or a control group ($N = 15$). Patients received 30 training sessions during 6 weeks. TSVS consisted of four standardized tasks (digit detection, reading/copying, copying drawings, and figure description). Moreover, a driving simulator task was integrated in the training procedure. Control patients practiced a single lane tracking task for 2 days a week during 6 weeks. The experimental group was administered the same training schedule, but in weeks 4–6 of the training, the TSVS digit detection task was combined with lane tracking on the same projection screen, so as to create a dual task (computerized visual reaction time task designed for training). Various neglect tests and driving simulator tasks were administered before and after training. No significant group and interaction effects were found that might reflect additional positive effects of dual task training. Significant improvements after training were observed in both groups taken together on most assessment tasks. Ameliorations were generally not correlated to post-onset time, but spontaneous recovery, test–retest variability, and learning effects could not be ruled out completely, since these were not controlled for. Future research might focus on increasing the amount of dual task training, the implementation of progressive difficulty levels in driving simulator tasks, and further exploration of relationships between dual task training and daily functioning.

Keywords: hemineglect, spatial attention, divided attention, virtual reality, driving simulator

INTRODUCTION

Visuospatial neglect is defined as "a disorder whereby a patient fails to explore the half-space contralateral to the cerebral lesion" (Heilman et al., 1993). To explain the deficit underlying this disorder, various theories have been formulated, like attentional, representational, and cerebral balance theories (see Kerkhoff, 2001 for a review). Corbetta and Shulman (2011) suggest that neglect results from a dysfunction of the distributed and interacting cortical networks responsible for the control of both spatial and non-spatial attention processes. For instance, neglect symptoms have been shown to vary with arousal and sustained or vigilant attention (Robertson et al., 1997; Samuelsson et al., 1998; Robertson, 2001) as well as with task complexity (Deouell et al., 2005; Vuillemier et al., 2008).

Neglect occurs more often after right hemisphere (RH) than after left hemisphere (LH) stroke. Reported rates of occurrence vary widely as a result of a number of factors, including assessment method and time post stroke (see Bowen et al., 1999 for a review). Also, large within-patient variability in test performance is reported. Machner et al. (2012) administered the Bells test, a symbol cancelation and a line bisection task on five consecutive days to 15 neglect patients. They observed large day-to-day variability, indicating that five more or less omissions on the Bells test and deviations of plus or minus 16 mm in the line bisection task could be due to test or within-patient variability, rather than indicating a reliable change of neglect severity. Similar results have been reported by Bailey et al. (2004).

Spontaneous recovery of neglect is mostly reported in the first weeks after stroke (Ferro et al., 1999; Appelros et al., 2004b; Jehkonen et al., 2007). However, a recent study of Nijboer et al. (in press) reports significant spontaneous recovery up to 14 weeks after stroke. Farnè et al. (2004) also report changes in the performance of neglect tasks until at least 3 months after stroke. The presence of neglect is generally associated with poor functional outcome after stroke (Jehkonen et al., 2006; DiMonaco et al., 2011; Vossel et al., 2012). Nijboer et al. (in press) point out that 40% of the neglect patients still show visuospatial neglect 1 year after stroke, indicating that rehabilitation of this disorder is of great importance.

Several interventions aimed at reducing neglect symptoms have been described, like visual scanning training, prism adaptation, limb activation training, and non-invasive brain stimulation techniques (see Zoccolotti et al., 2011; Kerkhoff and Schenk, 2012; Fasotti and Van Kessel, in press, for reviews). In a Cochrane review excluding all studies that were not considered properly randomized controlled trials, Bowen and Lincoln (2007) conclude that there is insufficient evidence to support the effectiveness of specific cognitive rehabilitation approaches for reducing disabilities due to neglect (see also Rohling et al., 2009; Paci et al., 2010). However, in two reviews of cognitive rehabilitation, Cicerone et al. (2000, 2005) recommend visual scanning training as a practice standard for the treatment of neglect. Also, in a meta-analysis of the reviews by Cicerone et al., Rohling et al. (2009) report a medium to large effect of visuospatial training. In an extensive review of 18 different treatments for neglect and their rationales, in which not only randomized controlled trials but also multiple baseline single case studies were included, Luauté et al. (2006) conclude that for 6 of the available methods there is some evidence for clinical relevant training effects, visual scanning training being the most extensively evaluated training method.

Visual scanning training was originally introduced by Diller and Weinberg (1977) and further developed and described by Pizzamiglio et al. (1990, 1992) (see Pizzamiglio et al., 2006 for a review). This type of training stems from the observation that neglect patients generally show very limited attention and exploration behavior toward the contralesional hemispace. The aim of training is to improve visual scanning behavior, i.e., to encourage neglect patients to actively and consciously pay attention to stimuli on the contralesional side. In the original training protocol by Pizzamiglio et al. (1990) (Training di Scanning Visuospaziale – TSVS), four standardized training tasks are used, i.e., a computerized digit detection task projected on a large screen, figure copying, picture exploring, and reading and writing tasks. Contralesional exploration behavior is encouraged by means of operant conditioning techniques (i.e., reinforcement of correct scanning movements) and repeated training of the use of compensatory strategies (for instance using a contralesional anchor and systematically starting to scan from this point and controlling one's performance starting from the contralesional side before finishing an activity). Guidelines for the use and gradual reduction of various stimulation methods and cues are provided. Moreover, in order to increase their awareness of the deficit, patients are given concrete feedback about their performance.

Significantly increased scores on paper-and-pencil tasks as well as on a semi-structured observation scale (Zoccolotti et al., 1992) were found after TSVS (Pizzamiglio et al., 1992; Antonucci et al., 1995). The authors stress that the duration and intensity of the training (40 h during 8 weeks) plays an important role in the attainment of positive results. Moreover, the gradual and systematic increase in difficulty levels of the materials and the reduction of feedback seem important ingredients of the training leading to improvement. Positive training results were replicated by Paolucci et al. (1996), who found improvements in test performance as well as in functional status linked to the timing of the training and additional to general rehabilitation. Despite these generally positive results, a large variability in patients' benefits from TSVS has also been observed in each of the abovementioned studies. It is unclear why some patients benefit from the training while others do not. One factor seems to be the improvement of the patients' awareness of deficit (Pizzamiglio et al., 1992). However, often it is not possible to predict whether improved awareness may be expected in an individual patient as a result of the training. In addition, since neglect may occur after lesions in different regions of the brain (see for instance Karnath et al., 2004), lesion site might also play a role in the variability of training effects.

As various authors (Pizzamiglio et al., 2006; Saevarsson et al., 2011) point out, individual variability in training results has led to the question whether training effectiveness can be improved by combining interventions. Until now, positive training results were found in both conditions in a study comparing regular TSVS with TSVS plus additional optokinetic stimulation (Pizzamiglio et al., 2004). However, no differences were observed between conditions. Luauté et al. (2006) also recommend the evaluation of combinations of existing methods. More specifically, these authors suggest that effective treatments be combined with techniques aiming at processes that contribute to the clinical manifestation of neglect (for example non-spatial attention and working memory) to further enhance training effects. Moreover, in another TSVS evaluation study, Piccardi et al. (2006) investigated whether TSVS might result in improved performances on various neglect and non-neglect measures (i.e., measures of vigilance, alertness, and attentional control/response inhibition). TSVS training effects were observed on neglect measures but not on non-spatial attention tasks. Therefore, Pizzamiglio et al. (2006) point out that in the rehabilitation of neglect, care must be taken to also treat non-spatial disorders.

In the present study, an attempt is made to further extend the scope of standardized TSVS by combining it with additional dual task training. The use of dual tasks in neglect may be preeminently useful because of the association between spatial and non-spatial attentional processes in this disorder. Robertson and Frasca (1992), for instance, assume that neglect patients are particularly vulnerable to a deterioration of performance in the face of additional attentional load because of this association. Robertson and Manly (2004) suggested that it is possible to detect the presence of well-compensated or even "recovered" neglect by increasing attentional load. This can be accomplished by means of a dual task. In line with this idea, it was found that computerized dual tasks elicit more contralesional omissions (Bonato et al., 2012, 2013) and slower contralesional reaction times (RTs) (Deouell et al., 2005) than single paper-and-pencil tasks. Moreover, clearly asymmetric task performance in the computerized dual tasks even occurred in some patients showing no signs of neglect in paper-and-pencil tasks. Thus, computer-based dual tasks, even though not always showing resemblance to contexts of daily living, have high diagnostic potential in the assessment of neglect and its recovery (Schendel and Robertson, 2002; Bonato and Deouell, 2013).

Furthermore, various authors describe that deficits in non-spatial attentional processes not only occur in association with neglect (for instance in the case of impaired arousal). Non-spatial attention processes involved in the exertion of top-down influence on lower level spatial perception may also play an important underlying role in this disorder (Corbetta et al., 2005; Vuillemier et al., 2008). Bartolomeo and Chokron (2002), for instance, suggest that a basic mechanism leading to neglect behavior is an impaired exogenous orienting toward left-sided targets. Nevertheless, patients may be able to compensate for their deficit by means of endogenous attentional processes, that may be spared but slowed in neglect. The ability to successfully compensate for neglect symptoms might thus depend on the patients' capacities to gain attentional control over their scanning behavior.

Neglect is often associated with frontoparietal damage in the RH (Farnè et al., 2004; Committeri et al., 2007) or in the white matter connecting parietal and frontal areas (Bartolomeo et al., 2007, 2012). According to Corbetta and Shulman (2011), lesions in the RH that cause neglect impair non-spatial functions mediated by a ventral frontoparietal attention network. This impairment may in turn induce abnormalities in an anatomically linked dorsal frontoparietal network that controls spatial attention. Singh-Curry and Husain (2009) point out that a frontoparietal system might allow the flexible reconfiguration of behavior between maintaining attentive control and responding to salient stimuli. Dual tasks might then not only generally increase attentional load, but might address this frontoparietal system more specifically.

Thus, dual tasks might not only appeal to attentional capacity, but also to the control over attention. Patients' performances on these tasks could be indicative for their abilities to compensate for neglect (Van Kessel et al., 2013). This raises the question whether these tasks might also be used as a training tool. As Robertson and Manly (2004) point out, the demands on neglect patients' impaired abilities in maintaining corrective "top-down" control over spatial attention might be minimized by attempting to train these corrective strategies to a point where they become more habitual. TSVS training is aimed at the conscious compensation for spatial attention deficits and thus appeals to top-down attentional control. Combining TSVS with additional dual task training might provide tools for accomplishing a higher degree of automation of scanning strategies and contribute to the enhancement of training results.

To investigate the additional value of dual task training, in the present study, a computerized visual RT task designed for training (CVRT-TR) will be used. The CVRT-TR was designed on the basis of two diagnostic tasks, i.e., a single and a dual CVRT task (CVRT and CVRT-D, respectively). These assessment tasks had been previously used to investigate spatial and non-spatial attention processes in neglect (Van Kessel et al., 2010, 2013). In concordance with the abovementioned findings of Deouell et al. (2005) and Bonato et al. (2012, 2013), more patients were classified as neglect patients by using RT asymmetries on the CVRT than by using scores on the Behavioral Inattention Test (BIT; Wilson et al., 1987). Moreover, the results suggested that some patients with defective RT asymmetries but normal BIT scores might compensate for their lateralized deficit in paper-and-pencil tasks. These patients might have engaged intact non-spatial attentional processes, especially attentional control (Van Kessel et al., 2010). When single (CVRT) and dual (CVRT-D) task performance were compared (Van Kessel et al., 2012), a clear increase in RT asymmetries between CVRT and CVRT-D was observed. Half of the patients meeting the BIT criterion for neglect showed increased RT asymmetries from CVRT to CVRT-D. Moreover, two LH and RH patients without neglect symptoms on the BIT and CVRT showed significantly increased asymmetries in the CVRT-D. This fostered the idea of an emergence of subtle neglect under increased attentional load.

In the CVRT-TR, a large screen driving simulation task was added to the computerized digit detection task used in the standardized TSVS protocol (Pizzamiglio et al., 1990). Thus, a dual task was created that can be used for training patients. The CVRT-TR could be referred to as a virtual reality (VR) task. Other VR methods include desktop simulator tasks or head-mounted devices. Recently, different kinds of VR tasks have been applied in the assessment and observation of neglect patients (Broeren et al., 2007; Buxbaum et al., 2008, 2012; Jannink et al., 2009; Kim et al., 2010; Fordell et al., 2011). Buxbaum et al. (2008, 2012) describe a virtual reality lateralized attention task (VRLAT) in which patients had to navigate through a VR environment while seated in front of a flat screen display in a powered wheelchair treadmill. These patients were asked to name objects projected on both sides of the road. Neglect symptoms were detected in more patients by using the VRLAT, compared to paper-and-pencil tasks. Moreover, left-sided collisions on the VRLAT showed significant correlations with real-world left-sided collisions.

Virtual reality tasks are also used as a rehabilitation tool (see Tsirlin et al., 2009 for a recent review). VR training in neglect is mostly aimed at improving performance on the task that is simulated, for instance navigating through a real-life wheelchair obstacle course (Webster et al., 2001) or street crossing (Katz et al., 2005). In an alertness training program used by Thimm et al. (2006), patients had to "drive" a simulated car or motorcycle as quickly as possible and avoid crashing into obstacles that appeared suddenly on the screen. After 3 weeks of training, both alertness and neglect deficits were significantly reduced. However, 4 weeks after the end of training, neglect symptoms had returned to the pre-training level. Finally, Akinwuntan et al. (2010) observed no differences between stroke patients receiving either simulator-based driving-related training or non-computer-based cognitive training over 5 weeks. In their RCT, both groups showed similar improvement after training on a test of driving-related visual attention skills.

Not only are VR techniques suitable to simulate daily activities, but in doing so, tasks can be created that allow for the combined training of visuospatial and non-spatial attention. In the present study, it will be investigated whether the effectiveness of the standardized TSVS protocol (Pizzamiglio et al., 1990, 1992) might be further enhanced using the CVRT-TR. In the CVRT-TR, patients are enabled to additionally practice their acquired scanning strategies while performing a secondary task. It is hypothesized that training patients with this task could contribute to an enhancement in TSVS training results and better performance on various diagnostic tasks for neglect.

MATERIALS AND METHODS

PARTICIPANTS

Patients with a first intracerebral infarction or hemorrhage admitted for clinical multidisciplinary rehabilitation to one of four local rehabilitation centers in the Netherlands were eligible for this study. Over a period of 2 years, 53 RH patients showing neglect symptoms as observed by their therapists and/or found in early neuropsychological screening, were referred for further assessment. This assessment was aimed at investigating whether TSVS and inclusion in the present study would be indicated. Tests were performed at least 8 weeks post-onset to minimize the role of spontaneous recovery. Six patients in the control group and 8 patients in the experimental group could be considered chronic neglect patients, since they had post-onset times of more than 3 months. Patients with omission scores above cut-off on at least three of the paper-and-pencil neglect tests and one of the observational scales (all listed below) were asked to participate in the present study. Patients with visual field deficits as observed by means of Donders' confrontation method were excluded. A total of 29 patients were included. All subjects gave informed consent to participate in this study and research was completed in accordance with the Declaration of Helsinki. In **Table 1**, medical and demographic data of the subjects are presented.

Patients were assigned to the experimental or control group using block semi-randomization. Of every four consecutive patients, the first two (in case these two were assigned to the same group) or three (if the first two patients each were assigned to a different group) were randomly allocated to one of the groups. The other(s) were classified in such a way that within every block of four, two patients were in the experimental and two in the control group.

PRE- AND POST-TRAINING ASSESSMENTS

Patients were administered various neglect tasks (see below) on two separate days within 1 week. The first session included the paper-and-pencil and driving simulator tasks and lasted for approximately 1 h. The semi-structured scales were administered on a second day, because another room (kitchen of the occupational therapy department) was necessary to administer these tasks. When a patient was included, training started 1 or 2 weeks after the first assessment. Post training assessments were scheduled 1 or 2 weeks after the end of the training.

Paper-and-pencil neglect tests

Line cancelation. Patients were asked to cross out 21 lines (2.5 cm) printed on a A3 sheet of paper (Albert, 1973). The occurrence of one or more omissions was considered as indicative for neglect.

Letter cancelation. Patients were instructed to cross out 104 uppercase "H"s interspersed among 208 distractor characters (Diller and Weinberg, 1977). All characters were printed in six horizontal lines on a A3 sheet of paper. Five or more omissions and a difference of two or more between contralesional and ipsilesional omissions were considered as indicative for neglect.

Bells test. Thirty-five bell-shaped figures, interspersed among 280 distractor figures and printed on a A4 sheet of paper, had to be crossed out (Gauthier et al., 1989). Four or more omissions were considered as indicative for neglect.

Table 1 | Medical and demographic data for both patient groups.

	Control ($N = 15$)	Experimental ($N = 14$)
Sex (male/female)	10/5	7/7
Mean age (SD)	59.07 (6.08)	61.86 (7.75)
Range	48–71	52–77
Days post onset (SD)	157.60 (117.16)	140.57 (133.56)
Range	63–431	57–569

Line bisection. Patients were asked to bisect 20 horizontal lines (printed on a A4 sheet of paper) by placing a pencil mark as close to the center of the line as possible (Schenkenberg et al., 1980). Two or more omitted lines were considered as indicative for neglect.

Word reading task. Patients were asked to read aloud 165 words and non-words, each printed on a different sheet of A4 paper (after Làdavas et al., 1997). All words consisted of three syllables and were composed of 6–11 letters. Fifty-five words were used in their natural form. Moreover, in every word two letters were replaced within the first syllable in one condition (left non-word) and within the last in a third condition (right non-word). All words (55) and non-words (110) were presented in random order. RH neglect patients tend to misread the first syllables. An index score was computed in which the difference between left and right errors was divided by the sum of left and right errors. Ignoring some letters or the complete first syllable, or (in case of left non-words) reading the original word as if no letters had been replaced in the first syllable were considered errors.

Grey scales. Twenty-six sheets of paper (A4, landscape) were presented to the patients (Tant et al., 2002). A pair of vertically aligned horizontal rectangular bars of equal length was printed on each page. The bars were filled with continuous scales of different gray shades varying from black to white at the extremes. The upper and lower bar of each pair were mirrored copies of each other. Hence, one of the gray scales was black on the left and white on the right and the other exactly the opposite. Pairs of stimuli of different lengths were randomly used. Patients were asked to judge which (top or bottom) bar of each pair appeared darker overall. RH neglect patients tend to show extreme rightward biases (consistently choosing bars that are black on the extreme right). An index score was computed, in which the difference between rightward and leftward biased responses was divided by 26.

Baking tray task. In this task, patients were asked to equally distribute 16 blocks (4 cm × 4 cm) on a "baking tray," i.e., a 75 cm × 100 cm board (Tham and Tegnér, 1996; Appelros et al., 2004a). A difference of two or more between the numbers of blocks placed left and right was considered as indicative for neglect. An index score was computed, in which the difference between the numbers of blocks placed right and left was divided by 16.

Observation scales and subjective questionnaire

Semi-structured scale for the evaluation of extrapersonal neglect. This task consisted of four subscales (serving tea, dealing cards, description of the environment, and of three large pictures), performed in the presence of the examiner and two additional persons seated at the left and right side of the table (Zoccolotti et al., 1992). Six scores for the extent of asymmetric performance were given on 0–3 point scales, so that the maximum total score of 18 indicated severe asymmetries on all subscales. A total score of 3 or more was considered as indicative for neglect.

Semi-structured scale for the evaluation of personal neglect. The patient was asked to show how he/she would comb his/her hair, using a razor (male) or powder her face (female) and putting on glasses (Zoccolotti et al., 1992). Three asymmetry scores were given on 0–3 point scales. A total score of 2 or more was considered as indicative for neglect.

Subjective neglect questionnaire. This questionnaire consisted of 19 items describing common problems associated with neglect (for instance bumping into door frames) (Towle and Lincoln, 1991). Patients were asked to indicate how frequently (1–5) each problem had occurred the last month. Thus, the minimum score of 19 indicated no reported problems, the maximum score was 95.

Driving simulator tasks

Three types of driving simulator tasks were used during the assessment. These were a single lane tracking task, a single target detection task, and a dual task consisting of both lane tracking and target detection (see also below). In all driving simulator tasks, patients were seated in front of a 2.13 m × 3.18 m projection screen at a distance of approximately 90 cm, thus creating a visual angle of approximately 110°. On the screen, a driving scene was projected. A steering wheel (Trust formula 1 race master) was fixed on a table in front of the participant and a white wooden board was placed on the table between the steering wheel and the projection screen, so as to prevent subjects from using the edges of the table as a spatial reference while driving.

Lane tracking. In the lane tracking task, a driving scene was projected on the same screen that was also used as a part of the standard TSVS training (e.g., large screen digit detection, see below). The simulated speed of the imaginary car was set at a constant 50 km/h. Patients were instructed to use the steering wheel to maintain the starting position in the middle of the right lane of the projected road, thereby compensating for what was indicated as "sidewind." This was a continuous signal fluctuating from left to right in a fixed pattern created by superimposing three low frequency sinus movements. Thus, patients were continuously "blown" off track, either right- or leftward. Patients' lateral positions during lane tracking were recorded every 15 s. Mean lateral position scores were computed from these values for each patient and the SD of the lateral position scores reflected the degree of oscillation.

Single detection task (CVRT). In the CVRT, patients were asked to detect large rectangular dot patterns on one of three horizontal positions within a driving scene that was projected on the screen. RTs for left, middle, and right stimuli were recorded and asymmetries (i.e., difference scores) between left and right RTs were computed. Steering was not required.

Dual task (CVRT-D). In the CVRT-D, lane tracking and CVRT dot pattern detection were combined to create a dual task. Lateral position and oscillation scores were computed together with RTs and RT asymmetries.

TRAINING TASKS

A translated version of the original TSVS manual (Pizzamiglio et al., 1990) was used. This was slightly adapted for use in the present study. Most importantly, patients received 30 training sessions (5 days a week, a 1-h session each day, during 6 weeks) instead of the original 40 h. Moreover, some changes had been made in the order of the digit detection sequences. Guidelines as to the use and fading of cues were provided in the manual. By individually adjusting difficulty levels of the sequences and the use of cues, patients were offered systematic training. Training sessions consisted of four standard tasks and additional control or experimental tasks.

Standard training

Large screen digit detection. Using a desktop computer and a projector, sequences of random digits (1–9) were projected from behind on a 3.18 m × 2.13 m screen. Each digit was projected at one of 48 (12 horizontal × 4 vertical) possible positions. Patients were seated in front of the screen, which was placed at approximately 90 cm from their eyes, so as to create a visual angle of the projection of around 110° horizontally and 70° vertically (see **Figure 1** for training set-up). Patients were free to move their head and eyes. They were asked to name each digit and at the same time press a button as quickly as possible. Sequences of progressive difficulty levels were used, the easiest sequences progressing stepwise from right to left at the same height and the most difficult ones randomly alternating between all possible positions. Verbal cues (encouragement of the trainer to look further to the left) and non-verbal auditory cues (signal tones accompanying each digit) could be given.

In general, during the first weeks of training, patients were trained to perform leftward scanning movements. To this end, training sequences were used that facilitated directing and preserving attention (supported by active head movements) to the left side of the screen, i.e., progressing stepwise to and (later) from the left side.

In the second half of the training, patients were taught to "center" their scanning behavior, i.e., using their straight ahead as a departing point from which to make scanning movements to either the left or right side. This technique is aimed at achieving symmetry in left and right detection times. The use of verbal and auditory cues was gradually faded during the training.

Copying line drawings on a dot matrix. Patients were instructed to copy lines, connecting some points of a dot matrix placed on the left halve of a page, into an empty matrix on the right. Matrices varied from 4 to 20 points. The use of verbal and visual cues was progressively reduced.

Reading and copying training. Patients were asked to read and/or copy sentences and newspaper headlines of progressive difficulty levels (based on size and length as well as the number and spatial distribution of lines). The use of verbal and visual cues was progressively reduced.

Figure description. Patients were encouraged to describe all elements on pictures printed on A3-sized pages. Picture complexity gradually increased over a total of 45–60 pictures. The most simple pictures represented small numbers of centrally placed large objects that had to be counted. In the most complex pictures, figural elements or portions of text that were essential to capture the meaning of the depicted scene were placed at the extreme left side of the paper.

Additional tasks for the control and experimental conditions

In **Table 2**, the training schedules for the experimental and control groups are displayed, including the number of minutes per task for each session. As can be seen, from the second half of the training on, the two groups had different training schedules for 2 days a week. On Thursdays and Fridays, the TSVS large screen scanning task was (partly or as a whole) replaced by either the lane tracking or CVRT-TR task.

In this training schedule, on Mondays to Wednesdays, the standardized TSVS protocol (Pizzamiglio et al., 1990) was practiced. The division of tasks on Thursdays and Fridays was based on clinical experience. It was chosen for two reasons: first, driving simulator tasks were only added for 2 days a week since it was considered important that patients in both the control and experimental condition were allowed sufficient time to practice TSVS digit detection. Second, the CVRT-TR dual was only introduced from week 4 of the training because it was presumed that patients should first learn the centering technique as a requisite skill for an adequate execution of the dual task.

Lane tracking task. This task was also used as a part of the pre- and post-training assessment, see for details under Section "Driving Simulator Tasks."

CVRT-TR dual task. The CVRT-TR dual task was designed as a training counterpart of the CVRT-D, that was used as a diagnostic task in the present study (see Driving Simulator Tasks). Instead of the large rectangular dot patterns on three possible positions used in the CVRT-D, sequences from the TSVS large screen digit detection task were projected in the driving scene in CVRT-TR conditions. Thus, besides maintaining their driving position, patients were instructed to detect and name digits that were projected on the upper half of the screen at one of 48 possible locations (see **Figure 2** for an example). The digit sequences that were projected were the same sequences that were used in the TSVS

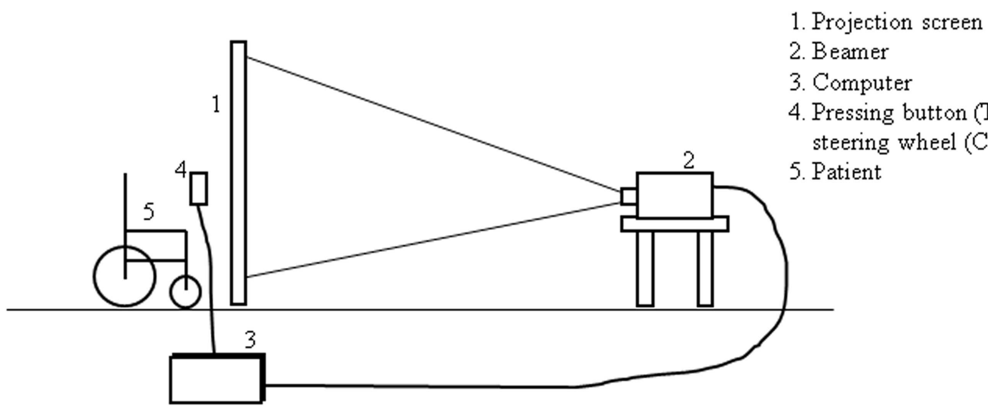

FIGURE 1 | TSVS visual scanning training set-up.

Table 2 | Training schedule for both groups.

	Monday–Wednesday	Thursday–Friday	
Week 1–3	**Both conditions: TSVS**	**Both conditions: TSVS + lane tracking**	
	Digit detection (30)	Digit detection (20)	
	Copying drawings (15)	*Lane tracking task (15)*	
	Reading/copying (10)	Copying drawings (15)	
	Figure description (5)	Reading/copying (10)	
Week 4–6		**Control condition: TSVS + lane tracking**	**Experimental condition: TSVS + dual task**
		Digit detection (20)	*CVRT-TR (35)*
		Lane tracking task (15)	Copying drawings (15)
		Copying drawings (15)	Reading/copying (10)
		Reading/copying (10)	

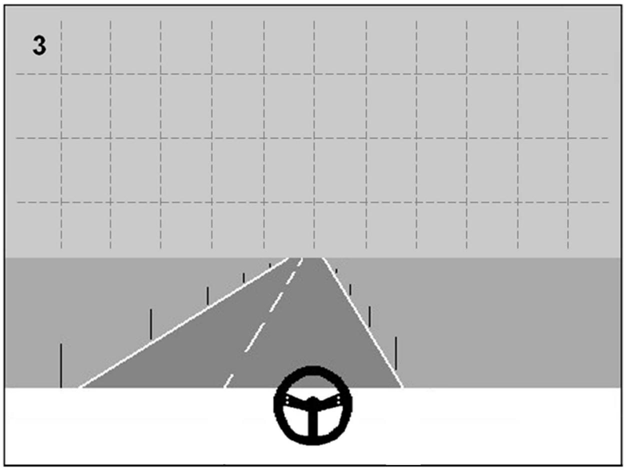

FIGURE 2 | CVRT-TR driving scene with digit projected at one of 48 possible locations.

for training patients to “center” their scanning behavior (see also Standard Training) during the second half of the training. Thus, patients were enabled to further practice this centering technique during the CVRT-TR, by choosing to focus on the straight ahead (i.e., the road in front of them) and regularly performing scanning movements to the left or right to detect digits while driving.

DATA ANALYSIS

Severity of neglect before and after training was analyzed using non-parametric (Mann–Whitney U) tests. Mixed models analyses were performed for relevant measures with time (before vs. after training) as a within subjects factor and condition (control vs. experimental) as a between-subjects factor ($N = 15$, 14). Mixed Models is a procedure in which alternative estimators are used for the parameters of a variance-analytic design; it is claimed to be more robust to violations of assumptions which are crucial for the conventional ANOVA estimators. The procedure used here was restricted maximum likelihood estimators (REML). For the covariance structure, we opted for “unstructured” (see also Rietveld, 2005). The same procedure and covariance structure are used in all Mixed Models analyses reported throughout the Results section.

RESULTS

PAPER-AND-PENCIL TASKS

Patients’ performances on the administered paper-and-pencil tasks before and after training are shown in **Table 3**.

As can be seen in **Table 3**, patients in both groups taken together showed significantly improved performances on almost all paper-and-pencil tasks. However, Mann–Whitney U tests did not show significant differences between groups on either of these scores, neither before nor after training.

A Mixed Models analysis was performed for a combined total score computed from the numbers of omissions on the line and letter cancelation tasks and the Bells test. The value of the −2 Restricted Log Likelihood information criterion was 510.08. The number of omissions in the cancelation tasks had decreased significantly after training in both groups as a whole [$F(1, 27) = 19.02$, $p < 0.001$], but no significant group effect [$F(1, 27) = 0.07$) or time × group interaction [$F(1, 27) = 0.02$] was found.

A Mixed Models analysis was also performed for a total score computed from the semi-structured scales for extrapersonal and personal neglect. The value of the −2 Restricted Log Likelihood information criterion for this analysis was 283.21. In general, patients in both groups showed significantly milder neglect symptoms on the semi-structured scales after training [$F(1, 27) = 68.13$, $p < 0.001$], but again, no significant group effect [$F(1, 27) = 0.002$] or time × group interaction [$F(1, 27) = 0.33$] was found.

DRIVING SIMULATOR DATA

Patients’ performances on the lane tracking, CVRT, and CVRT-D tasks before and after training are represented in **Table 4**.

The results in the last column of **Table 4** show that patients in both groups together had significantly improved on lateral positions in single as well as dual lane tracking after training. They also made less omissions and showed faster contralesional RTs in the CVRT as well as faster middle and ipsilesional RTs in the CVRT-D. However, again, Mann–Whitney U tests did not show significant differences between groups on any score, neither before nor after training.

A Mixed Models analysis was performed for left versus right RT asymmetries in the CVRT and CVRT-D. The values of the −2 Restricted Log Likelihood information criterion for these analysis were 753.34 and 710.29, respectively. No significant differences were found between asymmetries before and after training [CVRT: $F(1, 24.7) = 0.09$, CVRT-D: $F(1, 18.1) = 1.32$] or between groups [CVRT: $F(1, 25.6) = 0.73$, CVRT-D: $F(1, 21.4) = 0.01$]. Also, interaction effects were not significant [CVRT: $F(1, 24.7) = 2.68$, CVRT-D: $F(1, 18.1) = 0.91$]. It should be noted that since some patients omitted all left stimuli in the CVRT, CVRT-D, or both, this resulted in missing data for the RTs on this position. Therefore, varying degrees of freedom are reported. Moreover, as a result of the fact that only valid RTs were recorded, valid RTs might show an increase instead of a decrease in patients who after training did respond to stimuli they had omitted before.

CORRELATIONS WITH POST-ONSET TIMES

To account for the possible role of spontaneous recovery, two-tailed Pearson correlations were computed between days post-onset on the one hand and pre- vs. post-training differences on the other. These correlations were calculated for all measures showing significant differences in pre- vs. post-training performances (see **Tables 3** and **4**). Similar correlations were also computed between the post-onset period (in days) and pre-training as well as post-training performances. Bonferroni Holm corrections for multiple correlations (12 correlations for pre-training, post-training and pre- vs. post-training differences) were performed. No significant correlations of any measure with post-onset period were found.

DISCUSSION

In the present study, a computerized dual task was added to a standardized TSVS training (Pizzamiglio et al., 1990, 1992) for neglect patients. In this manner, patients were trained to use visual scanning strategies in an attention demanding task. It was hypothesized

Table 3 | Mean scores and SDs on paper-and-pencil and driving measures before and after training for the control (C) and experimental (E) group.

	Before training		After training		Before vs. after*
	C ($N = 15$)	E ($N = 14$)	C ($N = 15$)	E ($N = 14$)	Both groups ($N = 29$)
Line cancelation omissions (SD) cut-off: ≥1	1.53 (3.27)	2.07 (2.79)	0.40 (0.91)	0.71 (1.54)	$p < 0.01$
Letter cancelation omissions (SD) cut-off: ≥5, L vs. R ≥ 2	30.07 (29.23)	24.07 (24.15)	15.33 (20.11)	12.93 (21.55)	$p < 0.001$
Bells test omissions (SD) cut-off: ≥4	10.20 (6.84)	12.21 (8.83)	6.80 (5.13)	6.71 (7.52)	$p < 0.005$
Line bisection omissions (SD) cut-off: ≥2	1.53 (2.47)	2.43 (3.52)	0.67 (1.18)	2.21 (3.42)	ns
Reading errors (SD)	22.87 (27.28)	17.36 (22.38)	5.71 (4.82)	13.43 (11.59)	$p < 0.005$
Gray scales index (SD)	0.97 (0.10)	0.99 (0.03)	0.84 (0.32)	0.93 (0.17)	$p < 0.05$
Baking tray index (SD)	0.36 (0.59)	0.39 (0.55)	0.19 (0.57)	0.43 (0.40)	ns
Semi-structured scale extrapersonal (SD) cut-off: ≥3	6.33 (3.44)	6.79 (2.52)	3.07 (2.66)	2.71 (2.05)	$p < 0.001$
Semi-structured scale personal (SD) cut-off: ≥2	2.27 (1.58)	2.21 (2.61)	0.93 (1.10)	1.00 (0.96)	$p < 0.005$
Subjective neglect questionnaire (SD)	43.33 (13.54)	40.50 (11.11)	37.87 (11.90)	31.69 (9.46)	$p < 0.005$

Significance level $\alpha = 0.05$, Wilcoxon signed-rank tests for two related samples.

Table 4 | Mean scores and SDs on driving measures before and after training for each group.

		Before training		After training		Before vs. after*
		C ($N = 15$)	E ($N = 14$)	C ($N = 15$)	E ($N = 14$)	Both groups ($N = 29$)
Lateral position	Lane tracking (SD)	−214.00 (213.10)	−153.66 (153.77)	−131.15 (145.39)	−128.71 (120.26)	$p < 0.05$
	CVRT-D (SD)	−224.44 (209.29)	−181.36 (181.50)	−156.95 (170.56)	−111.03 (110.34)	$p < 0.05$
Oscillation	Lane tracking (SD)	71.12 (39.51)	89.08 (62.06)	68.38 (41.44)	80.00 (59.70)	ns
	CVRT-D (SD)	64.49 (37.24)	80.60 (49.15)	63.26 (28.29)	71.85 (38.11)	ns
Omissions	CVRT (SD)	5.60 (5.37)	2.69 (3.47)	2.33 (3.70)	1.83 (4.30)	$p = 0.057$
	CVRT-D (SD)	6.40 (5.51)	6.23 (6.39)	5.27 (5.35)	3.25 (5.45)	ns
RT CVRT	Left (SD)	1524.57 (1121.61)	1737.53 (1047.30)	1664.26 (1196.69)	1349.18 (928.02)	$p < 0.05$
	Middle (SD)	882.10 (677.78)	864.59 (609.41)	601.02 (275.94)	853.43 (574.88)	ns
	Right (SD)	733.04 (660.74)	845.01 (471.01)	616.55 (276.74)	857.84 (556.25)	ns
RT CVRT-D	Left (SD)	2176.96 (1280.29)	2105.93 (1460.54)	1786.43 (1071.84)	1759.81 (1154.38)	ns
	Middle (SD)	884.51 (634.93)	1106.57 (787.62)	679.57 (297.99)	987.30 (916.31)	$p < 0.05$
	Right (SD)	860.14 (475.40)	951.92 (649.09)	660.23 (276.52)	911.16 (542.13)	$p = 0.058$

Significance level $\alpha = 0.05$, Wilcoxon signed-rank tests for two related samples.

that this might enhance the automation of scanning strategies and thus contribute to an improvement of training results. Twenty-nine RH neglect patients, quasi-randomly assigned to one of two additional driving simulator training conditions, received TSVS training for 5 days a week during 6 weeks. In both conditions, for 2 days a week, the TSVS large screen digit detection task was replaced by a driving simulator task. In the control condition, patients trained with a lane tracking task two times a week during 6 weeks. In the experimental condition, lane tracking was replaced by CVRT-TR dual task training in weeks 4–6 of the training.

The primary research question of the present study was whether dual task training could contribute to an improvement of TSVS training results, as measured by various neglect tasks. No significant group or interaction effects reflecting additional positive training effects were found in the experimental group compared with the control group. Several explanations for the absence of group or interaction effects reflect the shortcomings of the present study and give clues for future research.

First, the amount of training time has to be considered. In the present study, the difference between control and experimental training time was two periods of 35 min per week during 3 weeks. This amount of time may be too small to find differences between conditions. The present results suggest that all patients had trained enough to show some improvement on most of the paper-and-pencil tasks as well as the simplest driving simulator subtasks, i.e., lane tracking and the detection of left stimuli in the CVRT single task. However, no improvement or practice effects were observed on the more complex CVRT-D.

Given the absence of a no-treatment control group, it can not be excluded that improved performance on the assessment tasks is due to spontaneous recovery, test–retest learning effects, or an interaction between these factors. Nijboer et al. (in press), for instance, found spontaneous recovery occurring up to 14 weeks after onset, on several paper-and-pencil tasks. Computerized dual tasks like the CVRT-D used in our study may show a higher sensitivity, even to slight signs of spontaneous recovery. Therefore, in future research, we recommend the use of longer post-onset times as an inclusion criterion and/or the inclusion of a no-treatment control group. Nevertheless, no significant correlations were found between pre- and post-training performances and differences in pre- vs. post-training performance on the one hand and post-onset time on the other. This indicates that spontaneous recovery does not explain all the observed improvements after training. Also, mean scores of both groups as a whole on the Bells test showed a reduction of approximately five omissions after training. This coincides with the maximum test–retest variability in the Machner et al. (2012) study (see also the Section Introduction). This result suggests that patients' progress can not entirely be ascribed to test–retest variability, although some learning effect may have been present. Our results seem in concordance with previous studies evaluating TSVS (Pizzamiglio et al., 1992; Antonucci et al., 1995; Paolucci et al., 1996). Nevertheless, the inclusion of a no-treatment control group is still recommended for future research. Including a control group might also be useful to rule out the possible role of other rehabilitation treatments that patients receive during the experimental or control training.

As in standardized TSVS, the mere amount of training time might be crucial also in dual task training (Antonucci et al., 1995; Kerkhoff, 1998). Therefore, in future research, increasing the amount of dual task training in the experimental group should be considered. The current training schedule was partly based on the standardized TSVS protocol (Pizzamiglio et al., 1990) and partly on clinical experience. Although it was presumed that patients first should learn the "centering" technique before moving on to the CVRT-TR task in the experimental condition, other training schedules allowing for more dual task practice might be considered. For example, after first introducing the centering technique during two or three training sessions in the fourth week of training using the TSVS digit detection task, the automatization of this skill might be further practiced using the CVRT-TR on a daily basis. Moreover, a repeated evaluation of the patients' performances with our assessment measures could have been useful. This might have unraveled the presence of a tendency to improve between the first half (equal for both groups) and the second half (different for the two groups) of the training. Moreover, repeated evaluation during training might reveal the time needed for substantial improvement and be useful to chart patients' progress during different training stages. Although 6 weeks of training may be considered time-consuming, the original TSVS training protocol by Pizzamiglio et al. (1990) envisages 8 weeks of training. Additional driving simulator training beyond 6 weeks might turn out to be necessary to allow the generalization of training results. This would also have minimized the demands on the patients' impaired abilities in maintaining corrective "top-down" control over spatial attention (Robertson and Manly, 2004).

In order to further evaluate the possible additional effects of dual task training and the design of future VR dual tasks for the training of neglect, it is important to address the issue of the large variability in neglect symptoms and training effects between patients. It may well be worth to evaluate larger groups of patients and to reconsider inclusion criteria for dual task training. For instance, despite the suggestion that it should be possible to also train patients with mild neglect using the CVRT and CVRT-TR, it must be noted that the groups participating in the present study consisted of patients with chronic and moderate to severe neglect. Although the CVRT-TR was, among other things, designed to allow patients with mild neglect to train visual scanning strategies up to a higher level of automation and under more challenging conditions, the inclusion criteria of the present study mostly led to the exclusion of patients with these milder degrees of neglect. Also, the CVRT-TR turned out to be too difficult for some of the participating patients. Two of them even complained that the dual task was unpleasant and had the impression that they were not improving. It might be worthwhile to evaluate which patients might really benefit from dual task training. To this end, data on the location and size of patients' lesions might be informative and aid in the tailoring of interventions.

Finally, no specific strategies were presently proposed to patients to systematically improve single and dual lane tracking. In future dual task training developments, the design of progressively increasing difficulty levels might be considered, coupled to the formulation of helpful cues and strategies to be learned accordingly. For instance, the addition (and gradual reduction) of spatial cues regarding their actual lateral position and a built-in control or "brake" function might be helpful for patients who have difficulties performing the dual task. For some patients, monitoring (the risk of) errors or omissions and exerting control over the situation by pausing and taking time to scan the environment might be an important strategy to compensate for neglect. Similarly, suitable strategies might be developed for patients suffering from neglect in combination with visual field deficits, who were excluded from the present study.

In conclusion, previous research has pointed out that computerized (dual) tasks may be very useful in the assessment of neglect (Schendel and Robertson, 2002; Bonato and Deouell, 2013). Before any recommendation can be made about the use of these tasks for training, further research is needed. Alongside the abovementioned methodological suggestions, future research might focus on the relationship between ameliorations on dual task performance and the performance on other outcome measures. For example, a robust relationships between CVRT-D performance and measures of mobility, balance, and daily functioning has recently been found (Van Kessel et al., 2012). It would be worthwhile to investigate whether possible training effects on driving simulator tasks might also be reflected in the reduction of neglect symptoms in real-life tasks like walking or (wheelchair) driving.

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Combined space and alertness related therapy of visual hemineglect: effect of therapy frequency

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The combined efficacy of space- and alertness related training in chronic hemineglect was tested behaviorally and in a longitudinal fMRI study. Earlier results had shown that both space as well as alertness related training as single intervention methods lead to short term improvement which, however, is not stable for longer time periods. The neurobiological data obtained in these studies revealed differential cortical reorganization patterns for the two training approaches thereby leading to the hypothesis that a combination of both trainings might result in stronger and longer lasting effects. The results of our current study, however, – at least at first glance – do not clearly corroborate this hypothesis, because neither alertness training alone nor the combination with OKS on the group level led to significant behavioral improvement, although four of the six patients after alertness and even more after combined training showed a higher percentage of behavioral improvement than during baseline. Despite the lack of clearcut behavioral training induced improvement we found right parietal or fronto-parietal increase of activation in the imaging data immediately after combined training and at follow-up 3 weeks later. The study design had called for splitting up training time between the two training approaches in order to match total training time with our earlier single training studies. The results of our current study are discussed as a possible consequence of reduced training time and intensity of both training measures under the combined training situation.

Keywords: neglect, therapy frequency, therapy duration, alertness, optokinetic stimulation, spatial attention, reorganization

INTRODUCTION

A main symptom of hemineglect is a lack of exploration of space contralateral to the lesion. There are different theories for the explanation of hemineglect. Neglect symptoms can be seen as a deficit in processing and integration of contralesional sensory information (Kinsbourne, 1993; Fink et al., 2000). Some authors suggest an impairment of mental representation of space (Bisiach and Luzzatti, 1978; De Renzi, 1982). Karnath (1994a) hypothesized that damage to a neural egocentric reference system leads to neglect symptoms (transformation hypothesis).

Other theories emphasize deficits of spatial directing of attention to be correlated with the phenomenon of neglect (Posner et al., 1984; Kinsbourne, 1993). Following Heilman and Van Den Abell (1980) or Mesulam (1999) the left hemisphere controls spatial directing of attention only for the right half of space whereas the right hemisphere represents both sides. Thus, right hemisphere lesions have a stronger and more generalized impact on spatial attentional processing while deficits after left hemisphere lesions can be compensated for by the bilateral attention processing capacity of the right hemisphere.

Recent findings suggest that persisting neglect symptoms are not solely caused by dysfunction of specific cortical regions but rather by the disconnection of larger networks comprising partially distant frontal and parietal regions of the right hemisphere (Bartolomeo et al., 2007). A central role of the superior longitudinal fasciculus (SLF II) as a connection between these regions was demonstrated by stimulation of the SLF II during neurosurgical intervention in patients suffering from a temporal glioma (without neglect symptoms): stimulation led to a considerable rightward shift in a line bisection task (Thiebaut de Schotten et al., 2005).

These findings might be a direct anatomical counterpart to the hypothesis by Fernandez-Duque and Posner (1997) of a close cooperation between control systems for alerting and orienting, i.e., between anterior and posterior attention systems (see also Sturm et al., 2006a) and a disconnection of these systems could explain the strong correlation between non-spatial (vigilance or sustained attention) attention deficits and hemineglect after right hemisphere damage.

SPACE-CENTERED THERAPY APPROACHES IN HEMINEGLECT

Most clinical therapy methods for hemineglect aim at improving the patient's exploration behavior. The following trainings led to amelioration of neglect symptoms although improvement was not stable over time: transcutaneous electroneutral stimulation of the left neck muscle (Karnath et al., 1993; Karnath, 1994b; Pizzamiglio et al., 1996); vestibular stimulation (Karnath, 1994b); visuomotor prism adaptation (Rossetti et al., 1998; Frassinetti et al., 2002, with repeated interventions yielding longer lasting effects); visual exploration training (Antonucci et al., 1995; Kerkhoff, 1998).

OPTOKINETIC STIMULATION THERAPY (OKS TRAINING)

Optokinetic stimulation is a procedure that displays visual stimuli on a screen which move coherently from the ipsilesional to the contralesional side thereby inducing smooth-pursuit eye movements if the patient follows the stimuli. This leads to an exogenously triggered directing of spatial attention to the neglected side.

Transient reduction of neglect under OKS has been demonstrated for the line bisection error (Mattingley et al., 1994), size, and space distortion (Kerkhoff et al., 1999; Kerkhoff, 2000), horizontal displacement of the sagittal midplane (Karnath, 1996), tactile extinction (Nico, 1999) as well as position sense deficit and motor weakness of the left limb (Vallar et al., 1993, 1995, 1997a,b). Unlike these studies, where OKS produced a passive, automatic stimulation via background movements, while patients were simultaneously engaged in another task, Kerkhoff et al. (2001, 2006) asked for active pursuit of the stimuli presented on the screen. After therapy, patients showed substantial improvement in digit cancelation, line bisection, visual size distortion, neglect dyslexia, and auditory neglect. These effects remained stable at a 2-week follow-up assessment. Compared to a conventional visual scanning training, OKS treatment showed stronger and more stable effects.

In our own therapy study (Sturm et al., 2006b; Thimm et al., 2009) seven neglect patients were treated daily for 45 min over a time period of 14 days with the OKS Training method introduced by Kerkhoff et al. (2001, 2006). After therapy, they showed a significantly higher number of improvements in a number of neglect tests (NETs) than after a 3 week baseline phase. Four weeks after the end of the training, however, lasting improvements could only be demonstrated in three of the patients. Longitudinal fMRT activation examinations revealed that a reduction of neglect symptoms after OKS training was accompanied by bilateral reactivation of parts of the posterior attention network (precuneus).

ALERTNESS RELATED THERAPY APPROACHES OF SPATIAL HEMINEGLECT

The presence and severity of spatial awareness deficits in hemineglect seem to depend greatly on the amount of attentional resources available for performance and thus can be strongly influenced by task demands (for a review see Bonato, 2012). Thus, spatial neglect subsequent to right hemisphere lesions often is closely associated with non-spatial deficits of attention like intrinsic alertness and sustained attention (Samuelson et al., 1988; Robertson, 1993, 2001; Hjaltason et al., 1996; Husain and Rorden, 2003; Corbetta and Shulman, 2011). Several studies have shown that the degree to which sustained attention is impaired is a strong predictor for the persistence of neglect (Samuelson et al., 1988; Robertson et al., 1997). The postulated interaction between an anterior alerting and a posterior spatial attention network (Heilman et al., 1978; Posner and Petersen, 1990; Fernandez-Duque and Posner, 1997; Sturm et al., 2006a) directly leads to the hypothesis that training of alertness may improve spatial neglect in right hemisphere stroke patients. First evidence supporting this hypothesis comes from a study by Robertson et al. (1995). In that study, attention training based on a self-instruction technique and on an enhancement of "phasic" alertness resulted in an improvement of neglect symptoms in all patients. Patients during the training were taught to give themselves the (silent, internal) instruction "be alert" before starting a task. In another study, Robertson et al. (1998) temporarily reduced the spatial bias of neglect patients by phasic alerting.

The concept of "alertness" on the one hand comprises a state of general wakefulness (tonic alertness) and the ability of top-down control of this state during phases of diminished external stimulation (Sturm et al., 1999, 2004b). On the other hand "phasic alertness" represents the ability to shortly improve the arousal level after a warning cue. In their rehabilitation study, Robertson et al. (1995) tried to activate the phasic alerting system, which may be intact, at least in part, after right hemisphere lesions (Sturm and Willmes, 2001; Yanaka et al., 2010) by using self-instructions. Degutis and Van Vleet (2010) found an improvement of sustained attention and neglect after a combined tonic and phasic alertness training (TAPAT).

In 1993 we (Sturm et al., 1993) developed a computerized training (AIXTENT) addressing different attention functions. During the AIXTENT alertness training, a car or motor cycle – driving at high speed – has to be stopped by the patient whenever an obstacle appears on the road. The impact of a 14-days treatment by this alertness training (45 min per day) on neglect initially was tested in a single case study (Sturm and Willmes, 2001) and later on in another study of seven neglect patients (Thimm et al., 2006). There was a significantly higher number of improvements after therapy than after a 3-week baseline phase, accompanied by significantly enhanced activations in the middle and medial frontal gyrus, in the anterior cingulate gyrus and in the right angular gyrus. The behavioral and functional changes, however – as for the OKS training (see above) – did not prove stable over a prolonged time period (3 weeks after the end of the therapy). There were, however, considerable interindividual differences, and in some patients (three out of seven) a stable effect of the alertness training on neglect symptoms in fact could be observed. Bilateral high frontal and anterior cingulate as well as left parietal reactivations corresponded to these long term effects and may represent a long lasting reorganization of the system for the top-down control of alertness.

COMPARISON OF ALERTNESS AND OKS TRAINING EFFECTS

Behaviorally, OKS and Alertness training led to comparable functional improvements (Thimm et al., 2009). A comparison of the patterns of functional reorganization after the two training approaches revealed a frontal increase of activation after alertness training and a superior parietal increase of activation after OKS training, thus being consistent with the theory of interacting anterior intensity and posterior orienting attentional networks (Fernandez-Duque and Posner, 1997). From the results it became evident that both space as well as attention/alertness related training approaches as single interventions lead to a more or less comparable short term improvement of neglect symptoms but that neither of the two could induce lasting, i.e., long term effects. The data furthermore suggest that the differential activation of frontal or parietal areas may reflect the specific impact of the two types of training either on an anterior system for the control of attention intensity (AIXTENT) or on the posterior system of spatial attention (OKS), respectively. Thus, a combination of both therapy approaches might lead to a supplementary or even reinforcing effect. Indeed, other studies have shown that more permanent training effects in neglect patients can be achieved by the combination of different training methods. The combination of two space related trainings [visual exploration and limb activation training (Brunila et al., 2002) or neck muscle vibration (Schindler et al., 2002)] was particularly successful. A similar long lasting effect was seen after combined limb activation and sustained attention training (Wilson et al., 2000). Accordingly, the goal of our present study was to examine the efficiency of a combined alertness and OKS training in patients suffering from visual hemineglect.

MATERIALS AND METHODS

STUDY DESIGN

The study design was comparable to our previous studies (Thimm et al., 2006, 2009) where we used either an alertness training as part of the computerized attention training system AIXTENT or an "OKS" training, but this time combining the two training methods. In order to keep the overall training time comparable to our former studies, the total training time was split between alertness and OKS training (see **Figure 1**). The study of patients started with a neuropsychological assessment of the neglect symptoms ("pre 1"). Neglect tests were repeated after 3 weeks in order to generate a baseline for the behavioral data ("pre 2"). This baseline served to control for behavioral improvements due to spontaneous recovery (although the fact that only patients in the postacute phase were included made spontaneous recovery effects less probable). When the inclusion criteria still held at the end of the baseline period, the first fMRI measurement took place, using a spatial attention paradigm (see below). During the following 4 weeks (excluding weekends and days reserved for Neuropsychological assessment or fMRI, see **Figure 1**), patients underwent seven sessions of alertness training followed by seven sessions of "OKS" training daily, each session lasting 45 min. We always started with the alertness training, because theoretically this is the more basic training procedure possibly enhancing overall activation level and thus enabling OKS training to be based on an improved level of arousal control. Immediately after the alertness training ("post 0.5"), at the end of the OKS period ("post 1") and 3 weeks after the complete training period ("post 2"), again a neuropsychological and an fMRI assessment were carried out to assess both specific and combined short and long term effects of alertness and alertness + OKS training on spatial neglect.

PATIENTS

Six (two female, four male) right-handed patients [as assessed by a German translation of the Edinburgh-Handedness-Inventory (Oldfield, 1971)] with cortical and subcortical right hemisphere vascular lesions and symptoms of visuospatial neglect were included. The patient characteristics are detailed in **Table 1**. Median age was 62.5 years (range 45–74 years). All patients showed stable neglect symptoms for at least 3 months post stroke (median time 4 months, range 3–6 months). For inclusion, at the second pretest ("pre 2") patients had to show neglect symptoms in at least two tasks of the "NET" (Fels and Geissner, 1996) or the "Test Battery of Attentional Performance" (TAP: Zimmermann and Fimm, 2007) described in detail later. Exclusion criteria were left-handedness, left hemisphere infarction, epilepsy, and any severe internal medical disease. Inclusion and exclusion criteria were the same as in our earlier studies (Thimm et al., 2006, 2009). Patients again were recruited from the inpatient service of the Neurological Clinic at the University Hospital Aachen and from the Neurological Rehabilitation Centre "Godeshöhe" in Bonn. The study was approved by the local Ethics Committee of the Medical Faculty of the University Hospital Aachen. Informed consent was given by all patients prior to participation in the study. Compared to our previous training studies (Thimm et al., 2006, 2009), the patients' sample was similar with respect to sex distribution, age, and lesion localization. **Figure 2B** depicts the individual lesion plots. Each patient had a typical infarction of the right middle cerebral artery (MCA). The patients had frontoparietal (M.R, H.H.), fronto-temporo-parietal (E.B., K.Z.), or temporoparietal (D.B., R.A.) lesions. In four patients (E.B., H.H., D.B., R.A.) the lesions protruded into subcortical areas, probably comprising the SLF

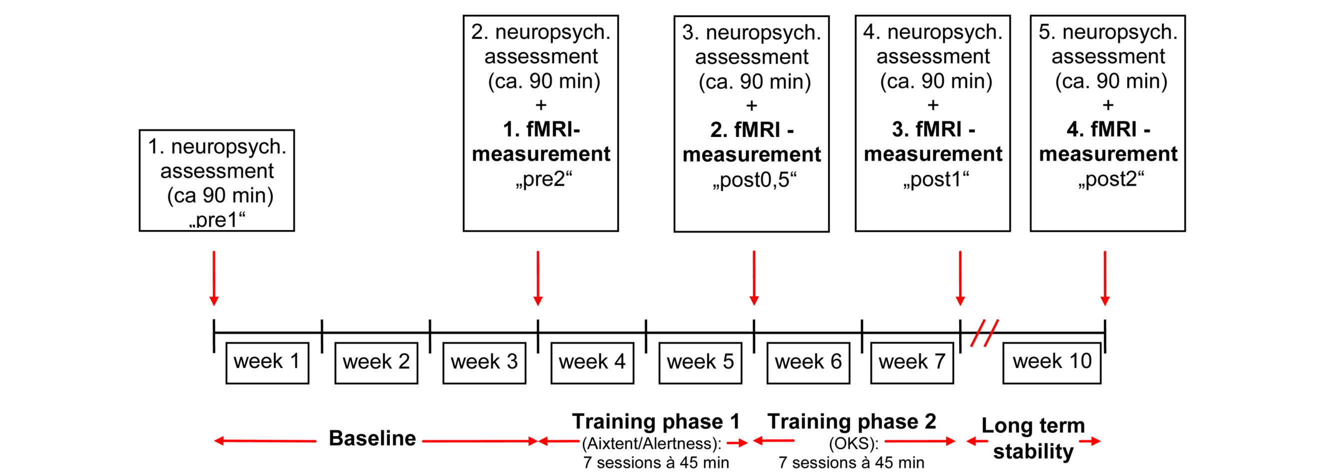

FIGURE 1 | Time schedule for the combined training alertness-OKS.

Table 1 | Patient characteristics and test results at the first pretest "pre 1."

Pat.	Sex	Age (years)	TPO (m)	NET LeC	NET LiC	NET SC	NET LB	NET Te	TAP VF (%)	TAP VF (RT)	TAP NEG (%)	TAP NEG (RT)	TAP VS
E.B.	F	45	6	+	–	–	–	–	+	–	+	–	–
M.R.	M	45	4	–	+	**–**	–	+	+	–	+	–	+
H.H.	M	74	3	**–**	+	+	+	–	+	**–**	+	–	–
K.Z.	M	69	3	**–**	+	+	+	+	+	–	+	–	**–**
D.B.	F	71	4	**–**	–	**–**	**–**	–	–	–	–	n.d.	–
R.A.	M	56	4,5	–	–	–	–	**–**	**–**	**–**	**–**	–	n.d.

+, normal score; –, pathological score; ***bold, significantly improved from "pre 1" to "pre 2;"*** *pat, patient; TPO, time post onset of neglect (months); NET, "Neglect-Test" (Fels and Geissner, 1996); LeC, letter cancelation; LiC, line cancelation; SC, star cancelation; LB, line bisection; Te, text; n.d., not done; TAP, "Test Battery of Attentional Performance" (Zimmermann and Fimm, 2007); TAP VF (%), visual field – % of detected left sided stimuli; TAP VF (RT), visual field – median reaction time (ms) on left sided stimuli; TAP NEG (%), neglect task – % of detected left sided stimuli; TAP NEG (RT), neglect task – median reaction time (ms) on left sided stimuli; TAP VS, visual scanning – overall number of detected stimuli in the left two columns.*

II, thus possibly causing a parieto-frontal disconnection. Interestingly, these four patients revealed the highest number of impaired test results in our neglect test battery (see **Table 1**). For comparison **Figure 2A** shows the lesion data of the patients included in our former two studies.

ALERTNESS TRAINING (COGNIPLUS)

The alertness training consisted of a subprogram of the Attention Training Program Package CogniPlus (Version 2.01: Sturm, 2007) and was developed from the AIXTENT alertness training described in the introduction. The patient watches on a computer screen a moving motorcycle from the driver's viewpoint in a realistic scene. Sudden events such as falling trees or rocks, cars crossing the street, traffic lights changing to red and animals crossing have to be responded to as fast as possible by pressing a large response key. The task mainly follows the theoretical framework of an alertness task (simple reaction time measurement mostly without need for a selection of targets: targets are easily detectable and there is not much need for a discrimination between target and non-targets). A recent study has shown that both this alertness training and a classical alertness task (simple visual reaction time measurement without warning) activate very comparable cortical and subcortical networks (Clemens et al., 2013).

There are two different modes of the training: (a) Training of phasic alertness: in order to evoke phasic alerting, the participant hears a warning signal and sees a traffic sign announcing possible target situations before the actual event happens. Feedback is given visually if an obstacle is overlooked or if the response was too slow. This feedback ensures that participants know when they have made an error so that they can try to improve their performance. (b) Training of intrinsic alertness: under this training condition, no warning signals are given in order to provoke an improvement of intrinsic, i.e., top-down controlled alertness. Furthermore, under the intrinsic alertness condition the whole scene is made less clearly visible (foggy) in order to prevent phasic alerting signals to be evoked by the surroundings.

Under both conditions the difficulty level is adjusted by the average speed of the motorcycle. To reach a specific level, a minimum response time is necessary ranging from 1.8 s for the lowest to 0.3 s for the highest level. Depending on the subject's mean response time the difficulty level is adapted automatically by the computer program. Before starting the training, during an instruction and practice period the mean response time of the patient is assessed which, in turn, defines the initial difficulty level for the subsequent training period.

OPTOKINETIC STIMULATION TRAINING

The OKS training used is part of the treatment program "EYEMOVE"[1]. Patients had to look at a computer screen (43° × 35°) where a pattern of randomly distributed, colored squares moving coherently from the right to the left side was displayed against a dark background. Patients were instructed to perform smooth-pursuit eye movements following the stimulus pattern until reaching the left margin and then to jump back to the right margin repeatedly. No head movements were allowed. To keep patients motivated, every few minutes the stimulus pattern was varied in color, speed (5–35°/s), size (0.2–2.5°), and number (30–70) of squares. The duration of each training session was 45 min. Every 10 min or whenever a patient asked for it, a break was allowed for a few minutes.

NEUROPSYCHOLOGICAL ASSESSMENT

Neglect symptoms were assessed using subtests of the TAP [(Zimmermann and Fimm, 2007) subtests "neglect," "visual field," and "visual scanning"] and the NET (Fels and Geissner, 1996), a German version of the "Behavioral Inattention Test" (BIT: Wilson et al., 1987), including letter, star and line cancelation, line bisection, and text reading (see also **Table 1**).

The subtests of the TAP repeatedly have proven their sensitivity as control tasks in attention rehabilitation studies (e.g., Sturm et al., 1997, 2003; Sturm et al., 2004a).

TAP, subtest "neglect"

Patients were instructed to fixate on a central square (size 3.8°) on a black screen. To ensure steady fixation, they had to read

[1] http://www.medicalcomputing.de

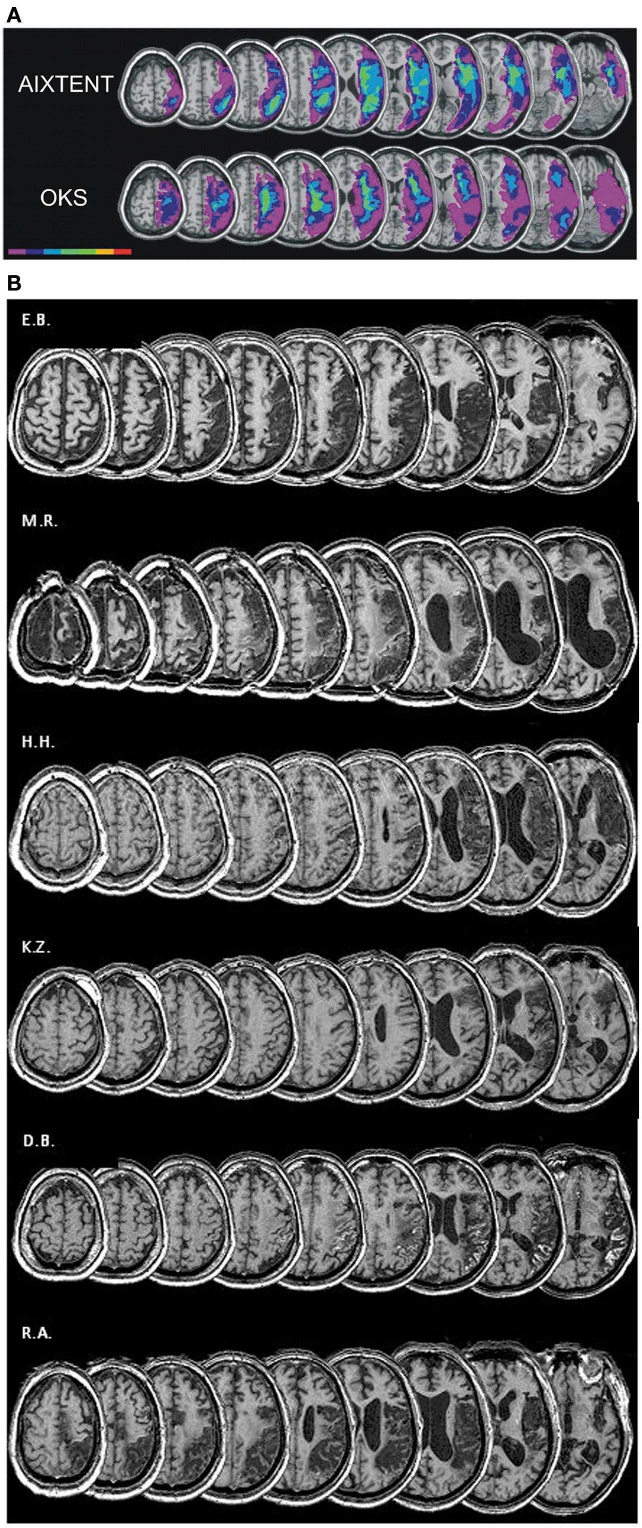

FIGURE 2 | (A) Overlay lesion plots for the AIXTENT (alertness-training) group ($n = 7$) and OKS group ($n = 7$; Thimm et al., 2009). The number of overlapping lesions is coded and indicated by the color bar from violet ($n = 1$) to red ($n = 7$). **(B)** Lesion plots of individual patients of the combined alertness + OKS training group.

aloud single letters appearing and changing every few seconds in the central square. Around the square in each visual hemifield the display showed 24 randomly distributed white distractors (small, hardly legible two, and three digit numbers). These stimuli were introduced to enhance possible neglect symptoms by distraction. In the gaps between these distractors a peripheral three digit target appeared at random locations in either the left or the right visual field within 13° from the central square. These three digit targets, however, appeared as flickering stimuli. Patients were instructed to press a key with the right index finger as soon as they detected the target. This was presented until the key was pressed or for a maximum of 3 s. In each visual half field 22 targets were presented at different positions. Dependent variable was the number of detected stimuli in the left visual half field.

TAP, subtest "visual field"

This test was very similar to the TAP-neglect test described above. In contrast to the neglect test, however, the screen was not filled with distractors. Thus stimuli could be detected more easily (as no distraction occurred). Forty-six stimuli were presented in each visual half field.

TAP, subtest "visual scanning"

Patients had to detect a target stimulus in a 5 × 5 matrix of similar distractors. The target stimulus was a square with an opening in the top line while the distractors had an opening in the left, right, or bottom line. Altogether 100 matrices were presented, half of them containing a target stimulus. Target stimuli were randomly distributed over the matrices, appearing two times at each possible position, thus 10 stimuli per column were presented. Patients were instructed to scan the matrix as fast as possible from the top left to the bottom right. They had to respond with their right hand by pressing either the left ("yes") or the right ("no") of two response keys deciding if the matrix contained a target stimulus or not. Dependent variable was the overall number of detected stimuli in the left two columns.

NET, cancelation tasks

These tasks required the patients to detect and cancel target stimuli distributed on a piece of paper. Dependent variable was the number of detected stimuli in the left half of the template.

Letter cancelation: targets: letter "E" or "R" (20 left, 20 right); with other letters serving as distractors.

Line cancelation: targets: lines of 26 mm length, rotated in different orientations (18 left, 18 right); no distractor.

Star cancelation: targets: little stars (28 left, 28 right); bigger stars, letters, and words served as distractors.

NET, line bisection: to assign the center of three lines of 20 cm length, located at the right, middle, and left side of an A4 sized sheet of paper. Dependant variable was the average deviation in millimeters across the three lines transformed into a percent score (100% = no deviation).

NET, text reading: to read aloud a newspaper article arranged in three columns.

fMRI ACTIVATION TASKS

Spatial attention task

A modified version of the subtest "neglect" of the TAP was used as activation paradigm in a box-car fMRI design. The task stimuli were presented via a head mounted video optical unit (VisuaStim XGA with eye tracker, Arrington Research Inc.). Patients were instructed to fixate on a central square. In each visual hemifield, the display contained 24 randomly distributed white distractors ("#"). In the gaps between these distractors, a peripheral flickering target (as well "#") appeared at random locations in either the left or the right visual field within 13° from the central square. The display covered a visual angle of 19.5° vertically and 30° horizontally. Each stimulus subtended 1.5° of visual angle. Target stimuli were presented in a pseudo-randomized sequence at varying positions in the left or right half of the screen. There were equal numbers of left- and right-sided targets (22 each). Stimulus onset asynchronies varied between 1500 and 4000 ms.

Patients were instructed to press a non-magnetic air pressure key with their right index finger as soon as they detected the target, which was presented until the key was pressed or for a maximum of 3 s.

Alertness task

This task was used to control for primary sensory and motor activation and for the alertness aspects of the neglect task (Sturm et al., 2006b). Patients had to respond to the same stimuli as in the neglect task. The only difference in the alertness task was the *location* of the stimuli, which were exclusively presented centrally, i.e., inside the fixation square. This condition undoubtedly also calls for some kind of spatial attention but this is much more focused centrally whereas under the neglect task condition a spatial distribution of attention is necessary (Sturm et al., 2006b).

fMRI DATA ACQUISITION

Each fMRI session consisted of two functional runs (alertness task, neglect task) in a box-car fMRI design which included 11 alternating periods of six times rest (15 s) and five times activation (37 s). Before each run, patients were informed about which kind of task would follow next. FMRI was performed on a 1.5 T Philips NT Gyroscan using a standard bird-cage head coil and T2*-weighted gradient echo EPI sequences (TR: 2900 ms, FA: 90°, Matrix 64 × 64, FOV: 250mm × 250 mm, 31 continuous slices parallel to the AC-PC line, comprising the whole brain, slice thickness 3.5 mm, no inter-slice gap).

STATISTICAL ANALYSIS OF THE BEHAVIORAL DATA

Test results were considered as indicative of neglect if they were below the test norm for healthy subjects (cancelation tasks, line bisection) or if the number of detected words/stimuli (text, TAP tests), or median reaction times (TAP visual field and NET) were significantly lower or slower, respectively, on the left than on the right side. This was assessed using Fisher's exact test or by t-Tests.

For the individual patient, improvements in text reading, the cancelation tasks of the NET, the neglect specific subtests of the TAP, and the fMRI neglect task were investigated by Fisher's exact test considering the number of left sided detected or canceled stimuli. Furthermore, cancelation tasks and line bisection (mean deviation from center to the right in millimeters transformed into a percent score: 100% = no deviation) were judged as improved, when a pathological score increased to within the normal range. Response times in the TAP and fMRI tasks were compared across the test sessions by means of ANOVA always considering only the left part of each test.

Due to this evaluation approach, patients served as their own control. As in our previous studies, the total number of improved test results after each training period was compared by Fisher's exact test with the number of improvements at the end of the baseline period. Tests showing normal results from the beginning and thus allowing no neglect related improvement were not considered.

Additionally, the percentage of improved vs. not improved test results was compared across patients between the baseline and different training phases by means of Wilcoxon's signed ranks test.

STATISTICAL ANALYSIS OF THE fMRI DATA

Analysis of the activation data was carried out using statistical parametric mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK[2]) using MATLAB version 6.5 (The MathWorks Inc., Natick, MA, USA). After discarding the first three volumes of each run, functional images were realigned to the new first scan of a session to compensate for movement artifacts. Realignment parameters showed no major translation (>one voxel size) or rotation (>2°), thus there was no reason to exclude any measurement. For the group analyses, realigned images were normalized to a standard EPI template based on the MNI reference brain following the Talairach convention (Talairach and Tournoux, 1988) resulting in a voxel size of 3mm × 3mm × 3 mm. To avoid image distortion caused by the lesions of the patients' brains, only affine normalization was chosen. Finally, all images were smoothed with a Gaussian filter of 8 mm to improve signal-to-noise ratio.

In order to assess the neural correlates of behavioral short term improvements induced by each single training, group contrasts were set up between post 0.5 and pre 2 (AIXTENT) as well as post 1 and post 0.5 (OKS). The effect of the entire training program was investigated by the contrast post 1 vs. pre 2. Long term effects were investigated by the contrast post 2 vs. pre 2. Contrasts were controlled for deactivation by using an inclusive masking procedure. Only clusters comprising at least 10 voxels with a threshold of $p < 0.05$ false discovery rate (FDR)-corrected will be reported.

RESULTS

BEHAVIORAL EFFECTS OF ALERTNESS TRAINING, OKS TRAINING, AND THE COMBINATION OF BOTH

As pointed out above, our design enabled us to use each patient as his or her own control. Thus, we compared short term effects resulting from the CogniPlus alertness training (post 0.5 vs. pre 2), the combined effects of Alertness plus OKS training (post 1 vs. pre 2), and long term effects (post 2 vs. pre 2) with any spontaneous changes during the baseline period (pre 2 vs. pre 1). Significant improvement during the baseline was found in a total of 12 of 38 originally impaired neglect scores across the six

[2]http://www.fil.ion.ucl.ac.uk/spm

patients (see **Table 2**). After the training periods, ameliorations were found in 12 of 39 test scores (CogniPlus alertness), and 17 of 39 test scores (CogniPlus alertness + OKS). Four weeks after the end of the last training procedure (long term effects) 13 out of 39 test scores remained improved. **Tables 2** and **3** show the original results of the different neglect tasks for the different training periods and **Table 4** presents the respective number of improvements resp. lack of performance changes plus the results of Fisher's Exact Test. For comparison, **Table 4** also presents the results of our former studies. In contrast to our former studies, neither alertness training alone nor the combination of alertness plus OKS training led to a significantly higher rate of improvement than the one caused by spontaneous remission in the baseline phase.

The percentage of improved vs. not improved test results across patients was 38.5% for the baseline, 36.5% for the alertness training, 64.8% for alertness + OKS training, and 36.5% for the long term phase 3 weeks after the end of both training procedures. The comparison of these improvement rates between the different phases by means of Wilcoxon's signed ranks test (one-tailed) revealed $p = 0.078$ for the comparison alertness with alertness + OKS and of $p = 0.094$ for alertness + OKS with the long term phase. All other comparisons were far from significant. Thus, in this analysis there was a trend for a higher percentage of improvements after the administration of alertness + OKS training than after alertness training alone and for an improvement decline during the long term phase after the end of both training procedures. The patients with the highest number of initially impaired test parameters tended to profit least especially from the combined training approach whereas the opposite pattern occurred for the initially less impaired patients as can be seen from the individual percentage improvement scores (percentage of number of improved test scores with reference to the number of impaired scores at the end of the baseline phase) in **Table 5**. Four of the six patients (E.B., M.R., H.H., and K.Z.) numerically either after alertness or after combined training showed a higher percentage of behavioral improvement than during baseline. Because not every patient underwent each of the several test procedures it is difficult to compare the sensitivity of the different tests to detect behavioral changes during therapy in the single case. It seems, however, that with the computerized tasks a higher number of

Table 2 | Results of paper and pencil tasks.

Pat.	CT letters					CT lines					CT stars					LB					Text				
	a	b	c	d	e	a	b	c	d	e	a	b	c	d	e	A	b	c	d	e	a	b	c	d	e
E.B.						83	n.d.	**100**	**100**	78	93	n.d.	89	**96**	**100**	67	n.d.	**100**	78	**100**	0	n.d.	**96**	**55**	**100**
M.R.	90	80	85	90	70											67	56	44	**89**	78					
H.H.																					100	55	55	**100**	**100**
K.Z.																									
D.B.	5	40	**80**	15	0	67	83	67	89	72	59	85	44	85	41	0	33	33	0	0	0	0	0	0	0
R.A.	70	35	50	**70**	**75**	72	78	67	94	89	81	70	63	81	74	67	67	89	56	89	0	55	55	55	55

Bold, significant improvement compared to pre 2 (pre 1 in patient E.B.)*; empty cells, not impaired at pre 2 (pre 1 in patient E.B.); n.d., not done; CT/text, cancelation tasks and text: % of detected left sided stimuli/words; LB, line bisection: score = average deviation in millimeters across the three lines transformed into a percent score (100% = no deviation); a, pre 1; b, pre 2; c, post 0.5; d, post 1; e, post 2.*

Table 3 | Results of computerized tasks.

Pat.	TAP VF (%)					TAP VF (RT)					TAP NEG (%)					TAP NEG (RT)					TAP VS				
	a	b	c	d	e	a	b	c	d	e	a	b	c	d	e	a	b	c	d	e	a	b	c	d	e
E.B.						785	n.d.	**448**	**553**	**512**						757	n.d.	930	755	712	50	n.d.	70	**100**	**95**
M.R.						558	506	**380**	**415**	**400**	91	82	77	**100**	95	704	1059	**519**	**586**	**486**					
H.H.						944	640	660	624	603	86	64	**86**	**91**	**91**	1103	1384	**1062**	**1157**	**817**	20	15	15	**45**	15
K.Z.						736	797	770	762	704						1180	966	968	**866**	**772**	45	70	75	**90**	75
D.B.	48	15	**41**	11	**48**	1378	1029	**725**	1770	**691**	5	0	0	0	5	n.d.	n.d.	n.d.	n.d.	n.d.	35	15	15	15	20
R.A.	78	93	96	89	91	962	672	693	621	696						1544	1459	**1052**	**773**	**968**	n.d.	20	15	15	30

Bold: significant improvement compared to pre 2*; empty cells, not impaired at pre 2; n.d., not done; TAP, "Test Battery of Attentional Performance" (Zimmermann and Fimm, 2007); TAP VF (%), visual field – % of detected left sided stimuli; TAP VF (RT), visual field – median reaction time (ms) on left sided stimuli; TAP NEG (%), neglect task – % of detected left sided stimuli; TAP NEG (RT), neglect task – median reaction time (ms) on left sided stimuli; TAP VS, visual scanning – overall number of detected stimuli in the left two columns; a, pre 1; b, pre 2; c, post 0.5; d, post 1; e, post 2.*

Table 4 | Number of improved or unchanged test results after the different training periods (see Figure 1) and results of Fisher's exact test for the current and for the preceding studies.

Training	Therapy phase	Comparison	Initial number of test results indicative of neglect (baseline: pre 1, training: pre 2)	Number of significantly improved test results per phase	Number of not improved test results per phase	Fisher's exact test for the comparison baseline/training resp. training/training (alertness/OKS)
Alertness (14 training sessions; Thimm et al., 2009) $n = 7$	Baseline	Pre 2–pre 1	32	3	29	$p = 0.025$
	Training	Post 1–pre 2	31	10	21	
OKS (14 training sessions;Thimm et al., 2009) $n = 7$	Baseline	Pre 2–pre 1	33	8	25	$p = 0.017$
	Training	Post 1–pre 2	30	16	14	
Alertness + OKS (7 training sessions each) $n = 6$	Baseline	Pre 2–pre 1	38	12	26	$p = 1.000$
	Alertness	Post 0.5–pre 2	39	12	27	
	Alertness + OKS	Post 1–pre 2	39	17	22	$p = 0.349$
	Alertness + OKS long term	Post 2–pre 2	39	13	26	$p = 1.000$

significant changes could be detected in the single case (TAP Visual field, response times for left sided stimuli: three improvements after Alertness training, two after OKS; TAP-Neglect, response times for left sided stimuli: three improvements after Alertness training, four after OKS; TAP Visual Scanning, no improvement after Alertness training but three improvements after OKS). This single case analysis shows the same trend for a higher efficacy of Alertness + OKS training compared with Alertness Training alone as the above reported group analysis. In contrast, most of the paper-and-pencil Tests could detect behavioral changes only in one patient.

In the fMRI neglect task, one patient (M.R.) showed significant behavioral improvement after alertness training and two other ones (H.H. and D.B.) after OKS Training (see **Table 6**).

fMRI DATA

After alertness training alone, concordant with the preponderance of absence of improvement at the behavioral level, no significant changes of neural activity were found (contrasts post 0.5 > pre 2). After combined training (alertness + OKS) a significant increase of activity (see **Table 7**) in the right superior parietal lobule (BA7) could be observed (post 1 > pre 2). Despite the fact that at follow-up (post 2 > pre 2) behaviorally some of the training induced improvements decreased, we not only still found the above mentioned increased right superior parietal activity (BA7) but also an additional increase in activity in the left inferior parietal lobule (PF) and in the dorsolateral prefrontal cortex (DLPF, BA9).

DISCUSSION

From the results of our previous studies (Thimm et al., 2006, 2009) it became evident that both space as well as attention/alertness related training approaches as single interventions lead to a more or less comparable short term improvement of neglect symptoms, but that neither of the two can induce long term effects. A comparison of the patterns of functional reorganization after the two training approaches revealed a stronger frontal increase of activation after alertness training and a stronger superior parietal increase of activation after OKS training. The data thus suggest that differential activation of frontal or parietal areas may reflect the specific impact of the two types of training either on an anterior system for the control of attention *intensity* (AIXTENT) or on the posterior system of *spatial* attention (OKS), respectively. Thus, it was our hypothesis for the present study that a combination of both training approaches might lead to a supplementary or even reinforcing effect. Other studies in fact corroborated this hypothesis: the combination of two space related trainings [visual exploration and limb activation training (Brunila et al., 2002) or neck muscle vibration (Schindler et al., 2002)] as well as a combined limb activation and sustained attention training (Wilson et al., 2000) led to more long lasting effects than the single training methods.

Thus, the main aim of this study was to prospectively investigate in right hemisphere stroke patients suffering from chronic spatial neglect the behavioral and neural effects (by fMRI) of a combined alertness and OKS training. As in our previous studies (Thimm et al., 2006, 2009) in which the effects of alertness training or of OKS were investigated separately, we applied a study design in which each patient served as his/her own control by comparing the effects of the single (only alertness training) or combined (alertness + OKS) treatment with a baseline phase. Furthermore, the study design enabled us to test for long time effects 3 weeks after the end of the last training procedure.

In our former studies, each training procedure was administered on 14 consecutive days (except weekends) for 45 min each day. In order to keep the overall training time comparable to our former studies, in our present study the total training time was split between alertness and OKS training. Thus, each patient underwent seven sessions of alertness training followed by seven sessions of "OKS" training, each session lasting 45 min.

Interestingly, in our current study we could not replicate our former behavioral findings, nor could we find a clearcut

Table 5 | Initial severity of impairment (number of neglect tasks outside normal range) and percentage of improvement (compared to the number of impaired parameters at the end of the baseline pre 2) during the different treatment phases for each individual patient.

Pat.	Number impair. param. at pre 1	Number improv. param. at pre 2	Number not improv. param. at pre 2	% Improv. param. during basel	Number impair. param. at pre 2	Number improv. param. at post 0.5	Number not improv. param. at post 0.5	% Improv. param. during alertn. training	Number improv. param. at post 1	Number not improv. param. at post 1	% Improv. param. during alertn. + OKS training	Number still improv. param. at post 2	Number no longer improv. param. at post 2	% Still improv. param. at post 2
R.A.	9	4	5	**44.4**	9	1	8	**11.1**	2	7	**22.0**	1	8	**11.1**
D.B.	9	3	6	**33.3**	9	3	6	**33.3**	0	9	**0.0**	2	7	**22.0**
E.B.	7	0	7	**0.0**	8	4	4	**50.0**	5	3	**62.0**	5	3	**62.0**
M.R.	5	1	4	**20.0**	5	2	3	**40.0**	4	1	**80.0**	2	3	**40.0**
H.H.	4	2	2	**50.0**	5	2	3	**40.0**	4	1	**80.0**	2	3	**40.0**
K.Z.	4	2	2	**50.0**	3	0	3	**0.0**	2	1	**67.0**	1	2	**33.0**

Percentage of improvement during baseline refers to pre 1.

Table 6 | Behavioral results in the fMRI tasks.

Pat.	fMRI spatial attention (%)				fMRI spatial attention (RT)			
	Pre 2	Post 0.5	Post 1	Post 2	Pre 2	Post 0.5	Post 1	Post 2
E.B.	39	23	9	16	945	1425	1249	1265
M.R.	27	**64**	18	11	1412	**764**	1026	606
H.H.	0	5	**9**	**11**	n.d.	1707	2135	1120
K.Z.	34	18	7	7	1957	1278	1685	2158
D.B.	11	18	14	**30**	2317	985	1105	1797
R.A.	7	2	5	7	1669	1328	1152	2553

Bold, significant improvement compared to pre 2*; fMRI spatial attention (%): % of detected left sided stimuli; fMRI spatial attention (RT), median reaction time (ms) of stimuli detected on the left side.*

Table 7 | Macroanatomical structure, cytoarchitectonical area ($Area_{cyto}$), cluster size in voxel, MNI coordinates (x, y, z), and maximum T value (T_{max}) of the local maxima from the direct contrasts of post combined training against baseline (post 1 > pre 2) and long term effects (3 > 1).

Local maximum in macroanatomical structure	$Area_{cyto}$	Cluster size (voxel)	MNI coordinates x	y	z	T_{max}
POST 1 > PRE 2						
R. superior parietal lobe	SPL_7P	18	18	−72	57	3.93
POST 2 > PRE 2						
L. inferior parietal cortex	IPC_PFcm	13	−57	−45	36	3.93
R. superior parietal lobe	SPL_7P	23	15	−69	63	4.17
R. prefrontal cortex	DLPF BA9	7	36	45	33	3.91

The significance level was set to $p < 0.05$, FWE corrected for small volumes using the image masks of the SPM Anatomy toolbox v1.8 (Eickhoff et al., 2005). A cluster size of ≥10 contiguous voxels extended the threshold. L., left; R., right.

beneficial effect of the combination of the former successful therapy approaches although in four of the six patients there was a trend favoring the combined approach. Patients E.B., M.R., H.H., and K.Z. numerically showed a higher percentage of behavioral improvement after alertness and especially after combined training than during baseline. This was mostly reflected in the results of the computerized neglect tasks which showed a somewhat higher sensitivity for training induced changes. This higher sensitivity in contrast to paper-and-pencil tests might be credited both to a higher attentional load evoked by these tasks (Bonato et al., 2010) and by providing scoring measures that are sensitive to specific deficits (Bonato and Deouell, 2013). The patients with the highest number of initially impaired test parameters (their lesions protruded into subcortical areas, probably comprising the SLF II, thus possibly causing a parieto-frontal disconnection) tended to profit least especially from the combined training approach whereas the opposite pattern occurred for the initially less impaired patients. In contrast to the single case findings the statistical analysis of the group results did not reveal an unequivocally significant behavioral improvement beyond effects during the baseline.

Neurobiologically, in the fMRI results there nevertheless were significant changes in activation patterns both immediately after the end of the combined training (though not after alertness training alone) and at the end of the 3-week follow-up period (right superior parietal resp. right superior and inferior parietal and right dorsolateral). This finding, too, might be interpreted as a specific benefit of combined Alertness + OKS training.

Our three efficacy studies were quite comparable with respect to the initial severity of neglect symptoms or lesion characteristics: in all our studies, neglect patients presented with 32–38 test parameters indicative of neglect at the end of the baseline phase, all patients had typical infarctions of the right MCA. In our recent study there was, however, a tendency for patients showing a higher number of initially impaired neglect test scores to benefit least, especially from the combined training approach. This should be reconsidered in future studies with a higher number of patients showing a comparable initial level of impairment.

Studies on the efficacy of aphasia therapy revealed a clear cut correlation between intensity and duration of therapy and its efficiency (e.g., Bhogal et al., 2003; Neininger et al., 2004). Moreover, in a recent study dealing with the impact of attention therapy on language function in aphasic patients, the authors neither found improvement of attention nor of language functions (Graf et al., 2011), although the same attention training procedure had been shown to be efficient in a couple of studies before (e.g., Sturm et al., 1997, 2003; Plohmann et al., 1998). The authors discuss the lack of efficiency in their study in the light of training frequency leaving the patients with only half of the training time for each approach as compared to former efficacy studies. This situation is quite comparable to our training study where we split total training time between Alertness and OKS training with the consequence of a lack of clearcut functional improvement by the single and only a trend for higher efficacy of the combined training approaches. Thus, the critical parameter of therapy outcome might be total time spent for the training. This hypothesis is corroborated by the observation that in our recent study the highest percentage of behavioral improvement and significant functional reorganization was achieved at the end of the OKS training, i.e., at the point in time during our study, when the total training time (summed up for alertness + OKS training) reached the same amount as that for the individual training procedures in our former studies (Sturm et al., 2004a; Thimm et al., 2006, 2009). The results of our combined approach, however, do not allow the conclusion that it is the combination of alertness plus OKS training which might be more efficient than alertness training alone. It might be either the addition of the OKS treatment which increases efficacy or just the fact that alertness plus OKS treatment sum up for a more adequate overall amount of therapy. Our former studies revealed significant functional improvement for both therapy approaches after 14 training sessions each. Even summing up the efficacy of both training approaches in combination in our current study does not lead to a comparable behavioral effect as for each approach *per se* in the earlier studies. This observation, again, points to overall training time for each training procedure as the critical parameter. On the other hand, the fact that after the follow-up period (3 weeks after the end of alertness + OKS training) there was a right fronto-parietal reorganization pattern (thus combining the frontal reorganization after alertness plus parietal reorganization after OKS, see Thimm et al., 2009) might, however, mirror a combined training and not only a summed up training time effect. Anyway it might be desirable to do another study administering both training procedures in the opposite order starting with OKS training or combining both methods in every therapy session keeping overall therapy time constant. Our earlier studies have shown that specific training approaches – if administered for at least 14 consecutive training sessions – besides behavioral improvement lead to reactivation of parts of the originally involved functional brain networks. It seems that only prolonged intensive training of the impaired cognitive function can provoke cerebral reorganization procedures in the networks subserving the impaired function which also holds true in our current study. Earlier, this has been revealed in animal studies where intensive and long lasting stimulation led to an enlargement of cortical sensory and motor areas (Jenkins et al., 1990; Nudo et al., 1996) and in human subjects after somatosensory discrimination training (Braun et al., 1999). Thus, our results are relevant for the ongoing discussion about the link between intensity and duration of cognitive retraining procedures and outcome in cognitive rehabilitation.

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Is two better than one? Limb activation treatment combined with contralesional arm vibration to ameliorate signs of left neglect

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In the present study, we evaluated the effects of the Limb Activation Treatment (LAT) alone and in combination with the Contralateral Arm Vibration (CAV) on left neglect (LN) rehabilitation. We conceived them as techniques that both prompt the activation of the lesioned right hemisphere because of the activation (with the LAT as an *active* technique) and the stimulation (with the CAV as a *passive* technique) of the left hemibody. To test the effect of the simultaneous use of these two techniques (i.e., LAT and CAV) on visuo-spatial aspects of LN, we described the case of an LN patient (GR), who showed high intra-individual variability (IIV) in performance. Given the high IIV of GR, we used an ABAB repeated-measures design to better define the effectiveness of the combined application of LAT and CAV, as a function of time. The results showed an improvement of GR's performance on the Bells test following the combined application of LAT and CAV, with respect to the application of LAT alone. We did not find, however, significant effects of treatment on two other LN tests (i.e., Line bisection and Picture scanning). We propose that the combined application of LAT and CAV can be beneficial for some aspects of LN.

Keywords: neglect, rehabilitation, intra-individual variability, repeated measures, limb activation, arm vibration

INTRODUCTION

One of the major neuropsychological syndromes following right-hemisphere lesion is left neglect (LN). LN patients fail to respond, report, or orient to stimuli in the contralesional left side of space (Heilman et al., 2003). LN comprises a heterogeneous, multifaceted, and highly variable set of behavioral symptoms and signs (Barrett et al., 2006; Adair and Barrett, 2008), which cannot be attributed to primary sensory or motor defects, given that double dissociations have been reported between LN and primary motor and sensory defects (Vallar, 1998). Although some spontaneous recovery occurs in the majority of LN patients after stroke, LN remains severe in many patients and may persist in the chronic phase (Stone et al., 1992; Jehkonen et al., 2000, 2007; Farnè et al., 2004; Rengachary et al., 2011; Nijboer et al., in press). Commonly associated with left hemiplegia, LN renders motor-associated deficits more severe and it is one of the major factors associated with poor functional outcome (Denes et al., 1982; Jehkonen et al., 2001; Buxbaum et al., 2004; Farnè et al., 2004). LN may limit the effectiveness of the rehabilitation interventions, often to a greater extent than more obvious motor, sensory, and speech deficits (Buxbaum et al., 2004). As a consequence, LN contributes to longer time of hospitalization (Katz et al., 1999; Cherney et al., 2001).

In the past decades, the growing of knowledge on the LN syndrome has suggested the implementation of several well-defined, theory-driven LN rehabilitation approaches (for review, see Luauté et al., 2006; Kerkhoff and Schenk, 2012; Riestra and Barrett, 2013). Evidence-based clinical trials that have evaluated the effectiveness of LN rehabilitation treatments are, until now, not sufficient to provide a general consensus for the efficacy of a given LN treatment approach (Riestra and Barrett, 2013). The main reasons for this failure are probably related to the problem of a definition of appropriate measurement criteria for treatment success (Riestra and Barrett, 2013), the limited assessment of LN subtypes (Barrett et al., 2006), and the lack of consideration of intra-individual variability (IIV) of the patients' performance and their individual complexity (Stuss, 2011).

To take into account the IIV and the individual complexity, several authors have provided evidence of the importance of conducting LN rehabilitation treatments, by using a repeated-measures approach (e.g., Robertson et al., 1998; Samuel et al., 2000; Bailey et al., 2002; Maddicks et al., 2003; Humphreys et al., 2006). In some of these studies, the Limb Activation Treatment (LAT; Robertson and North, 1992) has been used to reduce the visuo-spatial deficits of LN patients both in the acute and in the chronic phase. In a series of studies, Robertson and North (1992, 1993, 1994), and Robertson et al. (1992, 1998) showed that LN signs, on cancelation and reading tasks, decreased significantly when LN patients performed the task while moving their left hand in the left side of space. On the contrary, they showed that the total number of omissions on cancelation tasks did not decrease when one LN patient moved his left hand in the right side of space or his right hand in the left side of space (Robertson and North, 1992). In contrast, reading errors were not reduced by concurrent movements of both hands (Robertson and North, 1994). As a general result, a significant reduction of LN signs occurred only when two conditions were simultaneously accomplished: the active unilateral movement of the left limb (condition 1), took place in the left peripersonal space (condition 2). The same result was observed even when one LN patient could not see his own moving hand (Robertson and North, 1992), suggesting a specific effect of left limb activation, instead of a visual cueing effect, in reducing LN signs. In fact, visual cues have been often reported to reduce LN signs (Riddoch and Humphreys, 1983; Halligan et al., 1991), but they seem not to be as effective as active movements of the left upper limb. Robertson and North (1992), indeed, did not observe any improvement on letter cancelation when the LN patient they tested was instructed to gaze, at regular intervals, toward an irrelevant stimulus placed in the left side of space. Nevertheless, Cubelli et al. (1999) did not find positive effects of LAT in a group study (i.e., only 1 patient out of 10 ameliorated).

Several single-case studies, in which repeated measurements were used, have been reported providing some evidence on the effectiveness of the activation of the contralesional arm in reducing LN signs (e.g., see Bailey et al., 2002; Maddicks et al., 2003). Among the previous studies, Samuel et al. (2000) first reported the possible additive effect of LAT combined with the Visual Scanning Training (VST; Antonucci et al., 1995) in two LN patients, showing that LAT combined with VST may have additive effects to reduce the signs of LN in stroke patients. Nonetheless, these results are far from being clear to speculate on the effectiveness of combining the LAT with the VST. In addition to the single-case and group studies previously discussed, in which *active*, motor-intentional limb activation was used, it is also worth to mention that even *passive* left contralesional upper limb movements can improve LN signs (Frassinetti et al., 2001; Harding and Riddoch, 2009).

The positive effects of LAT reported in some LN patients can be interpreted in terms of the pre-motor theory of spatial attention (Rizzolatti and Camarda, 1987; Rizzolatti and Berti, 1990), for which the attentional and motor circuits are intimately linked in the brain. Thus, by activating the motor circuits of the damaged hemisphere (through the left arm/hand movement), associated attentional circuits in the damaged hemisphere would be recruited, improving the spatial attention orienting to the left side of space. On the bases of the pre-motor theoretical construct, it is possible that the somato-sensory activation in the left side of space through the use of LAT, activates and/or enhances the neural networks that subserve space representation. In fact, if spatial attention is a consequence of the activation of pre-motor neurons, the activation of pre-motor neural circuits of the lesioned hemisphere may improve the conscious perception of stimuli in the contralesional side of space. Therefore, even minimal movements of the contralesional limb, in the contralesional space, might induce sufficient activation of the lesioned hemisphere to reduce the inhibitory competition from the unimpaired hemisphere (Robertson et al., 1998).

Another LN rehabilitation technique is contralesional neck muscles vibration (Karnath et al., 1993; Karnath, 1995; Ferber et al., 1998; Schindler et al., 2002; Johannsen et al., 2003). The discharge induced by vibration of the left neck muscles leads to the "false" interpretation that the left neck muscles have lengthened (Karnath et al., 1993). This observation has been interpreted in terms of neural activation from the neck muscle proprioceptors, particularly from the muscle spindles, of cerebral areas subserving the processing of body-centered coordinates raising from the integration of visuo-spatial and body representational maps. A different interpretation, however, has been proposed by Vallar et al. (1995), who investigated the possibility that left neck muscles stimulation yields unspecific, general activation of the right hemisphere, rather than a selective modulation of the cerebral areas subserving the processing of body-centered coordinates. Vallar et al. studied the effect of unspecific stimulation of the right damaged hemisphere through the use of Transcranial Electrical Nerve Stimulation (TENS) applied on the left, contralesional LN patients' hemibody. Both the skin and the muscle mechanoreceptors may be stimulated by TENS (Vallar et al., 1995); then the pattern of sensory activation produced by the TENS could not be confined to proprioceptive input only. The stimulation could enhance the proprioceptive input toward the right lesioned hemisphere, given that the stimulation, delivered to the left hemibody, conveys the somato-sensory inputs to the right hemisphere. In contrast with the studies by Karnath et al. (1993) and Karnath (1995), in which no amelioration of LN signs was observed after the contralesional arm vibration (CAV) (used as a control condition), Vallar et al. (1995) showed that the stimulation of the left neck muscles and the stimulation of the dorsal surface of the left hand induced the same improvement of LN patients on a cancelation task, suggesting a role of the unspecific stimulation of the right damaged hemisphere in reducing LN signs.

Combining different rehabilitation methods may increase the effectiveness of cognitive treatments (e.g., Kerkhoff and Schenk, 2012). At least in some cases, there is evidence of the therapeutic effect of the combination of rehabilitation techniques, suggesting that combined treatments may be more effective than single rehabilitation treatments (e.g., Butter and Kirsch, 1992, Experiment 2; Schindler et al., 2002; Schröder et al., 2008; Saevarsson et al., 2010; for review, see Saevarsson et al., 2011). Nonetheless, some studies have reported no better effects of combined treatments with respect to single treatments for LN (e.g., Lafosse et al., 2003; Pizzamiglio et al., 2004; Keller et al., 2009; Polanowska et al., 2009). These findings suggest the need of better studying the combination of multiple treatments on LN rehabilitation, by means of the application of theory-driven cognitive interventions, instead of summing up casually two or more rehabilitation techniques. Probably, one successful way to obtain *additive* positive effects of two or more rehabilitation methods provided simultaneously, is the combination of methods that share a common theoretical framework and, consequently, a common network of neural activation. In fact, the use of cognitive interventions that induce conflicting activation of neural circuits has showed potentially harmful effects (e.g., Keller et al., 2009).

In the present study we tested, for the first time, the combined effect of two techniques: the LAT and the CAV, which have never been used together before for rehabilitation purposes (but see, Karnath, 1995, for a use of contralesional hand vibration as a control experimental task). We decided to evaluate the additive effects of LAT and CAV by using them as techniques that both prompt the enhancement of the right lesioned hemisphere, because of the activation (with the LAT) and the stimulation (with the CAV) of the left upper limb. Indeed, we used the LAT as an *active* limb activation technique (mainly top-down, although a bottom-up component is also present, because of tactile and proprioceptive feedback), whereas we used the CAV as *passive* (i.e., bottom-up) tactile activation technique. To test the possible additive effects of these two techniques (i.e., LAT and CAV) on visuo-spatial aspects of LN, we describe the case of an LN patient (GR) who showed high IIV in his performance. Given the high IIV of GR, we decided to use an ABAB repeated-measures design to better define the effectiveness of the combined application of LAT and CAV, as a function of time. In order to induce the strongest activation of the right lesioned hemisphere, we applied the vibration on the left forearm of the patient, to assure maximal stimulation of the left-forearm mechanoreceptors for maximizing the tactile sensory input toward the right lesioned hemisphere. We expected that the combined application of these two different, but complementary treatments (i.e., LAT and CAV) would be better than the application of only one (i.e., LAT).

MATERIALS AND METHODS

CASE DESCRIPTION

GR was a 44-year-old, right-handed man, with 13 years of formal education. GR suffered from hemorrhagic stroke in the right cerebral hemisphere (see **Figure 1**). As a consequence, GR sustained a neurosurgical intervention, to evacuate the intraparenchymal hematoma. During hospitalization, GR was complied with physical therapy for left hemiparesis and neuropharmacological treatment. GR underwent a formal neuropsychological evaluation 2 months after his right-hemisphere stroke. He was alert and oriented in time, space, and to personal information (Mini Mental State Examination (MMSE) score = 25.2/30, cut-off <24; Magni et al., 1996). GR was unaware of his cognitive and motor defects. GR was collaborative, but he was moderately abulic. Non-spatial cognitive functions, such as memory and language, were intact [*Rey 15*-Item Memory Test (RMT), immediate recall = 28.8/75, cut-off = 28.53; delayed recall = 5.1/15, cut-off = 4.69; Carlesimo et al., 1996 – verbal reasoning equivalent score = 3/4, cut-off = 0; Spinnler and Tognoni, 1987]. Clinical signs of LN, consisting in spontaneous head and gaze deviation toward the ipsilesional (right) side of space, were present. His score on the conventional and behavioral parts of the BIT (Wilson et al., 1987) was below the cut-off (BIT conventional = 27/149, cut-off <130; BIT behavioral = 4/81, cut-off <68), revealing that GR was affected by severe LN, which was exacerbated by the presence of his left homonymous hemianopia.

Because of his severe LN, GR was admitted to an intensive cognitive rehabilitation program (not the one described in the present study) in order to reduce his LN signs. After three months of intensive rehabilitation, and before entering in our study, GR suddenly showed signs of speech apraxia. A CAT scan, performed immediately after the onset of his speech apraxia, revealed a new hemorrhagic stroke in his left cerebral hemisphere (see **Figure 1**). After 1 month, GR underwent a new formal neuropsychological assessment, which confirmed his preserved non-spatial cognitive abilities (MMSE = 30/30, cut-off <24; Magni et al., 1996 – RMT immediate recall = 51.1/75, cut-off = 28.53; delayed recall = 9.5/15, cut-off = 4.69; Carlesimo et al., 1996 – verbal reasoning equivalent score = 2/4, cut-off = 0; Spinnler and Tognoni, 1987) and the persistence of LN signs (BIT conventional = 100/146, cut-off <130; BIT behavioral = 32/81, cut-off <68; Wilson et al., 1987).

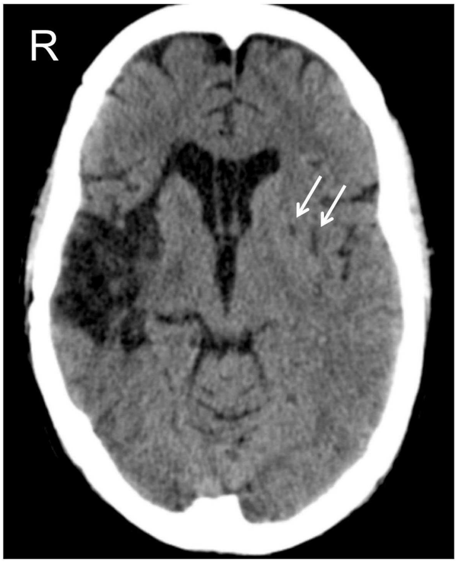

FIGURE 1 | CAT scan of patient GR, at the level of the basal nuclei. The right-hemisphere lesion involves the insula, the anterior part of the temporal lobe, and the lenticular nucleus. The left-hemisphere lesion is limited to the lenticular nucleus, indicated by the two white arrows.

The clinical neuropsychologist who treated GR reported that during the first neuropsychological rehabilitation program (i.e., after his right-hemisphere stroke), GR presented with high IIV of performance on several visuo-spatial tasks (e.g., figure description, drawing completion, etc.). High IIV of performance was also present after his left-hemisphere stroke. The impact of high IIV of GR during cognitive rehabilitation increased the difficulty of performing a comprehensive assessment of the real change achieved through the first rehabilitation program. In fact, a major principle underlying success in cognitive rehabilitation is the capacity of the brain to recover from damage (e.g., Nudo and McNeal, 2013; Sharma et al., 2013), and to re-organize itself in different neural pathways to maximize recovery. Nonetheless, this capacity may not be maximized for the benefit of each patient, because brain plasticity is influenced by many different variables. The success of an intervention, indeed, may not be evident because IIV might not have been appropriately considered. Thus, GR gave his consent to participate in the present rehabilitation study, which started 63 days after the onset of his left-hemisphere stroke. Our goal was to monitor the evolution of his behavioral changes, in order to disentangle his strong IIV in performance from the effects of treatment. GR gave his informed consent to participate in the study, according to the Declaration of Helsinki II.

NEUROPSYCHOLOGICAL TESTS

GR was assessed daily, after each cognitive rehabilitation session, through a brief battery of neuropsychological tests for neglect-related disorders in the peripersonal space. The battery included a Line bisection test (i.e., the Line bisection subtest from the BIT conventional; Wilson et al., 1987), a visual scanning test (i.e., the Picture scanning subtest from the BIT behavioral; Wilson et al., 1987), and a cancelation test (i.e., the Bells test; Gauthier et al., 1989). In addition, a non-spatial test (i.e., the Semantic verbal fluency test; Novelli et al., 1986) was also administered as a control test. The order of the daily-administered outcome measures was always the same (i.e., Picture scanning, Bells test, Line bisection, Semantic verbal fluency). The same examiner delivered all treatment sessions and she was aware of the aim of each treatment.

Picture scanning test

On this test, three large photographs were presented to the patient, one at a time (Wilson et al., 1987). The photographs depicted: a meal, a wash basin and toiletries, and a large hospital room containing various pieces of furniture and hospital aids. The midline of each photograph was aligned with the body midline of GR. He was asked to name the items in each photograph. Omissions of items were scored. There was no time limit for the patient to perform the test.

Bells test

On this test, different black drawings (i.e., shadows) including 35 targets (bells) and 280 distractors were printed on a white A4 sheet of paper (210 mm× 297 mm) (Gauthier et al., 1989). The drawings were positioned in an apparently random order, but they were equally distributed in seven columns (three on the left, three on the right, and one central), numbered from one to seven starting from the left. The midline of the A4 sheet of paper was aligned with the body midline of the patient. GR was asked to sign with a circle the targets (bells) in the A4 sheet of paper. Omissions of targets were scored. There was no time limit for the patient to perform the test.

Line bisection

The test consisted of three, 20-cm-long, horizontal, black line segments, one placed on the right side, one on the center, and one on the left side of a white A4 sheet of paper (210 mm × 297 mm) (Wilson et al., 1987). The midline of the A4 sheet was aligned with the body midline of the patient. GR was asked to find and mark the center of each line segment. The distance of the mark from each midline was measured. For each mark, a score from 0 (high displacement) to 3 (low displacement) was assigned according to the correction sheet. There was no time limit for the patient to perform the test.

Semantic verbal fluency test

On this test, GR was required to orally produce the highest possible number of words belonging to three semantic categories: car brands, fruits, and animals (Novelli et al., 1986). GR had 1 min to produce the names from each semantic category. Each correctly produced name received one point.

STIMULI

GR sat in front of a PC screen at a distance of about 60 cm. Stimuli comprised computerized exercises requiring simple and complex reaction times (http://www.schuhfried.com/cogniplus-cps/rehacom/), visuo-spatial word search exercises (De Tanti and Inzaghi, 1992), and visuo-spatial exercises in which the patient was asked to compare vertical bars presented at different distances. The vertical bars were moving at different speeds (De Tanti and Inzaghi, 1992). GR responded orally in the visual-search exercises, whereas he pressed a button with his right hand in the simple and complex reaction time exercises.

EXPERIMENTAL DESIGN

An experimental ABAB blocks design was used: block A consisted of repeated sessions of LAT, whereas block B consisted of repeated sessions of LAT + CAV. The rehabilitation program (i.e., ABAB blocks) was completed approximately in 8 weeks. Each rehabilitation block consisted of 10 sessions of 1 h each, held once a day at the same hour (whenever possible), for 5 days a week (see **Figure 2**).

APPARATUS AND REHABILITATION PROCEDURE

The examiner sat behind GR, out of the patient's sight, to avoid providing him with visual cues. During the rehabilitation sessions, the examiner prompted GR, whenever necessary, to carry out the computerized exercises. During the visual-search exercises and the visuo-spatial comparison of moving vertical bars, the examiner gave general verbal instructions to GR (e.g., "pay attention" or "check the stimuli in the whole visual field"), but avoided specific lateralized spatial suggestions (e.g., "pay attention to the left side

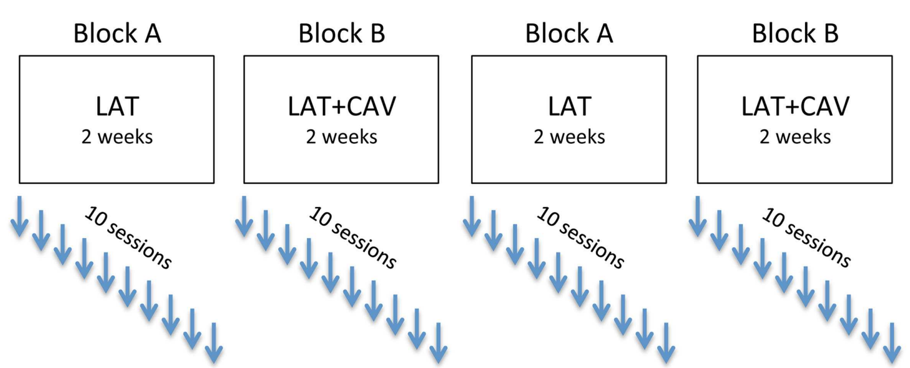

FIGURE 2 | Experimental ABAB design. After each rehabilitation session, the patient was administered four neuropsychological tests (see Materials and Methods section for details).

of the screen" or "check the stimuli both on the left and on the right side of the visual field"). The exercises remained the same through the whole rehabilitation protocol and were presented in fixed-sequence order to GR.

Limb activation treatment

In the block A, the training involved the use of the "Limb Activation Treatment Device" (LAT-D), a modified version of the original Limb Activation Device (LAD), employed by Robertson et al. (2002). The LAT-D comprised a central unit and a bellows. The central unit encompassed a small plastic box, measuring 11 cm × 6 cm × 3 cm (weight = 150 g). The box contained the power supply, a microcontroller, a timer, a buzzer, and a LED. The control unit could activate a buzzer and display a light, at random or fixed intervals. The bellows (measuring 15.2 × 2.5 cm) could be pressed by GR to stop the buzzing tone emitted by the buzzer. The central unit was connected with the buzzer with a spiral plastic air tube, so as the distance between the box and the bellows could be easily adjusted. The bellows was fixed between the patient's arm and the left armrest of the wheelchair. Then, the left arm of GR was placed on the bellows in order to compress it. By maintaining this setting, GR was asked to complete the computerized exercises. Each time GR heard the tone emitted by the buzzer, he was instructed to move his left arm to decompress the bellows to turn-off the tone. During the treatment, the buzzer was set to emit the tone at a fixed time interval of 120 s. If GR did not move his left arm within 30 s from the onset of the tone, the examiner verbally reminded him to move his left arm to decompress the bellows for turning-off the tone. This procedure remained the same through all the sessions of LAT. GR had sufficient proximal movement of his left arm to carry-on the rehabilitation protocol.

Contralateral arm vibration

The rehabilitation procedure of block B was the same as that of block A, except for the addition of a vibrating stimulus on the left, contralesional forearm of the patient. A portable vibration device (PVD) delivered the vibration. The device consisted of a small plastic unit, roughly 13 cm × 7 cm × 5 cm, with an elastomeric pressure-activated switch-pad, inside the PVD's plastic body, and a clamping component that permitted us to fix the PVD on the patient's left forearm. The PVD could be set up for the running time of vibration, for a fixed duration. The PVD remained attached on the left forearm of the patient during the entire rehabilitation session. The device was set to emit a constant vibration (frequency: ~86 Hz) on the patient's left forearm for a fixed time interval of 5 min. Among the fixed time intervals, a pause of 5 min was allowed to avoid the habituation of the patient's forearm skin mechanical receptors. During the 5-min interval following PVD vibration, a sensation of "vibration aftereffect" was reported by GR. The procedure was the same for all the sessions of blocks B (i.e., LAT + CAV).

RESULTS

THE *C*-STATISTIC ANALYSIS

We analyzed the data with the *C*-statistic test. The *C*-statistic is a statistical test that can be used to evaluate the trend in time-series measures, even when the number of observations is very low (e.g., at least eight observations for each experimental block; Young, 1941). By means of the *C*-statistic, the variability in successive data points is evaluated by examining the changes in slope from one block of an experiment to the next block of the same experiment (Tryon, 1982). In particular, the *C*-statistic estimates if, in a given dataset, there is a significant data trend. The *C*-statistic can be used to analyze separately each experimental block, but also it can be used to estimate if there are differences between successive blocks of the same experiment. To this aim, the data segments of the different blocks are joined in a unique vector (e.g., A + B, in an AB block design) and the statistical analysis on this joined vector is performed. In the present study, a significant *C*-statistic was considered as the evidence of a significant change between the different treatment blocks. To effectively use the *C*-statistic, a time-series of baseline scores is required. Given that multiple baseline scores were not available for GR, we assumed that the only baseline score available of GR could be a satisfying estimate of the patient's condition. We thus created a vector by replicating 10 times (as for all the other experimental blocks) the value of the patient's score at the baseline. Given this strong, but necessary assumption to use the *C*-statistic, we discussed the present results focused on the comparison between the treatment blocks (i.e., A and B), rather than on the comparisons between each treatment block and the baseline.

In the following analyses the experimental blocks have been labeled as follow: BAS is the baseline; LAT/1 is the first block of rehabilitation with LAT; LAT + CAV/1 is the first block of rehabilitation with LAT + CAV; LAT/2 is the second rehabilitation block with LAT; and LAT + CAV/2 is the second rehabilitation block with LAT + CAV. According to these labels, the treatment sequence was: BAS | LAT/1 | LAT + CAV/1 | LAT/2 | LAT + CAV/2 (see **Figure 2**). Separate *C*-statistics were calculated for all the tests administered (i.e., Picture scanning, Bells test, Line bisection, Semantic verbal fluency). Within each test, a *C*-statistic was calculated for each block, to investigate whether there was a significant trend within each block (i.e., LAT/1, LAT + CAV/1, LAT/2, or LAT + CAV/2). *C*-statistics were also calculated for each pair of consequent blocks, joined in a unique vector, to investigate whether there was a significant difference between two consequent blocks (i.e., BAS vs. LAT/1, LAT/1 vs. LAT + CAV/1, LAT + CAV/1 vs. LAT/2, LAT/2 vs. LAT + CAV/2).

RESULTS OF THE *C*-STATISTIC ANALYSES

The *C*-statistic analysis of the data from the Picture scanning test (Wilson et al., 1987) showed a significant trend between the LAT/1 and the LAT + CAV/1 blocks [analysis on LAT/1 vs. LAT + CAV/1 vector, $C = 0.42$, $z = 1.81$, $p < 0.05$; LAT/1 mean = 5.8, LAT + CAV/1 mean = 6.35]. No other significant trends were found within or between blocks (all $ps > 0.05$) – (see **Figure 3**). Although a significant difference was found between the LAT/1 and the LAT + CAV/1 blocks, it is impossible to attribute the improvement observed to an effect of the combined treatments (i.e., LAT + CAV) because of the absence of subsequent variability of GR's performance.

The *C*-statistic analysis of the data from the Bells test (Gauthier et al., 1989) showed a significant trend between the LAT + CAV/1 and the LAT/2 blocks [analysis on the

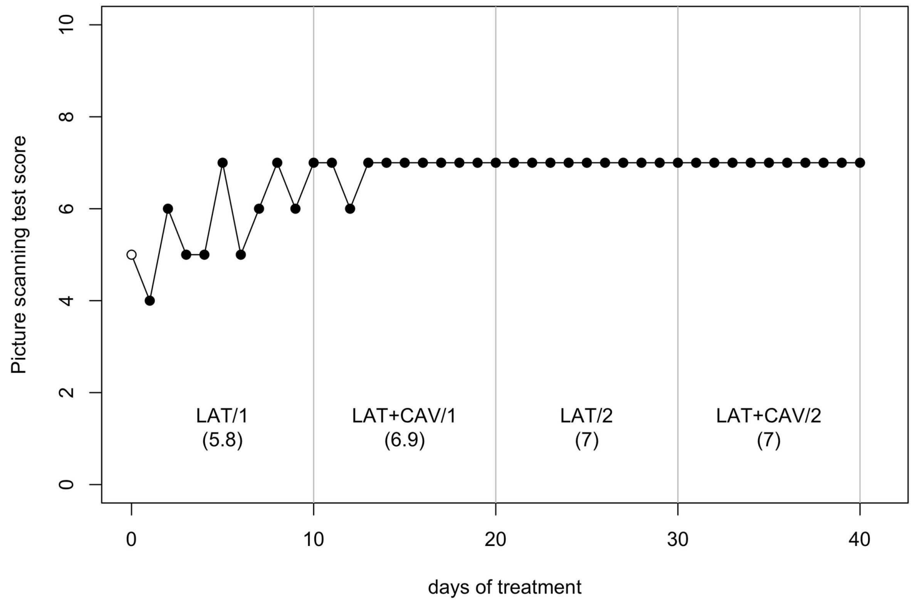

FIGURE 3 | Trend of GR's performance on the Picture scanning test. The first data point (empty dot) indicates the baseline score (5). The values under each block label indicate GR's mean score of the 10 sessions composing each block.

LAT + CAV/1 vs. LAT/2 vector, $C = 0.46$, $z = 1.97$, $p < 0.05$; LAT + CAV/1 mean = 26.2, LAT/2 mean = 20.8] and between the LAT/2 and the LAT + CAV/2 blocks [analysis on the LAT/2 vs. LAT + CAV/2 vector, $C = 0.44$, $z = 1.88$, $p < 0.05$; LAT/2 mean = 20.8, LAT + CAV/2 mean = 22.3] – (see **Figure 4**). Thus, GR's performance on the Bells test was better after the application of the combined treatments (i.e., LAT + CAV), rather than after the LAT alone. Although the mean score in the LAT1 condition was 26.1, a trend within this condition was not found. Given the absence of a meaningful baseline, it is impossible to infer the presence of an improvement in this condition with respect to the baseline.

The *C*-statistic analysis of the data from the Line bisection (Wilson et al., 1987) showed no significant trend neither in between blocks comparisons, nor in within-block comparisons (all $ps > 0.05$; see **Figure 5**).

The *C*-statistic analysis of the data from the Semantic verbal fluency test (Novelli et al., 1986) showed a significant difference between the BAS and the LAT/1 block [analysis on the BAS + LAT/1 vector, $C = 0.51$, $z = 2.16$, $p < 0.05$; BAS = 24, LAT/1 mean = 28.2] and a significant difference between the LAT/2 and the LAT + CAV/2 blocks [analysis on the LAT/2 | LAT + CAV/2 vector, $C = 0.44$, $z = 1.86$, $p < 0.05$; LAT/2 mean = 31.7, LAT + CAV/2 = 35]; see **Figure 6**.

DISCUSSION

We studied GR, a patient who initially suffered a right-hemisphere stroke and then a left-hemisphere stroke. Following the right-hemisphere stroke, GR presented with severe LN. After his left-hemisphere stroke, which was limited to the lenticular nucleus, we did not observe any further behavioral changes of GR, except of a temporary presence of speech apraxia. Indeed, he had no linguistic deficits in everyday life and on tests that require oral verbal comprehension and production (e.g., the MMSE and the Verbal reasoning test). Approximately 2-months after GR's left-hemisphere stroke, the present ABAB rehabilitation study started.

We tested the possible additive effects of two rehabilitation techniques (i.e., the LAT and the CAV). By using these techniques, we aimed to prompt the activation of the lesioned right hemisphere. The LAT was used as an *active* (i.e., mainly top-down) limb activation technique, whereas the CAV was used as a *passive* (i.e., bottom-up) tactile activation technique. GR showed high IIV in his performance on visuo-spatial tests. Some aspects of what is interpreted as change may be, therefore, attributable to short-term fluctuation and sampling variation, rather than true change (Salthouse, 2007). The success of an intervention, indeed, may not be evident because IIV and other types of variables (e.g., medical therapies, physiotherapy, unspecific environmental stimulation, etc.) might not have been appropriately considered. Thus, given the high IIV of GR, an ABAB repeated-measures design was used. The clearest of our results was that the combined application of LAT and CAV induced an improvement of GR's performance on the Bells test (Gauthier et al., 1989). This finding suggests that the amelioration of GR's performance could be the consequence of a specific sensori-motor activation effect of the right hemisphere after the combined activation (i.e., active with LAT and passive with CAV) of the contralesional left arm. It is, then, possible that the activation of the left contralesional arm in the left space has enhanced the neural networks that subserve space representation in the lesioned right hemisphere.

GR's performance on the Bells test got worse specifically from LAT + CAV/1 to LAT/2. That is, when CAV was not applied anymore, GR's performance got worse, whereas when CAV was re-applied GR's performance was improved again. Finally, there

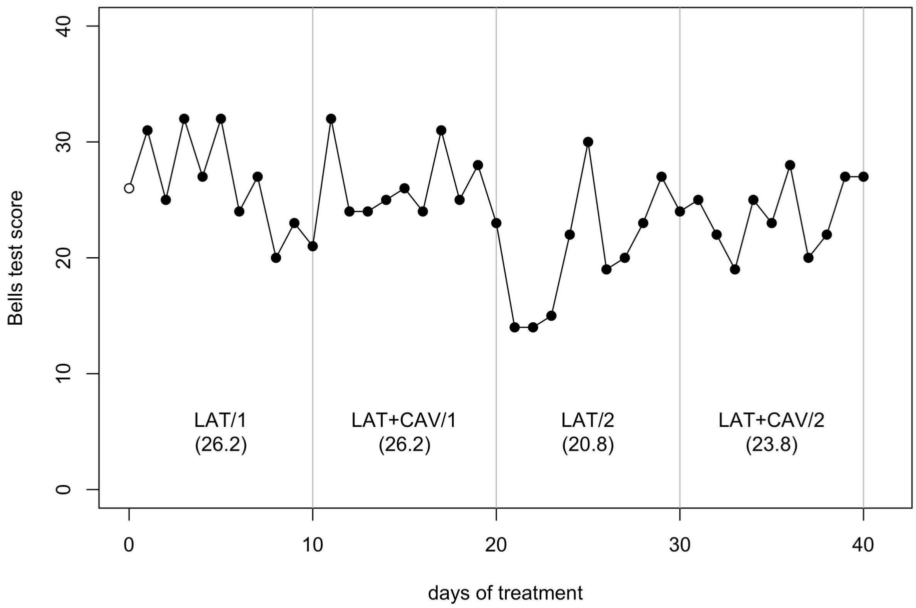

FIGURE 4 | Trend of GR's performance on the Bells test. The first data point (empty dot) indicates the baseline score (26). The values under each block label indicate GR's mean score of the 10 sessions composing each block.

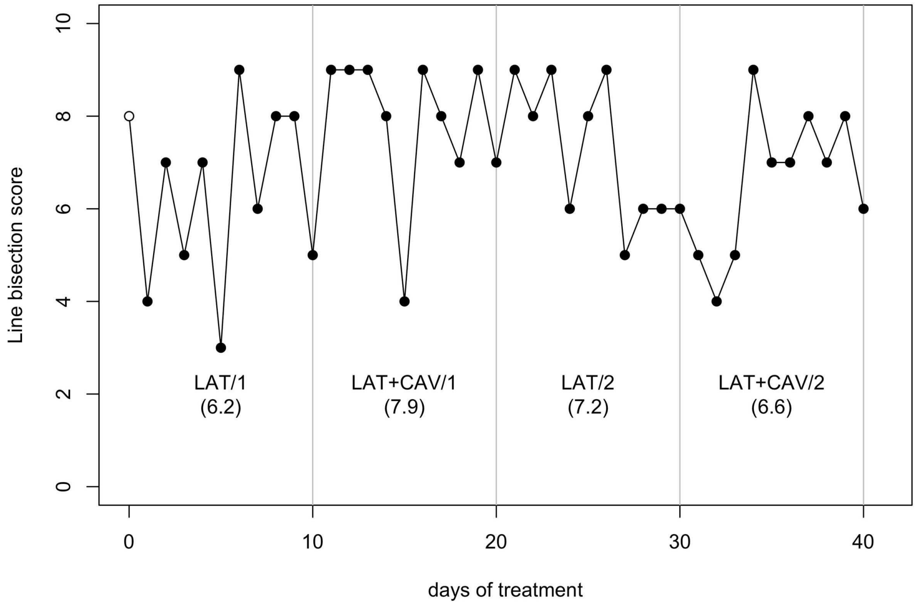

FIGURE 5 | Trend of GR's performance on the Line bisection test. The first data point (empty dot) indicates the baseline score (8). The values under each block label indicate GR's mean score of the 10 sessions composing each block.

were no intra-block differences in GR's performance on the Bells test. Taken together, these findings are in favor of a specific sensorimotor effect of LAT + CAV on the damaged circuits of the right hemisphere. A limitation of the present study, however, should be underlined. Given the lack of repeated measures on the baseline of GR, all results should be taken cautiously, and further studies with measures on baseline are necessary to corroborate the present results.

The positive effects of LAT + CAV were limited on one test measuring LN signs (i.e., the Bells test). In contrast, there were no positive effects of LAT + CAV on the other two LN tests (i.e., Picture scanning test and Line bisection test). Note, however, that

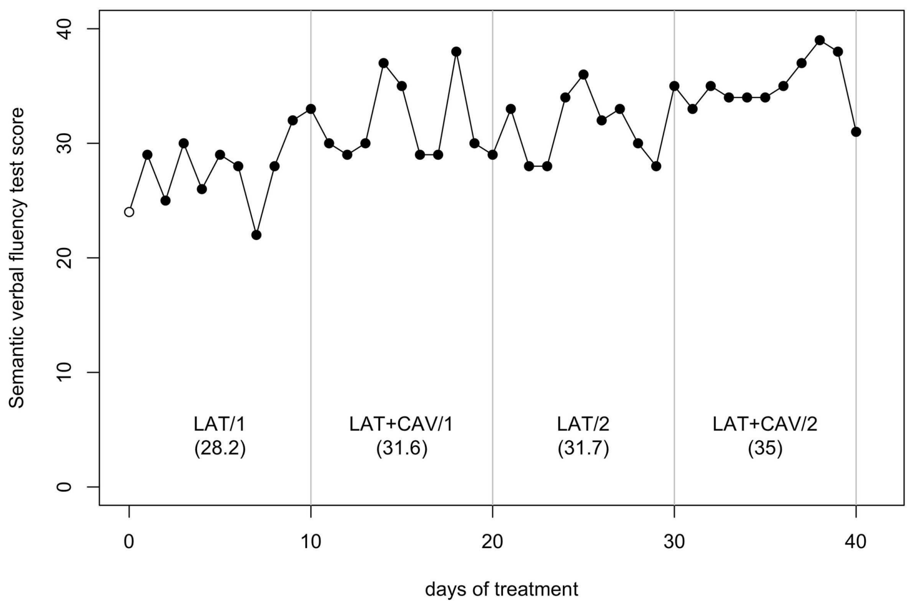

FIGURE 6 | Trend of GR's performance on the Semantic verbal fluency test. The first data point (empty dot) indicates the baseline score (24). The values under each block label indicate GR's mean score of the 10 sessions composing each block.

cancelation and bisection tasks are doubly dissociated in neurological patients (Halligan and Marshall, 1992; Keller et al., 2005). As a consequence, different rehabilitation techniques might be required to yield positive effects also on line bisection tasks. Finally, an important procedural difference between the Bells test and the Picture scanning test should be noted. On the Bells test, patients are required to perform actions with their ipsilesional limb toward the ipsi- and the contralesional side of space. In contrast, on the Picture scanning test no actions are required, given that patients are asked to verbally describe a picture placed in front of them. This limb-motor vs. verbal-motor output difference should be further investigated in future studies, given that these aspects of LN are doubly dissociated (e.g., see Heilman et al., 2003).

If our findings were a consequence of generalized and unspecific brain activation, we would have found exactly the same trend of amelioration, as that observed on the Bells test, also on the Semantic verbal fluency test. In contrast, GR's performance on the control task ameliorated only from LAT/2 to LAT + CAV/2. Thus, generalized and unspecific brain activation might explain GR's performance improvement from LAT/2 to LAT + CAV/2, but cannot explain GR's performance deterioration from LAT + CAV/1 to LAT/2. Note, however, that if the improvement in GR's performance between LAT/2 and LAT + CAV/2 was only due to generalized and unspecific brain activation, GR's performance amelioration would have been observed on all tests. This was not the case.

Karnath (1995) used the CAV as an experimental control task, with four LN patients who were asked to perform a cancelation and a copying task. He found no improvement on patients' performance on the two tasks following the CAV. There are, however, some methodological differences between our study and that of Karnath. First, in the Karnath's study the sequence of blocks was not counterbalanced (CAV was always applied in the last block), whereas we used an ABAB design. Second, Karnath applied CAV on the left hand of each patient, whereas we applied CAV on GR's left forearm. Third, Karnath applied CAV for a very brief duration (i.e., during the execution of cancelation and copying tasks), whereas we applied the CAV for 30′ on each LAT + CAV rehabilitation session, for 10 consecutive sessions. Finally, Karnath used the CAV alone, whereas we used a combination of LAT and CAV to reach a more enhanced activation of the sensori-motor circuits of the right lesioned hemisphere.

There is considerable evidence in the literature on the effectiveness of LAT for some LN patients (Robertson and North, 1992, 1993, 1994; Robertson et al., 1992, 1998; Samuel et al., 2000; Bailey et al., 2002). Nonetheless, the previous results are far from being clear because of the different methodologies used and the different neuropsychological measures adopted. In the present study, a reliable assessment of GR's performance was very difficult because of his high IIV. Our preliminary positive results might provide some new evidence on the possibility to obtain additive effects of cognitive rehabilitation procedures, if these procedures are based on a common theoretical framework and, consequently, share a common network of neural activation subserving the target function. The present findings suggest the need of more extensive LN rehabilitation studies that combine multiple treatments, by means of the application of theory-driven cognitive interventions. Although the simultaneous application of the LAT and the CAV, together with the use of a repeated-measures design (e.g., ABAB) is promising, future single case and group studies are needed to examine in depth the effects of the LAT combined with the CAV in order to reduce LN signs.

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Effects of pro-cholinergic treatment in patients suffering from spatial neglect

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Spatial neglect is a neurological condition characterized by a breakdown of spatial cognition contralateral to hemispheric damage. Deficits in spatial attention toward the contralesional side are considered to be central to this syndrome. Brain lesions typically involve right fronto-parietal cortices mediating attentional functions and subcortical connections in underlying white matter. Convergent findings from neuroimaging and behavioral studies in both animals and humans suggest that the cholinergic system might also be critically implicated in selective attention by modulating cortical function via widespread projections from the basal forebrain. Here we asked whether deficits in spatial attention associated with neglect could partly result from a cholinergic deafferentation of cortical areas subserving attentional functions, and whether such disturbances could be alleviated by pro-cholinergic therapy. We examined the effect of a single-dose transdermal nicotine treatment on spatial neglect in 10 stroke patients in a double-blind placebo-controlled protocol, using a standardized battery of neglect tests. Nicotine-induced systematic improvement on cancellation tasks and facilitated orienting to single visual targets, but had no significant effect on other tests. These results support a global effect of nicotine on attention and arousal, but no effect on other spatial mechanisms impaired in neglect.

Keywords: spatial neglect, fronto-parietal, attention, cholinergic network, nicotine

INTRODUCTION

Neglect patients typically fail to explore the left side of space. These symptoms are most frequently encountered after right hemisphere stroke (for review, see (Vuilleumier and Saj, 2013), and result from large lesions in fronto-parietal areas with extensive involvement of deep white-matter fibers (Doricchi et al., 2008; Verdon et al., 2010). A breakdown of spatial attention has been consistently put forward to account for many deficits encountered in unilateral spatial neglect (Kinsbourne, 1970b; Bartolomeo and Chokron, 2002). These patients typically present with an initial orienting bias toward stimuli in ipsilesional space (Kinsbourne, 1970a; D'Erme et al., 1992), together with a deficit in disengaging attention from these stimuli to reorient toward the left side (Gainotti et al., 1991; Bourgeois et al., 2012, 2013). This deficit can be explained in terms of a biased competition for attentional selection and conscious perceptual processing, with an advantage for ipsilesional sensory inputs at the expense of contralesional information. Neuroimaging studies in healthy subjects have further corroborated the hypothesis of right hemisphere specialization for controlling and reorienting attention in space (Gitelman et al., 1999).

In parallel, various lines of evidence indicate that the cholinergic system is also implicated in spatial attention (Voytko et al., 1994; Selden et al., 1998; Sarter et al., 2001). Studies in both animals (Voytko et al., 1994) and healthy humans (Witte et al., 1997) show that nicotine (a powerful cholinergic agonist) may increase selective attention and resistance to distractors; whereas cholinergic blockade (e.g., by scopolamine) can severely interfere with attention and increase distraction (see e.g., Bentley et al., 2003; Sarter et al., 2005; Mansvelder et al., 2006; Heishman et al., 2010). Numerous findings in rodents and primates point to a critical role of cholinergic inputs to cortical areas, which are conveyed by the basal forebrain cholinergic nuclei through widespread projections and act to enhance selective attention. Destruction of basal forebrain cholinergic neurons lead to severe impairments in focused attention (Voytko et al., 1994) and increased distracter vulnerability, an effect that seems to depend on cholinergic inputs to prefrontal cortex (Newman and McGaughy, 2008). Likewise, cholinergic deficits impair cue detection (Parikh et al., 2007), presumably subsequent to cholinergic losses in medial prefrontal cortex.

In humans, cholinergic pathways project to several cortical areas through discrete white-matter bundles traveling in the depth of human frontal and parietal lobes (Selden et al., 1998). Because of their anatomical location, it is likely that these pathways are often interrupted by large stroke lesions in patients with spatial neglect (Vuilleumier and Saj, 2013). These pathways are thought to provide modulatory inputs to fronto-parietal and sensory areas, acting on cortical synapses to boost signal-to-noise and prolong neuronal responses (Sarter and Bruno, 2000). A loss of cholinergic inputs to the cortex might potentially contribute to impaired attention and insufficient activation of sensory areas in these patients, in keeping with the fact that lesions in the white-matter tend to lead to more severe and persistent neglect (Samuelsson et al., 1997; Bartolomeo et al., 2007; Verdon et al., 2010; Corbetta and Shulman, 2011; Saj et al., 2012).

Recent functional brain imaging in healthy subjects further demonstrate that cholinergic drugs can modulate activity in frontal and parietal areas during spatial attention and working memory tasks (Lawrence et al., 2002; Bentley et al., 2004; Thiel et al., 2005; Giessing et al., 2006). In spatial orienting tasks, nicotine may also facilitate shifts of attention after "invalid cueing" on the opposite side (Thiel et al., 2005; Thiel and Fink, 2008), an aspect of attention typically impaired in patients with parietal lesions (Posner et al., 1984).

Thus, several lines of research converge to implicate the cholinergic system in attentional processes disrupted in spatial neglect, but no study so far investigated the effect of cholinergic drugs on a range of standard clinical neglect tests. Selective attention and reorienting of attention in space both are most conspicuously disrupted in spatial neglect, but also repeatedly reported to be modulated by cholinergic transmission in posterior parietal cortices (Witte et al., 1997; Murphy and Klein, 1998; Thiel et al., 2005). Moreover, nicotinic stimulation may also enhance sustained attention via inputs to prefrontal cortex (Hahn et al., 2003), and deficits in sustained attention are also common in neglect patients (Chatterjee, 1995; Robertson et al., 1998; Chatterjee et al., 1999). Therefore, brain lesions extending into white-matter regions traversed by cholinergic pathways (Selden et al., 1998) might exacerbate neglect deficits by disrupting cholinergic modulation of different attentional components. However, the role of a cholinergic component in neglect has not yet been systematically explored. To our knowledge, only one recent study was conducted where an oral gum with nicotine was administered to a group of nine chronic neglect patients (Vossel et al., 2010), showing a global effect on attention reorienting in a Posner cueing task. Other pharmacological treatment attempts in neglect patients have used dopaminergic (Fleet et al., 1987; Gorgoraptis et al., 2012) or noradrenergic (Malhotra et al., 2006) drugs, but with variable success.

In the present study, we predicted that attentional deficits associated with spatial neglect might partly be alleviated by a substitution of cholinergic loss through a pro-cholinergic drug. We hypothesized that deficits in attention in neglect patients, typically resulting from voluminous brain lesions extending widely into subcortical white matter, may often be combined with (or exacerbated by) a disruption of cholinergic transmission to cortical regions, even when the latter are spared by the lesion but deafferented from cholinergic inputs. In a proof-of-concept study, we tested the effect of a single-dose (10 mg) of transdermal nicotine patch on various symptoms of neglect using a double-blind placebo-controlled design. Based on previous research in both animals and humans, we expected some improvement in both lateralized and non-lateralized aspects of attention. In addition, we also performed an exploratory analysis of anatomical lesions to verify whether any treatment benefit would depend on particular components of the cholinergic pathways.

MATERIALS AND METHODS

PARTICIPANTS

The patient group consisted of 10 patients (8 women, 2 men) suffering from spatial neglect after a first-ever unilateral right-hemispheric stroke (except patient 1, who presented with right neglect after a left-hemisphere stroke). They were recruited from a consecutive series of stroke patients admitted to Geneva University Hospital and Plein Soleil Foundation (Lausanne). All patients gave their informed written consent to participate in this study according to the local ethics regulation of Geneva and Lausanne University Hospitals. Patients were all right-handed (except one), with mean age of 69.1 years (range: 51.2–79.2), and showed both clinical and radiological evidence of single focal lesion to the right hemisphere due to stroke, involving the middle cerebral artery (MCA) territory in all cases; while they had no other serious concomitant illness. Most patients had partial (five quadranopia) or full (three hemianopia) visual hemifield cuts as determined by clinical examination using confrontation (subsidiary analysis showed no systematic influence of hemifield defects on performance or treatment response). Patients were examined 6.45 months post-stroke on average (range: 1–15 months). They were included only if they had stable vigilance and sufficient cooperation to undergo a testing session of 45 min, and showed stable symptoms of neglect as assessed with a standard battery of tests (Rousseaux et al., 2001; Azouvi et al., 2003), including cancellation, line bisection, compound-word reading, and two computerized tests for lateralized target detection and cued target detection (**Table 1**). Patients were excluded if they were currently smoking ≥ 1 cigarette/day, and any past history of smoking was systematically quantified and registered (**Table 1**).

MATERIAL AND PROCEDURE

The effect of a medium dose transdermal nicotine patch on attention performance was studied in a double-blind placebo-controlled within-subject design, where each patient participated in a four day sequence. On day 1, baseline performance was measured on a standardized battery, comprising eight neglect tests, to establish initial neglect severity. On day 2, patients received either an active nicotine treatment patch (Nicorette®, 10 mg) or a placebo patch, the order being randomly assigned to successive patients. After 24 h of rest on day 3, allowing a complete washing-out of the active agent (when given), the second patch was given, complementary to the one applied on day 2 (i.e., day 2: placebo → day 4: nicotine; or day 2: nicotine → day 4: placebo). On days 1, 2, and 4, neglect was assessed using a similar battery of visuo-spatial attention tasks. For each subject, the testing took place at the same time of the day, reducing any contamination by circadian fluctuation in attention.

Each subject was treated once (on either day 2 or day 4) with the pro-cholinergic agent (Nicorette®, 10 mg), always administered by patch. Active and placebo patches were visually identical (provided by Pfizer, Inc.). The patch was applied in the morning between 7 and 8 a.m. and removed around 6–7 p.m. Neuropsychological effects were assessed 6–8 h after the patch was applied, given that peak absorption is reached 5–10 h after application (Swiss Medical Compendium). During each session, possible negative side effects were systematically monitored with a checklist, listing all

Table 1 | Demographic and clinical data of the neglect patients.

Patient	Sex	Age	Months post-accident	Cerebral vascular accident	Arterial territory	Visual field loss	Handedness	Sensory extinction	Smoking history	Nicotine side effects	Lesion volume (voxel)	Initial neglect severity (high: >group median; L: <group median)
hd	m	72.63	3.77	i	MCA	Yes	r	None	Nihil	No	498682	High
sh	f	51.18	7.83	i,h	ACA	No	r	None	Nihil	No	598567	Low
ro	f	59.45	5.37	i	MCA, ACA	Yes	l	None	Previously 30–40 UPA; stopped 5 years ago	No	496357	High
pa	m	68.20	1.73	i	MCA	Yes	r	None	Previously 60 UPA; stopped since accident	No	504154	High
fu	f	78.37	14.00	h	MCA, ACA	Yes	r	None	Nihil	No	Not available	Low
co	f	53.18	13.93	h	MCA, PCA	Yes	r	Tactile	Nihil	No	18841	High
sc	f	79.21	15.10	i	MCA	No	r	Tactile	Nihil	No	225924	High
ki	f	78.95	0.80	h	MCA	Yes	r		Nihil	Mild diarrhea in morning	131425	Low
lu	f	75.41	0.93	i	MCA	Yes	r	Visual and auditory	Nihil	0	391841	Low
go	f	74.58	1.00	h	MCA	Yes	r	visual and auditory	Nihil	0	89240	Low

f, Female; m, male; i, ischemic; h, hemorrhagic; MCA, middle cerebral artery; PCA, posterior cerebral artery; ACA, anterior cerebral artery; r, right; l, left; UPA, smoking habit magnitude (unity/packet/year).

symptoms declared by the producer on a three-level scale (0 = no effect, 1 = minor effect, 2 = major effect).

The battery for assessing symptoms of spatial neglect was composed of eight different tasks probing visuo-spatial exploration, perception, and orienting (see **Table 2** for details and **Figure 1**). For each of the tests, the stimulus support (paper-sheet or computer screen) was aligned with the midsagittal plane of the patient. The average assessment duration was around 45 min.

DATA ANALYSIS

The performance scores from each task (**Table 2**) were submitted to a repeated-measure ANOVA with the within-subject factor TREATMENT CONDITION (3) (baseline, placebo, nicotine), plus more specific factors related to the task itself.

For the cancellation tasks: we ran mixed ANOVAs using the within-subject factors TARGET SIDE (2) (contralesional; ipsilesional), TREATMENT CONDITION (3) (baseline, placebo, nicotine), and the between-subject factor TEST (3) (letter cancellation, shape cancellation, Bells' cancellation).

For the word reading task: repeated-measure ANOVAs using the within-subject factors TARGET SIDE (2) (contralesional; ipsilesional), and TREATMENT CONDITION (3) (baseline, placebo, nicotine), were conducted on the number of omissions/transformations per side of space relative to the midsagittal plane (egocentric frame of reference) and relative to the word-centered midline (allocentric frame of reference).

For the line bisection task: median deviations were calculated for each category of line length (16 and 20 cm) and for each patient, and then submitted to a repeated-measure ANOVA with the within-subject factor TREATMENT CONDITION (3) (baseline, placebo, nicotine).

In the Quadruplet detection task and the Cued target detection task: to reduce variables in a concise but sensitive measure, we combined hit rates and reaction times to compute efficiency scores (i.e., hit/RT ratio), which were then entered into repeated-measure ANOVAs with the within-subject factors TARGET SIDE (2) (contralesional; ipsilesional), CUE TYPE (3) (invalid, no cue; valid), and TREATMENT CONDITION (3) (baseline, placebo, nicotine).

Finally, we quantified initial neglect severity in all patients by calculating a global index of neglect deficits at baseline on day 1, dividing the number of tasks showing evidence of spatial neglect relative to the total number of tests given during this assessment, multiplied by 100. We distinguished patients with severe initial

Table 2 | Tests used to assess neglect (Rousseaux et al., 2001) and dependent variables used for ANOVAs.

Tests	Measure	ANOVA factor
PAPER AND PENCIL TASKS		
Bells' cancellation task	Omission (left-right)	Target side
2 Versions	Search time	Contralesional vs. ipsilesional
Letter cancellation task	Omission (left-right)	Target side
3 Versions	Search time	Contralesional vs. ipsilesional
Shape cancellation task	Total omission (left-right)	
1 Version		
Compound-word reading task	Omissions/transformations (left-right)	Frame reference
2 Versions		Egocentric vs. allocentric
Line bisection (16 or 20 cm)	Deviation of the subjective midline <5%	% Of deviation
1 Version		
COMPUTERIZED VISUAL TASKS		
Lateralized visual detection task	Response latencies (left-right)	% Rates
Cued detection task (Posner's paradigm)	Response latencies (left-right)	% Rates

Cancellation tasks: performance on the three cancellation tasks was evaluated using three different measures: number of omissions (per side of space), search duration (total time on the task, until the patient indicated to have finished the search or a maximum of 4 min), and the side of the first target canceled (right or left from the sheet midline).

Word reading task: the number of composite words omitted and the number of omissions/transformations of a composite-word part (typically its left part) were recorded for each side of space (right or left from the sheet midline).

Line bisection task: performance was measured as the deviation in mm of the subjective center relative to the true center of the line. Deviations exceeding 5% of total line length were considered pathological.

Quadruplet detection task: two dependent variables were measured, response latencies and detection rate (percentage of targets correctly reported for each side). To simplify our analysis and minimize multiple comparisons, both measures were collapsed into a single index of detection efficiency, by computing the ratio of the detection rate (number of hits) divided by the response latency (in milliseconds), multiplied by 100 to obtain speed-weighted percentage values. This quotient allows weighting the detection rate for a given condition as a function of the detection speed.

Cued target detection task (Posner's paradigm): performance was evaluated in the same way as above, by computing a single efficiency score that combined the two dependent variables of detection rate (number of hits) and detection latencies (milliseconds), multiplied by 100 to obtain speed-weighted percentage values.

All tests (except star cancellation and line bisection) were given in different versions (different shapes or colors but with same spatial distribution and task structure) in different session (counterbalanced across participants), in order to minimize habituation or learning effects due to repeating the same tests.

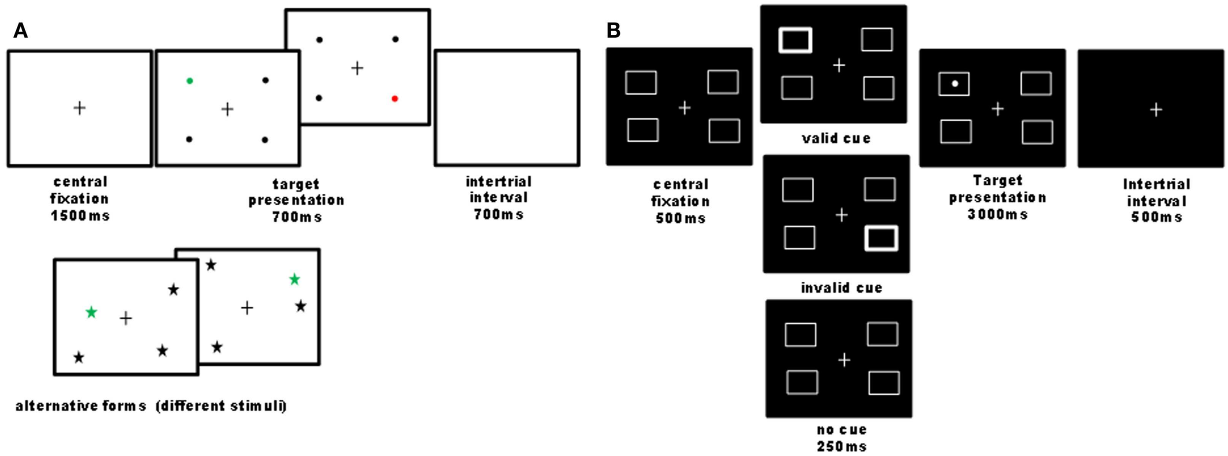

FIGURE 1 | Illustration of computer tasks. **(A)** *Quadruplet detection task*: participants had to detect a single colored visual target among three black distracters and to report its color (e.g., red or green) as fast as possible by pressing one of two possible keys. On each trial, four stimuli were always presented, one in each quadrant, while the exact stimulus position within the quadrant was pseudo-randomly varied across trials. Different shapes and colors were used in different sessions (baseline, nicotine, placebo), counterbalanced across participants. Overall 44 trials were administered. In 90% of trials, a target was presented (half on the left and half on the right side); 10% of trials were catch trials, where no target was presented, in order to control for guess responses. This task was designed to assess visual detection in condition of stimulus competitions across the two hemifields, similar to extinction conditions (Vuilleumier and Rafal, 2000). The criterion for neglect presence on this task was a significant slowing of response latencies or increase in omission rates for targets on the left as compared to the right side. **(B)** *Cued detection task*: we designed a four-position variant of Posner's paradigm with exogenous cues (24 trial by condition), where participants had to detect a lateralized target as quickly as possible, which could be preceded by a transient thickening of one of the four boxes or none. Validity and invalidity effects were calculated by comparing responses to targets following cues presented at the same or different locations. The cue validity was 50% to minimize the contribution of an endogenous allocation of attention. Patients reported detections by pressing on the computer space bar. The criterion for neglect presence on this task was a significant slowing of response latencies for targets on the left as compared to the right side.

neglect [(USN+), above group median] vs. patients with moderate initial neglect [(USN−), below group median] by applying a median split on the group data. Changes during under placebo or nicotine were assessed relative to baseline performance.

LESION ANALYSIS

Brain lesions were confirmed by MRI or CT scans in seven and two patients respectively (for one patient only the neuro-radiological report was obtained) and reconstructed on axial slices using MRIcro (Rorden and Brett, 2000), following previously described methods (Verdon et al., 2010; Vocat and Vuilleumier, 2010; Saj et al., 2012; Vuilleumier et al., 2007). In two patients, we used CT scan to delineate the lesion site on a corresponding MRI template, as MRI could not be performed for clinical reasons. The lesioned areas were transformed to a 3D region-of-interest (ROI) corresponding to the lesion volume, and then normalized to a standard brain template using standard MRIcro and SPM methods (Ashburner and Friston, 1997; Ashburner et al., 1997). The normalized lesion ROIs were superimposed on a T1 MRI template and submitted to exploratory mapping analyses using MRIcro (Rorden and Brett, 2000), in order to examine the correlations between behavioral performance and anatomical extent of brain damage on a voxel-by-voxel basis. Firstly, we determined the average lesion overlap across all neglect patients. Secondly, we delineated critical lesion sites as a function of specific behavioral deficits in individual patients (e.g., neglect severity), or as a function of their sensitivity to nicotine treatment based on the observed improvement on neglect tasks.

RESULTS

GOOD TREATMENT TOLERANCE

For the medium dose of nicotine administered here (10 mg), all patients in the present group showed a good treatment tolerance. Only two patients had a positive score for one item (diarrhea) on the negative symptom checklist. In one patient with a score of 2 on this scale (major symptom), the treatment was interrupted and the patient was not included into the study. The second patient presented a score of 1 (minor symptom) in the first few hours after patch application, but the symptom resolved after noon and the patient participated in the three sessions of the study without any further problem.

REDUCED NEGLECT IN CANCELLATION TASKS UNDER NICOTINE TREATMENT

We investigated visual exploration behavior on three different cancellation tasks (shape cancellation, letter cancellation, and Bells' cancellation), which have different degrees of difficulty (as a function of the number of targets to be found, distracters to be ignored, and spatial crowding). First we compared the influence of treatment on target detection, as measured by the number of omissions in the three cancellation tasks, using a mixed $3 \times 2 \times 3$ ANOVA, with the within-subject factors TREATMENT CONDITION (baseline, placebo, nicotine) and TARGET SIDE (contralesional, ipsilesional), plus the between-subject factor TEST (shape cancellation, letter cancellation, Bells' cancellation). Performance significantly varied as a function of treatment, with the number of omissions being significantly reduced under the *nicotine* treatment (mean number of omissions: 2.93 ± 0.5) as compared to both *baseline* (4.95 ± 0.8) and *placebo* (5.14 ± 0.9) [main effect of TREATMENT CONDITION: $F(2, 23) = 11.06$, $p < 0.0001$]. As expected, the number of omissions on the left (contralesional) side (mean: 6.7) was globally higher than on the right [mean: 1.9; main effect of TARGET SIDE: $F(1, 24) = 25.85$, $p < 0.0001$]. This pattern of was similar for the three cancellation tasks [no main effect of TEST: $F(2, 24) = 0.925$, $p > 0.05$; no interaction with the other factors [TEST × SIDE: $F(2, 24) = 0.75$; $p > 0.05$; TEST × TREATMENT CONDITION: $F(4, 48) = 0.4$; $p > 0.05$]. The average number of *omissions* across the three cancellation tasks, calculated for each side separately and each patient, is plotted in **Figure 2A**.

While the reduction of omissions under nicotine was numerically greater on the left than the right side, the spatial asymmetry in omission distribution persisted in all sessions (no two-way interaction TREATMENT CONDITION × TARGET SIDE [$F(2, 8) = 1.69$; $p > 0.05$]. However, the reduction of omissions under nicotine was primarily driven by enhanced exploration toward the contralesional part of space, and omissions of ipsilateral targets were not entirely abolished. When investigating the effect of treatment condition on exploration for each side separately, a significant effect was found for *contralesional* targets only [main effect TREATMENT CONDITION: $F(2, 8) = 9.92$; $p < 0.001$], with fewer omissions under *nicotine* (mean number: 5.0 ± 1.5) as compared to both *baseline* [mean: 7.9 ± 1.8; $t(9) = 4.67$; $p < 0.001$] and placebo [mean number of omissions: 7.8 ± 1.9; $t(9) = 3.92$; $p < 0.005$]. The reduction of omissions on the ipsilesional side was not statistically significant [$F(2, 8) = 1.39$, $p > 0.05$].

Enhanced target detection during cancellation tasks went along with longer exploration times. Following standard clinical practice, patients were free to interrupt the task whenever they felt they had marked all targets, but given a maximum of 4 min. We computed the average exploration time across the different cancellation tests and submitted these data to a repeated-measure ANOVA with the within-subject factor TREATMENT CONDITION (baseline assessment, placebo, nicotine). Patients searched the cancellation arrays significantly longer under nicotine treatment (mean: 186.9 ± 51.6 s), as compared to baseline assessment [mean exploration time: 141.4 ± 50.6 s; $t(8) = 3.5$; $p < 0.01$] and placebo [mean: 148.7 ± 58.5 s; $t(8) = 2.73$; $p < 0.05$] [main effect TREATMENT CONDITION, $F(2, 7) = 6.37$; $p < 0.01$]. **Figure 2B** illustrates the average search times in each treatment condition, and shows these were significantly longer under nicotine treatment relative to both placebo and baseline. This increase was observed in all three cancellation tasks (**Table 3**).

The rate of target detection over time was further examined in the Bells' cancellation task since this task allowed tracking the number and location of detected targets across successive time-bins of 60 s (Rousseaux et al., 2001). **Figure 3A** shows that at baseline and under placebo, the majority of targets was found during the first minute, while only few additional items were detected in the subsequent time-bins. By contrast, under nicotine, the increase in detection rate was associated with a more regular detection rate over time. Thus, patients self-terminated search earlier in both the baseline and placebo conditions (i.e., no longer detecting any new target after 3 min in two third of cases), while they tended to continue search much longer when treated by nicotine (i.e., still exploring and detecting new targets until the time-limits of 4 min in more than half of cases; see **Figure 3B**).

On the other hand, the side of the first target canceled (in the three cancellation tasks) remained unchanged throughout the three treatment conditions.

ENHANCED PERFORMANCE IN CUED TARGET DETECTION

Effects of spatial cues on attentional orienting and subsequent target detection (Posner task) were analyzed in a 3 × 3 × 2 repeated-measure ANOVA with the within-subject factors TREATMENT CONDITION (baseline assessment, placebo, nicotine), CUE TYPE (invalid, no cue, valid), and TARGET SIDE (contralesional, ipsilesional). Attentional orienting significantly varied as a function

Table 3 | Performance on individual cancellation tasks.

	Bells cancellation			Letter cancellation		
	Baseline	**Placebo**	**Treatment**	**Baseline**	**Placebo**	**Treatment**
Mean	14	14.2	9	7.9	7.2	4.7
SD	7.7	10.2	5.4	8.4	4.5	5.3

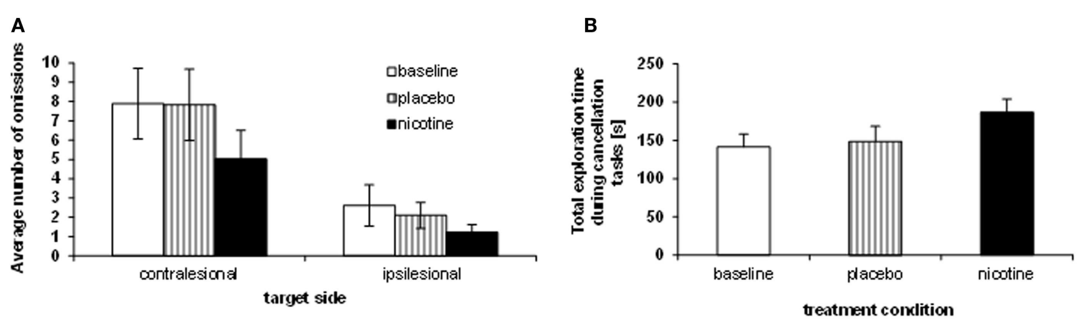

FIGURE 2 | Effects of treatment on neglect behavior. **(A)** Sum of omissions averaged over the three cancellation tasks, separately for each target side (contralesional, ipsilesional). **(B)** Average total exploration time, across the three cancellation tasks (millisecond), showing longer search periods under nicotine as opposed to placebo and baseline performance.

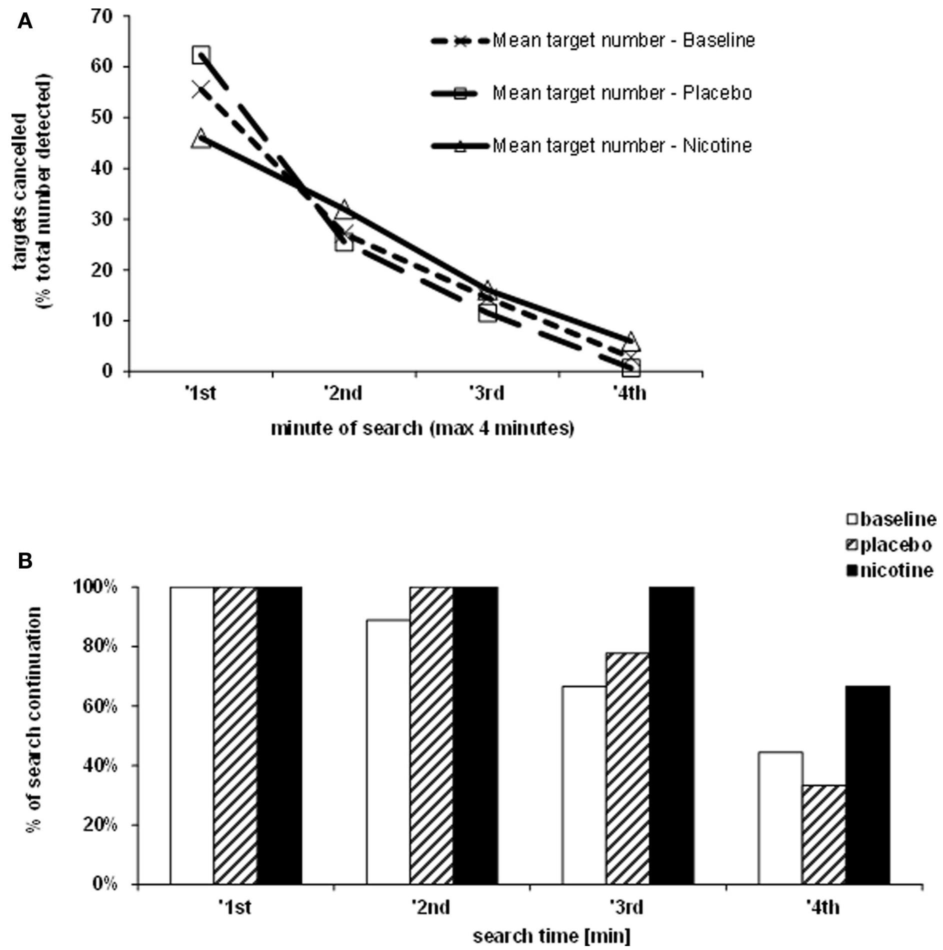

FIGURE 3 | Effects of treatment on exploration time. **(A)** Target detection during the Bells' cancellation task, plotted as the mean percentage of targets canceled per minute, relative to the total number of targets found by each participant in each test session. **(B)** Duration of search during the Bells' cancellation task represented as the percentage of patients continuing to search for targets in time bins and each treatment condition. Search was self-terminated until a maximum allocated time of 4 min.

of the cue type [main effect of CUE TYPE: $F(2, 7) = 18.65$; $p = 0.0001$], reflecting, as expected, a lower efficiency in the *invalid* condition (mean efficiency ratio of hits/RTs: 105.01 ± 9.56), relative to the two other cue conditions (all comparisons significant at $p < 0.05$; see **Figure 4**). Efficiency was intermediate in the *no-cue* condition (mean: 120.28 ± 12.12), and maximum in the *valid* cue condition (mean: 131.51 ± 12.12, significantly better than no cue, $p < 0.005$). Thus, the relative cost due to invalid cues and relative benefit due to valid cues both were reliably present in our patients. Note that the absence of an alerting signal in the no-cue condition was less harmful to performance than an invalid cue, consistent with the typical deficit in spatial attention associated with neglect.

As also expected, a robust difference in target detection efficiency was observed as a function of *target side* [main effect of TARGET SIDE: $F(1, 8) = 31.86$; $p < 0.0001$], with efficiency being overall better for targets in ipsilesional space (mean efficiency: 158.51 ± 10.83) as compared to targets in contralesional space (mean efficiency: 79.35 ± 15).

More importantly, attentional orienting was significantly influenced by the treatment [main effect TREATMENT CONDITION: $F(2,7) = 3.91$; $p < 0.05$], with nicotine enhancing the efficiency for target detection (mean efficiency: 128.65 ± 11.54) relative to both the baseline assessment (mean efficiency: 108.12 ± 9.67; $p < 0.05$) and to the placebo condition (mean efficiency: 120.04 ± 13.93; $p < 0.05$). This improvement in efficiency was generally more important for the contralateral visual field (six patients detected the target faster under nicotine than placebo), in comparison with the ipsilateral field (only four faster under nicotine than placebo). No such improvement occurred under placebo as compared to baseline ($p > 0.05$).

Furthermore, nicotine treatment did not enhance detection in all cueing conditions similarly, as indicated by a significant two-way TREATMENT × CUE TYPE interaction [$F(6, 3) = 2.05$; $p = 0.055$]. Subsequently, to examine the critical planned comparisons, we computed 3 × 2 ANOVAs for the factors TREATMENT CONDITION and TARGET SIDE for each cue condition separately, which revealed that nicotine enhanced performance

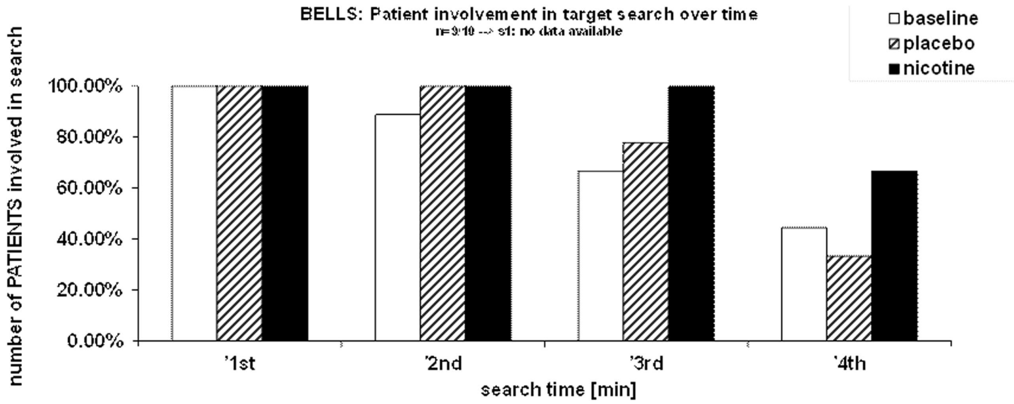

FIGURE 4 | Efficiency (hits/latencies) across different cueing conditions, for targets on both side of space relative to a mid-sagital plane separately.

exclusively in the *valid* condition [main effect TREATMENT CONDITION: $F(2, 7) = 4.42$; $p < 0.05$] and in the *no-cue* condition [$F(2, 7) = 3.46$; $p = 0.057$], but not in the *invalid* condition [$F(2, 7) = 1.87$; $p > 0.05$]. However, these effects did not interact with TARGET SIDE. Thus, overall, detection efficiency was significantly enhanced by nicotine on both sides of space upon *valid* cues (mean: 146.76 ± 13.67) as compared to the baseline condition [mean: 116.84 ± 9.94; $F(1, 8) = 16.22$; $p < 0.005$], which in turn was similar to the placebo condition [mean: 130.94; ± 16.01; $F(1, 8) = 1.32$; $p > 0.05$]. A similar improvement of detection efficiency was found for targets presented without a preceding cue (*no-cue* condition, mean: 130.53 ± 11.53), relative to both the baseline (mean: 111.36 ± 11.54; $p < 0.05$) and the placebo condition (mean: 119.13 ± 15.07; $p < 0.05$), again irrespective of target side [interaction TREATMENT CONDITION × TARGET SIDE: $F(2, 7) = 0.12$; $p > 0.05$]. However, a formal test of the full three-way interaction (TREATMENT CONDITION × TARGET SIDE × CUE TYPE) did not reach significance [$F(4, 6) = 0.543$], which is likely to result from the small sample size relative to the number of conditions.

NO EFFECT OF NICOTINE ON OTHER TASKS

No effect of nicotine treatment on neglect symptoms was found for the remaining tests. Nicotine did not induce any systematic amelioration on line bisection, a task where patients consistently showed rightward and highly variable deviation, irrespective of treatment condition (see **Table 4**).

No systematic effect was found for the composite-word reading task either. Nicotine did not induce systematic changes in the total number of words read on either side of the page. Neither did it modify the location of the first word read (egocentric neglect measures), nor did it reduce neglect dyslexia symptoms as determined by the number of omissions or transformations for the left part of compound words (allocentric neglect measures).

We note however that, in the present patient sample, *object-centered* neglect was consistently observed in one patient only (patient CF), for two different tests on different occasions (composite-word reading; shape cancellation, with discriminative target features on either their left or right side). No amelioration of these deficits was found under nicotine. Two other patients also showed signs of object-centered neglect but in the compound-word reading test only, and again none of them improved in this test under nicotine.

Finally, in the *Quadruplet detection* task, neither the number of misses nor the correct response time for contralateral targets were changed by nicotinic treatment. A 3 × 2 repeated-measure ANOVA was conducted on detection efficiency (ratio hits/RTs) with the factors TARGET SIDE (contralateral; ipsilateral) and TREATMENT CONDITION (baseline, placebo, nicotine), but only showed the neglect-specific spatial asymmetry [main effect of TARGET SIDE: $F(1, 9) = 44.91$; $p < 0.0001$]. Targets on the ipsilesional side were much more efficiently (more often and more rapidly) detected than targets on the contralesional side (mean efficiency: 151.4 ± 9.4 vs. 53.9 ± 13.2, respectively). However, nicotine did not reduce this asymmetry [main effect TREATMENT CONDITION: $F(2, 8) = 1.88$; $p > 0.05$; no interaction TREATMENT × TARGET SIDE: $F(2, 8) = 0.32$; $p > 0.05$].

NICOTINE TREATMENT INDUCES STRONGER IMPROVEMENT IN PATIENTS WITH MORE SEVERE NEGLECT

In order to quantify the severity of neglect in our patient sample at the beginning of our study, we computed a score of baseline performance, based on the percentage of tests positive for neglect (relative to the total number of tests administered, since some patients did not complete *all* tests). As shown in **Table 4**, at baseline, before any treatment took place, patients with *severe initial neglect* omitted 45.7% of targets on the Bells cancellation task, whereas patients in the *moderate* initial neglect group omitted 25.7% of targets. Moreover, patients in the *severe* group showed positive neglect signs on 90% (range: 63–100%) of the tests (according to standard criteria for each test; see details in Materials and Methods section), whereas patients in the *moderate* group showed positive neglect signs on 58.3% (range: 28–75%) of the tests.

Interestingly, patients showing more severe initial neglect also showed better improvement under nicotine, as reflected by a positive correlation ($r = 0.38$) between the scores of initial neglect severity and the scores of amelioration by nicotine (see **Figure 5**). However, this correlation did not reach significance ($p = 0.12$, two-tailed) presumably due to the small sample size.

Table 4 | Initial neglect severity in the baseline test session.

	Sj nr	No tests done	No tests positive	% Test positive	BELLS omtot	% BELLS omtot	% Mean
HIGH initial neglect	7	8	8	100.00	28	80.00	90.00
	4	8	8	100.00	25	71.43	85.71
	1	8	7	87.50	11	31.43	59.46
	8	8	5	62.50	16	45.71	54.11
	5	3	3	100.00	19	54.29	77.14
LOW initial neglect	6	7	5	71.43	11	31.43	51.43
	11	6	4	66.67	6	17.14	41.90
	10	8	6	75.00	9	25.71	50.36
	9	8	4	50.00	8	22.86	36.43
	3	7	2	28.57	7	20.00	24.29

Neglect severity was determined by computing two different scores: (1) percentage of tests positive for neglect (based on asymmetries in response latency and/or accuracy in each test), relative to the total number of tests given to the patient; (2) percentage of omissions on Bells' test, which is one of the most sensitive test for neglect and was given to all patients on all sessions. The same subgroups were constituted and the same results were obtained when defining the severity subgroup with either score.

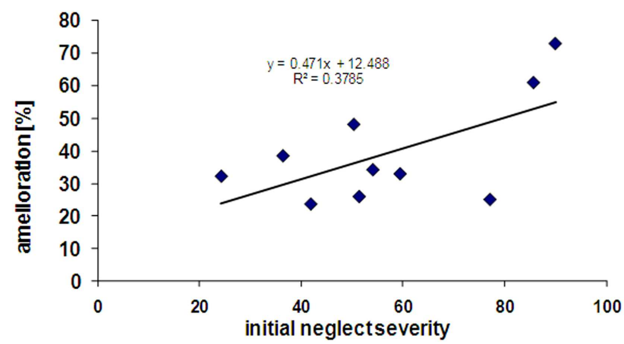

FIGURE 5 | Correlation between initial neglect severity (% tests failed at baseline) and extent of amelioration under nicotine treatment (% tests improved in the drug condition).

In addition, some patients were included at a relatively early stage post-stroke, whereas others were included at more chronic stages (range of days post-onset = 24–453). A moderate but again non-significant positive correlation between time since stroke onset (in number of days) and improvement was also found ($r = 0.42$, $p = 0.10$, two-tailed). This correlation nonetheless suggests that nicotine may exert some effects even at relatively late or chronic stages.

LESION ANALYSIS

Finally, we analyzed the patients' lesions in order to examine any possible relationship between behavioral performance and the site or extent of brain damage. As our population sample was small, these analyses were essentially exploratory. Normalized lesion ROIs obtained from MRI reconstruction were used to determine the common overlap and differences between patients. In this sample, neglect severity did not correlate with lesion volume: the total number of voxels covered by lesion on the MRIcro brain template did not correlate with scores of initial neglect severity ($r = -0.07$).

Areas most commonly damaged in the present patient group were centered on the peri-sylvian subcortical white matter, extending posteriorly toward the inferior parietal lobe (**Figure 6A**). The maximal overlap involved the sub-insular white matter, including tracts of the external capsula and claustrum, in a position that is likely to disrupt the major afferents in the lateral cholinergic bundle projecting from the nucleus basalis of Meynert to the posterior frontal, parietal, and temporal cortices (Selden et al., 1998).

Comparing patients with more severe initial neglect to those with less severe neglect showed that the former had more extensive damage in the sub-insular white-matter regions and internal capsule, extending into dorsal caudate, putamen, and globus pallidus (**Figure 6B**); whereas less severe deficit was associated with lesions affecting the temporal lobe and the depth of the inferior parietal lobe, without basal ganglia involvement (**Figure 6C**). A direct contrast between these two subgroups using a voxel-wise subtraction analysis (**Figure 6D**) indicates that brain damage associated with *severe* initial neglect (purple–yellow) predominated in posterior parietal cortex and posterior thalamus (particularly in a region corresponding to the pulvinar). Whereas lesions associated with *mild* neglect were centered on the white matter of the inferior temporal lobe (dark blue–turquoise).

Next, to determine whether different lesions accounted for different degrees of performance modulation by nicotine treatment, we distinguished patients showing a *low ameliorative effect* ($n = 4$) from those showing a *high ameliorative effect* ($n = 5$) under nicotine, based on a median split of improvement scores in each patient. Improvement was calculated as the difference in the global neglect severity score (% of positive tests) during nicotine treatment vs. baseline (cf. Materials and Methods section – **Table 4**). Note that the same patient subgroups were distinguished using a median split of changes in cancellation performance (difference in number of omission under nicotine vs. baseline). We then probed for the link between improvement and anatomical lesion sites using a voxel-wise subtraction analysis between patients with higher ($n = 5$) vs. lower amelioration ($n = 4$) under nicotine. As shown in **Figure 7**, reduced improvement was associated with

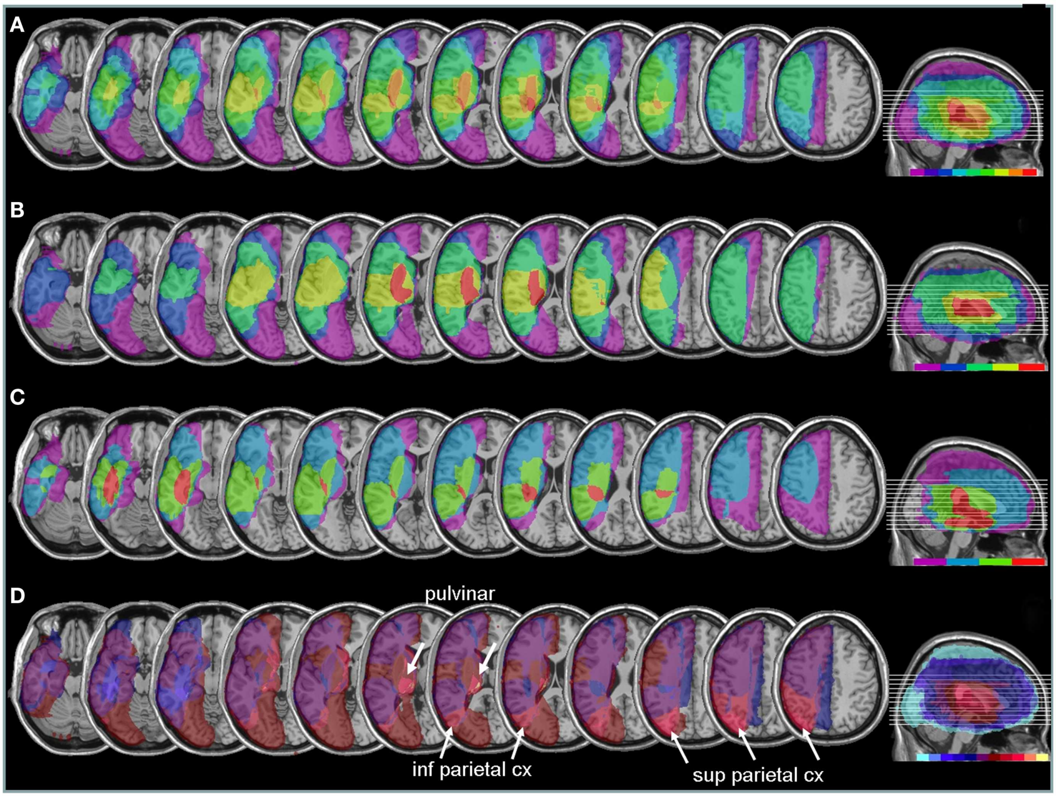

FIGURE 6 | Anatomical lesion analysis. **(A)** Lesion overlap for the 9/10 patients for whom CT or MRI scans were available. Colors code for the number of patients with damage to a given area, ranging from purple for areas affected in one patient only, to red for areas affected in all patients. Brain regions most consistently damaged in our patients were located in the posterior limb of the internal capsule and deep parietal lobe (orange-red, corresponding to at least eight patients). **(B)** Lesion overlap in a subgroup of four patients with the most severe neglect deficits at baseline showing more extensive lesions in the right peri-sylvian and subcortical temporo-parietal junction. **(C)** Lesion overlap in the five patients with less severe neglect deficits at baseline, showing predominant damage in the temporal lobe and deep paraventricular white-matter. Colors code for the number of patients with damage to a given area (from 1 = violet to 5 = red). **(D)** Median split subtraction analysis, comparing the lesion in patients with severe vs. moderate neglect at baseline. Each color in the scale bar codes for a 16.67% frequency of lesion in one or the other group, except for the central purple color that represents −16.67 to +16.67%. More severe initial neglect correlated with more frequent damage to posterior parietal cortex and pulvinar (purple to yellow shades), while less severe neglect correlated with temporal white-matter damage (blue to turquoise shades).

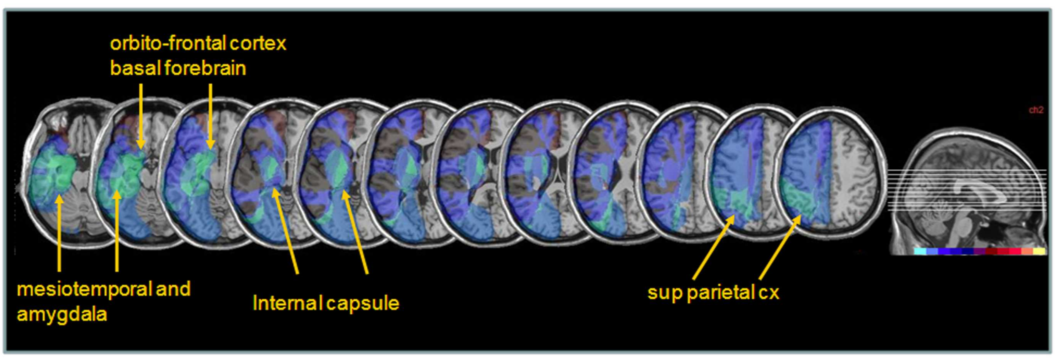

FIGURE 7 | Anatomical correlates of nicotine treatment efficacy. Median split subtraction analysis, comparing the lesion in patients with the least important vs. the most important modulation of neglect (% tests failed across the whole battery or number of target omissions in Bells' cancellation task) under nicotine relative to placebo. Each color in the scale bar codes for a 16.67% frequency of lesion in one or the other group, except for the central purple color that represents −16.67 to +16.67%. Lesions associated with the smaller improvement under nicotine were centered on subcortical white-matter fibers at the level of the basal forebrain, substantia innominata/sublenticular dorsal amygdala, as well as posterior parietal cortical areas.

lesions in the anterior mesial temporal lobe, with a maximum focus in dorsal amygdala (blue – turquoise voxels), as well as with lesions in the basal forebrain, internal capsule, and posterior parietal cortex (overlapping with intraparietal sulcus). Greater improvement was not found to correlate with consistent involvement of particular brain regions (dark purple and brown colored voxels).

DISCUSSION

The present study investigates the effects of pro-cholinergic treatment by nicotine in spatial neglect, using a series of classic neuropsychological tests and computerized measures of spatial attention. A significant improvement was found under nicotine for some tests but not others. This improvement tended to be more pronounced in patients with severe neglect, persisted in chronic stages, but depended on a relative sparing of parietal cortex, basal forebrain, and medial temporal lobe.

We employed a double-blind placebo-controlled within-subject design over three consecutive days, while spontaneous neglect recovery was unlikely to occur. Our major novel result is that a transdermal nicotine treatment with a single administration induced a consistent improvement of target detection and exploration behavior in three different cancellation tasks. Under nicotine, but not under placebo, the search performance of neglect patients was reliably improved, as reflected by a significant reduction of target omissions relative to both the placebo and baseline conditions. This improvement under nicotine was observed for targets on both sides of space, but with a more important reduction of omissions on the *contralesional* side. Nicotine also affected the duration of search behavior, by leading to more prolonged search times before terminating exploration and declaring all targets found (patients were free to continue or interrupt search until a maximum time limit of 4 min). This pattern suggests that nicotine enhanced the ability to progressively orient attention toward the contralesional side and/or disengage from previously explored locations on the ipsilesional side (Chatterjee et al., 1999), but without speeding target detection *per se.* Moreover, nicotine did not affect the *initial orienting bias* typically observed on cancellation tasks. Under nicotine, like at baseline or under placebo, patients invariably started their search on the ipsilesional (right) side of space (the first target canceled situated on the ipsilesional side of space).

By contrast, on tasks with a predominantly perceptual component, such as the line bisection and the quadruplet detection tasks, nicotine did not improve attentional biases of neglect patients. Both the extinction rate and detection latency asymmetries on the Quadruplet detection task remained unchanged, as did the rightward bias of the subjective midpoint during line bisection. A few previous studies have suggested a possible role for nicotine in boosting perceptual processing and representation in a *bottom-up* manner, either via enhanced selectiveness of thalamo-cortical transmission (Mooney et al., 2004; Disney et al., 2007) or through an amplification of early cortical visual processing (Stough et al., 1995; Thompson et al., 2000; Erskine et al., 2004), which would be expected to improve the detection of contralesional sensory stimuli in neglect patients (particularly in conditions of competition such as the quadruplet detection task here). However, such an effect of nicotine is not supported by the present findings, since detection efficiency in this task remained unchanged in our patients under the active drug treatment. Likewise, the distortion or compression in space representation underlying line bisection deficits (Bisiach et al., 1998) does not appear to be modulated by cholinergic function.

Finally, reorienting of spatial attention to the contralesional side subsequent to an invalid ipsilateral cue (i.e., Posner task), which is typically deficient in neglect patients (Bartolomeo and Chokron, 2002; Corbetta and Shulman, 2002), was not affected by nicotine in our study. However, we found an improvement in detection efficiency for targets presented after a valid cue or without a cue. Previous results from similar tasks in healthy human volunteers have been mitigated, with some studies reporting enhanced reorienting performance under nicotine with both endogenous (Thiel et al., 2005; Meinke et al., 2006) and exogenous cues (Witte et al., 1997; Murphy and Klein, 1998), while others failed to find reliable effects – with either exogenous (Meinke et al., 2006) or endogenous cues (Griesar et al., 2002; Meinke et al., 2006). A Posner task was also used to examine the effect of nicotine treatment in patients with spatial neglect in a recent study (Vossel et al., 2010), published after we reported our preliminary results elsewhere (Lucas et al., 2006). Results from this study showed that nicotine produced a non-specific speeding of RTs, without modulating the validity or invalidity effects of spatial cues, suggesting an influenced on tonic attentional processes like vigilance or sustained attention. These data accord with our own results, since we found that neither the detection rate nor the latency for reorienting to the contralesional side after invalid cues were improved.

Nevertheless, our results suggest an improvement in detection efficiency that was selectively observed for the uncued and validly cued targets. This improvement was spatially unspecific, i.e., not significantly lateralized to the contralesional or ipsilesional side. This improvement might reflect a nicotine-induced increase in cortical arousal and facilitation in processing task-relevant information, as reported by several behavioral studies after increased cholinergic levels through smoking or nicotinic drug (Knott et al., 1999; Gilbert et al., 2000). One study (Griesar et al., 2002) testing the effect of nicotine on alertness and covert orienting with endogenous cues reported similar findings in healthy non-smokers: participants showed a general improvement of latencies, in the absence of any spatially specific effect on orienting or reorienting of attention. Simultaneous EEG recordings also corroborated the hypothesis that the enhanced target detection was related to enhanced alertness. We note that, in our study, the absence of a similar improvement in the quadruplet detection task might possibly be due to the fact that that this task required a speeded discrimination, whereas the cued target detection task (Posner paradigm) required a simple detection response, and no-cue trials were unilateral without any competing distractors.

Consistent with our findings that nicotine may speed target information processing, a number of studies in different species have reported beneficial effects of nicotinic treatment on sustained attention (Trimmel and Wittberger, 2004; Spinelli et al., 2006). Therefore, we believe that the selective improvements in cancellation and cued target detection tasks in our patients might rely at least partly on an increase of sustained attention, possibly by enhancing arousal (Robertson et al., 1998) or general motivation factors (Mesulam, 1999), which are often impaired in neglect patients (Finke et al., 2012). In keeping with this assumption, both tasks for which neglect patients showed improvement were also the two tests with the longest duration: cued target detection task (7.5 min) and cancellation tasks (4 min); unlike the remaining tasks which all took on average $\leq$2.5 min.

It is important to note that, under nicotine, the improved exploration of contralesional space during cancellation tasks went along with longer search times. Patients were instructed to "*search and cancel targets, until they felt that there were no more targets left unmarked*." This suggests that, across the three cancellation tasks, nicotine apparently influenced the patient's criterion to stop search. This could also be related to sustained attention or motivational factors, in accord with putative cholinergic functions.

NEURAL SUBSTRATES FOR NICOTINIC EFFECTS ON ATTENTION

Neurobiology research suggests that cholinergic neurons in the basal forebrain are critically implicated in the analysis and/or response to the behavioral significance of sensory cues (Wilson and Rolls, 1990). In particular, the basal forebrain cholinergic corticopetal system has been hypothesized to operate as a relay for modulatory influences from the amygdala and other limbic areas (such as the dopaminergic reward pathways, see Rice and Cragg, 2004), which are exerted on cortical sensory areas (Bentley et al., 2003) as well as on other cortical systems involved in attention and top-down executive control (Sarter et al., 2005). Increased nicotine tone may thus enhance signals of behavioral saliency to amplify activity in visual cortices and/or boost fronto-parietal regions generating spatial or attentional saliency maps.

Indeed, neuroimaging studies after nicotine administration have shown consistent modulations of parietal and frontal activity. Using a working memory task in ex-smokers, Ernst et al. (2001) found that improved performance under nicotine depends on prefrontal and parietal cortices bilaterally. In non-smoking subjects, Kumari et al. (2003) also showed higher activation of parietal and frontal areas during a working memory task. Regarding attentional processes, several studies reported modulations of fronto-parietal cortex but with either reduced (Thiel et al., 2005; Vossel et al., 2008) or increased activation in attention-related networks (Lawrence et al., 2002). Using a sustained attention task, Lawrence et al. (2002) found that activity changes in bilateral inferior parietal cortices, precuneus, thalamus, and caudate nucleus mediated the behavioral costs of smoking abstinence and benefits of nicotine replacement on the sustained attention performance.

In sum, our data converge with these studies to suggest that nicotine might improve neglect by boosting the representation of behaviorally relevant target stimuli (as opposed to distracter stimuli), and by promoting sustained attention over longer periods of time, with such effects arising independently from spatial biases due to unilateral damage in the frontal and/or parietal attentional network.

DISTINCT MOTIVATIONAL AND ATTENTIONAL EFFECTS OF NICOTINE

An effect of nicotinic stimulation on arousal or motivational systems, rather than on spatial attention systems, is supported by two main findings: firstly, despite the fact that nicotine reduced omissions in cancellation tasks more markedly for the contralesional side, and non-significantly for the ipsilesional side, a formal statistical test for this difference remained non-significant (no reliable two-way interaction TARGET SIDE × TREATMENT CONDITION). Moreover, a differential improvement per side may partly depend on the number omissions committed at baseline (since few omissions at the beginning would result in a low potential for improvement; but numerous omissions would provide a high potential for improvement). In the same line, nicotine effects on the *Cued target detection* task arose for the *valid-cue* and the *no-cue* condition in both the contralesional and ipsilesional sides. As discussed above, these behavioral effects suggest a global facilitation without any spatially specific component. Such global effects might accord with other findings that neglect can be improved by transient arousal (Finke et al., 2009) and motivational incentives conveyed by reward (Malhotra et al., 2013; Mesulam, 1985) or reward learning (Lucas et al., 2013).

Secondly, the results of our exploratory anatomical analysis indicated that the nicotine-induced change in neglect behavior appeared to be lower in patients whose lesion extended into the basal forebrain region just dorsal to the amygdala and into the internal capsule, as well as (to a lesser degree) into more posterior parietal regions (see **Figure 6**). Though these interpretations must be taken with caution because of the small sample size and inherent variability of lesions in stroke patients, our data suggest that an effective impact of nicotine treatment might critically dependent on the integrity of the cholinergic projection systems in the basal forebrain region (Selden et al., 1998). Hence, patients suffering from lesions encompassing on this structure or its projections to parietal areas would show little amelioration under nicotine (unlike patients in whom these areas are spared). Although cholinergic enhancement due to nicotine might also take place at the synaptic levels in the target cortical zones, a preservation of some projections pathways from basal forebrain might be important to provide task-related modulations and more effective cholinergic activity in attention-demanding situations.

In addition, however, damage to superior parietal cortex was also found to reduce the benefit of nicotine (see **Figure 7**). This negative correlation accord with the notion that the pharmacological effect of nicotine on spatial attention might be mediated by modulation of parietal areas in healthy people (Thiel et al., 2005), and the related finding of Vossel et al. (2010) that such benefits might be absent in neglect patients when their lesions extent to parietal lobe. In our study, a sparing of superior parietal cortex in patients showing greater improvement in cancellation performance under nicotine suggests that this effect might depend on a boosting of attentional mechanisms subserved by these parietal regions (Corbetta and Shulman, 2011), which control endogenous orienting and promote active exploration.

Finally, we found that patients with more severe neglect at baseline tended to show greater amelioration effects under nicotine. Comparisons between initial neglect severity and changes under nicotine revealed a remarkable correlation between severity and nicotine benefit ($r = 0.58$). This relation may reflect the fact that more severe deficits gave greater opportunity to observe changes, or that more severe neglect symptoms may be associated with greater damage to brain systems mediating arousal functions sensitive to nicotine stimulation (Finke et al., 2012). We also note however that, in the present study, severe neglect was associated with more frequent damage to parietal areas, in line with previous anatomical findings in Mort et al. (2003) and Saj et al. (2012), as well as subcortical areas such as the pulvinar (Karnath et al., 2002). Future studies with larger patient groups are necessary to determine whether only patients with subcortical forms of neglect may benefit from pro-cholinergic therapy, and which aspects of neglect behavior may be improved in different patients as a function of their lesion sites.

CONCLUSION

To sum up, our study investigated the effects of pro-cholinergic treatment by nicotinic receptor stimulation in spatial neglect. Our results converge with those of a parallel study using nicotinic gums (Vossel et al., 2010) but also extend them by better delineating the range of improvement or non-improvement in different tasks. Another recent pharmacological study using the norepinephrine-enhancer guanfacine observed very similar results in two neglect patients, but not a third (Malhotra et al., 2006). In this study, the norepinephrine drug also improved search in multi-target displays, with better detection going along with prolonged search times, in the absence of any improvement for speeded tasks tapping into more perceptual functions. It is intriguing that globally similar effects were obtained on a similar cancellation tasks using different kinds of drug, targeting the norepinephrine in the latter study, and the cholinergic system in ours. Moreover, the effect was quantitatively similar to Malhotra et al. (2006) with a ∼20% of change in target detection. Although originating from different structures in brainstem (locus coeruleus for NE) and basal forebrain (Meynert nucleus cholinergic for ACH), cortical projections of these two neuromodulatory systems have partly overlapping distribution predominating in prefrontal and parietal areas (Russell et al., 2013). However, these two systems might modulate cortical arousal and information processing in different ways. ACH release in the cortex is increased both prior and during sustained attention demands, with further increase in response to distracters, presumably serving to enhance signal to noise of behaviorally relevant targets (Himmelheber et al., 2000; Klinkenberg et al., 2010). Conversely, tonic levels of NE are lower during search, allowing greater selectivity, but with phasic peaks to target detection, while higher tonic levels are present under state of inattentiveness in order to facilitate response to new or unexpected information (Aston-Jones and Cohen, 2005). Further studies would be useful to directly compare both drugs in the same patients and across various tasks. Variations in lesion site or extent might also lead to different therapeutic responses in different patients. Here, we found that subcortical limbic structures may be critically involved in the mediation of improved orienting and target detection during exploration, as nicotinic effects were reduced in patients whose lesions extended in mesial temporal lobe and basal forebrain, as well as internal capsule and posterior parietal cortex (see **Figure 7**). It remains to be seen if these patients showing little effects under nicotine would show greater benefits from guanfacine, and vice versa.

Future studies should also explore the possible benefits from more prolonged treatment with pro-cholinergic agents, compare them with other drugs such as noradrenergic or dopaminergic agonists, as well as use a combined stimulation of both the nicotinic and muscarinic cholinergic receptors. For example, in the treatment of Alzheimer's disease, other pharmacological cholinergic agents such as donepezil (an acetylcholine esterase inhibitor) are already used with a certain success, possibly leading to positive behavioral effects via improvement of attentional functions (Levy et al., 2000; Mansvelder et al., 2006; Heishman et al., 2010). These benefits of pro-cholinergic drugs in dementia and other clinical conditions (e.g., head injury) further show that such treatment may improve attentional deficits even in the absence of spatial neglect, perhaps by acting upstream on global arousal and motivational processes. It remains to be determined whether beneficial attention effects might also be obtained in neglect patients with such treatment, particularly when they present with low arousal or deficits in sustained attention.

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Dissociation in optokinetic stimulation sensitivity between omission and substitution reading errors in neglect dyslexia

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Although omission and substitution errors in neglect dyslexia (ND) patients have always been considered as different manifestations of the same acquired reading disorder, recently, we proposed a new dual mechanism model. While omissions are related to the exploratory disorder which characterizes unilateral spatial neglect (USN), substitutions are due to a perceptual integration mechanism. A consequence of this hypothesis is that specific training for omission-type ND patients would aim at restoring the oculo-motor scanning and should not improve reading in substitution-type ND. With this aim we administered an optokinetic stimulation (OKS) to two brain-damaged patients with both USN and ND, MA and EP, who showed ND mainly characterized by omissions and substitutions, respectively. MA also showed an impairment in oculo-motor behavior with a non-reading task, while EP did not. The two patients presented a dissociation with respect to their sensitivity to OKS, so that, as expected, MA was positively affected, while EP was not. Our results confirm a dissociation between the two mechanisms underlying omission and substitution reading errors in ND patients. Moreover, they suggest that such a dissociation could possibly be extended to the effectiveness of rehabilitative procedures, and that patients who mainly omit contralesional-sided letters would benefit from OKS.

Keywords: unilateral spatial neglect, optokinetic stimulation, neglect dyslexia, neuropsychological rehabilitation, eye movements

INTRODUCTION

Unilateral spatial neglect (USN) is defined as a neuropsychological disorder in which patients fail to detect or identify objects or to execute movements in the portion of space contralateral to the lesion side (Vallar, 2001; Halligan et al., 2003). USN is a syndrome that presents multiple symptoms (e.g., personal, peripersonal, and extrapersonal neglect, "motor" and "perceptual" neglect) and involves multiple cognitive functions (e.g., spatial cognition, attention, visual awareness). So, despite the fact that in the literature, particularly regarding rehabilitation, it has been treated as a unitary disorder, it is most likely due to multiple etiopathogenetic mechanisms.

Unilateral spatial neglect has a 40–80% incidence in acute stroke patients, and although evidence-based evaluation of rehabilitation of USN (e.g., Rohling et al., 2009) indicates positive effects, only a few studies have examined the effectiveness of treatments across several tasks and patients for specific domains of cognitive functioning. For example, adopting a meta-analytic approach and estimating effect sizes, Rohling et al. (2009) reported the effectiveness of cognitive rehabilitation with different treatments for focal impairments within cognitive domains. The results for the neglect syndrome show that gains are moderate in size (it persists chronically in one third of patients) and domain specific, indicating sufficient evidence for the effectiveness of visuo-spatial training in these patients. Overall, indications from the literature call for selective training on explorative symptoms (Bowen and Lincoln, 2007; Rohling et al., 2009).

Recently, Zoccolotti et al. (2011) made a systematic evidence-based review of the studies on rehabilitation training of neglect disorders up to 2007. They considered top-down techniques, such as visuo-spatial orientation training, characterized by a conscious learning of strategies to compensate for the lack of attention toward the neglected side of space, as well as bottom-up techniques, consisting of sensory stimulation aiming at "re-balancing" the representation of space. In particular, they considered prism adaptation, optokinetic stimulation (OKS), caloric vestibular stimulation, transcutaneous electrical neural stimulation, bio-feedback, eye patching, and some neuropharmacological approaches.

According to the analysis of the literature, the most highly recommended training is visuo-spatial orientation training and, among the bottom-up techniques, prism adaptation. However, the general quantitative approach used in the review (Zoccolotti et al., 2011) did not clarify which symptoms showed by the patients were really influenced by the different treatments.

As indicated in Rossetti and Rode (2002) and, more recently, in reviews about USN rehabilitation (Luauté et al., 2006; Kerkhoff and Schenk, 2012), it seems that some sensory and cognitive therapies have different impacts on different USN symptoms.

Prism adaptation seems to have a general rehabilitative effect, but no effect was found on perceptual tasks, such as single words reading (McIntosh et al., 2002), perception of chimeric faces (Ferber et al., 2003), object size estimation (Dijkerman et al., 2003), and haptic perception (Serino et al., 2007).

When different rehabilitation techniques are combined, it is possible to see dissociable effects, so that for example, different patients with both anosognosia and neglect respond differently to the combined treatments (Beschin et al., 2012).

Saevarsson et al. (2011) in their review conclude that "different therapeutic techniques used in combination that are applied repeatedly may currently be the most promising approach to treating the disorder and most likely produce the strongest and longest-lasting effects," but they state also that "... the current state of knowledge of specific aspects of neglect and their interaction for individual patients is not sufficient to serve as a basis for selecting a particular therapy."

While sharing the latter claim, however, we believe that it is precisely the direction in which the rehabilitation of the neglect syndrome will go in the future.

In this single cases study, we propose an approach to the rehabilitation of neglect more similar to that used with other neuropsychological disorders such as aphasia, where symptoms associated with comprehension, repetition, and production deficits, as indicators of the specific mechanisms that are compromised, are treated with specific procedures.

In particular, we focused on the acquired reading disorder often associated with USN, neglect dyslexia (ND). This symptom shows a high co-morbidity with USN and the reading impairment co-occurred with other spatial deficits in 40% of patients (Lee et al., 2009).

Neglect dyslexia determines errors in reading the contralesional side of words, sentences, and texts. Nevertheless, most experimental studies on ND are primarily concerned with single word reading where patients misread letters that occupy the contralateral side of the visually presented stimulus. The most common errors in single word reading are: (i) substitutions [e.g., the target word *albero* (tree) read as a non-word like *pobero*] and (ii) omissions [e.g., the target word *famiglia* (family) read as *miglia* (miles)]. However, for some patients a predominance of substitution errors has been reported (e.g., Ellis et al., 1987; Behrmann et al., 1990; Riddoch et al., 1990). These type of patients produce a smaller absolute number of errors and are more sensitive to the lexical status of the string (Arduino et al., 2002). Coherently, it has been concluded that a milder deficit accounts for the behavioral deficit expressed in substitution errors and that the two kinds of errors depend on a single mechanism, which can be disrupted along a continuum of severity (Mozer and Behrmann, 1990; Behrmann et al., 1991; Arduino et al., 2002).

However, Arduino et al. (2005), in describing RCG, a right-brain-damaged patient, who manifested a clear spatial reading disorder characterized mostly by left-sided substitutions without any other sign of USN, and in comparing the patient's performance with other similar cases in the literature, suggested that substitution errors could not be directly related to unilateral spatial disorder. Moreover, he was sensitive to spacing, that is, by increasing the inter-letter space to three times the letter size, despite the fact that letters occupied a larger portion of the left neglected space, the total number of reading errors was halved. This finding suggested that substitution errors may depend at least in part on a specific mechanism and that perceptual integration may play a crucial role in the reading performance of brain-damaged patients. Accordingly, Martelli et al. (2011) proposed a dual model, stating that substitution and omission errors could be due to different mechanisms: the first is visuo-spatial in nature and is responsible for omissions in both ND and USN (such as errors in detecting left-sided elements in cancelation tasks); the second mechanism, which causes a predominance of substitutions, is perceptual and does not depend on neglect. In the latter case, substitution errors depend on a well-described feature integration mechanism that impairs recognition for above acuity letters moving toward the visual periphery and limits letter identification when other letters surround the signal (the so called *crowding* phenomenon). This phenomenon characterizes the normal periphery and amblyopic fovea (Irvine, 1945; Stuart and Burian, 1962) and psychophysical studies indicate that correct letter recognition can be restored by increasing letter spacing (for reviews, see Pelli et al., 2004; Whitney and Levi, 2011). Evaluating ND patients, Martelli et al. (2011) found that increasing letter spacing reduced substitution errors while increasing omissions. In line with the assumption that omissions are affected by a visuo-spatial deficit and substitutions by a perceptual one, the Authors also found that omissions, but not substitutions tended to be related to the severity of neglect, measured by several visuo-spatial tasks. By adopting Martelli et al.'s (2011) dual model it still remains to be explained what causes the occurrence of reading errors only in a fraction of patients with USN. In a recent study by Primativo et al. (2013) eye movements were recorded in neglect patients with and without ND and in a matched group of right-brain-damaged patients without neglect, while reading pseudowords and during a saccadic task with non-orthographic material. The results indicated that only ND patients (all characterized by left lateralized omission errors) showed a distorted eye movement pattern in both the reading task and the non-verbal saccadic task. The main feature of the abnormal oculo-motor pattern was characterized by a large amount of inaccurate fixations (i.e., more than 50% of ND patients' fixations did not fall on the stimulus but they were distributed in different positions on the screen, both in the left and right hemispaces). The Authors also showed that USN patients without ND forced to read single words without eye movements produced a similar pattern of errors to that of ND patients with unlimited exposure time (i.e., left-sided errors). Primativo et al. (2013) concluded that the reading disorder in ND is the phenotypic expression of the exploratory deficit in USN when the fine eye movements required for reading are altered.

Accordingly, the two different error types would require specific diagnosis and treatments and a consequence of this hypothesis is that specific training for omission-type ND would aim to restore oculo-motor scanning, but would not improve reading in substitution-type ND.

Among all the possible techniques, we decided to adopt OKS (Pizzamiglio et al., 1990) since it facilitates the displacement of the oculo-motor exploration toward the neglected side of space and has the advantage of bottom-up techniques requiring neither consciousness of the deficit nor a goal-based behavior by the patient. This choice is also supported by recent studies which have shown that OKS significantly modulates many facets of the neglect syndrome, including ND, auditory neglect, subjective body midline, line bisection, and size distortions (Kerkhoff and Schenk, 2012) even though there are results which are not in accordance with such assumption (e.g., Antonucci et al., 1992; Pizzamiglio et al., 2004; Kerkhoff et al., 2006; Thimm et al., 2009).

In the present study two right-brain-damaged patients, with USN and no visual field defect, one affected by omission-type ND and the other affected by substitution-type ND, were selected by means of a pseudowords reading test (Vallar et al., 1996) and further investigated.

In order to confirm the relationship between omission errors and oculo-motor impairment, eye movements were recorded during a saccadic non-verbal task. Finally, the two patients were presented with a reading task before and after OKS (leftward moving dots) to test the sensitivity and specificity of the two types of reading errors to OKS.

CASE REPORTS

MA, a 62-year-old female, right-handed, with 11 years of education. In October 2012, she suffered a subarachnoid hemorrhage from a ruptured aneurysm of the right internal carotid artery, preceded by an episode of loss of consciousness. She underwent endovascular embolization treatment. The TC scan revealed the presence of hypodensity at the level of both the right frontal cortex and periventricular white matter (insula, supplementary motor area, middle cingulum, superior frontal gyrus, inferior frontal operculum, rolandic operculum, putamen). No occipital damage was present (see **Figure 1**) and no visual field defect was present. At the first neuropsychological assessment, the patient appeared alert, well oriented, with some short-term memory difficulties, a tendency to confabulation, and a gaze deviation toward the right. She showed a moderate to severe USN. The speech was fluid and informative, abundant, and no aphasic disorders were detected. MA's language comprehension was adequate for the demands of the present study. The performance in the naming tasks was not adequate, but was probably influenced by her visuo-spatial disorder. The speed of the lexicon access was reduced but within the limits. Performance in praxic-constructive tasks was insufficient, but again affected by the presence of neglect and perseverations. No evidence of visuo-perceptual integration deficit was observed (see **Table 1** for demographic and the neuropsychological assessment information). Finally, she had a pathological performance at a words and pseudowords reading test (Vallar et al., 1996), characterized by omission errors (see **Table 2**).

EP, a 60-year-old male, right-handed, with 13 years of education. He suffered a cerebrovascular ischemic stroke, confined to the right hemisphere. A MRI scan (see **Figure 1**) identified a right fronto-temporo-parietal lesion (heschl gyrus, rolandic operculum, superior fronto-occipital fasciculus, inferior frontal operculum, superior longitudinal fasciculus, superior temporal gyrus, external capsule, supramarginal gyrus, insula, superior corona radiata, putamen, middle temporal gyrus, superior temporal pole, inferior

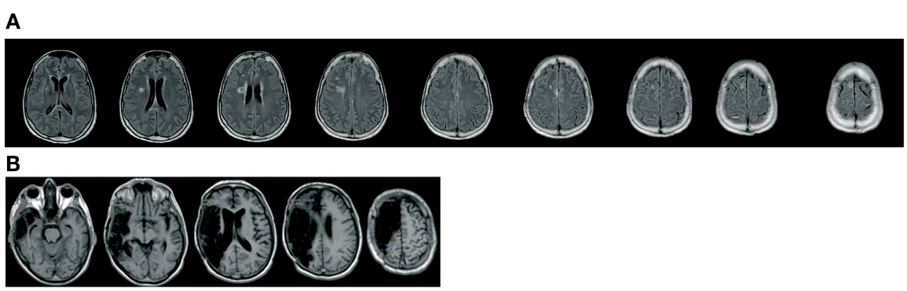

FIGURE 1 | MA (A) and EP (B) neuroradiological images. The first patient shows a cortico-subcortical frontal lesion, while the latter has a huge fronto-temporo-parietal cortico-subcortical lesion.

Table 1 | Demographic features and baseline assessment for unilateral spatial neglect.

Pat.	S	A	E	L	Letter Cancell.		Star Cancell.		Wundt-Jastrow		Sentence reading	Bisection
					Left	Right	Left	Right	Left	Right		
MA	F	62	8	F	42/53*	21/53	8/27*	3/27	4/20*	2/20	6/6*	5.4*
EP	M	60	10	FTP	4/53	1/53	13/27*	5/27	16/20*	0/20	1/6*	10.3*

*F, frontal lobe; P, parietal lobe; T, temporal lobe; S, sex; M/F, male/female; A, age; E, educational level; L, lesion location; Scores: (i) cancelation tasks: omission errors; (ii) Wundt-Jastrow area illusion test: "unexpected" responses; (iii) reading task: the number of sentences in which patients showed left-sided errors; 16 cm lines bisection error (mm). *Pathological score; L, left; R, right.*

Table 2 | Neglect dyslexia assessment (Vallar et al., 1996) for MA and EP.

	MA		EP	
	Words	Pseudowords	Words	Pseudowords
Errors	18/38 (47.4%)	25/38 (65.8%)	2/38 (5.3%)	25/38 (65.8%)
Neglect errors	17/18 (94.4%)	25/25 (100%)	2/2 (100%)	13/25 (52%)
Omissions	16/17 (94.1%)	22/25 (88%)	0/2 (0%)	3/13 (23.1%)
Substitutions	0/17 (0%)	1/25 (4%)	2/2 (100%)	10/13 (76.9%)

Absolute number and % of errors are reported for all types of items misread, neglect errors, omissions, and substitutions. Neglect errors refer to all misread items with left-sided errors, according to the Caramazza and Hillis (1990) criterion. Omissions refer to all neglect errors in which the produced item length was shorter than the target. Substitutions refer to all neglect errors in which the produced item had the same length as the target.

parietal gyrus). No occipital damage was present and no visual field deficit was detected.

The failure of an attempt at mechanical unblocking of a middle cerebral artery thrombosis, associated with an intraparenchymal hemorrhage in the caudal part of the right putamen, without involvement of the internal capsule, led to a decompressive right craniectomy.

After 6 months he was cooperative and oriented in time and space. He presented a complete left hemiparesis and the neuropsychological assessment still showed impulsiveness, distractibility, reduced cognitive flexibility and planning difficulties, as well as a medium to severe USN for extrapersonal and peripersonal space, and visuo-constructional and visual-spatial skills deficits (see **Table 1** for demographic and the neuropsychological assessment information). Finally, he showed ND by means of a words and pseudowords reading test (Vallar et al., 1996), characterized by substitution errors (see **Table 2**).

EXPERIMENT 1

NEGLECT DYSLEXIA ASSESSMENT

Material and procedure

The first experiment aimed to describe the type of reading errors in the two patients, according to the letter position analysis used by Martelli et al. (2011). Pseudowords were created by interchanging the syllables of existing words (taken from Burani et al., 2002; http://www.istc.cnr.it/grouppage/lexvar) in random positions in order to preserve pronunciation and minimize word similarity. We generated a list of 40, 5-to-8-letter pseudowords (10 for each length). The stimuli were written in capital Courier New font, which is characterized by consistent letter spacing. Letter size was kept constant (40 pt) and subtended 1.0°. Patients were shown two squared dots vertically displaced 1.5° apart in the center of the screen. These fixation marks remained on the screen for the entire experimental session. Stimulus onset was triggered when the patient steadily fixated the central marks for at least 50 ms. Each stimulus was presented at the center of the screen between the fixation marks (i.e., the central letter of each stimulus was vertically aligned to the fixation marks) and remained on the screen until onset of the patient's response. There was no time constraint for responding. Patients were asked to read aloud each stimulus as accurately as possible. Pseudowords appeared in a randomized order across participants. Responses were digitally recorded and errors were scored after listening to the recorded track later.

Results

We measured the letter omissions and substitutions errors for each stimulus. Following Martelli et al. (2011) we applied a letter-based approach treating each letter in the word independently. Caramazza and Hillis (1990) criterion is strict in that it considers that no processing occurs on the left-side of the string and the processing is completely spared on the right of the neglect point. This criterion excludes from the analysis substitution errors occurring on the right side of the stimulus and gives a less detailed description of performance. Therefore, we measured the omission and substitution errors over the entire stimulus, following a letter-based analysis (**Figure 1**). By comparing the two criteria it emerges that: (1) Caramazza's criterion underestimates the total number of omission and substitutions [e.g., the word "vacanza" (holiday) read fanza results in one omission error in that the production is shorter than the target, while according to a letter-based analysis two omissions, the letters v and a, and one substitution, f instead c, would be counted]. (2) Several errors although located on the left-side of the string are considered by Caramazza's criterion "visual" errors [e.g., the word "elefante" (elephant) read "etepante" would be considered a visual error since it preserved the identity of the first letter, while according to a letter positional analysis it would be counted as two left-side substitutions, "l" as "t" and "f" as "p").

Eye movements recording ensured that the first fixation landed on the center of the string. According to perceptual crowding the identificability of the letters falling around fixation and the external letters that only have one flanker nearby, should be spared when letter size is above acuity, as in the present case. Letters in intermediate positions should be unrecognizable because of crowding (Martelli et al., 2011). Thus we applied a two Gaussian distributions model to the data with picks on the left and right side of the centrally fixated string. On the converse if errors distribution is solely determined by the left lateralized neglect deficit data should be best described as an exponential decay.

Figure 2 reports the proportion of omission and substitution reading errors made by the patients as a function of letter position. From the figures it emerges that, while MA made a large number of omissions only on the left-side of the stimulus, EP made fewer errors, mostly substitutions, more evenly distributed across the entire stimulus. The same behavior has already been described in two other patients, AR and DNA (Martelli et al., 2011). The analysis of the error distribution in these two patients (**Figure 2**) showed that substitutions and omissions have different shapes as

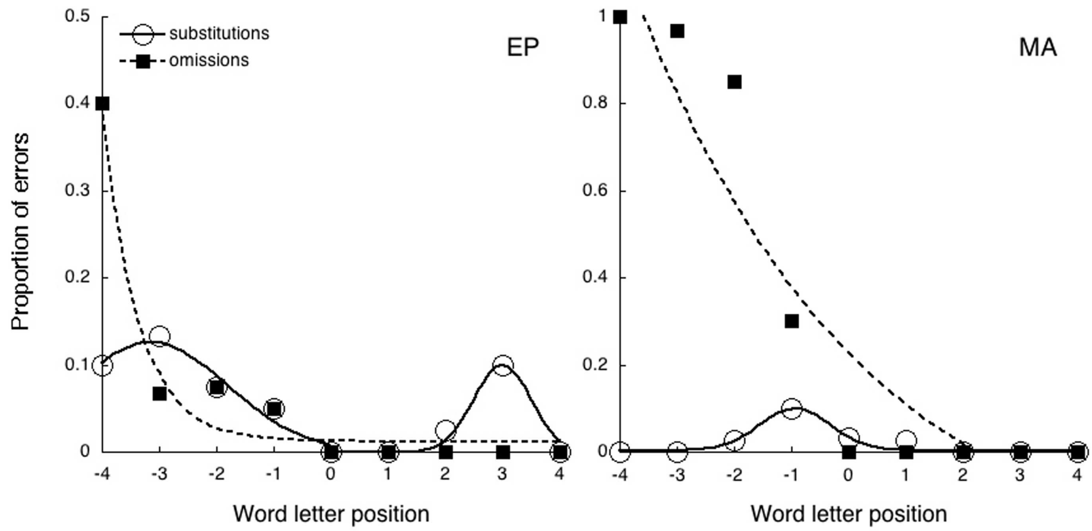

FIGURE 2 | The absolute number of reading errors made by the two patients, divided into substitutions and omissions as a function of letter position.

expected. The proportion of omission errors produced by MA and EP have been fit by a three parameters exponential decay model using the following equation

$$P_o = a + be^{(-c\,x)}$$

where *a* is the offset, *b* is the amplitude, and *c* is the rate of change.

In the case of EP the proportion of substitution errors has been fit by the sum of two Gaussian distributions according to the following equation

$$P_s = a + be\left(-(x-c)^2 / d^2\right)$$

where *a* is the offset, *b* is the area under the curve, *c* is the center of the distribution, and *d* is the width. In the case of MA substitution errors a unimodal Gaussian distribution has been applied.

In the case of omissions the exponential decay captures a large proportion of variance for both observers (MA $R^2 = 0.94$; EP $R^2 = 0.96$). In this case errors are confined to the left-side of the stimulus as predicted by USN. Substitution errors show a substantially different pattern. In the case of EP the pattern is well captured by the bimodal distribution ($R^2 = 0.97$) with picks at letter position –3.14 and 2.67, while the exponential fit doesn't capture the shape of the distribution ($R^2 = 0.44$). Errors are symmetrically distributed around the fixation point sparing the external letters that only have one flanker nearby (as predicted by crowding). In the case of MA the distribution is captured by a single Gaussian with a pick around letter position -1 ($R^2 = 0.88$). These data are in agreement with previous findings by Martelli et al. (2011) in that patients characterized by a majority of substitutions generally produce fewer and distributed errors. Additionally, the data indicate that omissions but not substitutions show the clear left-lateralization typical of USN disorder.

EXPERIMENT 2

EYE MOVEMENT IN A NON-VERBAL TASK

Material and procedure

As described in the introduction, Primativo et al. (2013) showed that the prevalence of omission errors in ND patients is associated with an impaired eye movement pattern. This was found not only during a reading task but also during a saccadic task which did not involve orthographic material but in which gaze simulated the sequential eye movements involved in reading. In order to assess whether a similar impairment is present in patient MA (who displays a prevalence of omissions) and thus could account for her reading difficulties, we conducted the same saccadic task used by Primativo et al. in which the patients had to follow a moving dot with their eyes on the horizontal meridian between five different spatial positions both right to left and left to right.

A black dot subtending 0.2° of visual angle and displayed on a white background, appeared along the horizontal meridian in five consecutive positions, 4.0° away from each other according to a synchronous paradigm (i.e., no gap). The dot appeared sequentially in the five positions and remained for 2 s in the two extreme positions and for 1 s in the three central ones. The sequence started with the extreme left dot and each dot appeared in turn until the extreme right dot appeared, then the reverse sequence took place. The rightward and leftward sequences were repeated twice in each trial. Three trials were administered. Patients were required to follow the dot as quickly and as accurately as possible.

Monocular eye movements were recorded in binocular vision via an SR Research Ltd., Eye Link 1000 eye tracker (SR Research Ltd., Mississauga, ON, Canada) sampling at 500 Hz, with spatial resolution of less than 0.04°.

Head movements were avoided by using a headrest.

Patients sat 57 cm away from a 17″ CRT monitor. A standard nine-point calibration procedure was run before collecting the data. The calibration targets were presented randomly in different positions on the screen. The experimental task started immediately after calibration.

Eye movement data were processed using EyeLink Data Viewer software (SR Research Ltd., Mississauga, ON, Canada).

Results

Accuracy (mean percentage of fixations on the dot when it was on the screen, in both directions, **Figure 3**) was measured.

Figure 4 shows the ocular behaviour of MA and EP during the saccadic task. We excluded analysis of fixations made on the first dot in the sequence and analysis of anticipatory saccades (i.e., saccades starting before the appearance of the following dot). We also excluded analysis of fixations that were far from the target with respect to its vertical axis (i.e., over 2 SD calculated on the vertical fixation positions of a control group collected and described in Primativo et al., 2013). The remaining fixations were considered "accurate" if they fell no more than 1° of visual angle away from the target.

MA and EP data were compared to that of four right-brain-damaged patients, by means of Crawford statistics (Crawford et al., 1998; Crawford and Garthwaite, 2002). The control subjects, one female and three males, were comparable in terms of age (mean age = 68.5 years, range 52–78) and education (mean education = 11.8 years; range 8–18) to the patients. The analyses of accuracy (**Table 3**) revealed that MA was significantly less accurate than the controls both when the dot was moving rightward and leftward [left to right: $t(3) = -55.365$; $p = 0.00001$; right to left: $t(3) = -15.426$; $p = 0.00059$; all: $t(3) = -28.235$; $p = 0.0001$], while EP did not significantly differ from the controls [left to right: $t(3) = 0.000$; $p = 1$; right to left: $t(3) = 0.446$; $p = 0.68573$; all: $t(3) = 0.447$; $p = 0.68504$].

The analyses of accuracy for the dot position (**Table 4**) revealed that MA was less accurate at each dot position [first: $t(3) = -0.448$; $p = 0.68469$; second: $t(3) = -13.86$; $p = 0.00081$; third: $t(3) = -67.082$; $p = 0.00001$; fourth: $t(3) = -29.784$; $p = 0.00008$; fifth: $t(3) = -89.443$; $p = 0.00000$], whereas none was different from the controls in the case of EP's fixations [1°: $t(3) = -8.497$; $p = 0.00034$; 2°: $t(3) = 0.446$; $p = 0.68573$; 3°: $t(3) = 0.000$; $p = 1$; 4°: $t(3) = 0.000$; $p = 1$; 5°: $t(3) = 0.000$; $p = 1$].

MA was profoundly impaired in performing a simple saccadic task on the horizontal axis. Although this result might be interpreted as a sign of premotor neglect (e.g., Saevarsson, 2013), the result that MA's performance was impaired in both directions (toward the ipsilesional side as much as toward the contralesional side) is unlikely to support this hypothesis. Moreover, the same result was obtained by Primativo et al. (2013), who showed how ND patients mainly characterized by letter omission errors showed both USN and an oculo-motor impairment.

On the other hand, EP, who was affected by USN and ND, as well, did show a preserved performance at the same saccadic task, confirming that substitution-type ND is a qualitatively different disorder to omission-type ND.

EXPERIMENT 3

OPTOKINETIC STIMULATION EFFECT

Material and procedure

The third experiment aimed to verify the effect of the OKS on ND and in particular to assess whether MA and EP, characterized by two different types of reading errors had a different sensitivity to it.

The OKS consisted of random black dots of 0.75° in diameter presented on a gray background of 16° cd/m^2 in luminance, moving from right to left with a speed of 11.3°/s. Before and after the OKS, two sets of 30 pseudowords of different length (6-7-8 letters; font: Courier New; font size: 22) were presented at the center of a CRT 17″ monitor screen (1024 × 768 pixel), without a fixation point.

Two lists of pseudowords were used in order to avoid repetition and learning effects. The lists were constructed so as to preserve

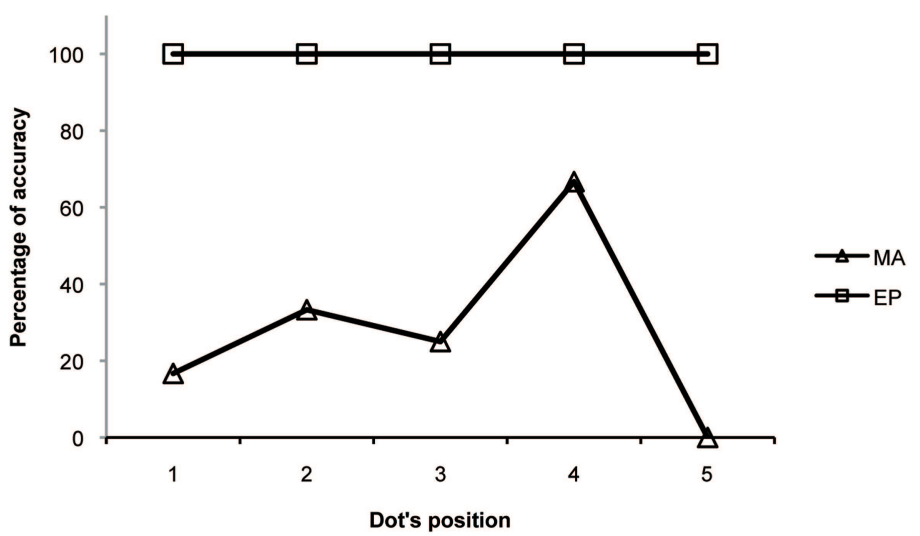

FIGURE 3 | The mean percentage accuracy in a non-verbal saccadic task (following a dot moving from left to right and from right to left) made by the two patients.

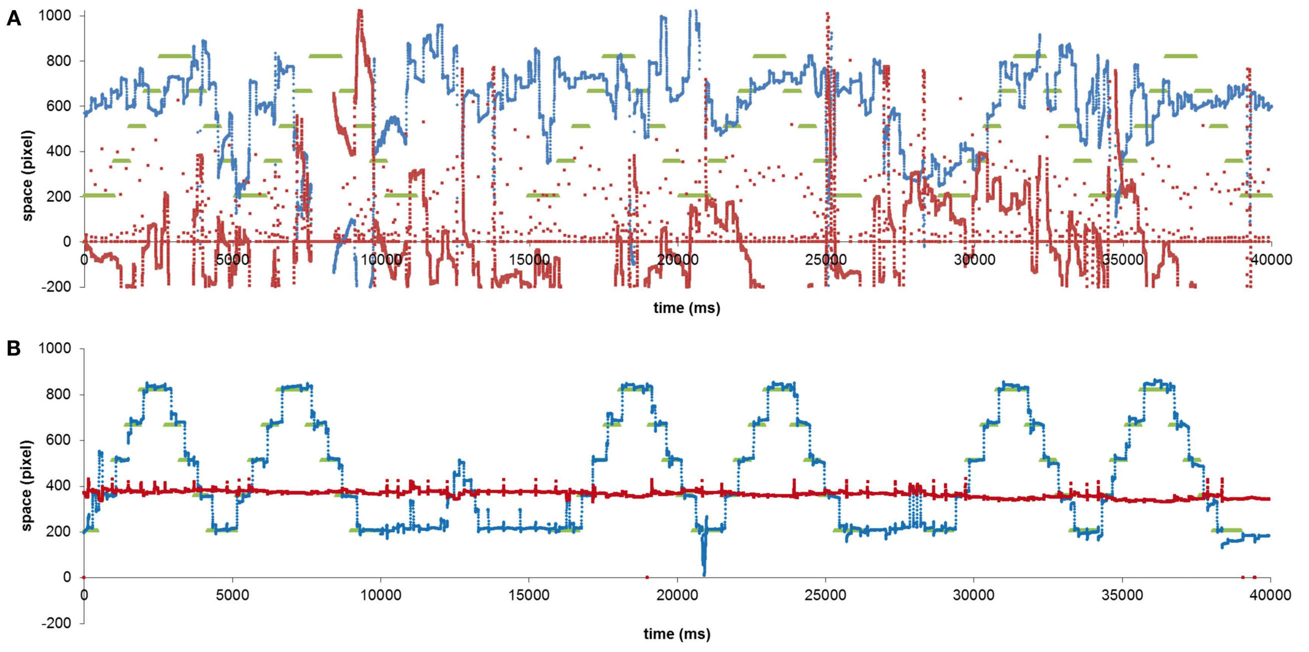

FIGURE 4 | MA (A) and EP (B) ocular behavior in a non-verbal saccadic task. The green lines indicate the dot positions, the red lines indicate the *y* coordinate of the eye movements and the blue lines the *x* coordinate.

Table 3 | Comparisons between the accuracy (% correct) of each one of the two patients affected by USN and ND and four right-brain-damaged patients without USN and ND (controls), in the conditions where the dot moved from left to right, from right to left, and in the two conditions together.

	DOT direction (% accuracy)		
	Left-right	Right-left	All
Controls	100.00	97.92	98.96
EP	100.00	100.00	100.00
MA	38.10**	26.00**	33.30**

$^*p < 0.05$; $^{**}p < 0.01$.

Table 4 | Comparisons between the accuracy (% correct) of each one of the two patients affected by USN and ND and four right-brain-damaged patients without USN and ND (controls), for each dot position.

	DOT position (% accuracy)				
	1	2	3	4	5
Controls	95.83	97.92	100.00	100.00	100.00
EP	100.00	100.00	100.00	100.00	100.00
MA	16.70**	33.30**	25.00**	66.70*	0.00**

$^*p < 0.05$; $^{**}p < 0.01$.

pronunciation and minimize word similarity (as in experiment 1). The two lists were matched for all relevant psycholinguistic variables such as length in terms of number of letters and syllables, bigram frequency, neighborhood size, and first phonemes and contained different stimuli from those of experiment 1.

The patients were seated in a dark and silent room facing a monitor displaying centrally presented visual stimuli. Their heads were positioned in an adjustable head-and-chin rest so that the distance between their eyes and the screen was approximately 57 cm. The experiment and the recording of the responses were carried out with MatLab 7.13.

The experimental session consisted of a reading task, before and after OKS. In each condition the patients had to read aloud 30 pseudowords presented at the center of the screen, written in white on a gray background. No fixation point was used. There were no time constraints and the 30 pseudowords were presented in the same fixed sequence for both patients. Only reading errors were recorded.

The same reading task was also presented to a control group of 10 healthy individuals who made no errors.

The experimental procedure consisted of two parts: a pseudowords reading task before the OKS (a), 10 min of OKS (b) and a pseudowords reading task (with different pseudowords) after the OKS (c).

During the OKS (b) the patients' task was to look at the screen with the moving dots, with the instruction not to fixate on any specific dot.

Results

Given that the performance of healthy subjects represented a ceiling in the pseudowords reading task, the chi-square analysis was used to test whether the number of reading errors was significantly different between the experimental conditions (before and after the OKS) in each patient and for each type of error.

In the pre-OKS condition MA misread 19 out of 30 pseudowords. According to a letter-based analysis she omitted 25 letters in 19 pseudowords. In the post-OKS condition MA misread 12 out of 30 pseudowords. In this condition she omitted 12 letters in the 12 misread pseudowords [a reduction of omission errors from 63.3 to 40%, $\chi^2(1) = 5.136$; $p = 0.023$].

MA showed a significant reduction in the number of omitted letters in the post-OKS stimulation compared to the pre-OKS condition [$\chi^2(1) = 6.72$; $p = 0.0095$], while substitutions (pre-OKS: 1; post-OKS: 0) were at ceiling level. Conversely, EP did not show any significant difference in terms of the number of substituted letters [$\chi^2(1) = 0.08$; $p = 0.7728$] or omitted letters [$\chi^2(1) = 0.25$; $p = 0.617$].

He misread 14 out of 30 pseudowords in the pre-OKS condition, making 13 substitutions in 12 pseudowords and 5 omissions in 5 pseudowords. In the post-OKS condition EP misread 10 out of 30 pseudowords. According to a letter-based analysis, he substituted 11 letters in 10 pseudowords and omitted 3 letters in 3 pseudowords [a reduction of omission errors from 16.7 to 10%, $\chi^2(1) = 1.816$; $p = 0.178$, and a reduction of substitution errors from 40 to 33.3%, $\chi^2(1) = 0.671$; $p = 0.413$].

Both letter and word based analyses showed a significant reduction only in the case of MA omission errors.

These results confirm the hypothesis of a dissociation in terms of the sensitivity to stimulation between the two types of reading errors, such that only omissions-type ND was affected by the OKS (see **Figure 5**).

DISCUSSION

Two patients affected by USN and ND were evaluated with a version of OKS (Pizzamiglio et al., 1990) presented with a small display (Reinhart et al., 2011) in order to validate the hypothesis that omissions could benefit from the slow leftward movement induced by this kind of stimulation. The two patients were identified as having ND using a words and non-words reading task (Vallar et al., 1996) and were then given a pseudowords reading task (experiment 1), and a non-verbal saccadic task (experiment 2) to assess the distribution of errors and their oculo-motor behavior.

One of the two patients, MA, showed mainly omission errors, an exponential distribution toward the contralesional side of space and an oculo-motor impairment at the non-verbal task in both spatial directions (as were all six ND patients described by Primativo et al., 2013). On the other hand, EP, did not show any exploratory deficit and his ND was mostly characterized by substitution errors, distributed in a bimodal manner (as were AR and DNA patients described by Martelli et al., 2011).

The result that substitution-type ND, in contrast to omission-type ND, was not associated with oculo-motor impairment, represents a new result and, even though it needs further evidence by group studies, it supports Martelli and Collaborators' dual model of ND.

As expected, only MA was shown to be sensitive to OKS and after 10 min of leftward moving dots stimulation, showed a significant reduction in omission errors, both at letter and word level.

Reinhart et al. (2011) found a similar result with paragraph reading. Leftward OKS was effective in reducing word omission errors, but not stimulus-centered errors. Their distinction is theoretically made on the basis of the model by Caramazza and Hillis (1990) and, from a phenomenological point of view their stimulus-centered errors included both omission and substitution errors on single words reading while omission errors alluded to the omission of entire words when reading texts.

This result suggests a double dissociation between word and sentence reading which is still a matter of debate (Vallar et al., 2010; Friedmann et al., 2011). However, the data are not helpful in assessing the specific effect of OKS since the authors did not distinguish between letter error types.

They conclude that OKS effectiveness on word omissions is due to a triggering of (pre-)attentional processes toward the

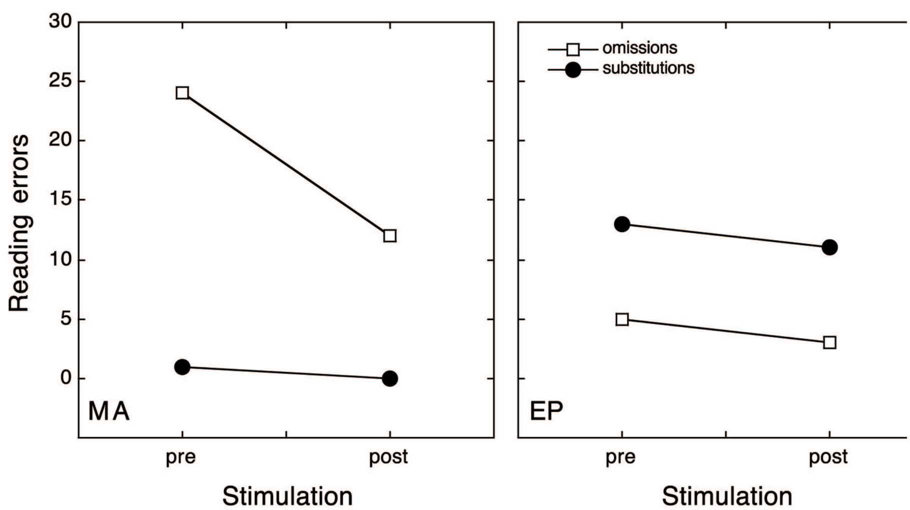

FIGURE 5 | The absolute number of letters omitted (open square) or substituted (filled dots) on the left-side of the stimulus while reading pseudowords, before and after OKS.

contralesional side of egocentric space. Nevertheless this account is not specific to ND and could be the reason why it has been shown to be effective also with other USN symptoms of visual and auditory neglect (Antonucci et al., 1992; Pizzamiglio et al., 1996; Kerkhoff et al., 2006; Thimm et al., 2009).

Here we suggest that a more specific mechanism is involved in ND. In the light of Primativo et al.'s (2013) results, letter omissions are due to the co-occurrence of USN and altered oculo-motor exploration, so, the automatic pursuit eye movements associated to OKS, could act specifically and directly to compensate or restore that mechanism. Indeed, our results show that OKS was able to benefit the specific exploratory behavior of the patient with ND characterized by omissions, by helping her in a single item reading task.

According to our hypothesis, OKS should be effective only for omissions but not for substitution errors.

Pizzamiglio et al. (2004) found a positive effect of OKS only on individual patients and the authors tried to determine if some characteristics could be linked to the effectiveness of OKS.

They considered the Barthel Index, visual field defect and motor impairment but none of those predictive variables could discriminate significantly between patients experiencing an improvement with OKS and patients showing no benefit. Unfortunately, they did not consider specific deficits of USN such as ND. An alternative interpretation of these results could be found in a model that was proposed by Ellis et al. (1993), which argued that omissions could reflect the co-presence of left ND and left homonymous hemianopia, whereas substitutions could reflect the pure presence of left ND without hemianopia. In the second case, residual information may activate contralesional positional coding of graphemes at the graphemic level. However, since it is true that many cases are in accordance with these predictions, other more recent studies have shown that this is not always the case (e.g., patient SVE by Miceli and Capasso, 2001; Martelli et al., 2011). In particular, in both Martelli et al. (2011) and in the present study, the absence of hemianopia was the condition *sine qua non* to participate in the research. The reason for this choice was precisely to avoid such a confounding variable.

In particular, it is also evident that MA (the patient with an omission-type ND) has a very small and anterior brain lesion, not compatible with a visual field defect.

Our study cannot shed light on the anatomical location for the two types of ND errors given that we had just two patients and they presented two very different lesions in terms of extension. Both of them showed cortical and subcortical frontal lesions, but EP showed a much bigger fronto-parieto-temporal lesion. In particular, the lesions of the two patients overlap on insula, putamen, inferior frontal operculum, and rolandic operculum, while they do not share the involvement of superior frontal gyrus, supplementary motor area, and middle cingulum (MA), other than the parieto-temporal areas (EP).

While further research will help in addressing the anatomical correlates issue, we think that our study suggests an interesting new approach to the treatment of reading errors in neglect patients.

Indeed, in contrast to the usual approach to USN rehabilitation, which considers the deficit to be due to the same core mechanism, we propose an approach to the rehabilitation of neglect in which symptoms and specific mechanisms are treated in a specific way.

Our study was not designed to be a full rehabilitation program, since this would require different methodologies and almost 10 sessions of OKS. Our aim was different: we wished to verify the sensitivity to OKS of different types of single stimuli reading disorder associated with USN.

In particular, here we presented a dissociation in the transient effects of OKS between omission and substitution types of ND. A systematic procedure is needed in the short to test its effectiveness in the rehabilitation of ND patients and the presence of long lasting effects.

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Visual scanning training, limb activation treatment, and prism adaptation for rehabilitating left neglect: who is the winner?

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We compared, for the first time, the overall and differential effects of three of the most widely used left neglect (LN) treatments: visual scanning training (VST), limb activation treatment (LAT), and prism adaptation (PA). Thirty-three LN patients were assigned in quasi-random order to the three groups (VST, LAT, or PA). Each patient received only one type of treatment. LN patients' performance on everyday life tasks was assessed four times (over a period of 6 weeks): A1 and A2 (i.e., the two pre-treatment assessments); A3 and A4 (i.e., the two post-treatment assessments). LN patients in each of the three treatment conditions were treated for the same number of sessions (i.e., 20). The results showed that improvements were present in the majority of the tests assessing the peripersonal space in everyday life activities. Our findings were independent of unspecific factors and lasted for at least 2 weeks following the end of the treatments. There were no interactions, however, between LN treatments and assessments. We suggest that all three treatments can be considered as valid rehabilitation interventions for LN and could be employed for ameliorating LN signs.

Keywords: prism adaptation, limb activation treatment, visual scanning training, neglect, rehabilitation, stroke

INTRODUCTION

Left neglect (LN) is one of the most frequent and disabling neuropsychological syndromes following right-hemisphere damage. LN patients fail to report, orient to, or verbally describe stimuli in the contralesional, left side of space (Karnath et al., 2002; Heilman et al., 2003). Although, to date, there is no comprehensive theoretical account of LN, most authors sustain that LN patients are not aware of events on the left side of space, because they do not orient their spatial attention leftward (for a brief review, see Priftis et al., 2011). Together with spatial attention deficits, LN is also associated with representational and non-spatial impairments (e.g., non-spatially lateralized sustained attention, spatial working memory, spatial remapping, etc.; for reviews, see Husain and Rorden, 2003; Pisella and Mattingley, 2004; Priftis et al., 2013). The lack of contralesional awareness in LN patients cannot be attributed to primary sensory or motor deficits. Indeed, double dissociations have been reported between LN and basic sensory-motor defects (Vallar, 1998). LN is not a unitary disorder because many LN subtypes have been described (for a taxonomy, see Vallar, 1998). For instance, LN may selectively impair the personal space (i.e., the space of the body), the peripersonal space (i.e., the reaching and grasping space), or the extrapersonal space (i.e., the locomotor space, beyond the reaching and grasping space; for review, see Vallar, 1998).

Functional recovery of LN patients can be severely affected (e.g., Paolucci et al., 1996; Kalra et al., 1997). Indeed, LN may considerably limit the overall effectiveness of rehabilitation interventions, often to a greater extent than more obvious motor, sensory, and speech deficits (Buxbaum et al., 2004). Although some spontaneous recovery occurs in the majority of LN patients after stroke, LN signs remain severe in many patients and may persist in the chronic phase (Stone et al., 1992; Jehkonen et al., 2000, 2007; Farnè et al., 2004; Nijboer et al., in press). Thus, LN is one of the major factors underlying poor functional outcome following stroke (Denes et al., 1982; Jehkonen et al., 2000; Buxbaum et al., 2004; Farnè et al., 2004).

Over the past 60 years, many different treatments for rehabilitating LN have been conceived and tested (for recent reviews, see Kerkhoff and Schenk, 2012; Riestra and Barrett, 2013). Early approaches to the treatment of LN were mainly based on the clinical experience of rehabilitation specialists, and they were less theory-driven than more recent approaches (Robertson, 1999). In contrast, in the last three decades a variety of different theory-driven LN-treatment techniques have been developed, on the basis of specific theories that aim to understand the underpinning mechanisms of LN (for review, see Robertson, 1999). Among other LN rehabilitation techniques, three of the most widely validated LN treatments are: visual scanning training (VST; Weinberg et al., 1977; Antonucci et al., 1995), limb activation treatment (LAT; Robertson and North, 1992), and prism adaptation treatment (PA; Rossetti et al., 1998; Frassinetti et al., 2002).

VISUAL SCANNING TRAINING

Systematic VST programs, employing voluntary orienting of spatial attention toward the left side of space, have been developed in the last 40 years (e.g., Diller and Weinberg, 1977; Pizzamiglio et al., 1992; Antonucci et al., 1995). In these programs, which are inspired by behavior modification techniques, LN patients are trained to actively explore the contralesional side of space on different tasks (e.g., picture scanning, copying, reading, etc.). Their visual search can be systematically guided by contralesional cues (e.g., a visual stimulus of reference on the left) and by the examiner's feedback. The difficulty and spatial extension of contralesional stimuli is progressively increased as a function of LN patients' performance. Using this paradigm, significant improvements of LN signs, both in group studies and in single-case studies, have been reported (for review, see Pizzamiglio et al., 2006). Some authors, however, have reported a significant amelioration of LN signs following rehabilitation, but only on the specific tests on which LN patients were trained (e.g., Lawson, 1962; Robertson et al., 1990; Wagenaar et al., 1992). This difference, however, might be due to the short duration, frequency, and intensity of some VST protocols with respect to others. For instance, Antonucci et al. (1995) showed that VST administered for 5 days a week (8 weeks) can lead to improvements of LN signs. Most important, improvements were generalized to untrained everyday life activities.

LIMB ACTIVATION TREATMENT

Limb activation treatment consists of the joint activation of spatiomotor brain maps that enhance conscious representation of specific spatial sectors (Rizzolatti and Berti, 1990). Robertson and North (1992) (see also Robertson et al., 1992; Robertson and North, 1993) empirically tested this assumption by asking LN patients to perform voluntary movements with their contralesional hemibody. The most important finding of the first studies that investigated the effects of LAT was that a significant reduction of LN signs occurred only when two conditions were concurrently satisfied: a voluntary movement of the contralesional limb (Condition 1), performed in the contralesional space (Condition 2). The same result was observed even when a patient could not see his own moving hand (Robertson and North, 1992), suggesting that the positive effects of the left-limb movement could not be ascribed to the fact that the left limb acted as a visual cue. In fact, visual cues are known to reduce LN (Riddoch and Humphreys, 1983; Halligan et al., 1991), but they seem not to be as effective as active movements of the contralesional limb. It is also worth to mention, however, that even passive contralesional limb movements can improve LN signs (e.g., Frassinetti et al., 2001). The relevance of Robertson and North's (1992, 1993) studies is undoubtedly remarkable. Nonetheless, the fact that only partially positive results of the application of LAT were observed in subsequent group studies (Kalra et al., 1997; Cubelli et al., 1999; Robertson et al., 2002) has raised some still unsolved questions about the effectiveness of LAT.

PRISM ADAPTATION

Prism adaptation is a phenomenon in which the motor system adapts to new visuo-spatial coordinates imposed by prisms that "misplace" the visual stimuli along the horizontal plane (Rossetti et al., 1998). When LN patients wear prismatic goggles inducing a visual field deviation toward the right, they show a rightward error in pointing to the visual targets. When the initial part of movement is not visible, LN patients perform a motor correction toward the contralesional (left) side of space to compensate for the prism-induced error. Thus, the initial ipsilateral displacement of the visuo-motor behavior is corrected through visuo-motor adaptation. When the prismatic goggles are removed and the distal part of the arm is not visible, LN patients show a systematic contralesional (leftward) deviation of visuo-motor responses, the so-called "after-effect." In the pioneering study by Rossetti et al. (1998) the performance of a group of LN patients was measured using standard neuropsychological tests (e.g., line bisection, line cancelation, drawing, reading), before and after a brief period of PA, with prisms inducing a 10°-rightward displacement of the visual field. Compared with a control group of LN patients exposed to goggles with neutral lenses, LN patients treated with PA showed significant improvements, which remained stable even when LN patients were tested 2 h after the end of PA. Positive and long-lasting effects of PA have been reported on both paper-and-pencil tasks and everyday life activities in a successive series of single-case and group studies (Rossetti et al., 1998; Frassinetti et al., 2002; Serino et al., 2006, 2007, 2009; Saevarsson et al., 2009; Vangkilde and Habekost, 2010; for reviews, see Luauté et al., 2006a,b; Barrett et al., 2012; Newport and Schenk, 2012; Jacquin-Courtois et al., 2013).

Some studies, however, have not confirmed the positive effects of PA. For instance, Rousseaux et al. (2006) failed to replicate the results of Rossetti et al. (1998). In a time series study, Nys et al. (2008) examined the effects of PA in LN patients who were tested within 4 weeks post-stroke. By using four treatment sessions, Nys et al. compared the PA treatment with a "placebo prism" treatment (i.e., goggles with normal, not prismatic lenses). Although PA resulted initially in faster improvements, no differences between the experimental group and the control group were found at 1-month post treatment. Note, however, that the number of treatment sessions employed by Nys et al. (i.e., four) was less than 25% of those employed by Frassinetti et al. (2002) and by Serino et al. (2007, 2009), who both used 20 sessions of PA. In addition, also Turton et al. (2010), in an RCT, did not find beneficial effects of PA. Nonetheless, the degree of the prismatic lenses used in that study (i.e., 6°) was "weaker" than that used in the studies by Frassinetti et al. (2002) and Serino et al. (2007, 2009), who both used 10° deviating, prismatic lenses. In conclusion, the number of treatment sessions and the type of lenses used, might have made the difference between studies reporting specific beneficial effects of PA and those reporting no specific effects (Nys et al., 2008) or no effects at all (Turton et al., 2010).

AIMS OF THE PRESENT STUDY

According to Kerkhoff and Schenk (2012), "[. . .] we need empirical evidence which identifies the best treatment, the optimal amount of treatment sessions, the best combination of treatments, and provides treatment-specific predictors for therapy responders." The present study aimed to test the effects of the three abovementioned treatments (i.e., VST, LAT, and PA), by means of a quasi-randomized clinical trial. To the best of our knowledge, the present study was the first that directly compared the effects of VST, LAT, and PA. We aimed to answer the following questions:

1) *What is the best treatment for ameliorating LN signs?* Our aim was to compare the three LN treatments (i.e., VST, LAT, and PA) to investigate which treatment could overall be the most suitable one for ameliorating LN signs.
2) *Are there differential treatment effects on specific subtypes of LN?* We wanted to investigate the possible differential treatment effects (VST, LAT, and PA) on subtypes of LN (i.e., personal, peripersonal, and extrapersonal), to find whether there could be interactions among treatments and LN subtypes.
3) *Are treatment effects observed on ecological tasks?* Bowen and Lincoln (2007) reviewed 12 RCTs regarding LN treatments. Only four RCTs had adequate allocation concealment (i.e., low risk of selection bias). Only 6 out of 12 RCTs measured disability and only 2 of them investigated whether the effects persisted. The overall effect of LN treatments on measures of disability was not statistically significant. Our aim was to investigate the effects of LN treatments on tests and tasks resembling activities of everyday life. For these reasons, in the present study we reported only outcome measures related to everyday life activities.
4) *Are treatment effects larger than those of unspecific factors?* We wanted to assess the effects of unspecific factors to differentiate their modulating role over the effects of LN treatments. The possibility of neural changes (e.g., positive spontaneous recovery and/or negative loss of neural connections) has been usually controlled by testing LN patients in the so-called "chronic phase" (e.g., about 2 or 3 months after the onset of the lesion). Nonetheless, this approach does not control appropriately the effect of neural changes because of unspecific factors (e.g., spontaneous neural reorganization, social and free-time activities, medical care, physiotherapy, environmental stimulation, etc.). In the present study, we employed a multiple baseline design with two pre-treatment assessments (i.e., A1 and A2) in order to control the role of unspecific factors affecting LN patients' performance.
5) *Are there long-lasting treatment effects?* The efficacy and effectiveness of LN treatments depend also on the post-treatment time interval, within which positive effects of treatments can be still observed. To this aim we included two post-treatment assessments (i.e., A3 and A4) separated by a 2-week interval.

MATERIALS AND METHODS

PARTICIPANTS

Thirty-three patients with right-hemisphere damage and LN were recruited. Sample numerosity was calculated *a priori*, by means of the software G∗POWER 3 (Faul et al., 2007)[1]. There were two dropouts. Thus, 31 LN patients (PA group: 11 LN patients; VST and LAT: 10 LN patients) took part in the study. All LN patients were assessed and received the rehabilitation treatments at the Neuropsychology Department of the IRCCS San Camillo Hospital (Lido-Venice, Italy).

Left neglect patients gave their written informed consent according to the Declaration of Helsinki II. Inclusion criteria comprised absence of dementia, documented both by neuropsychological history and interview, as well as by means of a neuropsychological battery involving global cognitive status [Mini Mental State Examination (MMSE); Magni et al., 1996], auditory verbal short-term memory (Digit span subtest; Orsini and Laicardi, 1997), auditory verbal long-term memory (Rey's 15 words; Carlesimo et al., 1996), verbal fluency (Novelli et al., 1986), and verbal reasoning (Spinnler and Tognoni, 1987). Patients with documented medical history of substance abuse and psychiatric disorders were excluded from the present study. LN patients had never received LN treatments before taking part in the present study. All patients had unilateral lesions because of first stroke. Lesion sites were confirmed by Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) scans. In addition, the presence of visual field defects was evaluated by means of visual perimetry. Gender, age, education, length of illness, lesion site, and stroke type are contained in **Table 1**.

ASSESSMENT AND TREATMENT SCHEDULE

Assessment was performed four times within a short time series. The first assessment (A1) was carried out to verify the presence and severity of LN signs. Two weeks after the end of A1, the second assessment (A2) was carried out to verify (i.e., A1 vs. A2) the effects of unspecific factors only (e.g., spontaneous neural changes, improvements to sustained attention, test–retest effects) or the effects of other therapies and activities, which were normally provided to the LN patients (e.g., pharmacological treatment, physiotherapy, social and free-time activities, environmental stimulation). Then, LN patients received the treatments for 2 weeks. The third assessment (A3) was carried out immediately after the end of the 2-week-long treatments (i.e., A2 vs. A3) to assess the effectiveness of each treatment (VST, LAT, and PA) and treatment-induced differences that were beyond and above those differences that were due only to unspecific factors (i.e., A1 vs. A2). The fourth assessment (A4) was carried out 2 weeks after the end of A3 (i.e., A3 vs. A4) to evaluate the presence of long-lasting effects of the treatments. In summary, there were two pre-treatment assessments (i.e., A1 and A2) and two post-treatment assessments (i.e., A3 and A4).

GENERAL PROCEDURE

All right-hemisphere-damaged patients who showed LN, both on Assessments 1 and 2, on at least one subtest of the Behavioral Inattention Test (Wilson et al., 1987), the Fluff test (Cocchini et al., 2001), the Bells test (Gauthier et al., 1989), or the Room description test, were assigned to one of the treatment groups (VST, LAT, or PA), on the basis of the order of patients' admission to the Department of Neuropsychology. That is, a quasi-randomized sequence (i.e., alternation) of the order of treatments was established. This fixed sequence was repeated in blocks (i.e., the first patient was assigned to the PA group, the second patient to the LAT group, the third patient to the VST group, the fourth patient to the PA group, and so on). All LN patients received the same neurological and neuropsychological assessments according to the rehabilitation protocol. The 2-week-long rehabilitation program consisted of 20 sessions (overall treatment duration: 2 weeks). Each session lasted approximately 20 min. There were two daily sessions

[1] http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/

Table 1 | Demographic and neurologic data of LN patients.

Patient ID	Treatment	Hemianopia	Gender	Education (years)	Age (years)	Lesion site	Stroke type	Time since lesion onset (days)
1	LAT	–	M	5	76	P	I	207
2	LAT	–	F	13	80	P, BN	I	40
3	LAT	+	M	17	54	TPO	H	89
4	LAT	–	M	8	39	FTP	H	95
5	LAT	–	F	17	81	LV	I	64
6	LAT	+	F	8	51	BN, IC	H	39
7	LAT	–	M	5	73	TPO	I	66
8	LAT	+	F	13	65	FTP	H	141
9	LAT	+	M	13	42	BN, IC	H	43
10	LAT	–	F	8	80	P	H	33
11	PA	–	M	8	57	T, BN	I	62
12	PA	–	F	8	75	P	I	31
13	PA	–	M	5	62	FP	H	345
14	PA	–	M	5	69	FP	I	57
15	PA	–	M	8	69	FTP	I	35
16	PA	–	F	5	59	P	I	207
17	PA	+	F	5	72	TP	I	58
18	PA	–	F	5	86	TP	I	65
19	PA	–	F	5	61	IC	H	92
20	PA	–	F	8	71	TP	I	58
21	PA	–	M	13	51	FTP	I	108
22	VST	–	M	13	70	BN	H	88
23	VST	–	M	5	86	FTP	I	132
24	VST	–	M	13	60	P, LV	I	41
25	VST	–	F	3	79	TP	I	82
26	VST	–	F	5	72	BN, LV	I	223
27	VST	–	F	8	78	FTP	I	54
28	VST	+	M	6	74	FTP	I	71
29	VST	+	M	5	57	TP, IC	H	43
30	VST	–	M	19	59	BN, IC	H	136
31	VST	+	F	13	41	TP	I	101

F, frontal; T, temporal; P, parietal; O, occipital; BN, basal nuclei; IC, internal capsule; LV, lateral ventriculus; I, ischemic; H, hemorrhagic; +, hemianopia present; –, hemianopia absent.

(i.e., one session in the morning and one in the evening), 5 days a week.

VISUAL SCANNING TRAINING

Apparatus and stimuli

Stimuli comprised black-and-white drawings. Each drawing was printed on an A4, landscape-oriented, white sheet of paper. Each drawing was divided into multiple parts. Each part had either a little black point inside or it was empty. Participants were asked to fill-out only those parts of the drawings, which had the little black point inside. The midline of each drawing was aligned with the patient's body midline. The drawings were presented to each patient following the same order. A vertical, wide, pink-colored stripe was placed along the left edge of each sheet of paper.

VST procedure

Patients were required to look at the pink-colored stripe before starting to scan and fill-out each drawing. After having filled each drawing, LN patients were verbally instructed and encouraged to look again at the pink-colored stripe and, then, to check-out the drawing for possible omissions. After having checked-out for omissions, patients were presented with a new drawing and the next trial started. The verbal cue ("look at the pink-colored stripe") remained the same through all the phases of the rehabilitation procedure; no other verbal cues were given by the examiner.

LIMB ACTIVATION TREATMENT

Apparatus and stimuli

This treatment involved the use of the LAT Device (LAT-D)[2], a modified version of the original "Limb Activation Device" (LAD) employed by Robertson et al. (2002). The LAT-D comprised a central unit and a bellows. The central unit encompassed a small plastic box, measuring 11 cm × 6 cm × 3 cm (weight = 150 g). The

[2] http://www.treatneglect.co.uk/prod01.htm

box contained the power supply, a microcontroller, a timer, a buzzer, and a LED. The control unit could activate the buzzer and display a light, at either random or fixed intervals. The bellows (measuring 15.2 cm × 2.5 cm) could be pressed by the patients to stop a buzzing tone emitted by the buzzer. The central unit was connected with the buzzer by means of a spiral plastic air tube, so that the distance between the box and the bellows could be easily adjusted. Drawings were the same as those used for the VST procedure.

LAT procedure

The bellows was fixed between each patient's left arm and the left armrest of the wheelchair. Then, LN patients were asked to fill-out the same drawings as those used in the VST. Each time LN patients heard the tone emitted by the buzzer, they were instructed to press the bellows with their left arm to turn-off the tone.

During the first week of treatment, the buzzer was set to emit the tone at a fixed time interval of 240 s, whereas in the second week of treatment the buzzer was set at a fixed time interval of 120 s. If LN patients did not move their left arm within 1 min from the onset of the tone, the examiner verbally cues reminded them to press the bellows with their left arm to turn-off the tone. No other verbal or non-verbal cues regarding the filling out of the drawings or the use of the LAT-D were given by the examiner during the task. All LN patients who completed the treatment had sufficient residual movement of the contralesional (left) arm to carry out the rehabilitation protocol.

PRISM ADAPTATION

Apparatus, stimuli, and procedure

Left neglect patients were seated at a table. In front of them, a wooden box was placed on the table (height = 30 cm, width = 75 cm, depth = 34 cm at the center and 18 cm at the periphery). The box was open on the side facing the patient and on the opposite side, facing the examiner. A visual target (a pen) was presented manually by the examiner at the distal edge of the top face of the box. The visual target was presented randomly in one out of three possible positions: one central position straight ahead of the patient (0°), and two lateral positions, one on the left and one on the right of the patient's body midline (−21 cm and +21 cm, respectively). Patients were asked to keep their right ipsilesional hand on their chest, at the level of the sternum (i.e., the hand starting position) and to point with the index finger toward the target (i.e., the pen), without hesitation. The pointing task was performed in three experimental conditions: pre-exposure (i.e., with visible and non-visible pointing), exposure (i.e., with visible pointing only), and post-exposure (i.e., with non-visible pointing only). The examiner recorded the patients' pointing movements, as the distance between the central position of the box (0°) and the final position of the patient's finger. A graduated scale (in cm) was used to assess the pointing deviation, which was recorded by the examiner.

The procedure was the same as that used by Frassinetti et al. (2002). All PA conditions (pre-exposure, exposure, and post-exposure) were run in each PA session.

Pre-exposure condition. Left neglect patients were required to point with their right index finger toward 30 targets, randomly presented at one of the three possible positions (10 targets in the center, 10 on the right, 10 on the left), with visible pointing (only first and eleventh session). Note that in visible pointing, the arm movement was performed below the top face of the box, but the index finger was visible at the final stage of pointing. Afterward, LN patients were required to point with their right index finger toward 30 new targets, which were again randomly presented at one of the three possible positions (10 targets in the center, 10 on the right, 10 on the left). The pointing movement was now performed entirely below the top face of the box, so that the index finger was not visible at any stage (i.e., non-visible pointing).

Exposure condition. Left neglect patients performed the same task wearing the prismatic goggles[3]. The goggles were fitted with wide-field prismatic lenses inducing a 10° shift of the visual field to the right. Patients were asked to point with their right index, without hesitation, to 90 targets presented in a random order in each of the three possible positions (30 targets in the center, 30 on the right, and 30 on the left). During the exposure condition, the arm movement was hidden below the top face of the box, except for the final part of the movement, where the index finger could emerge beyond the distal edge of the top face of the box to permit patients to see their finger.

Post-exposure condition. Immediately after removal of the prisms, LN patients were required to point toward 30 targets (10 in the center, 10 on the right, and 10 on the left). The pointing movement was performed entirely below the top face of the box, so that the index finger was not visible at any stage (i.e., non-visible pointing).

OUTCOME MEASURES

Tests for assessing personal LN

Comb and razor test. This test was based on Beschin and Robertson (1997) test, but we used a more sensitive formula to quantify LN patients' performance (McIntosh et al., 2000). The equipments consisted of a comb, a razor with shield on, and a powder compact. The examiner sat opposite to the patient and held up the comb, while saying: "I would like you to show me how this comb can be used." In the razor condition, which was used with men, the patient was told: "I would like you to show me how this razor can be used." In the powder compact case, which was applied to women, the patient was told: "I would like you to show me how this powder compact case can be used."

Left neglect patients were required to perform each task for 30 s. Each task was videotaped. The number of strokes on each task was analyzed off-line, by two examiners. Finally, each stroke was classified into three categories (left-sided, right-sided, or ambiguous).

The modified formula that we used to calculate the lateral bias of LN patients' behavior was:

$$\%bias = \frac{right - left\ strokes}{left + ambiguous + right\ strokes} \times 100$$

[3]http://www.optiquepeter.com/en/index.php

Rightward bias yielded a positive percentage score, whereas leftward bias yielded a negative percentage score (cut-off: % bias > 11).

Fluff test. This test encompassed 24 targets (i.e., round felt pads; diameter = 2 cm) (Cocchini et al., 2001). Each felt pad was self-adhesive to be easily attached to the patients' clothes, by using only little pressure. There were three targets on the right and three on the left of the trunk's midline, six targets along the patient's left arm, six along the right leg, and six along the left leg. No targets were placed on the right arm, because LN patients performed the task by using that arm. Each patient was blindfolded and seated, while the targets were attached. Patients were not told how many targets were attached. While the examiner attached each target, patients were distracted by engaging them in a conversation to prevent them from counting the targets. When the examiner finished attaching the targets, patients were asked to remove them, while the patients were still blindfolded. There was no time limit for the response and the test finished when the patients declared that they had collected all the targets. Only target omissions on the left were considered for determining the cut-off score, which was <13 out of 15.

Tests for assessing peripersonal LN

Picture scanning. In this test three large photographs were presented to the patients, one at a time (Wilson et al., 1987). The photographs depicted: a meal, a wash basin and toiletries, and a large hospital room containing various pieces of furniture and hospital aids. The midline of each photograph was aligned with the body midline of each patient. The patients were instructed to name and/or point to the items in each photograph. The number of identified targets was scored. There was no time limit for the patients to perform the test. The cut-off score of this subtest was ≤5 identified targets out of 9.

Menu reading. This task consisted of an "open-out" page containing 24 common words of food items arranged in four adjacent columns (two on the left page and two on the right page) (Wilson et al., 1987). Patients were asked to read aloud out all the words. Responses on each of the 24 words were scored as correct or incorrect. Incorrect responses consisted of partial/whole word substitutions or omissions. There was no time limit for the patients to perform the test. The cut-off score of this subtest was ≤8 correct responses out of 9.

Coin sorting. In this test the patient had to indicate coins of different values, as requested by the examiner (Wilson et al., 1987). Coins were distributed to the left, to the right, and in front of the patients, according to a standard arrangement scheme on a board. The midline of the board was aligned with the body midline of each patient. There were 3 coins for each value, for a total of 15 coins. The examiner recorded the indicated coins. There was no time limit for the patients to perform the test. The cut-off score of this subtest was ≤8 indicated coins out of 9.

Semi-structured ecological scale. This scale was developed to assess the qualitative/quantitative asymmetries present in the exploration of space in LN patients, in situations similar to those of everyday life (Zoccolotti and Judica, 1991). In the present study, we used only the subtests A (Serving tea) and C (Card dealing). During these subtests, patients sat at a table. They were required to take from the table and distribute the tea/the cards to three examiners, who were seated around the table (one examiner on the left, one on the right, and one in front of the patient). Patients' performance on these subtests was videotaped. Then two examiners evaluated off-line the patients' performance, according to the scoring system provided with the test. Scoring was based on a four-level scale, which evaluated how accurately LN patients served the tea or distributed the cards. The maximum score was 0 (i.e., no neglect), whereas the minimum score was 3 (i.e., severe neglect). There was no time limit for the patients to perform the test.

Test for assessing extrapersonal LN

We assessed the performance of LN patients in the extrapersonal space. There are not yet standardized measures of LN for the extrapersonal space, defined as the locomotor space beyond the reaching and grasping space. For this reason we tested LN patients in a room (7 m × 4 m), which was provided with various objects and pieces of furniture arranged symmetrically with respect to the room's midline (10 targets on the left and 10 targets on the right; maximum score: 20). LN patients sat on their wheelchair at the center of one of the two 10-meter-long walls of the room. Then, they were asked to describe all the targets that they could see. The examiner, standing behind each patient, recorded their responses on a map of the room depicting the positions of all the targets. There was no time limit for the patients to perform the test.

The Catherine Bergego Scale

We also assessed the presence and degree of LN in everyday life situations (Azouvi et al., 2006). To this aim we used the standardized 10-item checklist provided with the CBS. Each item of the CBS was responded on a four-point rating scale (range: 0 = "no LN-related difficulties"; 4 = "presence of severe LN-related difficulties"). In the present study the CBS was administered as a questionnaire to the patients' caregivers.

RESULTS

Left neglect patients in the three treatment groups did not differ for age, education, time since lesion onset, and on the MMSE (all *ps ns*). Only the performance of the patients with complete data on all four Assessments (i.e., 31) was subjected to the statistical analyses. Two-way, mixed ANOVAs were run, with Intervention type (VST, LAT, and PA) as the between-participants factor and Assessment (A1, A2, A3, and A4) as the within-participants factor. Wherever sphericity was violated, Huynh–Feldt corrections were applied.

PERSONAL SPACE

Fluff test

The main effect of Intervention type was not significant, $F(2, 28) = 1.015$, *ns*. The main effect of Assessment was significant, $F(3, 84) = 5.187$, $p < 0.001$, partial eta squared = 0.156. A repeated contrast showed that only the difference between Assessment 1 and Assessment 2 was significant, $F(1, 28) = 5.848$, $p < 0.05$, partial eta squared = 0.173 (see **Figure 1**). The interaction Intervention type by Assessment was not significant, $F(6, 84) = 0.835$, *ns*.

Comb and razor test

The main effect of Intervention type was not significant, $F(2, 29) = 0.149$, *ns*. The main effect of Assessment was not significant, $F(3, 87) = 1.428$, *ns*. A repeated contrast revealed no significant differences among the four levels of Assessment (all *ps ns*). The interaction Intervention type by Assessment was not significant, $F(6, 87) = 1.173$, *ns*.

PERIPERSONAL SPACE

Picture scanning subtest

The main effect of Intervention type was not significant, $F(2, 28) = 3.088$, *ns*. The main effect of Assessment was significant, $F(2.647, 74.112) = 7.414$, $p < 0.001$, partial eta squared = 0.209. A repeated contrast showed that only the difference between Assessment 2 and Assessment 3 was significant, $F(1, 28) = 7.003$, $p < 0.05$, partial eta squared = 0.2 (see **Figure 2**). The interaction Intervention type by Assessment was not significant, $F(5.294, 74.112) = 1.260$, *ns*.

Menu reading subtest

The main effect of Intervention type was not significant $F(2, 28) = 1.542$, *ns*. The main effect of Assessment was significant, $F(3,84) = 8.849$, $p < 0.001$, partial eta squared = 0.233. A repeated contrast showed that only the difference between Assessment 2 and Assessment 3 was significant, $F(1,28) = 7.582$, $p < 0.05$, partial eta squared = 0.213 (see **Figure 3**). The interaction Intervention type by Assessment was not significant, $F(6, 84) = 0.488$, *ns*.

Coin sorting subtest

The main effect of Intervention type was not significant $F(2, 28) = 2.323$, *ns*. The main effect of Assessment was not significant, $F(3, 84) = 2.390$, *ns*. A repeated contrast revealed no significant differences among the four levels of Assessment (all *ps ns*). The interaction Intervention type by Assessment was not significant, $F(6, 84) = 1.487$, *ns*.

Semi-structured ecological scale

Subtest A (serving tea). The main effect of Intervention type was not significant, $F(2, 28) = 1.819$, *ns*. The main effect of Assessment was significant, $F(3, 84) = 3.862$, $p < 0.001$, partial eta squared = 0.121. A repeated contrast showed that only the difference between Assessment 3 and Assessment 4 was significant, $F(1, 28) = 7.81$, $p < 0.05$, partial eta squared = 0.218 (see **Figure 4**). The interaction Intervention type by Assessment was not significant, $F(6, 84) = 1.972$, *ns*.

Subtest C (card dealing). The main effect of Intervention type was not significant, $F(2, 28) = 0.260$, *ns*. The main effect of

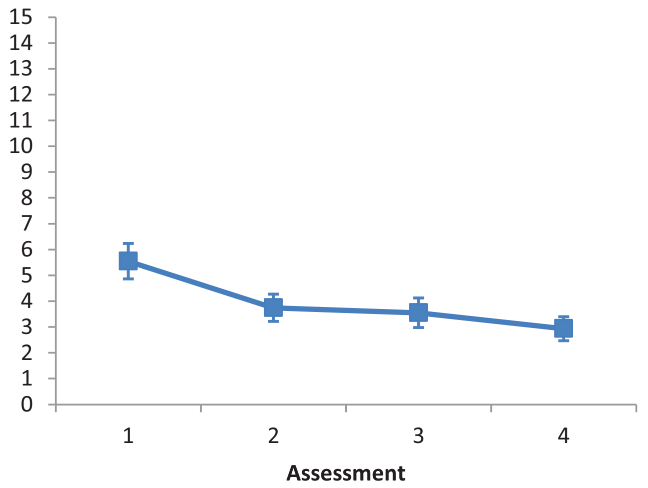

FIGURE 1 | LN patients' performance on the Fluff test as a function of assessment. Error bars represent 1 SEM.

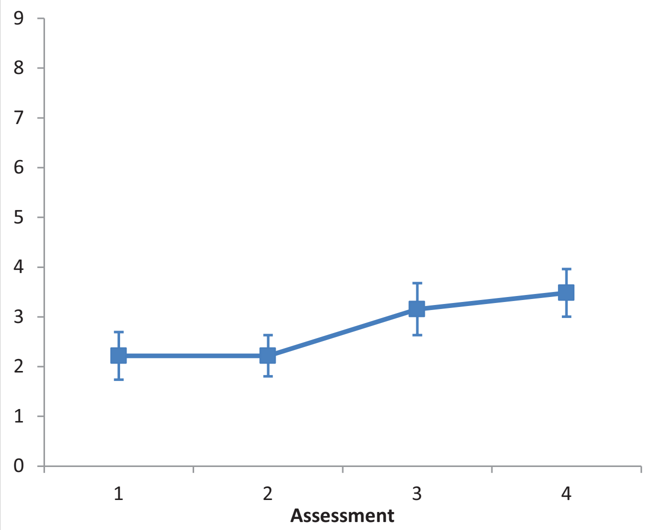

FIGURE 2 | LN patients' performance on the Picture Scanning subtest as a function of assessment. Error bars represent 1 SEM.

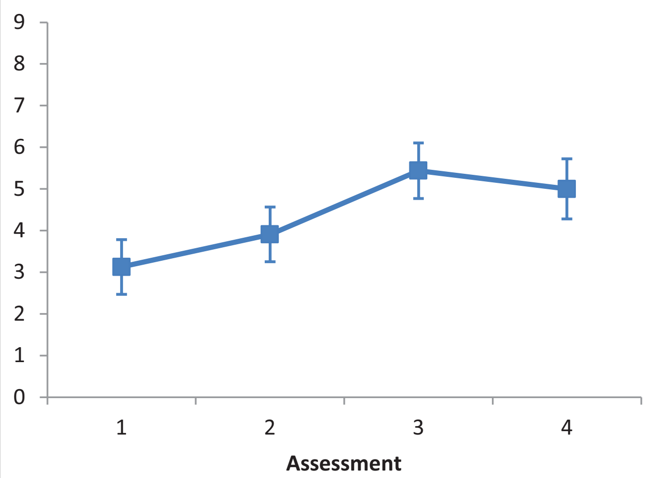

FIGURE 3 | LN patients' performance on the Menu Reading subtest as a function of assessment. Error bars represent 1 SEM.

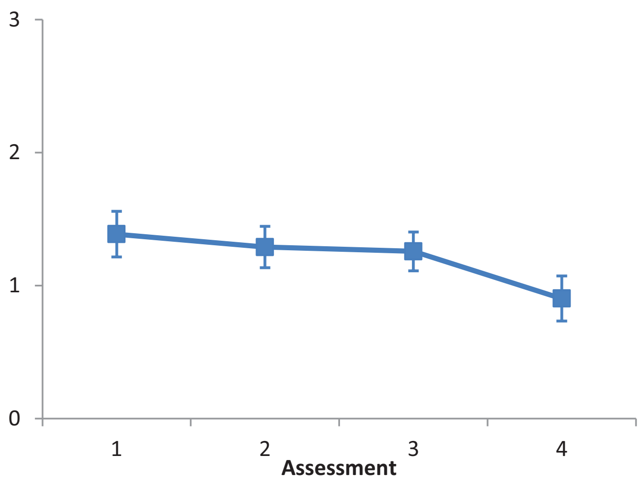

FIGURE 4 | LN patients' performance on the Serving tea subtest as a function of assessment. Error bars represent 1 SEM.

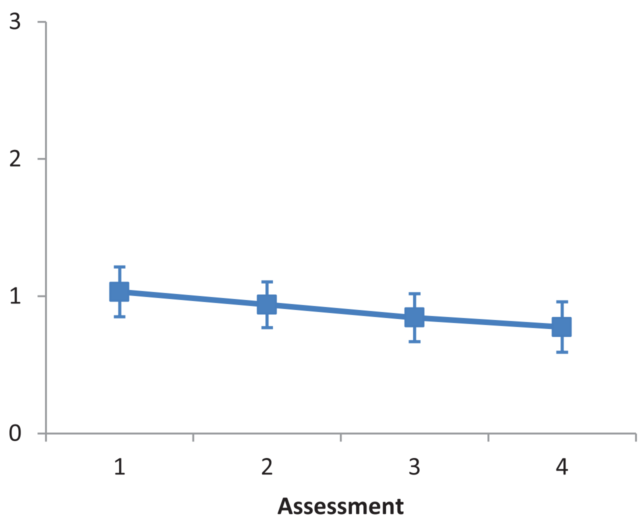

FIGURE 5 | LN patients' performance on the Card dealing subtest as a function of assessment. Error bars represent 1 SEM.

Assessment was significant, $F(1.271, 35.583) = 32.947$, $p < 0.001$, partial eta squared = 0.541. A repeated contrast showed that the differences between Assessment 2 and Assessment 3, and between Assessment 3 and Assessment 4 were significant: $F(1, 28) = 35.254$, $p < 0.05$, partial eta squared = 0.557, and $F(1, 28) = 35.637$, $p < 0.05$, partial eta squared = 0.560, respectively (see **Figure 5**). The interaction Intervention type by Assessment was not significant, $F(2.542, 35.583) = 1.874$, *ns*.

EXTRAPERSONAL SPACE

Room description

The main effect of Intervention type was not significant, $F(2, 28) = 0.436$, *ns*. The main effect of Assessment was not significant, $F(3, 84) = 1.093$, *ns*. A repeated contrast revealed no significant

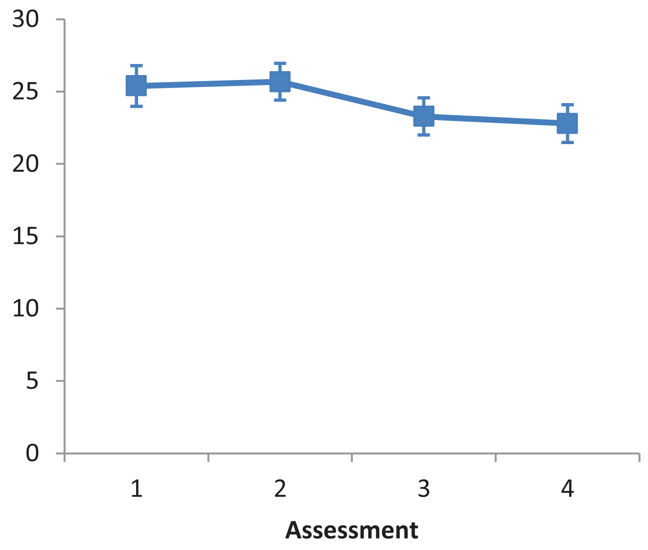

FIGURE 6 | LN patients' performance on the CBS as a function of assessment. Error bars represent 1 SEM.

differences among the four levels of Assessment (all *ps ns*). The interaction Intervention type by Assessment was not significant, $F(6, 84) = 0.581$, *ns*.

CBS

The main effect of Intervention type was not significant, $F(2, 25) = 0.274$, *ns*. The main effect of Assessment was not significant, $F(2.196, 54.9) = 2.615$, *ns*. A repeated contrast showed that the differences between Assessment 2 and Assessment 3 was significant, $F(1, 25) = 5.489$, $p < 0.05$, partial eta squared = 0.180 (see **Figure 6**). The interaction Intervention type by Assessment was not significant, $F(4.392, 54.9) = 0.220$, *ns*.

DISCUSSION

In the present study we compared, for the first time, the overall and differential effects of three of the most widely used LN treatments: VST, LAT, and PA. LN patients' performance was assessed four times: A1 and A2 (i.e., the two pre-treatment assessments); A3 and A4 (i.e., the two post-treatment assessments). LN patients were treated for the same number of sessions (i.e., 20). Our aims were to:

1. Test the overall efficacy and effectiveness of VST, LAT, and PA.
2. Test the differential effects of VST, LAT, and PA on specific subtypes of LN (e.g., personal, peripersonal, and extrapersonal).
3. Test the effects of VST, LAT, and PA on measures of everyday life activities.
4. Test the specific effects of LN treatments (A2 vs. A3) above and over the effects of unspecific factors (A1 vs. A2).
5. Test the long-lasting effects of LN treatments (A3 vs. A4).

In the following paragraphs each of our aims is discussed in relation to our findings.

1. We compared for the first time VST, LAT, and PA. In recent reviews, both PA and LAT, as well as VST have been proposed as the gold standard of LN rehabilitation: LAT and VST (Riestra and Barrett, 2013), PA (Mattingley, 2002). We found a main effect of treatments, but we did not find significant interactions between treatments and assessment sessions. That is, it seems that all three treatments can lead to similar positive outcomes concerning LN rehabilitation. Apparently VST, LAT, and PA are based on different principles of functioning. PA is thought to recalibrate ipsilesionally biased proprioceptive and visuo-spatial coordinates, LAT presumably activates joined spatio-motor representations of the contralesional space, and VST leads to compensatory, voluntary, contralesional scanning. To explain, however, the absence of differences in the present study, it can be assumed that beyond the supposed differences, VST and LAT activate some kind of voluntary orienting of spatial attention toward the contralesional space. Indeed, during both VST and LAT, LN patients are required to perform voluntary actions within (i.e., LAT) or toward the contralesional space (i.e., VST). This, in turn, may lead to the re-allocation of residual spatial resources toward the contralesional space. In contrast, PA does not activate some kind of voluntary orienting of spatial attention: left after-effect observed after removing the prismatic goggles is induced by automatic processes during the PA procedure.

   A working hypothesis can be that LN can have different underlying causes, each addressed by a different kind of treatment. If this is the case, then additive effects of LAT, PA, and VST should be observed. The additive effects of treatments can be addressed in future studies in which the combined use of the three treatments should be tested (e.g., LAT or PA vs. LAT plus PA; for reviews on additive effects of LN treatments, see Singh-Curry and Husain, 2008; Saevarsson et al., 2011). For instance, by combining neck vibration and PA, Saevarsson et al. (2010) have reported additive therapeutic effects on LN signs. Nonetheless, some studies have reported no better effects of combined treatments with respect to single treatments for LN (e.g., Pizzamiglio et al., 2004; Keller et al., 2009). Thus, further studies are required to explore the presence of possible additive effects of LN treatments and/or propose a global approach to the rehabilitation of LN patients.
2. We found different effects of treatments in relation to LN subtypes. That is, the effects of VST, LAT, and PA were present only on tests assessing the peripersonal space (i.e., the within-reaching space). Instead, we did not find any effects of LAT, PA, or VST on tests tapping the personal (i.e., the body space) or the extrapersonal (i.e., the locomotor space). We think that this finding is not surprising given that, in all three treatments, LN patients were required to perform actions only within their peripersonal space. Our findings are in accordance with Pizzamiglio et al. (1992). In contrast, our findings are partially different from those of Frassinetti et al. (2002) and Serino et al. (2007), who found positive effects of PA not only for the peripersonal space but also for the personal and the extrapersonal space. With reference to the peripersonal space, however, Frassinetti et al. (2002) and Serino et al. (2007) used totally or partially different procedures in administering the Fluff test (i.e., LN patients were not blindfolded while searching for the targets), whereas we used the standard procedure (i.e., patients were always blindfolded; Cocchini et al., 2001). In addition, neither Frassinetti et al. (2002) nor Serino et al. (2007) used the Comb and Razor test. Regarding the exploration of the extrapersonal space both Frassinetti et al. (2002) and Serino et al. (2007) tested their patients in a rather small room (3.6 m × 2.2 m), whereas we used a considerably larger room (7 m × 4 m). These procedural differences should be addressed in future studies. We propose that a possible way for extending the positive effects of LAT, PA, and VST, found in the peripersonal space, can be that of including versions of the three treatments, in which LN patients are required to perform actions not only in the peripersonal but also in the personal and the extrapersonal spaces. Note that some generalization to untreated tasks has been reported with reference to PA (e.g., reading, wheel-chair driving, auditory extinction, representational neglect, mental imagery; for review, see Jacquin-Courtois et al., 2013). Nonetheless, the exact extend of personal, peripersonal, and extrapersonal aspects in these tasks is unclear.
3. One of the major critiques regarding LN rehabilitation (Bowen and Lincoln, 2007) is that previously reported positive findings have used outcome measures of impairment (e.g., paper-and-pencil tests such as cancelation tests, drawing tasks, or line bisection), but not measures concerning disability (e.g., tasks resembling or directly investigating activities of everyday life). We tested the effects of LAT, PA, and VST on everyday life activities (Bergego questionnaire) and on tasks resembling everyday life activities (e.g., looking at photographs, reading, etc.). We found that positive outcomes were observed as a consequence of LN treatment. Our findings are in accordance and further extend the findings of previous single-case and group studies in which positive effects of VST, LAT, and PA on LN patients have been reported (e.g., Antonucci et al., 1995; Kalra et al., 1997; Frassinetti et al., 2002). We think, thus, that our study adds one more step toward accepting the efficacy and effectiveness of LAT, PA, and VST in the rehabilitation of LN. Note, however, that we did not find positive results of treatments on some tests, namely Coin sorting and Serving tea. A possible reason for these negative findings might be that both tests are the only ones in which patients are required to reach out to touch (Coin sorting) and reach out to grasp (Serving tea) real objects in the peripersonal space. Thus, this might be a case of task-specific effects of treatments, given that in none of our treatments the patients were required to interact with real objects. Nonetheless, instead of the requirement on reaching out and grasping, it could be that the "Coin sorting" and "Serving the tea" tests are just not very sensitive tasks for revealing treatment-associated changes in LN. In future investigations, the treatments used in the present study might be modified to include some interaction with real objects within more sensitive tests.
4. One might attribute the reported main effects of our treatments to unspecific factors (e.g., spontaneous neural reorganization, social and free-time activities, medical care, physiotherapy, environmental stimulation, test-retest effects, global improvements in sustained attention, etc.). We do not think that this is the case for the following reasons. First, there is no reason why an unspecific effect of treatments should be observed only in

the specific sector of space (i.e., the peripersonal space), which was the target space of all actions performed by LN patients tested. Second, the effects of unspecific factors cannot account for the absence of positive results regarding tasks performed in the peripersonal space that required reaching out or grasping of real objects (i.e., non-treated actions). Third, we controlled methodologically and statistically for the effects of unspecific factors only, by employing two pre-treatment assessments (A1 and A2), which were spaced by a 2-weeks interval. The results showed that there were no differences between the patients' performance on Assessment 1 and Assessment 2, for those measures where, instead, a significant difference between patients' performance on Assessment 2 and Assessment 3 was observed. Fourth, the danger that our effects were due only to unspecific factors was further controlled in the comparison between LN patients' performance on Assessment 1 and 2. In that time interval, all patients received daily sessions of physiotherapy. Patients are usually highly motivated to participate in physiotherapy sessions, given that motor defects are more obvious to the patients, than LN-related defects. During physiotherapy sessions, the patients were provided with unstructured cues to attend to the left, while the physiotherapist is placed for most of the time to the left of the patients' body midline. Thus, if our effects were due to simply "doing something" or to motivational factors, beneficial effects would have been observed in most comparisons between Assessment 1 and 2. By contrast, this was not the case. Finally, we reasoned that unspecific effects – not related to treatments – would have ameliorated LN patients' performance not only on spatial but also on non-spatial tasks. To this aim, we ran repeated contrasts, on the Intervention type factor, on three non-spatial tests: verbal reasoning, semantic verbal fluency, and digit span. The results showed that none of these contrasts was significant (i.e., A1 vs. A2; A2 vs. A3; A3 vs. A4). Instead, in our time series only the introduction of treatment leaded to improvements in the abovementioned comparisons. To the best of our knowledge this is the first study reporting specific effects of LAT and PA compared with the effects of unspecific factors (for evidence regarding VST, see Pizzamiglio et al., 1992; Paolucci et al., 1996).

Another possible critical point of our study is that we did not employ a "typical" "control" group. Note, however, that we have employed VST. In most of the previous studies on LN rehabilitation, VST has been employed as a control treatment (for review, see Riestra and Barrett, 2013). The VST, however, is one rehabilitation treatment (i.e., not a "doing nothing" or unspecific treatment). For this reason we did not name VST, in our study, a control treatment, but we considered it as an alternative treatment. We think that this is the most appropriate term (i.e., alternative treatment) to use when referring to VST. Each of the three treatments (LAT, PA, and VST) has been extensively compared with different control treatments (see Riestra and Barrett, 2013). Thus, it is thought that each of these treatments can be considered as a valid treatment for rehabilitating LN. Nonetheless, to date, no study has compared the differential effectiveness and efficacy of these three treatments. We conducted, indeed, the present study to test which would be the best LN treatment and which LN treatment would have worked better with specific LN subtypes. We considered that, in turn, each treatment would be compared with the two other treatments. In this sense, in the present study we had, for each comparison, not only one but two control treatments (LAT vs. PA/VST; PA vs. LAT/VST; VST vs. PA/LAT). Adding, for example, a non-treatment group would have been problematic for ethical reasons (see also discussion on the possible effects of unspecific factors).

5. An important point regarding LN rehabilitation is the stability of positive effects in time. Indeed, the efficacy and effectiveness of LN treatments is also based on the time interval during which positive effects of LN can be maintained. In the present study we showed that positive effects of treatments can be maintained for at least 2 weeks following the end of each treatment; further improvement was observed in one measure (i.e., Card dealing). Note, however, that on the Serving tea subtest we observed LN improvement only in the comparison between A3 and A4. A possible explanation is that beneficial effects of treatments on this test require more time to be consolidated. Further studies employing this test are required to clarify this point. Our findings are in accordance with those of Frassinetti et al. (2002) and Serino et al. (2007) with reference to PA, and with the findings of Pizzamiglio et al. (1992) with reference to VST. To the best of our knowledge our group study is the first one reporting long-lasting effects also of LAT on measures of LN in everyday life.

In summary, although we used only a small number of treatment sessions (20 sessions over a 2-week interval), an amelioration of LN signs was observed in the majority of the ecological tests assessing the peripersonal space and in everyday life activities measured with the CBS. Our findings cannot be attributed to unspecific factors, and lasted for at least 2 weeks after the end of each treatment. Further studies, however, are required to better investigate which is the most effective rehabilitation procedure for improving processing of the personal and the extrapersonal space, presumably by adapting existing treatment procedures. We employed standardized and rather varying tests for performing LN assessment. These tests are considered the "gold standard" for exploring and investigating different LN subtypes. On the basis of our findings we cannot advance any recommendation regarding the sensitivity of each of the tests that we used. Given that some dissociations were observed among tests of peripersonal space (and between tests of personal, peripersonal, and extrapersonal space) we recommend that comprehensive batteries, instead of single tests, be used to assess different LN subtypes.

Some authors have suggested that PA (Mattingley, 2002; Luauté et al., 2006a) or LAT and VST (Riestra and Barrett, 2013) might each be the best LN treatment. Nonetheless, these treatments had never been directly compared in previous studies. We suggest, instead, that all three treatments can be considered as valid rehabilitation interventions and should be employed for ameliorating LN signs.

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Motor neglect and future directions for research

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Here we present an opinion on "motor neglect," one of the several scotomas in neglect research (Kerkhoff and Schenk, 2012). We describe what it is, outline its anatomical substrate, and its frequency in a stroke population. We outline evidence to suggest that motor neglect reflects the impaired ability to generate movements and discuss a possible rehabilitation technique which may target this particular deficiency. We feel that it is a timely "opinion." Motor neglect may occur in the absence of visuospatial neglect (Laplane and Degos, 1983; Punt et al., 2005) and it can have a severe and detrimental effect on rehabilitation outcomes (Siekierka-Kleiser et al., 2006).

"Motor neglect," a term originally coined by Laplane and Degos (1983), refers to the underutilization of the affected limb compared to the healthy one following brain damage despite normal muscle strength, reflexes, and sensation. It may be distinguished from "directional hypokinesia" (originally described by Heilman et al., 1985) referring to slowness in the initiation of contralesional movements, reduced spatial exploration toward the contralesional side, and insufficient amplitude of contralesional limb movements. Patients with motor neglect typically underuse the contralesional side (even where this involves inconvenience); have little or no involvement of the contralesional limb in bimanual tasks (e.g., clapping, opening a bottle); have little or no involvement of the contralesional limb when automatically gesturing; however, they have relatively normal movement when encouraged *specifically* to use the contralesional limb (Laplane and Degos, 1983; Punt and Riddoch, 2006; Garbarini et al., 2012a,b). Unlike patients with hemiplegia, patients with motor neglect have no paresis, no increase in muscle tone, no pyramidal signs, or alterations in sensation (von Giesen et al., 1994). There is relatively no information on how these patients are able to manage their activities of everyday living. Laplane and Degos (1983) suggest that increased determination on the part of the patient results in tasks eventually being performed (they describe patients with right hemisphere lesions using verbal strategies, while with left hemisphere lesions patients become "left-handed").

There are differential reports as to the frequency of motor neglect. Siekierka-Kleiser et al. (2006), report an incidence of 33% incidence in an acute stroke population with 74% of the motor neglect sample having right hemisphere lesions, while Buxbaum et al. (2004) report an incidence of 12% in an acute and 8% in a chronic stroke population (all patients in the Buxbaum study had right hemisphere lesions). According to Siekierka-Kleiser et al., patients with motor neglect show poor motor recovery over the first 7 days post-stroke relative to the patients without motor neglect; although a sub-group (26.3%) recovered well, and two of the sub-group had left hemisphere lesions.

von Giesen et al. (1994), using positron emission tomography (PET) with four patients with motor neglect, demonstrated that while primary areas underlying the motor output system (the primary sensorimotor cortex, basal ganglia, and cerebellum) were unimpaired, there was poor glucose uptake in premotor, prefrontal, parietal, and cingulate cortex areas, as well as the thalamus. This substantiates the clinical manifestation of normal muscle strength, reflexes, and sensation in motor neglect. von Giesen et al. hypothesized that the intact motor cortical output system is deprived of sensory information and the voluntary drive needed for movement execution (see also Laplane and Degos, 1983).

Recent evidence implicating the parietal regions for movement generation comes from Desmurget et al. (2009). They contrasted the effects of direct stimulation of parietal and premotor regions. Stimulation of inferior parietal regions (IPL) produced a desire to move without any overt movement being produced or EMG activity recorded in the concerned muscles. If the intensity of stimulation was increased, patients reported that movement had occurred; however, again, no actual movement or EMG activity was observed. Desmurget et al. argue that the "wanting to act feeling," resulting from IPL stimulation, is indicative of intentions to move generated before any motor act (Desmurget and Sirigu, 2009, 2012; Desmurget et al., 2009). Sirigu et al. (2004) have also shown that lesions to the parietal lobe (involving the angular gyrus in particular) result in deficits in the subjective experience of wanting to move in a task where patients were free to execute a movement at a time of their own choosing. Thus, behaviorally, control participants demonstrated an anticipatory period prior to the actual movement, parietal patients reported the desire to movement at a time which was very close to the actual time movement was initiated.

The inability to generate actions in motor neglect is illustrated in a recent study. Garbarini et al. (2012a,b) contrasted the performance of patients with motor neglect (and a lack of voluntary drive to initiate action but intact ability to execute motor acts) with patients with anosognosia (who show the reverse deficit, intact voluntary drive but impaired motor ability). While blindfolded, the patients had to draw circles and lines, either performing unimanual drawing movements (the right hand drew unilateral lines) or bimanual movements (the right hand drew lines and simultaneously, the left hand drew circles). They showed that bimanual spatial coupling, as found in normal subjects is not present in patients with motor neglect, although such coupling was preserved in the anosognosic hemiplegic patients. This is a particularly striking finding given that anosognosic patients are unable to move the contralesional limb, while that ability is intact in patients with motor neglect.

As yet (as far as we know) there have been no studies specifically addressing rehabilitation for motor neglect. Exciting new techniques such as repetitive TMS and tDCS (used either to enhance the activity in the lesioned hemisphere or at suppressing the over-activity observed in the unaffected hemisphere) have been used for visuospatial neglect *in general* but not for motor neglect *in particular*. Thus, while suppressing over-activity in the contralesional hemisphere may facilitate ipsilesional performance, it is not clear how it may benefit contralesional action planning. Increasing the activity in lesioned hemisphere may not improve performance – Desmurget et al. (2009) report no benefit of increasing stimulation of IPL on movement generation. Rehme and Grefkes (2013) have argued that the best predictor for good recovery from stroke *in general* (from the acute phase to the chronic phase) is an increase of the coupling between ipsilesional premotor areas (supplementary motor area, ventral premotor cortex, and ipsilesional M1). Such coupling may be critical in patients with motor neglect. Recent studies suggest that noradrenergic (NA) stimulation may be the tool for the job. Grefkes et al. (2010) used a crossover design where healthy subjects were stimulated using the selective noradrenaline reuptake inhibitor reboxetine (RBX) or a placebo. The participants performed goal directed movements with a joy-stick. Drug-related changes in blood oxygen level – dependent activity and interregional connectivity were assessed using functional magnetic resonance imaging (fMRI) and dynamic causal modeling (DCM). The results showed that movement speed increased as a result of RBX (with a corresponding increase in regional activation), and that there were also complex network effects affecting both neural processing within and across the hemispheres. Within the right hemisphere, there this was enhanced activity in areas known to be involved in visuospatial attention and motor control (see Corbetta and Shulman, 2002). In addition, there was increased coupling of the right V1, IPS, and FEF/dPMC with left hemispheric areas, which was independent from task difficulty. Grefkes et al. suggest that the activation reflects enhanced engagement of transformation processes facilitating the integration of visual information into planned motor programs. Subsequently, Wang et al. (2011) studied the effects of NA stimulation at behavioral and neural levels using fMRI in sub acute patients. DCM was applied to fMRI data from key motor areas to assess the effects of NA stimulation on interregional connectivity within the cortical motor system. The results showed a reduction of cortical "hyperactivity" toward physiological levels observed in healthy control subjects, especially in the ipsilesional ventral PMC and SMA, but also in the TPJ and prefrontal cortex. Together these studies suggest that NA stimulation may help to modulate the pathologically altered motor network architecture in stroke patients, resulting in increased coupling of ipsilesional motor areas and improving motor function. Future studies may show NA stimulation to be of significance in patients with motor neglect showing impaired attention and visuomotor intention particularly in the acute phase of stroke when disconnectivity between motor areas is greatest (Rehme et al., 2011). As the time course of spontaneous neurological recovery of neglect as well as motor impairment shows a natural logistic curve up to the first 12–14 weeks post-stroke, after which severity becomes invariant (Kwakkel et al., 2004; Nijboer et al., 2012), NA stimulation may be most beneficial within this time-window in the facilitation of natural recovery.

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Videogame based neglect rehabilitation: a role for spatial remapping and multisensory integration?

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Post-stroke recovery is negatively affected by the presence of visuo-spatial neglect: patients with this diagnosis are more impaired in terms of independence, get lower scores on disability tests, and require longer rehabilitation period (Stone et al., 1992; Katz et al., 1999; Di Monaco et al., 2011). In light of the functional implications that characterize this pathology, it is not surprising that the development of efficient rehabilitation techniques is an important aim of the present research on neglect (Cappa, 2008). Videogames (VG) may offer an effective alternative to traditional behavioral and cognitive rehabilitation as they can integrate cognitive training with high flexibility in a daily life scenario (Rose et al., 2005; Tsirlin et al., 2009). The introduction of low cost, effective tracking devices like Sony's PlayStation Eye™ and PlayStation Move™, Nintendo's Wii Remote Plus™, and Microsoft's Kinect™ were soon recognized as a major source of inspiration for rehabilitation. However, commercially available VG, developed with the aim of amusement, do not match rehabilitation guidelines (i.e., use of meaningful functional activities, management of cognitive impairments through compensatory strategies and retraining skills (Wilson, 2008) posing the question of their applicability in this domain (Laver et al., 2011a). For this reason, *ad hoc* VG engines have been developed, based on these tracking devices, that do provide the monitoring and adaptation capabilities required by rehabilitation games (Pirovano et al., 2012). With a careful design of the virtual environments, rehabilitation sessions can become even more engaging for patients and increase their motivation (Thornton et al., 2005; Laver et al., 2011b; Pirovano et al., 2012). Enriched environments (Risedal et al., 2002), intense practice (Nudo et al., 2001), the possibility to tailor a rehabilitation session to patient's needs, to tune the degree of difficulty to patient's competences, and to enhance interaction during rehabilitation through an immediate feedback to the patient (Sveistrup, 2004) are the most promising features of VG approaches. It has also been suggested that a scenario including meaningful objects, rather than abstract geometric targets as stimuli, could be more motivating and encouraging for patients engaged in motor recovery programs leading to positive outcomes (Laver et al., 2011b; Sedda et al., 2013; Mainetti et al., 2013).

Nowadays, however, a simple view based only on the features of the programs cannot explain results obtained through VG platforms. Possible underlying mechanisms of brain reorganization after rehabilitation in virtual environments are unclear and could be far more complex. Nevertheless, there are several clues that they could ground mainly on two processes: (i) near/far spatial remapping, and (ii) multisensory integration. The role of these processes in recovery may be due to the multi-componential character of neglect syndrome (Milner and McIntosh, 2005; Hillis, 2006), as it may affect various domains, such as perception and mental representation in multiple sensory modalities.

Remapping of space (Berti and Frassinetti, 2000; Berti et al., 2001; Ansuini et al., 2006) is strongly connected to updating of the body schema representation (Neppi-Modona et al., 2007; Sedda et al., 2013; Mainetti et al., 2013), and may involve an action component which is associated with dorsal stream processing (Neppi-Modona et al., 2007; Sedda and Scarpina, 2012). The concepts of near/far space and reaching/locomotion can be can be taken into account as good examples to understand why more exhaustive models that considers the above mentioned concepts are needed. Reaching is an action that allows to bring the hand near to an object or to a spatial location. Consequently, space can be divided into within-reachable distance (near) and beyond-reachable distance (far). One peculiar feature of VG treatments is that although trained only in the far space, patients recover from neglect also in the peripersonal space (Kim et al., 2011; Sedda et al., 2013; Mainetti et al., 2013). In the past, the idea that an action could boost remapping of near-far space has been explored also with regards to locomotion (Berti et al., 2002), an action more often performed in everyday life than the grasping with tools. Locomotion involves the use of legs and allows humans and animals to move in space and change their position. The logic beyond this tentative experiment was mainly grounded on two assumptions: (i) far space is coded based on retinal coordinates, while near space is coded based on egocentric coordinates [meaning that in one case spatial position is reconstructed by computing the position of an object on the retina and the position of the eye in the orbit, while in the other case this computation is related not only to the body midline but also to body parts (Berti et al., 2002)] and (ii) locomotion is an effective action to reach the space in which a target object to be grasped is placed (Berti et al., 2002). However, this research highlighted that, at least for short, linear trajectories, remapping of space does not occur in neglect patients.

A possible explanation for the failure of spatial remapping during walking is that locomotion is only a mean to reach a location, but the action plans related to grasping are not active yet. In fact locomotion has its own neural networks (Sahyoun et al., 2004), makes use of different effectors than hand movements, and one can assume that during locomotion only the generic distance between the body and the object is computed, while fine graded movements representation are activated later, only when the hand is approaching the object. Furthermore, action representation for walking and for grasping are quite diverse and do not completely overlap (Sahyoun et al., 2004). The difference between these actions explains why models need to take into account also the concept of dorsal stream. The dorsal stream is devoted to planning and control of actions such as reaching and grasping, that require coordination between fingers, hands, and eyes as well as the computation of object size, their distance from the hand, their position in terms of egocentric coordinates, and in relation to a dynamic world in which targets and obstacles are moving (Sedda and Scarpina, 2012). Not all these features are considered in locomotion planning: for instance, object's size is not processed when planning to walk. Consequently, to parallel tools use to walking (Berti et al., 2002) one should assume that locomotion representations should transfer to hand grasping representations for a remapping to take place. Differently, when grasping with a tool and grasping with the hand, functionally related body segments are involved, allowing possibly an easier transferability of activations. Furthermore, the same features of the object are processed. Specifically, one can hypothesize that in case of a grasping movement the spatial remapping occurs due to the "action feedback" in the absence of a tactile or visual continuity obtained by means of a tool allowing to reach the far space (i.e., a long stick or a laser pointer) (Neppi-Modona et al., 2007). Congruently, recent studies suggest that the active visuo-motor learning of using a tool rather than its passive holding, leads to spatial adaptation and influences representation of space (Brown et al., 2011). This result strongly suggest an involvement of the dorsal stream in spatial remapping, at least when hand actions are required. This explanation might partially account for the success of VG based techniques making use of far (virtual) space to rehabilitate neglect also in peripersonal space. Performing real and functionally meaning actions could boost a spatial remapping more than a button press or walking toward the target. These hypotheses suggest that actions to be employed in VG base treatments should be carefully chosen.

In such view, however, it is necessary to consider that the well-known dissociation far and near space is not exhaustive to explain treatment success. One may speculate further that the multisensory integration facilitated by the immediate feedback provided by seeing one owns upper limb reflected in the far space while reaching objects, might facilitate the spatial remapping between far and near space through the updating of the body schema, which is strongly dependent on multisensory integration (Aglioti et al., 1996; Iriki et al., 1996; Berti and Frassinetti, 2000; Farne and Ladavas, 2000; Neppi-Modona et al., 2007; Sedda and Scarpina, 2012). Body schema refers to a dynamic representation of body parts in space, continuously updated during movement, distinct from the conscious and semantic description of the body that we can reach through awareness (Berlucchi and Aglioti, 2010). Implicit in this definition of body schema is its strong link with actions such as grasping and reaching. Importantly, VG treatments are more and more making use of the real dynamic silhouette of patients (Kim et al., 2011; Sedda et al., 2013; Mainetti et al., 2013). Rehabilitation platforms providing patients with their own image (Kim et al., 2011; Sedda et al., 2013; Mainetti et al., 2013) instead of avatars might favor the readaptation of a compromised body schema in an easier way than through cognition, as humans see their mirrored body since childhood (Beis et al., 2001). The patient is able to see his upper limb reflected into the virtual environment allowing him to perceive his movements time by time, benefiting unconsciously from the spatio-temporal congruency between real and virtual arm. Moreover the use of mirror images seems to improve the performance of right brain damaged patients with neglect when reaching objects located in the contralesional, ignored space (Ramachandran et al., 1999). In patients without cognitive dysfunctions such as spatial recalibration deficits or mirror ataxia (Beis et al., 2001) the real silhouette method might be a powerful mean to activate dorsal stream circuits, allowing a more fruitful rehabilitation path.

As a final remark, effectiveness of VG based treatments on diverse subtypes of neglect should be explored. For instance, these techniques might not be suitable for all neglect patients, considering that additional impairments such as somatoparaphrenia or perseverations might be present (Bottini et al., 2009). Somatoparaphrenia impacts body representation, while perseverations make visual search far more difficult. Together, somatoparaphrenia and perseverations undermine the interactive component of VG based tasks. Further, effectiveness of VG based treatment of patients with near or far only neglect might be different (Halligan and Marshall, 1991; Vuilleumier et al., 1998; Keller et al., 2005; Aimola et al., 2012) and should be explored. One could question whether patients showing only far neglect, not having near neglect, would not show the observed remapping between far and near space. It is not known whether these patients would improve in far space, as available studies only investigated the outcome in near space (Kim et al., 2011; Sedda et al., 2013; Mainetti et al., 2013). This implies that VG inspired studies should also adopt more fine graded assessment of neglect and related impairments, and samples selected *ad hoc* to allow within group contrasts, aimed at verifying the suitability of paradigms across different neglect subtypes.

Appropriate rehabilitation techniques may influence cognitive functions even in the chronic phase (Teasell et al., 2005). A *wider and enriched scenario* including *meaningful actions,* rather than abstract geometric targets as stimuli and movements that do not resemble reality, is more motivating, encouraging, and finally ecological for patients engaged in recovery programs (Laver et al., 2011b). For neglect patients, revisiting the classical visual search tasks (Bowen and Lincoln, 2007) through a VR environment might ensure more effective results not only because of the technological advanced equipment, but because this equipment allows to transfer classical theoretical concepts (such as those of body schema and action planning) in the rehabilitation field. New paradigms programing should take into account these theories and should try to integrate as many as possible of their principles, to reach optimal results in terms of impact on patients recovery.

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GENERAL COMMENTARY
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The influence of prism adaptation on perceptual and motor components of neglect: a reply to Saevarsson and Kristjansson

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A commentary on

A note on Striemer and Danckert's theory of prism adaptation in unilateral neglect
by Saevarsson, S., and Kristjansson, A. (2013). Front. Hum. Neurosci. 7:44. doi: 10.3389/fnhum.2013.00044

In a recent opinion paper we argued that prism adaptation (PA) primarily influences motor behaviors and spatial attention in neglect, but may have very little influence on perceptual biases (Striemer and Danckert, 2010b). Furthermore, we also suggested that the effects of PA on motor behaviors and spatial attention in neglect may arise via interactions with the dorsal "vision for action" pathway (Milner and Goodale, 2006), and the "dorsal attention network" that is important for allocating attention to specific locations in space (Corbetta and Shulman, 2002). Thus, we view alterations in shifts of attention following PA as being closely related to changes in motor behaviors (e.g., eye movements) following PA (i.e., the premotor theory of attention; Rizzolatti et al., 1987). See Striemer and Danckert (2010b) for discussion of the effects of PA on attention and motor behaviors and how this may lead to changes in visual imagery tasks.

Support for this hypothesis comes from a recent study (Striemer and Danckert, 2010b) in which we demonstrated that rightward PA reduced neglect patient's rightward bias on a manual line bisection task (i.e., marking the center of a line), but had no influence on their performance on a landmark task (judging whether a bisection marker was closer to the left or right end of a line). These results are consistent with other studies demonstrating that although PA influences exploratory motor behaviors (and covert attention) in neglect, they do not necessarily result in changes in perceptual biases (Dijkerman et al., 2003; Ferber et al., 2003; Sarri et al., 2006, 2010; for a review, see Striemer and Danckert, 2010a). For a similar dissociation between improved attention and bisection performance following PA with no changes in spatial working memory, see Saj et al. (2013).

In a recent opinion paper in *Frontiers in Human Neuroscience*, Saevarsson and Kristjansson (2013) suggest that the results of our recent study are not convincing because both of the tests we used involve "contralesional visual input, as well as eye movements, even when responses were made verbally" (i.e., the landmark task; Saevarsson and Kristjansson, 2013). Saevarsson and Kristjansson also highlight that "difficulties of many patients with shifting their gaze to the contralesional side" may be a critical factor in influencing performance. Based on these criticisms they suggest that the two tests were not capable of isolating "perceptual" and "premotor neglect."

There are a number of important points to note in reply to these comments. First, we never intended to use the line bisection and landmark tasks to *differentially* assess perceptual and premotor neglect. The purpose of using these tasks was simply to demonstrate that it is *possible* for PA to create beneficial effects for tasks that are completed with the motor effectors involved during adaptation (e.g., a motor response with the adapted hand) without necessarily changing the patient's perceptual bias.

Second, while it is clear that both the line bisection and landmark tasks require contralesional visual input and eye movements, it is unclear how this confounds our interpretation. Specifically, given that the stimuli for both tasks extended into both the left and right visual fields, that patients were allowed unlimited viewing time during both tasks, and that patients were free to make eye movements in both tasks, it is unclear how these factors could have led to the *dissociated* performance we observed (i.e., improvements on the line bisection but not the landmark task). Unfortunately, Saevarsson and Kristjansson (2013) do not construct a plausible alternative account of this dissociation.

Third, while difficulty in shifting gaze contralesionally may be a critical factor in influencing performance, previous studies have demonstrated that, following PA, patients do tend to make many more eye movements into contralesional space (Dijkerman et al., 2003; Ferber et al., 2003; Serino et al., 2006). However, this does not translate into changes in perceptual biases (Dijkerman et al., 2003; Ferber et al., 2003). Again, this provides additional support for our notion that changes in motor performance following PA do not translate into changes in perceptual biases. Of course Saevarsson and Kristjansson (2013) claim that these studies did not properly assess aspects of premotor neglect; however, neither study intended (or claimed) to do so.

Finally, while many studies have isolated the neural correlates of premotor neglect to the frontal lobes and basal ganglia (e.g., Sapir et al., 2007; Rossit et al., 2009a; Vossel et al., 2010), several authors have questioned whether premotor neglect is even an important component of the neglect syndrome (Coulthard et al., 2006; Himmelbach et al., 2007; Rossit et al., 2009b). Specifically, many of the premotor deficits in neglect are also present in right brain damaged patients without neglect. In this sense we view the issue as to whether the patient has been previously diagnosed as having "perceptual" or "premotor" neglect as largely irrelevant to interpreting the validity of our results. The fact of the matter is, regardless of how one attempts to fractionate neglect (in terms of patient diagnosis) it is clear that PA *can* influence motor behaviors *without* influencing perceptual biases (for an alternative view, see Newport and Schenk, 2012).

Saevarsson and Kristjansson (2013) also question our theory suggesting that it is unclear what role the dorsal stream might play in the beneficial effects of PA on premotor neglect. While we agree that it is not entirely clear what brain regions are responsible for the beneficial effects of PA in neglect, or what aspects of PA are critical for generating the beneficial effects (Aimola et al., 2012), it seems undeniable that the very brain regions that are directly involved in adaptation (which prominently include the dorsal stream) must play *some* role in generating the beneficial effects of PA in neglect (see Clower et al., 1996; Danckert et al., 2008; Shiraishi et al., 2008; Luaute et al., 2009; Saj et al., 2013).

In their opinion paper Saevarsson and Kristjansson (2013) proposed that in order for a neglect patient to demonstrate the beneficial effects of prisms they must have either premotor neglect, or a combination of visual neglect and premotor neglect, as visual neglect is assumed to play only a passive role in preventing de-adaptation. In essence, their proposal is quite similar to ours in that they suggest PA is more likely to exert its effects through influencing motor behaviors in neglect, although they focus more specifically on premotor neglect. While there is currently little data available to evaluate the validity of their hypothesis, it is certainly an interesting proposal that warrants future investigation.

In light of this, we are pleased to see that Saevarsson and Kristjansson (2013) and others have taken an active interest in this topic, as any additional knowledge obtained will only serve to help us better understand how PA remediates symptoms of neglect.

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Novel insights in the rehabilitation of neglect

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Visuospatial neglect due to right hemisphere damage, usually a stroke, is a major cause of disability, impairing the ability to perform a whole range of everyday life activities. Conventional and long-established methods for the rehabilitation of neglect like visual scanning training, optokinetic stimulation, or limb activation training have produced positive results, with varying degrees of generalization to (un)trained tasks, lasting from several minutes up to various months after training. Nevertheless, some promising novel approaches to the remediation of left visuospatial neglect have emerged in the last decade. These new therapy methods can be broadly classified into four categories. First, non-invasive brain stimulation techniques by means of transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), after a period of mainly diagnostic utilization, are increasingly applied as neurorehabilitative tools. Second, two classes of drugs, dopaminergic and noradrenergic, have been investigated for their potential effectiveness in rehabilitating neglect. Third, prism adaptation treatment has been shown to improve several neglect symptoms consistently, sometimes during longer periods of time. Finally, virtual reality technologies hold new opportunities for the development of effective training techniques for neglect. They provide realistic, rich, and highly controllable training environments. In this paper the degree of effectiveness and the evidence gathered to support the therapeutic claims of these new approaches is reviewed and discussed. The conclusion is that for all these approaches there still is insufficient unbiased evidence to support their effectiveness. Further neglect rehabilitation research should focus on the maintenance of therapy results over time, on a more functional evaluation of treatment effects, on the design and execution of true replication studies and on the exploration of optimal combinations of treatments.

Keywords: visuospatial neglect, treatment outcome, stroke, rehabilitation, novel treatments

INTRODUCTION

Visuospatial neglect is defined as an impairment whereby patients do not attend to visual stimuli or do not explore the visual half-space contralateral to their cerebral lesion (Heilman et al., 1993). It is usually the consequence of damage to the right hemisphere, most often due to an ischemic stroke. Visuospatial neglect is a major cause of disability, impairing the ability to perform a large range of everyday activities. Not eating food on the left part of the dish, bumping into obstacles on the left side, reading incomplete sentences in newspapers and ignoring objects on the left side are only a few impairments putting at risk the independence of stroke patients with left visuospatial neglect. Even without obvious signs of visuospatial neglect, stroke patients may suffer from subtle signs of neglect under increased attentional load (Bonato et al., 2010, 2013; Van Kessel et al., 2013a). Moreover, visuospatial neglect is often associated with other disabling symptoms like anosognosia and somatoparaphrenia. These co-morbidities may hamper the treatment of visuospatial neglect (see for example Borghese et al., 2013). Although some spontaneous recovery might take place until 2 or 3 months after stroke, visuospatial neglect persists in about one third of the patients (Kerkhoff and Schenk, 2012), leading to a chronic condition. More precisely, by using intensive serial measurements in the first months after stroke, Nijboer et al. (2013) were able to follow the exact course of recovery of visuospatial neglect in a group of 51 patients, using a line bisection and a letter cancelation test. The results show that after 12–14 weeks the recovery curves, as measured by a reduction of errors, grow flat, and spontaneous neurological recovery from neglect becomes invariant. Visuospatial neglect not only impairs patients in various visuospatial tasks, it is also associated with other consequences of stroke like problems with postural control, standing balance, and walking (Pérennou, 2006; Van Nes et al., 2009). It is considered to be a crucial factor influencing rehabilitation outcome, often leading to poor recovery from stroke (Jehkonen et al., 2006; DiMonaco et al., 2011; Vossel et al., 2013).

Given these premises, it is obvious that visuospatial neglect has been a target for rehabilitation since a long time. Starting in the early 1970s many rehabilitation techniques have been proposed to alleviate and reduce the problems generated by left visuospatial neglect. In a recent review Luauté et al. (2006a) distinguish and describe18 different approaches to the rehabilitation of neglect. In the present review we will describe the studies characterizing four of these approaches that have emerged since approximately a decade: prism adaptation (PA), virtual reality (VR) training, non-invasive brain stimulation (NIBS), and pharmacological therapies. Table S1 in Supplementary Material gives an overview of these studies (McIntosh et al., 2002, Angeli et al., 2004, Dijkerman et al., 2004, Jacquin-Courtois et al., 2008, Nijboer et al., 2011, Bauer et al., 2012, Luauté et al., 2012).

NON-INVASIVE BRAIN STIMULATION

The use of NIBS to improve impaired cognitive processes in neurologically impaired patients has recently received much attention (e.g., Miniussi and Vallar, 2011). More specifically, in neglect research, Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) have been used to ameliorate the symptomatology of patients with visuospatial disorders. With the aim to improve the duration of the after-effects of non-invasive stimulation methods, a particular form of TMS called Theta Burst Stimulation (TBS) has lately been introduced.

In order to understand the different forms of modulation of visuospatial functions by NIBS it is useful to describe the networks of attention involved in visuospatial neglect and to clarify the concept of interhemispheric rivalry. Visuospatial neglect is more and more seen as originating from a disruption of fronto-parietal networks of attention, particularly those of the right hemisphere (Thiebaut de Schotten et al., 2005; Bartolomeo et al., 2007; Committeri et al., 2007). Moreover, as proposed by Kinsbourne (1977, 1994), both parietal cortices also exert reciprocal interhemispheric inhibition. Therefore, injuries to the parietal areas of the right hemisphere do not only depress the activity of this area, they also cause disinhibition of the homolog areas of the left hemisphere. This overactivation of the left hemisphere aggravates the tendency of patients with visuospatial neglect to attend to the right and to neglect the left side. Empirical evidence for interhemispheric rivalry stems from the observation of patients with visuospatial neglect and from imaging research. Vuilleumier et al. (1996) observed a patient who had sequential strokes in both hemispheres. A first right-sided parieto-occipital infarct resulted in a severe left-sided neglect. However, about a week later, after a second infarct located in the left frontal lobe, the neglect symptoms abruptly subsided. In an fMRI study, Corbetta et al. (2005) noticed that in patients with visuospatial neglect, the intact left hemispheric orienting mechanism was relatively hyperactive. Recovery from neglect after 39 weeks showed a strong reactivation in several right hemisphere but also many left hemisphere regions, with a reduction of the activation imbalance between both hemispheres.

Starting from the idea of interhemispheric rivalry in visuospatial neglect, three non-invasive stimulation methods are basically conceivable: stimulation of the damaged right hemisphere brain areas, inhibition of the hyperactive intact left hemisphere, or both. Till now, the majority of NIBS studies targeting visuospatial neglect has been aimed at the inhibition of the left hemisphere.

Oliveri et al. (2001) were the first to apply contralesional parietal rTMS to five patients with right brain damage and two patients with left brain damage, all suffering from contralateral visuospatial neglect. rTMS was given during the presentation of bisected lines. Each transcranial stimulus train consisted of 10 stimuli delivered at a repetition frequency of 25 Hz during 400 ms. These trains started simultaneously with the appearance of the bisected lines on a monitor screen. After presentation, the subjects had to make a forced-decision about the length of the two bisected segments of each line with three response possibilities: equal, longer right, or longer left. To control for unspecific effects of rTMS, sham magnetic stimulation was intermingled with "real" rTMS trains. The results showed that rTMS of the unaffected hemisphere transiently decreased the magnitude of visuospatial neglect in both right and left lesioned patients as represented by wrong judgments, when compared with baseline (without rTMS) and sham rTMS trials.

Two years later, Brighina et al. (2003) applied low-frequency 1 Hz rTMS trains of 900 pulses in seven sessions over 14 days to three neglect patients with right brain damage. The pulses were given over the contralesional left parietal cortex. Visuospatial performance was assessed with the same task as in the Oliveri et al. (2001) study, namely making length judgments of prebisected lines presented on a computer screen. Unlike the Oliveri study, in which these judgments had to be given online, in the Brighina et al., study, the visuospatial line judgment task was administered four times: 15 days before treatment (T1), at the beginning of the treatment (T2), at the last day of the treatment (T3), and 15 days after (T4). At T1 and T2, a strong rightward bias was present in the patients. A significant amelioration of this bias was found after training (T3) and this improvement was still present 15 days after the end of the treatment (T4).

Other studies with small right brain lesioned patient groups and no control condition, using low-frequency rTMS inhibiting the left parietal cortex are those of Shindo et al. (2006), Koch et al. (2008), Song et al. (2009), and Lim et al. (2010). In the Shindo et al. (2006) study, six sessions of rTMS improved the performance of two right brain-damaged patients on several subtests of the Behavioral Inattention Test (BIT) up to 6 weeks after treatment. After a single low-frequency rTMS session, Koch et al. (2008) observed an improvement in the naming of visual chimeric figures in 12 right brain-damaged patients and in the Song et al. (2009) trial, two sessions of rTMS per day during 14 days ameliorated line bisection and line cancelation for up to 14 days after treatment in 7 patients with right brain damage. Lim et al. (2010) gave 1 Hz trains of 900 pulses for 5 days per week during 2 weeks to seven patients with right brain damage. They found that after training, line bisection had significantly improved, whereas line cancelation did not show gains. This dissociation can be explained by assuming that different brain areas underlie these tasks (see Ellison et al., 2004).

In contrast, one of the rare investigations in which the damaged right hemisphere was directly stimulated comes from Ko et al. (2008). Fifteen subacute stroke patients with visuospatial neglect after right hemisphere damage were recruited for this study. The study was designed as a double-blind, cross-over, sham-controlled experiment. All of the patients were stimulated with anodal (positive stimulation) and with sham tDCS in a counterbalanced and randomized order, with a 48-h interval between the two tDCS sessions. Anodal tDCS applied to the right posterior parietal cortex resulted in significant improvements of performance in a figure cancelation and a line bisection task immediately after brain polarization.

Sparing et al. (2009) tested the idea of interhemispheric rivalry most exhaustively. They treated 10 patients suffering from left visuospatial neglect with tDCS under the following conditions: (1) Anodal tDCS of the intact posterior parietal left hemisphere, (2) Cathodal (inhibiting) tDCS of the same area, (3) Anodal tDCS of the lesioned posterior parietal right hemisphere, and (4) Sham tDCS of the same hemisphere. The tDCS sessions were carried out on two separate days, with an intersession interval of at least 3 h and in a counterbalanced order of conditions across subjects. The authors conclude that both the inhibitory effect of cathodal tDCS applied over the intact left hemisphere as well as the facilitatory effect of anodal tDCS over the lesioned right hemisphere reduce symptoms of visuospatial neglect in a line bisection task but not on the neglect subtest of the TAP (Zimmermann and Fimm, 1995). Both tasks were administered before, immediately after and 20 min after the respective tDCS conditions.

Although the effects of rTMS seem to outlast the mere stimulation period, as shown above, these effects are only transient and their therapeutic benefits seem limited. In animal research, long-term potentiation (LTP) and long-term depression (LTD) of synaptic strength have been obtained with TBS. TBS is a high-frequency stimulation that is spaced at a frequency that mimics the theta wave, a spontaneous 5–7 Hz neural rhythm (Abraham, 2003).

As a proof-of-principle, Nyffeler et al. (2009) showed that several trains of TBS given to the left posterior parietal cortex of 11 neglect patient increased the number of perceived left visual targets for up to 32 h. Recently Koch et al. (2012) have investigated the efficacy of continuous TBS in 10 sessions over 2 weeks. The TBS trains were again applied to the left posterior parietal cortex of 18 neglect patients in the subacute stage of their illness. Scores on the BIT improved by 16.3% immediately after TBS application and by 22.6% at 1 month follow-up. In a double-blind, sham-controlled experiment, Cazzoli et al. (2012) applied four TBS trains to the left posterior parietal cortex of 16 neglect patients over two consecutive days. This resulted in a 37% improvement in the spontaneous everyday neglect behavior of the patients as measured by the Catherine Bergego Scale. This improvement was still present at 3 weeks after stimulation. The amelioration in neglect behavior was accompanied by better performances on several neglect tests. A control group of eight no-treatment (sham-stimulation) neglect patients did not show any progress.

PHARMACOLOGICAL THERAPIES

According to Singh-Curry and Husain (2010), two classes of drugs have been investigated for their potential therapeutical effects in the rehabilitation of neglect: dopaminergic and noradrenergic drugs. Dopamine and noradrenaline play essential roles in attention and thinking. They contribute to maintaining alertness, increasing focus and sustaining thought, and cognitive effort. A majority of trials have studied dopaminergic drugs, whereas noradrenergic compounds have only rarely been investigated.

The modulation of dopaminergic activity through pharmacological agents has produced mixed results in older as well as in more recent studies. Recent studies include the use of levodopa (Mukand et al., 2001) and amantadine (Buxbaum et al., 2007). Significant improvements were found on selected subtests of the BIT (conventional as well as behavioral subtests) and on the Functional Independence Measure (FIM, Keith et al., 1987) in three out of four neglect patients, after 1 week of treatment with carbidopa L-DOPA (Mukand et al., 2001). A small trial with amantadine administered to four neglect patients (Buxbaum et al., 2007) was performed using a double-blind, placebo-controlled design. Care was taken to obtain a stable baseline of performance in the first placebo phase, in order to make sure that changes in the amantadine administration stage were not due to random variation. Also, neglect was tested thoroughly with a large array of tests, a naturalistic action test (NAT, Schwartz et al., 2002) and the FIM. The results showed that a vast majority of the 17 measures employed showed no improvement. The most recent study (Gorgoraptis et al., 2012) investigated the effects of the dopamine agonist rotigotine on visuospatial neglect. The study was set-up as a double-blind, randomized, placebo-controlled ABA investigation with three phases: baseline, rotigotine administration, and return to baseline. The duration of each phase was randomized within limits and 16 neglect patients were included. Outcome measures were visual neglect tasks, visual working memory tests, selective attention and sustained attention tasks, and a measure of motor control. The results showed an improvement in visual search while on rotigotine, with the number of targets found on the left increasing by 12.8% and a spatial bias reduced by 8.1%, in comparison with being off rotigotine. Improvement in visual spatial search was associated with an amelioration of selective attention, but not with alterations in working memory, sustained attention, or motor performance.

Only one trial with noradrenergic medication has recently been performed. Malhotra et al. (2006) carried out a proof-of-principle trial with guanfacine, a noradrenergic agonist. Three chronic neglect patients participated in a double-blind cross-over trial and were tested six times with an extensive battery of paper-and-pencil tests and computerized tasks tapping spatial exploration. Two test sessions were for baseline purposes, after which a placebo (two measurements) or guanfacine (two measurements) was given. Two out of the three patients showed clear improvements in both tasks after the administration of guanfacine, but not after the placebo intake. Both patients also showed an improved ability to sustain attention during visual exploration following guanfacine. The authors attribute the absence of benefit for the third patient to the dorsolateral-prefrontal localization of his lesion, because animal research has evidenced that guanfacine exerts its beneficial effect through this area of the brain.

PRISM ADAPTATION

In the past decade, various authors investigated the effects of PA (a.o. Frassinetti et al., 2002; Serino et al., 2007, 2009; Vangkilde and Habekost, 2010 – see Table S1 in Supplementary Material) in neglect, as introduced in a seminal study by Rossetti et al. (1998). In PA, mostly rightward displacing prism goggles are used. Patients are asked to point to targets that are placed in front of them. The leftward compensatory shift in straight ahead pointing that is observed after removal of the prism goggles (i.e., the negative aftereffect) has been reported to alleviate neglect symptoms on paper-and-pencil tasks for some minutes after one training session (Rossetti et al., 1998), although Rousseaux et al. (2006) found no specific effects in a similar one-session study. PA is thought to create plastic changes in the sensori-motor system (Luauté et al., 2006b) and realignment of the egocentric coordinate system (Redding and Wallace, 2006) by means of the spatially remapping of patients' repeated pointing movements toward targets while they wear prism glasses, shifting the field of view to the right. Thus, PA may reduce the ipsilesional rightward bias that characterizes

RH neglect (Rode et al., 2003). For instance, in some uncontrolled trials, changes have been reported in eye movements (Shiraishi et al., 2008, 2010), global versus local processing of space (Bultitude et al., 2009) and wheelchair navigating toward left targets (Watanabe and Amimoto, 2010). However, a clear and unambiguous explanation of the working mechanism of PA is still lacking (Newport and Schenk, 2012).

Various authors investigated whether short-term ameliorations after PA could be converted into long-term therapeutic improvement. For instance, in a study by Frassinetti et al. (2002), seven neglect patients performed a pointing task wearing prismatic lenses in twice-daily sessions over a period of 2 weeks. Improvements on a series of paper-and-pencil and behavioral tests were observed in these patients, but not in six untreated controls. Training effects in the PA group were maintained till a final measurement 5 weeks after treatment, except in one patient who did not show the adaptation effect and had an unstable aftereffect. On the other hand, in a randomized trial, Nys et al. (2008) found greater improvement on paper-and-pencil tasks in acute neglect patients receiving PA for 4 days in a row when compared to control patients who did not, but this difference had disappeared after 1 month.

Using protocols of 2 weeks of repeated training sessions, longer lasting effects have been observed in other studies. For instance, Serino et al. (2009) compared PA to a neutral pointing control training in two matched groups of neglect patients. After 2 weeks of neutral pointing, the control group also received PA training. It was observed that patients' performances on paper-and-pencil tasks improved after both PA and neutral pointing, but the improvement was significantly more pronounced after PA. Moreover, after a second period of training using PA, the control group further improved up to the level reached by patients in the PA group. Improved performances on paper-and-pencil tasks were still observed a month after PA training.

Mizuno et al. (2011) conducted a RCT, comparing an experimental group ($N = 20$) of subacute neglect patients receiving PA training twice daily for 2 weeks to a control group ($N = 18$) that received similar training with neutral glasses. Pre- and post-training measures included the BIT, CBS, and FIM. Significantly more improvements on the FIM were observed in the PA group and significantly more improvement of both BIT and FIM in a subgroup with mild neglect symptoms receiving PA training. Effects lasting up to rehabilitation discharge (ranging from several weeks till few months after training) were observed.

However, in a similar RCT, Turton et al. (2010) found no differences between 16 post-acute neglect patients receiving a 2-week PA training and 18 patients receiving placebo treatment (i.e., wearing flat plain glasses) on neither self-care nor BIT performance, although both groups performed better after training than before.

In a study performed by Fortis et al. (2010), a comparison was made between a control condition consisting of a classic adaptation method (i.e., repeated pointing; Frassinetti et al., 2002) and an experimental adaptation method, involving ecological visuomotor activities. These were tasks like collecting coins, assembling puzzles, threading a necklace, and serving a cup of tea. Ten RH neglect patients were alternately assigned either to a program of 1 week of experimental followed by 1 week of control training or vice versa. Assessment tasks were administered at 1 week before treatment, at the beginning and ending of each treatment week and 1, 2, and 3 months after the end of treatment. Patients in both groups showed equal improvements after training on various neglect measures, the CBS and FIM. No relationship was found between neglect recovery and duration and disease.

Finally, PA has also been investigated in addition to other treatment methods, for instance neck muscle vibration. Saevarsson et al. (2010) applied neck muscle vibration in two groups of six RH neglect patients that were semi-randomly assigned to one of two conditions. Patients in both conditions received neck muscle vibration during a 20-min session. The experimental group received neck muscle vibration combined with PA for the same amount of time. Patients in both groups showed improved performance on a visual search task after treatment, but the patients that underwent the combined intervention showed clear improvements on visual search paper-and-pencil neglect tests that were not present in the group that only received neck vibration.

Various reviews on PA as a treatment method for neglect have been published recently (specifically Barrett et al., 2012; Newport and Schenk, 2012; Jacquin-Courtois et al., 2013). In each of these reviews, it is concluded that PA might be an effective therapy for patients with neglect. However, Barrett et al. (2012) emphasize that PA is not yet ready for broad administration in stroke rehabilitation and that it might be applied specifically for subgroups of patients presenting with motor-intentional "aiming" deficits. Newport and Schenk (2012) conclude that PA is only effective if training consists of 10 or more PA sessions. They argue that PA thus has become more and more similar to other, more traditional forms of neglect rehabilitation and might not fulfill initial promises. The authors stress the need for more research into the working mechanism of PA as well as the direct comparison with other rehabilitation techniques and more thorough investigation of ecologically relevant and long-term effects (see Shiraishi et al., 2010 for an exception: these authors performed a long-time follow-up using ecological measures). Fortis et al. (2010), based on the lack of a relationship between improvements after PA and duration of disease in their study, suggest that the treatment should be started as soon as clinically feasible and that the issue of post stroke intervals should be further explored. Finally, Jacquin-Courtois et al. (2013), despite some warnings about an ideal regime remaining to be defined more exactly, provide some practical guidelines for prism use in clinical practice. For instance, they recommend that 10–20 training sessions consisting of at least 60 pointing movements using sufficiently strong goggles (inducing at least 10° of visual displacement; see also Mancuso et al., 2012) are applied and that training only be given to patients showing a sufficient amount of aftereffect. Also, they indicate that the combination of techniques might provide future challenges as well as promises in neglect rehabilitation.

VIRTUAL REALITY

Virtual reality has been defined as "an advanced form of human-computer interface that allows the user to 'interact with' and become 'immersed in' a computer-generated environment in a naturalistic fashion" (Laver et al., 2011). In stroke rehabilitation, VR techniques have been evaluated predominantly in studies designed to improve motor function rather than cognitive function or activity performance. For instance, in their recent Cochrane review on the use of VR in rehabilitation, Laver et al. (2011) found limited evidence that the use of VR and interactive video gaming may be beneficial in improving arm function and ADL function when compared with the same dose of conventional therapy. They indicate that it is unclear at present which characteristics of VR are most important and that it is unknown whether effects can be sustained in the longer term.

In neglect patients, VR has been recently applied both for diagnostic purposes (Broeren et al., 2007; Buxbaum et al., 2008, 2012; Jannink et al., 2009; Kim et al., 2010; Van Kessel et al., 2010, 2013a; Fordell et al., 2011; Peskine et al., 2011; Dvorkin et al., 2012) and as a rehabilitation tool (Webster et al., 2001; Castiello et al., 2004; Katz et al., 2005; Ansuini et al., 2006; Kim et al., 2007, 2011; Smith et al., 2007; Sedda et al., 2012; Van Kessel et al., 2013b). In their review on the use of VR in the assessment and treatment of neglect, Tsirlin et al. (2009) argue that an important benefit of VR technologies is that they provide rich and realistic environments with a high level of control over their parameters and thus allow for training in a safe and cost effective way.

As a rehabilitation tool in neglect, VR has for instance been used to simulate grasping in space using a hand-motion tracking device (Castiello et al., 2004; Ansuini et al., 2006). In the VR tasks, dissociations were induced between real and simulated locations of stimuli, thus distorting the patients' representation of space. The authors argue that this might lead to the formation of novel neural circuitry governing visuo-proprioceptive integration, bearing resemblance to the effects of PA. Also Sedda et al. (2012), in a case study training a patient using a VR searching and grasping task, suggest that specific cognitive rehabilitation using VR may favor plastic reorganization of the brain.

In four case studies, Smith et al. (2007) had patients with mild neglect play computer games using a device translating the subjects' movements into the movements of an avatar on the screen. They report small improvements on paper-and-pencil tasks after six weekly training sessions. More recently, Kim et al. (2011) trained 24 RH neglect patients, randomly assigned to either a VR group or a control group. The VR group received training involving playing interactive computer games, the control group received conventional neglect therapy (i.e., reading, drawing, making puzzles). Both groups received therapy for 30 min a day, 5 days a week for 3 weeks. Differences in test scores between the start and end of training were significantly higher in the experimental group for two out of four measures (paper-and-pencil tasks and rating scales) that were used. The authors suggest that VR training may have a beneficial effect on unilateral spatial neglect after stroke.

Virtual reality has been applied to train patients to voluntarily compensate for their disorder in specific daily life situations. For instance, better performance on a real-life wheelchair obstacle course and less falling and accidents were reported in 20 neglect patients who received training by means of a desktop computer program involving sustained attention tasks and simulated wheelchair obstacle courses, compared to 20 untrained control patients with neglect (Webster et al., 2001). Katz et al. (2005) used a 12 session computer desktop-based training in which patients were required to press a button the moment they thought it safe to cross a virtual street. A group of 11 trained subjects improved more than eight controls on the practiced task and looked to the left more often in real street crossing after training, whilst performances on paper-and-pencil tasks did not differ between groups. In a preliminary study using a head-mounted device simulating crossing a street, Kim et al. (2007) found more symmetrical performance on the practiced task in 10 neglect patients after an unspecified number of training sessions, lasting till 3-month follow-up. Sedda et al. (2012), in a case study training a patient using a VR searching and grasping task, found significant amelioration on neuropsychological tests and self-reports of daily functioning. The authors suggest that specific cognitive rehabilitation using VR may favor plastic reorganization of the brain.

On the other hand, Akinwuntan et al. (2010) observed no differences between two groups of stroke patients with and without neglect participating in a large RCT ($N = 69$), receiving either simulator-based driving-related training or non-computer-based cognitive training for 15 h over 5 weeks. In fact, both groups showed significant but similar improvement in performance on a test of driving-related visual attention skills after training and benefits lasted up to 6 months after stroke. Van Kessel et al. (2013b) conducted a study in which visual scanning training (based on Pizzamiglio et al., 1990, 1992) was compared to an experimental condition consisting of a combination of visual scanning training and a VR driving simulator task. Twenty-nine subacute right hemisphere stroke patients were semi-randomly assigned to one of both conditions. On various neglect and driving simulator tasks, significant improvements after training were observed in both groups taken together, but no differences between groups were found. Thus, despite some promising results, no convincing evidence for the effectiveness of VR training has been reported till now.

CONCLUSION

The last decade has seen the emergence of four new treatment approaches in neglect rehabilitation: NIBS, pharmacological therapies, PA, and VR training have made their way through older and well-established treatment methods like visual scanning training and limb activation training. In the present review, a broad overview is given of the studies undertaken since the last decade to evaluate the effectivity of these new approaches in visuospatial neglect rehabilitation. A limitation of this survey is its non-systematic character, insofar as we did not include a scoring of the levels of evidence based on the used methodology. Therefore, it may contain a selection bias. Also, no meta-analyses of aggregated data are presented. Still, we believe that some conclusions may be drawn from the reported studies.

In general, the benefits of the new neglect rehabilitation techniques seem to be significant and may last for variable periods of time. In some cases the effects are still present after 2 months, especially when multiple training sessions have been applied. Unfortunately, in the majority of studies no long-term measurements have been performed. Moreover, visuospatial neglect is not an isolated symptom, but is often associated with symptoms like anosognosia, hemiparesis, or somatoparaphrenia. The absence of evaluation of these symptoms is clearly a limitation of the studies reviewed in the present paper. And lastly, the small sample sizes, the regular absence of control conditions and the explorative character of several studies restrict the reliability of their conclusions. So, despite encouraging results yielded by these new approaches Kerkhoff and Schenk's (2012) statement that "the initial hope for a quick cure for neglect after only one or a handful of treatment sessions has turned out to be unrealistic" still sounds true.

We think that the studies that we have reviewed are often proof-of-principle studies into new approaches in neglect rehabilitation. Therefore, much more research is needed in which several issues will have to be taken into account.

First, there is the point of generalization in time. Most studies have shown positive effects, but only for a limited time-window. In future studies it would be desirable to extend effect measurements up to 6 months after treatment, in order to establish the longer-term effects of the different treatments. TBS seems a promising candidate for LTP or depotentiation of synaptic plastic changes in patients with visuospatial neglect. More in general, one of the problems with novel treatments is also that they could be diversely effective depending on the time of treatment. Most studies do not consider this variable. A hypothesis might be that treatments stimulating an active participation by the patient might favor brain plasticity, but only in the chronic stage of the illness. Therefore, bottom-up techniques like drug treatments, PA, and NIBS (when no active tasks are used) might be more fitting in the acute stage, whereas VR treatments requiring an active (top-down) participation could be more useful in the chronic stage.

Second, there is the issue of measurement instruments. In the majority of studies, therapy effects are measured with neuropsychological tests. Only exceptionally, the efficacy of a treatment is also assesses on daily life neglect behavior. A more frequent use of instruments like the Catherine Bergego Scale (Azouvi et al., 2003) or the functional evaluation of neglect with a Semistructured Scale (Zoccolotti and Judica, 1991) is needed to evaluate the impact of treatment on the daily life neglect behavior of patients. This also applies to the above mentioned issue of subtle neglect revealed by increasing attentional load. Most studies use tests (e.g., paper-and-pencil) that are too coarse to identify these subtle forms of neglect and so these patients are not included in trials of neglect rehabilitation.

Third, true replication studies are needed. Within the approaches that we have reviewed, the difficulty was to make a true comparison between studies, due to differences in methodology, design, and patient populations. Although replication studies may seem less appealing, they are sorely needed in a field were much things are novel and risk to remain novel. Also, the number of studies that directly compare the effects of different training methods is very limited. Recently, Priftis et al. (2013) made an attempt to compare visual scanning training, limb activation training, and PA. Thirty-three neglect patients were quasi-randomly assigned one of these three training methods. All patients received 20 training sessions (two daily sessions during 2 weeks). Improvements on tests assessing the peripersonal space in everyday life activities were observed over the three conditions. However, no different treatment effects were observed between groups. Thus, the authors suggest that all three treatments might be considered as valid rehabilitation methods for neglect. We recommend that more studies investigating the differential effects of various training techniques are conducted.

Finally, Kerkhoff and Schenk's (2012) suggestion, that the true challenge will be to find the best combination of treatments for a given patient in order to maximize benefits, has not lost its strength. Likewise, Saevarsson et al. (2011) argue that combining various therapeutic techniques might be worthwhile, because of the heterogeneity of the neglect syndrome. A good mixture of treatment ingredients would be largely facilitated by more fundamental knowledge about the mechanisms of visuospatial neglect and research into these mechanisms should continue with the same intensity in the future. This knowledge might facilitate the choice of treatments suitable for individual patients.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/journal/10.3389/fnhum.2013.00780/abstract

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Rehabilitation interventions for unilateral neglect after stroke: a systematic review from 1997 through 2012

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A systematic review of the effectiveness of rehabilitation for persons with unilateral neglect (UN) after stroke was conducted by searching the computerized databases from 1997 through 2012. Randomized controlled trials (RCTs) of neglect treatment strategies for stroke patients which used the Behavioral Inattention Test (BIT) as the primary outcome measure were eligible for inclusion. Out of 201 studies initially identified, 12 RCTs covering 277 participants were selected for analysis. All had the same weakness of low power with smaller samples and limitation in the blinding of the design. Prism Adaptation (PA) was the most commonly used intervention while continuous Theta-burst stimulation (cTBS) appeared to be a new approach. Meta-analysis showed that for immediate effects, the BIT conventional subscore had a significant and large mean effect size (ES = 0.76; 95% CI 0.28–1.23; $p = 0.002$) whereas the BIT total score showed a modestly significant mean ES (ES = 0.55; 95% CI 0.16–0.94; $p = 0.006$). No significant mean ES in sensitivity analysis was found for long-lasting effects across all BIT outcomes. PA appeared to be the most effective intervention based on the results of pooled analysis. More rigorous studies should be done on repetitive transcranial magnetic stimulation (rTMS) before it can be concluded that it is a promising treatment for UN.

Keywords: systematic review, stroke, unilateral neglect, rehabilitation, Behavioral Inattention Test

INTRODUCTION

Unilateral neglect (UN) is a heterogeneous perceptual disorder that often follows stroke, especially after right hemisphere lesion. Its most typical feature is failure to report or respond to stimuli presented from the contralateral space, including visual, somatosensory, auditory, and kinesthetic sources. Sufferers may even fail to perceive their own body parts (Mesulam, 1999). The reported incidence varies from 10 to 82% following right- and from 15 to 65% following left-hemisphere stroke (Plummer et al., 2003). Subject selection criteria, lesion site, the nature and timing of the assessment, and lack of agreement on assessment methods are all responsible for the variability in these reported rates (Stone et al., 1991; Azouvi et al., 2002). UN has a significant negative impact associated with functional recovery at home discharge (Jehkonen et al., 2006; Mutai et al., 2012).

Different treatment approaches and assessment tools have been developed to evaluate and address UN. The most recent literature shows that rehabilitation can be classified under two types of behavioral approaches: recruiting the hemiplegic limbs to reduce spatial preference for the ipsilesional space, or improving awareness of the contralesional space to promote patients' attention (Pierce and Buxbaum, 2002; Paci et al., 2010). More than 18 methods using these general approaches have been put into practice (Luauté et al., 2006) with varying results based on a large number of outcome measures. Although the reported quality is moderate for most of the RCTs in neglect rehabilitation (Paci et al., 2010), some interventions appear to be more promising. Comments have also been made that the effects of treatment are often task-specific or transient and cannot be generalized to daily functioning (Pierce and Buxbaum, 2002; Bowen et al., 2007). Due to a lack of evidence, it is also hard to report which approach is the optimal recommendation for clinical practice (Luauté et al., 2006), and interestingly, professional therapists rarely use these scientifically proven interventions (Petzold et al., 2012).

Many RCTs have employed "pencil-and-paper" tasks, including line bisection, cancelation tasks, copying, and drawing, as treatment outcomes for UN. One of the commonest tests, and one that has been used extensively as an outcome measure for UN, is the Behavioral Inattention Test (BIT) (Bowen et al., 1999, 2007). This is a criterion-referenced test for UN or visual inattention in patients suffering from stroke or brain injuries, comprising two parts: the conventional and the behavioral subtests (Halligan et al., 1991). The conventional subtests include six traditional paper-and-pencil tasks: line crossing, letter cancelation, star cancelation, figure copying, line bisection, and representative drawing. The behavioral subtests consist of nine simulated daily living tasks: picture scanning, telephone dialing, menu reading, article reading, telling and setting the time, coin sorting, address and sentence copying, map navigation, and card sorting. Both parts can be used separately in clinical for impairment and function level assessments, and it has been recommended as a good predictor of functional performance in daily living with good construct and predictive validity (Hartmanmaeir and Katz, 1995).

The aim of this study was to develop a systematic review to assess the effectiveness of rehabilitation for UN as measured by the BIT and to evaluate the effects of the interventions reported in the RCTs using a meta-analysis.

METHODS

DATABASE

We searched the following electronic databases for trials published in English; PubMed/Medline (1965+ via EbscoHost), PsycINFO (1806+), physiotherapy evidence database (PEDro), Science Direct, CINAHL (Cumulative Index to Nursing and Allied Health Literature, 1982+), and Cochrane Central Register of Controlled Trials (CENTRAL). We also hand-searched the bibliographies of all studies ordered in full text. Date of publication was limited from January 1997 to June 2012 as most of the full-text electronic versions of journal papers are available since 1997.

The terms used in the search were: cerebrovascular accident OR stroke; neglect; visuo-spatial neglect; visual neglect; unilateral neglect; and hemisphere neglect. The search was limited to RCTs involving adults aged 19 or over.

SELECTION CRITERIA

We included all RCTs that sought to identify the effectiveness of any type of rehabilitation intervention in UN in adult stroke patients diagnosed by clinical examination and/or classical neuropsychological tests. Only studies which reported the BIT (Wilson et al., 1987) as the primary outcome measure were included. The BIT includes a score for the conventional subtest (BIT-C) and/or the behavioral subtest (BIT-B) as well as the total score [BIT (Total)].

We excluded observational studies and case reports as well as cross-over design studies; studies where full text was not available; studies with a sample size of less than five in each group; and those rated as 4 or less out of 10 by the PEDro in the quality assessment described below. Cross-over design studies were excluded in our review as they usually confounded the estimates of the treatment effects with carry-over and learning effects (Leslie and Mary, 2007).

QUALITY ASSESSMENT

After the database search, two reviewers assessed the methodological quality of the trials according to the PEDro scale. This was developed specifically for evaluating the quality of studies aiming to compare the effectiveness of rehabilitation (Verhagen et al., 1998; Sherrington et al., 2000) and has been proved to be valid in measuring the methodological quality of clinical trials. There are 11 items in the PEDro scale. The first criterion, item eligibility, is not scored as it is used as a component of external validity; the remaining items yield a total score from 10 (RCT that meets all items) to 0 (RCT that does not meet any item) (Paci et al., 2010). The PEDro scale item scores can be summed to obtain a total score that can be used as interval data for parametric statistical analysis (Bhogal et al., 2005; de Morton, 2009). The PEDro scale classifies studies as high or low quality based on a cut-off score of six (Maher et al., 2003). Articles scoring six or higher are considered of high quality and low-quality studies score less than six.

DATA EXTRACTION AND ANALYSIS

Each selected study was carefully assessed against the inclusion criteria, and the necessary information and characteristics summarized in a table. We calculated Cohen's d on individual treatment effect size (ES) for these studies and compared the effectiveness among different interventions. Meta-analysis on overall treatment effectiveness was done with Review Manager Version 5.0 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2012). The standardized mean difference (SMD) was presented as the ES and its 95% confidence interval (CI) computed. Because of the heterogeneity of the interventions, we could only perform a pooling for meta-analysis for a single intervention reported in two or more trials. The test of heterogeneity was used to assess the potential heterogeneity across studies. If heterogeneity existed, a random-effect model was used. The random-effect approach assumes that the ES from each trial is a random sample from a larger population of possible ES. Otherwise, the fixed-effect model was used. A sensitivity analysis was also used to assess the impact of overall treatment effectiveness by excluding each trial once at a time.

RESULTS

Figure 1 illustrates the selection process. The initial search yielded 201 citations from January 1997 through June 2012. After removing duplicates, 153 citations remained. Based on the title and abstract of the articles, 32 potentially relevant articles were selected. After careful evaluation by the reviewers, we identified 25 clinical trials (Wiart et al., 1997; Robertson et al., 2002; Harvey et al., 2003; Pizzamiglio et al., 2004; Katz et al., 2005; Fong et al., 2007; Nys et al., 2008; Schroder et al., 2008; Ertekin et al., 2009; Luukkainen-Markkula et al., 2009; Polanowska et al., 2009; Serino et al., 2009; Song et al., 2009; Tsang et al., 2009; Saevarsson et al., 2010; Turton et al., 2010; Ferreira et al., 2011; Kamada et al., 2011; Kim et al., 2011; Làdavas et al., 2011; Mizuno et al., 2011; Welfringer et al., 2011; Gorgoraptis et al., 2012; Ianes et al., 2012; Koch et al., 2012) to be included in the final assessment. Of these, 12 articles were included in our final review (Robertson et al., 2002; Harvey et al., 2003; Fong et al., 2007; Nys et al., 2008; Luukkainen-Markkula et al., 2009; Serino et al., 2009; Tsang et al., 2009; Turton et al., 2010; Ferreira et al., 2011; Làdavas et al., 2011; Mizuno et al., 2011; Koch et al., 2012) with the others excluded because the BIT was not used as the primary outcome measure.

The quality of all 12 RCTs was fair to good (**Table 1**). Four (33.3%) were identified as of fair quality as their scores were below six in the scale. Two studies (Mizuno et al., 2011; Koch et al., 2012) used double-blind designs whereas others were mostly single-blind.

CHARACTERISTICS OF THE STUDIES

Descriptions of the 12 articles reviewed are listed in **Table 2**. A total of 277 subjects with UN were included in this analysis. All were adults with right brain damage due to stroke; most had a diagnosis of first single right hemisphere stroke. The duration from stroke onset to study covered the period from the acute (≤4 weeks) to the chronic phase (≥6 months), but most studies were conducted in the subacute and chronic phases after stroke. All studies used similar selection criteria.

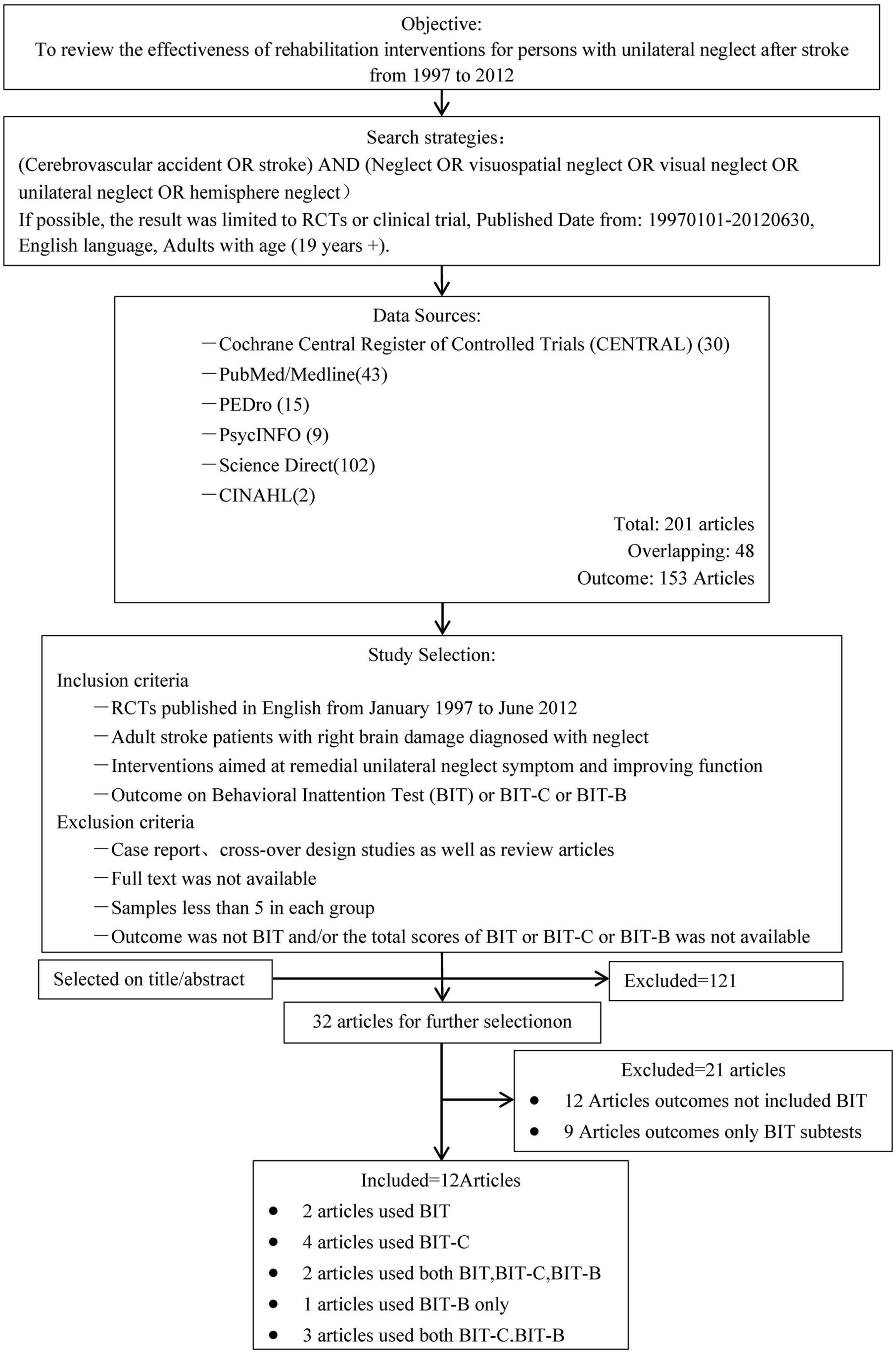

FIGURE 1 | Overview of the search and selection process.

Among the 12 studies, 5 (Nys et al., 2008; Serino et al., 2009; Làdavas et al., 2011; Mizuno et al., 2011) studied the effectiveness of prism adaptation (PA). There were differences in the PA procedure used; one study (Nys et al., 2008) used repetitive PA for a short period while another used different feedback strategies in PA (terminal and concurrent prism adaptation). During terminal PA, only the final part of the pointing movement is visible and PA relies most strongly on a strategic recalibration of visuomotor eye–hand (Làdavas et al., 2011). In contrast, in concurrent PA the second half of the pointing movement is visible, and thus adaptation mainly consists of a realignment of proprioceptive coordinates (Làdavas et al., 2011). All five studies used the same control methods with neutral goggles. Two articles (Robertson et al., 2002; Luukkainen-Markkula et al., 2009) applied limb activation. Other studies used

Table 1 | PEDro scores of included studies.

Studies	Eligibility	1, Random allocation	2, Concealed allocation	3, Baseline comparability	4, Blind subjects	5, Blind therapists	6, Blind assessors	7, Adequate follow-up	8, Intention-to-treat analysis	9, Between-group comparisons	10, Point estimates variability	Score	Quality
ITEMS													
Nys et al. (2008)	Yes	1	0	1	1	0	0	1	0	1	1	6/10	Good
Serino et al. (2009)	Yes	0	0	1	1	0	0	1	0	1	1	5/10	Fair
Turton et al. (2010)	Yes	1	1	0	0	0	1	1	0	1	1	6/10	Good
Mizuno et al. (2011)	Yes	1	1	1	1	0	1	1	0	1	1	8/10	Good
Làdavas et al. (2011)	Yes	1	0	1	1	0	1	0	0	1	1	6/10	Good
Robertson et al. (2002)	Yes	1	0	1	0	0	1	1	0	1	1	6/10	Good
Luukkainen-Markkula et al. (2009)	Yes	1	1	1	0	0	0	1	0	0	1	5/10	Fair
Fong et al. (2007)	Yes	1	0	1	0	0	1	1	0	1	1	6/10	Good
Tsang et al., 2009	Yes	1	1	1	0	0	1	0	0	1	1	6/10	Good
Harvey et al. (2003)	Yes	1	0	1	1	0	0	1	0	1	0	5/10	Fair
Koch et al. (2012)	Yes	1	1	1	1	1	1	1	0	1	1	9/10	Good
Ferreira et al. (2011)	No	1	0	1	0	0	0	1	0	1	1	5/10	Fair

different interventions; visuomotor feedback, virtual reality, repetitive transcranial magnetic stimulation (rTMS), and continuous Theta-burst stimulation (cTBS). Compared to a previous review (Luauté et al., 2006), no new intervention was reported in our review during the time period stated except for cTBS. All studies investigated a single treatment, except for one RCT (Fong et al., 2007) which investigated the effectiveness of a combination of two different methods, namely trunk rotation and eye patching.

The duration of treatment ranged from 4 days (Nys et al., 2008) to 5 weeks (Ferreira et al., 2011), but for half of the studies was 30 min per session for 5 sessions per week over 2 weeks, giving a total of 10 sessions. All the trials were conducted in hospitals except for one (Harvey et al., 2003) which involved self-administered home-based practice for 2 weeks.

Apart from the BIT, the outcome for neglect severity included the Catherine Bergego Scale (CBS), the Bell Cancelation Test, reading, computerized visual search tasks, and paper-and-pencil neglect tests. In all studies, functional outcomes were included, namely the Functional Independence Measure, the Barthel Index, upper limb motor functions (the Wolf Motor Function Test and the Modified Motor Assessment Scale), and the Stroke Impairment Assessment Set.

Three studies (Serino et al., 2009; Turton et al., 2010; Ferreira et al., 2011) used the BIT (Total) only; three (Nys et al., 2008; Làdavas et al., 2011; Mizuno et al., 2011) used both the BIT-C and the BIT-B separately as outcomes; and two (Fong et al., 2007; Koch et al., 2012) used the BIT (Total) and both the BIT-C and BIT-B as outcomes. Only one study (Robertson et al., 2002) used only the BIT-B as the outcome.

Effects of rehabilitation interventions

We applied a meta-analysis on all outcomes to calculate SMD and 95% CI using random-effects models. A comparison of the results of both the immediate and long-lasting effects is presented in forest plots (**Figures 2** and **3**).

Immediate effects of interventions

Figure 2 shows the forest plot of the immediate effects of the interventions covered in the 12 studies. The meta-analysis shows that there was significant heterogeneity across the studies, so the random-effect model was chosen. The BIT-C had a significant mean ES of 0.76 (95% CI, 0.28–1.23; $p = 0.002$). The BIT-B showed an insignificant mean ES of 0.37 (95% CI, −0.19 to 0.91; $p = 0.17$), and the BIT (Total) a statistically significant mean ES of 0.55 (95% CI, 0.16–0.94; $p = 0.006$). The sensitivity of each trial on the mean ES was also assessed by excluding each trial one at a time. The overall results were the same even when any single trial was eliminated.

Long-lasting effects of rehabilitation interventions

Figure 3 shows the forest plot of the long-lasting effects of the interventions studied. The meta-analysis shows that none of the ES were significant for the BIT outcomes except the BIT-C ($p = 0.05$). The sensitivity of each trial on the mean ES was also evaluated by excluding one trial at a time, but the results were not significant ($p > 0.05$).

To find out the optimal intervention for UN, Cohen's d was calculated on the individual ES of each approach as the difference between the pre- and posttest means for the single treatment group

Table 2 | Characteristics of included studies.

Studies	Methods					Interventions			BIT results	
	Type	Study design	Control	Groups subjects (*n*)	Duration from onset to treatment	Treatment	Regime	Duration	Immediate	Long-term
Nys et al. (2008)	PA	single-blind RCT	Placebo (neutral goggles)	$n = 16$ PA gp = 10 CT gp = 6	≤4 weeks	Wore pair of goggles fitted with wide-field point-to-point prismatic lenses shifted their visual field 10°/0° rightward and do some fast pointing movements	30 min/session 4-days-in-row sessions	4 days		BIT-C (−); BIT-B (−); follow-up = 1 month
Serino et al. (2009)	PA	single-blind pseudo-RCT	Placebo (neutral goggles)	$n = 20$ PA gp = 10 CT gp = 10	≥1 month	Wore prismatic lenses, which shifted their visual field 10°/0°rightward and pointing movements	30 min/Session 10 daily sessions within 2 weeks	2 weeks	BIT (+)	BIT (+); follow-up = 1 month
Turton et al. (2010)	PA	single-blind RCT	Placebo (flat plain glass)	$n = 36$ PA gp = 17 CT gp = 19 (1 drop-out) (1 drop-out)	≥20 days	Wore 10 diopter, 6 degree prisms using index finger to touch a bold vertical line on screen	Once a day, each working day	2 weeks	BIT (−)	BIT (−); follow-up = 8 weeks
Mizuno et al. (2011)	PA	double-masked RCT	Placebo (neutral glasses)	$n = 38$ PA gp = 18 CT gp = 20	≤3 months	Wore prism glasses shifted visual field 12° to right and repeat pointing tasks	20 min/Session bid, 5 days/week	2 weeks	BIT-C (−); BIT-B (−)	BIT-C (−); BIT-B (−); follow-up until discharge
Làdavas et al. (2011)	PA	single-blind pseudo-RCT	Placebo (neutral glasses)	$n = 30$ TPA gp = 10 CPA gp = 10 CT gp = 10	≥2 months	Wore wide-field prismatic lenses inducing a 10° shift visual field to right and repeat pointing tasks	30 min/Session one per day, 10 sessions	2 weeks	TPA:BIT-B (+); BIT-C (+); CPA:BIT-C (−); BIT-B (−)	No follow-up
Robertson et al. (2002)	LA	single-blind RCT	Dummy device	$n = 40$ LA + PT = 19 (2 drop-out) PT = 21 (2 drop-out)	LA: 152.8 ± 142.4 PT: 152.1 ± 117.9	Using a semi-automatic device for limb activation combined with perceptual training	45 min/Session once a week 12 sessions	12 weeks	BIT-B (−)	BIT-B (−); follow-up = 18–24 months
Luukkainen-Markkula et al. (2009)	LA	single-blind RCT	Conventional visual scanning training	$n = 12$ LA gp = 6 CT gp = 6	≤6 months	Arm activation training (determined by the individual hand and arm motor status assessed by WMFT)	Total 48 h of therapy	3 weeks	BIT-C (+)	BIT-C (+) follow-up = 6 months

(Continued)

Table 2 | Continued

Studies	Methods					Interventions			BIT results	
	Type	Study design	Control	Groups subjects (*n*)	Duration from onset to treatment	Treatment	Regime	Duration	Immediate	Long-term
Fong et al. (2007)	TRTR + EP	single-blind RCT	Conventional OT	$n=54$ TR gp = 19 TR + EP gp = 20 CT gp = 15	≤8 weeks	Trunk rotation was performed in three different positions: supine lying on a plinth, unsupported sitting on a plinth, and standing in a standing frame	1 h/Session 5 times/week	30 days	BIT-B (−); BIT-C (−); BIT (−)	BIT-B (−); BIT-C (−); BIT (−); follow-up = 60 days
Tsang et al. (2009)	EP	single-blind RCT	Conventional OT	$n=34$ EP gp = 17 CT: 22.18 ± 15.87 CT gp = 17	EP: 21.5 ± 21.67	Underwent occupational therapy with special glasses blocking the right half visual field	30 min ADL +30 min NDT for UL/day	4 weeks	BIT-C (+)	No follow-up
Harvey et al. (2003)	VF	RCT	Same activities but without feedback	$n=14$ VF gp = 7 CT gp = 7	5–25 months	Experimenter-administered practice of rod lifting with judge center grids for proprioceptive and visual feedback	1 h/day with 3 days, then 10 days of home-based intervention	3 days/ 2 weeks	BIT-C (+); BIT-B (−)	BIT-C (+); BIT-B (−); follow-up = 1 month
Koch et al. (2012)	TBS	double-blind RCT	Sham coil angled 90°	$n=18$ TBS gp = 9 CT gp = 9	≥1 months (43 ± 16 days)	3-pulse bursts at 50 Hz repeated every 200 ms for 40 s, 80% AMT over the left PPC	2 Sessions/day, 15 min interval; 5 days/week	2 weeks	BIT-B (+); BIT-C (+); BIT (+)	BIT-B (+); BIT-C (+); BIT (+); follow-up = 1 month
Ferreira et al. (2011)	MP VST	single-blind RCT	Conventional PT without any treatment for neglect	$n=15$ MP gp = 5 VST gp = 5 CT gp = 5	≥3 months	VS: the protocol included 4 tasks: 2 directed to the extrapersonal space and 2 addressing peripersonal neglect; MP: included 4 tasks: 2 tasks of motor imagery and 2 of visual imagery	1 h/Session twice per week	5 weeks	VST: BIT-C (+); MP: BIT-C (−)	VST: BIT-C (+); MP:BIT-C (−) follow-up = 2 months

PA, prism adaptation; LA, limb activation; TR, trunk rotation; EP, eye patching; VF, visuomotor feedback; TBS, theta-burst stimulation; MP, mental practice; VST, visual scanning training; BIT (Total), total score on Behavioral Inattention Test; BIT-C, BIT conventional subtest; BIT-B, BIT behavioral subtest; OT, occupational therapy; PT, physiotherapy.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 BIT-C								
Ferreira et al. 2011	123.8	9.84	5	106.2	16.64	5	2.7%	1.16 [-0.24, 2.56]
Fong et al(1). 2007	100.9	38.1	19	78.6	49.2	15	5.9%	0.50 [-0.19, 1.19]
Fong et al(2).2007	87.1	40.2	20	78.6	49.2	15	6.0%	0.19 [-0.48, 0.86]
Harvey et al. 2003	118.4	13.36	5	92.2	25.84	5	2.7%	1.15 [-0.25, 2.55]
Luukkainen-Markkula 2009	100.9	30.9	6	88.8	48.6	6	3.6%	0.27 [-0.87, 1.41]
Làdavas et al(1). 2011	129	6.2	10	110	6.2	10	2.9%	2.94 [1.59, 4.28]
Làdavas et al. (2)2011	118	6.2	10	110	6.2	10	4.3%	1.24 [0.26, 2.21]
Mizuno et al. 2011	117.5	26	17	117.2	33.9	17	6.0%	0.01 [-0.66, 0.68]
Tsang et al. 2009	25.06	30.81	17	8.29	10.35	17	5.9%	0.71 [0.02, 1.41]
Subtotal (95% CI)			**109**			**100**	**40.0%**	**0.76 [0.28, 1.23]**
Heterogeneity: Tau² = 0.29; Chi² = 19.39, df = 8 (P = 0.01); I² = 59%								
Test for overall effect: Z = 3.13 (P = 0.002)								
1.1.2 BIT-B								
Fong et al(1). 2007	44.2	20.8	19	40.4	26	15	6.0%	0.16 [-0.52, 0.84]
Fong et al(2).2007	44.6	27.3	20	40.4	26	15	6.0%	0.15 [-0.52, 0.82]
Làdavas et al(1). 2011	64	4.2	10	54	4.2	10	3.4%	2.28 [1.10, 3.46]
Làdavas et al. (2)2011	57	4	10	54	4.2	10	4.6%	0.70 [-0.21, 1.61]
Mizuno et al. 2011	62.5	15.2	17	65.7	20.8	17	6.0%	-0.17 [-0.85, 0.50]
Robertson et al. 2002	30.2	11.9	19	31.2	11.9	21	6.3%	-0.08 [-0.70, 0.54]
Subtotal (95% CI)			**95**			**88**	**32.4%**	**0.37 [-0.16, 0.91]**
Heterogeneity: Tau² = 0.29; Chi² = 15.07, df = 5 (P = 0.01); I² = 67%								
Test for overall effect: Z = 1.37 (P = 0.17)								
1.1.3 BIT(Total)								
Fong et al(1). 2007	145.6	55.7	19	119.1	74.1	15	5.9%	0.40 [-0.28, 1.09]
Fong et al(2).2007	131.7	66.1	20	119.1	74.1	15	6.0%	0.18 [-0.49, 0.85]
Koch et al. 2012	190	9.8	9	174	11	9	3.9%	1.46 [0.39, 2.53]
Serino et al. 2009	95	6	16	81	20	18	5.8%	0.90 [0.19, 1.61]
Turton et al. 2010	14.8	18.8	16	9.7	15.9	18	6.0%	0.29 [-0.39, 0.96]
Subtotal (95% CI)			**80**			**75**	**27.6%**	**0.55 [0.16, 0.94]**
Heterogeneity: Tau² = 0.06; Chi² = 5.66, df = 4 (P = 0.23); I² = 29%								
Test for overall effect: Z = 2.74 (P = 0.006)								
Total (95% CI)			**284**			**263**	**100.0%**	**0.57 [0.29, 0.84]**
Heterogeneity: Tau² = 0.21; Chi² = 43.50, df = 19 (P = 0.001); I² = 56%								
Test for overall effect: Z = 4.06 (P < 0.0001)								
Test for subgroup differences: Chi² = 1.13, df = 2 (P = 0.57), I² = 0%								

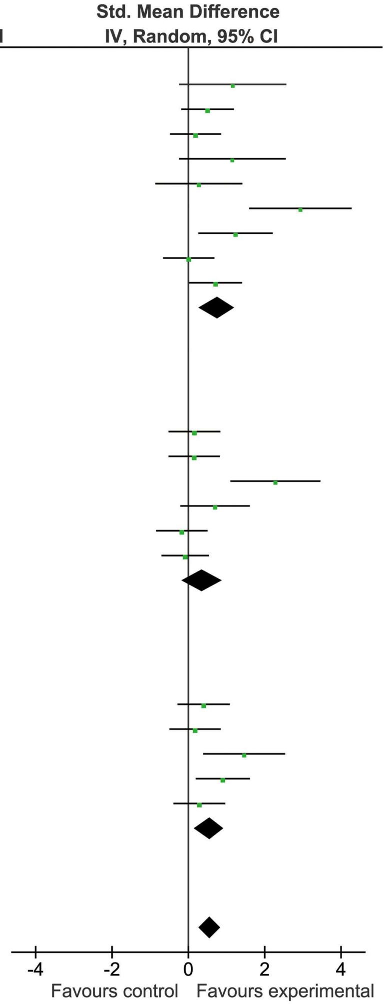

FIGURE 2 | Rehabilitation interventions versus any control, outcome: immediate effects.

divided by the SD of the pretest scores. There was more than one paper covering PA, so we pooled the ES of PA in three studies for the BIT-C, two for the BIT-B, and two for the BIT (Total) before conducting a relative comparison of the ES of all studies. The results showed that for immediate effects, after pooling, PA had the highest ES as measured by the BIT-C and the BIT-B, while cTBS had the highest ES measured by the BIT (Total). All interventions showed low ES for long-lasting effects (**Tables 3** and **4**).

Pooled effects of PA on UN

The pooled ES of the single intervention PA on each BIT outcome were also analyzed (**Table 5**). No statistically significant results were found for either immediate or long-lasting effects as reflected in the BIT outcomes with significant heterogeneity.

DISCUSSION

Our systematic review indicates that there is modest evidence for the use of PA to reduce UN in stroke, with immediate and long-lasting effects, and eye patching as shown by BIT-C scores for immediate effects. Other studies obtained positive effects from the use of visual scanning training (Ferreira et al., 2011), visuomotor feedback (Harvey et al., 2003), and TBS (Koch et al., 2012). Since Koch et al. (2012) only report the BIT (Total) and not the BIT-C and BIT-B subscale scores, it is impossible to draw any conclusion that rTMS is better than PA in improving the performance of tasks in the BIT-C and the BIT-B for neglect patients as no comparison could be done.

According to this review, PA is inclined to exhibit the highest ES for immediate effects, but this was not statistically significant as the 95% CI crossed over the zero point. The possible neural mechanism underlying the therapeutic effect of PA is that it reduces spatial neglect by enhancing the recruitment of intact brain areas responsible for visuo-spatial output through short-term sensorimotor plasticity pathways (Rossetti et al., 1998; Luauté et al., 2006). Although this technique has produced some improvement in a wide range of neglect symptoms, especially visual (Shiraishi et al., 2010; Mizuno et al., 2011; Rusconi and Carelli, 2012), some contradictory results have also been reported (Ferber et al., 2003;

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 BIT-C								
Fong et al(1). 2007	100.9	36.6	14	88.8	54.8	12	6.8%	0.26 [-0.52, 1.03]
Fong et al(2).2007	101.3	45.3	20	88.8	54.8	12	7.8%	0.25 [-0.47, 0.97]
Luukkainen-Markkula 2009	131	11.5	6	124.5	18.9	6	3.1%	0.38 [-0.76, 1.53]
Mizuno et al. 2011	133	10.1	16	119	26.9	15	7.6%	0.68 [-0.05, 1.41]
Nysa et al. 2008	123.2	25.1	10	116.5	36.5	6	4.0%	0.21 [-0.80, 1.23]
Subtotal (95% CI)			**66**			**51**	**29.3%**	**0.37 [0.00, 0.74]**
Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 4 (P = 0.91); I² = 0%								
Test for overall effect: Z = 1.96 (P = 0.05)								
1.2.2 BIT-B								
Fong et al(1). 2007	54.9	28.8	14	46.8	31.7	12	6.8%	0.26 [-0.51, 1.03]
Fong et al(2).2007	53.8	31.1	20	46.8	31.7	12	7.8%	0.22 [-0.50, 0.94]
Mizuno et al. 2011	70.3	13	16	69.5	13.5	15	8.1%	0.06 [-0.65, 0.76]
Nysa et al. 2008	60.2	21.5	10	61.2	21.2	6	4.0%	-0.04 [-1.06, 0.97]
Robertson et al. 2002	30.1	11.5	19	32.8	11.9	21	10.3%	-0.23 [-0.85, 0.40]
Subtotal (95% CI)			**79**			**66**	**37.1%**	**0.04 [-0.29, 0.37]**
Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 4 (P = 0.87); I² = 0%								
Test for overall effect: Z = 0.23 (P = 0.82)								
1.2.3 BIT(Total)								
Fong et al(1). 2007	156.4	62.9	14	135.6	85.74	12	6.8%	0.27 [-0.50, 1.05]
Fong et al(2).2007	155.1	75.5	20	135.6	85.74	12	7.8%	0.24 [-0.48, 0.96]
Koch et al. 2012	197	5	9	178	12	9	3.0%	1.97 [0.79, 3.14]
Serino et al. 2009	93	11	16	95	6	18	8.8%	-0.22 [-0.90, 0.45]
Turton et al. 2010	24.5	15.7	12	21.8	22	16	7.2%	0.13 [-0.62, 0.88]
Subtotal (95% CI)			**71**			**67**	**33.6%**	**0.36 [-0.21, 0.92]**
Heterogeneity: Tau² = 0.25; Chi² = 10.19, df = 4 (P = 0.04); I² = 61%								
Test for overall effect: Z = 1.23 (P = 0.22)								
Total (95% CI)			**216**			**184**	**100.0%**	**0.21 [0.01, 0.41]**
Heterogeneity: Tau² = 0.00; Chi² = 14.28, df = 14 (P = 0.43); I² = 2%								
Test for overall effect: Z = 2.01 (P = 0.04)								
Test for subgroup differences: Chi² = 2.03, df = 2 (P = 0.36), I² = 1.5%								

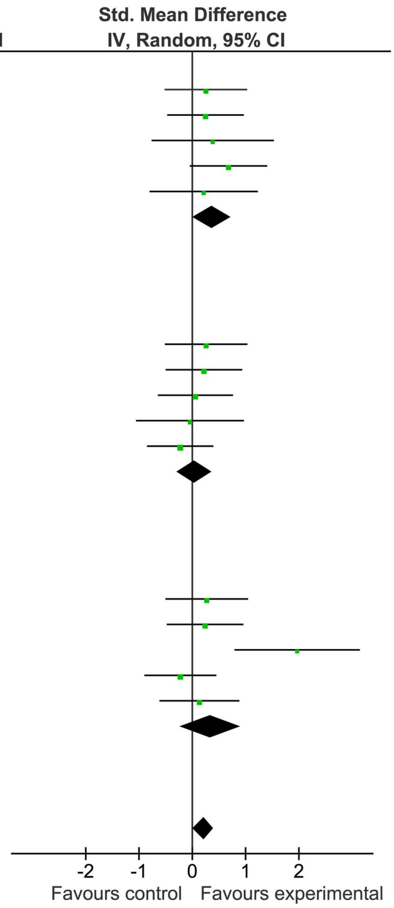

FIGURE 3 | Rehabilitation interventions versus any control, outcome: long-lasting effects.

Rousseaux et al., 2006). The inconsistent results are probably due to the lack of comparability of treatment apparatus, treatment duration, the tasks used to assess PA effects, and post-stroke duration. Similar to PA, hemiplegic half-field eye patching is another compensational intervention for neglect which works by blocking the ipsilesional visual field. The initial study by Tsang et al. (2009) demonstrates a significant result with an ES of 0.71 immediately after intervention. More good-quality RCTs are needed to assess its long-lasting effects on UN.

Transcranial magnetic stimulation is a safe and non-invasive procedure to detect or modulate brain activity by passing a strong brief electrical current through an insulated wired coil placed on the skull which generates a transient magnetic field in the brain (Hummel and Cohen, 2006). TBS is a kind of rTMS using a lower stimulation intensity and a shorter time of stimulation to induce long-lasting effects in the cortex (Cárdenas-Morales et al., 2010) which demonstrates a relatively high ES as measured by the BIT total scores discussed in this review. TMS has become a popular method to stimulate the human brain, with rTMS attracting particular interest for its therapeutic potential to modify cortical excitability (Funke and Benali, 2011), which sheds light on the use of the inter-hemispheric rivalry model in explaining the recovery after neglect disorder in stroke patients. According to the literature, rTMS induces and repairs the inter-hemispheric imbalance (a neglect-like behavior) in the left or right posterior parietal cortex in healthy humans (Kinsbourne, 1977, 1994; Oliveri et al., 2001; Rounis et al., 2007). Based on this model, some studies have explored whether the use of inhibitory rTMS over the contralesional hemisphere to reduce the pathological hyperactivity of either hemisphere may be useful in promoting recovery from neglect after stroke with promising results (Oliveri et al., 2001; Brighina et al., 2003; Shindo et al., 2006; Koch et al., 2008; Nyffeler et al., 2009; Song et al., 2009). Compared to traditional standard cognitive intervention, rTMS can accelerate clinical recovery (Oliveri et al., 2001; Shindo et al., 2006; Song et al., 2009; Paik and Paik, 2010). It seems that patients more severely affected at baseline also benefited more from this intervention. However, the small sample size of the TBS study makes it impossible to draw any conclusion based on robust evidence. There may be a publication bias whereby large studies will report small ES whereas small studies will report large ES.

This review cannot determine the best time to commence neglect rehabilitation interventions, because most participants in the studies included here were recruited in either the subacute or chronic phases. Only two studies implemented rehabilitation within 1 month of stroke (Fong et al., 2007; Nys et al., 2008). As most of the spontaneous recovery after stroke happens in the first month (Kerkhoff and Schenk, 2012), further research is necessary to determine the effects of early but specific intervention for UN compared to conventional rehabilitation in order to avoid the confounding effect of spontaneous recovery. Neglect is the best single predictor of long-term functional impairment and poor rehabilitation outcome in the early stage (Jehkonen et al., 2001; Nys et al., 2005). One study (He et al., 2007) based on neuroimaging shows that 2 weeks after stroke, the normally functional connectivity between the left and right dorsal parietal cortex was disrupted, with the degree of breakdown correlated with the severity of left spatial neglect. It is therefore reasonable that patients should start a neglect intervention as soon as possible in the acute stage, in order to avoid non-use of the hemiplegic limbs, by increasing multisensory inputs or stimulation to the ipsilateral brain regions, and thus slowing down the secondary changes in the brain related to neglect. For further research, we also recommend adequate follow-up to maximize the benefits and monitor the persistence of the effect of neglect rehabilitation interventions.

LIMITATIONS OF THE REVIEW

The review has some limitations. It is constrained by the quality of the studies included, none of which scored the intention-to-treat analysis. The blindness design was the biggest weakness of most of these RCTs. The heterogeneity of the studies means that this meta-analysis is less powerful and cannot identify conclusively the optimal treatment approach.

CONCLUSION

The results of this review confirm that PA appears to be the most common and effective rehabilitation intervention for UN, and that rTMS might be a promising approach for future treatment. As shown by the insignificant long-lasting effects, rehabilitation interventions often had a transient impact and could not be generalized across time to an improvement in daily functioning. All studies faced the same weakness of low power with smaller samples

Table 3 | Immediate effect size of each rehabilitation intervention.

Outcomes	Study	Intervention	Effect size
BIT-C	Làdavas et al. (2011) (1)	PA	1.31 (−0.26, 2.88)
	Làdavas et al. (2011) (2)		(pooled)
	Mizuno et al. (2011)		
	Ferreira et al. (2011)	VST	1.16 (−0.24, 2.56)
	Harvey et al. (2003)	VF	1.15 (−0.25, 2.55)
	Tsang et al. (2009)	EP	0.71 (0.02, 1.41)
	Fong et al. (2007) (1)	TR	0.50 (−0.19, 1.19)
	Luukkainen-Markkula et al. (2009)	LA	0.27 (−0.87, 1.41)
	Fong et al. (2007) (2)	TR + EP	0.19 (−0.48, 0.86)
BIT-B	Làdavas et al. (2011) (1)	PA	0.86 (−0.45, 2.18)
	Mizuno et al. (2011)		(pooled)
	Fong et al. (2007) (1)	TR	0.16 (−0.52, 0.84)
	Fong et al. (2007) (2)	TR + EP	0.15 (−0.52, 0.82)
	Robertson et al. (2002)	LA	−0.08 (−0.70, 0.54)
BIT (Total)	Koch et al. (2012)	TBS	1.46 (0.39, 2.53)
	Serino et al. (2009)	PA	0.55 (0.16, 0.94)
	Turton et al. (2010)		(pooled)
	Fong et al. (2007) (1)	TR	0.40 (−0.28, 1.09)
	Fong et al. (2007) (2)	TR + EP	0.18 (−0.49, 0.85)

Table 4 | Long-lasting effect size of each rehabilitation intervention.

Items	Study	Intervention	Effect size
BIT-C	Mizuno et al. (2011)	PA	0.52 (−0.07, 1.11)
	Nys et al. (2008)		(pooled)
	Luukkainen-Markkula et al. (2009)	LA	0.38 (−0.76, 1.53)
	Fong et al. (2007) (1)	TR	0.26 (−0.52, 1.03)
	Fong et al. (2007) (2)	TR + EP	0.25 (−0.47, 0.97)
BIT-B	Fong et al. (2007) (1)	TR	0.26 (−0.51, 1.03)
	Fong et al. (2007) (2)	TR + EP	0.22 (−0.50, 0.94)
	Mizuno et al. (2011)	PA	0.03 (−0.55, 0.60)
	Nys et al. (2008)		(pooled)
	Robertson et al. (2002)	LA	−0.23 (−0.85, 0.40)
BIT (Total)	Fong et al. (2007) (1)	TR	0.27 (−0.50, 1.05)
	Fong et al. (2007) (2)	TR + EP	0.24 (−0.48, 0.96)
	Koch et al. (2012)	TBS	1.97 (0.79, 3.14)
	Serino et al. (2009)	PA	−0.06 (−0.57, 0.44)
	Turton et al. (2010)		(pooled)

Table 5 | PA intervention on neglect.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
Immediate effects	5	216	Std. mean difference (IV, random, 95% CI)	0.89 (0.27, 1.51)
BIT-C	3	74	Std. mean difference (IV, random, 95% CI)	1.31 (−0.26, 2.88)
BIT-B	3	74	Std. mean difference (IV, random, 95% CI)	0.86 (−0.45, 2.18)
BIT (Total)	2	68	Std. mean difference (IV, random, 95% CI)	0.59 (−0.02, 1.19)
Long-lasting effects	4	125	Std. mean difference (IV, random, 95% CI)	0.15 (−0.20, 0.51)
BIT-C	2	47	Std. mean difference (IV, random, 95% CI)	0.52 (−0.07, 1.11)
BIT-B	1	16	Std. mean difference (IV, random, 95% CI)	−0.04 (−1.06, 0.97)
BIT (Total)	2	62	Std. mean difference (IV, random, 95% CI)	−0.06 (−0.57, 0.44)

and a limitation in the blindness design. More rigorous studies of various interventions should be done before coming to a firm conclusion.

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Non-invasive brain stimulation in neglect rehabilitation: an update

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Here, we review the effects of non-invasive brain stimulation such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) in the rehabilitation of neglect. We found 12 studies including 172 patients (10 TMS studies and 2 tDCS studies) fulfilling our search criteria. Activity of daily living measures such as the Barthel Index or, more specifically for neglect, the Catherine Bergego Scale were the outcome measure in three studies. Five studies were randomized controlled trials with a follow-up time after intervention of up to 6 weeks. One TMS study fulfilled criteria for Class I and one for Class III evidence. The studies are heterogeneous concerning their methodology, outcome measures, and stimulation parameters making firm comparisons and conclusions difficult. Overall, there are however promising results for theta-burst stimulation, suggesting that TMS is a powerful add-on therapy in the rehabilitation of neglect patients.

Keywords: review, rehabilitation, unilateral neglect, transcranial magnetic stimulation, theta-burst protocol, transcranial direct current stimulation

INTRODUCTION

Hemispatial neglect is a common neurological syndrome that may be particularly disabling after stroke. It is defined as the failure to detect, respond, or orient to the stimuli located in the portion of space contralateral to the lesion (Heilman et al., 1993). Neglect is common, occurring in up to 43% of patients suffering from an acute right-hemispheric stroke (Ringman et al., 2004). Depending on the assessment, the reported incidence may widely vary between 10 and 82% following right-hemispheric damage and between 15 and 65% following left-hemispheric damage (Plummer et al., 2003). Neglect patients show slower functional progress during rehabilitation and need longer hospitalization (Cherney et al., 2001; Gillen et al., 2005). Furthermore, neglect is an independent predictor of poor outcome, in terms of more limited functional independence (Stone et al., 1992; Di Monaco et al., 2011) and lower likelihood of being discharged home (Wee and Hopman, 2005, 2008).

Different therapeutic strategies to treat neglect have been evaluated, such as visual scanning, prism adaptation, sensory stimulation, neck muscle vibration, optokinetic stimulation, or pharmacologic treatments (see for a review Bowen et al., 2002; Kerkhoff and Schenk, 2012). Although these treatments attenuate the severity of neglect, they are often difficult to apply in rehabilitation – particularly during the acute or subacute phase of stroke – due to short duration of effects, patient discomfort, or the difficulty for patients to cooperate (Fierro et al., 2006).

THE CONCEPT OF INTERHEMISPHERIC RIVALRY IN NEGLECT

The concept of interhemispheric rivalry, based on the model by Kinsbourne (1987, 1993), is so far the most common basis for the application of non-invasive brain stimulation (NIBS) to modulate neglect [newer promising approaches are however also thinkable, such as, e.g., rhythmic transcranial magnetic stimulation (TMS) (see Thut et al., 2011) or network modulations (see van der Werf et al., 2010)]. According to this concept, both parietal cortices exert reciprocal interhemispheric inhibition. A damage of the right parietal cortex causes disinhibition of the intact, left hemisphere, and thus a pathological over-activation of the latter. This over-activation in the left, intact hemisphere further depresses the neural activity by an increased inhibition on the damaged hemisphere, aggravating the rightward, ipsilesional attentional bias.

Evidence supporting this concept comes from several experimental approaches. First, seminal works in animal models (Sprague, 1966) and a large body of subsequent studies (see, e.g., Payne and Rushmore, 2004; Rushmore et al., 2006; Valero-Cabré et al., 2006) showed that: (a) unilateral interventions (such as lesion, cooling, or TMS) generally introduce an imbalance in the physiological activity between the networks controlling visuospatial attention in the two hemispheres, favoring the intact hemisphere and leading to neglect; and (b) the experimental cancelation of this imbalance (and of neglect) is achievable through the reduction of the hyperexcitability (by lesion or cooling) of specific cortical or subcortical regions in the intact hemisphere. Second, fMRI studies showed a relative hyperactivity of the left, undamaged hemisphere in neglect patients, which correlated with neglect severity as measured by behavioral tasks (Corbetta et al., 2005). Moreover, the recovery of neglect correlated with the restoration and rebalancing of activity between both hemispheres, particularly in the dorsal parietal cortex (Corbetta et al., 2005; He et al., 2007). Third, clinical observations also indicate the relevance of the rebalancing of the activity between the two hemispheres as a functional mechanism accompanying neglect recovery. Vuilleumier et al. (1996) described the case of a patient who suffered from two sequential strokes. The first, right-hemispheric stroke, involving the parietal cortex, induced severe neglect, which completely recovered after a second, left-hemispheric stroke involving the frontal eye field. Fourth and finally, the pathological hyperactivity of intact, contralesional areas in neglect patients has also been directly demonstrated by means of a twin-coil TMS approach, allowing to assess the cortical excitability within parieto-motor circuits of the left hemisphere (Koch et al., 2008, 2012). Results showed a significantly higher excitability in neglect patients as compared to healthy controls and to patients with right-hemispheric lesions but no neglect. The degree of overexcitability was significantly correlated with neglect severity as measured by paper–pencil tests. Moreover, the application of inhibitory repetitive TMS (rTMS) over the left, contralesional posterior parietal cortex (PPC) could significantly reduce its overexcitability and triggered a significant amelioration in the behavioral measures of neglect.

The results illustrated above thus support the idea that the reinstatement of interhemispheric inhibitory balance is an important mechanism in neglect recovery.

NON-INVASIVE BRAIN STIMULATION

Non-invasive brain stimulation, i.e., TMS or transcranial direct current stimulation (tDCS), has been increasingly used to interfere with brain activity in healthy subjects and patients with brain lesions. Depending on the stimulation parameters, it is possible to facilitate or to suppress brain activity with measurable behavioral effects.

Transcranial magnetic stimulation is based on the application of very short-lasting, strong electric currents delivered through a coil generating a rapidly changing, high-intensity magnetic field. This magnetic field induces on its part perpendicular currents in the brain, which are strong enough to directly depolarize neurons and influence cortical excitability. rTMS can either enhance (5–20 Hz, so-called high-frequency stimulation) or suppress ($\leq$1 Hz, low-frequency stimulation) cortical activity and modulate excitability beyond the duration of the applied stimulation (see for a review Hallett, 2007).

More recently, the so-called "theta-burst stimulation" (TBS) has been introduced as a new protocol. Originally, such protocols were used to induce long-term potentiation (LTP) or long-term depression (LTD) in brain slices (Larson et al., 1986; Abraham, 2003). The protocol consists of three short trains of repetitive high-frequency TMS (30–100 Hz) in theta-frequency range (4–7 Hz). The stimulation pattern can have either excitatory (intermittent theta-burst, iTBS) or inhibitory (continuous theta-burst, cTBS) effects on brain activity (Huang et al., 2005). TMS can be used in a variety of ways to induce plastic changes in the brain. An effective way to modulate synaptic efficacy is to activate a cell with two or more inputs at brief intervals, such as in the bursts of the theta-burst protocol. A steady increase in synaptic strength is called LTP, a decrease LTD. In analogy, Huang et al. (2005) developed a modified TBS protocol with a pattern consisting of bursts of three pulses at 50 Hz, repeated every 200 ms intervals (i.e., at 5 Hz). The stimulation intensity was 80% of the activated motor threshold and the total number of pulses was 600. They found that a short and intermittent application of TBS (iTBS) facilitated motor-evoked potentials, i.e., increased their amplitude, whereas a continuous application of TBS (cTBS) suppressed motor-evoked potentials for up to 1 h. Nyffeler et al. (2006a, 2009) showed that such LTD-like effects could be disproportionately prolonged by repeated TBS application both in healthy subjects and in patients with neglect. They used a further modified theta-burst protocol with a burst frequency of 30 Hz, repeated with an inter-burst interval of 100 ms. The stimulation intensity was 80% of the resting motor threshold, and the total number of pulses was 801. The behavioral outcome was measured in healthy subjects with an oculomotor paradigm. The modified cTBS protocol has been shown to yield conspicuously longer inhibitory effects on the oculomotor cortex [i.e., the frontal eye field, in a head-to-head comparison with the commonly applied 1-Hz stimulation protocol (Nyffeler et al., 2006b)]. Moreover, Nyffeler et al. (2006a, 2009) showed that the behavioral effect of cTBS could be disproportionally prolonged: the behavioral effect after one, two, or four cTBS trains lasted on average up to 30 min, 3 h, or 11 h, respectively (Nyffeler et al., 2006a). Similar prolonged behavioral effects after repeated cTBS application were also found in patients with neglect. In a visual perception task, two cTBS trains significantly increased the number of perceived left visual targets for up to 8 h, whereas the application of four cTBS trains significantly increased the number of perceived left targets up to 32 h. No significant improvement was found after sham stimulation (Nyffeler et al., 2009).

While rTMS can generate strong currents capable to depolarize neurons, tDCS changes cortical activity by means of small electric currents. Suggested as a purely neuromodulatory approach, tDCS seems to alter brain activity by influencing the resting membrane potential, and does not evoke action potentials (Fregni and Pascual-Leone, 2007; Nitsche et al., 2008; Paulus, 2011). During tDCS, small currents (1–2 mA) are delivered to the brain transcranially via two large electrodes. The duration of the stimulation, its strength, and its polarity determine the excitability changes. Anodal tDCS leads to excitation of the brain, whereas cathodal tDCS results in brain inhibition (Nitsche and Paulus, 2000). tDCS effects seem to be mainly mediated by changes in the excitability of inhibitory or facilitatory interneuronal circuits that can outlast stimulation duration. tDCS has the advantage that the device is inexpensive, portable, and easy to use, in particular simultaneously with treatment sessions in the rehabilitation setting. Finally, the tingling sensation on the scalp at the beginning of the stimulation fades away shortly after. This is an advantage for a reliable sham condition (i.e., the device can be set to turn off a few seconds after the stimulation beginning, without the subject or the experimenter noticing it), and is also an important element for double-blind, controlled clinical trials.

The aim of the present study is to review the literature concerning the effectiveness of NIBS in the treatment of neglect patients.

METHODS

We searched the following databases for studies published in English: PubMed, PsychINFO, and Science Direct. Following search terms were used: neglect, visual neglect, unilateral neglect, rehabilitation, TMS, tDCS. Studies were included in the review if they satisfied following criteria: use of an offline TMS protocol, or use of an online or offline tDCS protocol; treatment of neglect or evaluation of the duration of NIBS effects on neglect as a goal of the study.

RESULTS

The characteristics of the included studies are presented in **Tables 1** and **2**. We found 10 studies that used TMS for neglect rehabilitation, and only 2 studies that used tDCS. In these studies, a total of 172 patients were involved, 147 patients in TMS studies and 25 patients in tDCS studies. The number of included patients varied considerably between studies, from 2 (Shindo et al., 2006) to 27 patients (Kim et al., 2013).

The methodological differences in the rTMS protocols between the studies were also considerable. Five studies used low-frequency rTMS (Brighina et al., 2003; Shindo et al., 2006; Koch et al., 2008; Song et al., 2009; Lim et al., 2010), with frequencies of 0.5, 0.9, or 1 Hz. Three studies used cTBS (Nyffeler et al., 2009; Cazzoli et al., 2012; Koch et al., 2012) with either 30 or 50 Hz bursts. Finally, two studies (Kim et al., 2010, 2013) compared the effects of low-frequency (1 Hz) stimulation over the contralesional, intact hemisphere with those of high-frequency rTMS (20 Hz) over the ipsilesional hemisphere.

Further differences included the number of applied pulses, the duration of the intervention and of the observation period after the intervention, the type of coil used, and the procedure used to determine the stimulation location. The number of TMS pulses varied between 450 (Song et al., 2009) and 1200 pulses per session (Kim et al., 2010, 2013), the cumulative number was between 600 (Koch et al., 2008) and 12,600 pulses (Song et al., 2009). The intervention duration varied between a single session (Koch et al., 2008; Nyffeler et al., 2009; Kim et al., 2010) and 14 sessions (Song et al., 2009).

All studies used a focal, figure-of-eight coil, with the exception of Nyffeler et al. (2009) and Cazzoli et al. (2012), who used a round coil.

Concerning the location of the stimulation site, only one study used a neuronavigation system (Koch et al., 2012). They targeted the left PPC, using individual anatomic MRI and positioning the coil over the angular gyrus close to the posterior part of the adjoining intraparietal sulcus. All other studies used the international 10–20 EEG System. Two studies stimulated over P5 (Brighina et al., 2003; Shindo et al., 2006), all other studies over P3 (or, respectively, P4 for the two studies that entailed ipsilesional stimulation; Kim et al., 2010, 2013).

Five studies were sham-controlled (Nyffeler et al., 2009; Kim et al., 2010, 2013; Cazzoli et al., 2012; Koch et al., 2012), the remaining studies had no sham control group. A control group of patients without neglect was included in three studies (Koch et al., 2008; Song et al., 2009; Lim et al., 2010). One study (Koch et al., 2012) fulfilled the criteria for Class III evidence, one study (Cazzoli et al., 2012) the criteria for Class I evidence.

In only one study (Brighina et al., 2003) patients had no rehabilitation therapy during the observation. The patients in Lim's study (Lim et al., 2010) received behavioral therapy, and the patients in Koch's study (Koch et al., 2012) received 20 sessions of 45 min therapy. In the remaining four studies (Shindo et al., 2006; Song et al., 2009; Cazzoli et al., 2012; Kim et al., 2013), the patients received a full neurorehabilitation program, including occupational therapy, physiotherapy, and neuropsychology.

The time between brain damage and inclusion varied also considerably between studies. Patients in the acute/subacute stage (first 3 months after brain damage) were included in the studies by Song et al. (2009), Koch et al. (2012), Cazzoli et al. (2012), and Kim et al. (2013). Patients with chronic neglect (more than 3 months after brain damage) were included in the studies by Brighina et al. (2003), Shindo et al. (2006), and Kim et al. (2010). The remaining studies included both patients in the subacute or in the chronic stage.

The follow-up time of the observation of the stimulation effects ranged from 3 days (Nyffeler et al., 2009), 2 weeks (Brighina et al., 2003; Song et al., 2009; Koch et al., 2012), 3 weeks (Cazzoli et al., 2012) to 6 weeks (Shindo et al., 2006). In all studies, no information is provided about a potential fade-out of the stimulation effects over time.

DISCUSSION

Our database search resulted in 12 studies fulfilling the inclusion criteria. The studies are heterogeneous concerning methodology, evaluation, patients, and post-stroke inclusion time, making firm conclusions about the efficacy of NIBS difficult. In the last few years, at least five reviews (Fierro et al., 2006; Cazzoli et al., 2010; Hesse et al., 2011; Oliveri, 2011; Mylius et al., 2012) specifically addressed the application of TMS or tDCS for the treatment of neglect, and at least another 11 more general reviews (Dobkin, 2004; Rossi and Rossini, 2004; Miniussi et al., 2008; Schlaug and Renga, 2008; Marshall, 2009; Bashir et al., 2010; Langhorne et al., 2011; Miniussi and Rossini, 2011; Stuss, 2011; Vallar and Bolognini, 2011; Schulz et al., 2013) included the topic of brain stimulation in neglect. The number of reviews emphasizes the great interest in the development and establishment of new and current NIBS approaches for the treatment of neglect in particular, and for cognitive rehabilitation in general. However, the mismatch between the number of reviews and the number of original studies represents a compelling call for further systematic investigations in this field.

We found 10 studies using rTMS, and only 2 studies using tDCS. All rTMS studies used inhibitory protocols (low-frequency stimulation or cTBS) and stimulated the contralesional parietal cortex. Two studies (Kim et al., 2010, 2013) also included a condition in which the ipsilesional parietal cortex was stimulated using a high-frequency, excitatory protocol. Nine studies showed a significant improvement after inhibitory stimulation of the contralesional parietal cortex, one study (Kim et al., 2013) found a significant improvement only after ipsilesional excitatory stimulation. The number of patients included in the studies varied between 2 and 27 patients. Four studies evaluated only immediate effects after

Table 1 | Studies evaluating treatment of neglect by TMS.

Study	No. of patients	Time post	Sham control	Stimulation site (contra/ipsilesional)	No. of pulses, frequency, intensity	No. of sessions	Time of assessment in relation to stimulation	Outcome measures	Main results	Descriptive magnitude of the changes in the main outcome measures
Brighina et al. (2003)	3 RH	3-5 m	No	Contra P5	900 Pulses, 1 Hz, 90% MT	7 sessions (every second d)	2 w/pre/post/2 w	Computerized length judgment task with prebisected lines. Clock drawing, line bisection	Sign. improvement in all tasks, at end and 2 w after stimulation	On average ∼ −0.6 pts (∼ −83%) at end and ∼ −0.57 pts (∼ −79%) at 2 w after stimulation in the mean scores of the computerized length judgment task (negative deflection = leftward bias)*; −4.6 mm (∼ −50%) between 2 w before and 2 w after stimulation in the mean rightward bias in the line bisection
Shindo et al. (2006)	2 RH	175, 186 d	No	Contra P5	900 pulses, 0.9Hz, 90% MT	6 sessions (3 per w)	2 w/1 d pre/1 d post/2 w/4 w/6 w	Two BIT subtests, MMSE, BRS, BI	Positive effects in BIT and BI for at least 6 w	Peak BIT-B of 38 pts and BIT-C of 100 pts after rTMS (pre = ∼20 and ∼60 pts*) in one patient, 35 and 83 pts (pre = ∼10 and 40 pts*) in the other
Koch et al. (2008)	10 RH, 5 RH without neglect	1–6 m	No	Contra P3	600 pulses, 1 Hz, 90% MT	1 session	Pre/post	MEP measures in the intact LH, naming test	Hyperexcitability of LH reduced after rTMS only in neglect patients. Sign. reduction of left-sided omissions	On average ∼ −40% in the MEP amplitude (% control, ISI of 4 ms)*; −13.9% in the left-sided omissions in the naming test
Song et al. (2009)	14 RH (7 treatment, 7 control)	15–60 d	No	Contra P3	450 pulses, 0.5Hz, 90% MT	14 sessions, 2 w (2 trains per d)	2 w/pre/post/2 w	Line bisection, line cancelation	Sign. improvement in both tasks in the rTMS group, up to 2 w after stimulation	Amelioration on average, according to the index values: ∼ −41% post and ∼ −38% at 2 w in the line bisection task; ∼ −79% post and ∼ −76% at 2 w in the line cancelation task*

(Continued)

Table 1 | Continued

Study	No. of patients	Time post	Sham control	Stimulation site (contra/ipsilesional)	No. of pulses, frequency, intensity	No. of sessions	Time of assessment in relation to stimulation	Outcome measures	Main results	Descriptive magnitude of the changes in the main outcome measures
Nyffeler et al. (2009)	11 RH	0.4–36.1 m	Yes	Contra P3	801 pulses cTBS, 30Hz, repeated at 100 ms, 100% MT	1 session (two or four cTBS trains)	Pre/1 h post/3 h/8 h/24 h/32 h/96 h	PVT	Sign. increase of detected left targets and reduction of RT only in the active cTBS condition. Stable effects up to 8 h after two cTBS trains, up to 32 h after four cTBS trains	On average: with two cTBS trains, from ∼8.1 omitted left targets pre to ∼3.5 at 8 h (≅ −57%); reaction times to left-sided targets from ∼6.9 s pre to ∼5.5 s at 8 h (≅ −21%). With four cTBS trains, from ∼7.1 omitted left targets pre to ∼1.7 at 32 h (≅ −76%); reaction times to left-sided targets from ∼7.4 s pre to ∼4.6 s at 32 h (≅ −38%)*
Kim et al. (2010)	19 RH	23.73 ± 12.3 m	Yes	Contra P3 and ipsi P4	1200 pulses, 1 Hz, 90% MT or 1000 pulses, 20Hz, 90% MT	1 session	Pre/post	Letter cancelation task, line bisection, Ota's task	Sign. improvement in the Ota's task after 1 Hz stimulation only	On average ∼ +1.6 responses to O in the left side, ∼ +1.85 correct responses to C in the left side, ∼ +1.8 correct responses to O in the left side as compared to sham in the Ota's task (all mean sham values = 0) *
Lim et al. (2010)	7 RH, 7 controls	9–313 d	No	Contra P3	900 pulses, 1 Hz, 90% MT	10 sessions (1 session per d)	Pre/post	Line bisection test, Albert test	Sign. improvement in the line bisection test for left-sided line sets	On average 33.4% improvement in the line bisection test for left-sided line sets (median = 28.5%)
Koch et al. (2012)	9 RH, 9 controls	24–102 d	Yes	Contra P3	600 pulses cTBS at 50 Hz, repeated every 200 ms, 80% MT	10 sessions (two cTBS trains per d for 2 w)	Pre/post/2 w	MEP measures in the intact LH, BIT	Sign. improvement in the BIT after real stimulation up to 2 w. Hyperexcitability of LH reduced after rTMS in neglect patients only	On average ∼ −50% in the MEP amplitude (% control) after cTBS, ∼ −40% at 2 w*; 16.3% improvement of the BIT scores after cTBS, 22.6% at 2 w

(Continued)

Table 1 | Continued

Study	No. of patients	Time post	Sham control	Stimulation site (contra/ipsilesional)	No. of pulses, frequency, intensity	No. of sessions	Time of assessment in relation to stimulation	Outcome measures	Main results	Descriptive magnitude of the changes in the main outcome measures
Cazzoli et al. (2012)	16 RH, 8 RH control group	Mean 27 d (SEM 4.5 d)	Yes	Contra P3	801 pulses cTBS at 30Hz, repeated every 100 ms, 100% MT	2 sessions (four cTBS trains per d)	1 w pre/1 w post/2 w/3 w	PVT, CBS, random shape cancelation test, two part picture test, reading texts	Sign. improvement in all outcome measures only after real stimulation, at least for 3 w	On average 37% improvement in the spontaneous everyday behavior as measured by the CBS
Kim et al. (2013)	27 RH	Mean 15 d	Yes	Contra P3 and ipsi P4	1200 pulses, 1 Hz, 90% MT or 1000 pulses, 20Hz, 90% MT	10 sessions over 2 w (5 d per w)	Pre/post	Motor-free visual perception test, line bisection test, star cancelation test, CBS, K-MBI	Sign. improvement in the line bisection test after high-frequency rTMS and in the K-MBI after high and low rTMS	On average: -36.9% rightward deviation in the line bisection test after high-frequency stimulation (sham = −8.3%); +27.6 pts after low-frequency rTMS and +30.6 pts after high-frequency rTMS in the K-MBI scores (sham = +15.1 pts)

stimulation, without any follow-up measurements. The remaining six studies performed follow-up examinations up to 6 weeks. Five studies were not sham-controlled and, in three studies, activities of daily living (ADL) were evaluated in addition to neuropsychological testing. One study (Cazzoli et al., 2010) fulfilled Class I evidence, and one study (Koch et al., 2012) Class III evidence. In both studies, cTBS of the contralesional parietal cortex was applied.

To the best of our knowledge, no study so far directly compared the different forms of NIBS (e.g., TMS, tDCS) in order to demonstrate the superiority of one method. Both techniques present advantages and disadvantages, and the preference for the application of one technique or the other may also largely depend on the experimental questions and design (see Priori et al., 2009). Moreover, the application of TMS and tDCS should not be seen as mutually exclusive. The combination of the two techniques has in fact been shown to yield promising results, e.g., applying preconditioning by means of tDCS followed by rTMS application (Siebner et al., 2004).

In summary, notwithstanding the limited number of studies, the current state of the evidence looks more promising concerning the studies using cTBS. In the following, we will discuss methodological key points for the future development of treatment concepts of neglect by NIBS.

DIFFERENT EFFECTS OF NIBS ON OUTCOME VARIABLES

In all studies, a battery of different neuropsychological tests, or test batteries specifically developed for neglect assessment (such as the behavioral inattention test, BIT) were used. Effects of stimulation were often strikingly different across outcome variables, suggesting possible dissociations. One explanation may be methodological: 8 out of the 10 rTMS studies used a focal figure-of-eight coil. Since neglect is associated with multiple lesion sites (e.g., Verdon et al., 2010; Corbetta and Shulman, 2011), a focal stimulation may not be sufficient to improve all aspects tapped by the different neuropsychological tests. It is noteworthy that Cazzoli et al. (2012), who used a non-focal round coil, found significant improvements in all tests. Thus, high focal precision may not be a primary goal for therapeutic rTMS application. However, further studies are needed to evaluate whether focal or non-focal rTMS stimulation of the network involved in neglect has a better clinical outcome.

Three studies also evaluated the effect of TMS on the ADL using the Barthel Index or the Catherine Bergego Scale. Shindo et al. (2006) used the Barthel Index and found a significant improvement after stimulation. Cazzoli et al. (2012) used the Catherine Bergego Scale and also found a significant improvement after real stimulation, but not after sham stimulation. Finally, Kim et al. (2013) used both the Barthel Index and the Catherine Bergego Scale and found a significant improvement only in the Barthel Index.

STIMULATION PROTOCOLS

Generally, inhibitory stimulation protocols are predominantly applied. Low-frequency (0.5–1 Hz) repetitive stimulation was used in seven studies. The total number of pulses and daily application varied considerably between studies. The stimulation strength more consistently used was 90% of the motor threshold. Three

Table 2 | Studies evaluating treatment of neglect by tDCS.

Study	No. of patients	Time post	Sham control	Stimulation site (contra/ipsilesional)	Protocol	No. of sessions	Time of assessment in relation to stimulation	Outcome measures	Main results	Descriptive magnitude of the changes in the main outcome measures
Ko et al. (2008)	15 RH	29–99 d	Yes	Ipsi P4	2.0 mA anodal stimulation for 20 min	1 session	Pre/post	Line bisection test, letter-structured cancelation test, shape-unstructured cancelation test	Sign. effects of real tDCS on line bisection test and shape-unstructured cancelation test	On average: −3.52 percent deviation score in the line bisection test (= ∼ −19%); −3.47 omissions in the shape-unstructured cancelation test (= ∼ −14.8%)
Sparing et al. (2009)	10 RH	0.5–12.4 m	Yes	Contra P3 and ipsi P4	1.0 mA anodal and cathodal stimulation for 10 min	2 sessions, cross-over	Pre/post	Line bisection test, visual detection task	Sign. improvement in line bisection test after anodal tDCS of the lesioned hemisphere and cathodal tDCS of the intact hemisphere	On average: in the line bisection test, from 3.4 mm deviation pre (rightwards bias) to -1.5 mm post (leftward bias) with anodal tDCS on P4; from 5.4 mm pre to −1.7 mm post with cathodal tDCS on P3

w, week; m, month; d, day; MT motor threshold; MMSE, Mini Mental State Examination; BRS, Brunnstrom Recovery Index; BI, Barthel Index; PVT, subtest of the Vienna Test System (detection of peripheral visual targets); CBS, Catherine Bergego Scale; MEP, motor-evoked potential; RH, right hemisphere; LH, left hemisphere; RT, reaction time; K-MBI, Korean-Modified Barthel Index; SEM, standard error of the mean; pts, points.

[*]These values have been visually inferred from the graphs provided in the respective studies.

studies used continuous inhibitory cTBS, one study (Koch et al., 2012) used the standard protocol described by Huang et al. (2005), two studies (Nyffeler et al., 2009; Cazzoli et al., 2012) the modified protocol described by Nyffeler et al. (2006a). The two protocols differ in the frequency of the bursts (50 versus 30 Hz), in the total number of pulses (600 versus 801 pulses), and in the definition of the stimulation strength (80% active motor threshold versus 100% resting motor threshold).

These two protocols were recently compared by Goldsworthy et al. (2012). They stimulated the human primary motor cortex in healthy subjects and recorded motor evoked-potentials (MEP) from the right first dorsal interosseous muscle before and at 0, 5, 10, 20, and 30 min after stimulation. The results showed that the standard protocol with 50 Hz induced a neuroplastic response that was short-lived and highly variable, whereas the modified protocol with 30 Hz induced a lasting change in MEP amplitude that was consistent between subjects. Such a lasting and consistent effect of cTBS may be an advantage for the therapeutic stimulation application. Furthermore, the fact that the repeated cTBS application at the same day can disproportionately prolong its effects (Nyffeler et al., 2009) is a further advantage.

TBS – THE WAY TO AN "IDEAL" STIMULATION PROTOCOL?

From a clinical and practical point of view, future stimulation protocols for therapeutical interventions should have the following properties: (1) the application should be easy to perform, i.e., no additional examinations such as neuroimaging or neuronavigation systems should be needed to localize the stimulation site. Indeed, only one study (Koch et al., 2012) used neuronavigation to localize the target site. The remaining studies localized the stimulation site by using the international 10–20 system. (2) The application time should be short. Protocols such as low-frequency stimulation protocols, with daily applications over several weeks, are difficult to perform in a rehabilitation clinic, and are often not well tolerated by patients. In contrast, cTBS application lasts about 40 s. Using the potential of disproportionate prolongation of the effects by repeated cTBS application, Cazzoli et al. (2012) could show that eight cTBS trains applied on 2 days have an ADL-relevant effect of up to 3 weeks.

CONCLUSION

Our update and review of recent studies using NIBS for neglect treatment shows an ongoing evolution of TMS application from proof-of-concept studies to clinical application. However, the limited number of studies indicates the need of further systematic investigations in this field, with the aim of developing and establishing the most promising stimulation parameters. For cTBS, two recent Class I and III studies demonstrated its clinical utility as add-on therapy in neglect treatment. For tDCS application in neglect, only two studies were found, indicating that this technique may still be in an earlier stage in the evolution toward clinical application.

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Effect of eye patching in rehabilitation of hemispatial neglect

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Eye patching (EP; monocular or right hemifield) has been proposed to improve visuospatial attention to the ignored field in patients with hemispatial neglect. The aim of this paper is to review the literature on the effects of EP in hemispatial neglect after stroke in order to convey evidence-based recommendations to clinicians in stroke rehabilitation. Thirteen intervention studies were selected from the Medline, EMBASE, Scopus, Cochrane Library, CINAHL, PsychINFO, EBRSR, and Health Star databases. Methodological quality was defined according to the Physiotherapy Evidence Database. Overall, seven studies used monocular EP, five used right hemifield patching, and one compared right monocular with right hemifield patching. Seven studies compared normal viewing to monocular or hemifield patching conditions. Six studies included a period of treatment. As to the monocular EP, four studies reported positive effects of right monocular patching. One study showed an improvement in hemispatial neglect with left monocular patching. Two studies found no superiority of right vs. left monocular patching. One study found no effects of right monocular patching. As to the right hemifield EP, one study showed improvements in neglect after right hemifield patching. Three studies found that right hemifield patching combined with another rehabilitation technique was more effective than that treatment alone. One study found no differences between right hemifield patching combined with another treatment and that treatment alone. One study found the same effect between right hemifield patching alone and another rehabilitation technique. Our results globally tend to support the usefulness of right hemifield EP in clinical practice. In order to define a level of evidence with the standard rehabilitation evidence rating tools, further properly powered randomized controlled trials or meta-analysis are needed.

Keywords: hemispatial neglect, rehabilitation, perceptual disorders, treatment, stroke, visual stimulation, superior colliculus, eye patching

INTRODUCTION

Hemispatial neglect is a common syndrome after stroke in which patients fail to report or respond or be aware of stimuli located contralateral to a brain lesion (Heilman and Valenstein, 1979; Kwon et al., 2012). The incidence of hemispatial neglect varies between 8 and 95% in individuals with stroke (Bowen et al., 1999), with a reasonable estimate of 23% (Pedersen et al., 1997). These epidemiological discrepancies are thought to result from inconsistencies in defining hemispatial neglect, differences in the timing of examination after stroke, the use of different tests to detect visual hemispatial neglect, and the use of small and insensitive test batteries in the available literature (Ogden, 1985; Stone et al., 1991).

Lesions involving the right inferior frontal gyrus, precentral gyrus, postcentral gyrus, superior temporal gyrus, middle temporal gyrus, middle occipital gyrus, insula, and surrounding white matter are those most frequently associated with hemispatial neglect (Chechlacz et al., 2012; Yue et al., 2012).

As left hemispatial neglect (after right brain damage) is the most frequent case in clinical practice, we will refer to this condition throughout the whole paper.

Testing of hemispatial neglect shows that patients misbisect lines to the right of true center, fail to cancel targets on the left side of a page, and fail to draw the left side of objects and scenes (Kwon et al., 2012). Diagnosis must exclude that these behavioral abnormalities arise from a primary sensory or motor deficit such as hemianopia or paralysis (Heilman and Valenstein, 1979).

An accurate estimate of the rates of hemispatial neglect recovery after stroke could not be derived to date (Bowen et al., 1999). However, a recent cohort study on a sample of 101 stroke patients described progress of time as an independent covariate that reflects neurological recovery of hemispatial neglect (Nijboer et al., 2013). The authors found that at 12 weeks after stroke, 54% of the initial hemispatial neglect patients recover from their impairment, and approximately 60% after 26 up to 52 weeks from the onset of stroke (Nijboer et al., 2013). Consequently, in clinical practice it is not unusual to have cases of chronic hemispatial neglect more than 1 year after stroke.

The presence of hemispatial neglect increases postural control abnormalities in patients with stroke. Indeed, they usually show trunk misalignment (van Nes et al., 2009), postural instability (Pérennou et al., 2000), and increased risk of falls (Paolucci et al., 2001; Jutai et al., 2003; Mackintosh et al., 2006). Hemispatial neglect is a recognized predictor of poor functional outcome, with a lower level of independence in activities of daily living (e.g., dressing, bathing, eating, and mobility), prolonged hospital stay, greater need of care-giver support (Katz et al., 1999; Cherney et al., 2001; Buxbaum et al., 2004; Franceschini et al., 2010), and a higher risk of functional deterioration at 1 year post-stroke (Paolucci et al., 2001). Thus, it is not surprising that over the past 60 years more than 18 different rehabilitation techniques have been put forward to alleviate, reduce, or remediate unilateral hemispatial neglect (Luauté et al., 2006; Ogourtsova et al., 2010). The most recent Cochrane review of cognitive rehabilitation for hemispatial neglect after stroke (Bowen and Lincoln, 2007) reports that although several types of neglect-specific approaches can improve performance on some, but not all, standardized neglect tests, evidence to support, or refute their effectiveness in reducing disability and improving independence is still insufficient.

Eye patching (EP) is an interesting approach to hemispatial neglect rehabilitation that has been proposed since the early 1990s as a method to improve visual-scanning and attention toward the neglected field (Butter and Kirsch, 1992). From a clinical point of view, EP may have remarkable gains over other treatment methods because of its high feasibility and low cost. However, the literature about EP reports non-unique evidences of effectiveness. Some of these studies display several methodological limitations. Furthermore, confounding factors in this debate are that studies differ in experimental design and that two different types of EP methods have been proposed.

Although some literature reviews dealing with the effects of hemispatial neglect rehabilitation have been published in the last decade (Butter and Kirsch, 1992; Diamond, 2001; Manly, 2002; Pierce and Buxbaum, 2002; Luauté et al., 2006; Bowen and Lincoln, 2007; Ogourtsova et al., 2010), none have been specifically dedicated to the EP approach.

The main aim of this paper is to review the literature on the effects of EP in post-stroke hemispatial neglect in order to convey evidence-based practice recommendations to clinicians in stroke rehabilitation. Furthermore, given the potential role of this approach in clinical practice, we aim at giving indications for guiding future studies in this field of research.

RATIONALE OF EYE PATCHING IN HEMISPATIAL NEGLECT

A number of studies on EP technique in post-stroke hemispatial neglect referred to the Sprague Effect theory (see below for details) (Sprague and Meikle, 1965; Sprague, 1966a,b), while others have interpreted their results in light of a different rationale (*Interhemispheric balance theory* and *Visual exploration constraint theory*) (Arai et al., 1997; Beis et al., 1999; Ianes et al., 2012). On this basis, we decided to propose three main theories in support of the potential benefit of EP in the treatment of hemispatial neglect after stroke.

THE SPRAGUE EFFECT THEORY

The Sprague effect was first described in 1966 by Sprague. In a remarkable series of studies on animal models (cat), Sprague showed that visually guided behavior is subserved by interactions involving the midbrain and cortical pathways (Sprague and Meikle, 1965; Sprague, 1966a). Sprague reported that hemianopia resulting from a contralateral, large posterior cortical lesion could be partially alleviated by ablation of the superior colliculus contralateral to the cortical lesion or transection of the commissure of the superior colliculus. He observed that cats with contralesional orienting deficits improved their ability to detect stimuli in the contralateral field after surgical ablation of the contralesional superior colliculus. Sprague's hypothesis that ablation of the contralateral superior colliculus disinhibited the ipsilesional colliculus and improved orientation of contralesional attention (Sprague, 1966b), met with some skepticism and the neural basis for this phenomenon continues to fire debate between supporters and opponents (Soroker et al., 1994; Walker et al., 1996; Arai et al., 1997; Barrett et al., 2001).

With regard to the use of EP in the treatment of left hemispatial neglect in patients with right brain damage, Posner and Rafal (1987) suggested that inhibiting contralesional (left) collicular activity might lessen orienting deficits. They hypothesized that input to the superior colliculi from the eyes may be predominantly monocular and contralateral and that a right eye patch may sensory deprive the left colliculus (Hubel et al., 1975).

THE INTERHEMISPHERIC BALANCE THEORY

Beis et al. (1999) suggested that wearing patches over both right half-fields in patients with left hemispatial neglect after right brain damage activates the right hemisphere, leading to an increase in the level of leftward attention. Unlike right monocular EP (which is thought to cause simultaneous activation of both hemispheres), covering both right half-fields should activate only the right hemisphere.

A balance between the hemispheres may be thus established between the "overactivated" damaged right hemisphere and the "non-activated" healthy left hemisphere (Beis et al., 1999) (see **Figure 1**).

THE VISUAL EXPLORATION CONSTRAINT THEORY

Some authors (Arai et al., 1997; Ianes et al., 2012) suggest that the use of EP might be viewed as an application of Constraint-Induced Therapy (CIT), a well-known rehabilitation program in patients with upper limb paresis. This treatment aims to reverse the affected limb "learned non-use" phenomenon (Taub et al., 2006). In hemispatial neglect, patients have a strong tendency to orient their exploratory eye movements toward the ipsilesional space. In keeping with a rationale similar to that of CIT in patients with hemispatial neglect, the use of ipsilesional hemifield EP may help patients to visually explore their neglected space (Arai et al., 1997; Ianes et al., 2012).

MATERIALS AND METHODS

Original articles were selected from the following electronic databases: Medline (1950–March 2013), EMBASE (1992–March 2013), Scopus (1992–March 2013), the Cochrane Library (2008–March 2013), CINAHL (1992–March 2013), PsychINFO (1992–March 2013), EBRSR (1992–March 2013), and Health Star (1992–March 2013). The following keywords were used: stroke, neglect, visual neglect, unilateral spatial neglect, spatial neglect,

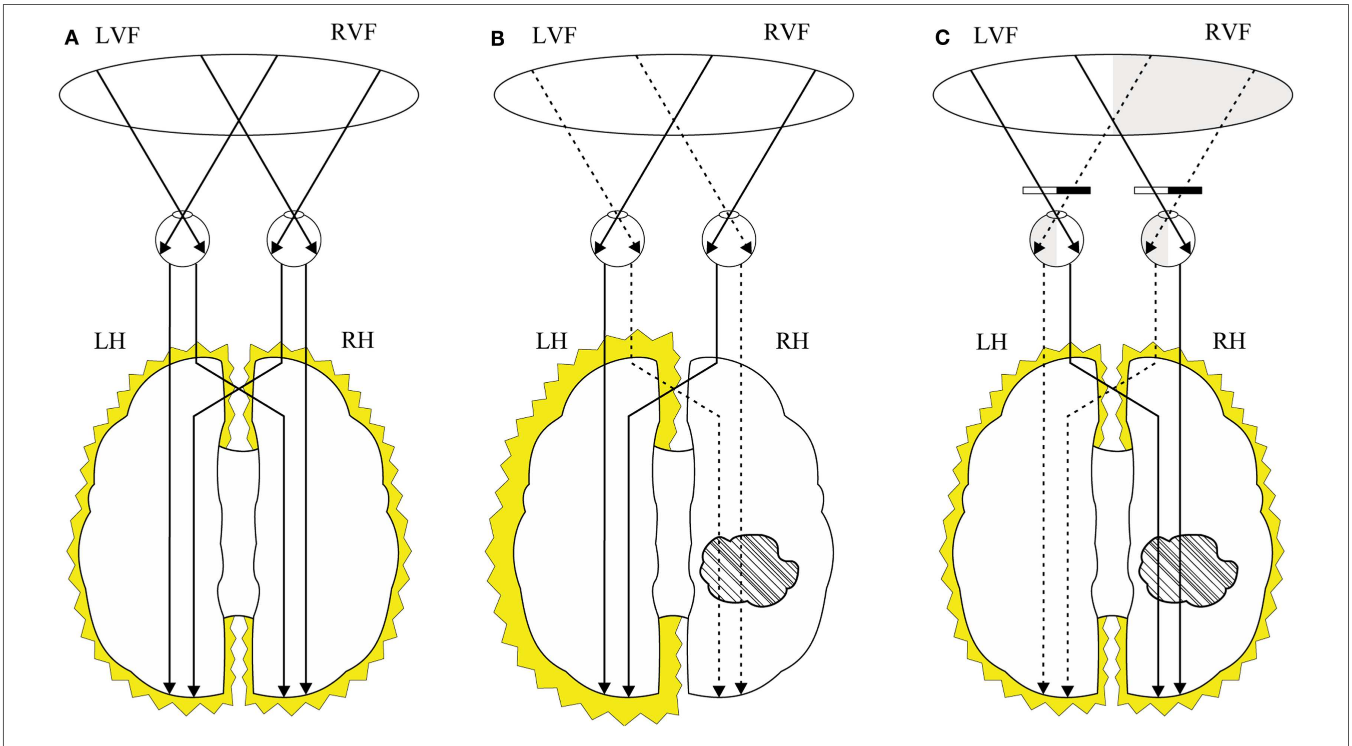

FIGURE 1 | Interhemispheric balance theory: (A) interhemispheric brain activation in individuals without stroke; (B) interhemispheric imbalance in individuals with right hemisphere stroke where the left hemisphere is activated and right hemisphere is under-activated; (C) patching bilateral right half-fields in individuals with left hemineglect and right hemisphere stroke stimulates the right hemisphere and reduces the stimulation of the left hemisphere leading to the interhemispheric re-balance. LVF, left visual field; RVF, right visual field; LH, left hemisphere; RH, right hemisphere.

hemispatial neglect, attention, eye patching, viewing, patching, glasses neglect, monocular, binocular. Different combinations of all these terms were used to source the articles.

Two independent reviewers (Valentina Varalta, Cristina Fonte) reviewed all abstracts retrieved from the initial search. Studies were included which evaluated the effects of monocular or hemifield EP in patients with hemispatial neglect (intervention studies) as a result of right brain damage. Excluded were non-intervention studies, animal studies, non-English language studies, studies enrolling only healthy subjects, studies involving stroke patients without hemispatial neglect and reviews. The two reviewers selected the relevant articles and performed the quality assessment of the studies. They independently read all the selected articles and listed the details in an appropriate grid (see **Table 1**). In addition to the electronic search, the reference lists of the selected full-text articles were checked for further articles. Three other investigators (Nicola Smania, Alessandro Picelli, and Marialuisa Gandolfi) read all the relevant articles and provided further assessment of data quality and validity. Disagreements were resolved by discussion. Heterogeneity in the selected studies precluded formal review. Thus, the results presented here are qualitative and represent the views of the investigators.

Methodological quality of the intervention studies was defined according to the Physiotherapy Evidence Database (PEDro) score as reported in the Physiotherapy Evidence Database (1999). The main author (Nicola Smania) verified all the scores.

RESULTS

A total of 83 papers were reviewed. Sixty-nine studies were excluded according to the above-mentioned criteria. Thirteen intervention studies were included in the review.

Five were case-series/case-control studies (Butter and Kirsch, 1992; Soroker et al., 1994; Serfaty et al., 1995; Walker et al., 1996; Arai et al., 1997), two were single-case studies (Barrett et al., 2001; Khurshid et al., 2009), and six were randomized controlled trials (RCTs) (Beis et al., 1999; Zeloni et al., 2002; Fong et al., 2007; Tsang et al., 2009; Ianes et al., 2012; Wu et al., 2013).

Seven studies investigated the effects of right monocular EP (five also analyzed the effects of left monocular EP) (Butter and Kirsch, 1992; Soroker et al., 1994; Serfaty et al., 1995; Walker et al., 1996; Barrett et al., 2001; Khurshid et al., 2009; Wu et al., 2013) and five assessed the effects of right hemifield EP (Arai et al., 1997; Zeloni et al., 2002; Fong et al., 2007; Tsang et al., 2009; Ianes et al., 2012). Only one study investigated the effect of right monocular EP and that of right hemifield EP (Beis et al., 1999).

Seven studies compared patient performance on neglect testing under two experimental conditions: normal viewing and viewing during EP (Butter and Kirsch, 1992; Soroker et al., 1994; Serfaty et al., 1995; Walker et al., 1996; Arai et al., 1997; Barrett et al., 2001; Khurshid et al., 2009). Six compared the effects of a rehabilitation technique with the same kind of treatment combined with EP (Beis et al., 1999; Zeloni et al., 2002; Fong et al., 2007; Tsang et al., 2009; Wu et al., 2013) or EP treatment applied alone (Ianes et al., 2012).

Table 1 | Short description of the studies considered for review.

Study	Study design	Patients (no.)	Time post onset (days)	Patients with VFD (no.)	Testing procedure	Intervention	Duration of intervention	PEDro score (0–10)
Butter and Kirsch (1992)	Case-series	13	112	8	Line and Letter Cancelation, Reading, Line Bisection, Clock Drawing	Normal viewing right monocular EP	1 Time	NA
		18	29.6	13	Line Bisection	Right monocular EP left visual stimulation right monocular EP + left visual stimulation	1 Time	
Soroker et al. (1994)	Case-series	6	135	3	Line Bisection	Normal viewing right monocular EP left monocular EP	1 Time	NA
Serfaty et al. (1995)	Case-series	26	67.2	12	Star Cancelation	Normal viewing right monocular EP left monocular EP	1 time	NA
Walker et al. (1996)	Case-series	9	506	9	Letter Cancelation, Line Bisection, Clock Drawing, Letter String Reading, Text Reading, Chimeric Face Recognition	Normal viewing right monocular EP left monocular EP	1 Time	NA
Arai et al. (1997)	Case-series	10	255	9	Line Bisection, Line Cancelation, Figures Copying	Normal viewing right hemifield EP	1 Time	NA
Barrett et al. (2001)	Single-case	1	ns	1	Line Bisection	Direct and indirect condition: normal viewing right monocular EP left monocular EP	1 Time	NA
Khurshid et al. (2009)	Single-case	1	365	1	Line Cancelation	Direct and indirect condition: normal viewing right monocular EP left monocular EP	1 Time	NA
Beis et al. (1999)	RCT	22	49.3	ns	Visual-scanning movements: time spent and number of movements, FIM	Group 1: VST + right hemifield EP; Group 2: VST + right monocular EP; Group 3: VST	12 weeks, 12 h/day	2/10
Zeloni et al. (2002)	RCT	11	236.2	9	Line, Letter and Bell Cancelation, Copy of Drawing, Line Bisection	Group 1: VST + right hemifield EP; Group 2: VST	1 week	NA
Fong et al. (2007)	RCT	60	11.9	ex	BIT-c, BIT-b, Clock Drawing, FIM	Group 1: TR + right hemifield EP; Group 2: TR; Group 3: OT	6 weeks, 5 days/week, 1 h/day	6/10
Tsang et al. (2009)	RCT	34	21.8	ns	BIT-c, FIM	Group 1: OT + right hemifield EP; Group 2: OT	4 weeks, 5 days/week, 1 h/day	7/10
Ianes et al. (2012)	RCT	18	12.9	ex	Line and Bell Cancelation, Line Bisection	Group 1: right hemifield EP; Group 2: VST	2 weeks, Group 1: 8 h/day; Group 2: 40 min/day	NA
Wu et al. (2013)	RCT	27	368	ns	CBS, Eye Movements, Trunk-arm Kinematic Analysis	Group 1: CIT + right monocular EP; Group 2: CIT; Group 3: OT	3 weeks, 5 days/week, 2 h/day	7/10

RCT, randomized controlled trial; VFD, visual field deficit; ns, not specified; BIT-c, behavioral inattention test-conventional subtest; BIT-b, behavioral inattention test-behavioral subtest; FIM, functional independence measure; CBS, Catherine Bergego scale; VST, visual-scanning training; TR, trunk rotation; OT, occupational therapy; CIT, constraint-induced therapy; NA, not applicable.

Three studies were performed in patients in the early stage after stroke (Fong et al., 2007: mean days = 11.9; Tsang et al., 2009: mean days = 21.8; Ianes et al., 2012: mean days = 12.9), while nine studies were conducted in patients in the sub-acute-chronic phase of illness (Soroker et al., 1994: mean days = 135; Serfaty et al., 1995: mean days = 67.2; Walker et al., 1996: mean days = 506; Arai et al., 1997: mean days = 255; Barrett et al., 2001: not specified; Khurshid et al., 2009: days = 365; Beis et al., 1999: mean days = 49.2; Zeloni et al., 2002: mean days = 236.2; Wu et al., 2013: mean days = 368). One study (Butter and Kirsch, 1992) tested patients at <1 month after the onset of stroke (mean days = 29.6) and patients in the chronic phase (mean days = 112).

The studies are summarized as follows (see also **Table 1** for methodological issues):

(1) Butter and Kirsch (1992) conducted two different experiments. In the first one, they tested the performance of 13 stroke patients with hemispatial neglect (co-morbidity: 8 patients with hemianopia; 11 patients with eye movement disturbances; 3 patients with visual extinction) during normal viewing and right monocular EP by means of the following test: Line Cancelation, Letter Cancelation, Reading, Line Bisection, and Clock Drawing. The authors observed that under the EP condition, 11 patients had modest clinical improvement in at least one of the five outcomes, noting statistically significant improvements only in the Line Bisection Test. In their second experiment, Butter and Kirsch tested 18 patients with hemispatial neglect (co-morbidity: 13 patients with hemianopia; 11 patients with eye movement disturbances; 1 patient with visual extinction) by means of a computerized test. Patients were required to bisect a line presented on the video screen at baseline and during presentation of visual warning stimuli on the left end of the line (warning condition). Both these conditions were carried out under normal viewing and under right monocular EP. The authors reported that patients performed significantly better under warning conditions compared to the baseline evaluation. Furthermore, they observed a smaller beneficial effect of right monocular EP compared to presentation of visual warning stimuli on the left end of the line during normal viewing (Butter and Kirsch, 1992).

(2) Soroker et al. (1994) analyzed the severity of hemispatial neglect in six stroke patients (co-morbidity: three patients with hemianopia; three patients with visual extinction) by means of a Line Bisection Test performed under three testing conditions: normal viewing; right monocular EP; and left monocular EP. The authors observed a significant improvement under the right monocular EP condition in one patient. Furthermore, three patients showed a significant worsening under the left monocular EP condition (Soroker et al., 1994).

(3) Serfaty et al. (1995) analyzed 26 stroke patients with hemispatial neglect (co-morbidity: 10 patients with left hemianopia and 2 with left quadrantanopia) by means of the Star Cancelation Test performed under the same conditions used by Soroker et al. (1994). The authors noted a significant improvement during right monocular EP compared to the normal viewing condition in 13 patients. Furthermore, two patients showed non-statistically significant improvements during left monocular EP (Serfaty et al., 1995).

(4) Walker et al. (1996) tested the presence and severity of hemispatial neglect in nine stroke patients (co-morbidity: all patients with left hemianopia) under the same conditions used by Soroker et al. (1994) by means of the following tests: Letter Cancelation, Line Bisection, Letter String Reading, Text Reading, and Chimeric Face Recognition. The authors observed that in the right EP condition three patients improved on at least one test and five patients worsened. In the left EP condition, five patients were found to worsen on at least one test, whereas two patients improved (Walker et al., 1996).

(5) Barrett et al. (2001) examined the effects of monocular EP on perceptual-attention and motor-intentional deficits in one stroke patient with hemispatial neglect (co-morbidity: left lower quadrantanopia) by means of a video Line Bisection Test performed directly (left/right on the video screen corresponded with workspace left/right) and indirectly (a 180°change in camera perspective reversed the image) under three testing conditions: normal viewing; right monocular EP; and left monocular EP. Paradoxically, under the right monocular EP condition, patient perceptual-attention deficit was found to significantly worsen, whereas there was a significant improvement under the left monocular EP condition (Barrett et al., 2001).

(6) Khurshid et al. (2009) analyzed the effects of monocular EP in one stroke patient with hemispatial neglect (co-morbidity: left homonymous hemianopia) by means of the video Line Cancelation Test performed under the same conditions used by Barrett et al. (2001). The authors showed that left monocular EP had no effect, whereas right monocular EP reduced left-sided omissions as compared with the un-patched condition (Khurshid et al., 2009).

(7) Arai et al. (1997) analyzed the performance of 10 stroke patients with hemispatial neglect (co-morbidity: 9 patients with visual field deficits) under normal viewing or during right hemifield EP by means of the following tests: Line Bisection, Line Cancelation, and Figure Copying. The authors found that nine patients showed improvement in hemispatial neglect on at least one of the three tests used during right hemifield EP as compared to the normal viewing condition (it was not specified if improvements were statistically significant). No effects were seen in the other two patients (Arai et al., 1997).

(8) Beis et al. (1999) randomized 22 stroke patients (co-morbidity not specified) into three groups: Group 1 ($n = 7$) received Visual-Scanning Training (VST) plus right hemifield EP; Group 2 ($n = 7$) underwent VST plus right monocular EP; Group 3 ($n = 8$) performed VST alone. All patients underwent 12-week training. They were evaluated before and after treatment by means of the Functional Independence Measure (FIM) and an analytical test recorded by photo-oculography (number of times the subject looked at the left zone; time spent looking at left zone). After treatment, significant improvements were found on the FIM and the number of times the subject looked at the left zone in Group 1 vs.

Group 3. No difference was found between Groups 2 and 3. Statistics for within-group comparisons were not reported (Beis et al., 1999).

(9) Zeloni et al. (2002) randomized 11 stroke patients (co-morbidity: 11 patients with left hemiplegia; 9 patients with visual field deficits) into two groups: Group 1 ($n = 5$) received VST plus right hemifield EP; Group 2 ($n = 6$) underwent VST alone. All patients underwent 1-week training. They were evaluated before, immediately after and 1 week post-treatment by means of the following tests: Line Cancelation, Letter Cancelation, Bell Cancelation, Copy of Drawing, and Line Bisection. After treatment, a significant improvement of visual spatial neglect was found in Group 1 vs. Group 2 as measured by the above-mentioned tests. Improvements were maintained at the follow-up evaluation. Within-group comparisons showed significant improvement only in Group 1 at all time points (Zeloni et al., 2002).

(10) Fong et al. (2007) randomized 60 stroke patients (co-morbidity: all patients with left hemiplegia) into three groups: Group 1 ($n = 20$) received voluntary trunk rotation treatment plus right hemifield EP; Group 2 ($n = 20$) underwent voluntary trunk rotation treatment alone; Group 3 ($n = 20$) received occupational therapy. All patients underwent 6-week training. They were evaluated before, immediately after and 1 month post-treatment by means of the Behavioral Inattention Test (BIT), Clock Drawing Test, and FIM. After treatment and at the follow-up evaluation, no significant difference for any outcome measure was found between groups. Statistics for within-group comparisons were not reported (Fong et al., 2007).

(11) Tsang et al. (2009) randomized 34 stroke patients (co-morbidity not specified) into two groups: Group 1 ($n = 17$) performed occupational therapy plus right hemifield EP; Group 2 ($n = 17$) performed occupational therapy alone. All patients underwent 4-week training. They were evaluated before and immediately after treatment by means of the BIT (conventional subtest) and FIM. After treatment, a significant improvement was found in Group 1 vs. Group 2 on the BIT. Within-group comparisons showed significant improvements for all outcome measures in both groups (Tsang et al., 2009).

(12) Ianes et al. (2012) randomized 18 patients (co-morbidity not specified) into two groups: Group 1 ($n = 10$) received right hemifield EP; Group 2 ($n = 8$) underwent VST. All patients underwent 2-week training. They were evaluated before, immediately after and 1 week post-treatment by means of the following tests: Line Cancelation, Bell Cancelation, and Line Bisection. After treatment, no significant difference was found between groups. At the follow-up evaluation, a significant improvement was found in Group 1 vs. Group 2 on the Line Cancelation test. Within-group comparisons showed significant improvements for all outcome measures in both groups (Ianes et al., 2012).

(13) Wu et al. (2013) randomized 27 stroke patients (co-morbidity: all patients with left hemiplegia and 8 patients with visual extinction) into three groups: Group 1 ($n = 9$) received paretic arm CIT plus right monocular EP; Group 2 ($n = 9$) underwent CIT alone; Group 3 ($n = 9$) received occupational therapy. All patients underwent 3-week training. They were evaluated before and immediately after treatment by means of the Catherine Bergego Scale (CBS), Eye Movements (namely: the fixation amplitude from leftmost to rightmost fixation points, the number of fixation points, and the fixation time in the left area), and Arm Kinematic Analysis. In particular, the authors used an eye tracker system to record eye movement by detecting the subject's pupil during the Line Bisection, as well as a seven-camera motion analysis system to evaluate reaction time, duration of the reaching movement, total distance (the path of the hand in three-dimensional space), planned control of the reaching movement (percentage of movement used for the acceleration phase), and trunk lateral shift to left. After treatment, a significant improvement was found in Group 1 and Group 2 vs. Group 3 for the CBS. Furthermore, a significant improvement was found in Group 2 and Group 3 vs. Group 1 for the left fixation point. As for the Arm Kinematic Analysis, a significant improvement in the pre-planned control of the reaching movements was found in Group 1 vs. Groups 2 and 3 and in trunk lateral shift to left in Group 1 vs. Group 2. Furthermore, a significant improvement in the reaction time was found in Group 2 vs. Group 3. Statistics for within-group comparisons were not reported (Wu et al., 2013).

Overall, seven studies used monocular EP (Butter and Kirsch, 1992; Soroker et al., 1994; Serfaty et al., 1995; Walker et al., 1996; Barrett et al., 2001; Khurshid et al., 2009; Wu et al., 2013), five used right hemifield EP (Arai et al., 1997; Zeloni et al., 2002; Fong et al., 2007; Tsang et al., 2009; Ianes et al., 2012), and one compared the effects of right monocular EP with right hemifield EP (Beis et al., 1999). The duration of intervention, the frequency and the duration of each session varied across studies. Six studies (Beis et al., 1999; Zeloni et al., 2002; Fong et al., 2007; Tsang et al., 2009; Ianes et al., 2012; Wu et al., 2013) compared outcomes before and after a period of treatment, while seven studies compared the performances on neglect tests during normal viewing and wearing monocular (Butter and Kirsch, 1992; Soroker et al., 1994; Serfaty et al., 1995; Walker et al., 1996; Barrett et al., 2001; Khurshid et al., 2009) or hemifield EP (Arai et al., 1997). Only three studies included follow-up evaluations (Zeloni et al., 2002; Fong et al., 2007; Ianes et al., 2012).

As to the monocular EP, four studies reported positive effects of right monocular EP (Butter and Kirsch, 1992; Serfaty et al., 1995; Khurshid et al., 2009; Wu et al., 2013) and one study (Barrett et al., 2001) showed a clear improvement in hemispatial neglect during left monocular EP. Two studies found no clear superiority of right vs. left monocular EP (Soroker et al., 1994; Walker et al., 1996) and one study found no effects of right monocular EP (Beis et al., 1999).

As to hemifield EP, one study showed a clear improvement in hemispatial neglect during right hemifield EP (Arai et al., 1997) and three studies found that the combination of right hemifield EP with another rehabilitation technique was more effective than the same treatment applied alone (Arai et al., 1997; Zeloni et al., 2002; Tsang et al., 2009). One study found no differences between the combination of right hemifield EP with another treatment and the same treatment applied alone (Fong et al., 2007), while one study found the same effect between EP applied alone and another rehabilitation technique (Ianes et al., 2012).

With regard to data interpretation, three studies showed results that were inconsistent with the presence of a *Sprague effect* during monocular EP (Soroker et al., 1994; Walker et al., 1996; Barrett et al., 2001). Indeed, according to Sprague's collicular hypothesis (Sprague, 1966b), patching the right eye should have decreased the tendency to make eye movements to the right and therefore reduce left hemispatial neglect. However, the results of these three studies showed no clear increase in leftward eye movements after right monocular EP. On the other hand, two studies (Arai et al., 1997; Ianes et al., 2012) suggested that their observations were consistent with the "forced use" intervention (*Visual exploration constraint theory*), and one study suggested that the findings were consistent with the *Interhemispheric balance theory* (Beis et al., 1999).

Finally, seven studies failed to interpret results in light of a specific theory (Butter and Kirsch, 1992; Serfaty et al., 1995; Zeloni et al., 2002; Fong et al., 2007; Khurshid et al., 2009; Tsang et al., 2009; Wu et al., 2013).

DISCUSSION

The results of the present review showed that EP is a promising procedure in the rehabilitation of patients with hemispatial neglect during the acute, subacute, or chronic phase of stroke. As to the type of EP, the data tend to favor right hemifield EP over monocular EP. The data available to date are insufficient to support or refute the effectiveness of EP at reducing disability and improving patient independence. Few studies investigated maintenance of improvements after EP by short-term follow-up evaluations. The effectiveness of this procedure should be further evaluated by future research.

EFFECTS OF MONOCULAR EP

Right monocular EP was the first approach to be examined in patients with hemispatial neglect. Its effects have been tested mostly in case-controls and single-case studies, which reported highly conflicting results. A few studies found that right monocular EP has some effects on improving patient performance during neglect visual search tests (Butter and Kirsch, 1992; Serfaty et al., 1995; Khurshid et al., 2009). Other studies found no clear superiority of right vs. left monocular EP (Soroker et al., 1994; Walker et al., 1996) and one study described unexpected improvement in hemispatial neglect after left monocular EP (Barrett et al., 2001). Only two studies tested the effects of right monocular EP (Beis et al., 1999; Wu et al., 2013) by means of an RCT design. They used specific analytical instruments to test these effects. The earlier study compared the effects of right monocular EP with those of right hemifield EP using photo-oculography and showed that the monocular EP approach was less effective than the right hemifield EP approach in regaining voluntary control over the deficit (Beis et al., 1999). The right hemifield EP indeed increased the number of times the subject looked at the left zone (Beis et al., 1999). This study reached a PEDro score of 2/10, thus indicating that it has some methodological shortcomings. The later study attempted to compare the effects of right monocular EP plus paretic arm CIT with those of CIT or occupational therapy alone. The main outcome was that CIT combined with monocular EP and CIT alone lead to similar beneficial effects on functional performance in patients' everyday life (Wu et al., 2013). However, these approaches had differential effects on eye movement and reaching kinematics. Indeed, while CIT alone improved eye movements and limb initiation, CIT plus EP facilitated pre-planned control of limb movement, and trunk control (see Results for details). This study reached a PEDro score of 7/10 indicating a fair methodological quality.

Taken together, the studies examining the effect of right monocular EP (Butter and Kirsch, 1992; Soroker et al., 1994; Serfaty et al., 1995; Walker et al., 1996; Beis et al., 1999; Barrett et al., 2001; Khurshid et al., 2009; Wu et al., 2013) on hemispatial neglect are not very convincing; when compared with the right hemifield EP approach, they tend to favor the second technique (Beis et al., 1999). Indeed, the majority were case-control or single-case studies (Butter and Kirsch, 1992; Soroker et al., 1994; Serfaty et al., 1995; Barrett et al., 2001; Khurshid et al., 2009), one RCT had methodological drawbacks (Beis et al., 1999), while another good quality RCT did not display any significant additional effect of monocular EP when combined with CIT (Wu et al., 2013). Moreover, the puzzling evidence that left monocular EP may occasionally lead to an improvement in hemispatial neglect has led some authors to suggest that there is no clear rationale for right monocular EP in hemispatial neglect rehabilitation (Soroker et al., 1994; Walker et al., 1996; Barrett et al., 2001).

EFFECTS OF RIGHT HEMIFIELD EP

Arai et al. (1997) were the first to examine the effects of right hemifield EP in patients with hemispatial neglect after stroke. In this study, 10 patients with hemispatial neglect were tested under normal viewing or while wearing glasses in which the right portion of the lenses was obscured. During right hemifield EP, 8 out of 10 patients improved their ability to explore the left hemispace (Arai et al., 1997). This study gave new insights into the potential effects of this technique on reducing hemispatial neglect. Following on the study by Arai et al. (1997), five RCTs tested the effects of right hemifield EP in hemispatial neglect (Beis et al., 1999; Zeloni et al., 2002; Fong et al., 2007; Tsang et al., 2009; Ianes et al., 2012). These studies tested the effect of right hemifield EP in conjunction with other rehabilitation procedures (VST, Trunk Rotation, Occupational Therapy, CIT), except for the study by Ianes et al. (2012) that compared the effectiveness of right hemifield EP with a conventional VST for hemispatial neglect (Ianes et al., 2012).

As to methodological quality, three of these RCTs (Beis et al., 1999; Fong et al., 2007; Tsang et al., 2009) were rated by means of the PEDro scale (Physiotherapy Evidence Database, 1999), reaching a score of 2/10, 6/10, and 7/10, respectively. Two other studies (Zeloni et al., 2002; Ianes et al., 2012) could not be rated with the PEDro score because they were not considered as physiotherapy interventions.

Beis et al. (1999), Zeloni et al. (2002), and Tsang et al. (2009) showed that the effect of right hemifield EP in combination with other treatments produced better improvement in hemispatial neglect deficit, than the same treatments applied alone. Only one study compared the effects of right hemifield EP treatment alone against another hemispatial neglect treatment (VST) and found that the right hemifield EP was as effective as conventional neglect treatment (I31). Taking into account that the hemifield EP procedure is far less expensive than VST, which requires one-on-one patient-therapist involvement, the results of this study are very relevant for the clinical practice.

Although the available literature on right hemifield EP is encouraging, some clear methodological limitations of the studies merit attention: small patient sample size (Arai et al., 1997; Beis et al., 1999; Zeloni et al., 2002; Ianes et al., 2012), lack of power, and sample size calculation (Arai et al., 1997; Beis et al., 1999; Zeloni et al., 2002; Ianes et al., 2012), lack of follow-up evaluations (Beis et al., 1999; Tsang et al., 2009), inclusion of patients with visual field deficits (because hemifield patching may be too penalizing in such cases) (Arai et al., 1997; Zeloni et al., 2002), use of unchallenging neglect tests (Arai et al., 1997; Ianes et al., 2012), lack of sample size homogeneity in terms of time from stroke (Arai et al., 1997; Zeloni et al., 2002), and severity of hemispatial neglect (Zeloni et al., 2002). All in all, given the potential of the right hemifield EP approach in remediating hemispatial neglect after stroke, future research with improved methodological quality is warranted.

Another potentially interesting research area is the basis of the effects of right hemifield EP. On the one hand, these effects could be explained by the *Interhemispheric balance theory* according to which right hemifield EP may allow or increase detection and selection of visual inputs from the neglected field. These inputs may enhance activation of the damaged (right) hemisphere, allowing a re-balance between the directional orientation processors of the right and left hemispheres. We may suggest that testing the effects of right hemifield EP in a functional Magnetic Resonance Imaging (MRI) or EEG mapping study in healthy subjects and in patients with hemispatial neglect may help further our understanding of the neural basis of this rehabilitation approach.

On the other hand, right hemifield EP might be viewed as another application of such "forced use" intervention (Arai et al., 1997). Following this conceptual model, use of a right hemifield EP may induce patients to visually explore their neglected space according to the *Visual exploration constraint theory* (Ianes et al., 2012).

ADVANTAGES OF EP

Several advantages of EP approaches should be acknowledged. First, it is an inexpensive and easily applicable procedure that requires that patients simply wear spectacles containing monocular or right hemifield EP. It may be used for many hours a day and provide long-term stimulation, a condition not applicable to conventional hemispatial neglect treatments. Second, patients may not be actively involved in one-on-one treatment sessions. This is particularly relevant in patients in whom the clinical condition may interfere with actively participating in treatment sessions due to medical reasons or to a lack of sitting tolerance. Finally, EP approaches may be easily coupled with other rehabilitation techniques or performed at home during daily activities with the support of a caregiver.

All these features make the EP particularly suitable for patients in the acute-sub-acute stage after stroke (Ianes et al., 2012). This last point is especially important because during the first post-stroke period patients may be unable to actively participate in rehabilitation treatment sessions, and could benefit from a treatment regime in which they are passive beneficiaries (Ianes et al., 2012). In addition, trunk misalignment or a lack of trunk postural control in the early stage after stroke may not allow the patient to receive conventional treatment.

RECOMMENDATIONS TO CLINICIANS

Taken together, the results of the present review show that right hemifield EP might be a promising procedure in treating hemispatial neglect. However, providing clear recommendations to clinicians is difficult for several reasons.

First, two RCTs rated 6/10 and 7/10 by the PEDro database displayed partially conflicting results on the effectiveness of right hemifield EP in the early phases after stroke (Fong et al., 2007; Tsang et al., 2009). However, the power of these studies was inadequate because of the small sample size. The authors, who suggested that a replication of the studies with an appropriate patient sample is warranted, admitted this. It is worth noting here that this point highlights a limit of the PEDro scale, in that the presence of an adequate patient sample size is not considered as a criterion for rating methodological quality (Geha et al., 2013).

Second, two RCTs relevant to our review were not found to be eligible for PEDro rating because they were not considered as physiotherapy interventions (Zeloni et al., 2002; Ianes et al., 2012). This precluded the possibility to rate the RCTs by Zeloni et al. (2002) and Ianes et al. (2012) who showed that right hemifield EP combined with another treatment (Zeloni et al., 2002) or applied alone (Ianes et al., 2012) is more effective or at least as effective as a standard VST.

To summarize, the results of the present review globally tend to support the usefulness of right hemifield EP in clinical practice. In order to define a level of evidence by means of the standard rehabilitation evidence rating tools, however, further research is warranted by means of adequately powered RCTs and/or a meta-analysis of the present literature data.

DIRECTIONS FOR FUTURE RESEARCH

Future studies in this field are recommended. These studies should be directed to investigate the effects of EP on reducing hemispatial neglect severity, disability, and to improve patient independence. It is also desirable that the limitations of the current literature are taken into consideration. First, RCTs in large patient samples and with multiple and long-term follow-up evaluation sessions (at least at 1 and 3 months after treatment) are warranted. This is crucial to have reliable evidence about the role of EP in stroke rehabilitation in order to convey a use/not use message to clinicians. Second, studies involving sub-acute patients should be implemented, where spontaneous recovery will need to be considered as a potential confounding factor. The most suitable method to control for the effects of spontaneous recovery would be to include an untreated group. However, the inclusion in the study of an untreated group is difficult to justify, because withholding treatment for hemispatial neglect from a patient is unethical. Instead, a specific study design such as "delayed treatment" should be applied

(Paolucci et al., 2000). Third, patients with hemianopia should be excluded or, if included, they should be analyzed separately. Finally, the assessment procedures should include both standardized batteries for the evaluation of hemispatial neglect severity, such as BIT, and the evaluation of disability.

CONCLUSION

To conclude, the results of the present review show that EP is a promising procedure in the treatment of hemispatial neglect after stroke and that further research in the evaluation of EP is needed.

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Spatial working memory deficits represent a core challenge for rehabilitating neglect

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Left neglect following right hemisphere injury is a debilitating disorder that has proven extremely difficult to rehabilitate. Traditional models of neglect have focused on impaired spatial attention as the core deficit and as such, most rehabilitation methods have tried to improve attentional processes. However, many of these techniques (e.g., visual scanning training, caloric stimulation, neck muscle vibration) produce only short-lived effects, or are too uncomfortable to use as a routine treatment. More recently, many investigators have begun examining the beneficial effects of prism adaptation for the treatment of neglect. Although prism adaptation has been shown to have some beneficial effects on both overt and covert spatial attention, it does not reliably alter many of the perceptual biases evident in neglect. One of the challenges of neglect rehabilitation may lie in the heterogeneous nature of the deficits. Most notably, a number of researchers have shown that neglect patients present with severe deficits in spatial working memory (SWM) in addition to their attentional impairments. Given that SWM can be seen as a foundational cognitive mechanism, critical for a wide range of other functions, any deficit in SWM memory will undoubtedly have severe consequences. In the current review we examine the evidence for SWM deficits in neglect and propose that it constitutes a core component of the syndrome. We present preliminary data which suggest that at least one current rehabilitation method (prism adaptation) has no effect on SWM deficits in neglect. Finally, we end by reviewing recent work that examines the effectiveness of SWM training and how SWM training may prove to be a useful avenue for future rehabilitative efforts in patients with neglect.

Keywords: neglect, spatial working memory, prism adaption, rehabilitation, parietal lobe

One of the most debilitating disorders arising from right hemisphere brain damage is known as neglect. Neglect typically results from damage to the right temporal-parietal or superior temporal cortex (Vallar and Perani, 1986; Karnath et al., 2001, 2004; Mort et al., 2003; Buxbaum et al., 2004; Verdon et al., 2010; Karnath and Rorden, 2012), or from damage to subcortical structures such as the basal ganglia or thalamus (Karnath et al., 2002). Clinically, neglect is characterized by an inability to attend to or interact with people or objects on the contralesional (i.e., left) side (for reviews, see Heilman et al., 2002; Mesulam, 2002; Husain and Rorden, 2003; Danckert and Ferber, 2006). In severe cases, patients may act as if the left half of their world has simply ceased to exist (Mesulam, 1981). This unique, lateralized deficit of awareness for objects and events in the environment can greatly reduce the patient's quality of life. Given that neglect is quite prevalent, occurring in 40–70% of all cases of right hemisphere stroke (Cherney and Halper, 2001; Buxbaum et al., 2004; Karnath et al., 2004; Ringman et al., 2004), and is a significant predictor of poorer overall functional recovery (Cherney et al., 2001), finding effective methods to rehabilitate the disorder is of great clinical importance.

Traditional models of neglect have focused on impaired spatial attention as the core deficit (e.g., Posner et al., 1984; Kinsbourne, 1993; Behrmann et al., 1997; Driver and Mattingley, 1998; Bartolomeo and Chokron, 2002). Specifically, neglect patients have been shown to have a rightward attentional bias (i.e., they preferentially attend to information on the right side). This is consistent with "gradient" models of neglect (Kinsbourne, 1987, 1993) which suggest that neglect severity increases for more leftward locations in space (i.e., even leftmost locations in right space are neglected more than locations further rightward). Neglect patients are also thought to have a "disengage deficit" such that they have great difficulty reorienting attention from right to left, neglected space (Posner et al., 1984; Bartolomeo and Chokron, 2002).

More recent studies have shown that neglect is a heterogeneous disorder comprised of a constellation of deficits including impaired temporal allocation of attention (Husain et al., 1997), poor time perception (Danckert et al., 2007; Merrifield et al., 2010; Oliveri et al., 2013), and spatial working memory (SWM) impairments evident throughout visual space (Husain et al., 2001; Ferber and Danckert, 2006). We will argue here that the deficits in SWM represent a core component of the disorder and as such, should be a target for rehabilitative strategies.

REHABILITATING NEGLECT

Given that neglect is such a debilitating disorder, a great deal of research has focused on developing effective rehabilitation methods. A full analysis of each of these rehabilitation methods is beyond the scope of the current review (for a systematic review, see Luaute et al., 2006). Although many different techniques, including visual scanning training (Weinberg et al., 1977), caloric vestibular stimulation (Rubens, 1985), optokinetic stimulation (Pizzamiglio et al., 1990), neck muscle vibration (Karnath, 1995), and limb activation (Robertson and North, 1993) have been shown to have some benefits for neglect patients, most are impractical for a variety of reasons. For example, although visual scanning training has been shown to be effective in some studies (e.g., Weinberg et al., 1977, 1979), it typically involves a lengthy training program (from weeks to months) and requires the patient to make a conscious effort to attend to left space which is difficult given that many patients lack insight into their rightward bias. Techniques such as caloric vestibular stimulation, optokinetic stimulation, and neck muscle vibration, which induce a temporary nystagmus, can be uncomfortable for the patient, are challenging to implement on a regular basis, and typically only lead to a brief amelioration of symptoms (i.e., lasting only around 30 min; Rubens, 1985; Pizzamiglio et al., 1990; Vallar et al., 1990; Karnath, 1995). Finally, limb activation, in which the patient is encouraged to utilize their left, contralesional limb (Robertson and North, 1993; Robertson et al., 1995; Eskes et al., 2003), is impossible for the most severely hemiparetic, and impractical for other patients who now rely more heavily on their intact ipsilesional limb for whatever degree of independence they can achieve.

PRISM ADAPTATION AND NEGLECT

One rehabilitation technique that does not suffer from many of these same limitations, and has been shown to be reasonably effective, is the prism adaptation procedure developed by Rossetti et al. (1998). In this procedure, patients wear prismatic lenses that shift vision temporarily further rightward. While wearing prisms, the patient points to targets located to the left and right of their body midline. Initially, the patient misses to the right due to the visual shift induced by the prisms. Over successive trials the patient must make leftward corrections for their initial rightward pointing errors (for reviews of the prism adaptation method, see Redding et al., 2005; Redding and Wallace, 2006). After only a brief (∼5 min) exposure period, once prisms are removed, the patient now makes *leftward* pointing errors – the so-called after-effect. This after-effect is associated with a range of changes in behavior including exploratory behaviors that now shift leftward, into neglected space, and dramatic improvements on standard clinical tests of neglect (**Figure 1**; Rossetti et al., 1998).

Since this original study a plethora of studies have shown that prism adaptation can influence a broad range of neglect symptoms, with positive effects seen for spatial attention (Berberovic et al., 2004; Striemer and Danckert, 2007; Nijboer et al., 2008; Schindler et al., 2009), extinction (Maravita et al., 2003), exploratory eye movements (Dijkerman et al., 2003; Ferber et al., 2003; Angeli et al., 2004; Serino et al., 2006), posture and balance (Tilikete et al., 2001), and somatosensory function (McIntosh et al., 2002; Dijkerman et al., 2004). There is, however, also some controversy surrounding whether or not prisms lead to changes in the strong perceptual biases evident in neglect – biases that favor right space or the right half of objects (Dijkerman et al., 2003; Ferber et al., 2003; Sarri et al., 2006, 2010; Striemer and Danckert, 2010a,b). Specifically, some studies have demonstrated that while prisms can induce a leftward shift in exploratory motor behaviors and covert attention (Dijkerman et al., 2003; Ferber et al., 2003; Striemer and Danckert, 2010a), these changes do not necessarily translate into changes in perceptual biases, which are a hallmark symptom of neglect (for a review, see Striemer and Danckert, 2010b). For example, when viewing vertically aligned chimaeric faces (faces shown as smiling on one side and neutral on the other) neglect patients typically report the face smiling on the right as appearing happier (Mattingley et al., 1993). Prior to any intervention, it can be shown that patients only *look* at the right side of such faces. We showed that after prism adaptation exploratory eye movements now took in the left side of the chimaeric faces as well as the right side (Ferber et al., 2003). Importantly, the patient continued to report that the right-sided smiling face appeared to be happier even though prisms had shifted his exploratory eye movements leftwards (Ferber et al., 2003). This dissociation between altered actions and attention, coupled with unchanged perceptual biases, is not unique to faces (Dijkerman et al., 2003; Ferber and Danckert, 2006; Striemer and Danckert, 2010a).

In addition, whereas some studies have shown that repeated exposure to prisms creates long-term benefits for neglect (Frassinetti et al., 2002; Serino et al., 2006, 2009; Shiraishi et al., 2008), recent randomized control trials have failed to observe any clear evidence for long-term improvements (Nys et al., 2008; Turton et al., 2009).

In summary, while prism adaptation is clearly beneficial for reducing attentional biases in patients, it may not be effective at addressing all of the cognitive deficits present in neglect. For example, one domain that has not been explored to any great extent (at least to our knowledge) is the influence of prism adaptation on non-spatially lateralized deficits in neglect such as SWM (Husain et al., 2001; Ferber and Danckert, 2006), time estimation (Danckert et al., 2007; Merrifield et al., 2010), and sustained-temporal attention (Husain et al., 1997). There is some controversy as to whether these deficits should be considered core symptoms of neglect (Danckert and Ferber, 2006), or viewed merely as *exacerbating* factors (Husain and Rorden, 2003). Given that attentional deficits can be rehabilitated (to some degree), while other perceptual biases remain unchanged, it is at least plausible that non-spatially lateralized impairments play a more central role in the disorder (Danckert and Ferber, 2006). Nevertheless, it remains undisputed that current therapeutic approaches cannot be considered unequivocally successful.

One deficit that would be particularly devastating for neglect patients is the inability to keep track of spatial information over time (i.e., SWM). Specifically, while a strong tendency to focus attention on right space undoubtedly biases the patient's initial exploratory behaviors, an inability to keep track of where one has *already attended* will mean that left space is rarely, if ever, explored.

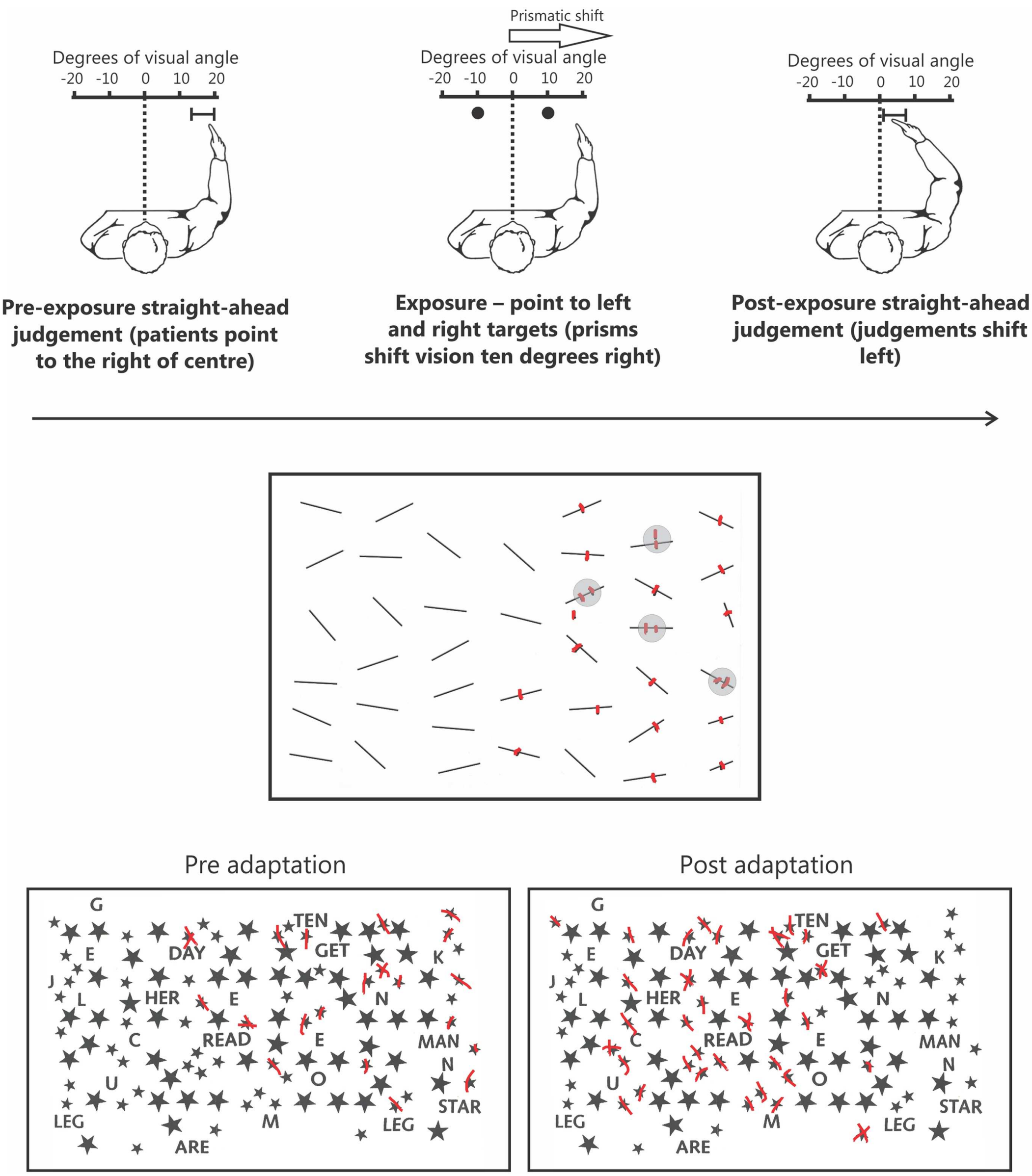

FIGURE 1 | The upper panel depicts the prism adaptation procedure used in neglect. Left: prior to adaptation the patient is blindfolded and asked to point straight ahead of their body midline. Owing to an altered egocentric reference frame, patients typically point far to the right. Middle: during the adaptation procedure patients wear prisms that shift their vision 10° to the right. When asked to point to targets to the left and right they initially miss to the right because of the visual shift induced by the prisms. Right: following ~5 min of prism adaptation, when the patient is again asked to close their eyes and point straight ahead, they now point much closer to true center. The middle panel depicts typical performance on a cancelation test. Specifically, in addition to missing numerous targets on the left side of the page the patient has also missed a target on the right side of the page. Note that the patient is also demonstrating "revisiting" behavior (highlighted by gray circles) by re-canceling previously canceled items as if they were new, indicative of impaired spatial working memory. The lower panel depicts an example of how prism adaptation improves performance on clinical tests of neglect. Prior to prism adaptation the patient misses targets on the left side of the page. However, following adaptation the patient now cancels many more targets on the left side of the page.

SPATIAL WORKING MEMORY

Working memory is conceptualized as a core cognitive skill that underlies human thought processes (for a review, see Baddeley, 2003). For example, studies have linked working memory capacity to general fluid intelligence (Engle et al., 1999), and attentional control (Kane et al., 2001; Cabeza et al., 2008). Working memory is typically defined as the ability to hold information online after it has been removed from view, and it is thought to have a limited capacity. The classic working memory model first proposed by Baddeley and colleagues (for recent reviews, see

Baddeley, 2003, 2012) suggested that working memory functions could be fractionated into three primary components: a phonological loop important for auditory and verbal working memory, a visuospatial sketchpad important for storing visual and spatial information, and a central executive that flexibly allocates attentional resources to the separate storage systems (Baddeley, 2003, 2012). Over the years, there have been several revisions to the model. Most notably for the purposes of the present review, is the division of the visuospatial sketchpad into visual and SWM. Specifically, this distinction suggests that remembering the location of an object requires separate visual codes to remember the identity and location. Indeed, research has shown that it is possible to observe selective deficits in either visual or SWM following brain damage (e.g., Della Sala et al., 1999). However, it is important to note that although it is possible to dissociate performance on tests of visual and SWM, many patients present with deficits on both measures (Della Sala et al., 1999). For our purposes we focus specifically on the relationship between neglect and SWM; that is, the maintenance of spatial information over time.

Interestingly, previous brain imaging studies have noted that SWM and spatial attention are controlled by many of the same brain regions including both the frontal and posterior parietal cortices (for reviews, see Awh and Jonides, 2001; Corbetta et al., 2002; Wager and Smith, 2003; Cabeza et al., 2008; Ikkai and Curtis, 2011). Based on these findings, and the fact that SWM performance can be enhanced at attended locations (Awh et al., 1998), some have argued that spatial attention is required in order to "rehearse" and maintain information in SWM (Awh et al., 1998; Awh and Jonides, 2001; Theeuwes et al., 2009). However, more recent behavioral studies have shown that SWM performance is not always enhanced at attended locations (Belopolsky and Theeuwes, 2009). This suggests that while spatial attention and SWM clearly involve overlapping brain networks, it is possible to dissociate them from one-another. Given that spatial attention and SWM involve largely overlapping brain networks it is not surprising that lesions to right fronto-parietal regions, in addition to leading to neglect, are also likely to cause deficits in SWM (e.g. Vallar and Perani, 1986; Mattingley et al., 1998; Karnath et al., 2001; Mort et al., 2003; Sapir et al., 2007).

SPATIAL WORKING MEMORY IN NEGLECT

Some of the most common clinical tests used to assess neglect are cancelation tasks in which patients must "cross out" target items embedded within an array of distracters (**Figure 1**). Densely neglecting patients will cancel out many more targets on the right than on the left side of the page. Although this pattern of performance is considered a classic manifestation of disordered spatial attention in neglect, recent data has shown that this deficit reflects impaired SWM independent of attentional biases (Husain et al., 2001; Wojciulik et al., 2001, 2004). On cancelation tasks, in addition to missing targets on the left, patients often fail to cancel targets presented in right, putatively non-neglected, space (**Figure 1**; see Danckert and Ferber, 2006). This deficit is suggestive of an inefficient search strategy in which the patient has trouble keeping track of where they have previously searched. A more direct confirmation of a SWM deficit comes from "revisiting" behavior in which patients will re-cancel items they have already canceled in right space, thus treating "old" items as if they were "new" (**Figure 1**; Husain et al., 2001; Wojciulik et al., 2001, 2004).

Wojciulik et al. (2001) had a neglect patient perform a variety of cancelation tasks to explore the role of SWM. In the first, the patient used a salient marker to indicate cancelations, whereas the second version had them make "invisible" marks (i.e., canceling targets with a capped marker). The patient made many more re-cancelations (i.e., "revisiting" errors) for targets in right space in the invisible compared to the visible marks condition. Thus, without a highly salient marker indicating that the patient had already canceled the item, she continued to treat previously canceled items as "new." These same findings were later confirmed in a larger group of patients (Wojciulik et al., 2004). Critically, studies have since demonstrated that revisiting errors were not simply a manifestation of perseveration, as a majority of cancelations were delayed revisits (i.e., cancelations of old targets occurring after other targets had been canceled; Parton et al., 2006).

Husain et al. (2001) had a neglect patient perform a variety of cancelation tasks while eye movements were monitored. Despite making an equal number of leftward and rightward saccades, the patient's search was largely restricted to the right half of the display. In addition, the patient also demonstrated significant revisiting behavior by re-fixating many items in right space. Importantly, follow-up experiments with the same patient demonstrated that this revisiting behavior was directly influenced by working memory load. That is, when the total search display was reduced, or the number of possible target items was decreased, revisiting behavior was also significantly reduced. Furthermore, the patient's revisiting behavior was positively correlated with the number of items missed on the *left* side of the display (see also Mannan et al., 2005).

A closely related concept that may explain SWM difficulties evident in neglect involves the updating of spatial locations across successive saccades (Duhamel et al., 1992a,b; Heide et al., 1995; Pisella and Mattingley, 2004; Vuilleumier et al., 2007; Vasquez and Danckert, 2008). The process of updating spatial locations across saccades is commonly referred to as saccadic remapping. Saccadic remapping is typically studied using the "double step" saccade task. In this task participants must saccade to successive targets presented in under 200 ms. Relying on retinal information alone would lead to an erroneous saccade to the second target. Instead, observers anticipate the sensory consequences of the first saccade, remap their internal representation of space accounting for those sensory consequences, and make an accurate saccade to the second target (Duhamel et al., 1992a). Patients with neglect commonly fail to accurately acquire the second target in a double step saccade task (Duhamel et al., 1992b; Heide et al., 1995; Pisella and Mattingley, 2004; Vuilleumier et al., 2007). Interestingly, saccadic remapping deficits in neglect have been shown to correlate with neglect severity as measured by standard clinical tasks (Vuilleumier et al., 2007).

Although saccadic remapping deficits might contribute to SWM deficits in search and cancelation tasks which by their nature require successive saccades to find targets (for reviews, see Pisella and Mattingley, 2004; Danckert and Ferber, 2006), other studies have demonstrated SWM impairments in neglect that are not easily explained by remapping deficits. For example, Malhotra et al. (2005) adapted the well-known Corsi Block Tapping test that is widely used to assess a participant's "spatial span" (a measure of SWM; Kessels et al., 2000). In this task, the patient is required to recall a sequence of spatial locations tapped out on blocks by the experimenter. In their version, Malhotra et al. (2005) presented the spatial sequences on a computer screen by illuminating colored disks in a pre-determined order. Following the presentation of the spatial sequence, the patient was asked to tap out the sequence in the correct order. Importantly, targets were aligned vertically in central space to avoid any confound from spatial orienting deficits. Results indicated that neglect patients had a significantly decreased spatial span ($M = 1.3$ positions) compared to right brain damaged patients without neglect ($M = 2.6$), and both young ($M = 3.5$) and elderly ($M = 2.6$) controls. Notably, this impairment of SWM was observed even though stimuli were presented in central, presumably non-neglected space.

In a task similar to that used by Malhotra et al. (2005), we showed that the SWM impairment in neglect extended to right space (Ferber and Danckert, 2006). In our SWM task, target locations were vertically aligned in right space (**Figure 2**). On each trial patients were presented with three targets, followed by a brief delay (3 s). A circle probe then appeared and patients had to indicate whether the probe occupied a target location or not. Compared to right brain damaged patients without neglect and healthy controls, neglect patients were severely impaired on this task (**Figure 2**). Importantly, all groups performed at ceiling on a verbal working memory task that mirrored the spatial layout used in the SWM task (**Figure 2**). Thus, neglect patients do not suffer from a generic impairment of working memory, but instead demonstrate a domain specific problem related to SWM.

In summary, early studies indicated that neglect patients had difficulty keeping track of previously searched locations during cancelation tasks, suggestive of a deficit in SWM (Wojciulik et al., 2001, 2004). Subsequent studies extended these findings by demonstrating that SWM deficits were evident in neglect independent of spatial orienting deficits and when stimuli were presented in non-neglected space (Malhotra et al., 2005; Ferber and Danckert, 2006).

Given the overwhelming evidence implicating SWM deficits in neglect, any attempt to rehabilitate the disorder will be successful only inasmuch as it deals with this core deficit. Unfortunately, no studies to our knowledge have attempted to examine the effectiveness of current rehabilitation protocols for neglect on SWM deficits. In the next section, we will explore the effectiveness of prism adaptation, which could be considered the best treatment currently available for neglect, and its effects on SWM.

PRISM ADAPTATION AND SPATIAL WORKING MEMORY IN NEGLECT

As mentioned previously, a number of studies over the last decade suggest that prism adaptation can reduce both the rightward attentional bias and the "disengage deficit" which are prominent in neglect patients (Maravita et al., 2003; Berberovic et al., 2004; Striemer and Danckert, 2007; Nijboer et al., 2008; Schindler et al., 2009). In addition, prisms have also been shown to reduce

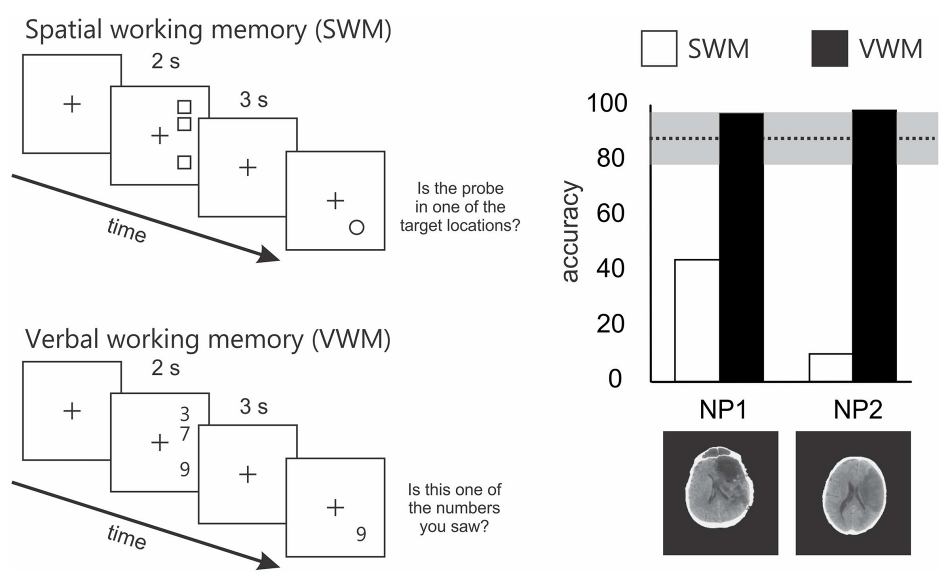

FIGURE 2 | Schematics of the spatial and verbal working memory tasks and results from 2 of the 4 patients tested by Ferber and Danckert (2006). The upper left panel depicts the layout of the spatial working memory task. Three squares were presented vertically aligned in right space for 2 s. Patients had to remember these locations over a 3-s delay. Following the delay a probe stimulus (a circle) appeared and the patient had to decide whether it was in a position previously occupied by one of the three squares. The lower panel depicts the layout for the verbal working memory task. Essentially the verbal working memory task used the same layout as the spatial working memory task. However, instead of remembering target locations patients had to remember three digits over a 3-s delay. Following the delay, the patient had to decide whether the probe digit was the same as one of the three previously presented digits. The right panel depicts the results of the spatial working memory task in a subset of two patients studied by Ferber and Danckert (2006). Specifically, both neglect patients performed extremely poorly on the spatial working memory task compared to right brain damaged controls ($n = 4$) without neglect (mean performance and standard deviation represented by the dotted line and gray bar). However, both neglect patients performed at ceiling on the verbal working memory task.

exploratory motor biases such that patients begin to re-explore previously neglected (left) space (Dijkerman et al., 2003; Ferber et al., 2003; Serino et al., 2006); however, many of the perceptual biases remain unaltered following prism adaptation (Dijkerman et al., 2003; Ferber et al., 2003; Sarri et al., 2010; Striemer and Danckert, 2010a,b). In other words, although prism adaptation may mean that a neglect patient *can* attend more efficiently to the left in some circumstances, their residual perceptual biases mean that they are still *not likely* to attend to the left and/or that attended information may not reach the level of conscious awareness (for further discussion of this issue, see Danckert and Ferber, 2006). The fact that perceptual biases are largely unaffected following prism adaptation further reinforces the notion that neglect is much more than simply a disorder of attention and that many non-spatially lateralized deficits (including SWM deficits in central and right space) contribute significantly to the disorder. Therefore, it is our contention that a failure to address these non-spatially lateralized deficits will result in only a partial rehabilitation of neglect. Importantly, while the directional visuomotor remapping induced by prisms might be beneficial in helping patients attend to and explore previously neglected space, it is unclear what effect prisms might have on non-spatially lateralized deficits in neglect such as deficits in SWM (Striemer and Danckert, 2010b).

We recently explored this in one neglect patient (patient NS) using our original SWM task in which targets are presented in right, putatively non-neglected space (**Figure 3**). Note that we have previously reported data from patient NS comparing the effects of prism adaptation on line bisection and landmark task performance (Striemer and Danckert, 2010a). Patient NS is an 80-year-old, right-handed female who presented with neglect (assessed via line bisection, cancelation, and figure copying) following a stroke affecting the right thalamus and surrounding white matter in right parietal cortex (**Figure 3**). Following prism adaptation patient NS demonstrated a significant leftward shift as measured by proprioceptive judgments of subjective straight ahead, that was evident by the end of the experiment (**Figure 3**). In addition, following prism adaptation, NS also demonstrated significant reductions in her rightward bias in line bisection, and an increase in the number of targets canceled on the left side of two cancelation tasks (**Figure 3**). Importantly, she showed no improvement whatsoever on our SWM task following prism adaptation (**Figure 3**). Note that in our previous study (i.e., Striemer and Danckert, 2010a) NS also failed to demonstrate any significant reduction in her rightward perceptual bias on the landmark task.

It is important to note that we have also found the same dissociation between beneficial effects of prisms on clinical tests of neglect but no changes in SWM performance in six additional right brain damaged patients, many of whom also had neglect (manuscript currently being prepared for publication).

Our contention that SWM performance is not altered by prism adaptation is further supported by a recent fMRI study by Saj et al. (2013) in which they examined performance in a bisection task, a spatial attention task, and a SWM task prior to and following prism adaptation in a group of seven neglect patients. Behavioral results indicated that prism adaptation improved performance on the bisection and spatial attention tasks, but did not improve SWM performance. Furthermore, their imaging results indicated that improvements in the bisection and spatial attention tasks were correlated with increased activity in the parietal, frontal, and occipital lobes bilaterally. However, no significant changes in activation were detected for the SWM task post prism adaptation.

Given that we are arguing that SWM represents a core deficit in neglect, one might question how prism adaptation can improve several aspects of neglect (i.e., exploratory motor biases, spatial attention) without influencing SWM? This is an important observation that we believe underscores two important points: (1) that it is *possible* to dissociate spatial attention from SWM performance (Belopolsky and Theeuwes, 2009); and (2) that neglect is a heterogeneous disorder comprised of a constellation of deficits and only by focusing on each of the deficits that comprise neglect will we be able to successfully ameliorate the disorder.

In summary, these results suggest that it is possible that prism adaptation may not be a effective treatment for SWM deficits in neglect, although further research in larger groups of patients is required for any definitive conclusions to be made. However, it is still important to highlight that even though research has clearly demonstrated that prisms can improve attention and exploratory motor behaviors, the research reviewed here suggests that it may not be effective for treating other aspects of neglect such as perceptual biases or SWM deficits. Therefore, developing new rehabilitation techniques that might reduce these additional components of neglect is necessary in order for a full recovery to occur. In the next section, we will discuss whether directed SWM training might be able to help further rehabilitate patients with neglect.

SPATIAL WORKING MEMORY TRAINING AND NEGLECT

As mentioned previously, working memory can be considered a foundational cognitive skill that underlies human thought (Engle et al., 1999; Baddeley, 2003), and may serve as an interface between attention, perception, and decision making processes (Baddeley, 2003). It has also been shown that SWM in particular may rely, at least partially, on spatial attention in order keep spatial information active in memory when it is no longer visible (Awh et al., 1998; Awh and Jonides, 2001). Critically, both attention and SWM share common neural substrates in the frontal and posterior parietal lobes (for reviews, see Awh and Jonides, 2001; Wager and Smith, 2003; Husain and Nachev, 2007; Cabeza et al., 2008; Ikkai and Curtis, 2011). Therefore, damage to right hemisphere frontal and parietal cortex, regions shown to be involved in neglect (Vallar and Perani, 1986; Mattingley et al., 1998; Karnath et al., 2001; Mort et al., 2003; Sapir et al., 2007), will also result in severe deficits in SWM. Given that SWM is a foundational cognitive skill, any attempt to rehabilitate neglect must address this core cognitive deficit. Unfortunately, no current therapies for neglect directly address SWM as a target for rehabilitation. In addition, as just demonstrated, prism adaptation, which could be seen as one of the most promising rehabilitation techniques available for neglect may not have any influence on SWM capacity. Therefore, we would suggest that what is needed is a targeted therapy that focuses on retraining SWM in neglect.

One of the most important questions to address at the outset is whether it is actually possible to increase working memory capacity using training procedures. A series of recent studies suggest both that working memory capacity can be improved through

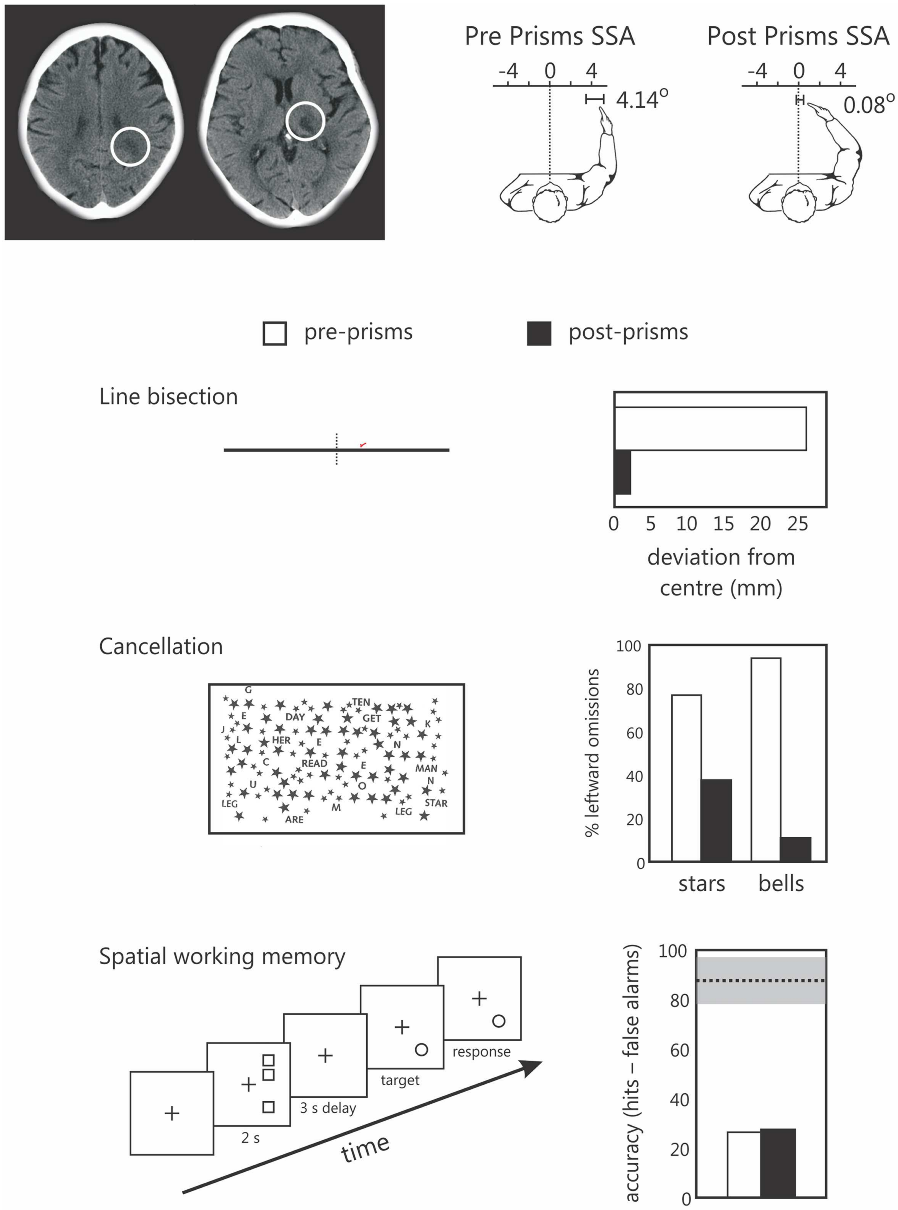

FIGURE 3 | Data from the single case study of patients NS, an 80-year-old right-handed female. The upper panel depicts NS's lesions to the parietal white matter (left) and thalamus (right) of the right hemisphere. To the right of these images are her subjective straight ahead (SSA) judgments made prior to prisms (left panel shows a 4.14° rightward bias) and after prism adaptation (SS = 0.08 degrees – not different from true center relative to her own body midline). The lower panels depict NS's performance on line bisection, two cancelation tests, and the spatial working memory task prior to (pre-prisms; open bars), and following (post prisms; black bars) prism adaptation. Note that NS demonstrated a significant reduction in her rightward bias in line bisection, and a reduction in the number of items missed on the left in both cancelation tasks, but no change in her spatial working memory performance following prism adaptation. Note that for the spatial working memory data the dotted line and gray bar represent the mean performance (and standard deviation) of a group of right brain damaged controls without neglect tested in a previous study (Ferber and Danckert, 2006). We have since found a similar failure to improve SWM following prism adaptation in a group of six additional right brain damaged patients (Locklin and Danckert, in preparation).

training, and that such training may transfer to other cognitive capacities (Klingberg et al., 2002, 2005; Klingberg, 2010). This is not a trivial matter. One of the more persistent and recalcitrant challenges to rehabilitation and training in general is that improvement on the trained task often fails to lead to any improvement on untrained tasks (i.e., transfer).

Klingberg and colleagues (e.g., Klingberg et al., 2002, 2005) recently developed a computerized working memory training procedure using a variety of tasks (both verbal and SWM) that focus on increasing working memory capacity by adjusting the working memory load on a trial-by-trial basis based on the individual participant's performance. Thus, the training procedure is tailored to the individual, and their current level of skill. Following the training regimen, participants demonstrate a significant improvement in working memory capacity as measured by the working memory training tasks (Klingberg et al., 2002, 2005; Westerberg et al., 2007). However, what is more impressive is the fact that the working memory training actually *transfers to untrained tasks* (Klingberg et al., 2002, 2005; Westerberg et al., 2007; Klingberg, 2010). That is, following training on a battery of verbal and SWM tasks, participants demonstrate improvements in other capacities including inhibition of unwanted responses (i.e., as measured by the Stroop; MacLeod, 1991), vigilance, and sustained attention (i.e., as measured by the continuous performance task and the paced auditory serial attention test; Beck et al., 1956; Tombaugh, 2006), SWM (as measured by other untrained tests), and reasoning (i.e., as measured by Raven's progressive matrices). In other words, verbal and SWM training led to improvements in a broad range of cognitive skills that were not directly targeted by the training program itself (for a review, see Klingberg, 2010). Such improvements in working memory capacity and other cognitive abilities have been demonstrated in healthy individuals (Klingberg et al., 2002; Olesen et al., 2004), children with ADHD (Klingberg et al., 2002, 2005), and more recently, in stroke patients (Westerberg et al., 2007).

Interestingly, studies have shown that individual differences in visual working memory capacity in healthy individuals are positively correlated with activity in the intraparietal sulcus (e.g., Todd and Marois, 2004; Vogel and Machizawa, 2004). Olesen et al. (2004) examined which brain regions responded to SWM training by scanning healthy participants (using fMRI) before, during, and after 5 weeks of SWM training. The results indicated that SWM improvements following training were related to increased activity in the middle frontal gyrus and superior, inferior, and intraparietal regions bilaterally. This bilateral activation is important for the proposition being put forth here, namely that SWM training may help rehabilitate neglect. Specifically, any training related benefits may depend on the capacity for perilesional regions to be "retrained" and for homologous contralesional brain regions to compensate for lost function.

In summary, a number of studies have demonstrated that both verbal and SWM can be improved using training programs, and these improvements transfer to a variety of untrained tasks (Klingberg et al., 2002, 2005; Olesen et al., 2004; Westerberg et al., 2007; Klingberg, 2010). In addition, improvements in SWM capacity following training were shown to be positively correlated with activity in the middle frontal gyrus and posterior parietal cortex bilaterally (Olesen et al., 2004). Based on these data, SWM training in neglect may be expected to not only improve SWM capacity (a core deficit in neglect, Danckert and Ferber, 2006), but also to transfer to other untrained cognitive functions like attention (Westerberg et al., 2007), and executive control (Klingberg et al., 2002, 2005; Westerberg et al., 2007) which are also deficient in patients with neglect (e.g., Husain et al., 1997; Bartolomeo and Chokron, 2002; Danckert et al., 2011). Furthermore, SWM training might also be able to increase activity in undamaged regions of the frontal and posterior parietal cortex (Olesen et al., 2004) in the right hemisphere which are known to be chronically underactive in patients with neglect (Corbetta et al., 2005), as well as bootstrapping onto intact left hemisphere regions that may support retrained functions (Olesen et al., 2004).

Finally, it should be stated explicitly that we are not trying to suggest that SWM training alone will constitute a "cure" for neglect. It is quite conceivable that SWM training could be combined with other existing techniques that target more specific attentional and exploratory motor biases in neglect such as prism adaptation (and/or other techniques). In this sense we see SWM as being a complementary approach to many of the methods already in use to treat neglect.

CONCLUSION

The evidence reviewed here suggests that SWM deficits are pervasive in neglect and thus constitute a core component of the syndrome. A severe limitation of the current strategies developed to rehabilitate neglect is that none of them specifically target SWM. What is needed then are rehabilitation strategies for neglect that are specifically aimed at increasing SWM capacity. The evidence reviewed here suggests that SWM training not only improves SWM performance, but also leads to improvements in untrained tasks (i.e., "transfer"; Klingberg, 2010). Furthermore, the improvements in SWM following training have been shown to rely on increased activity in frontal and parietal cortex bilaterally (Olesen et al., 2004). Therefore, we suggest that SWM training may constitute a promising avenue for future rehabilitative efforts in patients with neglect.

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Statistical learning as a tool for rehabilitation in spatial neglect

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We propose that neglect includes a disorder of representational updating. Representational updating refers to our ability to build mental models and adapt those models to changing experience. This updating ability depends on the processes of priming, working memory, and statistical learning. These processes in turn interact with our capabilities for sustained attention and precise temporal processing. We review evidence showing that all these non-spatial abilities are impaired in neglect, and we discuss how recognition of such deficits can lead to novel approaches for rehabilitating neglect.

Keywords: spatial neglect, rehabilitation, priming, statistical learning, updating

INTRODUCTION

The spatial impairments of neglect are striking and have dominated most research until the past few years (Pisella and Mattingley, 2004; Corbetta et al., 2005; Danckert and Ferber, 2006; Karnath and Rorden, 2012). As a result, a large number of rehabilitation programs, such as prism adaptation and vestibular stimulation, have focused on correcting those deficits (Luauté et al., 2006; Redding and Wallace, 2006; Bowen et al., 2007; Kerkhoff and Schenk, 2012). Unfortunately, success has been limited. This suggests that non-spatial impairments in neglect may contribute to its rehabilitory recalcitrance. Based on the results of recent studies, we have hypothesized that one such non-spatial deficit in neglect is the meta-level impairment of mental model building and updating, also referred to as representational updating (Danckert et al., 2012b).

Our everyday life is guided by regularities in the environment and also our ability to notice and adapt to those regularities: we dress with warm clothes if it has been snowing; based on our previous experiences, we guess what the weather will be like for the next few days. But if we have to visit a warm country, then we adapt to the new context and build a new model of the weather and the clothes needed for the higher temperatures.

The ability to learn environmental regularities and to be sensitive to their relationships is essential for building mental models. Detecting when a context has changed is the signal that a mental model needs to be adapted to the new context and updated. Therefore, representational updating impairments are revealed by the inability to learn environmental statistics. Ultimately, an impairment in this process leads to incorrect interactions with the environment, poor predictions about future states of the world, and an impaired ability to benefit from instruction and experience.

The ability to build successful representations depends on a number of interdependent sub-processes, where one of the most important is statistical learning: the ability to learn that some elements occur more often than others. Statistical learning in turn requires other, more elemental processes, such as priming. In addition, priming and statistical learning rely on intact temporal processing and working memory: to detect regularities in our environment, as for example whether something is frequently repeating its position, we must remember what has happened and be accurate in judging if it has occurred recently.

Working memory or temporal processing deficits, as well as difficulties in position priming and statistical learning, can all lead to a representational updating deficit. Those processes have also been demonstrated to be impaired in spatial neglect, which points the way to new tactics and targets that can be the focus of rehabilitation for this disorder.

In our review, we accept as givens that neglect is phenomenally heterogeneous, and that spatial impairments form the definitional core for the disorder. As the spatial components of neglect are well reviewed elsewhere (e.g., Danckert and Ferber, 2006; Karnath and Rorden, 2012), we do not review them here. Therefore, our review focuses on studies demonstrating non-spatial deficits in neglect. We show that those deficits in neglect include impaired priming, temporal processing, visual and auditory statistical learning, and working memory. We interpret other non-spatial impairments of neglect, such as prolonged attentional blinks and decreased sustained attention, as reflecting similar impairments. Lastly, we review evidence for updating impairments in neglect and conclude by suggesting that the hypothesis of neglect as a disorder of representational updating highlights new approaches for rehabilitation.

NON-LATERALIZED DEFICITS IN SPATIAL NEGLECT

Numerous recent studies have demonstrated deficits in neglect that are not lateralized spatially, but that contribute to the complexity of this disorder (Husain et al., 1997; Becchio and Bertone, 2006; Malhotra et al., 2006; Ptak et al., 2007).

Husain and Rorden (2003) suggest that a combination of non-lateralized and lateralized deficits might explain the difficulty in finding effective rehabilitation strategies.

The interest in non-lateralized deficits in neglect has grown in recent years with studies demonstrating a number of fundamental non-spatial impairments, such as decreased arousal, problems with sustained attention, spatial working memory impairments, and non-spatial attentional biases (for a review, see Husain and Rorden, 2003; Corbetta and Shulman, 2011; Danckert et al., 2012b).

Many neglect patients show decreased arousal and vigilance; this translates into a lower level of sustained attention (Robertson et al., 1997; Farné et al., 2004; Corbetta and Shulman, 2011). Several studies have implicated the right hemisphere in deficits of arousal or alertness (Robertson et al., 1995, 1997; Rueckert and Grafman, 1998; Sturm and Willmes, 2001; Corbetta et al., 2005; Fimm et al., 2006; Grahn and Manly, 2012). A correlation between neglect and a decreased level of sustained attention was first shown by Heilman and Valenstein (1979) and has been confirmed by multiple studies (Hjaltason et al., 1996; Robertson et al., 1997; Samuelsson et al., 1998; Barrett et al., 2007). In a study where right brain damaged patients were asked to count a series of tones, Robertson et al. (1997) found a correlation between sustained attention and the bias in spatial attention, confirming a connection between spatial and non-spatial aspects of neglect.

Another non-lateralized deficit that could contribute to spatial biases in neglect is a deficit of spatial working memory. Husain et al. (2001) recorded a neglect patient's eye movements while the patient judged whether a stimulus had been seen before. The authors found that a patient suffering from left neglect revisited old targets and identified them as new, even when they were presented on the right, ipsilesional side.

Neglect patients were also impaired when tested in vertical spatial working memory tasks, even though there was no left-right spatial component (Ferber and Danckert, 2006; Malhotra et al., 2006). The working memory deficit predicted the general degree of impairment in patients with neglect: the less patients can retain of their previous actions, the less liable are they are to undertake new actions (Husain et al., 2001).

An additional non-spatial impairment in neglect that has been linked to working memory is a prolonged attentional blink (Johnston et al., 2012). The attentional blink refers to the observation that when a person must detect multiple targets, the correct detection of one target impairs the ability to detect a subsequent target that follows it shortly thereafter in time. A recovery interval of between 200 and 500 ms is necessary for the detection of a second target to return to baseline (Dux and Marois, 2009). For many neglect patients, this interval is two to three times longer: after they have detected the first target, neglect patients are not aware of the second target unless there is an interval of about 1200 ms (Raymond et al., 1992; Husain et al., 1997; Shapiro et al., 1997, 2002; Johnston et al., 2012).

The non-lateralized deficits just highlighted demonstrate that neglect is more than a spatial disorder. We suggest that many of these different symptoms are related and reflect a mutual dependence. We now review data demonstrating that neglect patients also have impairments in priming, temporal processing, statistical learning and working memory, and suggest that those different deficits sum to a representational updating impairment.

NEGLECT AS A DISORDER OF GENERATING AND UPDATING MENTAL MODELS

POSITION PRIMING

Studies in visual search are greatly influenced by the research in priming and how the effect of the repetition of the target position or features influence participants' reaction time (for a review, see Neely, 1991; Kristjansson, 2008; Kristjánsson and Campana, 2010). Maljkovic and Nakayama (1994, 1996) were the first to report that when the features or the position of a target are repeated, participants are faster to detect it. In their study of position priming (1996), participants searched for a diamond with its left or right corner missing. There were two distractors. The stimuli were placed in an elliptical organization, and the target either repeated or switched its position on successive trials. The authors found that when the target was presented in the same position on successive trials, participants were faster and more accurate to respond than when the target's location was switched. Other studies have since confirmed those results for the priming of context, object features, movement, and presentation interval (Chun and Jiang, 1998; Goolsby and Suzuki, 2001; Los and Van Den Heuvel, 2001). The priming effect has also been tested in neglect patients (Kristjánsson et al., 2005; Saevarsson et al., 2008; Shaqiri and Anderson, 2012a,b). Saevarsson et al. (2008) repeated or switched the overall context in which a target was presented. They found a preserved priming effect in neglect. In their second experiment, they tested the priming effect in contralesional and ipsilesional space by repeating the context in both visual fields. Patients were faster to detect targets when the context was repeated, even when the presentation was in contralesional space.

We recently tested color and position priming in neglect with patients discriminating the color of a dot that could be either black or white (Shaqiri and Anderson, 2012a). Stimuli were biased to appear 75% of the time in a high probability region on the left side of space. Our results demonstrated that neglect patients had a preserved color priming, but their results for location priming were less consistent. Indeed, when the target repeated the same position, participants did not show significantly faster RTs than when the target was presented in another location – although there was a trend – which demonstrated that the benefit from position priming in neglect patients was attenuated (**Figure 1**). This was not the case for color priming: when the target repeated the same color, participants were faster to respond, even if the target appeared in contralesional space.

Although we did not control for eye position, we believe that the difficulty of neglect patients to benefit from position priming is not due to a remapping impairment, as has been hypothesized by Pisella and Mattingley (2004). In their review paper, the authors suggest that patients' gaze-shifts toward their contralesional side degrade all previously visited and remembered locations, creating a remapping problem. This hypothesis has been contradicted by the study of Vuilleumier et al. (2007), who tested how gaze-shifts affect the memory of location in neglect patients. The study revealed results that were different from the hypothesis of Pisella

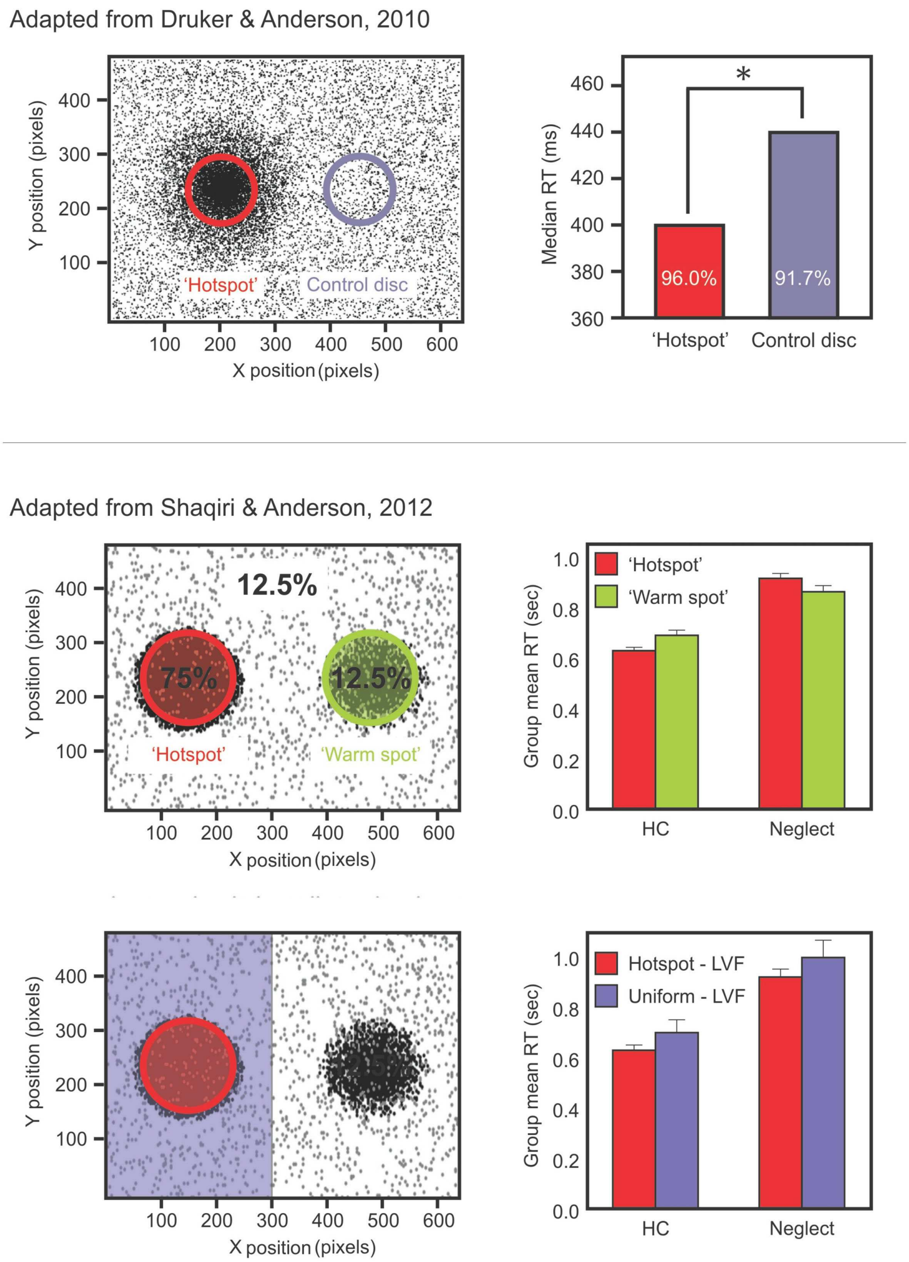

FIGURE 1 | Upper panels show data from the study of Druker and Anderson (2010) testing undergraduate students. Participants made color discriminations for targets that could appear anywhere on the screen but were more likely to come from a high probability "hotspot" region. Results (right panel) showed faster RTs and increased accuracy for targets in the hotspot despite participants being unaware of this high probability region. Middle panels show data from a different study: Shaqiri and Anderson (2012a). This is a modified version of the Druker and Anderson (2010) task in a group of healthy older controls (HCs) and right brain damaged (RBD) patients with Neglect. Contrary to HCs, Neglect patients failed to show a benefit in RT for targets presented in a contralesional, high probability region (Shaqiri and Anderson, 2012a). Lower panels show HCs and neglect patients' RT for the hotspot and the rest of the left-sided trials: although overall slower on the left, Neglect patients were sensitive to the biased distribution of the target.

and Mattingley (2004), as Vuilleumier et al. (2007) found that only gaze-shifts to the far right affect the location information in neglect patients, but when patients had to make a left gaze-shift, they showed a preserved ability to maintain and update the location information (see also Vasquez and Danckert, 2008 for similar results in healthy individuals). The results of Vuilleumier et al. (2007) consolidate our results of position priming. Indeed, we presented 75% of the targets on the patients' contralesional side (Shaqiri and Anderson, 2012a), therefore, we believe that patients' difficulty to benefit from position priming is not a demonstration of their remapping impairment, but is a more generic impairment of updating and benefiting from regularities of the environment.

These results are in accordance with Kristjánsson et al. (2005), who had neglect patients detect a distinctly colored diamond and report whether the top or the bottom corner was missing. The three diamonds were presented in a triangular array (i.e., bottom left, bottom right, and top middle). The authors found preserved color and position priming when participants had an unlimited time to respond to the target, although one of the two patients needed at least three repeats of the same position to show a priming effect. Moreover, when the time of the display was limited to 200 ms, patients did not show a position priming effect, unless they indicated that they had consciously detected the target, whereas color priming remained intact regardless of stimulus duration. Kristjánsson et al. (2005) concluded that awareness was necessary for patients to show position priming on their left side.

These studies included a spatial aspect in their design, as they presented stimuli on the contralesional and ipsilesional side. This complicates the interpretation of the impairment. In order to avoid a spatial bias, we adapted Maljkovic and Nakayama's (1996) study by presenting the target and distractors vertically aligned in central space (**Figure 2**). We assessed whether patients had preserved position priming, that is, if they were faster when the target repeated the same position successively (Shaqiri and Anderson, 2012b, under review). We found that although neglect patients had an overall priming effect, the magnitude was reduced compared to healthy controls. Further, the benefit did not show an increase with multiple spatial repeats, an effect that was seen with controls. Thus, a deficit in position priming was revealed in a task that eliminated lateral spatial biases (**Figure 2**). A generic priming deficit was not present though, as most studies, including our own, have demonstrated preserved color priming.

The brain regions associated with neglect may explain the differential results for color and position priming. In an fMRI study investigating the neural correlates of priming, Kristjánsson et al. (2007) found different brain regions activated by color and position priming conditions. While both of these priming effects were associated with regions traditionally linked with the control of attention, the so called "attention network" that includes the intraparietal sulci (Corbetta and Shulman, 2002, 2011), the color repetition condition also showed suppression of activity in the inferior temporal region. Position priming was more related with regions such as the right inferior parietal cortex and frontal areas. Kristjánsson et al. (2007) also found a greater involvement of the right hemisphere for position priming than for color priming. Although there is no single brain region where damage is both necessary and sufficient for causing spatial neglect, the right inferior parietal and the frontal lobe are frequently involved in the strokes that produce neglect (Corbetta and Shulman, 2002; Ricci et al., 2012). The correspondence between the regions involved in position priming and those involved with spatial neglect may explain why patients do not show as robust position priming effects as do controls and why different studies might find varying results.

TEMPORAL DEFICITS IN NEGLECT

The results discussed above reveal that neglect patients have difficulties benefiting from successive repeats of the same position by the target, and therefore demonstrate attenuated position priming. We make the hypothesis that this difficulty might be explained by the temporal processing impairments demonstrated by neglect patients (Berberovic et al., 2004; Danckert et al., 2007; Merrifield et al., 2010). Patients tend to underestimate multisecond intervals: Danckert et al. (2007) tested neglect patients in a temporal estimation task. Arranged in a circular shape, eight open circles were filled in one after another, following a clockwise motion. A trial could last 5, 15, 30, and 60 s and patients were asked how long the clockwise motion lasted on each trial. The authors found that neglect patients underestimated all durations, showing an impairment for estimating the passage of time: even for trials that lasted 60 s, neglect patients reported that the clockwise motion was present for no longer than 10 s. Those deficits have also been found in the processing of auditory stimuli (Cusack et al., 2000; Merrifield et al., 2010).

The temporal processing impairment is intrinsically linked with priming, as the importance of timing in priming has been demonstrated by Maljkovic and Nakayama (2000), who tested the ability of participants to benefit from position priming with different inter-trial intervals. While a break of 30 s between two trials did not affect priming magnitude, a break of 90 s did, as it reset any possible benefit from target position repetition to its initial pace. The authors demonstrated that priming was cumulative and that at short intervals (from 1 to 30 s) priming occurs, but at longer intervals there is some degradation of the implicit memory of previous information regarding target position. The difficulty neglect patients have in benefiting from more than one repeat of position in a priming task might be accounted for by temporal and memory impairments. To restate, since neglect patients have slower response times for any task in general (Kaizer et al., 1988; Shaqiri and Anderson, 2012a), it means that they have to keep in mind the association between the trials for a longer period of time and therefore, they are submitted to fewer trials from which they can accumulate information, compared to the healthy controls. A problem in keeping the relationship between the trials in their implicit memory might prevent patients from extrapolating to a more general regularity about their environment.

The importance of timing in the priming effect and the demonstration of an impairment in temporal processing in neglect affects other processes as well, such as statistical learning. Indeed, as we will demonstrate in the subsequent sections, priming, and statistical learning are closely related, to the point that some authors (Walthew and Gilchrist, 2006) have questioned whether statistical learning is not simply a form of priming, or if the latter is a necessary step for statistical learning to occur (Jones and Kaschak, 2012). We review different studies that have investigated the relationship between priming and statistical learning and how they are involved in building and updating mental models.

STATISTICAL LEARNING

Statistical learning is a form of implicit learning that occurs through mere exposure and observation and does not involve explicit feedback (Turk-Browne et al., 2008; Aslin and Newport, 2012). It has been demonstrated for both auditory and visual modalities. Bulf et al. (2011) found that newborn infants were able to extract the transitional probabilities of simple visual structures: they presented pairs of shapes to babies using a higher transition

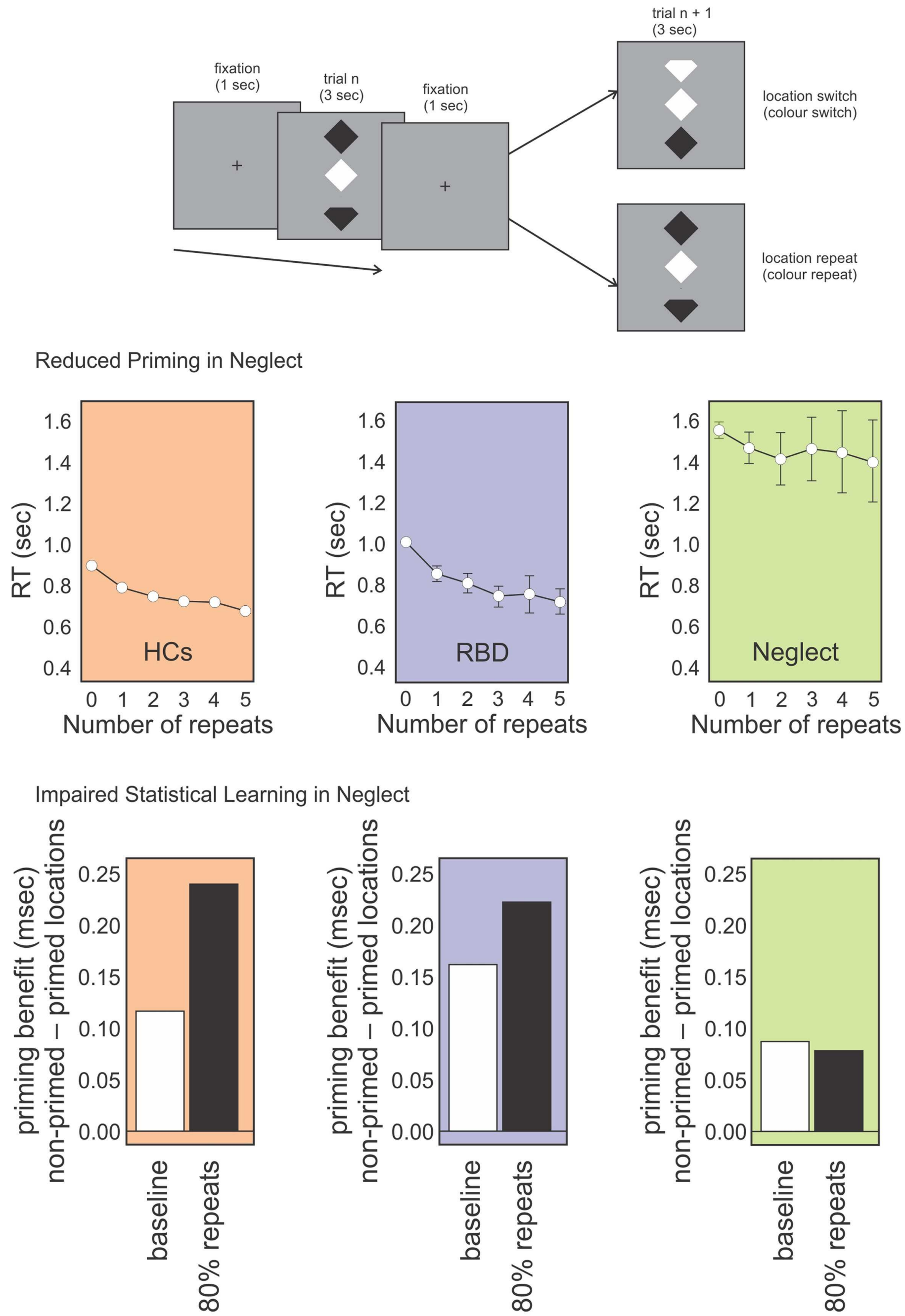

FIGURE 2 | Topmost panel: schematic representation of our position priming task (Shaqiri and Anderson, under review). Participants were required to detect if the top or bottom notch of the odd-colored diamond was missing (the schematic here exaggerates the actual physical distinction). Middle panel: RT data for healthy controls (HCs; orange panel), RBD patients (purple panel), and Neglect patients (green panel) for targets that repeated spatial locations on subsequent trials (up to five repeats). RBD patients show reduced priming relative to HCs who show increased priming over all five trials. In contrast, Neglect patients show no priming benefit after trial 1. Lower panel: priming benefit in conditions where repeated locations and switched locations are equally likely (baseline; white bars) vs. conditions in which location repeats were highly probably (i.e., location repeated on 80% of trials). Controls and RBD patients show an increased priming benefit on the highly probable repeat trials whereas Neglect patients do not.

probability within pairs of shapes and a lower transition probability between the shapes in a pair (for example, a circle was followed by a square 100% of the time, but the square was followed by a triangle or a diamond with equal probability). Results showed that the infants demonstrated preferential looking toward novel sequences. Bulf et al. (2011) concluded that newborns have the ability to detect regularities from the environment and learn which elements are being repeated more often.

Many early studies on statistical learning focused on very young children. Fiser and Aslin (2002), tested 9-month-old babies in a more complicated paradigm of visual statistical learning. They presented four base pairs of shapes combined with four noise elements, so that each baby was presented with consecutive base pairs and a noise element during the task. The data revealed that babies showed a greater preference for base pairs over non-base pairs, and the authors suggested that the infants learned the co-occurrence of the shapes.

While the phenomenon of statistical learning is well established, its relationship to priming is complex. When a statistical distribution leads to frequent repeats there are also more primed trials. Walthew and Gilchrist (2006) suggested that claims of statistical learning of spatial probability distributions in neglect might be explained on this basis; rather than learning underlying distributions, faster responses in areas of high probability could merely reflect the influence of a greater number of primed trials in those regions.

To address this issue and investigate further the relationship between priming and statistical learning, we conducted a study where undergraduate participants discriminated the color of a small dot. The main manipulation of the study was the spatial location of the target: 80% of the time stimuli were presented within a high probability region on one side of the display (Druker and Anderson, 2010). Participants were faster and more accurate to respond to targets presented in the high probability region compared to the rest of the screen. Given that exact locations were rarely if ever repeated (**Figure 1**), it is difficult to explain this result as simply a consequence of position priming: because target locations were free to be anywhere on the screen, and because targets were small, the risk of repeating target position was almost nonexistent. Furthermore, a questionnaire administered at the end of testing revealed that participants were not aware of the biased location for the target, demonstrating that the statistical learning of the high probability target zone was achieved implicitly.

Statistical learning has also been assessed in neglect patients. Geng and Behrmann (2002, 2006), had neglect patients detect the letters L and F that appeared among distractors (letters T and E). Targets were biased to appear 80% of the time on one side of the computer screen. The authors found that neglect patients were faster at detecting targets that appeared in the high probability region, even if this was in contralesional space. The results of Geng and Behrmann (2002, 2006), give promise for the use of statistical learning as a rehabilitation strategy for neglect patients. This technique does not need supervision or feedback. Patients' observations lead to an implicit learning of the distribution of elements in their environment. This could facilitate the direction of attention and help to overcome the ipsilesional attentional bias.

From this perspective we conducted two studies (Shaqiri and Anderson, 2012a,b, under review) where we tested statistical learning in neglect. Our first study adapted the paradigm of Druker and Anderson (2010) and tested whether neglect patients could learn a spatial statistical distribution and use it as an attentional cue in a color discrimination paradigm (**Figure 1**; Shaqiri and Anderson, 2012a). We biased the targets to appear 75% of the time in a high probability region on the left side of space. As was the case in our previous study in healthy controls (Druker and Anderson, 2010), target locations varied throughout the screen eliminating any concerns about position priming. Where priming did occur it was of a lesser magnitude in neglect patients compared to controls. To explore statistical learning in the same paradigm we first excluded trials where the previous target location was within 5 °of visual angle. With all trials considered, neglect patients were slower to respond to targets in the high (i.e., 75%) probability region in left space when compared with a low probability (12.5%) region in the mirror symmetric location in right space (**Figure 1**). With the primed trials removed, and considering only targets appearing in left, neglected space, we found that neglect patients were indeed sensitive to the high probability region of the screen (**Figure 1**). That is, when we compared the trials in the hot spot (i.e., the high probability region) with the other left-sided trials, neglect patients were faster to respond for the hot spot, although their RTs were slower compared with RTs to right-sided targets. These data demonstrated that patients are somewhat sensitive to the statistical distribution of targets, but also that they have difficulties benefiting from these regularities to the same extent as healthy controls (**Figure 1**).

In order to investigate whether the spatial elements of the task were central to the results, we tested neglect patients in a visual search task where we presented targets vertically in the middle of the screen (**Figure 2**; Shaqiri and Anderson, 2012b, under review). As with our previous task, here we could look both at priming and statistical learning within the same task. Priming was examined on trials in which target locations or colors repeated. To examine statistical learning we biased the transitional probability of stimuli positions to include a high repeat condition (an 80% probability of repeating target location), or a switch condition in which targets changed location on 80% of trials. As with our previous task that explicitly manipulated target locations throughout the visual field, results for this study showed that, contrary to healthy controls, who were faster to respond to targets on the high repeat condition, neglect patients did not learn the statistical distribution of the targets, independently from the spatial position of stimuli. Right brain damaged patients without neglect performed much like controls suggesting that the failure to benefit from statistical regularities (i.e., no RT benefit in the high repeat condition) was unique to neglect. This, despite the fact that *primed* trials were faster. In other words, the magnitude of the position priming effect was the same whether repeated trials were very likely or very unlikely (**Figure 2**). This demonstrates the difficulty neglect patients have in making use of environmental statistics and also that this difficulty is not simply a consequence of left-right biases of attention.

All these different paradigms tested the visual modality, but if such an impairment is generic, it ought to be present for other sensory modalities, given that numerous studies have reported multimodal impairments in neglect, including auditory and tactile deficits (for a review, see Pavani et al., 2003; Jacobs et al., 2012). For example, Cusack et al. (2000) found that neglect patients show auditory impairments for temporal aspects of stimuli, mapping a visual bias to the auditory modality (Bisiach et al., 1984; Tanaka et al., 1999), and they demonstrate a greater uncertainty for the location of sounds compared to healthy controls (Pavani et al., 2002).

Those studies, which demonstrated multimodal impairments in neglect, motivated our assessment of neglect patients' ability to learn the transition probability of nonsense words in an auditory statistical learning paradigm (**Figure 3**; Anderson and Danckert, 2013; Shaqiri et al., in preparation). This procedure relied on decades of results on auditory statistical learning exemplified by Saffran et al. (1999) and Aslin et al. (1998). They exposed 8-month-old infants to tri-syllabic nonsense words (for example bidaku, padoti, golabu) where the transitional probability of syllables within words was 100% (e.g., "go" was always followed by "la," "la" by ""bu" to create "golabu," etc.). In contrast, the transitional probability for syllables between words was 33% (e.g., "bu" of "golabu" was followed by "pa," "bi," or "go" equally often). The words had no breaks between them and were presented by computer to avoid clues to the word borders other than the statistics of syllable transitions. The continuous stream of speech presented to the children lasted 2 min. Saffran et al. (1999) found that 8-month-old infants were able to identify the words, extracting information about the word boundaries solely on the basis of the transitional probability of those words.

This effect has been confirmed for adults. Gebhart et al. (2009) used a similar paradigm for university undergraduates; some participants heard two different languages (5 min each). Participants were exposed to either one language, both languages without a break, or both languages with a 30 s break between the first and second language. Undergraduates learned the first language, as they were able to correctly identify the words with 80% accuracy in a 16 item forced-choice test. When presented with two languages, they learned both as long as they had a break between the exposures to each.

Adapting the paradigm of Gebhart et al. (2009), we tested neglect patients for their ability to learn the transitional probability of the tri-syllabic nonsense words (**Figure 3**; Anderson and Danckert, 2013; Shaqiri et al., in preparation). For all the studies, neglect was assessed using the letter cancelation, line bisection, and figure coping from the Behavioral Inattention Tests (BIT) (Wilson et al., 1987). Patients were diagnosed as having neglect when they missed more than 10% of the letters on the left in the letter cancelation test, when the rightward bias was higher than 5% of the total length of the line and finally, when patients missed parts of the figures for the figure coping task. Based on

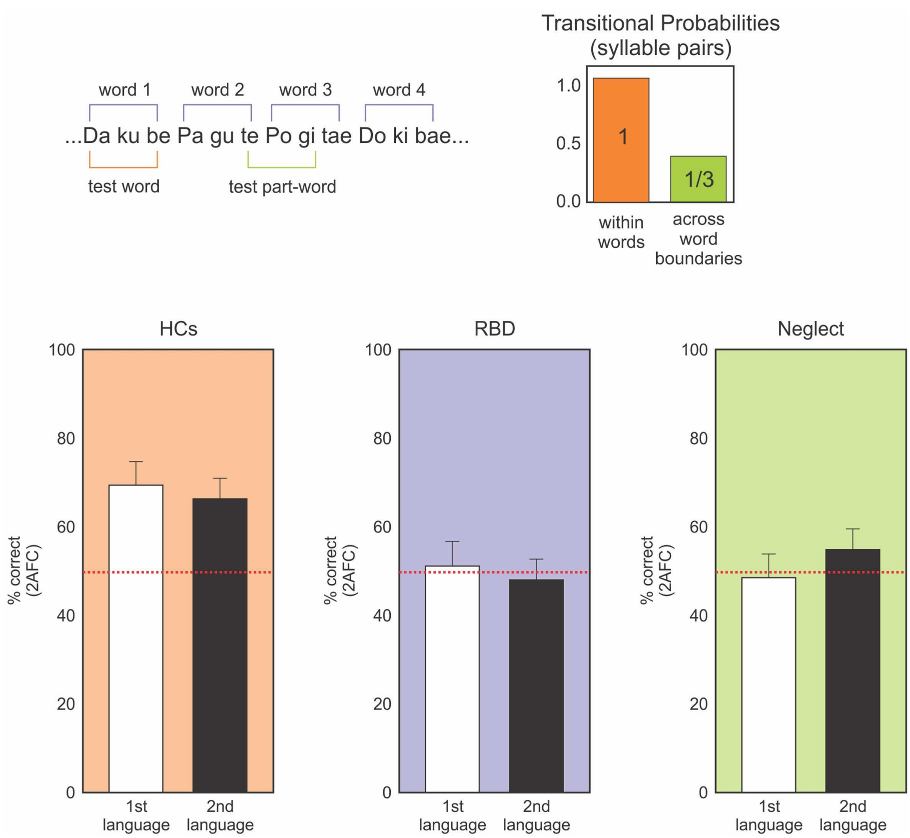

FIGURE 3 | Upper panel: representation of the nonsense language task. Participants heard a constant stream of nonsense syllables (no temporal gaps between syllables) for ∼10 min. Afterward they make forced-choice discriminations of "words" and "non-words" constructed from the same syllables. Words are defined by transitional probabilities with syllable pairs within word boundaries having 100% association (ku always follows da) and between word boundaries having 33% probability across all other syllables. Lower panels: forced-choice discrimination performance for two nonsense languages. HCs (orange) clearly perform above chance (red dotted line) on both languages. Neither the RBD (purple) or neglect (green) patients can discriminate the languages – task that was well performed by 8-month-old infants (data from Anderson and Danckert, 2013; Shaqiri et al., in preparation).

those criteria, we recruited eight neglect patients (main age = 72, SD = 9.02): three had lesions of the parietal lobe, two with lesion of the temporo-parietal lobeu, and finally, three with fronto-parietal lesions. The neglect patients listened to the stream of nonsense words forming the two different languages. Four patients heard both languages without a break (10 min) and four listened to the two languages for 5 min each, with the two languages separated by a 30 s break. After listening to the language streams, participants were tested in a forced-choice format where the words they heard were paired with part words made-up of syllables that spanned word borders (**Figure 3**). Neglect patients did not show any learning effect. Indeed, patients did not perform the task above chance, contrary to our healthy controls who learned the transition probability between syllables and identified the correct words about 80% of the time. These results demonstrate that the difficulty neglect patients have in learning statistical distributions is multimodal and is neither limited to visual or spatially presented material. Our study did not involve spatial aspects, but tested the general ability of those patients to be sensitive to the transitional probability between the syllables within the word, an ability shown to be present in 8-month-old infants (Saffran et al., 1999).

WORKING MEMORY AND STATISTICAL LEARNING

The different studies we conducted on statistical learning (Shaqiri and Anderson, 2012a,b) confirmed that neglect patients have difficulties benefiting from statistical regularities. We hypothesized that this might be, in part, because of the temporal processing impairment demonstrated by those patients (see above), and in part from working memory impairments. Spatial working memory has been shown to be deficient in neglect patients (Husain et al., 1997; Ferber and Danckert, 2006; Johnston et al., 2012) but based on the different studies we conducted, we extend those findings and hypothesize that neglect patients might demonstrate working memory deficits that exceed the spatial scope and are more generic, which contributes to patients' impairment of statistical learning.

To that end, we tested the involvement of working memory in statistical learning, in order to investigate whether these processes were interdependent and to what extent working memory plays a role in statistical learning. This study (Valadao et al., 2012) required participants to complete an n-back working memory task and a prediction task simultaneously. Participants had to predict the location of a target that was biased to appear in a specific quadrant of the display (**Figure 4**). They also had to do a 0-back or 2-back task based on the shape, location or color of the target, which tested feature and spatial working memory. We found that when participants did the 2-back task, they were not as accurate in learning the biased probability distribution of the target location, particularly if spatial working memory was involved. Another study that tested working memory while manipulating the statistical distribution of the target also found a close relationship between these two aspects: participants were better at storing in working memory targets that were presented within a high probability area, without necessarily being aware of this facilitation (Umemoto et al., 2010). These studies demonstrate that for statistical learning to occur, participants need free working memory resources. The impairment that neglect patients demonstrate in spatial working memory (Husain et al., 1997; Johnston et al., 2012) might extend and affect working memory more generally, which could contribute to the difficulty patients have in learning and benefiting from statistical regularities in their environment. If neglect patients cannot keep in memory the recent information about target locations and features, then they will not have access to the information necessary for building mental models of their environment. This difficulty in holding information in mind could also affect their ability to notice changes in the environment, changes that might require updating of mental models.

REPRESENTATIONAL UPDATING IMPAIRMENT IN NEGLECT

Combining the results of the various studies reviewed above, we hypothesize that neglect involves a disorder of representational updating (Danckert et al., 2012a,b) and consequently, that rehabilitation strategies need to address this deficit. Patients need to be trained to improve their ability to detect and exploit regularities within their environment. To interact efficiently with the environment, a representation of recent perceptual information is required (Tenenbaum et al., 2011). As Valadao et al. (2012) demonstrate, keeping in mind information that may be relevant for detecting changes in environmental statistics can affect the ability to learn the statistical distribution that gave rise to that data. An impairment in patients' abilities to integrate information, or to keep it in mind, will impair their ability to learn statistical regularities and affect their ability to create mental models of the environment. This will impact everything from adapting to new surroundings to benefiting from rehabilitation programs.

These ideas have guided our investigations of neglect patients' ability to learn and update mental models. One of the first studies demonstrating that neglect patients have a representational impairment is the very elegant and famous study of Bisiach and Luzzatti (1978). Patients were asked to imagine how they would see a famous square in Milan. What the authors found is that patients could represent all the buildings presented on their imagined right, but failed to report those on their left. When the experimenters asked patients to imagine themselves standing on the opposite side of the square, so that the buildings they had previously neglected were now on their right, the patients reported those building but missed (i.e., neglected) those they had previously reported. Bisiach and Luzzatti (1978) concluded that patients demonstrate neglect even for their mental representations.

Another demonstration of a representational impairment in neglect comes from motor imagery. Danckert et al. (2002) have shown in one neglect patient, that imagining and creating mental representations of motor movements is impaired, while they do not show any impairment while actually *performing* those movements. In their study, the researchers asked one neglect patient to imagine a motor action, such as pointing toward targets of different sizes. The patient demonstrated normal movements, that conformed to expected speed-accuracy trade-offs (i.e., movement duration decreased with increasing target size), whereas imagined movements did not show such a pattern. That is, contrary to the actual movement, where the patient was faster to point to larger targets – which corresponds to the performance of healthy participants – when asked to imagine a movement for a given target, the patient did not show a relation between the time to imagine the movement and the size of the presented target, further

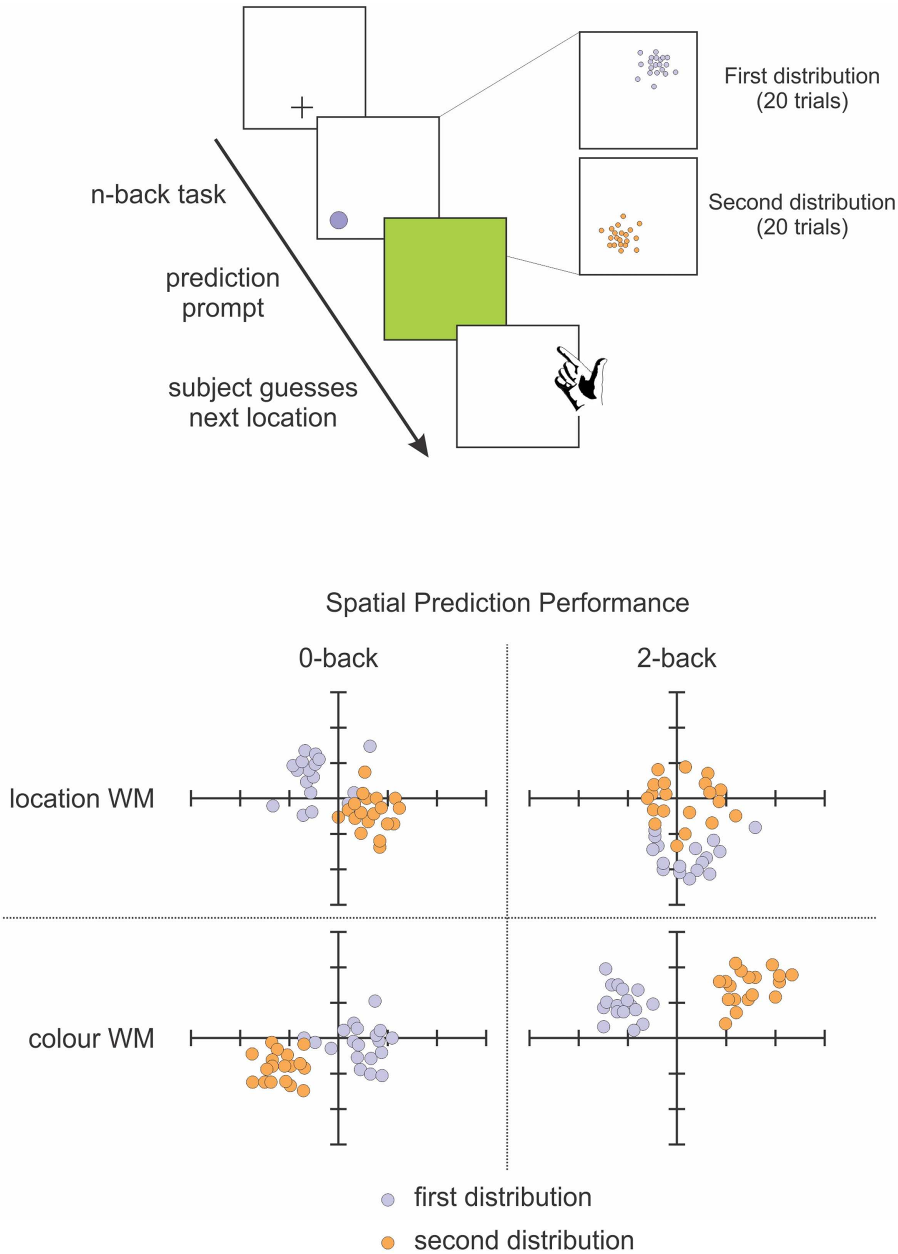

FIGURE 4 | Schematic representation of our spatial prediction and working memory task (Valadao et al., 2012). Participants first perform an n-back task related to the color or location of targets on a given trial. They are then required to predict the location of a target on the next trial. The distribution for target locations is chosen from 1 quadrant for 20 trials before being switched to another quadrant for 20 trials. Lower panel shows performance from a representative participant on the spatial prediction component of the task in the 0-back (left) and 2-back (right) tasks. The participant's predictions were less accurate when performing the 2-back spatial working memory task (upper right panel).

demonstrating the challenge neglect patients have in creating accurate mental models – in this instance a model of an intended action (Danckert et al., 2002).

Similarly, other studies have shown impairments of updating using the double step saccade task (Duhamel et al., 1992). In this task, participants saccade to two successive targets that are extinguished in under 200 ms (i.e., prior to initiation of the first saccade). In order to accurately acquire the second target, an individual must anticipate the sensory consequences of the first saccade to update a mental representation of space. Results showed that a neglect patient was unable to accurately saccade to the second target when the first target was presented in contralesional space and the second target appeared in ipsilesional space, demonstrating an impairment in updating a mental representation of intended eye movements in space (Duhamel et al., 1992; see also Heide et al., 1995, 2001).

Many studies investigating which brain regions are involved in updating, decision-making, statistical learning, and novelty detection have found sets of structures that overlap those often injured in neglect. For example, the right hemisphere generally appears critical for priming and statistical learning (Kristjánsson et al., 2007; Turk-Browne et al., 2009). Roser et al. (2011) presented sequences of shapes with varying transitional probabilities in the left or right visual field of a split-brain patient. The patient could learn the statistical relationship of the shapes when they were presented to his left visual field, but not when they were presented on his right. The authors concluded that the right hemisphere plays an important role in statistical learning (Roser et al., 2011). Finally, the temporo-parietal junction (TPJ), a region commonly involved in neglect, has been identified in several studies as being important for representational updating (Clark et al., 2000; Downar et al., 2002; Mort et al., 2003; for a review, see Corbetta and Shulman, 2002; Husain and Rorden, 2003). In a study where changes in event related potentials (ERP) were studied based on novel or unusual events, it has been shown that the P300 component, localized to the TPJ, is increased in amplitude for novel events (Dien et al., 2003). The authors found that when information coming from the environment required an update of existing mental models, the electroencephalographic activity at the TPJ increased. The TPJ is also believed to be activated when attention needs to be directed toward behaviorally relevant events (Corbetta and Shulman, 2002). In their review, the authors suggest that the TPJ acts as a "circuit breaker," important for redirecting attention toward salient information in the environment. Therefore, we hypothesize that TPJ might help to orient attention toward information that is useful to update mental models. Finally, other studies have identified the parietal cortex as being an important region involved in representational updating (Vuilleumier and Driver, 2007; Danckert et al., 2012a,b).

We designed a study to investigate the ability of neglect patients to learn statistical distributions and to use the incoming information for creating and updating mental models (**Figure 5**; Danckert et al., 2012a). We had patients play the children game rock-paper-scissors against a computer opponent that covertly varied its play strategy. In the first block of trials, the computer opponent chose uniformly from the three options rock, paper, and scissors, and did so independent of the participant's choice on any prior trials. The computer subsequently chose one item 80% of the time. Right brain damaged patients were not able to adapt their play to the heavily biased strategy of the computer, whereas control participants and left brain damaged patients did so without difficulty (**Figure 5**). We conclude that patients with right hemisphere injury (many of whom also had neglect) have difficulty using sequentially collected information from the environment to create mental models, to use such models to guide behavior, and to detect when the models need to be updated secondary to environmental changes. This type of impairment could easily depend on the deficits that we and others have observed in priming, temporal processing, statistical learning, and working memory capacity.

In order to evaluate impairments in mental model updating, and to do so in a way that was less dependent on statistical estimation, we tested the ability of right brain damaged patients to update mental representations of ambiguous figures (**Figure 6**; Christman et al., 2009; Stoettinger et al., 2013). We tested 12 patients (main age = 64, SD = 9): four had lesions of the parietal lobe and eight had lesions of the fronto-parietal area. A sequence of pictures began with a totally unambiguous representation of a common object (e.g., swan) and then gradually progressed through successive images that were slightly altered each time to eventually show a completely different, unambiguous item (e.g., cat; **Figure 6**). We used the number of stages for which patients retained their initial report of the original unambiguous figure in the sequence as a measure of updating. That is, when a person changed from reporting that they saw a swan to reporting a cat, they can be said to have updated their representation of the ambiguous figure. Results showed that right brain damaged patients persisted for longer than did controls in responding with the initial representation (e.g., swan) before adapting their responses to the figural changes (e.g., cat; **Figure 6**). Importantly, all subjects correctly identified the beginning and ending pictures, as well as catch trials in which simple geometric figures were inserted into the sequence. These data are in good agreement with those of Vocat et al. (2012), who tested right brain damaged patients with anosognosia on a riddle test. Participants listened to five increasingly specific clues (for example, for the targeted word "*airplane*," they were given the clues: "*I have wings*," "*I can fly*," and then the last clue was "*I have wheels*"). The authors found that anosognosic patients reported higher levels of certainty regarding their initial guesses associated with the first clue (even those that were not particularly informative) and to preserve their response, although the next clues disconfirmed their guess. For example, with the clue "*my weight is approximately 300 grams*" and the target word "*heart*," a patient guessed the word "*bread*," and then with the next clue, "*I produce a regular sound*," he persisted with the answer "*bread*" but justified it by saying it's the noise that the knife makes when we cut bread (Vocat et al., 2012). The authors concluded that patients were impaired in creating and adapting beliefs to new information: they were overconfident about their initial guesses and failed to revise those guesses when successive clues were incongruent with that guess. Data from our studies on rock, paper, scissors (Danckert et al., 2012a), the ambiguous figures task (Stoettinger et al., 2013) and Vocat's et al. (2012) riddle task are all consistent with the hypothesis that right brain damaged patients have difficulties in creating and updating mental models of the environment (Danckert et al., 2012a,b). Critically, these difficulties cannot be explained by recourse to deficits in spatial attention. So while previous rehabilitation attempts may succeed to some degree in improving deficits of spatial attention (Striemer and Danckert, 2007, 2010), they are unlikely to improve the more generic deficit in building accurate mental models and updating those models as environmental changes dictate.

IMPLICATIONS FOR REHABILITATION STRATEGIES

While neglect patients have trouble creating and updating mental models (Danckert et al., 2012a,b), this difficulty is not absolute. As the aforementioned studies of ambiguous figures (Stoettinger et al., 2013) and riddle tasks (Vocat et al., 2012) have shown, patients eventually get the correct answers; it just takes them longer to get there. The patients' need more information and longer

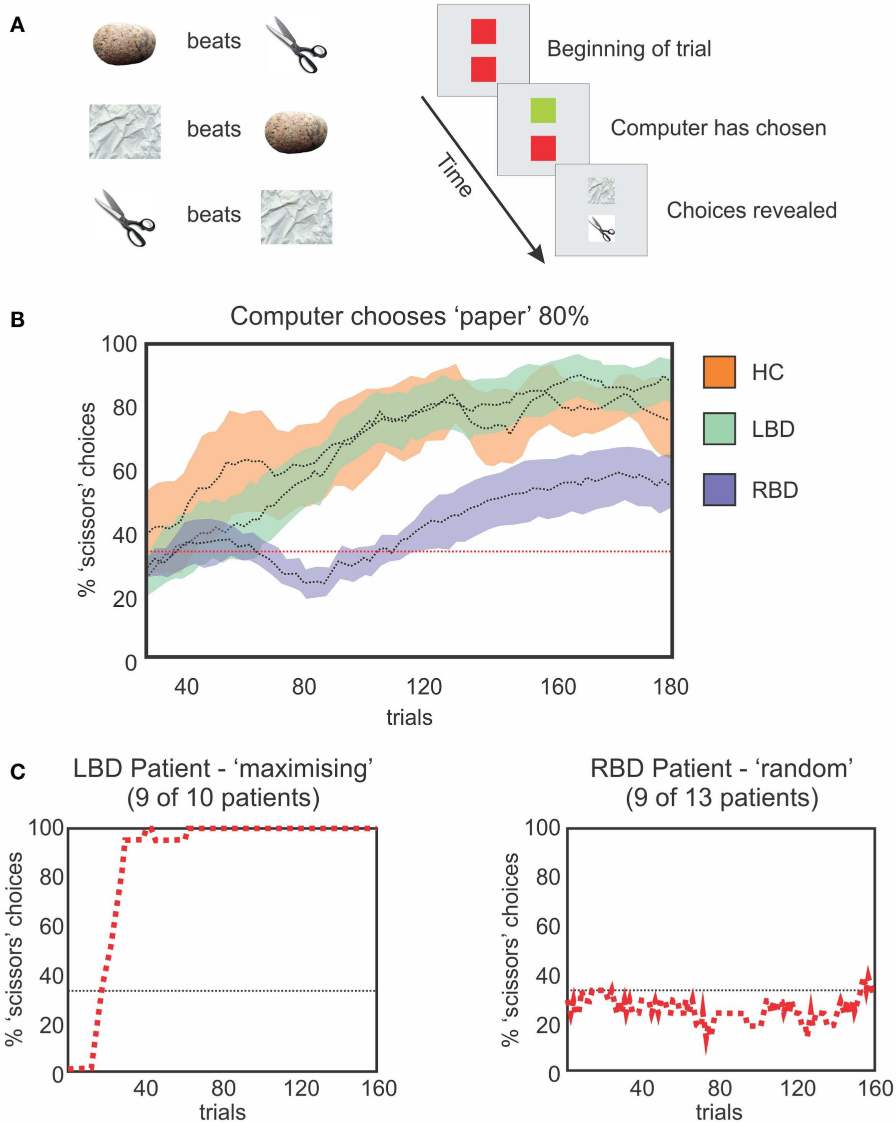

FIGURE 5 | (A) Schematic representation of the rules that govern the RPS task (left) and a single trial (right). The upper square represents the computer's choice, the lower square the participant's choice. The computer's square changes to green when a choice is made and the participant then make a choice, after which, both plays are revealed to indicate the result. **(B)** Moving average (20 trials) of optimal choices vs. the strong bias of the computer (i.e., 80% paper). HCs (orange) and LBD patients (green) exploit the bias. RBD patients fail to exploit the bias as efficiently. **(C)** Representative performances from a LBD (left) and RBD (right) patient. The LBD patient maximizes choosing the optimal play 100% of the time. The RBD patient continues to play randomly and uniformly.

periods of time compared to healthy controls and this is where the rehabilitation strategies should focus.

If statistical learning is inefficient in neglect then maybe massing trials would be another approach for training a corrective bias in patients' attention. This might make for an appropriate rehabilitation tool. To test this idea, we trained a chronic neglect patient by testing him over three different days on the paradigm of statistical learning adapted from Druker and Anderson (2010) (**Figures 1** and **7**). We analyzed whether the patient showed greater improvement in reaction time over trials for targets presented on the left compared to those on the right and found that after training, the patient was able to improve performance for the contralesional high probability region and become faster for targets in left, previously neglected space, although his performance did not reach the same speed as his RTs for right-sided targets (**Figure 7**). These results demonstrate that while patients with neglect have difficulties benefiting from the statistical distribution on their contralesional side, if they are given enough time to detect the targets (Kristjánsson et al., 2005) or if they are submitted to the regularities of the target position for a longer period of time (**Figure 7**), then they might benefit from the statistical regularities and improve their performance. Therefore, our data is in

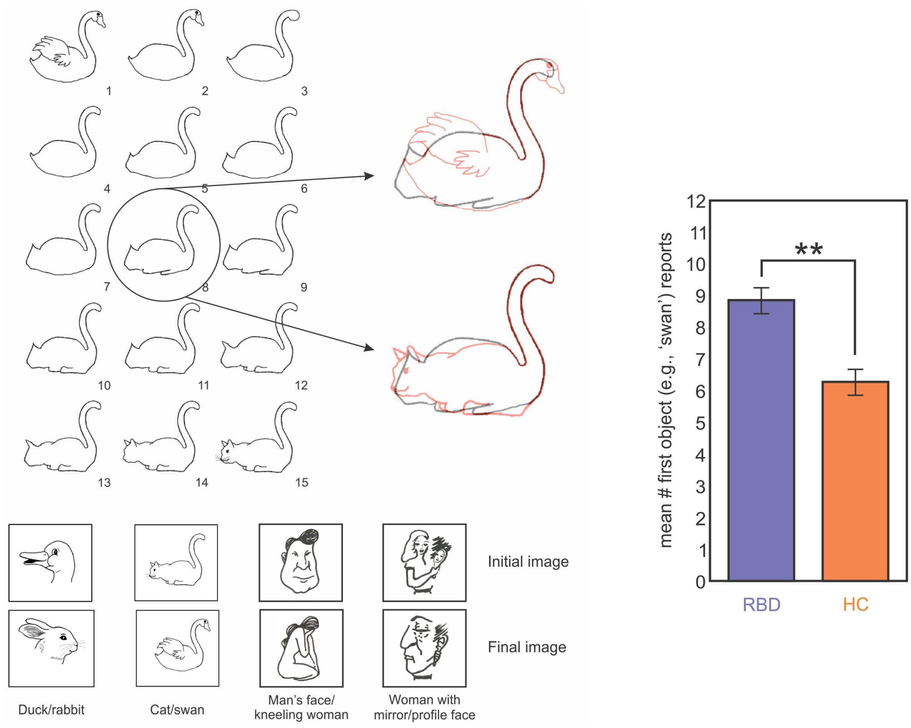

FIGURE 6 | Left panel: images used in one trial of the ambiguous figures task. In this example a swan morphs into a cat. The middle image (#8) is highlighted overlaid on the first (swan) and last (cat) images in red to highlight the ambiguous interpretation for the middle image. The four image sets used are indicated below. Right panel: data from RBD (purple) and HC (orange) participants showing mean report of the first object (i.e., how long does the first perceptual model persist before participants switch to the second?). RBD patients reported the first object for significantly more trials than did HCs (Stoettinger et al., under review).

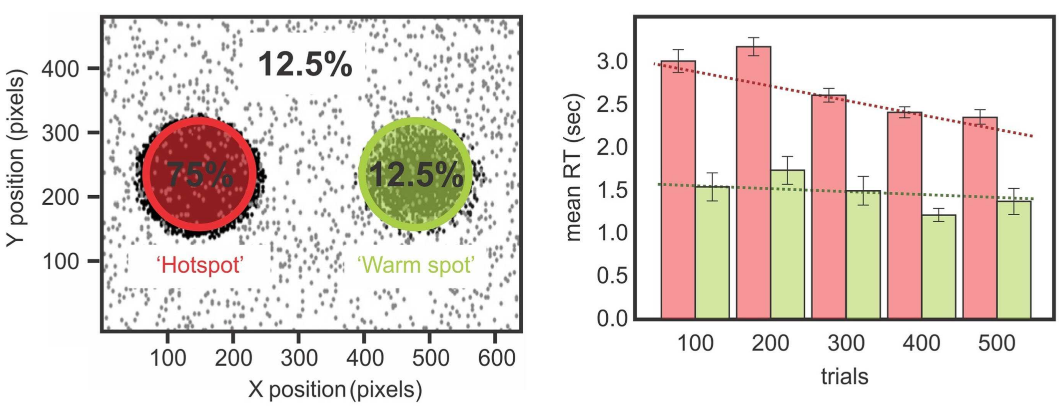

FIGURE 7 | Left panels show the distribution of the biased target positions while a chronic neglect patient performed a color discrimination task (Shaqiri and Anderson, 2012a, see also Figure 1). Targets were biased to appear 75% on a hotspot on the patient's contralesional side and 12.5% on a mirrored region on his ipsilesional side called the warm spot. Right panels show the chronic neglect patient's RT for the hot spot and the warm spot. There is a difference on the RT for the left and right-sided targets over the sessions. The patient improved his RT over the sessions for the targets presented on the hotspot, which was not the case for the targets presented on the warm spot.

agreement with the studies of Geng and Behrmann (2002, 2006): although their protocol had a reduced number of positions and could have suffered from the confound of position priming, their patients with neglect were sensitive to the probability of the stimulus location, and this acted as a cue for directing attention. We demonstrated (Shaqiri and Anderson, 2012a,b, under review) that neglect patients have a preserved but attenuated priming effect, but are also sensitive to some extent to probability distributions, although a longer exposure duration is needed to demonstrate this sensitivity.

Taken together, these data could have important implications for the rehabilitation of neglect patients. First, the non-spatial features of neglect must be understood to be important contributors to the nature and recalcitrance of the clinical symptoms. Second, deficits in domains such as priming, temporal processing, and working memory may underlie deficits in mental model building and updating that can have pervasive effects on daily behavior and limit the benefits due to conventional rehabilitation. Our data also suggest that if given enough time and experience, neglect patients can benefit from regularities of their environment, as we have shown by training a neglect patient over three different days (**Figure 7**; Shaqiri and Anderson, 2012a). If considered when designing and testing rehabilitation techniques for neglect, the observations suggest new domains for intervention and emphasize that constant, regular biases with training over multiple sessions may help patients to develop the intrinsic biases that will improve performance across multiple tasks, and in activities of daily life. A rehabilitation approach that could exploit these data is virtual reality (VR). VR permits the flexible modulation of stimulus timing, exposure duration, and environmental regularities. This technique also permits creating personalized environments that match individual patients' impairments. VR approaches to rehabilitation have already shown some promise for neglect patients (for a review, see Rose et al., 2005; Tsirlin et al., 2009), where, for example, VR rehabilitation has been used for training how to cross the street safely (Weiss et al., 2003; Katz et al., 2005).

CONCLUSION

In the present review paper, we have presented different studies that demonstrate that beyond the spatial aspect of neglect, the disorder is linked with a range of other deficits, including working memory, temporal processing, motor imagery, statistical learning, and priming impairments. Taken together, this range of impairments make it extremely difficult for neglect patients to build accurate mental models of the environment and to update those models when contingencies change. In essence, this makes neglect a disorder of representational updating: a difficulty in using incoming information from the environment in order to create and then update mental models about that environment. It is a difficulty that most rehabilitation techniques available have not succeeded in overcoming. We have demonstrated that with enough time and information, some neglect patients can be trained to be sensitive to the statistical distribution and regularities from their environment and use that information to their benefit. As such, this may be a fruitful avenue for developing novel rehabilitative techniques for what has proven to be an extremely difficult disorder to treat.

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Motor extinction: a deficit of attention or intention?

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Motor extinction refers to a deficit of motor production on the side opposite a brain lesion that either only becomes apparent or disproportionately worsens during bilateral motor activity. It may arise due either to a contralesional deficit in setting the motor activation level (an intentional deficit) or a deficit in contralesional awareness of the sensory consequences of movement (an attentional deficit). In this study, we investigate the nature of motor extinction in a patient (LR) with a right fronto-temporal lesion through the kinematic analysis of unimanual and bimanual circle-drawing movements. While the ipsi- and contralesional limbs performed comparably for unimanual movements, the contralesional limb demonstrated marked bradykinesia and hypometria during bimanual movements. Furthermore, these deficits were not overcome when visual feedback of the contralesional limb was provided (Experiment 1). However, when performing bimanual movements in the presence of a visual template (Experiment 2), LR was able to overcome the contralesional hypometria but not the bradykinesia which proved intractable across both experiments. Both the bradykinesia and hypometria could result from an intentional deficit of motor production. However, in Experiment 2, LR also demonstrated an abnormal level of positional drift in the contralesional limb for bimanual movements indicative of an additional attentional deficit. We conclude that LR's presentation of motor extinction is the result of a primary intentional deficit and a secondary attentional deficit.

Keywords: motor extinction, neglect, intention, attention, frontal lobe

INTRODUCTION

It is now generally accepted that unilateral spatial neglect (USN) involves a wide range of deficits within an overall syndrome. While the sensory and perceptual ramifications of the disorder continue to attract attention, the effects on motor control have received relatively little interest. Neglect-related movement problems take many forms but can be broadly divided into two categories; those affecting the visuo-spatial control of movement and may affect both sides of the body (see Harvey and Rossit, 2012 for a recent review), and those relating to the "underuse" of a contralesional limb. This study is concerned with the latter of these, most often referred to as "motor neglect" (Laplane and Degos, 1983; see below).

Patients who demonstrate elements of USN show a strong competitive element to their behavior that is perhaps best characterized by the related problem of "extinction," where a contralesional stimulus fails to register awareness only when presented simultaneously with an ipsilesional stimulus (Driver and Vuilleumier, 2001). Similarly, motor extinction refers to a deficit of motor production that either worsens disproportionately or only becomes apparent when the patient is involved in bilateral activity (Punt and Riddoch, 2006; Coulthard et al., 2008). As with perceptual neglect and extinction, motor extinction is related to motor neglect, an underutilization of a limb which cannot be explained by primary motor or sensory deficits (Laplane and Degos, 1983). Motor neglect tends to be measured by clinical observation alone (Laplane and Degos, 1983; de la Sayette et al., 1989; Chamorro et al., 1997; Manabe et al., 1999) or by relatively crude clinical tests (Heilman et al., 2003). By definition, one measures motor extinction by comparing the performance of the contralesional limb on unilateral and bilateral movement tasks. Comparing performance during unilateral and bilateral movements in this way, one is able to measure the contribution of directing resources to both sides of the body even when concurrent sensory and motor deficits are present. However, the precise nature of the motor deficit may differ across cases. In some instances, contralesional hypokinesia (slowness to initiate movement) has been reported (Valenstein and Heilman, 1981; Meador et al., 1986) whereas in others contralesional impersistence (an inability to sustain a movement) has been noted (Mattingley and Driver, 1997; Mattingley, 2002). There are at least two accounts for the deficit in contralesional motor production found in motor extinction. Firstly, motor failure may be an expression of an underlying problem in monitoring the sensory consequences of movement (e.g., proprioception). For instance, it may be the case that when attentional resources are devoted to monitoring the movement of a contralesional limb alone, movements unfold in a normal manner. However, during bilateral movements, a competitive bias between the two movements may arise resulting in only ipsilesional movements being monitored effectively (proprioceptive extinction). Such an account would be in line with accounts of perceptual awareness and extinction (Driver and Vuilleumier, 2001) and would suggest an "attentional" basis for the disorder. The patient may produce equal bilateral activity but only be aware of the sensory consequences of moving the ipsilesional side. As movements unfold, the lack of awareness for contralesional movement would likely lead to a movement deficit becoming apparent.

A second possible explanation for the failure of contralesional motor activity is that it represents a failure of "intention." Intention may be thought of as a physiological readiness to respond (Heilman et al., 2003) or the forming of a plan to move (Andersen and Buneo, 2002). Impaired intention has been linked to motor neglect, where the patient fails to automatically move the contralesional limb (Watson et al., 1978; Meador et al., 1986). In motor extinction on the other hand, intention would only fail during bilateral movement. If the underlying basis of motor extinction was isolated to one of intention, then the patient may be aware of the failure but unable to correct the problem. However, it has also been proposed that patients with a deficit in motor intention may not demonstrate normal motor awareness. Gold et al. (1994) proposed a "feed forward hypothesis" to understand anosognosia for hemiplegia, suggesting that motor intention fails in anosognosic patients. There is consequently no mismatch between the predicted and actual states of the limb as no attempt to move is made. The "forward model" of movement that this hypothesis draws on is consistent with current understanding of motor control (Wolpert et al., 1995). A recent study of patients with either anosognosia or motor neglect proposes dissociation between the two disorders with regards to the contribution of motor intention. It is suggested anosognosic patients have intact motor intention in the absence of the ability to execute movements whereas for patients with motor neglect, motor execution is spared while motor intention is impaired (Garbarini et al., 2012). Further work by the same group suggests motor awareness can be impaired in both conditions (Garbarini et al., 2013).

Of course, patients who demonstrate motor extinction may have a combination of both intentional and attentional deficits but the issue remains to be established. In this study, we examine the relation between intentional and attentional factors in motor extinction, by analyzing the performance of a patient with motor extinction on a series of unimanual and bimanual circle-drawing tasks.

BIMANUAL CIRCLE-DRAWING MOVEMENTS

Circle drawing has a history of use as a method of measuring both unimanual and bimanual coordination, providing the opportunity to measure a range of parameters including amplitude, circularity, cycle duration, velocity, drift, and temporal coupling. For example, when moving bimanually, coupling is most stable when mirror-symmetrical movements are performed compared with parallel or asymmetrical movements (Semjen et al., 1995). There is also evidence that, while there is a strong tendency for synchrony, small but distinct inter-limb asynchronies arise which may be modulated by focusing visual attention toward a particular hand (Swinnen et al., 1996; Franz et al., 2002; Franz, 2004). Performance may also be affected by other factors such as hand dominance, direction of movement (Franz et al., 2002), and proprioception (Verschueren et al., 1999a).

Normal proprioception is important for optimal performance in unimanual and bimanual circle drawing. In a series of studies, Verschueren et al. (1999a,b) demonstrated the effects of proprioceptive disturbances in normal subjects on these tasks. Proprioception was disturbed by placing small vibrators (60–70 Hz) on the distal tendons of the biceps and anterior deltoid muscles while subjects performed circle drawing using the dominant limb while blindfolded. For unimanual circle drawing, tendon vibration caused the circle diameters (CDs) to be smaller; it reduced circularity and introduced a systematic drift of the hand toward the body. CDs were significantly reduced when both tendons (biceps and anterior deltoid) in the same arm were vibrated, but the reduction was relatively small (control condition = 17.63 cm, vibration of both tendons = 16.70 cm). Similar results were found for the dominant, vibrated limb when subjects performed bimanual circle drawing. Interestingly, the non-dominant, non-vibrated limb showed a significant increase in CD when the dominant limb was vibrated but again this was a relatively small change (<1 cm).

Spatial coupling is a strong feature of bimanual circle-drawing movements as demonstrated by the work of Franz (1997). Normal subjects have great difficulty in maintaining asymmetrically sized (amplitude) circles with a strong tendency for coupling. Franz argues that amplitude coupling reflects interactions at the planning (intentional) stages of movement.

Reports of the use of bimanual circle drawing to investigate bimanual coordination in subjects with brain pathology are limited, but studies relating to subjects with damage to the parietal lobe and the corpus callosum have been conducted. Serrien et al. (2001a) studied mirror or symmetrical, and parallel or asymmetrical movements in three patients with left parietal damage. The subjects showed a phase lag for the contralesional limb which was most apparent for the more difficult parallel task. Studies of subjects with acquired corpus callosum damage reveal a problem in maintaining synchronization across the limbs (Serrien et al., 2001b; Kennerley et al., 2002). Such studies add weight to the proposal that skilled bimanual coordination relies on the transmission of information from one hemisphere to the other.

In this study, we investigate the spatial and temporal characteristics of circle drawing in a subject with motor extinction. We hypothesize that contralesional unimanual movements will be relatively well-maintained. However, for bimanual movements, we predict that while ipsilesional movements will be unaffected, contralesional movements will be degraded with reduced CDs. Crucially, we measure velocity to indicate the intensity of motor production. As stated above, motor extinction may represent a contralesional deficit of proprioception (awareness) or intention under bilateral conditions, or possibly elements of both problems. Different kinematic parameters during circle drawing may be considered to primarily reflect either intentional or attentional factors. For example, movement velocity and CD can provide a measure of motor production related primarily to the intentional control of movement. Disturbing proprioception in normal subjects has only small effects on CD (see Verschueren et al., 1999b above), so that marked reductions in CD together with a reduction in movement velocity can be considered more suggestive of an intentional deficit rather than a sole deficit in awareness of the sensory consequences of movement. On the other hand, the amount of drift away from the starting position should provide a measure of the proprioceptive awareness of movement (Verschueren et al., 1999b). Drift provides a strong indication of position sense which is modulated by proprioceptive awareness.

We do not expect to find substantial difficulties with bimanual coupling but nevertheless measured the relations between temporal and spatial characteristics of the movements produced. It is important to establish whether aspects of bimanual coupling may remain even under extinction conditions. We also manipulate direction of gaze. Visual feedback will provide compensation for abnormal performance in a limb due to a deficit in proprioceptive awareness so that deficits due to poor proprioceptive awareness should decrease.

BACKGROUND

CASE STUDY: LR

LR was a previously fit 52-year-old man, formerly employed as a security guard, with a keen interest in aquarium fish and the martial arts. In June 2002, he suffered a right middle cerebral artery infarction and was hospitalized for 6 weeks. Subsequent MRI of his head showed the infarction to be primarily restricted to the right temporal lobe and posterior aspects of the right frontal lobe. More specifically, there was involvement of the inferior, middle, and superior temporal gyri on the right, and the inferior frontal and middle frontal gyri on the right (see **Figure 1**). LR underwent a neuropsychological screen following admission to the hospital. He also underwent additional neuropsychological testing prior to participating in the two experiments described below. Together, this information provides insights into LR's initial difficulties and his abilities at the time of testing.

INITIAL NEUROPSYCHOLOGICAL ASSESSMENT

LR was assessed 8 days following stroke. He was oriented in time and space and performed within normal limits on picture naming, single word comprehension, complex commands, and digit span (forwards and backwards). He scored 46/54 on the Star Cancelation Test (Wilson et al., 1987), "missing" seven stars in the lower left quadrant. He scored at ceiling on tests of visual and tactile extinction. Visual extinction was tested by confrontation using the examiner's fingers as visual stimuli either side of the examiner's nose (central fixation). Tactile extinction was also tested by confrontation using light strokes (delivered using the examiner's fingers) to the backs of LR's hands (with eyes closed). LR did not present with a visual deficit.

He was tested on a novel test for motor extinction using two electronic "tappers" (WPS Electronic Tapping Test). Here, the participant places either their left, right, or both index fingers on a spring-loaded platform, and at a given signal, depresses and releases the platform as frequently as possible. The devices record the number of "taps" made in a 10-s period. When tapping with the right hand, LR made 46 taps. When tapping with the left hand, he made 41 taps. However, when tapping both hands together (each hand operating a separate device), he made 42 taps with the right hand and only 1 tap with the left hand. This pattern of performance is diagnostic of motor extinction. At this early stage post-stroke, the general impression was that LR demonstrated no language deficits, showed some deficit of executive functions as shown by impaired performance on the Brixton Test (Burgess and Shallice, 1997) and had intact memory. He showed some mild elements of neglect and in particular demonstrated motor extinction.

At this time, neurological examination revealed the following information. Muscle power was 4/5 on the left and 5/5 on the right. Assessment of tone showed no abnormalities, with equal tendon reflexes left and right. Plantar responses were downward bilaterally and there was no clonus. LR was accurate in detecting light touch and reported no differences from side to side.

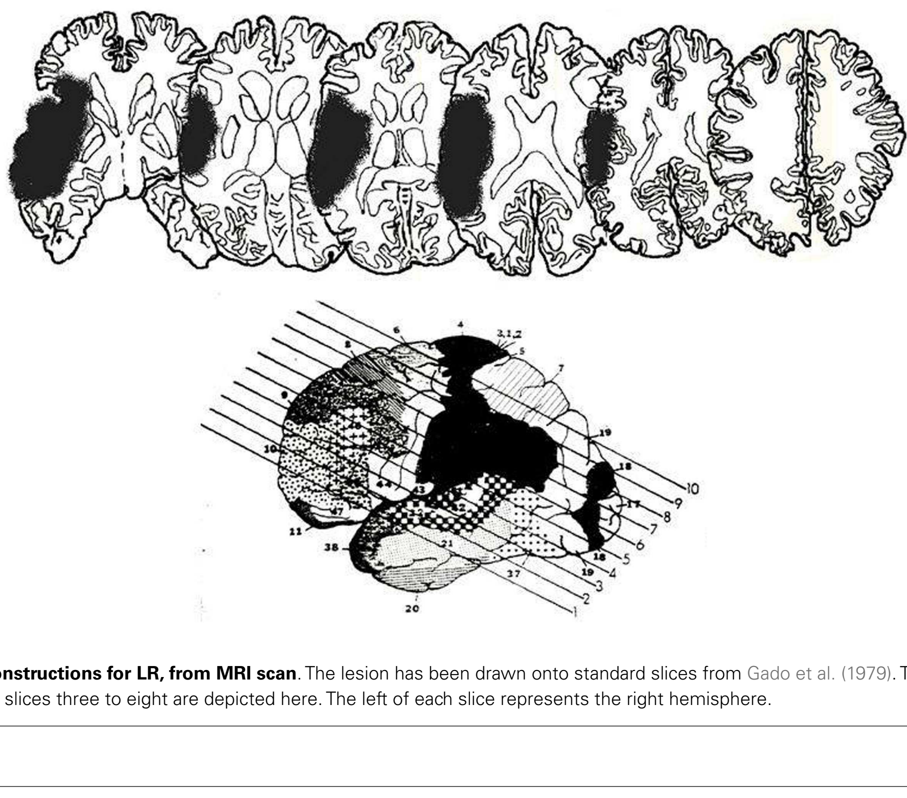

FIGURE 1 | Lesion reconstructions for LR, from MRI scan. The lesion has been drawn onto standard slices from Gado et al. (1979). The bottom figure shows the 10 slices used. Only slices three to eight are depicted here. The left of each slice represents the right hemisphere.

FURTHER TESTING

The examination was repeated at 9 months post-stroke. At this time, the neurological examination was as above except that power appeared to have fully returned on the left (5/5). LR scored 9/9 on the Abbreviated Mental Test (Hodkinson, 1972). He performed at ceiling on tests of long term memory. Forward and backwards digit span were within normal limits. His performance on the Brixton Test for executive functions was improved but still fell within the "poor" range. LR performed normally on the Star Cancelation subtest of the Behavioral Inattention Test (Wilson et al., 1987). To assess visual attention more sensitively, LR completed a test based on the Spatial Cueing Paradigm developed by Posner et al. (1987). In this test, the subject responds to targets that can appear at locations on either side of central fixation. The appearance of a target is proceeded by a 300-ms brightening of one of these locations (50% valid and 50% invalid). In addition, targets appear at various asynchronies following the onset of the cue. Patients with lateralized attentional deficits have particular difficulties in responding to contralesional targets that follow the brightening (cueing) of the ipsilesional location. LR was slightly slower in responding to contralesional targets but the pattern for valid and invalid cues was the same on the left and right sides suggesting that he did not have a particular difficulty disengaging attention from the ipsilesional side as previously reported in patients with parietal injury and neglect (Posner et al., 1984).

LR was tested for tactile extinction using transcutaneous nerve stimulation set just above sensory threshold applied to each arm (left and right intensity thresholds were equal. Using computer-controlled presentations of these stimuli, LR was 100% accurate in responding to unilateral stimuli on the ipsilesional and contralesional sides but reported "right only" for 39% of bilateral stimuli (61% correct). He performed normally on the "sharp/dull discrimination," "surface pressure touch," "surface localization," "sensory extinction," "proprioceptive movement discrimination," and "proprioceptive direction discrimination" subtests of the "Rivermead Assessment of Somatosensory Performance" (Winward et al., 2002).

Prior to the current experimental study, the novel tapping test for motor extinction that LR had performed during the acute phase of stroke was repeated. He now scored equal numbers of taps on the left and the right, both for unimanual and bimanual conditions (blindfolded) suggesting that he no longer demonstrated motor extinction for discrete tasks. However, as our experiments (below) demonstrate, he did continue to manifest motor extinction in continuous movement tasks (continuous circle drawing). In addition, he was also tested on the crossed-response task developed by Watson et al. (1978). This task aims to dissociate between sensory and motor neglect by demanding a response contralateral to a stimulus (e.g., the subject has to move the left arm when the right is stimulated and vice-versa). If there is no ipsilesional response to a contralesional stimulus, then the subject is considered to have a sensory deficit or sensory neglect. If there is no contralesional response to an ipsilesional stimulus, this is indicative of an exo-evoked akinesia, and suggests a motor deficit or motor neglect. LR performed at ceiling on this task.

EXPERIMENT 1: A COMPARISON OF UNIMANUAL AND BIMANUAL CIRCLE-DRAWING MOVEMENTS

LR sat at a table which had no markings except for two small crosses placed 30 cm from the near edge of the table. These two crosses were equidistant from his mid-sagittal plane and were 55 cm apart. The crosses acted as start points for the circle-drawing movements to be performed. LR was instructed to draw circles rhythmically and repetitively with the extended index finger of either the left, the right, or both hands when given a start signal. Each trial lasted for 30 s and the participant was asked to maintain a constant speed and size of movement throughout the trials. In addition, there were three visual conditions where LR's gaze position was manipulated ("look at the left hand," "look at the right hand," or "look at a fixation point straight ahead"). There were therefore nine different experimental conditions, and each one was performed five times (45 trials in all). The conditions were randomized across trials. All movements of the left hand were performed in an anticlockwise direction, whereas all the movements with the right hand were performed in a clockwise direction. Thus, bimanual movements were of a mirror or symmetrical type and directionally thought to relate to the natural tendencies of each hand (Franz et al., 2002). Movements were recorded using a 3-camera 3-D motion analysis system (ProReflex, Qualisys Ltd., Sweden) sampling at 200 Hz. Spherical reflective markers (5 mm diameter) were placed on the index finger nail of each hand. An auditory cue indicated the beginning and end of each trial. LR completed a small number of practice trials prior to the experimental trials in order to familiarize himself with the procedure. All trials were completed within one experimental session which lasted approximately 1 h.

DATA ANALYSIS

The x- and y-axis components of movement were analyzed offline using customized software (QTools, Qualisys Ltd., Sweden and LabVIEW, National Instruments Inc., USA). The measures of interest were the spatial and temporal characteristics of each limb and the relations between the two limbs. More specifically, we report the measurements summarized below.

Circle diameter

The peaks of the x- and y-axes were used to calculate CD in each plane. For the y-axis, each proximal peak was subtracted from the previous distal peak and for the x-axis, each medial peak was subtracted from the previous lateral peak.

Cycle duration

The mean time taken for each hand to produce a full circle was calculated.

Drift

Movement of the limb began with the index finger placed on the cross. As each trial progressed, any tendency for the limb to drift either in the x- or y-axis was quantified by the slope of the linear regression of displacement as a function of time.

Velocity

Mean velocity was calculated across each entire trial to provide a further indication of force production.

Inter-limb temporal coupling

The relative time that each hand reached particular landmarks was used to provide a simple indication of temporal coupling between the two limbs. The specific points used were the peaks of the x and y trajectories. The lag was calculated by subtracting the time when the right limb reached each point from the time that the left hand reached each point. Thus, a negative value refers to a "left lead" and a "right lag," and a positive value refers to a "right lead" and a "left lag."

RESULTS

For most of the analyses, mean values from each trial were treated as independent replications and submitted to a univariate analysis of variance (ANOVA). There were four factors leading to a $2 \times 2 \times 3 \times 2$ (Hand × Condition × Gaze Position × Axis) analysis. The factors were: hand (left vs. right), Condition (unimanual vs. bimanual), Gaze Position (left vs. central vs. right), and Axis (x vs. y).

CIRCLE DIAMETER

The mean CDs are shown in **Figure 2**. The main finding was the marked reduction in contralesional CD when LR made bimanual movements leading to a significant Hand × Condition interaction [$F(1,96) = 37.7$, $p < 0.0001$]. While unimanual CDs were within a few millimeters of each other (left = 39.3 mm, right = 46.3 mm), bimanual CDs were markedly different (left = 17.4 mm, right = 50.1 mm). There was a significant main effect of Hand [$F(1,96) = 89.7$, $p < 0.0001$] and Condition [$F(1,96) = 18.7$, $p < 0.0001$]. No other main effects or interactions proved reliable. Importantly, there was no significant main effect of Gaze Position, nor was Gaze Position involved in any significant interactions. As can be seen from **Figure 2**, vision failed to improve contralesional CDs when directed at the contralesional hand. CDs were comparable across all gaze position conditions. **Figure 3** shows representative trajectories for unimanual and bimanual trials when vision was directed centrally.

CYCLE DURATION

The ANOVA revealed a significant main effect for Condition [$F(1,48) = 4.9$, $p < 0.05$]. Duration means were 891 ms for unimanual movements and 937 ms for bimanual movements. There was also a significant main effect of Gaze Position [$F(2,48) = 7.8$, $p < 0.005$] and a significant Condition × Gaze Position interaction [$F(2,48) = 5.2$, $p < 0.01$]. Further analysis showed Gaze Position was only a significant factor for the bimanual condition [$F(2,24) = 7.7$, $p < 0.005$]. Contrasts revealed cycle duration to be shorter when vision was directed to the right hand (833 ms) than when gaze position was directed centrally (986 ms) or to the left hand (993 ms) [gaze right compared with gaze central, $F(2,24) = 11.1$, $p < 0.005$; gaze right compared with gaze left, $F(2,24) = 12.2$, $p < 0.005$]. Durations were comparable when gaze was directed leftwards or centrally [$F(2,24) < 1.0$, $p = 0.9$]. For unimanual movements, there was no significant effect of Gaze Position [gaze left = 890 ms, gaze central = 904 ms, gaze right = 880 ms; $F(2,24) < 1.0$, $p = 0.5$].

DRIFT

The mean slope of the linear regressions of limb position over time provided a measure of drift; the larger the number, the larger the amount of drift measured. Drift in the x-axis indicated movement toward or away from the mid-sagittal plane. Drift in the y-axis indicated movement toward or away from the body. There was a Hand × Axis interaction [$F(1,96) = 5.8$, $p < 0.05$]. Exploring the simple effects of this revealed drift in each axis to be comparable for the right hand [$x = 0.32$, $y = 0.33$, $F(1,48) < 1.0$, $p = 0.80$], whereas there was significantly more drift in the x-axis for the left hand [$x = 0.62$, $y = 0.28$, $F(1,48) = 6.2$, $p < 0.025$].

Directing gaze vision toward a limb reduced the amount of drift leading to a significant Hand × Gaze Position interaction [$F(2,96) = 5.6$, $p < 0.01$]. This was best explained by considering the difference in drift across the hands depending on gaze position. The left hand (0.20) drifted less than the right hand (0.37) when gaze was directed toward the left hand [$F(1,32) = 6.8$, $p < 0.016$]. When gaze was directed centrally, drift across the hands was comparable [left hand = 0.54, right hand = 0.44, $F(1,32) < 1.0$, $p = 0.41$]. The left hand (0.61) drifted more than the right hand (0.18) when gaze was directed toward the right hand [$F(1,32) = 6.54$, $p < 0.016$]. There were no other significant main effects or interactions. Importantly for this study, Condition was not found to have a significant effect on drift and neither did it appear in any interaction. While excessive drift is indicative of a proprioceptive deficit, it should be noted that in normal subjects, the non-dominant limb tends to drift more than the dominant

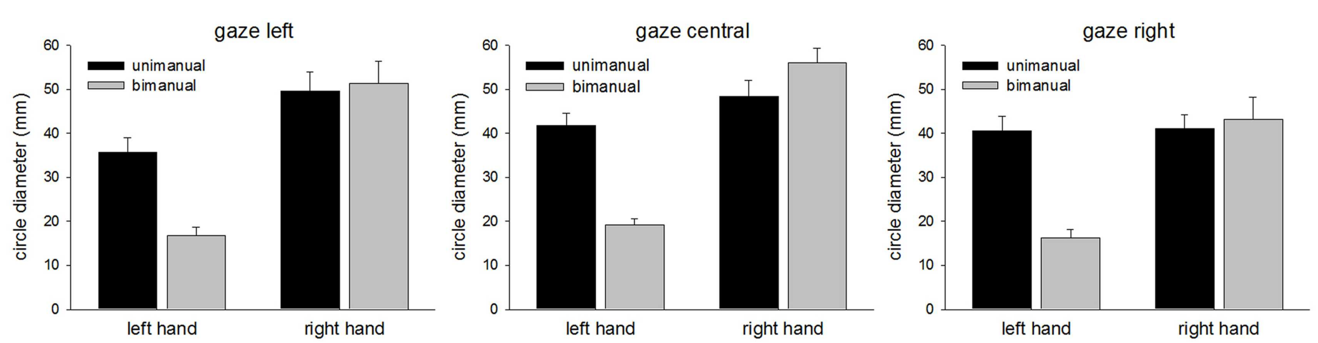

FIGURE 2 | Circle diameters for each condition in Experiment 1.

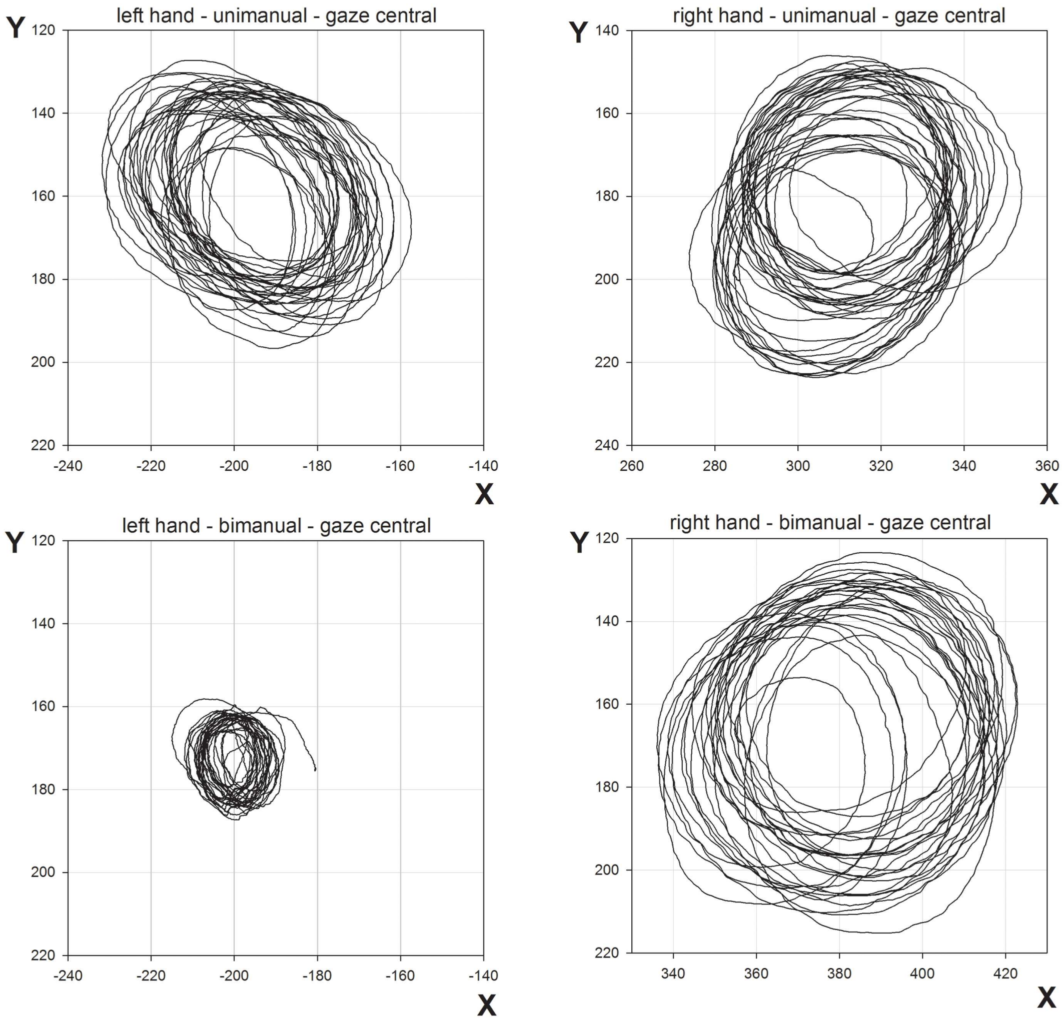

FIGURE 3 | Representative movement trajectories of unimanual and bimanual conditions from Experiment 1, when gaze was directed centrally.

limb and this may be sufficient to explain LR's performance (Verschueren et al., 1999a). In comparison with the Verschueren study, LR showed increased drift in both limbs, possibly a function of the reduced circle size in this study. However, the relative drift for the dominant vs. the non-dominant hand is less in our study.

VELOCITY

The left and right hands demonstrated comparable velocities for unimanual movements [$F(1,24) = 3.2$, $p = 0.09$] but while the right hand maintained similar velocity for bimanual movements [$F(1,24) < 1.0$, $p = 0.9$], the left hand showed a marked reduction in velocity [$F(1,24) = 78.8$, $p < 0.0001$]. The relevant means are displayed in **Figure 4**. There were corresponding significant main effects of Hand [$F(1,48) = 62.8$, $p < 0.0001$], Condition [$F(1,48) = 23.7$, $p < 0.0001$], and a significant Hand × Condition interaction [$F(1,48) = 25.9$, $p < 0.0001$]. No other main effects or interactions reached significant levels.

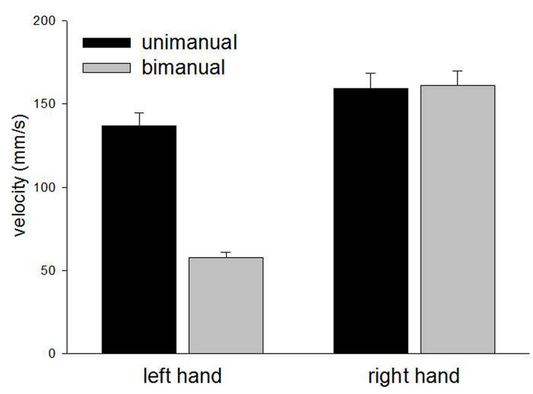

FIGURE 4 | Mean velocity for unimanual and bimanual movements in Experiment 1.

INTER-LIMB TEMPORAL COUPLING

Despite some of the profound asymmetries reported above, movements of the left and right hands were tightly coupled with an overall mean right lag of only 18 ms. However, there were small but significant asynchronies which were modulated by the Gaze Position [$F(2,27) = 12.2$, $p < 0.0005$]. The left hand lead was strongest when gaze was directed toward the left hand (−36 ms), less strong when gaze was directed centrally (−29 ms) and the asynchrony was reversed to a right hand lead when gaze was directed toward the right hand (12 ms). Contrasts showed a significant difference between right gaze and central gaze [$F(1,27) = 15.3$, $p < 0.001$] and between right gaze and left gaze [$F(1,27) = 21.0$, $p < 0.0001$] but not between central gaze and left gaze [$F(1,27) < 1.0$, $p = 0.5$].

DISCUSSION

The results from Experiment 1 show a clear deterioration in contralesional circle drawing under bimanual conditions, consistent with LR showing motor extinction. Moreover, extinction was reflected most clearly in the reduced CD and velocity, measures of motor production. This is important as it suggests that LR's motor extinction was the result of a deficit in the intentional system that has been implicated in previous studies of motor neglect (Heilman and Valenstein, 1972; Watson and Heilman, 1979; Meador et al., 1986). We propose that an intention to move "sets" the level of activation for motor output, and LR's clear contralesional hypometria and bradykinesia reflect difficulties in setting this level during bimanual movements. However, it may also be argued that LR showed a deficit in the awareness of movement, as CD does reduce for unimanual and bimanual circle drawing in subjects with proprioceptive disturbances (Verschueren et al., 1999a,b). Against this is the magnitude of the effects shown by LR and the normal subjects with reduced proprioception tested by Verschueren and colleagues. For example, the reduction in the proprioceptively impaired limb was <1 cm for circles drawn using a 16-cm diameter template (Verschueren et al., 1999b). Here, in Experiment 1, with no template, LRs contralesional limb reduced from 39.3 mm for unimanual movements to 17.4 mm for bimanual movements, a relatively large reduction. Also, a proprioceptive deficit would be expected to reduce accuracy in circle drawing in both directions (Meador et al., 1986) rather than the consistently hypometric movements shown by LR here. Furthermore, if a deficit in proprioceptive awareness was the primary reason for LR's impairment, gaze position ought to have compensated in the "gaze left" condition, but this was not found. Indeed, LR was aware of the difficulties he was having with the contralesional limb when moving bimanually but was unable to correct them[1]. Such behavior is reminiscent of Meador et al.'s (1986) patient who was also described as having an intentional deficit of motor production (see General Discussion later). In addition, LR's ipsilesional limb showed relative hypermetria in the bimanual condition (see **Figures 2** and **3**) possibly as a result of LR's awareness and his attempts to correct for the hypometric movements of the contralesional limb. Further support for an intentional rather than an attentional basis for the asymmetry of bimanual movements comes from inter-limb coupling. LR generally demonstrated a "left lead" during bimanual movements which is indicative of attention being directed toward that side (Swinnen et al., 1996).

In summary, we conclude that LR does not demonstrate an attentional deficit for the sensory consequences of contralesional movements during bimanual circle drawing. Rather, his performance reflects a contralesional deficit in the maintenance of appropriate force that can generally be considered a deficit in the intentional control of movement. In LR's case, contralesional movement initiation was preserved, but bradykinesia and hypometria became evident on bimanual movements (motor extinction).

We were surprised that LR was unable to prevent the contralesional hypometria when his vision was directed toward the left arm. To examine this further, in Experiment 2 we provided more explicit visual guidance by providing a visual template for the action (Semjen et al., 1995; Verschueren et al., 1999a; Serrien et al., 2001a; Kennerley et al., 2002). In doing this, we assessed whether, by increasing the visual cues available, we would "force" LR's contralesional limb to make comparable movements with both limbs in the bimanual condition when gaze was directed toward the contralesional limb. Experiment 2 was performed 2 weeks after Experiment 1.

EXPERIMENT 2: A COMPARISON OF UNIMANUAL AND BIMANUAL CIRCLE-DRAWING MOVEMENTS CONSTRAINED BY A VISUAL TEMPLATE

The procedure was identical to that in Experiment 1 except for the inclusion of a visual template. This template involved two circles (60 mm diameter) drawn on the table with the crosses from Experiment 1 at their center. This size of circle was chosen as it was similar to the size of the unconstrained circles performed in Experiment 1. The circles provided guidance for the movements in Experiment 2. The crosses from Experiment 1 acted as start points for each trial. The data were analyzed as for Experiment 1.

RESULTS

CIRCLE DIAMETER

The mean CDs are shown in **Figure 5**. As in Experiment 1, the main finding was the marked contralesional hypometria when LR made bimanual movements. However, in Experiment 2, contralesional hypometria did not occur when gaze was directed toward the contralesional limb. Thus, provision of a visual template appeared to facilitate performance. These results are supported by significant main effects of Hand [$F(1,96) = 77.8$, $p < 0.0001$], Condition [$F(1,96) = 21.3$, $p < 0.0001$], and Gaze Position [$F(2,96) = 7.8$, $p < 0.001$]. Contrasts for Gaze Position revealed significant differences between "left gaze" and "central gaze" [$F(1,96) = 13.9$, $p < 0.0005$] and between "left gaze" and "right gaze" [$F(1,96) = 8.8$, $p < 0.005$] but not between "central gaze" and "right gaze" [$F(1,96) < 1.0$, $p = 0.4$]. Significant interactions included Hand × Condition [$F(1,96) = 17.8$, $p < 0.0001$], Hand × Gaze Position [$F(2,96) = 4.8$, $p < 0.05$], and

[1] LR appeared frustrated during bimanual trials, complaining of the arm letting him down and occasionally telling his arm to "move."

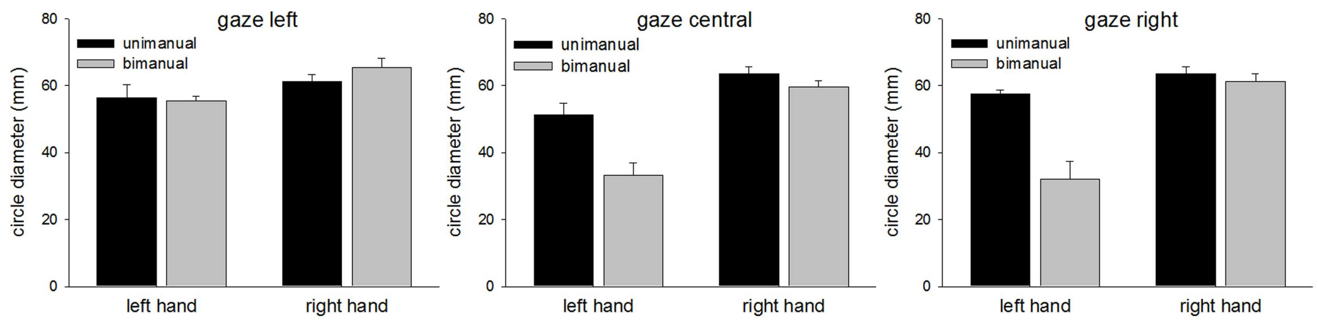

FIGURE 5 | Circle diameters for each condition in Experiment 2.

Condition × Gaze Position [$F(2,96) = 8.2$, $p < 0.001$]. Representative bimanual trajectories from Experiment 2 are shown in **Figure 6**.

CYCLE DURATION

Cycle durations were equivalent for the left and right hands [left = 1750 ms, right = 1773 ms, $F(1,48) < 1.0$. $p = 0.7$]. Unimanual durations were shorter than bimanual durations (unimanual = 1706 ms, bimanual = 1817 ms) but this just failed to reach normal levels of significance [$F(1,48) = 4.0, p = 0.05$]. There was a significant main effect of Gaze Position [$F(2,48) = 59.5$, $p < 0.0001$]. Contrasts revealed that durations were on the borders of being significantly different for "central gaze" (1484 ms) and "right gaze" (1620 ms) [$F(1,48) = 4.1$, $p = 0.05$], while "left gaze" (2180 ms) was significantly different from both "central gaze" [$F(1,48) = 105.9$, $p < 0.0001$] and "right gaze" [$F(1,48) = 68.6$, $p < 0.0001$]. There were significant two-way interactions between Hand × Gaze Position [$F(2,48) = 6.4$, $p < 0.005$] and Condition × Gaze Position [$F(2,48) = 19.0$, $p < 0.0001$], and a significant three-way interaction [$F(2,48) = 6.5$, $p < 0.005$]. To understand this interaction; when gaze was directed centrally, there was no significant main effect of Hand [$F(1,16) = 1.6$, $p = 0.2$], Condition [$F(1,16) = 1.6$, $p = 0.2$], or a significant interaction [$F(1,16) = 1.4$, $p = 0.2$]. When gaze was directed rightwards, there was a clear increase in cycle duration for the right hand making unimanual movements (left = 1474 ms, right = 1957 ms), leading to a significant Hand × Condition interaction [$F(1,16) = 18.7$, $p < 0.005$]. When gaze was directed leftwards, bimanual cycle durations were clearly lengthened (left = 2471 ms, right = 2476 ms), leading to a significant main effect of Condition [$F(1,16) = 15.8$, $p < 0.005$].

DRIFT

The ANOVA revealed significant main effects of Hand [the left hand drifted more than the right; left = 0.76, right = 0.34; $F(1,96) = 40.9$, $p < 0.0001$], Condition [unimanual movements drifted less than bimanual movements; unimanual = 0.38, bimanual = 0.73; $F(1,96) = 28.6$, $p < 0.0001$], and Axis [drift was more severe along the x-axis rather than the y-axis; x-axis = 0.67, y-axis = 0.44, $F(1,96) = 12.6$, $p < 0.001$]. A significant main effect of Gaze Position [$F(2,96) = 19.4$, $p < 0.0001$] was further investigated through a series of contrasts. Drift was most severe when gaze was directed centrally (0.77) and this was significantly greater than both when gaze was directed either leftwards [0.28; $F(1,96) = 37.7$, $p < 0.0001$] or rightwards [0.60; $F(1,96) = 4.7$, $p < 0.05$]. The difference between drift when gaze was directed leftwards or rightwards was also significant [$F(1,96) = 15.8, p < 0.0005$]. A significant Condition × Axis interaction [$F(1,96) = 10.5$, $p < 0.005$] revealed that, while drift was equivalent for each axis for unimanual movements ($x = 0.39$, $y = 0.37$), for bimanual movements, drift along the x-axis was much greater ($x = 0.95$, $y = 0.51$). There were also significant two-way interactions for Hand × Condition [$F(1,96) = 21.3$, $p < 0.0001$], Hand × Gaze Position [$F(2,96) = 29.3$, $p < 0.0001$], Condition × Gaze Position [$F(2,96) = 6.3$, $p < 0.005$], and a significant three-way interaction for Hand × Condition × Gaze Position [$F(2,96) = 5.0, p < 0.01$]. The three-way interaction occurred because contralesional drift increased disproportionately to ipsilesional drift as a function of both Condition and Gaze Position. Thus, for the right hand, drift was comparable for unimanual and bimanual movements [unimanual = 0.32, bimanual = 0.37, $F(1,48) < 1$, $p = 0.4$] and there was no Gaze Position × Condition interaction [$F(2,48) < 1.0$, $p = 0.4$]. The significant effect of Gaze Position [$F(2,48) = 19.0$, $p < 0.0001$] can be explained as follows. Visually monitoring the right limb led to reduced drift (0.11) compared with "central gaze" [0.52, $F(1,48) = 36.1$, $p < 0.0001$] and "left gaze" [0.40, $F(1,48) = 17.6$, $p < 0.0005$]. However, there was no significant difference for the "central gaze" and "left gaze" conditions [$F(1,48) = 3.3, p = 0.08$]. For the left hand, drift was significantly greater for bimanual movements (1.09) than unimanual movements [0.44, $F(1,48) = 30.5$, $p < 0.0001$] and here, there was a significant Condition × Gaze Position interaction [$F(2,48) = 6.7$, $p < 0.005$]. This interaction is best explained by considering the difference in drift for unimanual and bimanual movements when gaze was directed at the three possible locations. Drift was significantly greater for the left hand during bimanual movements relative to unimanual movements when gaze was directed rightwards [unimanual = 0.70, bimanual = 1.49, $F(1,16) = 18.1$, $p < 0.005$] and centrally [unimanual = 0.47, bimanual = 1.58, $F(1,16) = 13.74$, $p < 0.005$], but not when gaze was directed leftwards [unimanual = 0.13, bimanual = 0.20, $F(1,16) = 1.74$, $p = 0.2$]. Representative linear regression slopes for the x- and y-axes during bimanual movements are shown in **Figure 7** (when gaze

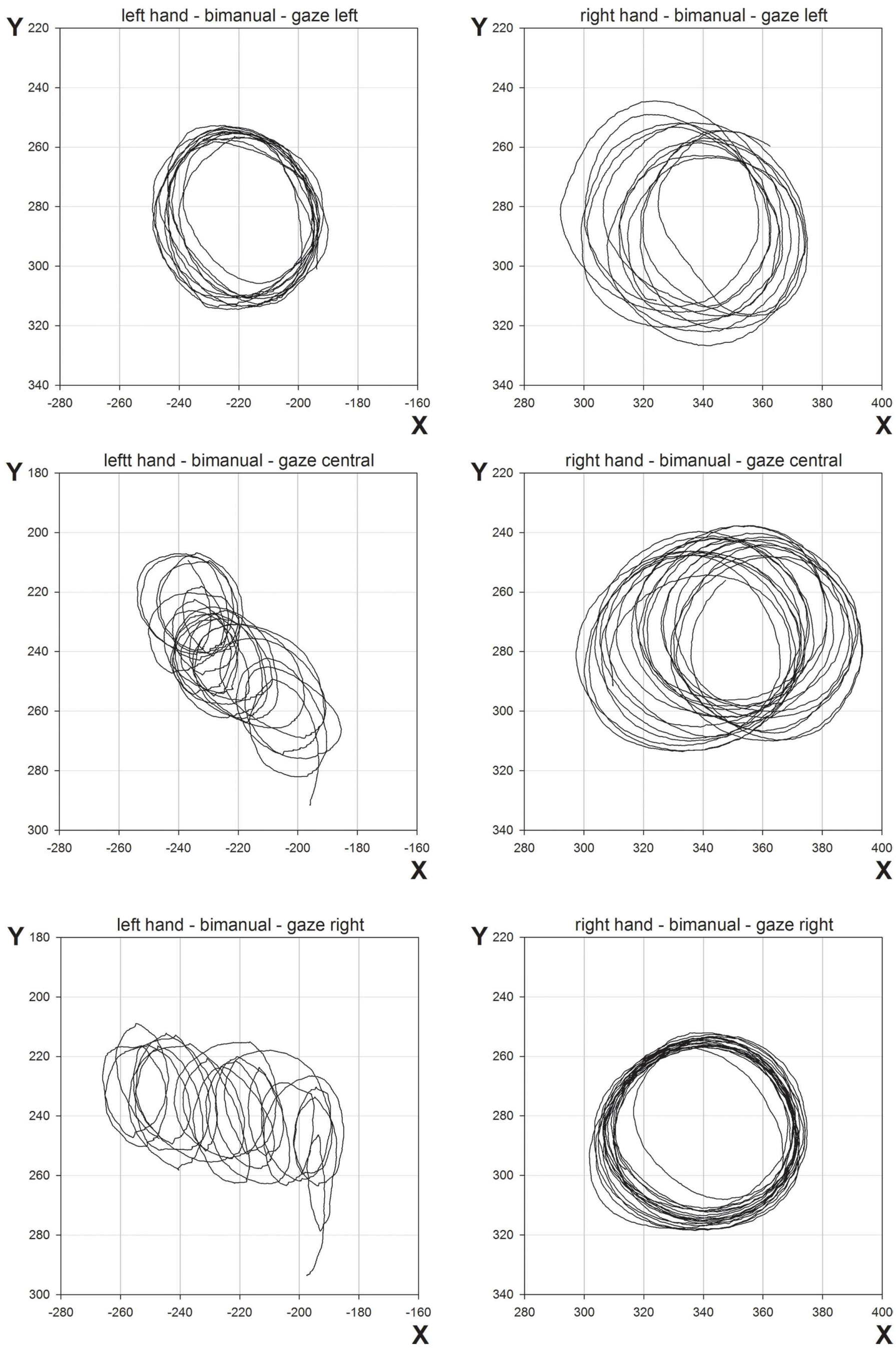

FIGURE 6 | Representative movement trajectories of bimanual conditions from Experiment 2.

was directed leftwards) and **Figure 8** (when gaze was directed rightwards).

VELOCITY

As with Experiment 1, unimanual velocity was relatively equal across the hands (left = 104.85 mm/s, right = 115.98 mm/s) but there was a clear uncoupling of velocity for bimanual movements due to contralesional bradykinesia (left = 62.92 mm/s, right = 108.79 mm/s). There were associated significant main effects of Hand [$F(1,48) = 91.8$, $p < 0.0001$] and Condition [$F(1,48) = 68.1$, $p < 0.0001$], and a significant Hand × Condition interaction [$F(1,48) = 34.1$, $p < 0.0001$]. In addition, in Experiment 2, there was a main effect of Gaze Position [$F(2,48) = 13.3$, $p < 0.0001$] and a significant three-way Hand × Condition × Gaze Position interaction [$F(2,48) = 24.4$, $p < 0.0001$]. Most strikingly, while contralesional bradykinesia was found for all visual

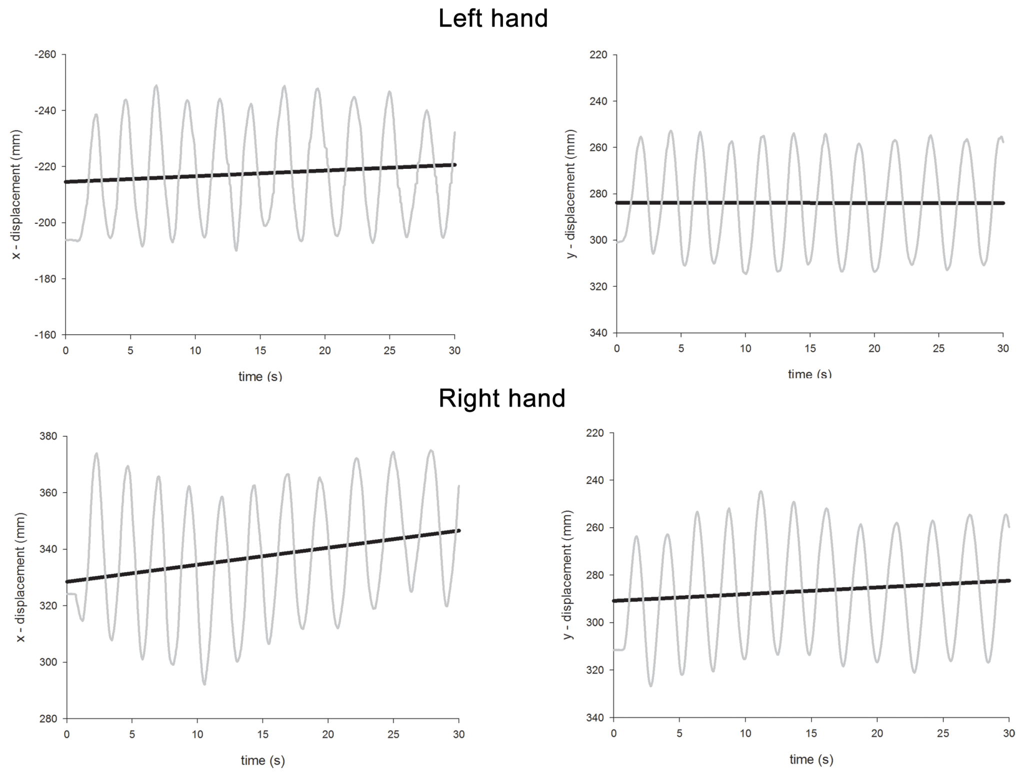

FIGURE 7 | Representative linear regression slopes for the *x*- and *y*-axes in the bimanual movement conditions when gaze was directed leftwards in Experiment 2.

conditions when LR made bimanual movements, when directing gaze at the contralesional hand, velocity was coupled with ipsilesional velocity appearing to "follow" contralesional velocity (left = 66.21 mm/s, right = 75.82 mm/s).

INTER-LIMB TEMPORAL COUPLING

Again, there was tight coupling of the temporal elements of bimanual circle drawing. Overall the bimanual trials, there was a right lead of just 2 ms, and asynchrony was affected by Gaze Position [$F(2,24) = 15.5$, $p < 0.0001$]. There was a left lead of 33 ms when gaze was directed centrally. This was markedly reduced to 3 ms when gaze was directed to the right [$F(1,24) = 4.7$, $p < 0.05$]. When gaze was directed to the left, there was a right lead with the left lagging behind by some 42 ms. This was significantly different to when gaze was directed to the right [$F(1,24) = 11.4$, $p < 0.005$] or centrally [$F(1,24) = 30.6$, $p < 0.0001$]. This is remarkable as one might have expected the left lead to increase with gaze toward the left rather than reverse to a left lag.

DISCUSSION

Experiment 2 differed from Experiment 1 in that a visual template was included. This change caused some marked differences in LR's performance. As in Experiment 1, LR's performance was again characterized by relatively normal unimanual movements with notable contralesional hypometria and bradykinesia on bimanual movement. However, in Experiment 2, gaze toward the contralesional hand prevented hypometria but bradykinesia persisted. Indeed, bradykinesia was shown to be the most intractable feature of bimanual contralesional performance. In addition, in Experiment 2, the contralesional limb showed a tendency to both drift as a function of both Condition and Gaze Position. That is, contralesional drift became more evident when LR moved bimanually and directed gaze away from his contralesional limb. Directing gaze at the ipsilesional right hand appeared to increase the asymmetry still further as compared with directing gaze centrally. These data suggest that, in addition to the intentional deficit apparent in the hypometric movements in Experiment 1, there was also an attentional deficit revealed. Here, visual feedback was able to compensate for the increased drift under bimanual conditions, consistent with the extra visual information compensating for reduced proprioception. In contrast, the bradykinesia remained a feature of LR's performance. We attribute this to an intentional deficit under bimanual conditions.

Experiment 2 also showed a striking difference from Experiment 1 in terms of inter-limb coupling. While coupling was broadly similar between the two experiments when gaze was directed rightwards and centrally, there were differences when gaze was directed to the left. In Experiment 1, there was a left lead of 36 ms. In Experiment 2, this was replaced by a right lead and a left lag of 42 ms. Interestingly, this is a similar lag to that reported in three patients with left parietal damage on mirror or symmetrical circle drawing in a recent study (Serrien et al., 2001a).

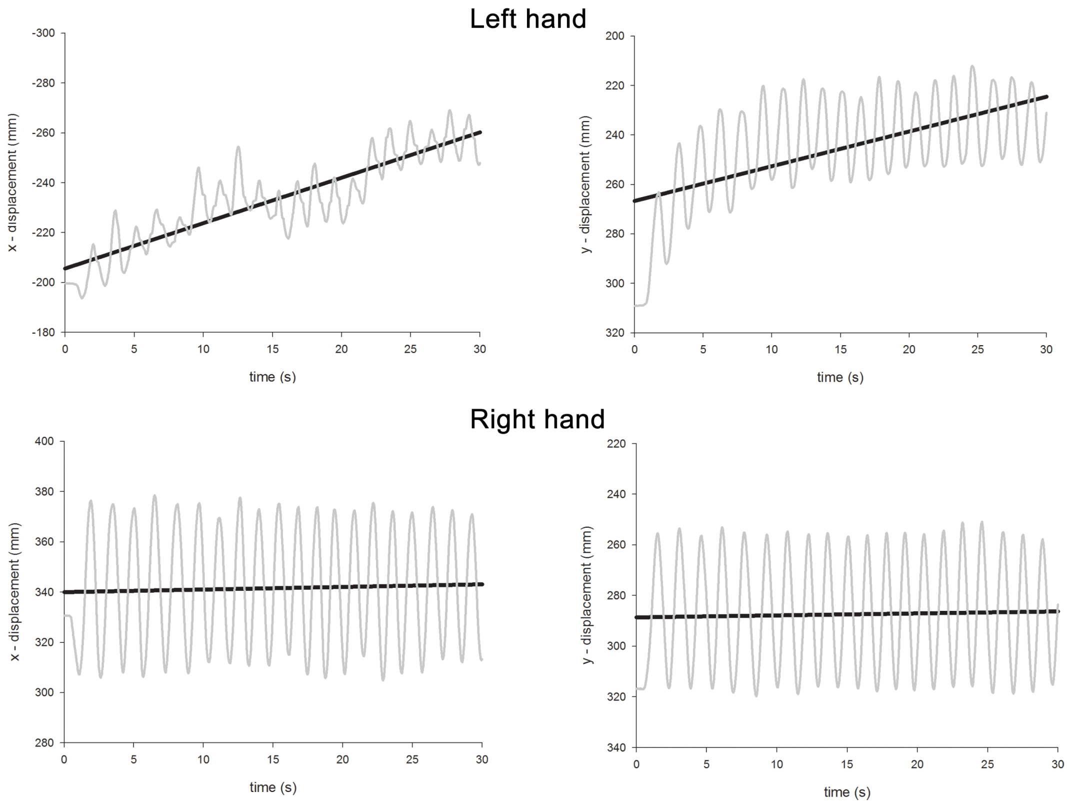

FIGURE 8 | Representative linear regression slopes for the *x*- and *y*-axes in the bimanual movement conditions when gaze was directed rightwards in Experiment 2.

The study by Serrien and colleagues only addressed the temporal relationship between the limbs in a task with a visual template; the spatial relationship was not examined and the role of vision was not assessed. It seems likely that patients would direct their vision toward the "affected" limb in conditions of free vision, which would have produced a very similar situation to our condition in Experiment 2. It also further stresses the crucial role played by task constraints in temporal coupling for circle drawing (see also Franz et al., 2002).

GENERAL DISCUSSION

Bilateral motor function is a primary feature of human movement. This study demonstrates a patient with a right fronto-temporal lesion who was able to maintain temporal coupling but who showed a selective deficit for coupling the amplitude of movements. We interpret the deficit as a result of a competitive bias in the control of bimanual movements introduced by LR's brain lesion – this bias reduced the intention to act with the contralesional limb when a concurrent intention to act was activated for the ipsilesional limb. The resulting bradykinesia was not influenced by visual feedback, as would be expected if it were due to reduced proprioceptive feedback. Nevertheless, LR did show evidence of "proprioceptive extinction" in Experiment 2, where there was a contralesional deficit in drift which was corrected in the presence of visual feedback (when gaze was directed to the contralesional limb). We discuss how these results relate to other patients and accounts of motor extinction.

LR IN RELATION TO OTHER PATIENTS

LR demonstrated hypometria and bradykinesia of the contralesional limb during bimanual movements. These deficits were first described in a patient with motor neglect by Meador et al. (1986). Their patient also demonstrated a deficit in the initiation of contralesional movement (hypokinesia) not seen in LR. The patient studied by Meador et al., had suffered a hemorrhage into the right supplementary motor area (SMA) and anterior cingulate gyrus. Their explanation for the deficit was that the patient's intentional system had been disrupted and it was argued that the right SMA may be specialized for the initiation and amplitude of movement. Motor neglect is thought to be a result of a disruption in the intentional system (Heilman, 2004) and, as with sensory neglect, has been shown to occur most frequently on the left side of the body as a result of a right-sided brain lesion (Laplane and Degos, 1983). Consistent with this, it has been shown that a lesion in the dorsolateral frontal lobe causes an intentional deficit with no related sensory deficit or sensory neglect in the crossed-response task in monkeys (Watson et al., 1978). The few reports of motor neglect and motor extinction argue for a dissociation between different motor deficits related to intention or motor planning (e.g., initiation, amplitude, velocity).

Studies relating to bilateral upper limb activity following stroke have produced conflicting results. The use of bilateral movements as a method of enhancing movement in the affected limb has become an influential approach in stroke rehabilitation (Stewart et al., 2006). However, some studies have not demonstrated such enhanced activity (Lewis and Byblow, 2004; Rice and Newell, 2004). In the case of motor extinction, by definition, affected patients will show deterioration in the performance of the affected limb. Together, these findings perhaps suggest that a "one size fits all" approach to stroke rehabilitation is inappropriate and intervention should be based on individual characteristics that patients present with.

As noted in the introduction, recent interest has centered on the motor awareness of patients with motor neglect (Garbarini et al., 2012, 2013). While we did not test this formally, it seemed clear during testing that LR was aware of the difficulties he had moving his left hand during bimanual trials. As described above, he appeared frustrated at times, occasionally "urging" his left hand to "move." While this level of awareness has previously been reported during bimanual movements in patients with motor neglect (Meador et al., 1986; Mattingley, 2002), it stands in contrast to recent evidence suggesting a lack of motor awareness characterizes both anosognosia and motor neglect (Garbarini et al., 2013). The differing profiles of patients may reflect varying severities of motor neglect as well as varying underlying mechanisms (e.g., intention, attention). The case of LR suggests that it is possible to have a deficit in motor intention without a corresponding deficit in motor awareness.

MOTOR DEFICITS IN THE NEGLECT SYNDROME

Our study also raises issues regarding motor impairments within the neglect syndrome. Motor neglect is generally related to a deficit of intention or motor planning. However, as discussed in the introduction, deficits in either intention, attention or both may contribute to motor deficits. Just as extinction has served as a reliable measure of attentional bias in perception (Driver and Vuilleumier, 2001), so we compared unimanual vs. bimanual movements as a means of exploring similar biases in action. Our objective here was to make a first attempt in demonstrating the separation of intentional and attentional contributions to motor extinction within a single task. We hypothesized that contralesional deficits which became apparent during bimanual movements, but that could be compensated for by directing gaze toward the contralesional limb, were due to an attentional deficit. Vision would compensate for a lack of proprioceptive awareness under bimanual conditions. However, contralesional deficits during bimanual movements which were not compensated for by directing gaze toward the limb were assumed to be of intentional origin. Experiment 1 supported a purely intentional form of motor extinction. Experiment 2 also showed intention-related problems but directing gaze toward the contralesional limb led to improved performance in amplitude and drift. Only the deficit in velocity proved intractable. We interpret these results as demonstrating both intention and attention-related difficulties.

INTER-LIMB COUPLING

There are at least two important issues relating to inter-limb coupling observed in LR's performance. Firstly, one of the striking aspects of his movement was that inter-limb coupling remained ostensibly intact, despite marked asymmetries in the spatial parameters of action (e.g., amplitude). Such a dissociation is in direct contrast to callosotomy patients who can maintain spatial symmetry while temporal parameters of bimanual coordination become uncoupled (Kennerley et al., 2002). Together, these findings suggest the control of temporal and spatial elements of bimanual action are independently controlled. It was recently claimed that patients with motor neglect do not show normal spatial coupling effects when asked to simultaneously draw a line with one hand and a circle with the other (Garbarini et al., 2012); however, only movements of the ipsilesional limb were reported. Secondly, while the modulation of small asymmetries in temporal coupling as a consequence of visual guidance are generally in line with previous studies, there is one exception to this. Directing gaze toward a limb during bimanual, mirror-symmetrical movements has a tendency to either increase its lead or reduce its lag, compared with the neutral situation (Swinnen et al., 1996; Franz et al., 2002; Franz, 2004). While this was true for LR in Experiment 1 and when gaze was directed rightwards in Experiment 2, when gaze was directed leftwards in this experiment, the opposite modulation was seen with the left lag increasing. This finding is difficult to explain but suggests the correction to trajectories implemented by LR had a "knock-on" effect to temporal coupling. It is also the case, that in this particular condition, cycle duration was lengthened and this may too have had an effect on temporal coupling. The lag for the contralesional limb described above is in line with that shown by three patients with left-sided parietal lesions (Serrien et al., 2001a). However, this study neither controlled for visual guidance nor examined spatial aspects of movement. Our findings highlight the importance of vision and task constraints in bimanual circle drawing (Swinnen et al., 1996; Franz et al., 2002; Franz, 2004).

CONCLUSION

In conclusion, we report the case of a patient (LR) who demonstrates motor extinction for the amplitude and velocity of movements. A comparison of unimanual and bimanual circle drawing, while manipulating gaze position, provided a means of kinematically separating movement components that reflect intentional and attentional aspects of movement. The main finding was one of contralesional bradykinesia and hypometria during bimanual activity, with the bradykinesia remaining intractable even in the presence of visual feedback. Visual feedback was able to improve secondary deficits related to attention (e.g., drift), but amplitude only normalized when direct visual guidance for action was given (i.e., a visual template). In contrast to the deficits on spatial aspects of motor performance, temporal coupling between the limbs remained. We suggest that LR demonstrates a primary deficit for intention with a secondary deficit of attention for the sensory consequences of action. Motor extinction can result from either intentional or attentional deficits in action.

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