# SPATIAL AND NON-SPATIAL ASPECTS OF NEGLECT

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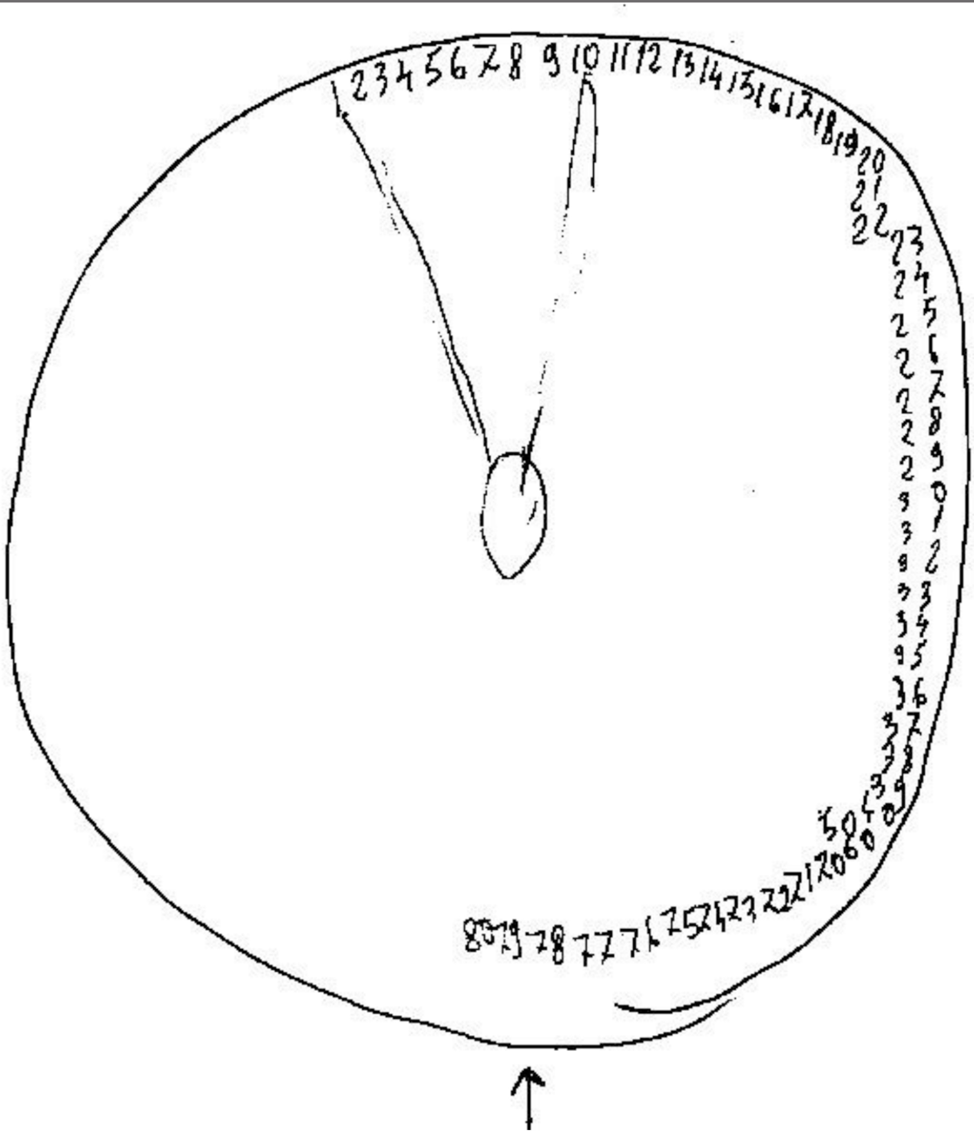
and Mario Bonato

PUBLISHED IN: Frontiers in Human Neuroscience



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**ISSN 1664-8714**
**ISBN 978-2-88919-584-8**
**DOI 10.3389/978-2-88919-584-8**

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# SPATIAL AND NON-SPATIAL ASPECTS OF NEGLECT

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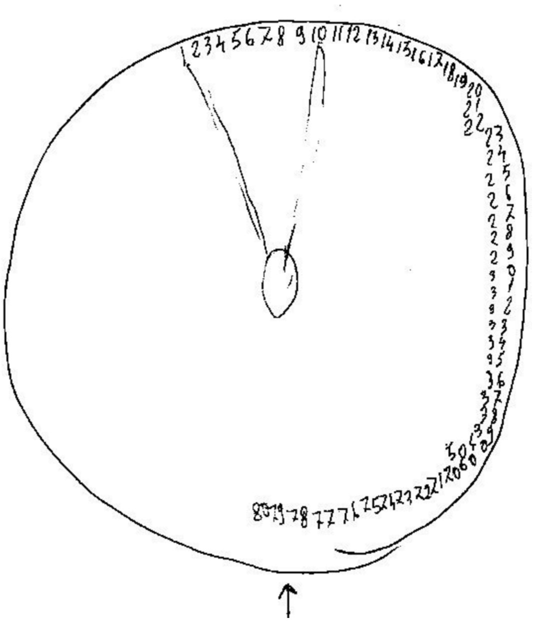

The image shows the drawing of a clock made by a right-hemisphere damaged patient with left neglect. Both spatial and non spatial disorders are visible.
Image by Mario Bonato

Neglect is one of the most impressive neuropsychological disorders, for both its theoretical and clinical relevance. Besides being very common and disabling, it is highly informative for understanding normal cognitive functioning.

The hallmark of neglect is the failure to attend to the contralesional hemispace. However, several studies have recently highlighted that additional deficits, not attributable to a spatial bias, are associated to the impaired contralesional hemispace processing. Moreover, manifestations of neglect tend to be particularly heterogeneous and often dissociate according to the spatial domain being investigated (e.g., body space, space within reaching, space beyond reaching, imaginal space). Heterogeneity in neglect patients also means that dissociations across different tasks in a single patient are more the rule than the exception. Evidence suggests that some of these dissociations can be readily explained by taking into account the amount of available attentional resources as a major determinant for the presence and the severity of neglect. There is no doubt that neglect patients provide a wealth of information about the functioning of systems subserving attentional orienting and spatial processing. Moreover, their performance also show that some non-spatial deficits are tightly coupled with more classic contralesional spatial deficits. It seems however still unclear to what extent these non-spatial deficits are an intrinsic characteristic of neglect or whether they are to be considered unspecific effects of the often massive brain lesions suffered by the patients.

From the clinical point of view, neglect is a disorder that dramatically affects patients and their caregivers, because it severely limits the individuals' autonomy and motor recovery after brain damage. For these reasons neglect is a disorder that is worth rehabilitating. To be effective, neglect rehabilitation should be based on the knowledge of what cognitive aspects are impaired and it should be focused on improving daily-life performance. For these reasons, it is also important to detect and quantify subtle forms of neglect.

**Citation:** Priftis, K., Umiltà, C., Zorzi, M., Bonato, M., eds. (2015). Spatial and Non-Spatial Aspects of Neglect. Lausanne: Frontiers Media. doi: 10.3389/978-2-88919-584-8

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frontiers in
HUMAN NEUROSCIENCE

EDITORIAL
published: 05 February 2013
doi: 10.3389/fnhum.2013.00025

# Spatial and non-spatial aspects of neglect

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**Reviewed by:**
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Deficits of contralesional space awareness (neglect and extinction) often follow right hemisphere damage and are typically attributed to the disruption of neurocognitive mechanisms subserving orienting of attention in space (Driver and Vuilleumier, 2001). Neglect affects awareness of contralesional stimuli, whereas extinction affects contralesional awareness only when competing stimuli are presented in the ipsilesional space. The difference between neglect and extinction contributes to the complexity of the disorders of contralesional spatial processing, in which the heterogeneity of symptoms can be hardly reconciled with the impairment of a single underlying mechanism. A widely accepted theory (Posner et al., 1984) maintains that neglect and extinction are caused by a deficit in disengaging spatial attention from ipsilesional stimuli. This theory is based on the observation that patients with parietal brain damage are particularly slow to detect a target presented in the contralesional visual field when it is preceded by a spatial cue that directs attention to the ipsilesional visual field. Posner et al., therefore, suggested that parietal damage produces a bias toward the ipsilesional hemispace, so that spatial attention is pathologically stuck to the stimuli shown there (i.e., hyperattention). Because of this bias, contralesional stimuli would remain undetected because patients' spatial attention is prevented from disengaging from ipsilesional stimuli. Another hypothesis adds a non-spatial aspect to the explanation of extinction (Desimone and Duncan, 1995). The idea is that, because attentional resources are limited, the neural representations of the stimuli have to compete for these limited resources. In brain-damaged patients, this competition would be biased because of their unilateral lesion. As a consequence, the contralesional stimuli lose the competition with the ipsilesional stimuli for attracting attention. The hypotheses that non-spatial attentional (or processing) resources are limited and that non-spatial and spatial components interact in neglect and extinction are helpful in order to explain these complex phenomena (for reviews see Husain and Rorden, 2003; Bonato, 2012). For example, it has been shown that increased attentional demands, generated by a concurrent task, can impair contralesional space awareness in brain-damaged patients (Robertson and Frasca, 1992; Bonato et al., 2010, 2012).

The studies collected in the present Research Topic cover both spatial and non-spatial aspects of neglect and extinction. With respect to the anatomical basis of these disorders two studies use a meta-analytic approach based on anatomical likelihood estimation to investigate the heterogeneous nature of the neuroanatomical underpinnings of neglect. Molenberghs et al. (2012; see commentary by Bartolomeo, 2012) found specific anatomical clusters for distinct neglect subtypes (e.g., personal vs. extrapersonal neglect). Chechlacz et al. (2012) focuses on the dissociation between egocentric and allocentric signs of neglect. Both studies suggest that different forms of neglect are linked to both distinct and common lesion patterns involving gray and white matter. Two review articles (Bartolomeo et al., 2012; Bonato, 2012) draw a picture of the rather complex interactions between attentional networks devoted to attentional orienting and highlight the role of non-specific attentional resources in compensating contralesional biases given that neglect clearly emerges on computer-based presentation of transient targets. Two studies (Dukewich et al., 2012; Fellrath et al., 2012) investigate visuospatial attention asymmetries in the processing of brief visual targets. Fellrath et al. (2012), using a preview paradigm, show a serial search strategy in the left hemifield of neglect patients, as opposed to the pop-out effect characterizing healthy controls. Dukewich et al. (2012) compare temporal order judgments and speed of detection in a spatial cueing task; they highlight the lack of correlation between the two tasks in terms of disengage deficit. Yamanashi Leib et al. (2012) investigate the extraction of summary statistics (mean object size) in the left and right hemifield of patients with mild neglect. One long-standing issue in neglect is the difference between premotor and attentional disorders. Loetscher et al. (2012) propose a neat method to disambiguate output-related components from input-related components by asking patients to perform line bisection first and then to judge their own performance in a landmark task. Two studies explore the boundaries between rehabilitation procedures and the study of body schema, which could be distorted when neglect extends to personal space. Reinhart et al. (2012) show that limb activation (but not alertness cueing) ameliorates the judgment on the orientation of visually presented hands. Bolognini et al. (2012) show that bisection of real body parts dissociate from bisection of fake body parts and that both can be ameliorated by means of prismatic adaptation. Body schema, however, has several dynamic properties and can be modulated by different inputs. The interaction between body schema and vision has been highlighted in the study by Sambo et al. (2012), who show that bringing the patient's left hand in the right hemispace modulates both reaction times and early somatosensorial evoked potentials to tactile stimuli, particularly when the hand is in the patient's sight. An intriguing perspective comes from the study of Maravita et al. (2012), who show that tactile extinction decreases following hypnotic suggestion. This is the first study demonstrating that hypnosis can be useful not only to induce but also to ameliorate a neuropsychological disorder, in this case contralesional awareness deficits emerging when competitive stimuli are presented ipsilesionally (i.e., extinction). The variety of studies reported in the present Research Topic confirms that deficits of contralesional space awareness can substantiate into a variety of forms. Advanced approaches, as those presented in the present Research Topic, go well beyond the current clinical and experimental standards, and seem to be the key to better understand the nature of contralesional hemispace awareness deficits.

## ACKNOWLEDGMENTS

This work was supported by a grant from Compagnia di San Paolo (Neuroscience program).

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*Received: 24 October 2012; accepted: 21 January 2013; published online: 05 February 2013.*

*Citation: Priftis K, Bonato M, Zorzi M and Umiltà C (2013) Spatial and non-spatial aspects of neglect. Front. Hum. Neurosci. 7:25. doi: 10.3389/fnhum.2013.00025*

frontiers in
HUMAN NEUROSCIENCE

REVIEW ARTICLE
published: 04 May 2012
doi: 10.3389/fnhum.2012.00110

# Brain networks of visuospatial attention and their disruption in visual neglect

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Visual neglect is a multi-component syndrome including prominent attentional disorders. Research on the functional mechanisms of neglect is now moving from the description of dissociations in patients' performance to the identification of the possible component deficits and of their interaction with compensatory strategies. In recent years, the dissection of attentional deficits in neglect has progressed in parallel with increasing comprehension of the anatomy and function of large-scale brain networks implicated in attentional processes. This review focuses on the anatomy and putative functions of attentional circuits in the brain, mainly subserved by fronto-parietal networks, with a peculiar although not yet completely elucidated role for the right hemisphere. Recent results are discussed concerning the influence of a non-spatial attentional function, phasic alertness, on conscious perception in normal participants and on conflict resolution in neglect patients. The rapid rate of expansion of our knowledge of these systems raises hopes for the development of effective strategies to improve the functioning of the attentional networks in brain-damaged patients.

**Keywords: attention, neglect, consciousness, parietal lobe, frontal lobe**

## TAXONOMIES OF ATTENTIONAL PROCESSES

Biological organisms live in an environment cluttered with a multitude of objects. To behave in a coherent and goal-driven way, organisms need to select stimuli appropriate to their goals. On the other hand, because of capacity limitations, they must be capable of ignoring other, less important objects. Thus, objects in the world compete for recruiting the organism's attention in order to be the focus of the organism's subsequent behavior. Neural mechanisms of attention resolve this competition by taking into account both the goals of the organisms and the salience of the sensorial stimuli (Desimone and Duncan, 1995). However, attention and its neural correlates cannot be subsumed under a single concept. Attentional phenomena consist of a set of distinct, though interacting, neurocognitive mechanisms. For example, Parasuraman (1998) identified at least three independent but interacting components of attention: (1) *selection*, that is, mechanisms determining more extensive processing of some input rather than another; (2) *vigilance*, the capacity of sustaining attention over time; (3) *control*, the ability of planning and coordinating different activities. The concept of spatial selective attention refers operationally to the advantage in speed and accuracy of processing for objects lying in attended regions of space as compared to objects located in non-attended regions (Posner, 1980). In ecological settings, agents usually orient toward important stimuli by turning their gaze, head and trunk toward them (Sokolov, 1963). This is done in order to align the stimulus with the part of the sensory surface with highest resolution (e.g., the retinal fovea). This allows further perceptual processing of the detected stimulus, for example its classification as a useful or as a dangerous object. Even very simple artificial organisms display orienting behavior when their processing resources are insufficient to process the whole visual scene in parallel (Di Ferdinando et al., 2007).

Spatial selective attention must allow an organism to successfully cope with a continuously changing environment, while maintaining its goals. This flexibility calls for mechanisms that (A) allow for the processing of novel, unexpected events, that could be either advantageous or dangerous, in order to respond appropriately with either approaching or avoidance behavior; (B) allow for the maintenance of finalized behavior in spite of distracting events (Allport, 1989). For example, attention can be directed to an object in space either in a relatively reflexive way (e.g., when a honking car attracts the attention of a pedestrian) or in a more controlled mode (e.g., when the pedestrian monitors the traffic light waiting for the "go" signal to appear). It is thereby plausible that different attentional processes serve these two partially conflicting goals. A traditional distinction in experimental psychology refers to more exogenous processes for orienting attention to novel events (Yantis, 1995), as opposed to more endogenous orienting processes, which would be responsible for directing the organism's attention toward relevant targets despite the presence of distractors in the environment (Laberge et al., 2000). A further important notion concerns the fact that attention can not only be directed to a region of space, but also (and perhaps more importantly) to visual objects in space (Egly et al., 1994; Valdes-Sosa et al., 1998). Exogenous attention directed on an object part automatically spreads to the entire object (Macquistan, 1997).

Posner and Petersen (1990) have further refined the taxonomy of attention by proposing to distinguish the orienting processes of spatial attention from alerting and executive control. Executive control requires both monitoring and conflict solving, such as in flanker paradigms, where participants have to respond to targets while inhibiting the processing of adjacent flankers (Eriksen and Eriksen, 1974). Alerting mechanisms prepare the system for fast reactions by means of a change in the internal state, sometimes at the expense of motor control (Posner and Petersen, 1990; Callejas et al., 2005). Two types of alerting have been described: tonic alerting refers to a sustained activation over a period of several minutes, whereas phasic alerting refers to a non-specific activation occurring when a warning signal is presented a few hundred milliseconds prior to a target (Sturm and Willmes, 2001; Callejas et al., 2005).

## ARCHITECTURE OF ATTENTIONAL CIRCUITS IN THE BRAIN

Today, we know a fair amount of detailed information on the anatomy, functions, dynamics, and pathology of the brain networks that subserve the orienting of gaze and attention in the human brain[1]. Important components of these networks include the dorsolateral prefrontal cortex (PFC) and the posterior parietal cortex (PPC). Physiological studies indicate that these two structures show interdependence of neural activity. In the monkey, analogous PPC and PFC areas show coordinated activity when the animal selects a visual stimulus as a saccade target (Buschman and Miller, 2007). Importantly, PFC and PPC show distinctive dynamics and seem to use two different "languages" when attention is selected by the stimulus (bottom-up or exogenous orienting) or when it is directed by more top-down (or endogenous) goals. In particular, bottom-up signals appear first in the parietal cortex and are characterized by an increase of fronto-parietal coherence in the gamma band (25–100 Hz), whereas top-down signals emerge first in the frontal cortex and tend to synchronize in the beta band (12–30 Hz) (Buschman and Miller, 2007).

Functional MRI studies in healthy human participants (reviewed by Corbetta and Shulman, 2002) indicate the existence of multiple fronto-parietal networks for spatial attention (**Figure 1**, right panel).

A dorsal attentional network (DAN), composed by the intraparietal sulcus/superior parietal lobule and the frontal eye field/dorsolateral PFC, shows increased blood oxygenation level dependent (BOLD) responses during the cue—target period. As a consequence, the DAN is supposed to be important for spatial orienting. Functional MRI also demonstrated a more a ventral attentional network (VAN), which includes the temporoparietal junction and the ventral frontal cortex (inferior and middle frontal gyri), and shows increased BOLD responses when participants have to respond to invalidly cued targets. Thus, the VAN is considered important for detecting unexpected but behaviorally relevant events. Importantly, the DAN is bilateral and symmetric, whereas the VAN is strongly lateralized to the right hemisphere.

Not surprisingly given the postulated architecture of these networks, PFC and PPC are directly and extensively interconnected. In particular, three distinct fronto-parietal long-range pathways can be identified in the monkey on the basis of cortical terminations and course (Petrides and Pandya, 1984; Schmahmann and Pandya, 2006) (see **Figure 1**, left panel). Recently, advanced tractography techniques and post-mortem dissections demonstrated that a similar architecture seems to exist in the human brain (Thiebaut de Schotten et al., 2011) (see the middle panel in **Figure 1**). In humans, the most dorsal branch (SLF I) originates from BA 5 and 7 and projects to BA 8, 9, and 32. In contrast, the middle pathway (SLF II) originates in BA 39 and 40 within the inferior parietal lobule (IPL) and ends in prefrontal BA 8 and 9. Lastly, the most ventral pathway (SLF III) originates in BA 40 and terminates in BA 44, 45, and 47. These results permitted to

[1]The relationship between attention and gaze shifts is a debated one. According to the so-called "premotor theory" (Rizzolatti et al., 1987), an attention shift always entails the programming of an eye movement, which can then be executed (overt attention) or not (covert attention). Consistent with this view, nodes of the fronto-parietal attentional networks such as the FEF and the IPS do contribute to saccade programming (Corbetta, 1998).

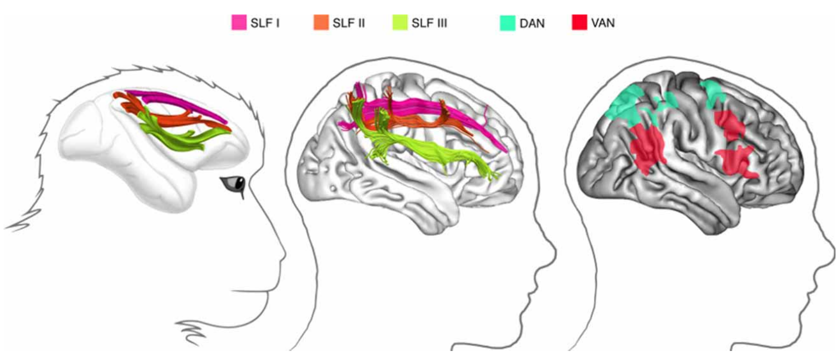


**FIGURE 1 | Fronto-parietal networks linked by the three branches of the superior longitudinal fasciculus.** Left: in the monkey brain (from Schmahmann and Pandya, 2006): middle: in the human right hemisphere (from Thiebaut de Schotten et al., 2011); right: attentional networks in the right hemisphere, according to Corbetta and Shulman (2002).

fit anatomical pathways to the fMRI evidence on attentional networks mentioned above. Thiebaut de Schotten et al. (2011) were able to show that the SLF III connects brain regions within the VAN, whereas the DAN is connected by the human homologue of SLF I. The SLF II connects the parietal component of the VAN to the prefrontal component of the DAN, thus allowing direct communication between ventral and DANs. Importantly, in good agreement with asymmetries of BOLD response during fMRI, with larger right hemisphere response for the VAN and more symmetrical activity for the DAN (Corbetta and Shulman, 2002), the SLF III (connecting the VAN) is anatomically larger in the right hemisphere than in the left hemisphere, whereas the SLF I (connecting the DAN) is more symmetrically organized. The lateralization of the SLF II is instead strongly correlated to behavioral signs of right hemisphere specialization for visuospatial attention such as pseudo-neglect in line bisection (i.e., small leftwards deviations of the subjective midline produced by normal individuals) (Bowers and Heilman, 1980; Jewell and Mccourt, 2000; Toba et al., 2011), and asymmetries in the speed of detection between the right and the left hemifield (Thiebaut de Schotten et al., 2011).

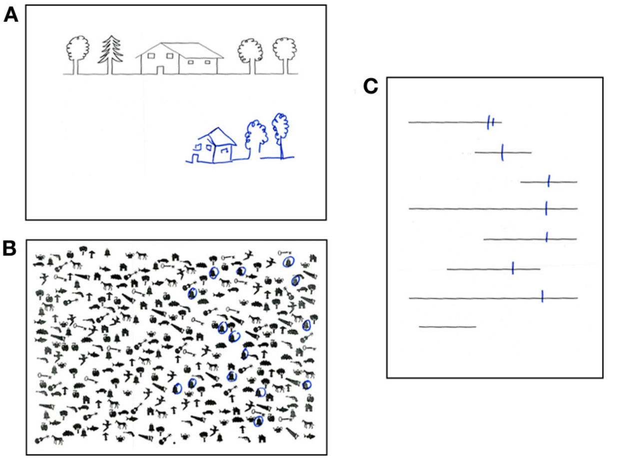


**FIGURE 2 | Performance of a patient with left spatial neglect on paper-and-pencil tests. (A)** copy of a linear drawing with omission of left-sided elements; **(B)** target cancellation task, with omission of left-sided targets (bells); **(C)** bisection of horizontal lines, with rightward deviation of the bisection mark and complete omission of one left-sided line.

## IMPAIRED ATTENTION AFTER BRAIN DAMAGE: VISUAL NEGLECT

### THE NEGLECT SYNDROME

Temporary inactivation of the SLF II in the human right hemisphere impairs the symmetrical distribution of visual attention (Thiebaut de Schotten et al., 2005). Damage to SLF networks in the right hemisphere is frequently associated to a disabling condition known as left visual neglect (Bartolomeo, 2006, 2007; Doricchi et al., 2008; Thiebaut de Schotten et al., 2008). About half of the patients with a lesion in the right hemisphere suffer from neglect for the left side of space (Azouvi et al., 2006). The cause is most often vascular strokes, but signs of neglect may also be observed as a consequence of brain tumors (Hughlings Jackson, 1876/1932; Bartolomeo, 2011) and of neurodegenerative conditions, such as Alzheimer disease (D'Erme et al., 1991 (abstract); Bartolomeo et al., 1998) or posterior cortical atrophy (Andrade et al., 2010; Migliaccio et al., 2011). Neglect patients are unaware of events occurring in a portion (usually the left half) of their environment, sometimes up to the dramatic extent of "forgetting" to eat from the left part of their dish or of bumping into obstacles situated on their left. Patients with left neglect also display a tendency to look to right-sided details as soon as a visual scene deploys, as if their attention were "magnetically" attracted by these details (Gainotti et al., 1991). They are usually unaware of their deficits (anosognosia), and often obstinately deny being hemiplegic. Patients with left brain damage may also show signs of right-sided neglect, albeit more rarely and usually in a less severe form (Bartolomeo et al., 2001a; Beis et al., 2004). Neglect is a substantial source of handicap and disability for patients, and entails a poor functional outcome. Diagnosis is important, because effective rehabilitation strategies are available, and there are promising possibilities for pharmacological treatments (Bartolomeo, 2007). Furthermore, in many cases the "negative" nature of neglect deficits (impaired active exploration of a part of space) renders the diagnosis difficult or impossible if signs of neglect are not searched for. This is unfortunate, because simple paper-and-pencil tests can easily make the diagnosis at patient's bedside (**Figure 2**).

### ATTENTION AND NEGLECT

In addition to its clinical importance, neglect also raises important issues concerning the brain mechanisms of consciousness, perception and attention. In particular, the study of patients with visual neglect has given a substantial contribution to the analysis of attentional processes and of their neural substrates (Bartolomeo and Chokron, 2002; Corbetta and Shulman, 2011). Neglect is characterized, among other symptoms, by severe problems in orienting attention toward left-sided objects (Bartolomeo and Chokron, 2002; Rastelli et al., 2008). Typically, however, neglect patients' deficits of spatial attention are not generalized, but concern first and foremost exogenous orienting (see Bartolomeo and Chokron, 2002, for review), with a relative sparing of endogenous orienting (Bartolomeo et al., 2001b). For example, Rastelli et al. (2008) demonstrated that the onset, but not the offset, of right-sided visual objects was able to induce a pathological attentional bias in neglect patients (see also D'Erme et al., 1992). Thus, it is right-sided objects (and not spatial regions) that tend to capture patients' attention, consistent with the peculiar relationships between object-based and exogenous forms of attention (Macquistan, 1997) (see Section Taxonomies of attentional processes above)[2].

Importantly, recent accumulating evidence from behavioral, neurophysiologic, neuropsychological and neuroimaging

[2]Instances have been described of "object-based" neglect, whereby patients fail to process information coming from the intrinsic left side of an object, whether or not it corresponds to the left of patient's midline. However, the left-right border is variable in neglect, and some of these cases have been reinterpreted as examples of relative egocentric neglect (Driver and Pouget, 2000).

experiments in normal participants (reviewed by Chica and Bartolomeo, 2012) indicate that while endogenous attention has weak influence on subsequent conscious perception of near-threshold stimuli, exogenous attention appears instead to be a necessary, although not sufficient, step in the development of reportable visual experiences. Thus, there is an impressive convergence of findings between the striking spatial unawareness shown by neglect patients, their severe impairment of exogenous orienting of attention, and the importance of exogenous attention for conscious visual perception in normal individuals (Bartolomeo, 2008b).

How do these notions map on the hypotheses concerning the organization of the attention networks in the brain? A plausible model of intra-and inter-hemispheric interactions in neglect (He et al., 2007) stipulates that damage to right hemisphere VAN causes a functional imbalance between the left and right DANs, with a hyperactivity of the left dorsal fronto-parietal network, which would provoke an attentional bias toward right-sided objects and neglect of left-sided items. Consistent with this hypothesis, suppressive TMS on left fronto-parietal networks correlated with an improvement of patients' performance on cancellation tests (Koch et al., 2008). However, an alternative proposal has been made recently by Singh-Curry and Husain (2009) on the role of the right IPL, which is not fully captured by the Corbetta and Shulman (2002) model. In particular, the authors argued that the VAN is not only dedicated to salience detection in a stimulus-driven way but is also responsible for maintaining attention on goals or task demands, which is a top-down process. In support of this proposal, functional MRI has suggested a role for the inferior frontal junction (parts of BA 9, 44, 6) in mediating interactions between bottom-up and top-down attention (Asplund et al., 2010). Furthermore, TPJ, the caudal node of the VAN, demonstrates increased BOLD response for behaviorally relevant distractors, but not for non-relevant but highly salient ones (Indovina and Macaluso, 2007). Thus, deficits in these non-spatial aspects of attention may lead to an exacerbation of the spatial bias in neglect patients (Husain and Nachev, 2007).

Another important characteristic of neglect-related deficits is that spatial attention and gaze are prone to be captured by right-sided objects (Gainotti et al., 1991), often in a repeated fashion. For example, in cancellation tasks patients may keep cancelling the same right-sided lines over and over again. Perhaps normal individuals do not show this perseverative behavior because of processes inhibiting repeated orientations toward the same event. When two consecutive visual events occur at the same spatial location, there can be an early facilitation to respond to the second event. However, when the interval between the two events is longer than 300 ms, responses to the second event are typically slower that those to the first. This phenomenon, dubbed inhibition of return (IOR, Posner et al., 1985; Klein, 2000; Lupiáñez et al., 2006), is thus important for thoroughly exploring the visual environment, by avoiding repeated processing of the same location (Klein, 1988). IOR occurs both with manual responses (such as a keypress) and with saccades to peripheral visual stimuli. Not surprisingly, IOR can be abnormal in visual neglect (Bartolomeo et al., 1999). When pressing a key in response to peripheral visual targets which were occasionally repeated on the same side of space, patients with left neglect presented abnormal facilitation, instead of IOR, for repeated right-sided items, i.e., for items appearing in their supposedly normal hemispace (Bartolomeo et al., 1999). Other patients with right hemisphere damage but without neglect had, instead, normal IOR for both sides of space (Bartolomeo et al., 1999). These results were later confirmed in neglect patients with cue-target paradigms (Bartolomeo et al., 2001b; Lupiáñez et al., 2004; Sieroff et al., 2007). Patients with parietal damage also demonstrated decreased IOR (but not facilitation) on the ipsilesional side, even in the absence of neglect signs (Vivas et al., 2003, 2006). These results are important in suggesting that cortical networks including the right parietal lobe, which are typically dysfunctional in neglect patients (Mort et al., 2003; Thiebaut de Schotten et al., 2005; Bartolomeo et al., 2007; He et al., 2007), are implicated in the occurrence of IOR. However, in these studies eye movements were not controlled; if patients looked at ipsilesional first targets or cues (a frequent occurrence in right brain-damaged patients, Gainotti et al., 1991), they received the second stimulus on the fovea; then fast responses to foveal stimuli could have offset IOR. To address these questions, Bourgeois et al. (2012) explored IOR with central fixation and manual responses (covert attention, Experiment 1), as well as IOR generated by saccadic responses (overt attention, Experiment 2). Bourgeois et al. used a target-target paradigm similar to the one used in the seminal study on IOR in neglect (Bartolomeo et al., 1999), while eye movements were monitored at all times. Neglect patients' performance was compared to that of right brain-damaged patients without neglect. Confirming the previous results obtained by Bartolomeo et al. (1999), neglect patients demonstrated facilitation, instead of inhibition, for repeated right-sided targets with manual responses. However, they had normal IOR for the same right-sided targets with saccadic responses. All neglect patients had damage to the supramarginal gyrus in the right parietal lobe, or to its connections with the ipsilateral PFC. Bourgeois et al. (2012) concluded that IOR with manual responses relies on fronto-parietal attentional networks in the right hemisphere, whose functioning is typically impaired in neglect patients. Saccadic IOR may instead depend on circuits less likely to be damaged in neglect, such as the retinotectal visual pathway.

## PERCEPTUAL ASYMMETRIES IN NEGLECT

As these results indicate, the multiform character of visual neglect calls for finely articulated models of attentional deficits in this condition. One important question concerning spatial attention in neglect is: are rightward attentional capture and leftward orienting deficits two (consecutive) sides of the same coin, or should they be considered as distinct components of neglect behavior? To answer this question, Charras et al. (2010) asked neglect patients to draw the horizontal segment of left- or right-directed Ls, on the basis of a given vertical segment (**Figure 3A**).

Neglect patients drew longer left-directed segments than right-directed segments. However, comparison with controls' performance revealed that neglect patients did over-extend horizontal lines toward the left, but did not under-extend rightwards lines. This result invites the conclusion that the left–right imbalance observed in length estimation resulted more

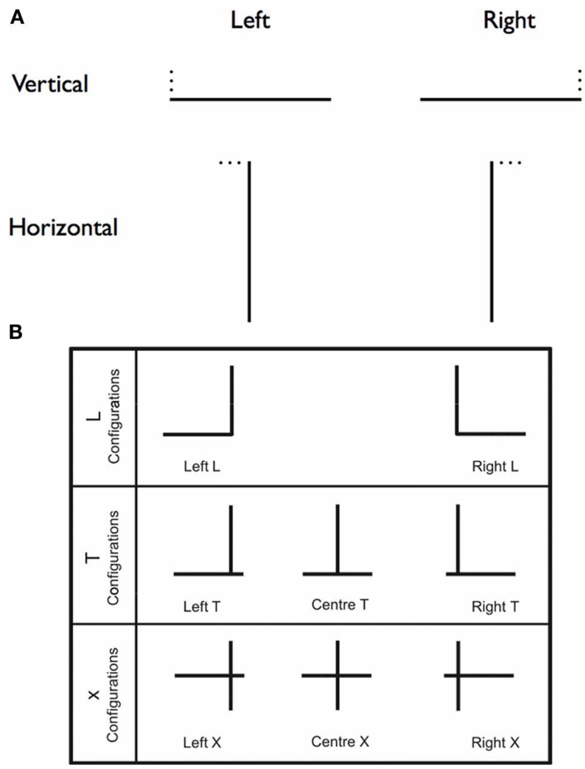


**FIGURE 3 | Neglect and length estimation. (A)** A schematic depiction of the stimuli used by Charras et al. (2010). A single black line, either horizontal or vertical (40 mm long, 1 mm thick), was printed in the center of the sheet. Participants performed a line extension task in which they were to draw either a horizontal or a vertical line to complete an L figure. The missing line was located either to the left or right of the presented line. The position of the missing line was indicated by three small black dots. **(B)** Schematic depiction of the stimuli used by Charras et al. (2012). The L configurations enabled to test leftwards and rightrightwards biases separately. In the T and X configurations, there was a left/right competition between the horizontal line segments left and right of the bisection line. The results showed that, in the T configuration, the vertical line was overestimated, while in the X configuration, the horizontal line was overestimated.

from left impairment in stimulus processing than from right attentional capture. However, in a different series of patients, Urbanski and Bartolomeo (2008) found that right attentional capture exerted by the right extremity of horizontal lines did have an important role in patients' performance in bisection-related tasks. Their patients were selected on the basis of the presence of a pathological rightward deviation on line bisection. However, when they had to set the left endopoint of an imaginary line on the basis of a central point, their performance depended on the presence/absence of a (presumably attention-capturing) right endpoint. The two virtual segments were asymmetric, mimicking ordinary line bisection, when the right endpoint was visible, but much more symmetrical when it was not. To account for the apparent discrepancy between the outcome of these two studies, Charras et al. (2010) noted that in their L-shaped figures there was no right-sided horizontal line whose extremity could capture patients' attention (see Gainotti et al., 1991), which presumably led to the absence of right overestimation. In this sense, Charras et al. (2010) results are perfectly consistent with the effects of right attentional capture effect in imaginary line bisection described by Urbanski and Bartolomeo (2008).

In a second study, Charras et al. (2012) were able to confirm and refine their previous conclusions. Patients were asked to estimate the length of left- and right-sided segments with L-, T-, or cross-shaped (X) configurations (see **Figure 3B**). When there was no competition between left and right horizontal segments, such as in the L configurations, the left-right imbalance resulted from left underestimation, in the absence of right overestimation, thus confirming the previous results (Charras et al., 2010). Similar results occurred with the T configurations, when emphasis was put on the vertical dimension of the stimulus (as shown by participants' strong tendency to overestimate the vertical portion of the stimulus), thus presumably preventing left-right integration of the horizontal segments. However, when left- and right-segments competed to be integrated in a single percept, as in the X configurations, then, right attentional capture did contribute to patients' performance. Interestingly, the presence of left homonymous hemianopia worsened left underestimations, but did not modulate right overestimations. Based on these results, Charras et al. (2012) proposed the existence of distinct neural bases for right overestimation, resulting from the activity of an isolated left hemisphere (see the section on interhemispheric disconnection in Bartolomeo et al., 2007), and left underestimation, dependent on impaired functioning of right hemisphere attentional networks (Bartolomeo, 2006). In different patients, these two component deficits might have different weights, perhaps depending on individual differences in anatomical asymmetries of fronto-parietal networks linked by SLF II and III (Thiebaut de Schotten et al., 2011).

### NEGLECT AND NON-SPATIAL ATTENTION: THE ROLE OF ALERTNESS

Thus far, we have examined the role of different sorts of imbalance of spatial attention mechanisms in neglect. However, other attentional capacities have been shown to be impaired in neglect patients (Husain and Rorden, 2003). For example, it has long been shown that non-spatial aspects of attentional mechanisms, such as alerting, can be defective in neglect, and contribute in substantial ways to patients' patterns of performance (Robertson, 2001). Thus, a further question of interest is: given the complex patterns of interaction between selective attention, alerting, executive functions and perceptual consciousness in normal individuals (Callejas et al., 2005; Kusnir et al., 2011), what happens when brain damage intervenes?

First of all, it is worth noting that there are relatively under-explored links between alerting and perceptual consciousness in normal individuals. For example, the manipulation of phasic alertness in healthy participants has been shown to affect perceptual discriminations and conscious perception of targets presented near the threshold of conscious perception (Kusnir et al., 2011). In this study, near-threshold visual targets were presented, accompanied or not by a short acoustic tone. Acoustic tones (which increase phasic alerting) ameliorated both speed (as manifested in decreased response times to discriminate targets) and discrimination performance (as manifested in increased accuracy) when the target was presented in a temporally non-predictive manner (Kusnir et al., 2011). This constitutes a piece of evidence in favor of the idea that phasic alerting can directly affect perceptual processing, rather than just motor readiness. Phasic auditory alerting also improved the subjective perception of near-threshold visual stimuli, perhaps through the activation of right hemisphere fronto-parietal networks whose dysfunction may determine visual unawareness in neglect patients (Bartolomeo, 2006). This is consistent with observations suggesting that visual neglect patients with extensive right hemisphere damage show, in addition to spatial deficits, non-spatial deficits in sustaining alertness (Robertson et al., 1998). There is evidence from neuroimaging that tonic alertness, like spatial attention, relies on fronto-parietal networks in the right hemisphere (Sturm and Willmes, 2001). In contrast, the attentional system underlying phasic alertness depends on ascending thalamic-mesencephalic, noradrenergic projections from the locus coeruleus (Mesulam, 1981; Posner et al., 1987), as well as additional left-hemisphere cortical networks (Sturm and Willmes, 2001). All these structures are typically intact in visual neglect patients. Thus, it has been proposed that in visual neglect ascending subcortical projections may phasically activate what is spared of the fronto-parietal cortical networks subserving spatial attention and alerting in the damaged right hemisphere, thus shifting spatial attention leftwards and compensating for neglect deficits (Robertson et al., 1998).

The importance of the interplay between attentional networks implicated in alerting, orienting and executive control has been explored in a group of patients with right hemisphere damage (Chica et al., 2011). Patients were evaluated by using a modified computerized battery test (Attention Network Test, ANT), originally designed to determine the functional independence and efficiency of the three attentional networks (Fan et al., 2002). The introduction of an alerting tone before the occurrence of the visual cue permits to assess the efficiency and independence of each network, but also their interactions. If the attentional networks interact, the phasic alerting produced by the tone could ameliorate neglect patients' orienting deficits, who might be faster and/or more accurate for validly cued left-targets. Better orienting might in turn be able to improve conflict resolution at the attended location. The results of the Chica et al. (2011) study demonstrated that modulating alertness is an important way of improving basic mechanisms typically impaired in neglect. In particular, neglect patients' orienting abilities improved after the phasic alerting tone, which enhanced conflict resolution in the neglected hemispace. However, three patients out of 16 were not able to benefit from auditory alerting tones. These patients had damage implicating the right insula and the underlying white matter. The right insula has been associated with sustained attention (Thakral and Slotnick, 2009) and has important connections to the anterior cingulated cortex (Augustine, 1996), a structure crucial for cognitive control and conflict resolution (Botvinick et al., 1999; Fan et al., 2003). Thus, the Chica et al. (2011) results suggest that conflict resolution can be improved in neglect patients by modulating alerting and orienting, provided that structures critical for conflict resolution such as the insula are spared by the lesion.

## IMAGINAL NEGLECT

To further complicate the semiotics of spatial neglect, about a third of neglect patients may also neglect the left part of their mental images (Bartolomeo et al., 1994). When describing places from memory, these patients omit to mention the left side of the mental space (**Figure 4**), thus demonstrating "imaginal" neglect (Bisiach and Luzzatti, 1978).

However, not all patients with visual neglect show imaginal neglect, perhaps because imagined details have less attention-capturing power than real ones (Bartolomeo et al., 1994). Imaginal neglect can also occur in the absence of signs of perceptual neglect, either at onset or, perhaps more commonly, as a result of selective compensation for the perceptual aspects of the syndrome. Patients often learn with time (and possibly the help of people around them) to explore more thoroughly their visual environment. However, compensation may be more difficult to obtain in the more abstract imaginal domain, which is rarely the object of rehabilitation or of more informal reminders to "look to your left" (Bartolomeo and Chokron, 2001). Thus, similar to other domains of visual mental imagery (Bartolomeo, 2002, 2008a), several studies have reported the existence of double dissociations between imaginal and perceptual neglect (Anderson, 1993; Guariglia et al., 1993; Beschin et al., 1997; Coslett, 1997; Ortigue et al., 2001).

However, the study of imaginal neglect raises peculiar methodological problems. Often, very different task are used to evaluate spatial perception and spatial imagery. In particular, in several studies, paper-and-pencil tests were used for perception and description from memory for imagery (Rode and Perenin, 1994; Rode et al., 2007). Moreover, description from memory might rely more on verbal semantic memory than on visual imagery, and thus produce symmetrical descriptions even in the presence of imaginal neglect (Rode et al., 2004). To encourage the use of a visual mental strategy, a response time "geographical" test was devised (Bartolomeo et al., 2005), with strictly comparable

**FIGURE 4 | Imaginal neglect.** In their seminal paper, Bisiach and Luzzatti (1978) reported two left neglect patients who, when asked to imagine and describe from memory familiar surroundings (the Piazza del Duomo in Milan), omitted to mention left-sided details regardless of the imaginary vantage point that they assumed.

perceptual and imaginal conditions (Bourlon et al., 2008, 2011a). In different tasks, participants either saw towns/regions on a map of France or heard their names, and pressed one of two keys according to the stimulus location (left or right of Paris). Interestingly, when normal participants performed such a task, their eye movements mimicked those produced with real displays, thus lending support to the hypothesis that similar attentional mechanisms may be engaged in perception and in mental imagery (Bourlon et al., 2011b). In patients, however, the results obtained with these tasks confirmed the rarity of imaginal neglect with respect to perceptual neglect.

In a recent case report of imaginal neglect (Rode et al., 2010), structural and diffusion MRI demonstrated damage to several white matter tracts in the right hemisphere and to the splenium of corpus callosum. The same study reported on a second right-brain-damaged patient, who showed signs of perceptual but not imaginal neglect, and had damage to the same intrahemispheric tracts; the callosal connections, however, were spared. Imaginal neglect might thus result from the association of fronto-parietal dysfunction, which impairs orienting toward left-sided items (see Bartolomeo et al., 2007) and additional posterior callosal disconnection, which might prevent the symmetrical processing of spatial information from long-term memory.

In clinical settings, drawing from memory is often used to assess imaginal abilities and then directly compared to drawing copying. However, visual feedback provided by drawing may influence final performance by inducing an attentional capture of the right-sided details the patient has just drawn (Chokron et al., 2004). To address this issue, recent studies employed drawing without visual feedback, e.g., while blindfolded (Chokron et al., 2004) or by using a pen which leaves no visible traces on the sheet (Cristinzio et al., 2009). While in general patients show more neglect with visual feedback than without visual feedback (Chokron et al., 2004), thus confirming the attention-capturing effect of right-sided visual items (Bartolomeo et al., 1994), one recent case report (Cristinzio et al., 2009) demonstrated the opposite effect, perhaps as a consequence of additional working memory impairment (Wojciulik et al., 2004). In conclusion, a possibility to account for the rarity of imaginal neglect is that this form of neglect might depend on additional deficits of top-down processes, such as endogenous attention or active rehearsal of spatial knowledge, that are typically less impaired than exogenous attention in patients with perceptual neglect (Bourlon et al., 2011a).

### THE ANATOMY OF VISUAL NEGLECT

Signs of visual neglect have been traditionally related to damage to the IPL (Vallar and Perani, 1986; Mort et al., 2003). More recent evidence suggested that neglect signs do not result from focal cortical lesions, but correlate with dysfunction of large-scale networks, whose nodes include the PPC, the lateral prefrontal cortex (LPFC), the TPJ and the occipital lobe (Bartolomeo et al., 2007; Doricchi et al., 2008). As mentioned before, these cortical nodes show increased BOLD response during spatial orienting of attention (Nobre, 2001; Corbetta and Shulman, 2002; Bartolomeo et al., 2008). Consistent with the hypothesis of a causal link between neglect signs and impairment of large-scale fronto-parietal networks in the right hemisphere (Bartolomeo, 2006), accumulating evidence has demonstrated an associated injury to white matter pathways connecting these networks in monkey studies (Gaffan and Hornak, 1997) and in human neglect patients with vascular damage (Urbanski et al., 2008, 2011; Chechlacz et al., 2010; Verdon et al., 2010) or neurosurgical lesions (Thiebaut de Schotten et al., 2005; Shinoura et al., 2009; Roux et al., 2011). It must be noted that in all these studies on human brain-damaged patients the lesions affected both the gray and the white matter. However, a recent single case report demonstrated that severe, if transitory, neglect signs can result from small lesions restricted to the white matter and affecting components of the SLF (Ciaraffa et al., 2012).

## DISCUSSION

### PUTTING THINGS TOGETHER: TOWARDS A NEURAL MODEL OF ATTENTIONAL INTERACTIONS IN NEGLECT

Several neural models have been proposed to explain neglect, but no single model can plausibly account for all the complex and sometimes contradictory features of this syndrome. A perusal of the vast literature on neglect invites the conclusion that the refinement of behavioral analysis has not yet been matched by completely satisfactory neural models of neglect-related deficits and compensatory processes. We outline here some ideas which could offer starting points for the enterprise of mapping behavioral deficits to brain networks.

Despite the obvious links between left neglect and dysfunction of large-scale fronto-parietal networks in the right hemisphere (Bartolomeo, 2006, 2007; Bartolomeo et al., 2007; Doricchi et al., 2008), the most severe and persistent signs of left neglect typically occur after retro-Rolandic lesions. This apparent paradox may be explained by the architecture of fronto-parietal connections in the human brain (Thiebaut de Schotten et al., 2011) (**Figure 5**; see also **Figure 3**).

As mentioned in Section *Architecture of attentional circuits in the brain*, the SLF II, whose caudal cortical origin is in part shared with that of the SLF III in the IPL, connects the parietal component of the VAN to the prefrontal component of the DAN

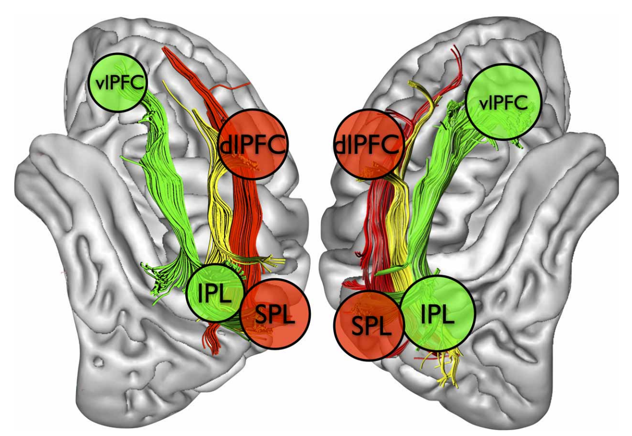


**FIGURE 5 | Schematic depiction of fronto-parietal attentional networks for visuospatial processing in the two hemispheres, based on Corbetta and Shulman (2002) and Thiebaut de Schotten et al. (2011).** IPL and SPL, inferior and superior parietal lobules. dlPFC and vlPFC, dorsolateral and ventrolateral prefrontal cortex.

(Thiebaut de Schotten et al., 2011). Thus, it is plausible that damage to the IPL (Mort et al., 2003), when accompanied by injury to the underlying white matter (Doricchi and Tomaiuolo, 2003; Verdon et al., 2010), can produce severe and persisting signs of neglect because it can jointly disrupt the functioning of both the VAN (through SLF III disconnection) and its communication with the DAN (through SLF II damage). On the other hand, less extensive lesions, perhaps sparing a significant part of SLF II, might allow for intra-hemispheric compensation mechanisms relying on the possibility of communication between VAN and DAN offered by SLF II. In this case, an initial imbalance between the dorsal fronto-parietal networks, with the left hemisphere DAN being relatively more active than its right hemisphere counterpart, might subside after the acute phase, with consequent recovery from neglect signs (Corbetta et al., 2005).

Another possible mechanism of neglect recovery might depend on inter-hemispheric interactions. Individual variability in the asymmetry of SLF II and III, which only recently is starting to be explored (Thiebaut de Schotten et al., 2011), could account for different patterns of recovery/compensation. It is possible that patients who happen to have a relatively large SLF III in the left hemisphere may use resources pertaining to a left-hemisphere homologue of the right-sided VAN to partially compensate for neglect signs. Along similar lines, one might speculate that the larger the left-hemisphere SLF II, the better the communication between the DAN and the left hemisphere homologue of the VAN. A relatively efficient left homologue of the VAN might control the ipsilateral VAN and ensure a relatively functional exploration of the whole space after right brain damage, thus leading to (apparent) recovery from neglect.

If these considerations are true, however, neglect compensation by using alternative (left-hemisphere-based) attentional routes is likely to be partial and subject to task demands. Indeed, it has repeatedly been shown that even patients who do not demonstrate anymore neglect on paper-and-pencil tests often show lateralized impairments on more demanding, time-constrained tasks (Posner et al., 1984; Bartolomeo, 1997, 2000; Bonato et al., 2010). This evidence is consistent with the common clinical observation of chronic patients who perform perfectly on paper-and-pencil tasks but, as soon as they exit the testing room, start again bumping into left-sided obstacles.

## CONCLUSIONS

Attentional processes, mainly subserved by frontoparietal brain networks, with a peculiar although not yet completely elucidated role for the right hemisphere, are at the basis of our capacity to actively explore the external world. Their impairment as a result of brain damage can hamper the conscious perception of objects in space, and is a source of significant disability for patients. Our knowledge of these systems is still too limited to enable us to offer specific interventions for the whole range of attentional impairments, but it is expanding at fast pace, raising hopes for the development of effective strategies to improve the functioning of the attentional networks in brain-damaged patients.

## ACKNOWLEDGMENTS

Supported by postdoctoral grants from the Neuropôle de Recherche Francilen (NeRF), Marie Curie Intra-European Program (FP7), and Ramón y Cajal fellowship from the Spanish Ministry of Education and Science to Ana B. Chica.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.


*Received: 17 January 2012; accepted: 11 April 2012; published online: 04 May 2012.*

*Citation: Bartolomeo P, Thiebaut de Schotten M and Chica AB (2012) Brain networks of visuospatial attention and their disruption in visual neglect. Front. Hum. Neurosci.* ***6****:110. doi: 10.3389/fnhum.2012.00110*

frontiers in
HUMAN NEUROSCIENCE

REVIEW ARTICLE
published: 17 July 2012
doi: 10.3389/fnhum.2012.00195

# Neglect and extinction depend greatly on task demands: a review

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This review illustrates how, after unilateral brain damage, the presence and severity of spatial awareness deficits for the contralesional hemispace depend greatly on the quantity of attentional resources available for performance. After a brief description of neglect and extinction, different frameworks accounting for spatial and non-spatial attentional processes will be outlined. The central part of the review describes how the performance of brain-damaged patients is negatively affected by increased task demands, which can result in the emergence of severe awareness deficits for contralesional space even in patients who perform normally on paper-and-pencil tests. Throughout the review neglect is described as a spatial syndrome that can be exacerbated in the presence and severity by both spatial and non-spatial tasks. The take-home message is that the presence and degree of contralesional neglect and extinction can be dramatically overlooked based on standard clinical (paper-and-pencil) testing, where patients can easily compensate for their deficits. Only tasks where compensation is made impossible represent an appropriate approach to detect these disabling contralesional deficits of awareness when they become subtle in post-acute stroke phases.

**Keywords: awareness, cognitive resources, attention, dual-task, extinction, neglect, neuropsychology, computer-based testing**

## NEGLECT: DEFINITION, SPATIAL (AND NON-SPATIAL) CHARACTERISTICS

Neglect is a disabling condition which often follows a brain lesion. Symptoms of neglect consist of the failure to report, respond, or orient to stimuli presented to the side opposite that of the damaged hemisphere (i.e., the contralesional hemispace), which cannot be explained by sensory-motor deficits (Heilman, 1979). According to this definition, any attentional deficit in contralesional processing which has an impact on everyday life, or on the experimental task performed by a patient with known – or suspected – brain damage can be, in the absence of an alternative explanation, attributed to neglect.

The characteristics of neglect change substantially in time. Its symptoms, striking and common in the acute phase, become less evident and frequent with time. In the first hours/days after the occurrence of a neurological insult (commonly, although not necessarily, a stroke) the presence of neglect is often self-evident in the form of the head and eyes deviating toward the ipsilesional space (Becker and Karnath, 2010; Karnath and Rorden, 2012). As time progresses, this deviation tends to decrease on its own. The presence and degree of neglect are then typically quantified according to the patients' performance on specific paper-and-pencil tests, including cancellation (crossing of all target items within a sheet) and bisection (marking of the midpoint of a line) tasks.

Remarkably, the characteristics of neglect also change considerably according to the affected hemisphere. In the acute phase, neglect following right hemisphere damage is relatively more common than neglect following left hemisphere damage. In contrast, in the post-acute and chronic phases (left) neglect after right hemisphere damage is much more common and severe than (right) neglect after left hemisphere damage (Ringman et al., 2004; Stone et al., 1991, 1992, 1993). When considering patients with right hemisphere brain damage, the prevalence of neglect ranges from 13 to 82% (Bowen et al., 1999; Azouvi et al., 2002). This surprisingly high variability (see Barrett et al., 2006 for a thorough discussion) might depend on time from lesion onset, inclusion criteria and, crucially for the purposes of this review, on the heterogeneous methods used to diagnose neglect (e.g., number and complexity of tests, domain of space under investigation, see Azouvi et al., 2002). Critically, these factors can also interact in a dramatic manner. Recovery rates from acute neglect range from 60 to 90% within 3–12 months from the injury (Karnath et al., 2011). From these observations it might be concluded that the majority of patients with right hemisphere damage show neglect in the acute phase, and that many show a remission of the deficits in the chronic phase. However, it is possible that the perception of a "recovery" process may be illusory when based only on improved performance on paper-and-pencil tests, where patients can compensate for their deficits and hide the real extent of their impairment. In contrast, when testing procedures are adopted that do not allow patients to compensate for their deficits, apparently recovered patients often return to show severe contralesional deficits (Cherney and Halper, 2001; Robertson and Manly, 2002; List et al., 2008; Rengachary et al., 2009).

In the chronic phase, many right hemisphere damaged patients do not show neglect but extinction, i.e. difficulty in reporting a contralesional stimulus when it occurs simultaneously with a correctly reported ipsilesional stimulus. Extinction presumably results from the "winner-takes-all" functioning of the attention and awareness mechanisms within the parietal lobes (Driver and Vuilleumier, 2001). Although neglect and extinction frequently co-occur, several double dissociations have been described (Cocchini et al., 1999; Vossel et al., 2011) questioning whether extinction should simply be considered a "weak" expression of neglect in remission.

Although there is no doubt that the hallmark of neglect is the failure to attend to the contralesional hemispace, several studies have shown that additional deficits, not attributable to a spatial bias (i.e., non-lateralized), are associated with impaired processing of the contralesional hemispace (Husain and Rorden, 2003; Corbetta and Shulman, 2011, for review). Indeed, neglect patients may present several additional deficits, such as a lack of awareness of their impaired spatial processing (Karnath and Rorden, 2012), visuospatial working memory impairment (Wojciulik et al., 2001), increased variance in line bisection (Bonato et al., 2008), an abnormally long attentional blink (Husain et al., 1997; see also di Pellegrino et al., 1998), and, more generally, reduced alertness and sustained attention (Robertson, 2001). I will now focus on the latter two characteristics.

Reduced arousal and vigilance are often associated with right hemisphere injury (Heilman et al., 1978; Yokoyama et al., 1987; Lazar et al., 2002) and can also interact with spatial deficits (Robertson et al., 1995, 1997; Malhotra et al., 2009; Corbetta and Shulman, 2011). This interaction may be critical for the pathogenesis and preferential right hemisphere lateralization of neglect (Robertson et al., 1997; Corbetta and Shulman, 2011).

Studies by Ian Robertson and his collaborators have shown that the link between neglect and sustained attention is so close that the rehabilitation of the latter leads to benefits in the former (Robertson et al., 1995; see also De Gutis and Van Vleet, 2010), and that the presence and level of sustained attention deficits in right brain-damaged (RBD) patients accurately predicts the presence of neglect (Robertson et al., 1997).

In short, RBD patients have "disproportionate problems with a cluster of non-spatial attentional capacities" (Manly, 2002). However, to directly address the aims of this research topic, it is unclear to what extent non-lateralized deficits are caused by unspecific effects due to the size and lateralization of the cerebral lesion (often quite massive in RBD patients with neglect), or are instead an intrinsic characteristic of the neglect syndrome. The influential review by Husain and Rorden (2003), often quoted to support the view that neglect syndrome would be characterized by non-lateralized deficits, in fact cautiously suggested that non-lateralized deficits are often associated with neglect, but did not state that these deficits are to be considered an intrinsic characteristic of neglect.

One methodological caveat worth discussing in this context is that the presence of non-spatial deficits in neglect patients might be, at least in some studies, due to the presence of more severe, yet non-specific, cognitive impairments within the neglect group.

This could be due to two potential selection biases in studies where brain-damaged patients are assigned to a group according to the presence of a single clinical criterion. The first bias is that (severely impaired) left brain-damaged patients with large lesions and severe aphasia are systematically excluded from testing protocols because their comprehension deficits do not allow clinical or experimental tests to be performed. This may result in the selection of more severely impaired RBD (vs. left BD) patients (Kertesz et al., 1979; De Renzi, 1982). The second potential selection bias comes from the fact that a group of patients selected based on the presence of a specific deficit (e.g., neglect) present with more severe general cognitive impairments (as empirically indexed by lower scores neuropsychological tests and overall slower reaction times) than the complementary group (e.g., patients without neglect) derived from the same sample (Bonato et al., 2012b). In turn, this bias may result in the selection of more severely impaired neglect (vs. non-neglect) patients.

From a clinical perspective, the studies by Robertson et al. (1995, 1997) clearly showed that the diagnosis and rehabilitation of neglect can be more effective if the role played by sustained attention is taken into account. In addition, it is well established that the ubiquitous slowing down observed after right hemisphere damage is more prominent in the presence of neglect (Schürmann et al., 2003) and can be detected also when non-spatial aspects are investigated (see Howes and Boller, 1975; Samuelsson et al., 1998). This slowing down, however, cannot be *a priori* taken as indexing impairments in sustained attention rather than general, unspecific, impairments. The question thus becomes whether non-lateralized aspects of neglect are relatively independent from the severity of general and specific impairments suffered by patients or whether they are instead closely connected with spatial impairments. Only a few studies attempted to unravel these tangled issues (e.g., Hjaltason et al., 1996; Samuelsson et al., 1998). Even assuming that a genuine dissociation between neglect severity and non-specific impairments emerged in these two studies, this cannot be generalized by default to all studies where neglect patients show a more prominent slowing of processing.

Given that severe cognitive impairments often result in sustained attention deficits, caution is mandatory when considering as causal the several correlations between the indexes of neglect and sustained attention.

## SPECIFIC/NON-SPECIFIC COGNITIVE RESOURCES IN THE ATTENTIONAL PROCESSES OF HEALTHY PARTICIPANTS AND NEGLECT PATIENTS

Regardless of whether it should be considered solely spatial in nature, neglect is by and large considered an attentional disorder. There are several definitions of attention and every theory on "attention" aims to characterize one of several attentional processes, from visuospatial orienting to executive functions. Posner (1980) made an influential proposal, mostly focused on the characteristics of attentional orienting in visual space. He adopted a simple and informative method for dissociating components of visual attention (see **Figure 2**). Despite the presence of a more complete model encompassing the mechanisms for alerting/sustained attention (Posner and Petersen, 1990) most of the studies that adopted Posner's cueing paradigm focused on clearly defining the differences between voluntary and automatic orienting, where unspecific non-spatial attentional resources are of little importance. This approach was very fruitful and showed that automatic (exogenous) components of attentional orienting in neglect are more impaired than voluntary ones (Losier and Klein, 2001; Bartolomeo and Chokron, 2002).

In contrast, other theoretical frameworks designed to account for dual-task performance suggested the crucial role played by task demands (see Kahneman, 1973, for a classic account) to determine the performance outcome. In particular, Wickens (2002) focused on dual-task interference and assigned an important role to non-specific cognitive resources for performance. According to him the term "resources" indicates, by definition, something which is limited and can be allocated. He distinguished between the characteristics of "resource demand" determined *a priori*, such as in the case of different experimental conditions, or *a posteriori*, by analyzing performance through subjective ratings, physiological measures, and, also by behavior. This differentiation allows to address the issues of resources, task difficulty, and resource demands and limits the risk of incurring in circular issues. It avoids stating that a task is more demanding because it results in slower responses and more errors, while maintaining that a task presents slower responses and more errors because it is more demanding. La Berge and Brown (1989) also highlighted the important role played by cognitive resources in attentional performance. Although their approach mainly focused on shape identification, it also addressed the debate on the mechanisms underlying orienting of spatial attention. They argued that attention operates in space not as a moving spotlight-model but as a gradient model of processing resources according to which peaks of resources and processing efficiency are formed at the location in space where attention is directed. To our knowledge the stances of Wickens and of Laberge and Brown are mostly confined to studies in ergonomics and experimental psychology, and have not been systematically addressed by studies conducted on brain-damaged patients.

A recent approach relevant for our purposes is the "load theory of attention" (Lavie et al., 2004), where the influence of lateralized distracters depends on the level and type of load required by the task. High perceptual load would reduce distracter interference, whereas working memory load or dual-task load would increase distracter interference. The load theory distinguishes between a perceptual selection mechanism and a cognitive control mechanism. The first reduces the perception of distracters in situations of high perceptual load that "exhaust perceptual capacity in the processing of relevant stimuli," whereas the second is thought to reduce interference from perceived distracters as long as cognitive control functions are available to prioritize the tasks (i.e., under low cognitive load). This theory integrates the debate on the locus of selection of irrelevant information (early vs. late) into a unique, flexible system which processes (or does not process) lateralized distracters according to the amount and nature of the resources required by the task. It has been implemented directly to assess the performance induced by ipsilesional distracters in neglect (Lavie and Robertson, 2001; Snow and Mattingley, 2008).

Finally, two accounts of neglect are worth mentioning for the purposes of this paper.

The first suggests a key role for arousal, alertness, and sustained attention deficits in determining impaired visuospatial performance (Robertson, 2001), to the extent that the latter can be improved when on-the-spot alertness is increased (Robertson et al., 1998) or when it undergoes specific training (Thimm et al., 2009).

A second influential model of neglect focuses on the occurrence of three components: an initial, automatic orienting of attention toward the ipsilesional side; a general non-directional attentional deficit, and an impairment in reorienting attention toward the contralesional side (Karnath, 1988). According to this proposal, persisting deficit in the first two components would account for the residual deficits found in patients who have otherwise regained some contralesional orienting abilities.

After this brief theoretical overview, evidence will be presented showing that impairments in the processing of the contralesional hemispace can be detected more sensitively by tasks that do not allow any compensation.

## COMPUTER-BASED TESTING AND INCREASED TASK DEMANDS RESULT IN AWARENESS DEFICITS FOR CONTRALESIONAL HEMISPACE

### COMPUTER-BASED TESTING DETECTS HIDDEN CONTRALESIONAL DEFICITS

The adoption of computer-based testing is a promising solution for neglect assessment (Schendel and Robertson, 2002, for review) because it is potentially more sensitive than paper-and-pencil tests in detecting slowed processing of contralesional hemispace. Computerized assessments allow presenting patients with stimuli of brief durations and recording response latencies with a millisecond precision and can be adapted to the individual degree of impairments (List et al., 2008).

There is a long tradition of computer-based studies that have assessed the performance of RBD patients in computer-based detection tasks, which typically require patients to press a response key when a lateralized target is perceived. These computer-based approaches often highlighted slower responses for targets appearing in the contralesional hemispace, also in patients without evidence of neglect on paper-and-pencil tests. For instance, the difference between the detection of validly cued left vs. right targets is biased toward the ipsilesional hemispace in chronic RBD patients, even in the absence of neglect (Posner et al., 1984; Losier and Klein, 2001) and even when patients without neglect or extinction are included in the sample (Friedrich et al., 1998). These studies mainly focused on contralesional slowing rather than on omission rate because targets of relatively long durations (e.g., never shorter than 2 s according to Losier and Klein, 2001) were presented, whereas shorter durations are required to obtain a consistent number of omissions.

It may be argued that the disadvantage found in contralesional targets detection may be due to biased orienting in valid trials. However, this explanation can be refuted by the results of studies where RBD patients without neglect at clinical testing were required to detect single, brief light-emitting diode (LED) flashes occurring at several eccentricities (up to 40°; Smania et al., 1998; Marzi et al., 2002). Despite the fact that there were no cueing procedures (and therefore, valid trials) this LED-based testing procedure allowed detecting severe contralesional slowing and omissions. In particular, when the same patients were presented with stimuli that always appeared in the same location within each block, their performance returned to normal (Marzi et al., 2002). The method adopted by Marzi et al. (2002) and by Smania et al. (1998) required to simultaneously monitor several spatial positions where the target could potentially appear. It is plausible that the sensitivity of this device in detecting attentional biases for contralesional hemispace therefore derives from a high recruitment of monitoring resources, due to both the wide range of locations where the target could appear and to its brief duration. Indeed, spatial predictability improves target detection performance (Geng and Behrmann, 2005). From this perspective, it seems plausible that the deployment of resources for spatial monitoring would result in an increase in the cognitive load required by the task. The recruitment of visuospatial resources might then, in turn, hamper the implementation of compensatory strategies and allow subtle deficits to emerge. This testing method is sensitive enough to detect signs of contralesional slowing in both left and RBD patients (Smania et al., 1998). Target duration of computer-based testing can be calibrated individually in order to avoid floor and ceiling effects. This procedure allows analyzing, for each patient, both RTs and omission rates and is particularly suitable for exploring the effects of changes in the task instructions, while keeping the same stimuli across the different tasks (Vuilleumier and Rafal, 2000). Patients with right hemisphere damage are also particularly slow at detecting a contralesional target when it is preceded by an ipsilesional cue. In the seminal study by Posner et al. (1984) this "disengage deficit" occurred despite the fact that the study included several patients with mild or no neglect according to clinical testing, based on easy everyday activities, and one case without extinction at standard finger confrontation testing. The disengage deficit can persist, in the absence of neglect on paper-and-pencil tests, for several years after lesion onset (Friedrich et al., 1998). It also emerges when attention is oriented rightwards by a non-predictive arrow cue presented at fixation (Bonato et al., 2009).

Most, if not all, the detection studies performed with brain-damaged patients (Losier and Klein, 2001, for review) focused on theoretical issues and did not highlight the possible clinical (i.e., diagnostic) usefulness of these tasks. Contralesional slowing (or omissions when brief target durations are adopted) commonly occur in computer-based (but not in paper-and-pencil) experimental tasks, even when the non-neglect group is based upon performance on sensitive and complex diagnostic batteries as the Behavioral Inattention Test (BIT; Wilson et al., 1987), which is considered the "gold standard" for neglect diagnosis (Halligan et al., 1989).

Increased visual (Lavie et al., 2004; Dell'Acqua et al., 2006) or visual and auditory (Webster and Haslerud, 1964) load in healthy participants hampers processing at peripheral locations. A number of studies with RBD patients manipulated visual demands at fixation. The mere presence/absence of a fixation point can determine whether a brain-damaged patient will show neglect, hemianopia, or both (Walker et al., 1991; Müller-Oehring et al., 2003). Furthermore, RBD patients show a bias in disengaging attention from fixation (Posner et al., 1984; Ptak et al., 2007).

Crucially, the deployment of attention in brain-damaged patients may be differentially affected in the two hemispaces by increasing the attentional resources deployed at fixation. Increasing perceptual demands at fixation (e.g., by asking the discrimination of a shape) can result in an asymmetric reduction of spatial performance with a significant "shrinkage" of the contralesional hemifield in RBD patients without neglect (Russell et al., 2004). A similar manipulation resulted in a more efficient rejection of ipsilesional distracters in neglect patients, as predicted by the load theory of attention (Lavie and Robertson, 2001; but see Snow and Mattingley, 2008). Two recent studies of RBD patients with left neglect (Vuilleumier et al., 2008; Eramudugolla et al., 2010) have confirmed that increased load at fixation deeply affects contralesional hemispace processing (see also Maravita et al., 2007). The f-MRI study by Vuilleumier et al. (2008) demonstrated that increased load at fixation can reduce or even eliminate brain activations selectively for (ipsilesional) visual areas which process the opposite hemispace. Instead, Eramudugolla et al. (2010) showed that impairments for the contralesional hemispace exerted by increased load at fixation are so strong that they are relatively unaffected by prismatic adaptation.

In summary, several studies unite to show that brain-damaged patients without neglect on paper-and-pencil tests are slow to detect computer-presented contralesional targets, and that increased visual demands at fixation can result in the complete disruption of contralesional processing.

## CLINICAL RELEVANCE OF COMPUTER-BASED, SENSITIVE TESTING

Only a few studies have examined the clinical implications of how neglect can (re)emerge with computer-based presentation.

In a seminal study, Anton et al. (1988) presented a group of right hemisphere damaged patients with a series of unilateral or bilateral lights appearing on a semicircular array covering a wide visual angle, and three paper-and-pencil tests. Occupational therapy scores were also collected. The sample was then categorized according to the presence of neglect in the computerized test (54%), in the standard tests (20%), and in the occupational therapy test (28%). In other words, the light detection task resulted to be more sensitive than the standard clinical measures (see also Beis et al., 1994; Eschenbeck et al., 2010).

More recently, a compelling study (Deouell et al., 2005) directly compared results from the computer-based Starry Night Test (SNT, see **Figure 1**) and paper-and-pencil tests (BIT). A higher sensitivity emerged in the SNT compared the BIT when assessing each patient's individual performance. In the SNT, relatively brief targets can appear in several spatial positions. As previously noted for the studies by Marzi et al. (2002) and Smania et al. (1998) spatial uncertainty plausibly deploys attentional monitoring resources and hampers the implementation of compensatory strategies. Moreover, in the SNT, the presence of distracters does not allow patients to respond (key press) as soon as something appears on the screen but forces them to identify the target before responding. Crucially, Deouell and collaborators also described in detail the deficits shown in everyday life by two patients whose neglect was only evident in the SNT (see also Erez et al., 2009).

As already mentioned, Posner-like detection tasks can also be more sensitive than paper-and-pencil tests in unveiling neglect (e.g., Friedrich and Margolin, 1993). This occurs not only in the chronic but also in the acute phase (Rengachary et al., 2009). Relatively brief target durations (**Figure 2**) increase the sensitivity of these tasks (Rengachary et al., 2009, 2011, where a variant of the Posner paradigm with very long SOAs was adopted).

Non-spatial characteristics of a task can also increase the amount of resources required for performance. For instance, the mere introduction of trials where no response is required can increase the left-right asymmetry in RBD patients without neglect (Bartolomeo, 2000). This suggests that apparently intact RBD patients tested by previous studies often presented hidden neglect and were able to compensate for their spatial bias through the task (Plummer et al., 2003; see also Appelros et al., 2003; Behrmann et al., 2004).

The connection between subclinical neglect and the demanding tasks which often characterize everyday life became even more evident in a visual dual-task study where a sample of stroke patients were divided into two groups according to whether they were/were not still driving at the time of testing (Marshall et al., 1997). Despite intact performance at paper-and-pencil tests for neglect assessment, the better dual-task performance obtained by the drivers group was interpreted as though these patients were more efficient in dealing with complex visuospatial tasks requiring intact divided attention skills. A simple yet challenging driving environment, where lateral items had to be detected, was reproduced in an experimental study where more patients were classified as affected by neglect according to reaction time asymmetry in the "driving" task than the BIT criteria (van Kessel et al., 2010). Within the RBD group, patients with both RT asymmetries and pathological BIT scores showed longer ipsilesional RTs than patients with RT asymmetries only. Once again, neglect symptoms were detected when more demanding tests were conducted on patients who were able to compensate for their lateralized deficit in paper-and-pencil tasks.

To our knowledge only Peers et al. (2006) reported that, contrary to the previously discussed evidence, an increase in task demands result in a rightward shift of attention, independent from lesion lateralization.

### DETECTING UNRECOVERED NEGLECT

Some studies addressed the clinical potential of tasks that do not allow compensation by exploring whether these testing procedures can still detect neglect in the specific case of patients who had a clinical history of neglect and then recovered. Severe impairments of the contralesional hemispace in (apparently) recovered patients can re-emerge if sensitive testing procedures and scoring criteria are implemented (Campbell and Oxbury, 1976). RBD patients without signs of neglect exhibit an early rightward orienting of attention when identifying complex stimuli such as overlapping figures (Gainotti et al., 1991). This supports the view of Karnath (1988) who maintains that a strong tendency toward rightward orienting is a core deficit in chronic neglect. Once again, the RBD group in Gainotti et al. (1991) may have included neglect patients who were, in fact, able to inhibit their initial rightward orienting after its occurrence, and to redirect their attention toward the left (i.e., to compensate for their deficit) in standard clinical tests, characterized by less complex stimuli and less sensitive, accuracy-based, scoring criteria.

Bartolomeo (1997) studied the individual performance changes within a computer-based detection task. He found that

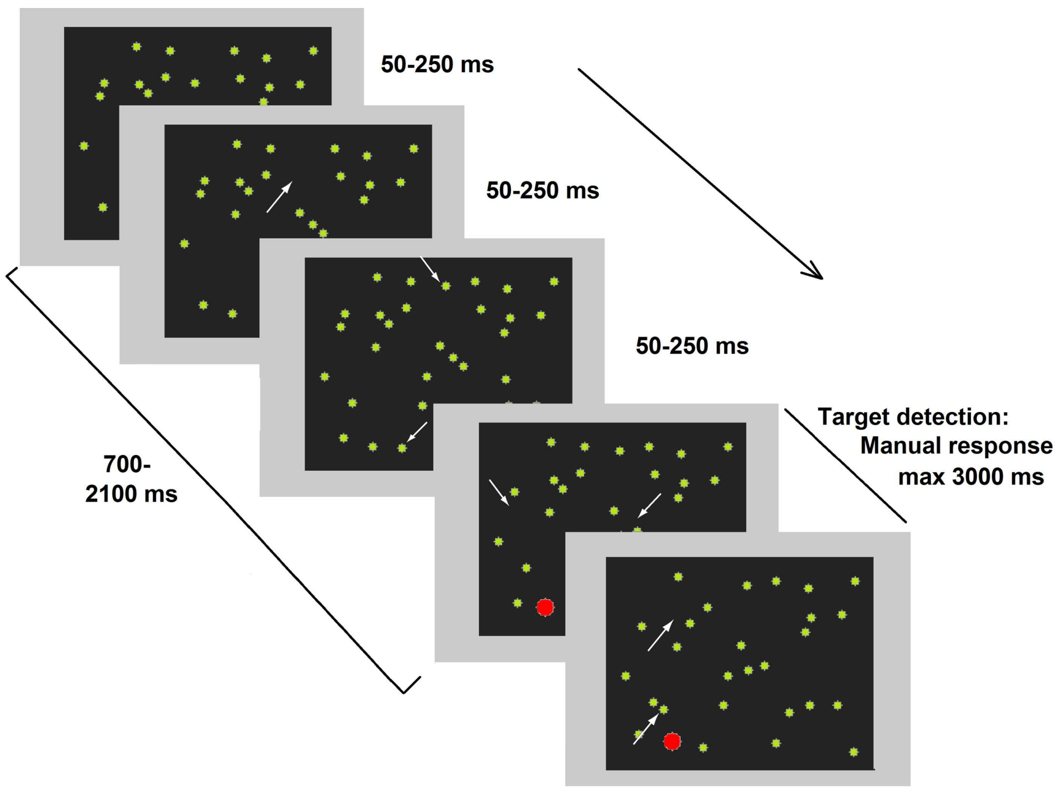



**FIGURE 1 | Representative frames of one trial of the dynamic Starry Night Test (SNT).** White arrows (not present in the real test) point to spatial positions where a distracter (green dot) appeared or disappeared along the trial. The target (in red) was embedded in the continuously changing background. Adapted from Deouell et al. (2005), image not to scale.

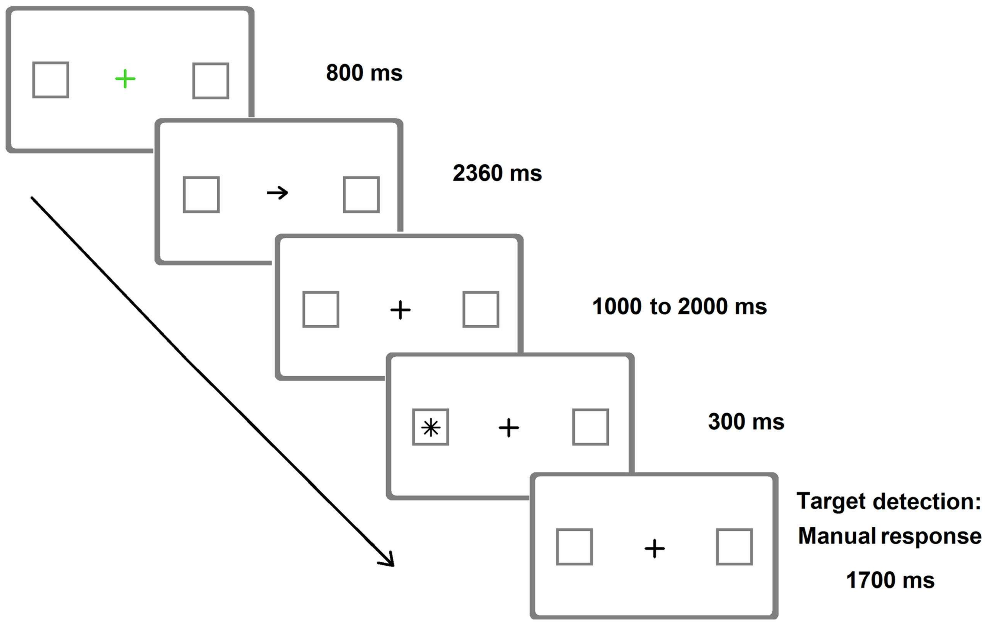



**FIGURE 2 | Representative frames of one (invalid) trial of the Posner Cueing Paradigm resembling the version adopted by Rengachary et al. (2009).** Arrows predicted the location of appearance of the target on 75% of the trials. The image is only indicative of the stimuli adopted and is not to scale.

(apparently) recovered neglect patients showed longer RTs to left-sided visual stimuli than to right-sided stimuli at the beginning of the test, but fell within the controls' range by the end of the test. Patients with mild albeit hidden neglect thus seemed to be rather effective in recruiting attentional resources to compensate for their deficits when performing tasks engaging visuospatial attention. It may seem that this finding is in contrast with the hypothesis of a sustained attention deficit in neglect. Instead, it supports the idea that only neglect patients with severe general/sustained attention deficits are unable to compensate for their spatial deficits. The ubiquity of these compensatory strategies makes it difficult to clarify whether the majority of patients who seem to spontaneously recover from the spatial biases of the disorder in the first phases, have genuinely recovered or are, in fact, implementing corrective compensatory (voluntary) strategies (Robertson and Manly, 2002).

As already mentioned, the SNT is also successful in detecting patients who had apparently recovered from neglect. It was sensitive enough to detect slower RTs for contralesional (as compared to ipsilesional) stimuli in a RBD patient tested 12 years after a stroke, who had severe but hidden deficits in everyday life, including a severe problem in driving as indicated by several crashes involving the left side of his car (Deouell et al., 2005).

As suggested by Campbell and Oxbury (1976), an accurate analysis of behavioral performance may also reveal that the recovery from neglect in several patients is only apparent. Post-acute stroke patients who were diagnosed with neglect and then re-tested on average about 5 months after stroke may show unimpaired performance on standard paper-and-pencil tests but mild impairments in their movements (Goodale et al., 1990). While post-stroke patients had the same overall accuracy of their arm reaching movements of healthy controls, kinematics revealed significant rightward deviations in their trajectories that were only corrected in the final (pre-target) stage. Patients who had (apparently) recovered from left neglect also showed biased visual exploration with a shift toward the right side of items (Mattingley et al., 1994; see also Pflugshaupt et al., 2004). In cancellation tasks, patients with left neglect show several markers of biased performance (e.g., rightward starting point, slowness, increased speed variability, and incoherent organization), which typically are not taken into account by standard, accuracy-based, criteria (Manly et al., 2009). A careful assessment of these performance details also confirmed the presence of visuospatial impairments for those patients whose scores were borderline (around the cut-off) on paper-and-pencil tests and for which the appropriateness of the neglect diagnosis can be questioned (Manly et al., 2009).

## LACK OF SENSITIVITY IN NEGLECT DIAGNOSIS: SENSITIVE DIAGNOSIS REQUIRES DIFFICULT TASKS

It is a truism to maintain that a more difficult task results in a worse performance and that only difficult tests achieve higher diagnostic sensitivity. Indeed, several studies adopting cancellation tasks have shown that the performance of neglect patients decreases when attentional demands are increased and more complex visual searching strategies are implemented (Rapcsak et al., 1989; Eglin et al., 1991; Aglioti et al., 1997; Sarri et al., 2009). Surprisingly enough, the implementation of difficult tasks to increase the sensitivity of diagnostic tests is far from being a standard in assessing neglect and extinction.

On the contrary, several clinical studies in different research domains have shown that difficult tasks result in more sensitive diagnosis and allow to infer performance in everyday contexts. For example, research in the field of fall risk in older people has shown that dual-task performance (e.g., walking combined with a simultaneous cognitive task), hampers motor performance, particularly when cognitive deficits are also present (Camicioli et al., 1997). A second example comes from the study of patients with cirrhosis, which shows that a highly demanding visuospatial task (i.e., performing a sustained attention task on briefly presented letters) is sensitive in detecting the presence of minimal hepatic encephalopathy (Amodio et al., 2010). Therefore, it seems appropriate to implement more demanding visuospatial tasks in order to obtain a more sensitive diagnosis of neglect, a disorder which in itself is visuospatial.

Apart from its theoretical consequences, the misdiagnosis of neglect raises a number of important clinical implications since patients in the chronic phase may be allowed to return to their pre-morbid activities where they may be at risk (driving, road crossing, and use of dangerous objects/devices). Experienced clinical neuropsychologists know that paper-and-pencil tests can detect only moderate-to-severe forms of neglect (Barrett et al., 2006; Buxbaum et al., 2004) and do not allow deducing a patient's disability in natural settings (Deouell et al., 2005; Hasegawa et al., 2011). Nonetheless, these tests are still considered the "state of the art" for diagnosing contralesional awareness deficits, despite several studies showed that, in the chronic phase, computer-based testing is the best option for obtaining a more sensitive diagnosis of neglect (Friedrich and Margolin, 1993; Schendel and Robertson, 2002; Deouell et al., 2005; Rengachary et al., 2009; Bonato et al., 2010, 2012a,c).

Moreover, although studies by Bartolomeo (1997, 2000) suggest a positive answer, the question as to whether a non-specific (non-visual) increase in the amount of attentional resources worsen neglect, and to whether this might also occur in patients with intact performances on paper-and-pencil tests have been scarcely addressed so far. Robertson and Frasca (1992) directly addressed the first issue by showing that the performance of left neglect patients in cancellation and reaction time tasks can be modulated by different engagements of working memory in a concurrent task (e.g., from an easy task like counting forward to a hard one like counting backward by threes from 100). In their study some (but not all) neglect patients showed a peculiar contra-ipsilesional increase in the detection of lateralized targets when performed with a simultaneous attentionally demanding concurrent task (i.e., counting backward in threes from 100). The study adopted a multiple single-case approach where each patient's individual performance could be tested for asymmetries and dual-task modulation. Nevertheless, the experimental paradigm did not highlight an increased bias in patients without neglect. If volitional orienting plays an important role in functional recovery from neglect, a re-emergence of the contralesional deficit under challenging dual-task conditions (Robertson and Manly, 2002) could be predicted. We empirically confirmed this prediction.

## COMBINING COMPUTER-BASED PRESENTATION WITH DEMANDING TASKS

We recently combined brief stimuli presentation with resource-demanding tasks, namely two characteristics that have been shown to maximize the possibility to detect contralesional omissions in a multiple single-case study of four post-acute (1–2 months from stroke) RBD patients (Bonato et al., 2010).

Patients were first tested for the presence of neglect with the BIT and then for the presence of extinction with the finger confrontation procedure. One of them had neglect and extinction, whereas the remaining three had no signs of neglect and only one of them showed signs of extinction. Patients were required to verbally report the position of briefly presented unilateral and bilateral targets (**Figure 3**). Target duration was individually determined by means of a calibration procedure performed before the experiments (Vuilleumier and Rafal, 2000). Upper and lower limits were set to 50 and 700 ms, respectively. Within the calibration procedure for each bilateral trial (of a given duration) the accuracy was calculated online and determined the duration of the subsequent trial, which was increased or decreased by 35 ms, depending on whether the patient extinguished or correctly reported the contralesional target, respectively. The calibration procedure yielded individual target durations between 50 and 650 ms. For control participants, target duration was set at the minimum allowed (50 ms).

The average extinction rate for bilateral trials dramatically increased under dual-task conditions from 18.4% in the single task to 90% in the visual dual-task and to 84% in the auditory dual-task. Impairments for contralesional space processing, thus, emerged as soon as the quantity of attentional resources available for performing the task were reduced, regardless of the nature of the concurrent task (i.e., visual vs. auditory). Two patients, despite the absence of neglect on paper-and-pencil tests, omitted a significant number (30 and 80%) of single contralesional targets (i.e., they showed neglect), once again only under dual-task conditions. In contrast, the performance of healthy participants was symmetric and virtually errorless, and unaffected by the dual-task manipulation. A left brain-damaged patient without neglect, tested 4 months from stroke, also showed severe contralesional (this time, right) awareness deficits for single and double targets (neglect and extinction, respectively), under dual-task conditions only. The performance of healthy controls and of the left brain-damaged patient demonstrate that the spatial deficits found in RBD patients are genuinely contralesional and not due to an unspecific rightward shift that may occur under dual-task conditions (Peers et al., 2006 vs. Śmigasiewicz et al., 2010).

Bonato et al. (2010) explicitly focused on the bias resulting from manipulations in task difficulty and highlighted its diagnostic potential. It is worth reiterating that neglect severity is closely determined by the task at hand. Surprisingly enough, until our study, computer-based and demanding testing had never been coupled to assess the potential presence of neglect in patients whose contralesional awareness was apparently spared. Moreover, previous studies on patients (except Robertson and Frasca, 1992) assessed the effects of load manipulations in visuospatial modality only. As a result, it is difficult to disentangle whether the severe impairments in contralesional awareness resulting from an increase in demands at fixation were caused by an increase in the visuospatial load or by an unspecific recruitment of attentional resources, or the combination of both. Consequently, a crucial and novel aspect of our findings is that, regardless of whether visual or non-visual processing resources are recruited, and the extent to which the two manipulations can be considered similar, both

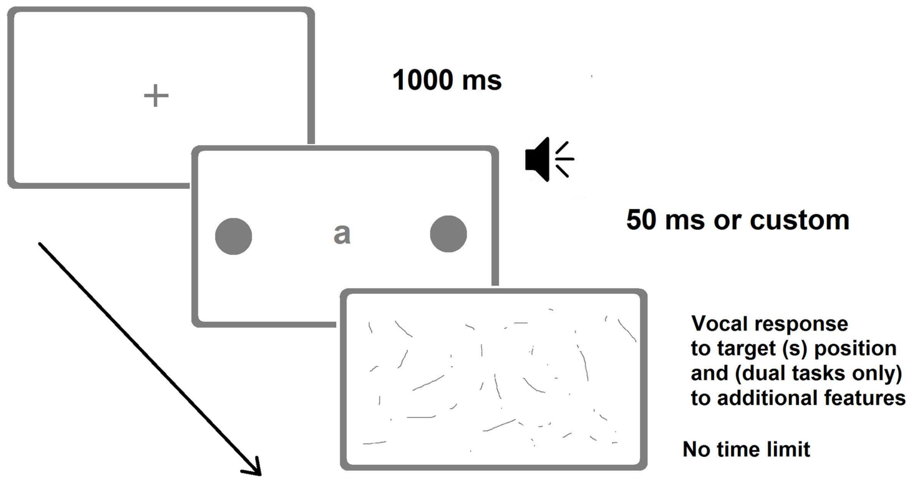



**FIGURE 3 | Representative frames of one (bilateral) trial of the Dual-Task Paradigm in the version adopted by Bonato et al. (2012a).** There were also trials with a single unilateral target. The loudspeaker indicates the auditory presentation of a number. In the last screenshot (response collection) patients verbally reported either the position of the target(s) only (in the single-task condition) or the identity of the letter and the position of the target(s) (visual dual-task) or counted twice by two from the number they heard and then reported the position of the target(s) (auditory dual-task). Image not to scale.

dual-task manipulations can have a detrimental effect on awareness. Finally, the choice to adopt a multiple single-case approach (and statistics) was fundamental to allow us to monitor performance at the individual level (Robertson and Frasca, 1992; Deouell et al., 2005).

The lack of a systematic discussion about the need to implement more sensitive testing procedures may be due to the absence of strong connections between everyday life performance and subtle awareness deficits that emerge in a computer-based task. Researchers may believe that deficits detected by computer-based testing procedures are so mild that they do not exert any effect on everyday performance. Moreover, the few studies assessing patients' behavior in everyday life generally rely on standard instruments to obtain an "ecological" assessment (e.g., FIM, Barthel index, Bergego scale). To our knowledge only a few studies (e.g., Deouell et al., 2005; Hasegawa et al., 2011) described in detail the impairments shown by chronic patients without neglect according to paper-and-pencil tests in complex, truly ecological, everyday settings. The main disadvantage of the FIM, Barthel and Bergego scales is that the resulting scores only allow quantifying disability in easy tasks such as eating or dressing, but do not appear to be precise enough to detect subtle neglect in complex everyday life activities, and lack scores related to dual-task performance (but see Eschenbeck et al., 2010 for a more sensitive neglect-related ADL assessment). Additionally, they do not clarify whether contralesional performance is impaired because of motor or attentional deficits when patients, as commonly occurs, have concurrent motor deficits. In order to answer both criticisms, we (Bonato et al., 2012a) recently performed a longitudinal investigation on the deficits shown by GB, a 63-year-old woman who, after a stroke affecting most of the territory of her right middle cerebral artery, showed no motor impairment and presented normal performance on paper-and-pencil tests for neglect (see the Tutorial in the Supplementary Material). We tested her with computer-based, resource-demanding dual-task procedures and repeated ecological observations at home, for more than 6 months after her discharge from the hospital. Surprisingly enough, both computer-based and observation-based approaches highlighted severe difficulties in contralesional hemispace processing which selectively emerged under dual-task conditions, not only in the computer-based paradigm (she neglected almost all contralesional targets in the first testing session) but also in everyday life (with repeated bumping into objects on her left).

The uncommon absence of any motor deficits (Azouvi et al., 2002) allowed us to rule left leg/arm weakness as a potential explanation for her accidents involving bumping into objects on her left and to ascribe to neglect her impaired performance for contralesional hemispace found in everyday life contexts. Longitudinal testing allowed us to detect the spontaneous remission of GB's deficits over time, which began from the easiest conditions (single task) and continued to intermediate difficult conditions (dual task, single stimulus), resulting, after more than 1 year, in the sole persistence of extinction for 1/3 of the trials performed under dual-task conditions only (Bonato et al., unpublished data).

She was also presented with several cancellation tasks (Bonato et al., 2012a), see Videos 1–3 in the Supplementary Material. She was very accurate and relatively fast, although her starting point, an index of subclinical neglect (Azouvi et al., 2002) was consistently located in the right half of the page. Her performance on the TMT-A was normal, whereas her TMT-B performance was very slow (Videos 4 and 5). This confirmed that she suffered from severe visuospatial impairments under dual-task (in the case of the TMT-B: task shift) conditions, exacerbated also when two spatial positions had to be monitored to determine the order of appearance of two targets (Video 6). Cued-detection tasks (e.g., Posner, 1980; Rengachary et al., 2009) revealed a persisting contralesional slowing in target detection which was, however, not coupled with a significant number of contralesional omissions or with a disengage deficit when the test was performed in the chronic phase.

In the same study we also tested, with the same computer-based dual-tasks, five post-acute right stroke patients (one with left neglect and four without neglect; four with extinction rate of ≤35% at finger confrontation) and one healthy participant (sex and age-matched with GB). Contralesional extinction and omissions also dramatically emerged for these patients, confirming that subclinical awareness deficits in post-acute stroke patients are more the rule than the exception. Across the same group, the effects of different target durations were also compared across patients. Each patient was presented both with a customized target duration – calculated using the "calibration procedure" described above (resulting range of 50–600 ms) – and with the minimal (50 ms) target duration. These two conditions succeeded, respectively, in maximizing the emergence of (i) contralesional awareness deficits under dual-task conditions and (ii) contralesional awareness deficits regardless of dual-task manipulations. In no case did the BIT (for neglect) or the finger confrontation procedure (for neglect/extinction) detect a deficit that did not emerge under dual-task conditions. In contrast, our dual-task succeeded, both at an individual and group level, in highlighting deficits that were much more severe than those detected by standard clinical testing. This was maximally evident when target duration was as short as 50 ms, with an average left omission rate above 80% for bilateral targets and around 50% for left unilateral targets.

In a third study (Bonato et al., 2012c) we grouped the data from ten RBD patients who had been presented with the shortest (50 ms) target duration in our computer-based, resource demanding task. We directly compared their omission rates when performing the BIT cancellation subtests and when performing the computer-based tasks. The difference in performance found was, once again, striking. Across all cancellation tests, only 7% of omissions for left targets vs. 5.5% for right targets emerged (i.e., no left-right difference was observed). In contrast, under dual-tasks, computer-based conditions, patients omitted 70% of unilateral targets on the left and 4.5% on the right (i.e., a significant left-right difference was observed).

Our approach therefore allows to couple a bottom-up (e.g., long vs. brief stimuli presentation) with a top-down manipulation (e.g., single vs. dual-task condition). Several patients already showed impaired contralesional performance under single-task conditions and custom target duration. The deficits became even more evident when the presentation time was reduced, and the awareness for contralesional hemispace further decreased under dual-task conditions (Bonato et al., 2012c). Our data were interpreted by maintaining that the reduction in the presentation time and the introduction of a concurrent task both contributed to the recruitment of attentional resources, which in turn resulted in contralesional awareness deficits.

Even though both manipulations seemed to converge in increasing awareness deficits selectively for contralesional hemispace, in future they may be useful for providing different information on the individual characteristics of the awareness deficit of the tested patient. Indeed, some patients may be more sensitive to dual-task manipulations whereas some may be more sensitive to reduced presentation time.

Although fully addressing the complex relation between neglect and extinction goes beyond the aims of this review, our results reliably show more severe extinction than neglect (Bonato et al., 2010, 2012a) at a group level. At the same time, however, it is worth mentioning that the only left hemisphere damaged patient we tested (Bonato et al., 2010) presented with more severe neglect than extinction, as if the presence of a left target was, in his case, facilitating the detection of a right, synchronous target. Whether this phenomenon is a general characteristic of left brain-damaged patients and/or whether it can also be found in RBD patients remains unanswered.

Further evidence is also needed to clarify differences between dissimilar dual tasks. At present, group data show a similar modulation in the number of neglected targets (Bonato et al., 2012c) regardless of the version of the dual task adopted. At an individual level, however, some patients seem to be more affected by a specific load manipulation (Bonato et al., 2010, 2012a). If our interpretation of hampered performance as a function of attentional resources engaged by the task is correct, dual tasks with different levels of difficulty should result in better performance for the easier one.

Our results suggest that deficits in awareness emerge drastically in the contralesional hemispace when attentionally demanding tasks are performed and compensatory strategies cannot be implemented. Resource-demanding dual-tasks appear to be one of the best options available for detecting and monitoring the presence of awareness deficits from lesion onset over time (see Deouell et al., 2005; and Rengachary et al., 2009 for recent alternative, sensitive, computer-based assessment methods). A comparison with the average evolution of performance on standard tests is shown in **Table 1**. Our approach might be useful for neuropsychologists not only because it is sensitive but also because it is flexible and informative. It is flexible because it allows the use of different indicators according to the severity of the awareness deficits, the easiest conditions being single task and unilateral target presentation and the more difficult (and sensitive) being bilateral target presentation under dual-task conditions. It is informative because it allows identifying patients whose visuospatial performance in everyday life can be kept within the boundaries of normality by avoiding dual-task recruitments.

In summary, we (Bonato et al., 2010, 2012a,c) provided a concrete diagnostic tool, and confirmed that: (a) the degree of contralesional impairments was closely dependent on the amount of resources required by the task and (b) apparently spared contralesional awareness may simply reflect the general availability of attentional resources that just suffice to perform single tasks.

## FINAL CONSIDERATIONS

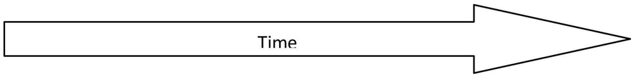
### SUMMARY

We have reviewed evidence that:

– Neglect patients have non-lateralized deficits which interact with the severity of lateralized deficits and can enhance them (Husain and Rorden, 2003; Corbetta and Shulman, 2011). It seems very difficult to separate the overall role played by non-specific cognitive impairments (De Renzi, 1982; Bonato et al., 2012b).

– Computer-based detection tasks highlight contralesional impairments which are not detected by paper-and-pencil tests

**Table 1 | A simple graphical representation of hierarchy of spatial impairments presented by a "typical" patient following a stroke of the middle right cerebral artery in the acute, post-acute, and chronic phases, respectively.**




| Symptom | Acute phase (first days) | Post-acute phase (1 month) | Chronic phase (3–6 months) |
|---|---|---|---|
| Rightward gaze | Y | N | N |
| Left omissions: easy (e.g., no distracters) cancellation tasks | Y | N (but right starting point) | N (but right starting point) |
| Left omissions: difficult (e.g., with distracters) cancellation tasks | Y | Few/inconsistent | N (but right starting point) |
| Contralesional omissions at computer-based single tasks | Y | Several | N |
| Contralesional omissions at computer-based dual tasks | Y | Several | Y (Variable) |
| Contralesional extinction at finger confrontation | Y | Y | N |
| Contralesional extinction at computer-based dual tasks | Not possible to assess | Y | Y |

*In the post-acute phase, computer-based dual tasks are more sensitive than cancellation tasks in detecting neglect. In the chronic phase, computer-based dual tasks are more sensitive than finger confrontation in detecting extinction.*

(Posner et al., 1984; Friedrich et al., 1998; Smania et al., 1998; Losier and Klein, 2001; Marzi et al., 2002; Bonato et al., 2009).

– The true impairment suffered by patients is revealed, in the chronic phase, only when attentional resources, otherwise implemented to contrast and compensate for the contralesional bias, cannot be effectively allocated (e.g., Bartolomeo, 1997, 2000; Marzi et al., 2002; Deouell et al., 2005; Rengachary et al., 2009; Bonato et al., 2010, 2012a; van Kessel et al., 2010; Hasegawa et al., 2011).

– These tasks can be useful for clinical (e.g., diagnostic) purposes (Deouell et al., 2005; Rengachary et al., 2009; Bonato et al., 2010, 2012a,c).

## INTEGRATION WITH THE THEORETICAL POSITIONS

The findings above supplement the theories of normal attention accounting for a crucial role of non-specific cognitive resources in dual-task performance (Wickens, 2002), as well as those claiming a gradient of resources in space (La Berge and Brown, 1989). With specific reference to the load theory (Lavie et al., 2004), we found that contralesional orienting/awareness can be hindered similarly and independently from whether attentional load is increased visually at fixation (Russell et al., 2004; Vuilleumier et al., 2008) or by a second task irrelevant to visuospatial processing (Bonato et al., 2010, 2012a). We highlighted the importance of compensatory strategies (Bartolomeo, 1997; Robertson and Manly, 2002) the persistence of extinction after neglect remission (Karnath, 1988) and the presence of a disengage deficit from fixation (Posner et al., 1984; Ptak et al., 2007).

## TAKING ADVANTAGE OF THE ASYMMETRY IN NEGLECT

Studies that suggested an individual-level comparison took advantage of a peculiarity characterizing neglect syndrome: the possibility to use the ipsilesional hemispace performance of an individual patient as their own control (e.g., Robertson and Frasca, 1992; Deouell et al., 2005; in part also Bonato et al., 2010, 2012a). This simple approach maximizes sensitivity and can be summarized as follows: poorer performance in the contralesional as compared to the ipsilesional hemispace indicates neglect. In contrast, the diagnosis of neuropsychological impairments other than neglect requires a comparison with the performance of a sample of healthy controls. This comparison results in lower sensitivity because inter-individual variability must be considered. Nevertheless, many studies based the diagnosis of neglect on the comparison with the performance shown by a standardized sample (e.g., the cut-off scores of the BIT) or, less frequently, on the cut-off scores shown by the worst of the healthy participants (e.g., Stone et al., 1992).

It is worth highlighting, however, that this approach does not necessarily assume that the ipsilesional hemispace is intact in patients with neglect. In fact, a neglect patient's performance for the ipsilesional hemispace is far from "normal." We have already mentioned several studies suggesting that disengaging from both ipsilesional and central cues is particularly difficult for RBD patients (Posner et al., 1984; Russell et al., 2004; Ptak et al., 2007). Considerable evidence suggests that attentional orienting toward the ipsilesional hemispace is characterized by slower and more error-prone detection of targets within the less eccentric ipsilesional positions (Smania et al., 1998). Extinction itself can be seen as an indicator of pathological reflexive orienting toward the "good" hemispace (but see di Pellegrino et al., 1997). At the same time, however, increased severity of neglect is coupled with slower reaction times for ipsilesional stimuli (Bartolomeo and Chokron, 1999). Finally, in several clinical tests (e.g., cancellation tasks), the performance of neglect patients is often characterized by perseverations (e.g., repeated marks on the same target), typically more evident for the most ipsilesional items (Ronchi et al., 2009) and potentially interacting also with deficits of monitoring/executive functions.

#### PROS AND CONS OF COMPUTER-BASED TESTING PARADIGMS

Apart from high sensitivity, computer-based tests have several additional advantages; short administration time, low cost, and the possibility to easily modify and control the characteristics of the stimuli. Nonetheless, they also have some disadvantages. Firstly, the specific programs are currently not available from software companies[1] and, therefore, their implementation requires specific software allowing for brief presentation time, RT recording, and some basic programming and statistical skills for calculating the individual statistics. Moreover, they are not suitable if the patient has hemianopia. In addition, they cannot be used to test for the presence of neglect in spaces other than the peripersonal one, although this limitation also holds for paper-and-pencil tests.

#### CHALLENGES FOR FUTURE STUDIES

Future studies are required to increase both the theoretical and clinical relevance of tasks where no compensation is allowed. Their theoretical relevance could be increased by better defining the role played by general cognitive impairments in determining the performance of a single patient. Their clinical relevance can be increased by addressing three main questions. One relates to the incidence of subclinical neglect and to the factors resulting in the implementation of compensatory strategies in neglect patients. This question could be primarily answered by testing larger samples of patients. A second question regards the sensitiveness of these methods in disability prediction. This could be answered by implementing instruments to quantitatively determine performance across several, highly demanding, everyday life tasks. Within this specific domain, it would be interesting to explore, by analogy, whether extinction in computer-based tasks is coupled with contralesional impairments in complex environments when several ipsilesional distracters are presented. The third question relates to understanding which approach, among the few options available, is more sensitive (e.g., Bonato et al., 2010, 2012a vs. Deouell et al., 2005 vs. Rengachary et al., 2009). Regardless of whether computer-based testing is used, it seems important that future studies take advantage of the contra-ipsilesional comparison to obtain more sensitive tests.

The last step, and potentially the most difficult one, would involve implementing and testing successful rehabilitation procedures, which could even adopt a complex paradigm similar to the one used for the diagnosis. As noted elsewhere (Erez et al., 2009; Bonato et al., 2012a), only by coupling effective rehabilitation procedures with sensitive assessment it is possible to guarantee that any potential improvements in a patient's performance are captured by the testing methods. More sensitive instruments will help to determine the most effective solutions to reduce impairment and disability in patients affected by this syndrome, which fascinates researchers but is a major obstacle in a patient's steep and long road back to recover autonomy (Katz et al., 1999).

[1]Neuropsychologists interested in receiving and developing the E-prime script adopted for stimuli presentation in our studies can write to mario.bonato@unipd.it


## ACKNOWLEDGMENTS

This study was supported by a grant from "Compagnia di San Paolo" (Neuroscience Program) for the project entitled "Modulation of attention and spatial awareness by concurrent task demands: implications for right hemisphere stroke patients." The author is grateful to S. Cutini, K. Priftis, and M. Ranzini for their valuable comments and suggestions.


## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/Human_Neuroscience/10.3389/fnhum.2012.00195/abstract

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**Conflict of Interest Statement:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 13 February 2012; accepted: 14 June 2012; published online: 17 July 2012.*
*Citation: Bonato M (2012) Neglect and extinction depend greatly on task demands: a review. Front. Hum. Neurosci.* ***6****:195. doi: 10.3389/fnhum.2012.00195*

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 10 August 2012
doi: 10.3389/fnhum.2012.00230

# Neuroanatomical dissections of unilateral visual neglect symptoms: ALE meta-analysis of lesion-symptom mapping

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Unilateral visual neglect is commonly defined as impaired ability to attend to stimuli presented on the side of visual space contralateral to the brain lesion. However, behavioral analyses indicate that different neglect symptoms can dissociate. The neuroanatomy of the syndrome has been hotly debated. Some groups have argued that the syndrome is linked to posterior parietal cortex lesions, while others report damage within regions including the superior temporal gyrus, insula, and basal ganglia. Several recent neuroimaging studies provide evidence that heterogeneity in the behavioral symptoms of neglect can be matched by variations in the brain lesions, and that some of the discrepancies across earlier findings might have resulted from the use of different neuropsychological tests and/or varied measures within the same task for diagnosing neglect. In this paper, we review the evidence for dissociations between both the symptoms and the neural substrates of unilateral visual neglect, drawing on ALE (anatomic likelihood estimation) meta-analyses of lesion-symptom mapping studies. Specifically, we examine dissociations between neglect symptoms associated with impaired control of attention across space (in an egocentric frame of reference) and within objects (in an allocentric frame of reference). Results of ALE meta-analyses indicated that, while egocentric symptoms are associated with damage within perisylvian network (pre- and postcentral, supramarginal, and superior temporal gyri) and damage within sub-cortical structures, more posterior lesions including the angular, middle temporal, and middle occipital gyri are associated with allocentric symptoms. Furthermore, there was high concurrence in deficits associated with white matter lesions within long association (superior longitudinal, inferior fronto-occipital, and inferior longitudinal fasciculi) and projection (corona radiata and thalamic radiation) pathways, supporting a disconnection account of the syndrome. Using this evidence we argue that different forms of neglect link to both distinct and common patterns of gray and white matter lesions. The findings are discussed in terms of functional accounts of neglect and theoretical models based on computational studies of both normal and impaired attention functions.

**Keywords: unilateral neglect, lesion-symptom mapping, allocentric, egocentric, spatial attention**

## INTRODUCTION

The complexity of the visual world requires us to have the ability to select and process behaviorally relevant stimuli while ignoring the rest of the scene. We also need to have the capacity to shift attention between different elements as we search for relevant stimuli. The cognitive processes that underlie these abilities are collectively known as visuospatial attention. These cognitive mechanisms are indispensable for numerous daily activities, as illustrated by the immense problems experienced by individuals suffering from visuospatial deficits after brain damage. The most widely studied disorder of visuospatial attention is unilateral visual neglect (a lack of awareness of space contralateral to the side of brain damage; Heilman and Valenstein, 1979). In extreme cases unilateral neglect manifests itself when patients ignore food on one half of their plates or dress only half of their body. The unilateral neglect syndrome has a significant impact on daily activities and is correlated with poor recovery and return to independent living following the stroke (e.g., Campbell and Oxbury, 1976; Denes et al., 1982; Luaute et al., 2006). This disorder not only has a significant impact on the overall outcome following brain damage but also has proved to be difficult to understand and treat (e.g., Kerkhoff, 2001; Parton et al., 2004; Singh-Curry and Husain, 2010).

In the past three decades, there has been much clinical interest in understanding both cognitive symptoms and the underlying lesion anatomy of unilateral neglect. Notably, many important insights into the functional and structural organization of the neural networks involved in visuospatial attention come from neuropsychological studies examining patients with cognitive deficits associated with unilateral neglect. Specifically, these reports support notion that a distributed neuronal network of frontal and parietal areas, the fronto-parietal network, controls, and allocates visual attention (e.g., Mesulam, 1981; Corbetta and Shulman, 2002). However, the neuroanatomy of the syndrome has been hotly debated with various groups presenting different arguments for critical lesion site associated with unilateral neglect. Interestingly, the behavioral analyses indicate that unilateral neglect is a heterogeneous disorder and different neglect symptoms can dissociate, both within and across patients (e.g., Humphreys and Riddoch, 1994, 1995; Walker and Young, 1996; Doricchi and Galati, 2000; Olson, 2003). Our aim here was to provide an overall review and statistical analysis of the neuroanatomical findings, focusing on whether heterogeneity in the behavioral symptoms of neglect can be matched by variations in the brain lesions associated with different deficits. We ask whether some of the discrepancies across findings might have resulted from a failure to take into account the behavioral dissociations between patients.

The textbook diagnosis of unilateral neglect is made when patients fail to attend to stimuli presented on the side of space contralateral to their lesions (Heilman and Valenstein, 1979). However, this diagnosis does not take into account that unilateral neglect represents a complex syndrome with different patients showing a varied combination of impairments (Kerkhoff, 2001; Buxbaum et al., 2004). Although unilateral visual neglect is the most commonly diagnosed problem, the presence of neglect symptoms in different modalities has been also reported, though the prevalence varies across patients (Halligan and Marshall, 1994b; Vuilleumier et al., 1998; Kerkhoff, 2001; Hillis et al., 2005; Marsh and Hillis, 2008). Dissociations between symptoms of neglect syndrome have also been found for different sectors of space and the severity of deficits observed in individual patients depends on the magnitude and type of cognitive process affected. For example the extent of visuospatial impairments characteristic of neglect may be exacerbated by deficits in non-spatial cognitive process (Singh-Curry and Husain, 2010) and difficulty in assessment of neglect can be linked to the fact that some heterogeneity across tasks might be due to differences in (non-spatial) attentional demands (see for example Bonato et al., 2010; Bonato et al., 2012). Overall the heterogeneous deficits associated with unilateral neglect syndrome can be categorized into spatial (e.g., spatial attention, spatial bias, and visuospatial short term memory) and non-spatial (e.g., target detection, reorienting, and overall vigilance) impairments (for a recent review, see Corbetta and Shulman, 2011). Due to the variety of cognitive deficits contributing to neglect, the diagnosis of the syndrome based on any one single clinical measure may obscure the heterogeneity of symptoms. Dissociable cognitive deficits within the neglect syndrome have been previously reported both across a variety of different measures (e.g., line cancelation versus bisection) and even within the same task, perhaps depending on the way stimuli are spatially represented (Buxbaum et al., 2004; Rorden et al., 2006; Chechlacz et al., 2010; Verdon et al., 2010; Bickerton et al., 2011). Importantly, the heterogeneity in the cognitive deficits and symptoms reported in unilateral neglect patients can be matched by variations in the brain lesions associated with these different cognitive problems (Hillis et al., 2005; Mannan et al., 2005; Rorden et al., 2006; Kleinman et al., 2007; Butler et al., 2009; Malhotra et al., 2009; Medina et al., 2009; Rossit et al., 2009; Chechlacz et al., 2010; Verdon et al., 2010). This is of particular significance as it could account for the discrepancies across earlier studies using lesion-symptom mapping, which might have resulted from a failure to take into account the behavioral dissociations between patients (see also Rorden et al., 2006; Saj et al., 2012). Specifically, some groups have previously argued that the syndrome is linked to damage to the posterior parietal cortex, while others have reported damage within brain regions including the superior temporal gyrus, insula, and basal ganglia (on the one hand, see Vallar and Perani, 1986; Mort et al., 2003; Vallar et al., 2003; on the other, see Karnath, 2001; Karnath et al., 2001, 2004a). It should be noted that neglect symptoms often observed in acute stroke patients with sub-cortical lesions including the basal ganglia and thalamus (e.g., Vallar and Perani, 1986; Karnath et al., 2002) have been linked to dysfunction (abnormally perfused but structurally intact brain tissue) of cortical areas such as inferior parietal lobule and/or superior temporal gyrus (e.g., Hillis et al., 2002; Karnath et al., 2005). Thus direct contribution of the sub-cortical lesion to neglect is still debatable.

The most common tests used to diagnose neglect include various cancelation, line bisection, word reading, and copying scenes. Depending on their design, the tests measure deficits of spatial attention either across space in relation to the body (in an egocentric frame of reference; Riddoch and Humphreys, 1983; Doricchi and Galati, 2000) and/or across parts within objects (in an allocentric frame of reference; Walker and Young, 1996; Walker et al., 1996; Doricchi and Galati, 2000; Olson, 2003; Kleinman et al., 2007). Several different cancelation tests have been used to measure the ability to attend to stimuli presented on the right and left side of visual space (see for example **Figures 1A–C**). Typically such tests are administered by asking patients to cross targets evenly distributed on a centrally placed sheet of paper. In contrast to exceptions such as the line crossing test (Albert, 1973; **Figure 1C**), cancelation measures often require participants to select targets appearing amongst mixed sets of distractors (Mesulam, 1985; Gauthier et al., 1989; Halligan et al., 1989; **Figures 1A,B**). Perhaps not surprisingly, since the tests involve both target detection and selection, it has been demonstrated that these are more sensitive to mild to moderate symptoms than tasks such as line crossing (Vanier et al., 1990). Other common clinical tasks involve drawing and copying, which requires both producing elements within an egocentric frame whilst also aligning parts in their correct co-locations, perhaps using allocentric coding (e.g., either to code parts relative to a whole object or objects relative to one another; see Ishiai et al., 1993; **Figure 1D**; Ogden, 1985; **Figure 1H**). Assessments which attempt to behaviorally tease apart egocentric and allocentric symptoms include gap detection tests, such as the Ota test (Ota et al., 2001; Hillis et al., 2005; Medina et al., 2009; **Figure 1E**) and the Apples Cancelation test (Chechlacz et al., 2010; Bickerton et al., 2011; Humphreys et al., 2011; **Figure 1F**), and also word reading tests (Subbiah and Caramazza, 2000; Medina et al., 2009; Ptak et al., 2012). Gap detection tests are administered by asking patients to cross only full targets (e.g., full circles and full apples as illustrated in **Figures 1E,F**). Egocentric deficits are then measured by counting missing targets on either left or right side of the page while allocentric deficits are measured by counting false-positive responses (i.e., by crossing out distractors with either left or right openings; see **Figures 1E,F**). Finally, line bisection (Heilman and Valenstein, 1979; **Figure 1G**) typically involves asking patients to mark the middle of a series of horizontally presented lines. Some researchers have suggested that bisection is not a sensitive

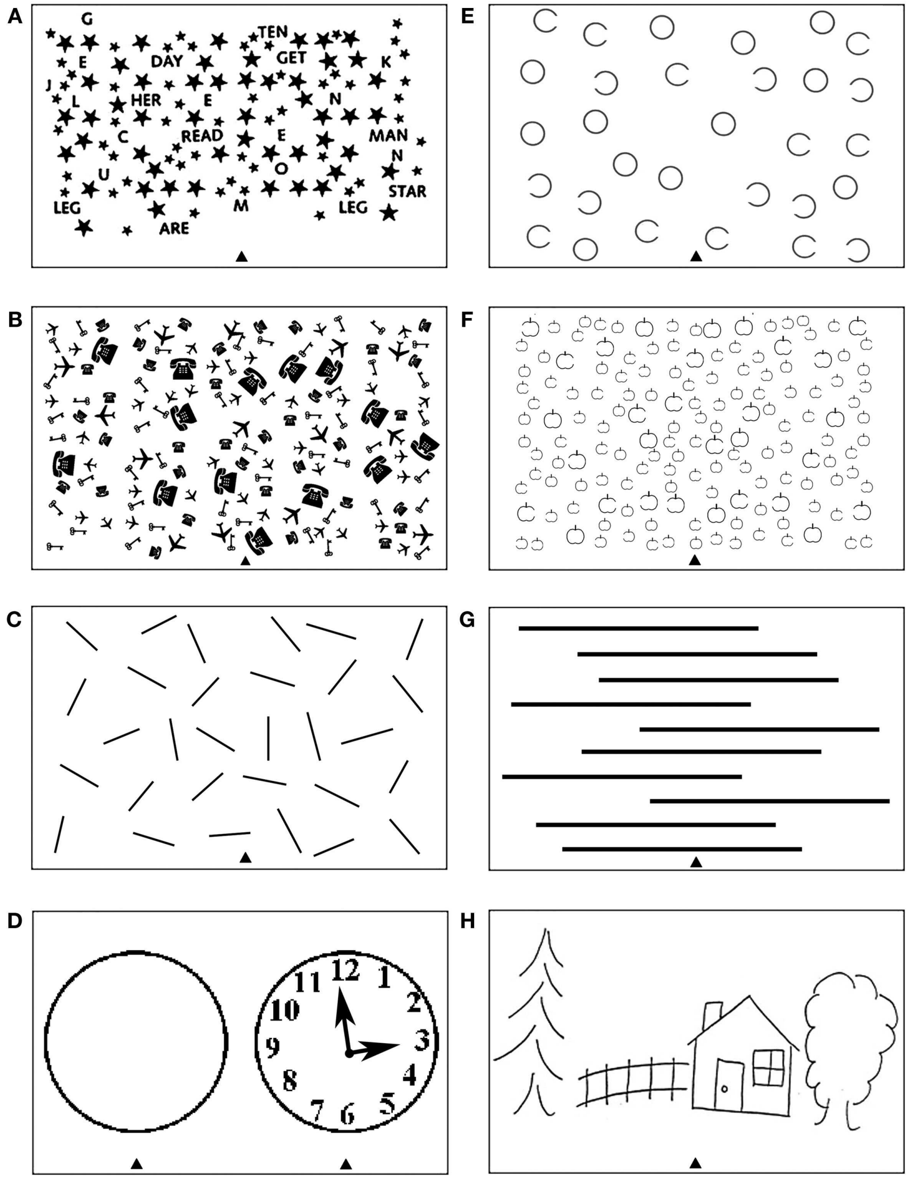


**FIGURE 1 | Examples of tests frequently used to diagnose heterogeneous symptoms associated with unilateral visual neglect, which can provide measure of deficits associated with impaired control of attention either (A–D) across space, i.e., egocentric frame of reference and/or (E–H) within objects, i.e., allocentric frame of reference (see Introduction for further details).** Common cancelation tests: **(A)** star cancelation, **(B)** key cancelation, and **(C)** line crossing, all administered by asking patients to cross targets (small stars, keys, or lines respectively) evenly distributed on the centrally placed sheet of paper – deficits are measured by target omissions on either left or right side of space. **(D)** Clock drawing test that can be administered by either asking patients to place numbers on the face of the clock or asking patients to copy the fully drawn clock (the face of the clock or fully drawn clock are centrally presented on the sheet of paper). Gap detection tests: **(E)** Ota test and **(F)** Apples Cancelation, both administered by asking patients to cross only full targets (full circles or full apples respectively) evenly distributed on the centrally placed sheet of paper – deficits are measured by counting missing targets on either left or right side of space as well as false-positive responses, i.e., crossing objects with either left or right openings). **(G)** Line bisection test, which is administered by asking patients to mark middle of a series of horizontally presented lines – deficits are measured by deviation from the center of each line. **(H)** Scene copying task, which is administered by asking patients to copy multi-object scene consisting of several elements horizontally distributed on the centrally presented sheet of paper – deficits are measured by omissions of left or right sided elements of the scene as well as omissions of either left of right side of individual elements/objects).

tool to detect neglect while others have debated whether bisection performance can reflects either deficits in separate coding of the ends of the lines in relation to the patient using an egocentric frame of reference, or the perception of the line as a single object in an allocentric frame of reference (Ferber and Karnath, 2001; Rorden et al., 2006; Chechlacz et al., 2010; Karnath and Rorden, 2012; see also Molenberghs and Sale, 2011 for a contrasting view).

The differences between the various diagnostic tests are of particular relevance if they underlay contrasting results on lesion-symptom mapping. Here we attempted to formally test this based on ALE meta-analyses examining whether there is a concurrence in findings dissociated based on the different neglect measure criteria. While some earlier analyses tended to assess neglect mainly in terms of line bisection tasks or deficits pooled across line bisection and cancelation (Mort et al., 2003; Mannan et al., 2005; Bird et al., 2006), other studies have diagnosed neglect using a battery of tasks which all include some degree of spatial exploration (Karnath et al., 2002, 2004a, 2009, 2011). By contrast, many recent studies following Binder et al.'s (1992) and Rorden et al.'s (2006) suggestion that different neglect symptoms may be associated with damage to discrete brain areas, have made attempts to distinguish the neuroanatomical basis of different neglect symptoms (Binder et al., 1992; Rorden et al., 2006). The emerging evidence indicates that different spatial symptoms of neglect (e.g., within allocentric and egocentric frames of reference) are associated with contrasting brain lesions (Hillis et al., 2005; Medina et al., 2009; Chechlacz et al., 2010; Verdon et al., 2010; Ptak et al., 2012; see below). For example, we have previously demonstrated that, after right hemisphere damage, left allocentric neglect is associated with lesions to the right posterior superior temporal sulcus, angular, middle temporal/inferior temporal, and middle occipital gyri, while left egocentric neglect is linked to more right anterior lesions within perisylvian network including the middle frontal, postcentral, supramarginal, and superior temporal gyri as well as the insula (Chechlacz et al., 2010). Several other research groups have reported similar dissociations (e.g., Hillis et al., 2005; Medina et al., 2009; Verdon et al., 2010; Ptak et al., 2012). Importantly, these dissociations have been noted across a variety of different tasks including gap detection and figure copy tests which can simultaneously measure both symptoms (e.g., Hillis et al., 2005; Medina et al., 2009; Chechlacz et al., 2010) as well as variety of word reading tests (e.g., Medina et al., 2009; Ptak et al., 2012).

It should also be noted that, in addition to the gray matter lesions associated with unilateral neglect, many reports have linked the symptoms of neglect to the presence of white matter lesions, which disrupt connectivity within the brain's attentional networks. This has led some researchers to regard neglect as a disconnection syndrome (Doricchi and Tomaiuolo, 2003; Bartolomeo et al., 2007). Specifically, neglect has been reported following damage to the superior longitudinal (SLF; Doricchi and Tomaiuolo, 2003;Thiebaut de Schotten et al., 2005, 2008; He et al., 2007; Karnath et al., 2009; Shinoura et al., 2009;Chechlacz et al., 2010, 2011; Urbanski et al., 2011), the inferior longitudinal fasciculi (ILF; Bird et al., 2006; Chechlacz et al., 2010; Riddoch et al., 2010), and the inferior fronto-occipital fasciculi (IFOF; Urbanski et al., 2008, 2011; Karnath et al., 2009; Chechlacz et al., 2010; Riddoch et al., 2010).

The lesion-symptom mapping procedures used to understand the neuroanatomical basis of neglect are not un-controversial (see for example Karnath et al., 2004b versus Mort et al., 2004). Traditional lesion-symptom mapping approaches have used lesion overlap/lesion subtraction methods, contrasting lesion maps for different groups of patients categorically defined as having a particular deficit (Damasio and Damasio, 1989). More recent procedures have been developed to enable continuous behavioral measures to be used and formal statistical comparisons to be made (voxel-based lesion-symptom mapping, VLSM or voxel-wise lesion-behavior mapping, VLBM; Bates et al., 2003; Rorden et al., 2007, 2009; Karnath et al., 2009; voxel-based morphometry, VBM; Ashburner and Friston, 2000). These emerging approaches facilitate the direct quantitative examination of dissociations between the heterogeneous symptoms that contribute to disorders such as unilateral neglect (e.g., Medina et al., 2009; Chechlacz et al., 2010; Verdon et al., 2010).

In the current study, we review the evidence for dissociations between both the symptoms and the neural substrates of unilateral visual neglect, drawing on meta-analyses of published lesion-symptom mapping studies. The work evaluates the concurrence between findings from various lesion-symptom mapping studies examining the neuroanatomy of the neglect syndrome by employing coordinate based anatomic likelihood estimation (ALE) meta-analyses. Specifically, our analyses examined (i) the overall convergence between the results from different lesion-symptom mapping studies concerned specifically with visual neglect (we included here all studies that matched this criterion regardless of the assessment tools they employed), (ii) the concurrence in the damage within white matter pathways associated with neglect symptoms, and (iii) the concurrence in lesion sites associated with deficits in the control of attention either across space (egocentric frame of reference) or within objects (allocentric frame of reference), to evaluate whether behavioral dissociations within the neglect syndrome are matched by different lesion patterns. For this last analysis we fractionated data from studies using different assessment tools to measure neglect symptoms. It should be noted that our classification of the differential assessments of neglect depends on inferences about the underlying processes. For example, we assume that tasks such as line cancelation require that multiple stimuli are coded in relation to the patient's body (e.g., using an egocentric reference frame). In contrast, tasks such as line bisection could reflect either separate coding of the perceived ends of the lines in relation to the patient (i.e., egocentric spatial coding) or perception of the line as a single object (i.e., allocentric spatial coding; Humphreys and Riddoch, 1994, 1995). Thus we examined concurrence in findings based on both line bisection and other measures of within object deficits grouped together as well as treating them as separate behavioral measures.

Based on the evidence from our meta-analyses we argue that different forms of neglect link to both distinct and common patterns of gray and white matter lesions. The results provide insights into the discrepancies that exist between different reports examining the lesion site(s) associated with unilateral visual neglect as well as providing evidence for disconnection accounts of the syndrome. The findings are discussed in terms of functional accounts of neglect and theoretical models based on computational modeling of both normal and impaired attention functions.

## MATERIALS AND METHODS

### LITERATURE SEARCH AND SELECTION CRITERIA

For the purpose of the current study we conducted a systematic literature search to indentify relevant papers reporting the neuronal substrates of the heterogeneous symptoms associated with unilateral visual neglect. All searches were carried out using PubMed[1] and Web of Knowledge[2] databases. The database searches were conducted using the following keywords: (visual neglect OR unilateral neglect OR spatial neglect OR line bisection OR target cancelation) AND (anatomy OR neuroanatomy OR tractography OR diffusion tensor imaging OR perfusion weighted imaging OR diffusion weighted imaging OR lesion-symptom mapping OR VBM OR VLSM OR computed tomography OR magnetic resonance imaging). In addition, we also identified studies through references cited by review papers and through references from relevant papers found via database searches.

The inclusion criteria were as follows: (1) studies published in peer-reviewed journals; (2) use of lesion-symptom mapping approaches as defined in the Introduction, i.e., either lesion subtraction methods (based on either comparisons between the lesion overlap plots from patients with and without neglect or formal subtraction plots between the groups), VBM, or VLSM/VLBM methods; (3) the studied sample consisted of mainly brain injured patients and both experimental and control patients groups were described/defined clearly; (4) the findings were reported using spatial coordinates in either Montreal Neurological Institute (MNI; Evans et al., 1993) or Talairach space (Talairach and Tournoux, 1988); (5) papers defined neglect based on common assessment tools including at least one of the following: target cancelation, bisection, word reading, and figure copy (see **Figure 1**). In cases where standard coordinates were not reported in the lesion-symptom analyses, we contacted the authors to request this information. If the authors agreed to provide the information, the studies were included in our meta-analyses (we thank the following authors for providing these additional data on our request: Bird et al., 2006; Medina et al., 2009; Eschenbeck et al., 2010; Karnath et al., 2011; Vossel et al., 2011; Saj et al., 2012). We excluded studies that were (1) not published in English; (2) reported either preliminary findings or conference presentations; (3) single case studies or multiple-case studies based on patients pre-selected according to either lesion location or cognitive deficits without comparison to appropriate patient control groups (studies using traditional lesion overlap analysis based on overlapping the lesion maps of patients with certain deficit and defining an area of maximum overlap as the brain region critically sub-serving the cognitive function impaired in the patients); (4) functional neuroimaging studies (fMRI, PET, etc.) in either patients or healthy controls.

Following the literature search, we created lists of reported peak coordinates (foci) for each individual study entered into our ALE meta-analyses. In **Table 1** under Analysis 1 we list the number of all foci as reported/defined by the authors of each study based on all relevant analyses of the neuroanatomy of neglect (for example if authors report both peak coordinates from lesion subtraction and VLSM, all these were listed). We entered into analysis all coordinates that were given by the authors to describe their results, i.e., all coordinates listed in text, tables, or figures excluding only these that were repeated for example both in text and tables, etc. In case of studies that do not provide a single peak coordinate but border coordinates of maximum overlap for neglect group versus controls (studies exclusively based on lesion subtraction analyses), we entered an "averaged" peak to prevent misrepresentation of data and inflating results by a number of peaks entered into analysis. In the subsequent analyses we only used the foci that were relevant to either specific types of neglect (these were selected based on reported measures of neglect as listed in **Table 5**) and/or specifically white matter substrates of neglect.

### DATA ANALYSES – DESIGN

In order to examine dissociations between both the symptoms and the neural substrates of neglect, we performed several different ALE meta-analyses (see below for Materials and Methods description). The relevant papers included in these analyses are listed in **Table 1** (see also Results). *Analysis 1* included data from all relevant papers reporting the neural substrates of unilateral visual neglect considering it as a unitary syndrome, not separating out patients according to different types of symptom as well as not differentiating between gray versus white matter lesions associated with the syndrome. Specifically, in *Analysis 1* we included all the data from studies examining neglect, diagnosing neglect either from one of the commonly used tests or a battery of measures without applying any prior selection criteria. *Analyses 2* and *Analysis 3* directly examined the link between the heterogeneity of neglect and any associated neural substrates by fractionating lesion sites associated with deficits in allocating attention either across space (using an egocentric frame of reference, *Analysis 2*) or within objects (using an allocentric frame of reference, *Analysis 3*). The data included in *Analysis 2* came from studies that defined neglect exclusively using either target cancelation tests or both target cancelation and figure copying tests, measuring the patient's ability to attend to stimuli presented on the right and left side of egocentric space (see **Figure 1**; **Table 5**). In contrast the data included in *Analysis 3* came from studies that defined neglect using a variety of tests measuring spatial deficits in relation to an allocentric frame of reference. This analysis included data from studies that employed different gap detection tests, multi-object scene copying tasks, word reading tests, and line bisection (see **Figure 1**; **Table 5**). Line bisection tests (**Figure 1G**) are administered by asking patients to mark the middle of horizontally presented lines and it has been suggested that the performance on this test may reflects deficits in the perception of the line as a single object (i.e., coding space within an allocentric frame of reference; Chechlacz et al., 2010; Karnath and Rorden, 2012). However, despite the fact that neglect symptoms measured using line bisection can dissociate from these measured by target cancelation (Ferber and Karnath, 2001; Rorden et al., 2006; for an opposite view however, see Molenberghs and Sale, 2011), it has been suggested that bisection deficits can reflect problems in coding of the perceived ends of the lines in relation to the patient (i.e., within an egocentric frame of reference); for example, it has been observed that the magnitude of any asymmetries in bisection increase when the lines are presented further to the contralesional side of a patient's body (Riddoch and Humphreys, 1983). Consequently we also examined the concurrence in lesion sites associated with poor performance on line bisection test only (*Analysis 4*)

[1] http://www.ncbi.nlm.nih.gov/pubmed
[2] http://apps.webofknowledge.com

followed by analysis of concurrence in lesion sites associated more specifically with deficits in the control of attention within objects (in an allocentric frame of reference) after excluding reports using line bisection (*Analysis 5*). As recently much attention has been given to white matter lesions and disconnection accounts of the syndrome, *Analysis 6* was performed on a subset of data specifically describing the link between neglect symptoms and white matter damage based on data from identified studies diagnosing neglect based on either one of the commonly used tests or on battery of neglect diagnostic measures without applying any selection criteria. Finally, *Analyses 7* and *Analysis 8* examined the link between white matter lesions and the specific symptoms of neglect associated with the control of attention either in relation the patient's body (egocentric deficits, *Analysis 7*) or within objects (allocentric deficits, *Analysis 8*).

### ALE META-ANALYSES

We performed the meta-analyses using BrainMap GingerALE 2.1 software[3] to estimate the concurrence between the reported neuroanatomy of unilateral visual neglect from different published studies and to examine the evidence for dissociations between neglect symptoms and the underlying neural substrates of the syndrome. The inputs for the different analyses were as defined above and all source papers are listed in **Table 1**. We performed all analyses in MNI space and if necessary we converted coordinated reported by authors in Talairach space to MNI space using the coordinate conversion tool implemented in GingerALE software.

Traditionally GingerALE is used for activation likelihood estimation (ALE) meta-analyses using as inputs coordinates describing foci identified in functional neuroimaging studies (Turkeltaub et al., 2002; Laird et al., 2005). However, GingerALE also performs anatomic likelihood (ALE) meta-analyses (Ellison-Wright et al., 2008; Glahn et al., 2008; Di et al., 2009; Ferreira et al., 2011) that assess the overlap between anatomical foci identified by different research groups using voxel-wise analyses of structural neuroimaging data, as for example here the foci obtained based on various lesion-symptom mapping approaches. In the current paper we applied the revised version of the ALE method (Eickhoff et al., 2009) after implementing the modified ALE algorithm design to minimize within-experiment and within-group effects (Turkeltaub et al., 2012). The ALE algorithm of Turkeltaub et al. (2012) was used here to control for dependent within-group effects as some of the papers included here report findings based on different data analysis approaches (e.g., lesion overlap and VLSM) or included data based on cognitive measures obtained in the same group of patients but at two separate time points (e.g., in the subacute and chronic phases following stroke) and these were input as separate coordinates lists (i.e., separate experiments; see **Table 1**). The ALE approach models the anatomical foci from different published reports (here studies listed in **Table 1**) as Gaussian probability density distribution at a given coordinate. First Gaussian widths are calculated based on the expected between-template variability in spatial normalization and the relationship between the sample size and inter-subject localization uncertainty. Next for each individual experiment (here referring to single analysis reported in each lesion-symptom mapping paper), a Modelled Activation Map (MA map) is calculated by taking the voxel-wise union of the Gaussians for all the foci reported by that specific experiment (Eickhoff et al., 2009). Following that, an ALE map (experimental ALE map) is generated as the voxel-wise union of all MA maps from the full datasets (all included experiments from published studies). To differentiate true concurrence of foci from random clustering (random spatial associations), the calculated experimental ALE map is tested against ALE null distribution maps generated by permutation test to represent the same number of foci as the real analysis but randomly redistributed throughout the brain. In the current study we used a statistical threshold of $p < 0.05$ FDR (False Discovery Rate) corrected for multiple comparisons and a minimum cluster size of 200 $mm^3$ (Eickhoff et al., 2009). ALE maps were overlaid onto the MNI template using MRIcron software MRICro (Chris Rorden, McCausland Center for Brain Imaging, University of South Carolina, SC, USA). The anatomical localization of the significant clusters identified by the meta-analyses was based on the Duvernoy Human Brain Atlas (Duvernoy et al., 1991), the Woolsey Brain Atlas by (Woolsey et al., 2008), and the Mori MRI Atlas of Human White Matter (Mori, 2005).

[3]http://brainmap.org/

## RESULTS

**Table 1** presents a list and details of all the reviewed studies that fulfilled the inclusion criteria as specified in the Section "Materials and Methods" and were included in ALE meta-analyses. All studies that were included in the ALE meta-analyses presented below reported the neuronal substrates of left unilateral visual neglect. Twenty-two studies (1306 participants; total of 32 experiments with 238 relevant foci identified) that met the inclusion criteria were identified and their data entered into *Analysis 1* (overall concurrence in the reported neural substrates of unilateral visual neglect; not applying any selection criteria with regards to the tests of neglect).

For *Analysis 2* we identified 15 studies (1043; total of 20 experiments with 149 relevant foci identified; **Table 1**) that met the selection criteria and for *Analysis 3* we included ten studies (688 participants; total of 13 experiments with 75 relevant foci identified; **Table 1**) examining concurrence in the neuronal substrates associated with egocentric and allocentric neglect respectively. We included four studies (164 participants; total of 4 experiments with 13 relevant foci identified; **Table 1**) reporting the neural substrates associated with asymmetric line bisection (*Analysis 4*) and six studies (524 participants; total of 9 experiments with 62 relevant foci; **Table 1**) reporting the neural substrates associated with deficits in the control of attention within objects – in this case using measures excluding line bisection (*Analysis 5*). Ten of the identified studies (554 participants; total of 16 experiments with 101 relevant foci identified) reported neglect associated with damage within white matter (not applying any selection criteria with regards to the tests of neglect) and these data were included in *Analysis 6* (**Table 1**). Seven of these studies (438 participants; total of 11 experiments with 54 relevant foci identified; **Table 1**) specifically reported white matter lesions associated with egocentric symptoms (included in *Analysis 7*) and four studies (332 participants;

**Table 1 | Studies included in the ALE meta-analyses.**

| No | Study | Type of patients/time | No. of patients‡ | Modality | Methods | | No. of Foci* |
|---|---|---|---|---|---|---|---|
| | | | | | Lesion reconstruction | Data analysis* | |
| **ANALYSIS 1** | | | | | | | |
| 1 | Bird et al. (2006) | SO/AS | 15 | CT, MRI | M | LO/LS | 1 |
| 2 | Chechlacz et al. (2010) | SP/CH | 38 (19) | MRI, DTI | A | VBM, VLSM, VA-FA | 55 |
| 3 | Chechlacz et al. (2011) | SP/CH | 50 | MRI | A | VBM | 9 |
| 4 | Chechlacz et al. (2012) | SO/AS and CH** | 160 | CT | A | VBM (AS and CH) | 30 |
| 5 | Doricchi and Tomaiuolo (2003) | SO/AS | 31 | CT, MRI | M | LO/LS, VLSM | 12 |
| 6 | Eschenbeck et al. (2010) | SO/AS | 68 | CT, MRI | M | VLSM | 5 |
| 7 | Golay et al. (2008) | SO/AS | 50 | CT, MRI | M | VLSM | 2 |
| 8 | Grimsen et al. (2008) | SO/AS + CH | 21 | CT, MRI | M | LO/LS | 6 |
| 9 | Karnath et al. (2001) | SO/AS | 50 | CT, MRI | M | LO/LS | 4 |
| 10 | Karnath et al. (2002) | SO/AS | 32 | CT, MRI | M | LO/LS | 7 |
| 11 | Karnath et al. (2004a) | SO/AS | 140 | CT, MRI | M | LO/LS, VLSM | 2 |
| 12 | Karnath et al. (2011) | SO/AS and CH** | 54 | CT, MRI | M | VLSM (AS and CH) | 1 |
| 13 | Lee et al. (2010) | SO/AS | 42 | SPECT | A | VLSM | 12 |
| 14 | Medina et al. (2009) | SO/AS | 171 | PWI, DWI | M | VLSM | 4 |
| 15 | Molenberghs and Sale (2011) | SO/AS | 44 | MRI | A | VLSM | 2 |
| 16 | Mort et al. (2003) | SO/AS | 35 | MRI | M | LO/LS | 3 |
| 17 | Ptak et al. (2012) | SO/AS | 54 | CT, MRI | M | LO/LS, VLSM | 20 |
| 18 | Rorden et al. (2006) | SO/AS | 22 | CT, MRI | M | LO/LS | 2 |
| 19 | Saj et al. (2012) | SO/AS and CH** | 69 | MRI | M | VSLM (AS and CH) | 4 |
| 20 | Urbanski et al. (2011) | SO/AS + CH | 24 (12) | DTI | A | VA-FA | 11 |
| 21 | Verdon et al. (2010) | SO/AS | 80 (41) | CT, MRI | M | LO/LS, VSLM | 9 |
| 22 | Vossel et al. (2011) | SO/AS | 56 | CT, MRI | M | VLSM | 5 |
| **ANALYSIS 2** | | | | | | | |
| 1 | Chechlacz et al. (2010) | SP/CH | 38 (19) | MRI, DTI | A | VBM, VLSM, VA-FA | 55 |
| 2 | Chechlacz et al. (2011) | SP/CH | 50 | MRI | A | VBM | 9 |
| 3 | Chechlacz et al. (2012) | SO/AS and CH** | 160 | CT | A | VBM (AS and CH) | 17 |
| 4 | Grimsen et al. (2008) | SO/AS + CH | 21 | CT, MRI | M | LO/LS | 5 |
| 5 | Karnath et al. (2001) | SO/AS | 50 | CT, MRI | M | LO/LS | 4 |
| 6 | Karnath et al. (2002) | SO/AS | 32 | CT, MRI | M | LO/LS | 7 |
| 7 | Karnath et al. (2004a) | SO/AS | 140 | CT, MRI | M | LO/LS, VLSM | 2 |
| 8 | Karnath et al. (2011) | SO/AS and CH** | 54 | CT, MRI | M | VLSM (AS and CH) | 1 |
| 9 | Medina et al. (2009) | SO/AS | 171 | PWI, DWI | M | VLSM | 1 |
| 10 | Molenberghs and Sale (2011) | SO/AS | 44 | MRI | A | VLSM | 1 |
| 11 | Ptak et al. (2012) | SO/AS | 54 | CT, MRI | M | VLSM | 4 |
| 12 | Saj et al. (2012) | SO/AS and CH** | 69 | MRI | M | VSLM (AS and CH) | 2 |
| 13 | Urbanski et al. (2011) | SO/AS + CH | 24 (12) | DTI | A | VA-FA | 3 |
| 14 | Verdon et al. (2010) | SO/AS | 80 | CT, MRI | M | VSLM | 5 |
| 15 | Vossel et al. (2011) | SO/AS | 56 | CT, MRI | M | VLSM | 3 |
| **ANALYSIS 3** | | | | | | | |
| 1 | Chechlacz et al. (2010) | SP/CH | 38 (19) | MRI, DTI | A | VBM, VLSM, VA-FA | 29 |
| 2 | Chechlacz et al. (2012) | SO/AS and CH** | 160 | CT | A | VBM | 17 |
| 3 | Grimsen et al. (2008) | SO/AS + CH | 21 | CT, MRI | M | LO/LS | 1 |
| 4 | Lee et al. (2010) | SO/AS | 42 | SPECT | A | VLSM | 5 |
| 5 | Medina et al. (2009) | SO/AS | 171 | PWI, DWI | M | VLSM | 3 |
| 6 | Molenberghs and Sale (2011) | SO/AS | 44 | MRI | A | VLSM | 1 |
| 7 | Ptak et al. (2012) | SO/AS | 54 | CT, MRI | M | VLSM | 11 |
| 8 | Rorden et al. (2006) | SO/AS | 22 | CT, MRI | M | LO/LS | 2 |

*(Continued)*

**Table 1 | Continued**

| No | Study | Type of patients/time | No. of patients‡ | Modality | Methods | | No. of Foci* |
|---|---|---|---|---|---|---|---|
| | | | | | Lesion reconstruction | Data analysis* | |
| 9 | Verdon et al. (2010) | SO/AS | 80 | CT, MRI | M | VSLM | 1 |
| 10 | Vossel et al. (2011) | SO/AS | 56 | CT, MRI | M | VLSM | 2 |
| **ANALYSIS 4** | | | | | | | |
| 1 | Lee et al. (2010) | SO/AS | 42 | SPECT | A | VLSM | 5 |
| 2 | Molenberghs and Sale (2011) | SO/AS | 44 | MRI | A | VLSM | 1 |
| 3 | Rorden et al. (2006) | SO/AS | 22 | CT, MRI | M | LO/LS | 2 |
| 4 | Vossel et al. (2011) | SO/AS | 56 | CT, MRI | M | VLSM | 2 |
| **ANALYSIS 5** | | | | | | | |
| 1 | Chechlacz et al. (2010) | SP/CH | 38 (19) | MRI, DTI | A | VBM, VLSM, VA-FA | 29 |
| 2 | Chechlacz et al. (2012) | SO/AS and CH** | 160 | CT | A | VBM | 17 |
| 3 | Grimsen et al. (2008) | SO/AS + CH | 21 | CT, MRI | M | LO/LS | 1 |
| 4 | Medina et al. (2009) | SO/AS | 171 | PWI, DWI | M | VLSM | 3 |
| 5 | Ptak et al. (2012) | SO/AS | 54 | CT, MRI | M | VLSM | 11 |
| 6 | Verdon et al. (2010) | SO/AS | 80 | CT, MRI | M | VSLM | 1 |
| **ANALYSIS 6** | | | | | | | |
| 1 | Chechlacz et al. (2010) | SP/CH | 38 (19) | MRI, DTI | A | VBM, VLSM, VA-FA | 37 |
| 2 | Chechlacz et al. (2011) | SP/CH | 50 | MRI | A | VBM | 3 |
| 3 | Chechlacz et al. (2012) | SO/AS and CH | 160 | CT | A | VBM | 12 |
| 4 | Doricchi and Tomaiuolo (2003) | SO/AS | 31 | CT, MRI | M | LO/LS, VLSM | 11 |
| 5 | Golay et al. (2008) | SO/AS | 50 | CT, MRI | M | VLSM | 1 |
| 6 | Karnath et al. (2002) | SO/AS | 32 | CT, MRI | M | LO/LS | 3 |
| 7 | Mort et al. (2003) | SO/AS | 35 | MRI | M | LO/LS | 1 |
| 8 | Ptak et al. (2012) | SO/AS | 54 | CT, MRI | M | VLSM | 6 |
| 9 | Urbanski et al. (2011) | SO/AS + CH | 24 (12) | DTI | A | VA-FA | 11 |
| 10 | Verdon et al. (2010) | SO/AS | 80 (41) | CT, MRI | M | LO/LS, VSLM | 5 |
| **ANALYSIS 7** | | | | | | | |
| 1 | Chechlacz et al. (2010) | SP/CH | 38 (19) | MRI, DTI | A | VBM, VLSM, VA-FA | 26 |
| 2 | Chechlacz et al. (2011) | SP/CH | 50 | MRI | A | VBM | 3 |
| 3 | Chechlacz et al. (2012) | SO/AS and CH | 160 | CT | A | VBM | 7 |
| 4 | Karnath et al. (2002) | SO/AS | 32 | CT, MRI | M | LO/LS | 3 |
| 5 | Ptak et al. (2012) | SO/AS | 54 | CT, MRI | M | VLSM | 2 |
| 6 | Urbanski et al. (2011) | SO/AS + CH | 24 (12) | DTI | A | VA-FA | 3 |
| 7 | Verdon et al. (2010) | SO/AS | 80 | CT, MRI | M | VSLM | 1 |
| **ANALYSIS 8** | | | | | | | |
| 1 | Chechlacz et al. (2010) | SP/CH | 38 (19) | MRI, DTI | A | VBM, VLSM, VA-FA | 21 |
| 2 | Chechlacz et al. (2012) | SO/AS and CH | 160 | CT | A | VBM | 7 |
| 3 | Ptak et al. (2012) | SO/AS | 54 | CT, MRI | M | VLSM | 4 |
| 4 | Verdon et al. (2010) | SO/AS | 80 | CT, MRI | M | VSLM | 1 |

*‡Numbers in brackets indicate that some of the included data were based on the subset of patients participating in the given study; *the information in the table only includes data analysis methods and number of foci from the identified papers that were included in the ALE meta-analysis; **these studies present separate findings for subacute and chronic phase following stroke (AS and CH) and thus the findings were included as separate experiments (see Materials and Methods); Type of patients: SO, stroke only; SP, stroke plus other brain damaged patients; Time: AS, acute and/or subacute patients; CH, chronic; AS + CH, both subacute and chronic patients were included in the same data analyses presented in the given study; Lesion reconstruction: A, automated/semi-automated; M, manual demarcation of lesion; Neuroimaging modality: CT, computed tomography; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging, mainly structural anatomical scan such as T1- and/or T2-weighted scans); PWI, perfusion weighted imaging; SPECT, single photon emission computed tomography; Data analyses methods: LO/LS, lesion overlap/lesion subtraction plots (please note that all included studies are based on subtraction analysis, i.e., either comparisons between the lesion overlap plots from patients with and without neglect symptoms or formal subtraction plots between patients with and without neglect symptoms; VA-FA, voxel-wise analysis of fractional anisotropy maps; VBM, voxel-based morphometry; VLSM, voxel-based lesion-symptom mapping; findings from the same paper from on separate analyses based on different methods were included as separate experiments (see Materials and Methods).*

**Table 2 | Significant ALE clusters and corresponding MNI coordinates identified in Analysis 1.**

| Cluster | | | ALE value | MNI coordinates | | | No. of Exp.* |
|---|---|---|---|---|---|---|---|
| **No** | **Anatomical label** | **Size (mm$^3$)** | | ***X*** | ***Y*** | ***Z*** | |
| 1 | Right SLF | 5784 | 0.026 | 36 | −36 | 26 | 16 |
| | Right SLF, superior thalamic radiation | | 0.02 | 30 | −24 | 22 | |
| | Right SLF | | 0.017 | 22 | −30 | 24 | |
| | Right inferior parietal lobule (IPL)/BA40 | | 0.016 | 34 | −46 | 34 | |
| | Right superior temporal gyrus/BA 22 | | 0.021 | 54 | −28 | 2 | |
| | Right superior temporal gyrus | | 0.016 | 50 | −22 | −4 | |
| | Right superior temporal gyrus | | 0.015 | 48 | −24 | 14 | |
| | Right superior temporal gyrus | | 0.016 | 60 | 18 | 8 | |
| | Right superior temporal gyrus | | 0.013 | 44 | −34 | 20 | |
| | Right lateral fissure, TPJ junction BA 21/22/39 | | 0.013 | 50 | −38 | 18 | |
| 2 | Right IFOF, superior corona radiata | 1776 | 0.025 | 26 | −10 | 36 | 7 |
| | Right insula/BA 13 | | 0.018 | 36 | −12 | 26 | |
| | Right SLF | | 0.014 | 20 | 0 | 34 | |
| | Right insula/BA 13 | | 0.013 | 36 | −6 | 22 | |
| 3 | Right postcentral/BA 2 and supramarginal gyrus/BA 40 | 1464 | 0.031 | 26 | −40 | 52 | 7 |
| 4 | Right middle temporal gyrus/BA 21 | 1312 | 0.03 | 54 | −64 | 4 | 6 |
| 5 | Right supramarginal gyrus/BA 40, TPJ BA 40/22 | 816 | 0.017 | 56 | −34 | 38 | 5 |
| | Right angular gyrus/BA 39 | | 0.016 | 54 | −48 | 34 | |
| 6 | Right IFOF | 664 | 0.018 | 36 | −46 | 12 | 4 |
| | Right posterior thalamic radiation | | 0.018 | 36 | −42 | 14 | |
| 7 | Right putamen | 544 | 0.017 | 22 | 4 | 8 | 4 |
| 8 | Right putamen | 400 | 0.019 | 20 | 8 | −10 | 3 |
| 9 | Right ILF, IFOF | 368 | 0.018 | 34 | −26 | 4 | 3 |
| 10 | Right precuneus/BA 7 | 336 | 0.019 | 8 | −38 | 18 | 2 |
| 11 | Right middle occipital gyrus/BA 19 | 320 | 0.016 | 34 | −74 | 8 | 2 |
| 12 | Right superior temporal gyrus/BA 22 | 304 | 0.016 | 52 | −2 | −12 | 3 |
| 13 | Right angular gyrus/BA 39 | 240 | 0.016 | 50 | −62 | 30 | 3 |
| 14 | Right middle occipital gyrus/BA 19 | 232 | 0.015 | 38 | −76 | 34 | 2 |
| 15 | Right inferior occipital/lingual BA 18 | 200 | 0.015 | 26 | −86 | −8 | 2 |

**Number of contributing experiments (No, number); BA, Brodmann Area; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; TPJ, temporo-parietal junction.*

total of 7 experiments with 33 relevant foci; **Table 1**) specifically reported white matter lesions associated with allocentric neglect (these were included in *Analysis 8*).

## NEURAL SUBSTRATES OF UNILATERAL VISUAL NEGLECT SYNDROME – ANALYSIS 1

The ALE meta-analysis for the main effect, i.e., the overall concurrence in the reported neural substrates of unilateral visual neglect (not differentiating between either different symptoms or gray versus white matter lesions) revealed 15 significant clusters (**Table 2**; **Figure 2**). However, we found that the agreement between different studies was not very strong with only one cluster showing high convergence with 16 out of 32 experiments contributing and 4 other clusters with 5 or more contributing experiments. The most concurrent cluster was located sub-cortically within long association pathways including the SLF (ALE peaks at MNI 36, −26, 26 and 22, −30, 24) and superior thalamic radiation (ALE peak at MNI 30, −24, 22). Part of this cluster also covered some areas of right cerebral cortex including the superior temporal gyrus (BA 22, ALE peak at MNI 54, −28, 2) and the inferior parietal lobule (BA 40, ALE peak at MNI 34, −46, 34) and extending into TPJ (BA 21/22/39, ALE peak at MNI 50, −38, 18). The four other clusters were located in the right insula (BA 13, ALE peak at MNI 36, −12, 26), the middle temporal gyrus (BA 21 54, −64), the postcentral gyrus (BA2, ALE peak at MNI 26, −40, 52), and the inferior parietal lobule (both supramarginal and angular gyrus/BA 40 and BA 39) extending into TPJ (BA 40/22, ALE peak at MNI 56, −34, 38).

## DISSOCIATING THE NEURAL SUBSTRATES OF EGOCENTRIC AND ALLOCENTRIC NEGLECT – ANALYSES 2–5

The ALE meta-analyses examining concurrence in the lesion sites associated with the control of attention either in relation to the patient's body or within objects (in egocentric or allocentric frames of reference) revealed 16 significant clusters associated with egocentric symptoms and 10 clusters associated with allocentric symptoms (**Table 3**; **Figures 3A,B**). The convergence between studies included in both *Analysis 2* and *Analysis 3* was not as robust as in the case of the white matter analysis reported below but the

**Table 3 | Significant ALE clusters and corresponding MNI coordinates identified in Analyses 2, 3, 4, and 5.**

| Cluster | | | ALE value | MNI coordinates | | | No. of Exp.* |
|---|---|---|---|---|---|---|---|
| **No** | **Anatomical label** | **Size (mm$^3$)** | | ***X*** | ***Y*** | ***Z*** | |
| **ANALYSIS 2** | | | | | | | |
| 1 | Right superior temporal gyrus/BA22 | 2160 | 0.02 | 54 | −28 | 2 | 7 |
| | Right superior temporal gyrus | | 0.017 | 62 | −22 | 8 | |
| | Right insula/BA13 | | 0.014 | 46 | −22 | 14 | |
| | Right superior temporal gyrus/BA22 | | 0.014 | 50 | −20 | −2 | |
| | Right insula/BA13 | | 0.013 | 44 | −14 | 0 | |
| 2 | Right putamen | 1360 | 0.018 | 20 | 4 | 8 | 5 |
| | Right putamen, thalamus | | 0.012 | 22 | −6 | −2 | |
| | Right thalamus | | 0.013 | 22 | −2 | 0 | |
| 3 | Right supramarginal gyrus/BA40 | 640 | 0.018 | 24 | −42 | 52 | 3 |
| 4 | Right caudate | 464 | 0.016 | 24 | −30 | 24 | 3 |
| 5 | Right putamen | 576 | 0.019 | 20 | 8 | −10 | 3 |
| 6 | Right ILF, IFOF | 552 | 0.017 | 34 | −24 | 4 | 3 |
| 7 | Right precentral gyrus/BA4 | 344 | 0.015 | 42 | −8 | 60 | 2 |
| 8 | Right insula/BA13 | 216 | 0.014 | 50 | −10 | 10 | 2 |
| 9 | Right supramarginal gyrus/BA40 | 240 | 0.014 | 54 | −46 | 36 | 2 |
| 10 | Right superior temporal gyrus/BA22 | 232 | 0.014 | 58 | 2 | 0 | 2 |
| 11 | Right precentral gyrus/BA4, SLF | 272 | 0.012 | 34 | −24 | 50 | 3 |
| 12 | Right SLF | 240 | 0.014 | 44 | −22 | 26 | 2 |
| 13 | Right precentral gyrus/BA4 | 224 | 0.014 | 32 | −14 | 50 | 2 |
| 14 | Right postcentral gyrus/BA2/3 | 216 | 0.013 | 54 | −12 | 26 | 2 |
| **ANALYSIS 3** | | | | | | | |
| 1 | Right middle temporal gyrus/BA21/BA37 | 816 | 0.02 | 54 | −64 | 4 | 4 |
| 2 | Right SLF | 912 | 0.015 | 36 | −36 | 28 | 6 |
| | Right lateral fissure, TPJ/BA21/22/39 | | 0.012 | 44 | −34 | 22 | |
| | Right angular gyrus/BA39 | | 0.012 | 42 | −48 | 30 | |
| 3 | Right middle occipital gyrus/BA19 | 372 | 0.013 | 40 | −76 | 12 | 2 |
| 4 | Right intraparietal sulcus/BA2/3 | 384 | 0.014 | 50 | −20 | 26 | 2 |
| 5 | Right angular gyrus, TPJ/BA39/22/40 | 344 | 0.016 | 54 | −48 | 34 | 2 |
| 6 | Right IFOF | 312 | 0.016 | 36 | −48 | 12 | 2 |
| 7 | Right SLF | 304 | 0.012 | 28 | −24 | 28 | 2 |
| 8 | Right superior parietal lobule/BA5 | 304 | 0.014 | 22 | −44 | 50 | 2 |
| 9 | Right intraparietal sulcus, TPJ/BA40/22 | 208 | 0.012 | 56 | −34 | 36 | 2 |
| 10 | Right inferior temporal gyrus/BA20 | 208 | 0.012 | 58 | −32 | −14 | 2 |
| **ANALYSIS 4** | | | | | | | |
| 1 | Right middle occipital gyrus/BA19 (extending into superior temporal sulcus) | 278 | 0.012 | 40 | −78 | 14 | 2 |
| **ANALYSIS 5** | | | | | | | |
| 1 | Right SLF | 952 | 0.015 | 36 | −36 | 28 | 6 |
| | Right lateral fissure, TPJ/BA22/39 | | 0.012 | 44 | −34 | 22 | |
| | Right angular gyrus/BA39 | | 0.012 | 42 | −48 | 30 | |
| 2 | Right middle temporal gyrus/BA21 | 600 | 0.019 | 54 | −62 | 4 | 3 |
| 3 | Right intraparietal sulcus/BA2/3 | 384 | 0.013 | 50 | −20 | 26 | 2 |
| 4 | Right angular gyrus, TPJ/BA39/22/40 | 368 | 0.016 | 54 | −48 | 34 | 2 |
| 5 | Right IFOF | 312 | 0.016 | 36 | −48 | 12 | 2 |
| 6 | Right SLF | 312 | 0.012 | 28 | −24 | 28 | 2 |
| 7 | Right superior parietal lobule/BA5 | 304 | 0.014 | 22 | −44 | 50 | 2 |
| 8 | Right inferior temporal gyrus/BA20 | 208 | 0.012 | 58 | −32 | −14 | 2 |
| 9 | Right intraparietal sulcus, TPJ/BA40/22 | 208 | 0.012 | 56 | −34 | 36 | 2 |

**Number of contributing experiments (No, number); BA, Brodmann Area; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; TPJ, temporo-parietal junction.*

**Table 4 | Significant ALE clusters located within white matter and corresponding MNI coordinates identified in Analyses 6, 7, and 8.**

| Cluster | | | ALE value | MNI coordinates | | | No. of Exp.* |
|---|---|---|---|---|---|---|---|
| No. | Anatomical label | Size ($mm^3$) | | X | Y | Z | |
| **ANALYSIS 6** | | | | | | | |
| 1 | Right SLF | 8416 | 0.026 | 36 | −36 | 26 | 14 |
| | Right superior corona radiata, IFOF | | 0.025 | 26 | −10 | 36 | |
| | Right superior thalamic radiation | | 0.024 | 28 | −22 | 22 | |
| | Right SLF | | 0.018 | 36 | −12 | 26 | |
| | Right superior thalamic radiation, SLF | | 0.017 | 22 | −30 | 22 | |
| | Right SLF | | 0.014 | 20 | 0 | 34 | |
| | Right SLF | | 0.014 | 36 | −6 | 22 | |
| | Right IFOF | | 0.011 | 32 | −54 | 32 | |
| 2 | Right ILF, IFOF | 616 | 0.018 | 34 | −26 | 4 | 3 |
| 3 | Right IFOF | 488 | 0.017 | 36 | −48 | 12 | 3 |
| 4 | Right posterior thalamic radiation | 384 | 0.014 | 22 | −42 | 50 | 3 |
| 5 | Right internal capsule (posterior limb) | 256 | 0.012 | 16 | −14 | −8 | 2 |
| **ANALYSIS 7** | | | | | | | |
| 1 | Right superior thalamic radiation, SLF | 1520 | 0.016 | 24 | −28 | 24 | 5 |
| | Right SLF | | 0.013 | 34 | −36 | 26 | |
| | Right superior thalamic radiation | | 0.011 | 30 | −20 | 24 | |
| | Right SLF, ILF | | 0.011 | 30 | −28 | 24 | |
| | Right SLF | | 0.011 | 28 | −12 | 24 | |
| 2 | Right ILF, IFOF | 640 | 0.017 | 34 | −24 | 4 | 3 |
| 3 | Right internal capsule (posterior limb) | 368 | 0.011 | 16 | −14 | −8 | 2 |
| 4 | Right posterior thalamic radiation | 360 | 0.014 | 22 | −44 | 50 | 2 |
| **ANALYSIS 8** | | | | | | | |
| 1 | Right SLF | 1184 | 0.021 | 36 | −34 | 30 | 5 |
| | Right IFOF, posterior thalamic radiation | | 0.012 | 32 | −48 | 30 | |
| 2 | Right posterior thalamic radiation | 544 | 0.014 | 22 | −44 | 50 | 3 |
| | Right IFOF, posterior thalamic radiation | | 0.011 | 26 | −40 | 44 | |
| 3 | Right IFOF | 352 | 0.016 | 36 | −48 | 12 | 2 |
| 4 | Right SLF, anterior thalamic radiation | 224 | 0.012 | 22 | 0 | 36 | 2 |

**Number of contributing experiments (No, number); IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus.*

findings were nevertheless striking. The two most concurrent clusters (contributed respectively by 7 and 5 out of 20 experiments) identified in *Analysis 2* (egocentric neglect) were located within the right superior temporal gyrus (BA 22, ALE peak at MNI 54, −28, 2), right insula (BA 13, ALE peak at MNI 46, −22, 14), and sub-cortical structures including the right putamen (ALE peak at MNI 20, 4, 8) and thalamus (ALE peak at MNI 22, −2, 0). The two most concurrent clusters (contributed respectively by 4 and 6 out of total of 13 experiments) identified in *Analysis 3* (allocentric neglect) were located within the right angular gyrus (BA39, ALE peak at MNI 42, −48 30), right temporo-parietal junction (BA 22/39, ALE peak at MNI 44, −34, 22), right middle temporal gyrus (BA 21, ALE peak at MNI 54, −64, 4), and sub-cortically within the right SLF (ALE peak at MNI 36, −36, 28). Strikingly, these two analyses indicated that, while egocentric symptoms were associated with damage within perisylvian network (the pre- and postcentral, supramarginal, and superior temporal gyri) and damage within sub-cortical structures, more posterior lesions including the angular, middle temporal, and middle occipital gyri were associated with allocentric symptoms (**Figure 3C**).

We next examined whether there was a difference in the neural substrates associated with neglect symptoms defined by poor line bisection performance (*Analysis 4*) and the neural substrates associated with allocentric symptoms as measured by diagnostic tests excluding line bisection (*Analysis 5*). The ALE meta-analysis on biases in line bisection revealed one significant cluster (**Table 3**; **Figure 3D**) located within the right temporo-occipital junction, the right middle occipital gyrus extending into the superior temporal sulcus (BA 19, ALE peak at MNI 40, −78, 14). However, it should be noted that this finding was based on a comparison across only four papers (total of 4 experiments with total of only 13 foci). In contrast to this, after excluding the data based on line bisection, we found strong concurrence in the reported damage associated with allocentric symptoms with six out of nine experiments contributing to the largest of the identified clusters (**Table 3**). This cluster indicated high convergence of reported lesions in the right hemisphere within the right angular gyrus (BA 39, ALE peak at MNI 42, −48, 30), the right TPJ (BA 22/39, ALE peak at MNI 44, −34, 22), and the right SLF (ALE peak at MNI 36, −36, 28).

**Table 5 | Neglect measures and reported symptoms in studies included in ALE meta-analyses.**

| No | Study | Neglect measure(s) | Reported symptoms |
|---|---|---|---|
| 1 | Bird et al. (2006) | Battery of different measures including BIT* plus other cancelation, bisection, and drawing tests | Overall neglect (across various measures) |
| 2 | Chechlacz et al. (2010) | Apples cancelation test** | Allocentric, egocentric |
| 3 | Chechlacz et al. (2011) | Apples cancelation test** | Allocentric, egocentric |
| 4 | Chechlacz et al. (2012) | Apples cancelation test** | Allocentric, egocentric |
| 5 | Doricchi and Tomaiuolo (2003) | Cancelation and line bisection tests | Overall neglect (across various measures) |
| 6 | Eschenbeck et al. (2010) | Behavioral inattention test (BIT)*, daily living activities assessment | Overall neglect (across various measures) |
| 7 | Golay et al. (2008) | Battery of different measures including cancelation, line bisection, and drawing tests | Overall neglect (across various measures) |
| 8 | Grimsen et al. (2008) | Battery of different measures based on BIT* plus search paradigms | Allocentric (across different measures), egocentric (across different measures) |
| 9 | Karnath et al. (2001) | Battery of different cancelation and copying tests plus baking tray task | Egocentric (across different measures) |
| 10 | Karnath et al. (2002) | Battery of different cancelation and copying tests plus baking tray task | Egocentric (across different measures) |
| 11 | Karnath et al. (2004a) | Battery of different cancelation and copying tests plus baking tray task | Egocentric (across different measures) |
| 12 | Karnath et al. (2011) | Battery of different cancelation and copying tests | Egocentric (across different measures) |
| 13 | Lee et al. (2010) | Battery of different measures including cancelation, line and letter bisection, scene, and figure copying tests | Overall neglect (across different tests), allocentric (line bisection bias) |
| 14 | Medina et al. (2009) | Battery of different measures including cancelation, line bisection, gap detection scene copy, clock drawing, word reading tests | Allocentric (across different tests not including line bissection), egocentric (across different tests) |
| 15 | Molenberghs and Sale (2011) | Cancelation and line bisection tests | Allocentric (line bisection bias), egocentric (cancelation laterality) |
| 16 | Mort et al. (2003) | Cancelation and line bisection tests | Overall neglect (across different tests), |
| 17 | Ptak et al. (2012) | Battery of different measures including cancelation, line bisection, and scene copy tests plus tests for neglect dyslexia | Overall neglect (across different tests), allocentric (object-centered reading errors), egocentric (page-centered errors) |
| 18 | Rorden et al. (2006) | Battery of different measures including cancelation, line bisection, scene copy, and clock drawing tests | Allocentric (line bisection bias) |
| 19 | Saj et al. (2012) | Battery of different measures including cancelation, line bisection, scene copy, clock drawing, writing, and text reading tests | Overall neglect (across different tests), egocentric (across cancelation and copying tests) |
| 20 | Urbanski et al. (2011) | Battery of different measures including cancelation, line bisection, scene copy, and overlapping figures tests | Overall neglect (across different tests), egocentric (cancelation laterality) |
| 21 | Verdon et al. (2010) | Battery of different measures including cancelation, line bisection, scene copy, gap detection, word, and text reading tests | Overall neglect (across different tests), allocentric, egocentric, visuo-motor |
| 22 | Vossel et al. (2011) | Behavioral inattention test (BIT)* | Allocentric (line bisection bias), egocentric (overall cancelation laterality) |

**BIT, battery of tests including line bisection, line and star cancelation, copying of figures, text reading, and clock drawing (Wilson et al., 1987b); **type of gap detection test (Bickerton et al., 2011).*

### WHITE MATTER SUBSTRATES OF VISUAL NEGLECT – ANALYSES 6–8

The ALE meta-analysis examining concurrence in the reported damage within white matter pathways associated with left neglect, not differentiating between the different symptoms of neglect (*Analysis 6*), revealed six significant clusters (**Table 4**; **Figure 4A**) located within the long association and projection pathways including the SLF, IFOF, ILF, corona radiata, thalamic radiation, and internal capsule in the right hemisphere. Strikingly, we found high concurrence between the studies with 14 out of 16 experiments contributing to the largest of the identified clusters (cluster 1; **Table 4**; **Figure 4A**). This cluster covered two of the long association pathways – the SLF (ALE peaks at MNI 36, −36, 26 extending till 36, −6, 22) and the IFOF (ALE peak at MNI 26, −10, 36 and 32, −54, 32) as well as superior parts of the corona radiata

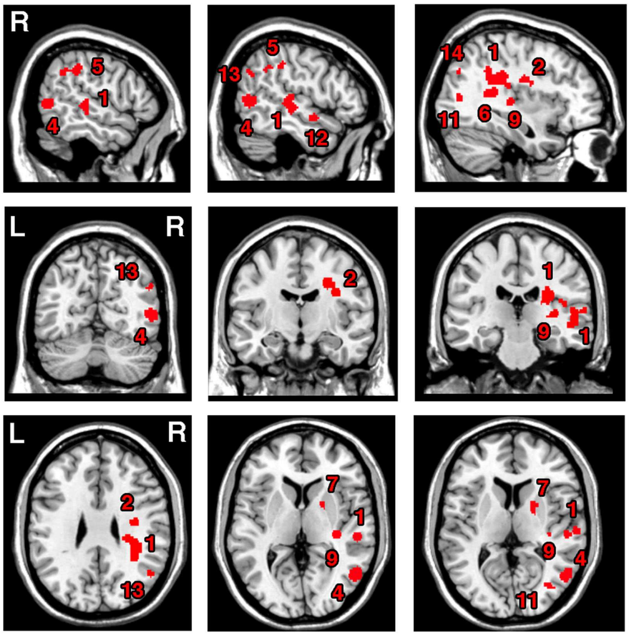


**FIGURE 2 | Significant clusters identified in *Analysis 1* (ALE meta-analysis, $p < 0.05$, FDR corrected for multiple comparisons, cluster size $>200\,mm^3$) – the convergence between results from different lesion-symptom mapping studies concerned with neuroanatomy of the unilateral visual neglect syndrome.** The numbers denote indentified ALE clusters as listed in **Table 2**.

(ALE peak at 26, −10, 36) and the thalamic radiation (ALE peak at MNI 28, −22, 22). Subsequent, ALE meta-analyses examining concurrence in white matter lesions associated with the control of attention across either egocentric space (*Analysis 7*) or allocentric space (*Analysis 8*) revealed four significant clusters associated with egocentric symptoms and four clusters with allocentric symptoms (**Table 4**; **Figure 4B**). Overall, we found higher concurrence between studies reporting white matter damage associated with allocentric symptoms compared to that between studies reporting white matter damage associated with egocentric symptoms. The most concurrent cluster (contributed respectively by 5 out of total of 11 experiments) identified in *Analysis 7* examining neural substrates of left egocentric symptoms was located within right SLF (ALE peak at MNI 34, −34, 26), right superior thalamic radiation (ALE peak at MNI 30, −20, 24), and right ILF (ALE peak at 30, −28, 24). The most concurrent cluster (contributed to respectively by five out of seven experiments in *Analysis 8*) was located within the right SLF (ALE peak at MNI 36, −34, 30), the right IFOF, and the right posterior thalamic radiation (ALE peak at MNI 32, −48, 30). Strikingly, these two analyses (*Analyses 7* and *8*) indicated that egocentric and allocentric symptoms were associated with lesions within common long association and projection pathways, in particular the SLF and the thalamic radiation.

## DISCUSSION

Here, we examined data indicating dissociations between the heterogeneous symptoms and the neural substrates of unilateral visual neglect based on ALE meta-analyses of lesion-symptom mapping studies. There is a substantial body of evidence demonstrating that different neuropsychological tests and/or even varied measures within the same task used for diagnosing neglect can reveal different symptoms of this heterogeneous syndrome whilst also varying in their overall sensitivity for detecting mild to moderate symptoms (e.g., Vanier et al., 1990; Ferber and Karnath, 2001; Rorden et al., 2006; Bickerton et al., 2011). Past studies have hotly disputed the neuroanatomy of unilateral neglect, while, in contrast, more recent studies have suggested that at least some of the previously reported differences between studies can stem from the heterogeneity of the syndrome and the associated lesion sites. In the current paper, we provide statistical evidence supporting this notion based on the ALE meta-analyses. We first examined whether there was commonality across studies when the different tests of neglect are not taken into account. In this overall assessment (*Analysis 1*), the consistency across the reported findings was relatively poor, though one of the identified clusters was contributed to by approximately 50% of all experiments. This covered regions within posterior parietal cortex (IPL), the insula, and the thalamus as well as within white matter pathways. Strikingly, when the different tests were not differentiated, there was high overall concurrence in white matter lesions within the long association SLF (inferior fronto-occipital and ILF) and projection (corona radiata and thalamic radiation) pathways. This provides strong evidence for a disconnection account of the syndrome, which can generate a common pattern of deficit across different tests. While the assessment of common cortical damage across the different tests of neglect generated moderate results, the results were stronger when we separated out tests sensitive to the positions of elements in egocentric and allocentric reference frames. Here our concurrence analyses indicated that egocentric symptoms were associated with damage within the perisylvian network (the pre- and postcentral, supramarginal, and superior temporal gyri) along with damage within sub-cortical structures, while more posterior lesions including the angular, middle temporal, and middle occipital gyri) were associated with allocentric symptoms.

## UNILATERAL VISUAL NEGLECT – THE CONTROVERSIAL QUEST FOR A KEY LESION SITE

Understanding lesion-symptom relations in patients with cognitive deficits has both clinical and basic scientific implications. Data from individuals who have impaired cognitive processes due to the specific patterns of neural damage allow researchers to shape and test theories of how the human brain works and is organized. Importantly, information about the extent and location of any lesion, and the associated cognitive problems, also carry direct implications for clinical care – specifically if predictions of outcome and plans for rehabilitation can be informed by lesion data. Unilateral visual neglect has been extensively studied by both basic scientists and clinicians as, on the one hand, the syndrome provides a unique opportunity to study human visuospatial attention, while on the other neglect-related problems have proved difficult to understand and treat. Not surprisingly, there have been numerous research efforts toward understanding the lesion patterns associated with neglect but not without controversies (e.g., see Mort et al., 2003 versus Karnath et al., 2001; Karnath et al., 2004a). Some groups have argued that the syndrome is linked

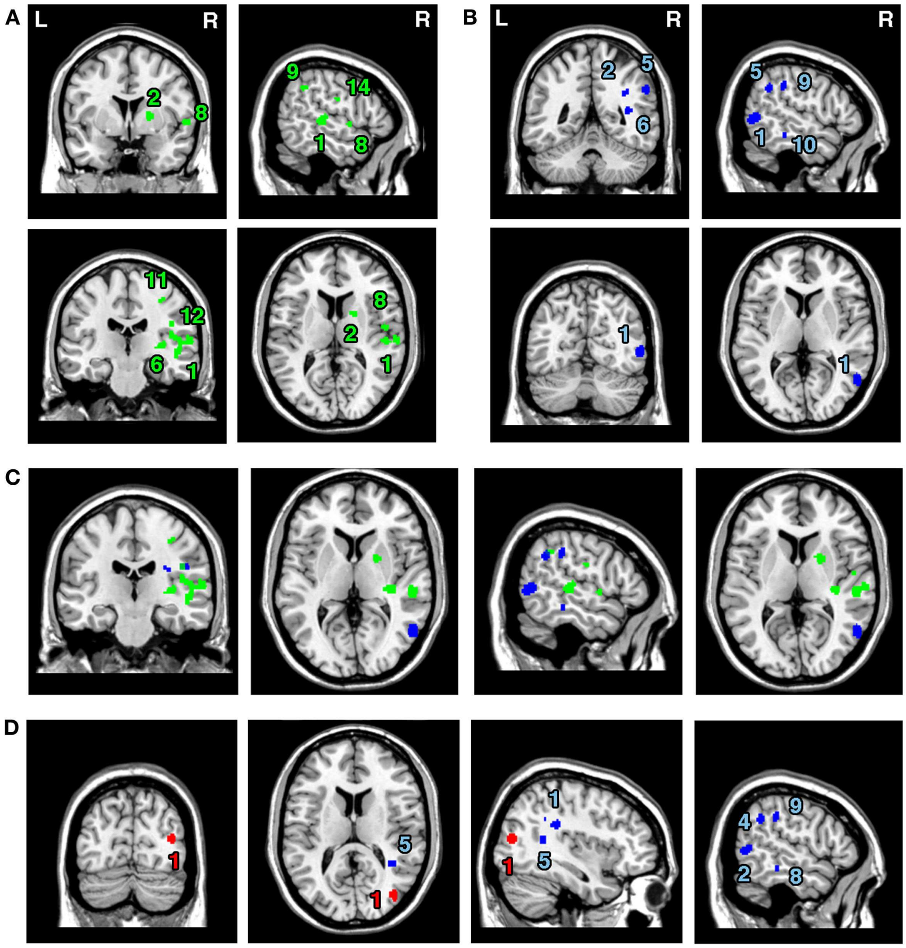


**FIGURE 3 | Significant clusters identified in *Analyses 2, 3, 4,* and *5* (ALE meta-analyses, $p < 0.05$, FDR corrected for multiple comparisons, cluster size >200 mm³).** The concurrence in lesion sites associated with impaired control of attention either **(A)** across space, i.e., egocentric frame of reference (green; *Analysis 2*) or **(B)** within objects, i.e., allocentric frame of reference (blue; *Analysis 3*) including lesion sites associated with impaired performance on line bisection test. **(C)** Distribution of ALE clusters indentified in both analyses (*Analysis 2* in green and *Analysis 3* in blue). **(D)** The concurrence in lesions associated with either impaired performance on line bisection (red; *Analysis 4*) or impaired control of attention within objects, i.e., allocentric frame of reference as measured by various neglect diagnostic tests excluding line bisection (*Analysis 5*; blue). The numbers in **(A,B,D)** denote indentified ALE clusters as listed in **Table 3**.

to posterior parietal cortex lesions, while others report damage within regions including the superior temporal gyrus, insula, and basal ganglia (Vallar and Perani, 1986; Mort et al., 2003; Vallar et al., 2003; on the other, see Karnath, 2001; Karnath et al., 2001, 2004a). Interestingly, this debate has not only centered on the critical lesion site itself but also on the methods used to determine the link between site of brain damage and the behavioral symptoms and on patient selection criteria and assessment (e.g., Rorden et al., 2006; Medina et al., 2009; Chechlacz et al., 2010; Verdon et al., 2010). We provide here evidence across studies for dissociations between both the symptoms and the neural substrates of unilateral visual neglect, illustrated by both low and high concurrence in our ALE meta-analyses. The results presented here support the notion that the tests used to diagnose neglect symptoms are critical when studying the neuronal substrates of this heterogeneous syndrome, since the correlations between the brain lesions vary according to the cognitive process assessed in different tasks. The process rather than the test *per se* seems important and our analyses indicate that common lesion-symptom mapping occurs across different tasks, which "tap" the same process. Our conclusion is that the quest for identifying a key lesion site for unilateral neglect is an impossible task as this heterogeneous syndrome itself is not a "theoretically coherent but rather meaningless entity" (Halligan and Marshall, 1992). Our study points to the coherent evidence indicating that behavioral dissociations between particular neglect symptoms are closely coupled with anatomical dissociations and thus it seems more appropriate to define separately the key lesion site for allocentric neglect and separately for egocentric neglect, etc.

The symptoms associated with neglect are traditionally diagnosed with a battery of tests including target cancelation, line bisection and scene/figure copying (Wilson et al., 1987a,b).

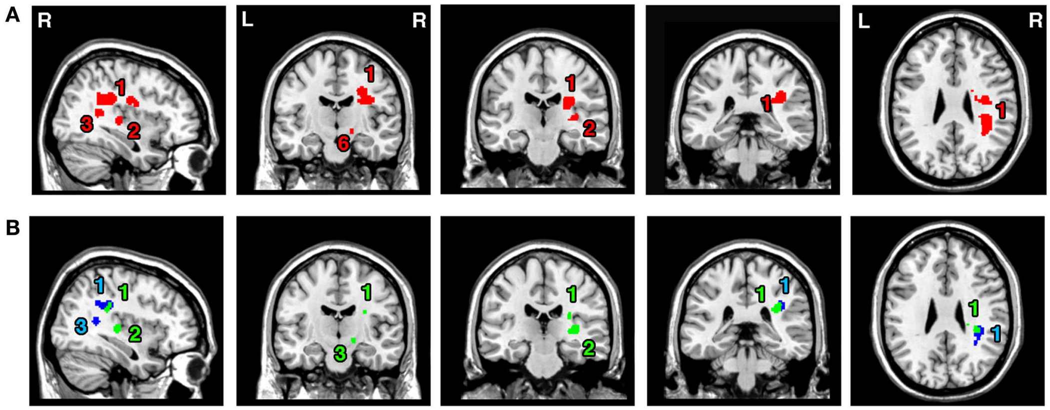


**FIGURE 4 | Significant clusters within the white matter identified in *Analyses 6, 7,* and *8* (ALE meta-analysis, $p < 0.05$, FDR corrected for multiple comparisons, cluster size >200 mm³). (A)** The convergence between results from different lesion-symptom mapping studies examining link between damage within white matter pathways and unilateral visual neglect syndrome (*Analysis 6*). **(B)** The concurrence in white matter lesions associated with impaired control of attention either across space, i.e., egocentric frame of reference (*Analysis 7*; green) or within objects, i.e., allocentric frame of reference (*Analysis 8*; blue). The numbers denote indentified ALE clusters as listed in **Table 4**.

Additionally, gap detection and single word or sentence/paragraph reading task can be used (Subbiah and Caramazza, 2000; Ota et al., 2001; Bickerton et al., 2011). Karnath and colleagues suggested that while cancelation tests provide a good measure of core deficits associated with neglect (including biases in gaze direction, exploration, and cancelation), other diagnostic tools measure deficits behaviorally distinct from these symptoms (Ferber and Karnath, 2001; Rorden et al., 2006; Karnath and Rorden, 2012). Specifically, it has been demonstrated that line bisection bias and allocentric spatial coding, as measured on gap detection tasks, multi-object scene copying, and single word reading, can differentiate anatomically allocentric symptoms from egocentric symptoms with substantial concurrence across studies using different methods (Rorden et al., 2006; Medina et al., 2009; Chechlacz et al., 2010; Verdon et al., 2010; Ptak et al., 2012). Strikingly, our ALE analyses confirmed previously reports indicating that egocentric symptoms are associated with the damage to more anterior cortical regions, while allocentric symptoms are associated with more posterior lesions. To conclude, though there may not be a key lesion site, there are different key lesion sites according to the forms of spatial representation mediating performance.

## WHITE MATTER LESIONS – UNILATERAL VISUAL NEGLECT AS A DISCONNECTION SYNDROME

The data presented here also provide strong evidence linking white matter disconnections to neglect. Previously there have been arguments that neglect can be viewed as a disconnection syndrome, following a simple idea that neglect symptoms result from structural disruption of connectivity within fronto-parietal attention networks (Doricchi and Tomaiuolo, 2003; Bartolomeo et al., 2007). Consistent with this, there is now a growing body of evidence that neglect is associated with damage to the SLF (Doricchi and Tomaiuolo, 2003; Thiebaut de Schotten et al., 2005, 2008; He et al., 2007; Karnath et al., 2009; Shinoura et al., 2009; Chechlacz et al., 2010, 2011), the ILF (Bird et al., 2006; Chechlacz et al., 2010; Riddoch et al., 2010), and the IFOF (Urbanski et al., 2008, 2011; Karnath et al., 2009; Chechlacz et al., 2010; Riddoch et al., 2010), i.e., the long association pathways associated with spatial attention, spatial orienting, visual selection, and spatial working memory (Aralasmak et al., 2006; Schmahmann and Pandya, 2006; Schmahmann et al., 2007). We examined here the existing evidence linking neglect symptoms with white matter lesions across different lesion-symptom mapping studies. We found convergent lesion patterns across all studies without applying any selection criteria based on the type of test used to diagnose neglect, covering both allocentric and egocentric symptoms. The high concurrence in the reported white matter lesions was found within long association (SLF, IFOF, ILF) as well as projection (corona radiata and thalamic radiation) pathways. There is a consensus on the cortical areas connected by the SLF (Petrides and Pandya, 1984, 2002; Makris et al., 2005; Schmahmann and Pandya, 2006; Schmahmann et al., 2007; Thiebaut de Schotten et al., 2012) and ILF (Catani et al., 2003; Schmahmann and Pandya, 2006) and their anatomy conserved between the monkey and the human brain. By contrast the anatomy of IFOF is somewhat controversial. Some post-mortem dissections and tractography reconstructions indicate the existence of IFOF, a white matter pathway providing direct connection between frontal and occipital lobes in the human brain (Crosby, 1962; Catani et al., 2002; Thiebaut de Schotten et al., 2012). However, since IFOF is not present in the monkey brain and since there is a documented poor correspondence between cytoarchitectonic probabilistic post-mortem histology and *in vivo* tractography based reconstructions of IFOF (Burgel et al., 1999; Thiebaut de Schotten et al., 2011), the anatomy of IFOF remains questionable. Interestingly, recent study examining the comparative anatomy of the long association pathways (including IFOF) in the rhesus monkey and human brain, has demonstrated that the anterior fibers of the extreme capsule in the monkey brain overlap with those of the human IFOF and project to similar frontal regions. On the other hand, the posterior fibers differ in human and monkey brain – in the monkey brain the posterior projections do not reach the occipital lobe and project to the temporal lobe, while human IFOF projects to the occipital lobe (Thiebaut de Schotten et al., 2012).

The concept of a "disconnection syndrome" can be traced back to the forefathers of cognitive neuropsychology such as Carl Wernicke, Hugo Liepman, and Jules Dejerine. However, the popularity of the concept can be credited to the work of Geschwind who presented a revised disconnection account of many neurological disorders (Geschwind, 1965a,b; for review, see also Catani and Ffytche, 2005; Catani and Mesulam, 2008). According to the classical disconnection concept as put forward for example by Wernicke, a disconnection syndrome can be viewed as a disorder of higher cognitive function resulting from a breakdown of associative connections between cortical areas due to white matter lesions (Wernicke, 1874). In contrast to this, Geschwind viewed disconnection syndromes as disorders of higher cognitive functions resulting from either white matter lesions or lesions within association cortices, which serve as relay posts between primary motor, primary sensory, and limbic cortical areas (Geschwind, 1965a). Regardless of the specifics of the disconnection concept, it has a very appealing applicability to syndrome of unilateral neglect and here we provide evidence supporting this notion. First, it can be argued that the cognitive processes underlying spatial attention and visual selection are derived from a widely distributed neuronal network subserved by long association fronto-parietal and fronto-occipital white matter pathways (Makris et al., 2005; Petrides and Pandya, 2006; Schmahmann and Pandya, 2006). This is in accordance with arguments such as those made by Corbetta and Shulman (2011), that neglect is better explained by the dysfunctions of distributed neuronal networks rather than by specific cortical damage. Secondly, many previous reports have demonstrated a strong relationship between white matter lesions and neglect, fitting our meta-analyses. The interesting point about our analyses, though, is that neglect symptoms which fractionate in terms of their cortical underpinning, can be linked back to common white matter damage. We consider this point below.

### FUNCTIONAL ACCOUNTS OF UNILATERAL VISUAL NEGLECT

Our ALE meta-analyses supports the argument that distinct cortical regions control attention across egocentric space and within objects ("between" and "within object" spatial representations; see Humphreys, 1998). An alternative account is that egocentric neglect reflects a problem in global space perception while allocentric neglect reflects a problem in representing space at a more local scale. Halligan and Marshall (1994a) proposed that left neglect after right hemisphere damage is brought about by the combination of poor global space perception along with a spatial bias in attention. Poor attention to local spatial areas is associated with left rather than right hemisphere damage (Delis et al., 1983) and, if coupled to a spatial bias in selection, then there may be poor detection of missing parts on one side of individual objects – allocentric symptoms. However we found no evidence for this (please note that while some lesion-symptom mapping studies only included patients with right hemisphere lesions, others applied no such selection) and there was certainly no evidence that allocentric neglect was particularly associated with left hemisphere damage, as might be expected on this account. Another possibility is that both forms of neglect stem from a gradient of attention across egocentric space (e.g., Driver and Pouget, 2000). On this gradient account, there will be a bias against elements on one side of objects, even when the objects fall in the ipsilesional visual field. Again, this account has problems with the data. For example, it predicts that allocentric and egocentric neglect should co-occur behaviorally and they should be associated with common lesion sites. In contrast to this the behavioral data accumulated by various research groups (e.g., Medina et al., 2009; Chechlacz et al., 2010; Ptak et al., 2012) indicate dissociations between patients with one or other form of neglect and, in addition, egocentric, and allocentric neglect are associated with contrasting lesions. This gradient account also fails to explain prior results where opposite egocentric and allocentric biases have occurred even in the same patient, which also arose in some cases in the present sample (Humphreys and Riddoch, 1994, 1995).

The evidence supporting anatomical and behavioral dissociations between egocentric and allocentric symptoms is in agreement with computational modeling of visual attention (Heinke and Humphreys, 2003). It can be proposed that the different neural regions support the allocation of attention to the distinct spatial representations held in other areas, or the regions may support processes that read-in visual information (egocentric symptoms) or that read-out information (allocentric symptoms) from neural networks involved in selecting between stimuli as they compete for object recognition. One framework was proposed by Heinke and Humphreys (2003). In their model visual information is fed-into a selection network where separate objects compete for entry into a focus-of-attention, and activity within the focus-of-attention gates access to stored object knowledge, which is translation invariant across the retina. Selected objects are subsequently registered in a location map reflecting the salience of stimuli in the visual field (the Selective Attention for Identification Model, SAIM). Subsequently, Heinke and Humphreys demonstrated that damage affecting the visual information coming into one side of the competition network led to egocentric neglect, with there being poor recovery of stimuli on one side of retinally defined space. In contrast, damage affecting the output from the selection network going into one side of the focus-of-attention led to allocentric neglect, with the contralesional parts of objects being neglected irrespective of their lateral position in the field (Heinke and Humphreys, 2003). This argument, for distinct spatial codes being derived for different computational reasons in object processing, fits with the data on lesion dissociation that we report. Note though that common communication pathways might be set up from these different representations to output systems for motor responses, so that damage to the communication pathways leads to problems within both egocentric and allocentric space.

### METHODOLOGICAL CAVEATS

We employed here an approach based on ALE meta-analysis that traditionally is applied to data from functional neuroimaging studies and uses coordinates describing brain activation foci (GingerALE, Turkeltaub et al., 2002; Laird et al., 2005). However, GingerALE also performs anatomic likelihood (ALE) meta-analysis and in the past this method has been successfully used to assess the overlap between anatomical foci identified by voxel-wise analyses of structural neuroimaging data (Ellison-Wright et al., 2008; Glahn et al., 2008; Di et al., 2009; Ferreira et al., 2011). As the method uses as input coordinates corresponding to the statistical peak from the lesion-symptom mapping analysis, it could be argued that such points poorly represent the usually large lesions associated with neglect symptoms. This is even more problematic when using peak coordinates representing the results from lesion subtraction analyses (based on either comparisons between the lesion overlap plots from patients with and without neglect symptoms or from formal subtraction plots between patients with and without neglect symptoms), as such methods describe the areas where the groups differ quantitatively and not necessarily statistically. Furthermore, many early lesion subtraction papers differ in terms of their definition of the critical area(s) associated with neglect. While some authors provide peak coordinates of lesion overlap, others provide border coordinates of maximum overlap for neglect group versus controls. As many early influential reports examining the neuroanatomy of neglect are based on lesion subtraction methods and not statistical VLSM analyses, despite the methodological problems with peak coordinates definition, we included all such studies in the meta-analysis in order to have a full representation of published findings. Furthermore, these arguments and methodological caveats should be weighted against the fact that the ALE approach is based not on simple point plotting but on estimations of probability (see Materials and Methods for details) followed by statistical analyses corrected for the observation of false positives. Furthermore, this approach allows investigators to factor differences in the methods and sample sizes that are used by different research groups, and it appears to provide a useful way to gain an overview across lesion-symptom data.

## CONCLUSION

In conclusion, we argued here that different symptoms of unilateral visual neglect link to both distinct patterns of gray matter lesions and common patterns of white matter lesions. We provide here statistical evidence based on ALE meta-analyses (e.g., low overall concurrence between different studies and higher concurrence after fractionating neglect symptoms) that multiple factors arising from variability in the neglect diagnosis explain the discrepancies reported in the literature on the neuronal substrates of unilateral visual neglect. It is plausible that other modulating factors, such as for example the neuroimaging modality used (we combined here findings based on CT, anatomical MRI, DTI, and PWI), the data analysis methods (we combined here findings based on different lesion-symptom mapping approaches including both simple lesion overlap/subtraction methods as well as methods based on statistical analysis, e.g., VBM and VLSM) and the time of assessment, i.e., acute versus chronic brain injury, may also be important. However, because of the much higher concurrence demonstrated after fractionating the symptoms of neglect, we believe that the diagnostic tools are adequate to explain the literature discrepancies.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 06 February 2012; accepted: 18 July 2012; published online: 10 August 2012.*

*Citation: Chechlacz M, Rotshtein P and Humphreys GW (2012) Neuroanatomical dissections of unilateral visual neglect symptoms: ALE meta-analysis of lesion-symptom mapping. Front. Hum. Neurosci.* ***6****:230. doi: 10.3389/fnhum.2012.00230*

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 10 April 2012
doi: 10.3389/fnhum.2012.00078

# Is there a critical lesion site for unilateral spatial neglect? A meta-analysis using activation likelihood estimation

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The critical lesion site responsible for the syndrome of unilateral spatial neglect has been debated for more than a decade. Here we performed an activation likelihood estimation (ALE) to provide for the first time an objective quantitative index of the consistency of lesion sites across anatomical group studies of spatial neglect. The analysis revealed several distinct regions in which damage has consistently been associated with spatial neglect symptoms. Lesioned clusters were located in several cortical and subcortical regions of the right hemisphere, including the middle and superior temporal gyrus, inferior parietal lobule, intraparietal sulcus, precuneus, middle occipital gyrus, caudate nucleus, and posterior insula, as well as in the white matter pathway corresponding to the posterior part of the superior longitudinal fasciculus. Further analyses suggested that separate lesion sites are associated with impairments in different behavioral tests, such as line bisection and target cancellation. Similarly, specific subcomponents of the heterogeneous neglect syndrome, such as extinction and allocentric and personal neglect, are associated with distinct lesion sites. Future progress in delineating the neuropathological correlates of spatial neglect will depend upon the development of more refined measures of perceptual and cognitive functions than those currently available in the clinical setting.

**Keywords: unilateral spatial neglect, extinction, lesion mapping, ALE meta-analysis, line bisection, cancellation task**

## INTRODUCTION

Unilateral spatial neglect is typically defined as an inability to detect, attend or respond to stimuli in spatial locations contralateral to the side of cerebral damage (Heilman et al., 1993). The symptoms of spatial neglect are typically associated with cerebral damage involving the right hemisphere, although neglect also arises after left-sided lesions (Stone et al., 1993; Kleinman et al., 2007). Within the right hemisphere, neglect symptoms have been reported following damage to different brain regions, including the angular gyrus (Mort et al., 2003; Molenberghs and Sale, 2011), superior temporal cortex (Karnath et al., 2001, 2004), parahippocampus (Mort et al., 2003), temporo-parietal junction (Vallar and Perani, 1986; Karnath et al., 2003), inferior frontal lobe (Husain and Kennard, 1996; Rengachary et al., 2011), intraparietal sulcus (Molenberghs et al., 2008; Gillebert et al., 2011), insula (Karnath et al., 2004; Rengachary et al., 2011), putamen (Karnath et al., 2002, 2004), caudate nucleus (Karnath et al., 2002, 2004; Medina et al., 2009), pulvinar (Karnath et al., 2002), parieto-frontal cortex (Bartolomeo et al., 2007) and occipital lobe (Bird et al., 2006). Recent work also suggests that a common cause for spatial neglect is a disruption of white matter pathways connecting parietal and frontal areas (Doricchi and Tomaiuolo, 2003; Thiebaut de Schotten et al., 2005; Bartolomeo et al., 2007; Doricchi et al., 2008; Urbanski et al., 2008; Ptak and Schnider, 2010; Urbanski et al., 2011) and damage in a particular area could potentially cause functional changes well outside the critical lesion site (Corbetta et al., 2005; Hillis et al., 2005; He et al., 2007; Corbetta and Shulman, 2011). It should be noted, however, that a focal lesion within a circumscribed brain area does not invariably alter cerebral perfusion in functionally relevant, but structurally unaffected, regions (Zopf et al., 2009) and some authors have argued that gray matter damage is the most common cause of neglect (Karnath et al., 2009). Yet this latter study was based on white matter damage on the Jülich brain atlas (Bürgel et al., 2006), which is built on coronal anatomical slices of post-mortem brains, and as a consequence could underestimate the extension of caudo-rostral pathways such as the superior longitudinal fasciculus.

Different lesion sites have been associated with different aspects of the neglect syndrome and the condition is now widely accepted as a heterogeneous syndrome (Stone et al., 1998; Hillis, 2006; Karnath and Rorden, in press). For example, patients with visual extinction, but without neglect, can detect single stimuli presented briefly and in isolation in either hemispace, but fail to detect the more contralesional event when two stimuli occur simultaneously on both sides (Karnath et al., 2003). Other subdivisions in the neglect syndrome have been made. Personal neglect, for example, refers to cases in which the patient is unaware of the contralesional side of the body (Committeri et al., 2007; Baas et al., 2011). By contrast, extrapersonal neglect refers to patients who ignore the contralesional side of the external environment beyond the body, either within or beyond reaching space (Committeri et al., 2007). Allocentric neglect concerns a failure to perceive the contralesional side of individual objects (e.g., items in a complex scene or words) regardless of their orientation or position relative to the body (Medina et al., 2009; Chechlacz et al., 2010). By contrast, egocentric neglect refers to a deficit in perceiving stimuli located on the contralesional side of space relative to the body midline (Chechlacz et al., 2010).

In order to probe these different symptoms of the neglect syndrome, a wide variety of clinical tests have been developed (Karnath et al., 2003; Rorden et al., 2006; Grimsen et al., 2008; Marsh and Hillis, 2008; Verdon et al., 2010), the majority of which test for neglect within the visual modality. Most common among these are cancellation tasks, in which patients use a pen to mark individual targets scattered on a page (Albert, 1973; Gauthier et al., 1989; Ota et al., 2001), and line bisection tasks in which patients are required to indicate the midpoint of several horizontal lines (Schenkenberg et al., 1980; Wilson et al., 1987; Halligan et al., 1990). These tests were designed to be easy to administer and score, but lack specificity in terms of the underlying perceptual and cognitive deficits they measure (Vandenberghe and Gillebert, 2009; Verdon et al., 2010). Some consideration of the underlying properties of these clinical tests is important when attempting to determine whether there is a critical brain region whose damage most commonly causes symptoms of neglect. We addressed this issue by undertaking anatomical analyses separately for lesion maps obtained from studies that employed either cancellation or line bisection tasks to define neglect.

To date, the published group studies that have investigated the anatomy of neglect have been limited by small sample sizes and wide variability in lesion sites. The principal motivation for the present study was thus to add clarity to the information presently available by determining for the first time which, if any, lesion sites are consistently associated with the neglect syndrome *across* different studies. Our main goal was to summarize the data currently available and do this in an unbiased way. Therefore, we performed an activation likelihood estimation (ALE) meta-analysis (Laird et al., 2005; Eickhoff et al., 2009), which has been used previously as an objective measure to quantify the relationship between brain anomalies and different syndromes (Glahn et al., 2008; Rotge et al., 2010; Ferreira et al., 2011).

Since spatial neglect is often used as a broad term to describe different behavioral deficits in clinical settings and research studies, we first identified all published group studies of neglect in which lesions had been mapped and that reported the peak coordinates of the critical lesion site. We also performed an additional qualitative analysis by subdividing the peak coordinates from different subtests such as target cancellation and line bisection. Likewise, we examined peak coordinates for subgroups of neglect-like symptoms such as extinction, personal, extrapersonal, egocentric and allocentric neglect and provide them in an objective framework. The findings, which imply an objective and coherent network of brain areas associated with different neglect measures and symptoms, should prove useful for researchers and clinicians involved in the management and rehabilitation of patients with this debilitating neurological condition. They should also assist experts in the field to develop more refined measures of perceptual and cognitive functions associated with the spatial neglect syndrome in the future.

## MATERIALS AND METHODS

### LITERATURE SELECTION AND EXCLUSION CRITERIA

We searched the Web of Science database (http://apps.isiknowledge.com) in January 2012 using the keywords "spatial neglect," "lesion mapping," "extinction," "inattention," "hemineglect," "hemispatial neglect," and "unilateral neglect". The inclusion criteria for our analyses were as follows:

1. Studies that dealt with spatial neglect in human patients were included, whereas those that did not were excluded (e.g., the search also uncovered studies focused on lesions in non-human species, as well as review articles).
2. Studies that used lesion localization were included, whereas those that employed other techniques (e.g., behavioral tests, positron emission tomography (PET) or perfusion studies) were excluded.
3. Because we were only interested in consistent lesion sites across patient groups, we only included studies that performed group lesion-overlap analyses; other studies (e.g., single case studies) were excluded.
4. Studies that did not report the coordinates of damage or for which the coordinates could not be obtained through personal communication were excluded.

A total of 20 studies that were found in the Web of Science database or that were known to the authors matched all the inclusion criteria and were thus entered into the meta-analysis (see **Table 1** for a complete list of the included studies).

### SELECTION OF PEAK COORDINATES

From the 20 studies that passed the inclusion criteria listed above, we extracted the peak coordinates reported on the basis of the authors' lesion mapping analyses. To minimize over-representation by one particular region based on a single study, we only included peak coordinates that were separated by more than 10 mm from each other in *x*, *y*, and *z* space in the same study and for the same test. Additionally, if the voxels reported in the original study were reported in Talairach space we transformed them into Montreal Neurological Institute (MNI) space using the icbm2tal algorithm (Lancaster et al., 2007) implemented in the Ginger ALE software (Eickhoff et al., 2009). In total, 69 foci were included in the overall analysis (see **Table 1** and **Figure 1** for details).

### ACTIVATION LIKELIHOOD ESTIMATION (ALE)

To identify the brain regions consistently lesioned in the included studies, we performed an ALE analysis (Eickhoff et al., 2009). Although ALE analysis was originally developed to quantify consistent activation patterns in neuroimaging studies, it has also been used in meta-analyses of brain anomalies in such syndromes as obsessive-compulsive disorder (Rotge et al., 2010), schizophrenia (Glahn et al., 2008; Cheung et al., 2010), Alzheimer's disease (Ferreira et al., 2011) and autistic spectrum disorders (Cheung et al., 2010). We used Version 2.0, which has advantages over earlier ALE algorithms (Turkeltaub et al., 2002; Laird et al., 2005) in that rather than testing for an above-chance clustering between activated foci, it assesses above-chance clustering of activated foci

**Table 1 | Overview of the 20 studies and peak coordinates used in the ALE analysis.**

| Number | Reference | Number of patients | MNI coordinates | Class | Description lesion mapping result |
|---|---|---|---|---|---|
| 1 | Molenberghs and Sale, 2011 | 44 | 31, –77, 37 | B | Cancellation task |
| | | | 34, –74, 34 | A | Line bisection task |
| 2 | Mort et al., 2003 | 35 | 51, –42, 31 | C | MCA neglect patients |
| | | | 36, –10, 18 | C | PCA neglect patients |
| 3 | Karnath et al., 2004 | 140 | 67, –18, 5 | C | Neglect vs. non-neglect patients |
| 4 | Verdon et al., 2010 | 80 | 29, –29, 18 | C | Neglect on all tasks |
| | | | 20, –2, 30 | C | |
| | | | 33, –47, 37 | A | Perceptive/visuo-spatial egocentric neglect |
| | | | 28, –60, 28 | A | |
| | | | 49, 29, 15 | B | Exploratory/visuo-motor egocentric neglect |
| | | | 38, 49, 8 | B | |
| | | | 52, 2, 33 | B | |
| | | | 35, –26, –10 | D | Allocentric neglect |
| 5 | Committeri et al., 2007 | 52 | 64, 4, 16 | C | Extrapersonal neglect |
| | | | 44, 44, 20 | C | |
| | | | 60, –24, 4 | C | |
| | | | 50, –28, –8 | C | |
| | | | 37, 6, –20 | C | |
| | | | 37, –36, 32 | E | Personal neglect |
| | | | 40, –19, 39 | E | |
| | | | 56, –29, 40 | E | |
| | | | 35, 13, 38 | E | |
| 6 | Golay et al., 2008 | 19 | 24, 26, 8 | C | Neglect minus non-neglect patients |
| | | | 40, –44, 26 | C | |
| 7 | Chechlacz et al., 2010 | 41 | 54, –58, 6 | D | Allocentric neglect |
| | | | 50, –58, 44 | D | |
| | | | 50, –62, 30 | D | |
| | | | 52, –32, 40 | B | Egocentric neglect |
| | | | 48, –24, –8 | B | |
| | | | 44, –8, 62 | B | |
| | | | 4, –22, –2 | B | |
| | | | 16, 8, –10 | B | |
| | | | 50, –38, 18 | C | Allocentric and egocentric neglect |
| | | | 50, –22, 40 | C | |
| 8 | Vossel et al., 2011 | 56 | 52, –72, 33 | F | Visual extinction |
| | | | 41, –77, 18 | C | Unilateral left performance (p.c.) |
| | | | 44, –71, 38 | C | |
| | | | 37, 6, 43 | C | |
| | | | 26, –17, 53 | C | |
| | | | 39, –77, 13 | A | Line bisection task (p.c.) |
| | | | 37, 45, 28 | A | |
| | | | 41, 39, 33 | B | Cancellation task (p.c.) |
| | | | 31, 12, 53 | B | |
| | | | 28, –41, 53 | B | |
| 9 | Grimsen et al., 2008 | 21 | 37, –26, 60 | C | Egocentric impairment |
| | | | 40, 2, 57 | C | |
| | | | 35, –7, 49 | C | |
| | | | 37, –19, 50 | C | |
| | | | 38, –9, –13 | D | Allocentric impairment |
| 10 | Mannan et al., 2005 | 8 | 42, –53, 43 | C | MCA neglect patients |
| 11 | Urbanski et al., 2011 | 12 | 34, 8, 22 | C | neglect patients vs. non-neglect patients |
| 12 | Molenberghs et al., 2008 | 20 | 43, –67, 33 | F | More interference from an ipsilesional distractor (p.c.) |

*(Continued)*

**Table 1 | Continued**

| Number | Reference | Number of patients | MNI coordinates | Class | Description lesion mapping result |
|---|---|---|---|---|---|
| 13 | Shallice et al., 2010 | 42 | 34, –48, 29 | B | Cancellation task (p.c.) |
| 14 | Karnath et al., 2003 | 27 | 69, –9, 0 | C | Neglect |
| | | | 65, –35, 34 | F | Extinction |
| | | | 63, –55, 27 | F | |
| | | | 67, –49, 8 | F | |
| | | | 69, –34, 7 | F | |
| 15 | Eschenbeck et al., 2010 | 68 | 26, –4, 58 | C | Neuropsychological (NP) neglect test battery (p.c.) |
| | | | 29, –38, 53 | C | |
| 16 | Doricchi and Tomaiuolo, 2003 | 21 | 39, –8, 26 | C | All neglect patients minus controls |
| | | | 30, –5, 35 | C | |
| 17 | Baas et al., 2011 | 22 | 47, −42, 20 | E | Patients with minus without personal neglect |
| 18 | Ptak and Schnider, 2010 | 29 | 30, –22, 22 | C | Neglect patients minus control patients |
| | | | 27, 3, 30 | C | |
| | | | 44, –46, 32 | C | |
| 19 | Rengachary et al., 2011 | 30 | 28, –10, 22 | C | Consistent lesion site in neglect patients (p.c.) |
| 20 | Medina et al., 2009 | 171 | 28, –27, 28 | D | Stimulus-centered neglect (p.c.) |
| | | | 55, –21, 13 | C | Viewer-centered neglect (p.c.) |

*Class A = neglect tested with line bisection task, B = neglect tested with cancellation task, C = neglect tested in general, D = allocentric neglect, E = personal neglect and F = spatial extinction. p.c. = coordinates obtained through personal communication.*

*between experiments*, thus permitting random-effects inference. The ALE analysis was conducted using the standard settings in the Ginger ALE software (Eickhoff et al., 2009). The test was corrected for multiple comparisons using the false discovery rate (FDR) method with $p < 0.05$, and a suggested minimum volume of 200 mm³ voxels was used to define a cluster. The maps of the ALE values were superimposed on a ch2better.nii.gz atlas using MRIcron software (http://www.mricro.com/mricron).

## SUBDIVISIONS

As noted in the Introduction, spatial neglect is increasingly considered a heterogeneous syndrome (Stone et al., 1998; Verdon et al., 2010; Karnath and Rorden, in press). Distinctions have been drawn between spatial neglect and extinction (Ogden, 1985; Liu et al., 1992; Di Pellegrino and De Renzi, 1995; Cocchini et al., 1999; Karnath et al., 2003), personal and extrapersonal neglect (Guariglia and Antonucci, 1992; Beschin and Robertson, 1997; Committeri et al., 2007; Baas et al., 2011), and egocentric and allocentric neglect (Hillis et al., 2005; Grimsen et al., 2008; Marsh and Hillis, 2008; Medina et al., 2009; Chechlacz et al., 2010). Moreover, it has been suggested that different tests for visual neglect, such as cancellation and line bisection, are associated with different lesion sites (Karnath et al., 2004; Rorden et al., 2006; Verdon et al., 2010). Therefore, in addition to the main analysis we subdivided the coordinates into six subclasses (See **Table 1** and **Figures 1** and **3** for details). Subclass A included all coordinates in which neglect was specifically tested for using a line bisection task (purple spheres); Subclass B included all coordinates in which neglect was specifically tested for using a cancellation task (red spheres); Subclass C was used for coordinates derived from studies in which several different tasks (e.g., target cancellation, line bisection, copying, clinical observation) were used in combination to test for the presence of neglect (green spheres); Subclass D included coordinates for allocentric neglect (blue spheres); Subclass E included coordinates for personal neglect (black spheres); and Subclass F included coordinates for spatial extinction (orange spheres). Since dividing the data into separate subclasses did not provide enough coordinates to justify separate ALE meta-analyses, we plotted the individual coordinates on an inflated cortical surface to give a qualitative overview of the anatomy derived from the different studies.

# RESULTS AND DISCUSSION

## META-ANALYSIS ACROSS ALL INCLUDED STUDIES

The ALE meta-analysis of all included studies (**Table 1**) revealed nine significant clusters in total (See **Figure 2** and **Table 2** for details), all of which were located in the right hemisphere. The largest area of damage consistently associated with neglect included white matter corresponding to the posterior part of the superior longitudinal fasciculus (Mori et al., 2005). Other significant clusters were located in: (1) An area located at the border region between the posterior middle temporal gyrus and angular gyrus; (2) The inferior parietal lobule; (3) The caudate nucleus; (4) An area located at the border between the horizontal segment of the intraparietal sulcus and postcentral sulcus; (5) The precuneus; (6) An area including the superior temporal gyrus and superior temporal sulcus; (7) The posterior insula; and (8) The middle occipital gyrus.

## SUBDIVISIONS

### *Line bisection vs. target cancellation*

Our analysis shows that most of the lesions associated with line bisection deficits (purple spheres in **Figure 3A**) are located more posteriorly than those associated with target cancellation deficits (red spheres in **Figure 3B**), although one set of coordinates for line bisection, from the study by Vossel et al. (2011),

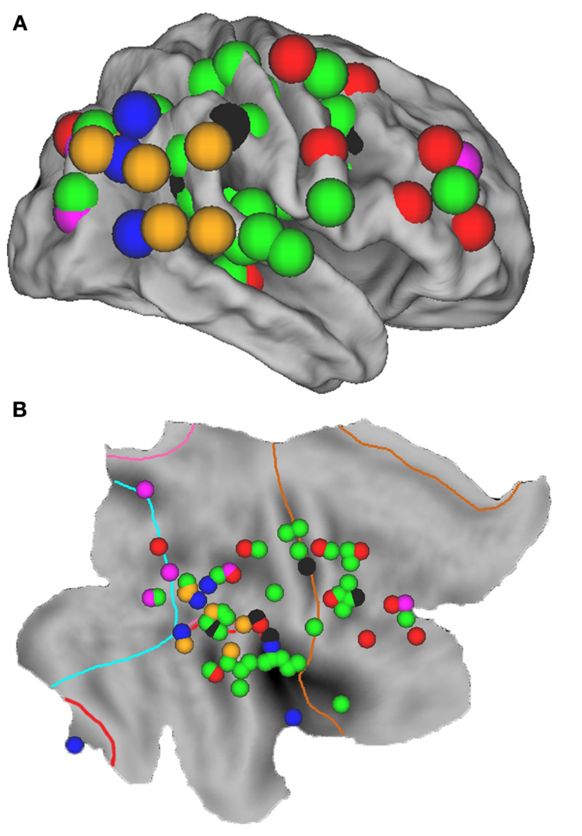


**FIGURE 1 | Overview of all regions associated with unilateral spatial neglect, based upon 20 lesion mapping studies (see Table 1), superimposed on the cortical surface of the right hemisphere using CARET software (v5.64 http://brainmap.wustl.edu/caret.html).** **(A)** Fiducial map. Purple spheres = neglect tested with line bisection tasks; red spheres = neglect tested with cancellation tasks; green spheres = neglect tested with a combination of tasks; blue spheres = allocentric neglect; black spheres = personal neglect; orange spheres = spatial extinction. **(B)** Flat map with identical spheres as in A. Cyan line indicates the occipital lobe border; pink line = parietal lobe; red line = temporal lobe; brown line = frontal lobe; regions outside borders = limbic lobe.

is located in the right middle frontal gyrus. The coordinates associated with neglect on target cancellation are quite widely distributed over dorsolateral prefrontal and parietal areas. It has been suggested that poor performance on the line bisection task is associated with more posterior lesions (Rorden et al., 2006; Verdon et al., 2010) because line bisection involves a more "perceptual or representational" deficit, whereas target cancellation deficits could also result from problems with "motor exploration" (Binder et al., 1992). This explanation is consistent with our finding of more frontal foci across studies that used target cancellation to assess neglect (**Figure 3B**). On the other hand, a recent study (Molenberghs and Sale, 2011) has shown that performance on line bisection and target cancellation in an unbiased clinical sample of left and right hemisphere stroke patients was highly correlated ($r = 0.76$), and that both tasks are associated with lesions in the right posterior angular gyrus. In more homogeneous (i.e., pre-selected) patient groups these correlations seem to be less pronounced (Binder et al., 1992; Ferber and Karnath, 2001), probably because of the reduced variance in the behavioral data. Another explanation for the discrepancy could be a difference in the approach to administering the line bisection task. For example, in the study by Ferber and Karnath (2001), the lines had been placed at the rightmost part of the sheet, which likely resulted in reduced or absent deviations from the midline in neglect patients (Schenkenberg et al., 1980).

#### *Allocentric vs. egocentric neglect*

Four of the studies that met our inclusion criteria (Grimsen et al., 2008; Medina et al., 2009; Chechlacz et al., 2010; Verdon et al., 2010) specifically examined allocentric neglect. Grimsen et al. (2008) found that allocentric neglect was associated with ventral lesions involving areas including the parahippocampal gyrus, whereas egocentric neglect was associated with more dorsal lesions in the premotor cortex. A similar dorsal versus ventral distinction between ego- and allocentric neglect was also found in the study by Medina et al. (2009). The parahippocampal gyrus was also implicated as the critical lesion site for allocentric neglect in a study by Verdon et al. (2010). In addition, these authors found that the critical lesion site for allocentric neglect extended into the middle temporal gyrus, as did Chechlacz et al. (2010), although in the latter study the damaged area also extended into posterior regions including the posterior temporal and angular gyrus (**Figure 3D**).

#### *Personal vs. extrapersonal neglect*

Personal neglect has been associated with more dorsal lesions than observed in patients with extrapersonal neglect (Committeri et al., 2007). These regions, which are shown in **Figure 3E**, are thought to be involved in coding proprioceptive body information such as the somatosensory cortex and more abstract body information such as the supramarginal gyrus (Committeri et al., 2007) and temporo-parietal junction (Baas et al., 2011).

#### *Spatial neglect vs. spatial extinction*

All studies that included a measure of extinction yielded lesions lying within posterior cortical regions, including the angular gyrus (Karnath et al., 2003; Molenberghs et al., 2008; Vossel et al., 2011) and temporo-parietal junction (Karnath et al., 2003). This is consistent with the view that spatial extinction is associated with more posterior parietal regions subserving stimulus competition (Karnath et al., 2003; Molenberghs et al., 2008; Gillebert et al., 2011), whereas the spatial neglect syndrome which is usually measured with a wider variety of behavioral measures is associated with multiple lesion sites. We note, however, that some previous studies have suggested that extinction arises as a nonspecific consequence of any unilateral lesion, perhaps reflecting a general competitive imbalance in sensory or other cortical areas (Birch et al., 1967; Farah et al., 1991; Vallar et al., 1994; Duncan et al., 1997). While this may be true to some extent, we note that these conclusions were based on clinical investigations that lacked high-resolution MRI data and statistical analytic techniques, such as voxel-based lesion-symptom mapping (Bates et al., 2003; Rorden et al., 2007), which can uncover subtle but consistent lesion foci across patients.

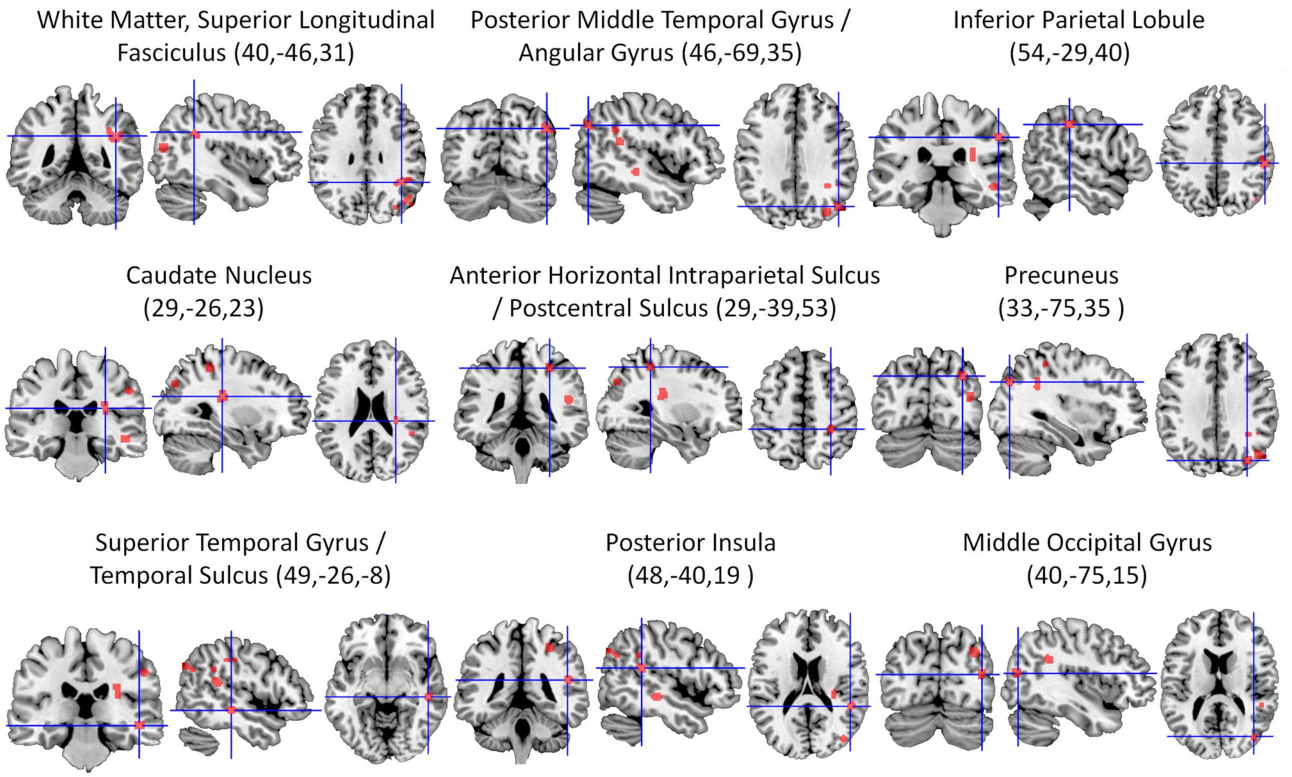


**FIGURE 2 | Overview of all significant clusters (FDR, $p < 0.05$) derived from the ALE analysis of 20 lesion mapping studies (listed in Table 1), superimposed on a ch2better template using MRIcron.** Numbers in parentheses are *x*, *y*, and *z* coordinates of the center of the cluster in MNI space. All lesion clusters are in the right cerebral hemisphere.

**Table 2 | Significant clusters (FDR, $p < 0.05$) revealed by the ALE analysis of the 20 lesion mapping studies.**

| Cluster | Cluster size in mm³ | Center MNI coordinates (*x, y, z*) | Anatomical region | Brodmann area |
|---|---|---|---|---|
| 1 | 704 | 40, −46,31 | White matter (right superior longitudinal fasciculus) | |
| 2 | 448 | 46, −69,35 | Right posterior middle temporal gyrus/right angular gyrus | 39 |
| 3 | 376 | 54, −29,40 | Right inferior parietal lobule | 40 |
| 4 | 352 | 29, −26,23 | Right caudate nucleus | |
| 5 | 336 | 29, −39,53 | Right anterior horizontal intraparietal sulcus /postcentral sulcus | 40 |
| 6 | 320 | 33, −75,35 | Right precuneus | 19 |
| 7 | 288 | 49, −26, −8 | Right superior temporal gyrus / right superior temporal sulcus | 22 |
| 8 | 256 | 48, −40,19 | Right posterior insula | 13 |
| 9 | 240 | 40,−75,15 | Right middle occipital gyrus | 19 |

## GENERAL DISCUSSION

### COMMON REGIONS ASSOCIATED WITH SPATIAL NEGLECT

From the wide variety of brain areas associated with unilateral spatial neglect (**Figure 1**), nine regions emerged consistently across the studies included in our meta-analysis (**Table 2** and **Figure 2**). These included regions typically associated with spatial neglect, such as the posterior temporal cortex (Karnath et al., 2004) and inferior parietal lobule (Mort et al., 2003), but also other regions less commonly associated with spatial neglect such as the occipital lobe. Although neglect is less common after posterior cerebral artery (PCA) infarction than after middle cerebral artery (MCA) infarction (Mort et al., 2003), it is not uncommon for PCA patients with occipital lobe lesions to suffer from neglect, probably because of damage to white matter pathways connecting the parahippocampal and angular gyrus (Bird et al., 2006). This probably explains why the right middle occipital gyrus was one of the critical lesion sites identified in our meta-analysis. Specific gray matter structures are more localized than long-range white matter pathways, and different sectors along a long-range white matter pathway can

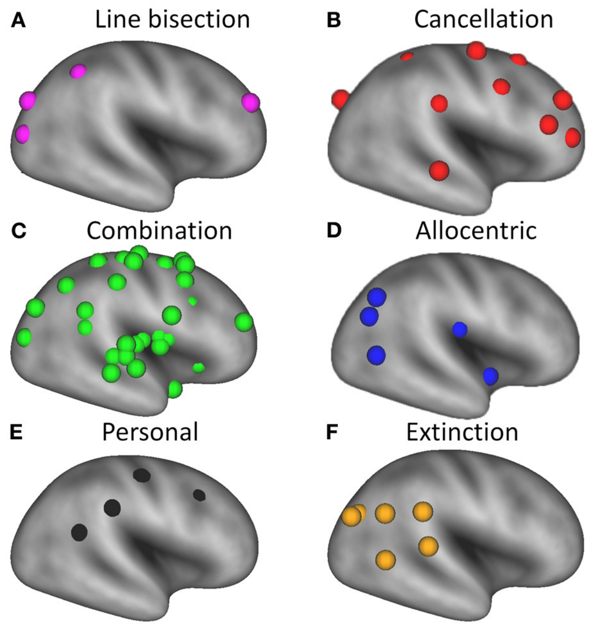


**FIGURE 3 | Overview of brain regions associated with different deficits in patients with unilateral spatial neglect, superimposed on a very inflated template brain using CARET software (v5.64 http://brainmap.wustl.edu/caret.html).** Purple spheres = neglect tested with line bisection tasks; red spheres = neglect tested with cancellation tasks; green spheres = neglect tested with a combination of tasks; blue spheres = allocentric neglect; black spheres = personal neglect; orange spheres = spatial extinction.

produce similar effects by disconnecting the fascicle, independent of the precise location of the interruption (Catani and Mesulam, 2008). It is possible, therefore, that our meta-analytic method under-represents the contribution of white matter lesions to spatial neglect. Nevertheless, consistent with the view that neglect can arise from white matter lesions connecting parietal and frontal areas (Doricchi and Tomaiuolo, 2003; Bartolomeo et al., 2007; Doricchi et al., 2008; Ptak and Schnider, 2010), our meta-analysis revealed that the largest region involved in the development of spatial neglect was a white matter lesion corresponding to the superior longitudinal fasciculus (Mori et al., 2005). Most of the significant regions in our analysis form the core of a previously described, "circuit-breaking" ventral frontoparietal attention network (Corbetta and Shulman, 2002; Corbetta et al., 2008), and lesions in this area can also lead to functional changes in the dorsal frontoparietal selective attention network (Corbetta et al., 2005; He et al., 2007; Corbetta and Shulman, 2011). Given the fact that most of these regions are situated around the center of the vascularization territory of the MCA it is no surprise that they emerged consistently and reliably from our meta-analysis. Vascular brain damage normally respects arterial territories and therefore will inevitably involve some brain regions more than others. This consideration should be borne in mind when interpreting the results of any lesion-based analysis, and our ALE approach is no exception. More posterior parietal regions that form the core components of this dorsal network, such as the intraparietal sulcus and superior parietal lobule, which are typically activated in neuroimaging studies on selective attention (Corbetta and Shulman, 2002; Woldorff et al., 2004; Molenberghs et al., 2007; Serences and Yantis, 2007; Molenberghs et al., 2008; Vandenberghe and Gillebert, 2009; Vandenberghe et al., in press), are less likely to be affected by stroke because they are situated at the border of the MCA and therefore have a smaller chance of being affected by stroke than the more central regions (Tatu et al., 2001). Recent evidence (Gillebert et al., 2011; Vandenberghe et al., in press), however, suggests that small focal lesions restricted to these regions can cause the same neglect-like symptoms as typically found in patients with more ventral damage.

### NEGLECT AS A HETEROGENEOUS SYNDROME

The term "unilateral spatial neglect" is used to describe a range of functional impairments, and the condition has increasingly become viewed as heterogeneous (Stone et al., 1998; Verdon et al., 2010; Karnath and Rorden, in press). This view is supported by the current meta-analysis, which shows that symptoms of the neglect syndrome considered together are associated with a widely distributed matrix of brain regions (**Figure 1**). A more detailed analysis of the different subclasses of neglect symptoms, such as visual extinction, allocentric, egocentric, personal and extrapersonal neglect, is important for characterizing the neural circuits that underlie these dissociable functional deficits (**Figure 3**). Further clues to this underlying circuitry can be gleaned from neuroimaging studies of neurologically healthy participants as they undertake conventional neglect-type tasks. For example, brain imaging studies of line bisection have implicated posterior cortical regions including the inferior and superior parietal lobule (Fink et al., 2000). Likewise, imaging studies of visual search, a task which in some respects at least resembles target cancellation, have shown that activity in the superior frontal sulcus is associated with effortful, conscious visual search (Leonards et al., 2000). These findings in healthy participants are consistent with data from our lesion meta-analysis, which showed that deficits on cancellation tasks tend to be associated with more anterior lesions (**Figure 3B**), whereas those with deficits on line bisection were associated with more posterior lesions (**Figure 3A**).

### DIFFERENT CRITERIA, TESTS AND TECHNIQUES PRODUCE DIFFERENT LESION PATTERNS

The 20 studies included in the meta-analysis used different criteria to identify neglect in their patient samples. For example, in the study by Mort et al. (2003) the criterion for classifying a patient as having neglect on line bisection was a 3 percent rightward deviation from the midline, whereas in the study of Molenberghs and Sale (2011) the criterion was 9.5 percent. It follows that a given patient identified as having neglect in one study might not be classified as such in another. It will therefore be critical in future studies for investigators to use a continuous behavioral score in lesion mapping analyses, so that the severity of symptoms can be taken into account. In previous studies (Karnath et al., 2001, 2003; Mort et al., 2003; Rorden et al., 2006) patients were divided into dichotomous groups according to arbitrary cut-offs, but recent developments in lesion mapping approaches (Rorden et al., 2007), and the inclusion of continuous behavioral scores as variables (Molenberghs et al., 2008; Verdon et al., 2010; Karnath et al., 2011; Molenberghs and Sale, 2011; Vossel et al., 2011) has improved the inferences that can be drawn from such studies. In addition, the time of testing post stroke (acute vs. chronic stage) is also an important factor that differs between studies and this can result in different lesion sites (Karnath et al., 2011).

The studies included in our meta-analysis also varied widely in the actual tests administered to assess neglect. Across the 20 studies there were seven different cancellation tasks [Line crossing (Albert, 1973), Ota's search task (Ota et al., 2001), Apple Cancellation Task (Chechlacz et al., 2010), Letter Cancellation Test (Weintraub and Mesulam, 1985), Star Cancellation Test (Halligan et al., 1989), cancellation tests from the BIT (Wilson et al., 1987), Bells Test (Gauthier et al., 1989) and Mesulam shape cancellation task (Mesulam, 1985)] and five different line bisection tasks [110 lines of varying length (Halligan et al., 1990), 18 lines of varying length (Schenkenberg et al., 1980), 8 lines of varying length (Urbanski et al., 2011), 10 lines of equal length (Ferber and Karnath, 2001), and three lines of equal length from the Behavioural Inattention Test (Wilson et al., 1987)]. These differences might well have contributed to inconsistencies in critical lesion sites reported across studies. Thus, for example, the targets in the Bells test (Gauthier et al., 1989) are small and densely interspersed amongst many distractor items, whereas the line crossing test (Albert, 1973) consists of sparsely distributed line segments with no visual distractors.

In addition to different behavioral measures, the studies employed different neuroimaging techniques. For example, some included low-resolution CT scans from which lesions were drawn manually onto standard templates (Karnath et al., 2004), while others used high-resolution MRI scans in which the lesions were mapped directly onto the original image (Mort et al., 2003; Molenberghs et al., 2008).

## THE WAY FORWARD

In addition to revealing the critical lesion sites associated with the various clinical manifestations of visual neglect, a key message of the current investigation is that there is a need to develop more sensitive and nuanced assessment tools to characterize the different facets of this heterogeneous syndrome. For example, a typical test for spatial neglect, such as target cancellation, involves both visuo-spatial and visuo-motor components. Impairment in either domain could therefore result in the same, abnormal score on the test, but due to deficits in different underlying functional processes. It will be important to bring laboratory tests into the clinic in an effort to identify specific cognitive functions by examining each in isolation [e.g., selective visual attention (Corbetta et al., 2005; Molenberghs et al., 2008; Bays et al., 2010; Gillebert et al., 2011; Vossel et al., 2011)]. Combining more specific descriptions of the neglect syndrome with better clinical measures that isolate specific cognitive functions should yield more consistent lesion mapping results in the future.

## ACKNOWLEDGMENTS

This work was supported by a University of Queensland Postdoctoral Fellowship awarded to Pascal Molenberghs, a National Health and Medical Research Council (NHMRC) Postdoctoral Training Fellowship awarded to Martin V. Sale, and an NHMRC Project Grant awarded to Jason B. Mattingley and Pascal Molenberghs. We would like to thank Jared Medina, Mikolaj Pawlak, Jennifer Rengachary, Simone Vossel, Philipp Eschenbeck and Tim Shallice for kindly providing us with the coordinates from their papers.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 22 January 2012; accepted: 20 March 2012; published online: 10 April 2012.*

*Citation: Molenberghs P, Sale MV and Mattingley JB (2012) Is there a critical lesion site for unilateral spatial neglect? A meta-analysis using activation likelihood estimation. Front. Hum. Neurosci. **6**:78. doi: 10.3389/fnhum.2012.00078*

frontiers in
HUMAN NEUROSCIENCE

GENERAL COMMENTARY
published: 03 August 2012
doi: 10.3389/fnhum.2012.00229

# The elusive nature of white matter damage in anatomo-clinical correlations

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**A commentary on**

**Is there a critical lesion site for unilateral spatial neglect? A meta-analysis using activation likelihood estimation**
*by Molenberghs, P., Sale, M. V., and Mattingley, J. B. (2012). Front. Hum. Neurosci. 6:78. doi: 10.3389/fnhum.2012.00078*

Molenberghs et al. (2012) contributed a clearly written meta-analysis on the debated issue of the anatomy of spatial neglect. They looked for a critical lesion site for neglect, and found several distinct regions whose damage has been associated with signs of neglect. Lesioned clusters were located in virtually the whole lateral surface of the right hemisphere (see their Figure 1), as well as in the white matter.

Molenberghs et al.'s study is timely and much needed after the recent publication of new evidence concerning this debate (see, e.g., Saj et al., 2012). Despite a fairly complete covering of the literature, however, a general methodological point prevents studies such as the present one from giving adequate weight to lesions to long-range white matter pathways.

As the authors acknowledge in the general discussion, while their method based on "the peak coordinates of the critical lesion site" is certainly appropriate for gray matter lesions, it seems problematic for long-range white matter bundles. At variance with gray matter lesions, where one can look for maximum overlap (Vallar and Perani, 1986) or analogous topological data (Bates et al., 2003), lesions in different sectors along a long-range white matter fascicle can produce similar effects by disconnecting the fascicle, independent of the precise location of the interruption (Catani and Mesulam, 2008). This is a general problem for studies looking for a "critical lesion site" in brain-damaged patients (Bartolomeo, 2011). Theoretically, similar behavioral deficits should be observed when a gray matter functional module is damaged as well as when white matter injury disconnects this module from the rest of the brain. Historically, neurologists have described neurological and neuropsychological deficits as disconnection syndromes (Geschwind, 1965; Catani and ffytche, 2005). However, the recent dominance of functional MRI (which identifies activation patterns in gray matter) and lesion symptom mapping based on gray matter injury (Bates et al., 2003) have led scholars to focus purely on the role of gray matter. Advances using techniques such as diffusion weighted imaging and the resulting tractography can help reveal the role of white matter (Catani, 2006). There is a clear need for methods that can integrate information from both gray and white matter injury, as these will likely provide better clinical significance and theoretical insight.

At present, the only way to explore the possibility that a deficit results from disconnection of a particular fascicle is to track the relevant fascicle, draw the lesions, and see whether or not they are located along the fascicle (see, e.g., Bourgeois et al., 2012). Methods based on this idea are being developed for group studies (Rudrauf et al., 2008). Concerning meta-analyses on neglect anatomy, Bartolomeo et al. (2007) mapped the hotspots defined by a small number of previous studies on fronto-parietal white matter, and found that the maximum lesion overlaps invariably occurred on or near the right superior longitudinal fasciculus (see also Doricchi et al., 2008; Thiebaut de Schotten et al., 2008). Such a procedure, however, would be much more cumbersome in larger meta-analyses such as the present one.

Despite these caveats, Molenberghs et al.'s results did reveal that "the largest region involved in the development of spatial neglect was a white matter lesion corresponding to the superior longitudinal fasciculus", consistent with the meta-analysis of Bartolomeo et al. (2007). However, other white matter sites of damage might have been more difficult to pinpoint. For example, the possibility that a disconnection of the inferior fronto-occipital fasciculus (IFOF) may determine neglect in some patients (Urbanski et al., 2008) does not appear in the meta-analysis results. This might well depend on the relative rarity of such patients; however, it could also result from the fact that the IFOF is a particularly long white matter pathway; thus, IFOF-damaging lesions might be dispersed along its length and go undetected by methods based on lesion clustering.

To conclude, Molenberghs et al. (2012) made an important attempt to clarify a complex problem such as the anatomy of neglect. Their results, however, also highlight demanding methodological issues that need to be solved in future research.

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*Received: 11 April 2012; accepted: 18 July 2012; published online: 03 August 2012.*

*Citation: Bartolomeo P (2012) The elusive nature of white matter damage in anatomo-clinical correlations. Front. Hum. Neurosci.* ***6****:229. doi: 10.3389/fnhum.2012.00229*

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 18 April 2012
doi: 10.3389/fnhum.2012.00093

# Visual search in spatial neglect studied with a preview paradigm

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Impaired visual search is a hallmark of spatial neglect. When searching for an unique feature (e.g., color) neglect patients often show only slight visual field asymmetries. In contrast, when the target is defined by a combination of features (e.g., color and form) they exhibit a severe deficit of contralesional search. This finding suggests a selective impairment of the serial deployment of spatial attention. Here, we examined this deficit with a preview paradigm. Neglect patients searched for a target defined by the conjunction of shape and color, presented together with varying numbers of distracters. The presentation time was varied such that on some trials participants previewed the target together with same-shape/different-color distracters, for 300 or 600 ms prior to the appearance of additional different-shape/same-color distracters. On the remaining trials the target and all distracters were shown simultaneously. Healthy participants exhibited a serial search strategy only when all items were presented simultaneously, whereas in both preview conditions a pop-out effect was observed. Neglect patients showed a similar pattern when the target was presented in the right hemifield. In contrast, when searching for a target in the left hemifield they showed serial search in the no-preview condition, as well as with a preview of 300 ms, and partly even at 600 ms. A control experiment suggested that the failure to fully benefit from item preview was probably independent of accurate perception of time. Our results, when viewed in the context of existing literature, lead us to conclude that the visual search deficit in neglect reflects two additive factors: a biased representation of attentional priority in favor of ipsilesional information and exaggerated capture of attention by ipsilesional abrupt onsets.

**Keywords: visual search, pop-out, saliency, selective attention, spatial neglect, temporal processing, parietal lobe**

## INTRODUCTION

Impaired visual search is one of the primary characteristics of spatial neglect. Patients with this disorder may fail to find personal belongings or may bump into obstacles when these are presented in contralesional space (Halligan and Marshall, 1993; Milner and McIntosh, 2005). Consequently, visual search tasks are among the most sensitive tests of spatial neglect. Several reports have shown that the visual search deficit of neglect patients varies as a function of the extent to which the task engages serial or parallel mechanisms of spatial attention. These studies were strongly influenced by work with healthy participants showing that performance in visual search for targets defined by a unique feature (*feature search*, e.g., a red *O* among red *X*s) is largely independent of the number of distracters (Treisman and Gelade, 1980; Treisman and Gormican, 1988) whereas when the target is defined by a unique combination of features (*conjunction search*, e.g., a red *O* among red *X*s and green *O*s) search times linearly increase with increasing numbers of distracters (Treisman and Gormican, 1988). Feature search is effortless and the target automatically "pops-out" among the distracters, suggesting that the search items are examined pre-attentively and in parallel. Conjunction search is effortful and search times depend on the number of distracters, suggesting that they are processed attentively and serially (Bricolo et al., 2002). The time necessary to examine an individual item in the display (i.e., the search rate) is expressed as the slope of a simple regression computed with search times for targets embedded in displays with increasing display size. In pop-out search the search rate approaches zero whereas in serial search it is in the order of several tens of milliseconds (Treisman and Gormican, 1988).

Functional imaging and virtual lesion studies using transcranial magnetic stimulation indicate that the posterior parietal cortex (PPC) plays a special role in feature binding and conjunction search (Corbetta et al., 1995; Ashbridge et al., 1997). This is confirmed by several reports of patients with damage to PPC exhibiting visual binding deficits in the form of illusory conjunctions (Cohen and Rafal, 1991; Friedman-Hill et al., 1995). Previous visual search studies examined the question whether the contralesional impairment of spatial attention characterizing neglect affects serial and parallel search mechanisms to the same degree, or whether pre-attentive processing—as is required in search for pop-out targets—is preserved. However, these studies have produced equivocal results. Regarding serial search for feature combinations, most studies agree that neglect patients have much slower search rates for contralesional targets (Riddoch and Humphreys, 1987; Humphreys and Riddoch, 1993; Aglioti et al., 1997; Esterman et al., 2000). In contrast, while some studies found that search for pop-out targets is impaired in the contralesional visual field (Eglin et al., 1989; Pavlovskaya et al., 2002; Behrmann et al., 2004; Eramudugolla and Mattingley, 2009), others reported intact performance (Aglioti et al., 1997; Esterman et al., 2000).

Several factors might account for these differences. Ipsilesional distracter stimuli strongly capture attention of patients with neglect (Posner et al., 1984; Morrow and Ratcliff, 1988; Golay et al., 2005), and this effect is particularly strong when distracters share perceptual properties with the search target (Ptak and Schnider, 2006). Some studies have shown that the number of ipsilesional distracters strongly affects visual search for a contralesional target (Eglin et al., 1989; Grabowecky et al., 1993), suggesting that impaired attentional disengagement might underlie deficient visual search performance (Posner et al., 1984; Bonato et al., 2009; Schnider et al., 2011). Peru and Chelazzi (2008) proposed that visual search in neglect is better described as result of interactions between a focused or distributed mode of processing rather than by the distinction between pre-attentive and attentive mechanisms. According to this proposal, patients with slight forms of neglect have difficulty directing focused attention to the contralesional hemifield while patients with severe neglect have an additional ipsilesional bias preventing distribution of attention across the hemifields. Finally, differences in search performance of patients with neglect might also be related to the anatomical location of brain damage. Thus, neglect patients with damage involving the inferior temporal cortex show particularly slow search for contralesional conjunction targets (Ptak and Valenza, 2005).

Reconciling these different proposals is difficult, as feature and conjunction search likely rely on distinct, but partially overlapping attentional mechanisms. Rather than using distinct feature and conjunction tasks we investigated the underlying attentional processes by presenting the different items of a conjunction display separated in time. We showed neglect patients a feature display and added supplementary distracters following a variable preview period, which transformed the display into a conjunction display. This is a variant of the preview paradigm (Olivers and Humphreys, 2004) in which participants are shown a preview of a set of distracters (e.g., green *H*s) some time (e.g., 1000 ms) prior to adding the second set of items (e.g., blue *A*s), which includes the target (blue *H*). Thus, apart from the preview period the task conforms to a standard conjunction search task. Nevertheless, healthy participants exhibit search rates compatible with fast, parallel search, indicating that the preview period effectively reduces the task to a feature search task.

In the present study the target (a green *T*) was presented together with the previewed items (red *T*s), before adding the remaining distracters (green *L*s). Thus, during the preview period the task was a standard feature task, and it only became a conjunction task once the remaining distracters were added. The search rate (expressed as a function of preview duration) in the modified preview task is therefore an indicator of the time needed to activate pre-attentive search mechanisms.

## MATERIALS AND METHODS

### PARTICIPANTS

Nine patients (three females) with left spatial neglect following recent right-hemispheric brain injury and 13 neurologically healthy control participants (eight females) participated in this study. Approval was obtained from the ethical committee of the University Hospital Geneva, and all participants gave written informed consent. The demographic data and results of clinical testing are presented in **Table 1**. Control participants and neglect patients had comparable age ($t_{20} = 0.89$), and all but one ambidextrous control subject were right-handed. All neglect patients manifested behavioral symptoms of visual neglect (e.g., unawareness of persons or objects placed contralesionally; difficulty with dressing, eating, grooming etc.) as well as objective neglect signs in at least three out of five neglect tests: the "Bells" cancellation test (Gauthier et al., 1989), cancellation of inverted among upright *T*s (Ptak et al., 2007), line bisection (Schenkenberg et al., 1980) and sentence copying (Wilson et al., 1987). Patients had preserved visual fields, as assessed on clinical confrontation and/or computerized perimetry (white dot presented on black background).

### VISUAL SEARCH TASK

In the visual search task participants were required to search for a green *T* presented on black background among varying numbers of distracters (green *L*s and red *T*s). The search displays were constructed by plotting letters on an imaginary circle (diameter: 11.4°), divided in sixteen equal sectors (**Figure 1**). Letters, uppercase *L* and *T*, were bright red (RGB-values: 255, 0, 0) or green (RGB-values: 0, 255, 0), and were 0.76° high × 0.67° wide. Search displays contained 4, 8, or 16 elements. On target-present trials (two thirds of all trials) one of these was the target (green *T*) and the remainder distracters; on target-absent trials all search elements were distracters. On 67% of all target-present trials the target was presented at position 4 in the right visual field (RVF) or position 12 in the left visual field (LVF). On the remaining trials it could appear at one of the positions 2, 6, 8, 10, 14 or 16, selected randomly, while distracters could appear at all positions. Thus, when the search display contained 16 elements, all positions were occupied, while when it contained 4 or 8 elements positions were selected randomly with the constraint that at least two items appeared in each hemifield.

Stimuli were presented on a 15′ laptop screen running at a resolution of 1280 × 768 pixels, placed at a distance of 60 cm from the participant. In the preview conditions, the search display was separated into a first display (preview) and a second display (final view). The preview display contained the target as well as all distracters that differed from the target only by their color (i.e., red *T*s). The final view contained distracters that differed from the target by their form (i.e., green *L*s). In the no-preview condition the target and all distracters were presented simultaneously. Each trial started with the presentation of a white fixation cross

**Table 1 | Demographic and clinical characteristics of neglect patients and control participants.**

| Patients | Age | Days post-injury | Aetiology | Bells cancellation (left omissions, out of 15) | Inverted T cancellation (left omissions, out of 27) | Line bisection (ipsilesional bias in %) | Sentence copying (words missed) |
|---|---|---|---|---|---|---|---|
| **N1** | 63 | 39 | CVI | 11 | 27 | 31.4 | 6 |
| **N2** | 68 | 48 | Haemorrhage | 14 | 13 | 20.1 | 6 |
| **N3** | 73 | 44 | CVI | 15 | 27 | 10.7 | 5 |
| **N4** | 51 | 43 | Haemorrhage | 15 | 27 | 33.7 | 4 |
| **N5** | 86 | 20 | CVI | 11 | 14 | 8.8 | 10 |
| **N6** | 69 | 19 | Haemorrhage | 15 | 27 | 23.7 | 15 |
| **N7** | 80 | 44 | CVI | 15 | 18 | −12.4 | 0 |
| **N8** | 80 | 111 | CVI | 8 | 7 | 9.6 | 2 |
| **N9** | 68 | 134 | CVI | 15 | 27 | 1 | 4 |
| Neglect mean | 70.9 ± 10.6 | 55.7 ± 39.7 | | 13.2 ± 2.6 | 20.8 ± 7.9 | 14 ± 14.8 | 5.8 ± 4.4 |
| Controls mean | 68 ± 10.6 | | | | | | |

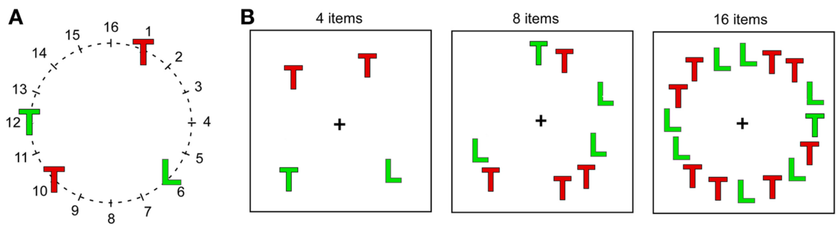


**FIGURE 1 | Displays used in the visual search task. (A)** Schematic presentation of the 16 positions on an imaginary circle, on which search items were presented. **(B)** Three examples of search displays with different display sizes and the target (green T) presented at different positions. Note that in reality letters were shown on black background and that their size is exaggerated in comparison to the circle.

in the middle of the screen. After 1000 ms either the final display appeared (no-preview condition) or a preview display, followed after 300 ms or 600 ms by the final display. In both preview conditions the task was therefore reduced to a color search task and only became a conjunction search task once the preview period ended. The final display stayed on until there was a response, or for a maximum duration of 5000 ms. Thus, the design of the task was a 2 (Target Position: *LVF, RVF*) × 3 (Display Size: *4, 8, 16 items*) × 3 (Preview Condition: *0, 300, 600 ms*) factor experiment. Stimuli were presented in blocks of 63 trials consisting of two trials per Target Position × Display Size × Preview Condition cell, nine trials with the target-presented randomly at other than the left/right positions, and 18 target-absent trials.

Participants were instructed to press the space bar as soon as they detected a green *T* and to withhold reaction when the target was absent. Control participants completed 10 blocks, resulting in 20 trials per cell; neglect patients completed up to 30 blocks, resulting in up to 60 trials per cell.

### TEMPORAL JUDGMENT TASK

Three neglect patients (N7, N8, N9) and seven controls (C7–C13) were tested in a temporal judgment task, which examined participants' perception of the temporal order of events. The experimental setup was the same as in the visual search task, with two important modifications. First, only target-present displays were shown. Second, participants were informed that some items of the display might appear earlier than the remaining items. Their task was to indicate whether all items were presented *at the same time*, or whether the target *T* was presented *prior to* a subset of distracters. Participants gave their answer orally, and the experimenter registered the answer by pressing on one of two different keyboard buttons. Each participant completed at least ten blocks of 45 trials, resulting in at least 20 trials per Target Position × Display Size × Preview Condition cell.

## RESULTS

### RESPONSE ACCURACY

The number of false alarms was very low in both groups (1.04 and 2.78% in controls and neglect patients, respectively) and was therefore not analyzed. **Table 2** shows the percent targets missed by control participants and neglect patients. Omission rates were close to zero in the control group and were therefore not analyzed. Across conditions neglect patients missed on average 0.8–7.4% ipsilesional targets. Not surprisingly their omission rates were much higher for contralesional targets (between 11.6–34%). These results were analyzed with repeated-measures

**Table 2 | Average percent missed targets in the control and neglect group as a function of target position (LVF, RVF), display size (4, 8 or 16 items) and preview condition (0, 300 or 600 ms).**

| | Controls | | | | | | Neglect | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LVF | | | RVF | | | LVF | | | RVF | | |
| | 4 | 8 | 16 | 4 | 8 | 16 | 4 | 8 | 16 | 4 | 8 | 16 |
| **0 ms** | 1.1 ± 3.3 | 0.6 ± 1.7 | 0.6 ± 1.7 | 0 | 1.1 ± 2.2 | 1.7 ± 3.5 | 12.2 ± 9.7 | 16.8 ± 11.4 | 34 ± 12.1 | 3.3 ± 4.2 | 4.6 ± 5.7 | 7.4 ± 8 |
| **300 ms** | 0 | 0 | 0.6 ± 1.8 | 0 | 0 | 0.6 ± 1.7 | 13.5 ± 12.7 | 17.7 ± 12.9 | 24.4 ± 15.7 | 1.8 ± 2.6 | 0.8 ± 1.8 | 4.1 ± 5.4 |
| **600 ms** | 0.6 ± 1.8 | 0 | 0 | 0 | 0 | 0.6 ± 1.7 | 11.6 ± 12 | 12.4 ± 11.7 | 17.7 ± 15.4 | 2.1 ± 2.8 | 4.1 ± 5.5 | 3.1 ± 3.3 |

ANOVA with the factors Target Position, Display Size and Preview Condition. Significant effects were followed-up computing *post-hoc* pairwise comparisons (Fisher test) with Bonferroni-adjusted level of significance. The analysis revealed significant main effects of Target Position [$F_{(1, 8)} = 30.25$, $P < 0.001$], Display Size [$F_{(2, 16)} = 16.62$, $P < 0.001$] and Preview Condition [$F_{(2, 16)} = 13.55$, $P < 0.001$], as well as significant interactions of Target Position × Display Size [$F_{(2, 16)} = 10.83$, $P < 0.01$], Target Position × Preview Condition [$F_{(2, 16)} = 3.99$, $P < 0.05$] and Display Size × Preview Condition [$F_{(4, 32)} = 8.05$, $P < 0.001$]. We did not analyze these effects further because of the presence of a significant three-way interaction of Target Position × Display Size × Preview Condition [$F_{(4, 32)} = 3.11$, $P < 0.05$]. *Post-hoc* comparisons revealed that whereas there was no difference across conditions for target omissions in the RVF, the percentage of LVF omissions significantly increased with increasing display size, but only in preview conditions 0 and 300. Thus, neglect patients found the search task hardest when the target was presented in the LVF, when many distracters were present, and when all display items were presented simultaneously or with a short preview. As will be seen in the following section this pattern is similar to the pattern of reaction times (RTs) and the findings can therefore not be explained by a speed-accuracy trade-off.

### REACTION TIME

Before analyzing possible effects of search conditions on RT, we examined the possible contribution of a bias resulting from the fact that targets appeared more often at positions 4 (right) and 12 (left) than any other position (this constraint being introduced in order to limit the number of experimental trials). We argued that, if participants were influenced by the biased probability of target occurrence, their omission rates and RTs for the most frequent positions of the target would gradually decrease. In order to test this prediction, we analyzed RTs of neglect patients to all LVF and RVF targets across 10 experimental blocks. Repeated-measures ANOVAs did not reveal any change in omission rates (LVF: [$F_{(9, 72)} = 0.58$]; RVF: [$F_{(9, 72)} = 1.22$)] or RTs (LVF: [$F_{(9, 72)} = 1.34$]; RVF: [$F_{(9, 72)} = 1.94$)] in neglect patients. Though this finding does not definitely exclude a bias due to different location probabilities, it suggests that the contribution of such a bias was negligible.

As **Figure 2** shows the pattern of RTs to ipsilesional targets is comparable between groups. In contrast, neglect patients were differently affected by search conditions when searching for contralesional targets.

In an initial analysis, results were submitted to a mixed ANOVA with Group (control, neglect), Target Position, Display Size and Preview Condition as factors. This analysis revealed significant main effects of Group [$F_{(1, 16)} = 23.23$, $P < 0.001$], Target Position [$F_{(2, 16)} = 23.36$, $P < 0.001$], Display Size [$F_{(2, 32)} = 51.11$, $P < 0.001$], and Preview Condition [$F_{(2, 32)} = 107.31$, $P < 0.0001$]. All two-way and three-way interactions were significant: Group × Target Position [$F_{(1, 16)} = 28.67$, $P < 0.0001$], Group × Display Size [$F_{(2, 32)} = 7.98$, $P < 0.01$], Group × Preview Condition [$F_{(2, 32)} = 7.87$, $P < 0.01$], Target Position × Display Size [$F_{(2, 32)} = 9.65$, $P < 0.001$], Target Position × Preview Condition [$F_{(2, 32)} = 5.99$, $P < 0.01$], Display Size × Preview Condition [$F_{(4, 64)} = 58.71$, $P < 0.0001$], Group × Target Position × Display Size [$F_{(2, 32)} = 16.71$, $P < 0.0001$], Group × Target Position × Preview Condition [$F_{(2, 32)} = 16.98$, $P < 0.0001$], Group × Display Size × Preview Condition [$F_{(4, 64)} = 6.60$, $P < 0.001$], and Target Position × Display Size × Preview Condition [$F_{(4, 64)} = 8.18$, $P < 0.0001$]. Finally, the four-way interaction between all factors was also significant [$F_{(4, 64)} = 17.96$, $P < 0.0001$].

In order to better understand this complex pattern, we decided to follow up these results with separate repeated-measures analyzes of RTs to LVF and RVF targets, focusing on the factors Group, Display Size and Preview Condition.

For targets presented in the RVF this analysis revealed significant effects of Display Size [$F_{(2, 32)} = 49.4$, $P < 0.0001$] and Preview Condition [$F_{(2, 32)} = 66.48$, $P < 0.0001$], as well as an interaction between these two factors [$F_{(4, 64)} = 29.59$, $P < 0.0001$]. Pairwise comparisons showed that in both preview conditions RTs were comparable across different display sizes, but increased from display size 4–16 when all items were presented simultaneously. In addition, RTs were longer in the no-preview condition compared to both preview conditions for all three display sizes. The main result of these comparisons was that no interaction with the factor Group reached significance, indicating that in the RVF neglect patients had a pattern of results comparable to healthy participants.

The same analysis on RTs to LVF items revealed significant effects of Group [$F_{(1, 16)} = 32.46$, $P < 0.0001$], Display Size [$F_{(2, 32)} = 30.89$, $P < 0.0001$] and Preview Condition [$F_{(2, 32)} = 67.95$, $P < 0.0001$]. The two-way interactions of Group × Display Size [$F_{(2, 32)} = 12.95$, $P < 0.0001$], Group × Preview Condition [$F_{(2, 32)} = 16.92$, $P < 0.0001$] and Display Size × Preview Condition [$F_{(4, 64)} = 37.4$, $P < 0.0001$] were significant. Most importantly, the three-way interaction of Group × Display

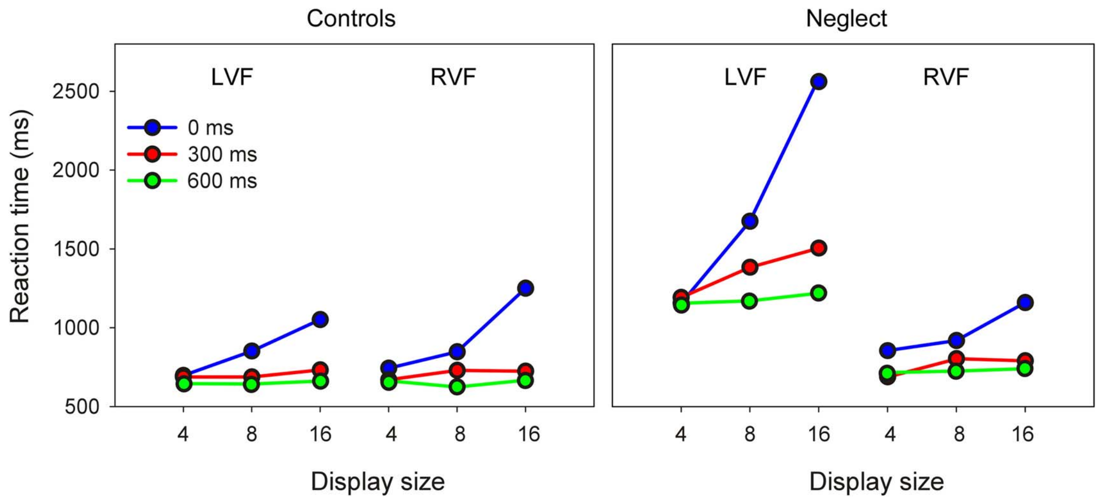


**FIGURE 2 | Mean reaction time of controls and neglect patients as a function of target position, display size and preview condition (LVF/RVF: left/right visual field).**

Size × Preview Condition was significant [$F_{(4, 64)} = 15.12$, $P < 0.0001$]. Pairwise comparisons showed for the control group very similar results as for RVF targets: RTs increased with increasing display size only when all items were presented simultaneously, and RTs were longer in this condition compared to both preview conditions at display sizes 8 and 16. The same differences were also found for the data of neglect patients. However, in addition patients showed also a significant increase of RTs in the 300 ms preview condition when the display contained 16 items compared to when it contained only four items. Only when the preview was as long as 600 ms were RTs independent of display size.

Thus, the main finding of these analyzes is that visual search of healthy participants depended on display size only when all items were presented simultaneously, while previewing the target for 300 ms or more was sufficient to turn the task into a pop-out task. This pattern was comparable for items shown in the LVF and RVF. In contrast, neglect patients showed a clear difference between visual fields: their search RT was independent of display size in both preview conditions when the target was shown in the RVF, while for LVF targets it was only independent of display size when the preview was 600 ms. These effects of item preview were further examined with analyzes of search rate.

## SEARCH RATE

**Figure 3** shows the mean search rate of controls and neglect patients as a function of preview condition. The search rate is the time necessary to examine one individual item in conditions when the target is present (having used a go-nogo task we did not sample search times for target-absent trials and were therefore unable to compute search rates for these trials). Search rates close to zero indicate that search time is independent of the number of items in the display—a marker of pop-out search.

A mixed ANOVA revealed significant main effects of Group [$F_{(1, 16)} = 16.24$, $P < 0.001$], Target Position [$F_{(1, 16)} = 16.83$, $P < 0.001$] and Preview Condition [$F_{(2, 32)} = 110.51$, $P < 0.0001$]. The two-way interaction between Group and Target Position was also significant [$F_{(1, 16)} = 25.11$, $P < 0.001$], but was not further analyzed because of the presence of a significant three-way interaction [$F_{(2, 32)} = 16.2$, $P < 0.0001$]. Pairwise comparisons showed that the search rate of neglect patients was comparable to healthy controls when the target was presented in the RVF, irrespective of preview condition. In contrast, for targets in the LVF neglect patients had slower search rates than controls in the no-preview condition or when the preview was 300 ms. However, even at the longest preview interval neglect patients seemed to benefit less from the preview than controls. We therefore performed additional paired $t$-tests evaluating whether search rates reliably differed from zero. For control participants, this was the case only when all items were presented simultaneously (LVF: $t_8 = 6.1$, $P < 0.0001$; RVF: $t_8 = 10.6$, $P < 0.0001$).

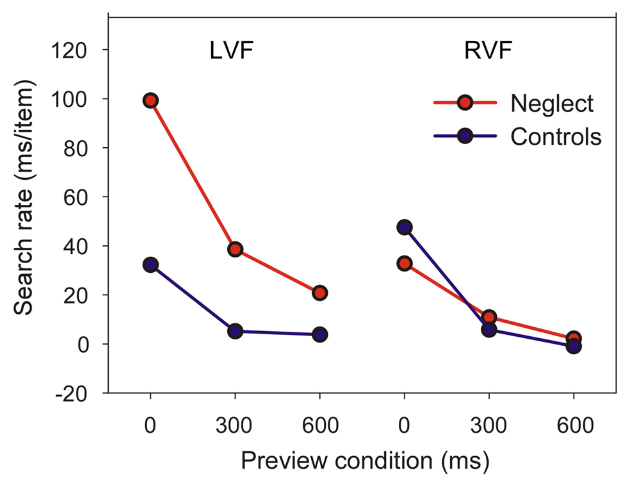


**FIGURE 3 | Mean search rates of the control and neglect group (LVF/RVF = left/right visual field).**

Similarly, neglect patients had a search rate significantly greater than zero when all items were presented simultaneously (LVF, mean 99 ms: $t_8 = 10.7$, $P < 0.0001$; RVF, mean 33 ms: $t_8 = 7.15$, $P < 0.0001$). However, in contrast to healthy participants their slope also differed from zero when the target was presented in the LVF and was previewed for 300 ms (mean 39 ms: $t_8 = 3.39$, $P < 0.01$).

Together, these findings show that while visual search of neglect patients for RVF targets is comparable to healthy participants, patients benefit less from item preview when targets are shown in the LVF.

### TEMPORAL JUDGMENT

In order to examine to what extent the preview benefit might depend on the explicit recognition of temporal separation, three neglect patients (N7, N8, N9) and seven age-matched controls (C7–C13) were tested in a temporal judgment task. The results of these subgroups in the visual search task were similar to the whole group. **Figure 4** shows the mean percentage of trials on which the target was judged being presented simultaneously with all distracters. As the figure shows, the performance of control participants in this "slow" task was close to ceiling, and made it therefore difficult to compare with performance of neglect patients. We therefore asked six additional healthy participants (four females; mean age, 27 years) to make judgments of simultaneity using much shorter time intervals ("fast" task: 15 and 30, instead of 300 and 600 ms). Performance of neglect patients was profoundly impaired, and differed in several respects compared to healthy participants. First, patients made more "simultaneous" judgments when the number of display items increased (Friedman test, no-preview condition, LVF: $\chi^2 = 6.0$, $P < 0.05$; RVF: $\chi^2 = 4.67$, $P = 0.097$). This appeared to be due to a generalized response bias that affected temporal judgments independently of preview condition, and was not beneficial for performance. This conclusion is supported by the observation that healthy participants performing the much more difficult "fast" task were positively influenced by item number: their performance was better with increasing display size in the no-preview condition as well as the 30 ms preview condition.

Second, neglect patients' temporal judgments were much less influenced by preview condition than controls. In the "slow" task healthy controls had a ratio of "simultaneous" judgments close to 0% in both preview conditions and 100% in the no-preview condition. A similar pattern was found in the "fast" task, when the 30 ms preview condition was compared with the no-preview condition. Only in the 15 ms preview condition were healthy participants' judgments of simultaneity close to chance performance. In comparison, the difference between preview and no-preview conditions was much less for neglect patients. We analyzed these data by computing average scores for preview and no-preview conditions across all display sizes, and compared these within each group with non-parametric tests. Control participants made more "simultaneous" judgments for no-preview items than preview items in the "slow" task (Wilcoxon Test, LVF: $Z = 2.37$, $P < 0.05$; RVF: $Z = 2.36$, $P < 0.05$) and the "fast" task (LVF: $Z = 2.20$, $P < 0.05$; RVF: $Z = 2.2$, $P < 0.05$) whereas there was no effect of preview on neglect patients' judgments of simultaneity (LVF: $Z = 1.6$; RVF: $Z = 1.6$). Finally, in strong contrast to the visual search task neglect patients showed comparable performance for targets presented in the LVF and targets presented in the RVF (Wilcoxon test, average across all conditions: $Z = 0$).

## DISCUSSION

The use of a preview paradigm to study visual search reveals several characteristics of search performance in patients with spatial neglect. When all items were presented simultaneously and the task corresponded to a conjunction search task, control participants exhibited search rates reflecting serial search. In contrast, when there was a preview of parts of the search display, their average search rate approached zero milliseconds in both preview conditions, suggesting parallel search. Neglect patients showed comparable performance when searching for targets in the right

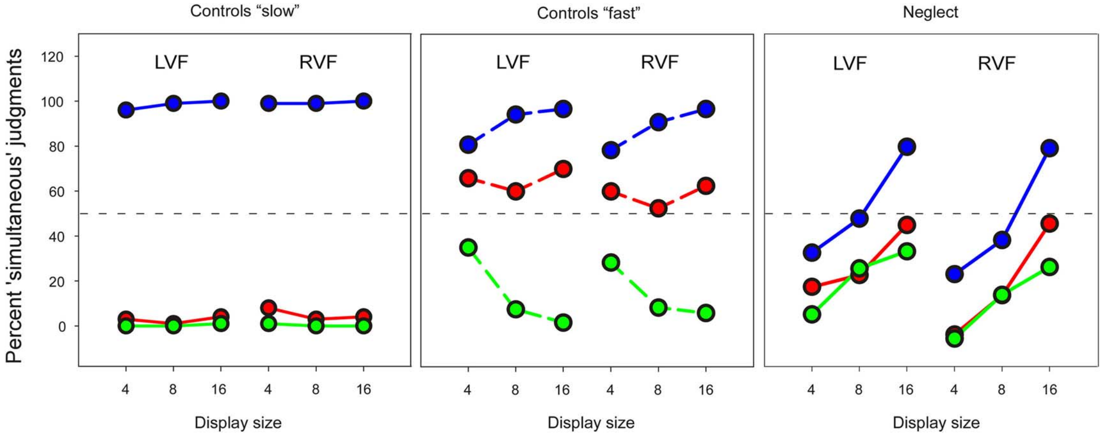


**FIGURE 4 | Mean percent "simultaneous" responses in the temporal judgment task.** Left and right panel: blue—no preview; red line—300 ms preview; green—600 ms preview. Middle panel: blue—no preview; red—15 ms preview; green—30 ms preview. The stippled horizontal line represents chance performance.

hemifield. In contrast, for left hemifield targets their search data were characterized by two major trends. First, when all search items were presented simultaneously patients showed increasing RTs with increasing numbers of distracters, which is compatible with previous conjunction search studies (Eglin et al., 1989; Esterman et al., 2000; Behrmann et al., 2004). More importantly, though search rates were strongly reduced in the preview conditions neglect patients' visual search remained inefficient at 300 ms preview, and partly even at 600 ms preview, when the target appeared in the LVF. Thus, while neglect patients benefited from item preview of LVF items, previewing did not reduce the search task to a pop-out task.

The preview search task used in our study resembles a paradigm used in previous reports to examine a phenomenon known as visual marking, thought to result from top-down inhibition of a subset of distracters presented prior to the rest of the display (preview display; Watson and Humphreys, 1997). However, in a visual marking experiment the preview display only contains distracters and the search target is shown in the final display. By contrast, in our study the preview display contained the target and the final display only distracters. Though the methodological difference appears to be small, the processing requirements of the two paradigms are different: in the visual marking paradigm, search is faster because previewed items are inhibited and search is restricted to items appearing in the final display. In our paradigm, search is restricted to the subset of items presented during preview (provided the deployment of attention during preview is sufficiently fast), resulting in a pop-out effect. If the target is not found during the preview period attention may drift away due to capture by the upcoming final display.

One might be tempted to explain the failure of neglect patients to show pop-out search in the preview conditions by impaired explicit judgment of temporal simultaneity. Indeed, neglect patients exhibit deficits suggesting an altered perception of time intervals and of the temporal order of events (Becchio and Bertone, 2006). Thus, neglect patients have deficits perceiving the duration of stimuli both for intervals below one second (Basso et al., 1996) and up to 60 s (Danckert et al., 2007). More relevant to the present study is the observation that in situations of asynchronous presentation, a contralesional stimulus must be presented with substantial lead in order to be perceived by neglect patients as simultaneous to an ipsilesional item (Rorden et al., 1997; Robertson et al., 1998). Here, we used a similar paradigm, but varied the display size. The results of the temporal judgment task–though influenced by a response bias (patients made more "simultaneous" judgments with increasing display sizes)—revealed two important findings that are helpful in identifying the processes involved in visual search: First, the number of "simultaneous" judgments was not significantly different in the preview compared to the no-preview condition. Second, in contrast to visual search the temporal judgment deficit was independent of target side. These observations are based on a limited number of participants who did not complete the search tasks. Although they suggest that the effect of item preview on visual search is not dependent on explicit knowledge of temporal order, a more confident conclusion to this effect must await a study in which a sufficient number of patients and controls are tested on both search and temporal processing tasks.

Our findings are better explained by impaired deployment of spatial attention in neglect. Cognitive and computational models of visual search distinguish two stages of visual processing (Treisman and Gelade, 1980; Treisman and Gormican, 1988; Wolfe, 1994; Itti et al., 1998): a feature stage, at which individual features are analyzed in separate visual maps, and a conjunction stage, at which features are combined to form spatially coherent objects. According to these models spatially focused attention is necessary for the binding of individual features and the prioritization of important objects. Neurophysiological studies have shown that the activity of neurons in the PPC reflects a combination of bottom-up saliency information and top-down signals carrying information about the behavioral relevance of a stimulus (Gottlieb et al., 1998; Constantinidis and Steinmetz, 2001; Bisley and Goldberg, 2010). Other characteristics of the PPC—such as feature-independent coding of information and integration of inputs from several modalities—suggest that this region contains a priority map of the environment (Bisley and Goldberg, 2010; Ptak, 2011; Vandenberghe et al., 2012). Recent evidence from lesion studies supports this conclusion. Whereas several reports localized the greatest lesion overlap associated with neglect in the inferior parietal (Vallar and Perani, 1986; Mort et al., 2003; Golay et al., 2008), superior temporal (Karnath et al., 2004) or premotor and ventral frontal cortex (Rengachary et al., 2011), some have found that damage to the PPC is a predictor of specific attention deficits in neglect. Thus, damage affecting the intraparietal sulcus impairs processing of contralesional targets under bilateral stimulation (Vandenberghe et al., 2005), contributes to the appearance of object-based deficits (Ptak et al., 2011), and predicts deficits of attentional shifting and target selection in patients with neglect (Ptak and Schnider, 2011). Moreover, damage to the superior longitudinal fasciculus, which is a major fiber tract connecting the PPC with lateral premotor cortex (Schmahmann and Pandya, 2006), is a predictor of the occurrence of spatial neglect (Thiebaut de Schotten et al., 2005; Bartolomeo et al., 2007), of the preference for ipsilesional locations that characterizes this disorder (Bourgeois et al., 2012), and of the degree to which relevant stimuli capture attention of neglect patients (Ptak and Schnider, 2010). Together, these findings indicate that a frontoparietal network involving the PPC and premotor cortex is crucially involved in the elaboration and representation of attentional priority.

The question arising from these findings is how the failure of neglect patients to fully benefit from item preview can be accommodated with the idea of a parietal priority map. An influential theoretical position holds that neglect results from a spatial selection bias favoring ipsilesional information (Desimone and Duncan, 1995; Duncan, 2004). Applied to the visual search task this hypothesis postulates that due to the right-hemispheric brain damage of patients with neglect ipsilesional items have a higher level of priority than contralesional items. Priority is of importance when search is effortful and requires relatively focused examination of individual items. Therefore, ipsilesional stimuli are found faster when all stimuli are presented simultaneously (conjunction search) because search proceeds from right to left according to the degree of priority. In both preview conditions visual search is effortless (feature search) only during the preview period, and attentional priority is less biased in favor of right-sided information. However, in these conditions an additional bias likely affects performance, which is the abrupt onset of additional items at the end of the preview period. Visual onsets capture attention (Yantis and Jonides, 1990) and they do so particularly strongly in patients with lateralized deficits of spatial attention (de Renzi et al., 1989; D'Erme et al., 1992). Right-sided abrupt onsets may therefore delay the activation of search mechanisms or interrupt the on-going search of neglect patients for a left-sided item.

In conclusion, the present findings suggest two additive processes that contribute to the deficit of neglect patients in conjunction search tasks: a biased representation of attentional priority in favor of ipsilesional information and exaggerated capture of attention by ipsilesional abrupt onsets. The preview paradigm provides a tool for the investigation of distinct attentional processes contributing to impaired search performance in spatial neglect.

## ACKNOWLEDGMENTS

Study supported by the Swiss National Science Foundation (grant 320030–134591).

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 30 January 2012; accepted: 31 March 2012; published online: 18 April 2012.*

*Citation: Fellrath J, Blanche-Durbec V, Schnider A, Jacquemoud A-S and Ptak R (2012) Visual search in spatial neglect studied with a preview paradigm. Front. Hum. Neurosci.* ***6****:93. doi: 10.3389/fnhum.2012.00093*

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 13 June 2012
doi: 10.3389/fnhum.2012.00176

# Disentangling input and output-related components of spatial neglect

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***Reviewed by:***
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Spatial neglect is a heterogeneous disorder with a multitude of manifestations and subtypes. Common clinical paper and pencil neglect tests fail to differentiate between these subtypes. For example, neglect patients typically bisect lines to the right. This bias can be caused by an underestimation of the left half of the line (input-related deficit), by the failure to direct actions toward the left side of space (output-related deficit), or by a mixture of these impairments. To disentangle these impairments, we used a test consisting of a line bisection task on a touch screen monitor (manual motor task) and the subsequent judgment of one's own bisection performance (visual perceptual task). It was hypothesized that patients with mainly output-related neglect should be better able to recognize their misbisected lines than patients with purely input-related neglect. In a group of 16 patients suffering from spatial neglect after right brain damage, we found that patients were three times more likely to suffer from a predominantly input-related than from an output-related subtype. The results thus suggest that neglect is typically an input-related impairment. Additional analysis of the line bisection task revealed that temporal (slowness in initiation and execution of contralateral movements) and spatial (insufficient movement amplitude toward the contralesional side) aspects of output-related neglect were mutually unrelated. This independence raises the possibility that a fine-grained differentiation of output-related neglect is required. That is, impairments in lateralized temporal and spatial aspects of movements may underlie different neglect subtypes.

**Keywords: spatial neglect, rehabilitation, neglect subtype, motor neglect, perceptual neglect, attention, proof of concept, stroke**

## INTRODUCTION

Spatial neglect is a disabling disorder of lateralized cognition and behavior (Bradshaw and Mattingley, 1995). It is characterized by a failure to report, respond, or orient to stimuli presented to the side opposite a brain lesion, which cannot be attributed to elementary sensory-motor impairments (Heilman, 1979). The presence of neglect is associated with an unfavorable prognosis in terms of rehabilitation outcome, length of hospital stay, and daily living activities after discharge to home (Robertson and Halligan, 1999; Nys et al., 2005). Knowledge of the processes guiding spontaneous recovery and effective therapeutic approaches for spatial neglect is very sparse (Bowen and Lincoln, 2007a,b). This is surprising, given that spatial neglect occurs in a substantial number of patients suffering from brain damage (about 45% of patients after right and 20% of patients after left brain damage, see Bowen et al., 1999). There is, therefore, an obvious clinical need for a better understanding of the cognitive mechanisms underlying spatial neglect to advance therapeutic interventions.

A fundamental difficulty in advancing neglect therapy derives from the inherent heterogeneity of the disorder. Numerous subtypes and forms of spatial neglect have been described in the literature (Bartolomeo and Chokron, 2001; Buxbaum et al., 2004; Barrett et al., 2006). Some patients with right brain damage, for example, may primarily neglect the left side of their body (personal neglect), whereas other patients neglect the left in reaching (near) space, and still others only neglect the left side of space beyond their reach (far space, see Halligan and Marshall, 1991; Vuilleumier et al., 1998). Furthermore, some patients may be particularly affected when detecting left-sided stimuli, while others are impaired during the initiation, execution and/or aiming of motor responses toward those stimuli (Heilman, 1979, 2004). The wide variety of behavioral neglect profiles is commonly thought to originate from damage to distinct neural substrates in a widely distributed cortical network, which mediates attention in the brain (Mesulam, 1999; Verdon et al., 2010). It is conceivable, therefore, that therapeutic success could be improved if treatments are targeted to the specific pattern of the impairment. In support of this view, there is preliminary evidence that patients with different forms of neglect may respond differently to specific treatments (Barrett et al., 1999, 2001; Adair et al., 2003).

While the potential importance of isolating neglect subtypes is emphasized in authoritative reviews on neglect therapy (Barrett et al., 2006; Bowen and Lincoln, 2007a), standard clinical tests, such as line bisection, copying or cancellation tasks, all fail to provide information on the subtypes of neglect. For example, while a marked rightward deviation in the bisection of horizontal lines indicates left-sided neglect, the reason for this deviation can differ between patients. Some patients may deviate to the right because of a perceptual-attentional bias toward the right-side (input-related deficit) while others deviate to the right because of a failure to direct actions toward the left side of space (output-related aiming deficit). There may also be individuals with a mixture of input and output impairments, which makes them difficult to sort neatly into either category (Bisiach et al., 1990; Schwartz et al., 1999; Bartolomeo and Chokron, 2001). Performance on the traditional line bisection task, however, does not allow the clinician to distinguish between these possibilities.

A number of techniques have been devised to disentangle input- and output-related accounts of neglect. The general rationale in many of these techniques is to uncouple the direction of hand movements (output) from the location of the corresponding visual target (input). One study used, for example, a horizontal pulley device with a pointer mounted on the upper pulley string (Bisiach et al., 1990). Participants were asked to move the pointer to the midpoint of a line. In one condition, participants grasped the pointer on the upper string and moved it to the subjective midpoint. The directions of hand and pointer movements were therefore congruent. In a second condition, participants controlled the pointer by moving the lower pulley string. Consequently, hand and pointer movements were in opposite directions: pulling the lower string leftwards resulted in rightward pointer movements, and vice-versa, when the lower string was moved rightward. Neglect was classified to be predominantly input-related if an identical rightward deviation was found in both conditions. Conversely, output-related neglect was indicated by marked leftward deviations in the incongruent pulley condition, because impairments in pulling the lower pulley string leftwards resulted in a failure to shift the pointer toward the right. Other studies have reported similar perceptual/motor dissociations using devices such as reversing mirrors (Tegner and Levander, 1991), video cameras (Na et al., 1998), and overhead projectors (Nico, 1996) to present left/right mirror-reversed visual feedback on a display. These techniques also allow the assessment of input and output-related biases, not only in clinical populations, but also in healthy (Garza et al., 2008; Fortis et al., 2011) and aged participants (Chen et al., 2011).

While the ingenuity of the above techniques is not disputed, the interpretation of the data is not quite as straight-forward as one might wish. Some researchers have pointed out that coordinating spatially incongruent movements from visual feedback is highly confusing and some patients might simply fail to handle the high task-demands (Mattingley et al., 1998; Husain et al., 2000; Vallar, 2001). That is, deficits in the execution of mirror-reversed movements are not necessarily exclusive to output-related deficits of neglect, but might also derive from frontal executive dysfunctions in resolving the cognitive conflict between movement direction and visual feedback (Fink et al., 1999). Such conflicts might particularly arise during the initial phases of learning motor responses to incongruent visual feedback. Once the new motor skills are fully acquired frontal executive conflicts might be less common as motor responses are now thought to be implicit and automatic (Halsband and Lange, 2006).

A paradigm that does not involve conflicting visuo-motor movements is the passive line bisection task. In this task, patients observe an experimenter as he/she moves the tip of a pen along a line. The patient then indicates verbally when the subjective midpoint has been reached by the pen's tip (Reuter-Lorenz and Posner, 1990). However, the use of moving stimuli (see also Halligan and Marshall, 1989; Chiba et al., 2006 for related methods) is not ideal because the stimuli may act as a visual cue and cues are well known to modulate spatial neglect (Riddoch and Humphreys, 1983). The paradigm may therefore not provide an uncontaminated indication of input-related neglect.

A compelling alternative to the use of a moving marker is the presentation of pre-bisected lines ("landmark task", Milner et al., 1993; Harvey et al., 1995). The landmark task requires patients to point to the end of the line closer to the transaction mark. Patients with input-related neglect are assumed to perceive the left-side of accurately bisected lines as shorter and to point to that side. Conversely, those patients consistently pointing to the right side are thought to suffer from output-related neglect. Harvey et al. (1995) required neglect patients to carry out a relatively difficult landmark task where the bisector was placed only up to 5 mm to the left or right of the true middle. While the ability of the task to detect input-related neglect is not disputed, the task's sensitivity to output-related neglect has been questioned (Husain et al., 1998; Harvey, 2004). Bisiach et al. (1998) modified the landmark task used by Harvey et al. (1995) using stimuli where the difference between the left and right halves of the line ranged from 30 to 150 mm. By making the task easier, Bisiach et al. (1998) identified more patients with output-related neglect. That said, because the task was easy, it was less able to identify patients with input-related neglect. Thus, while it appears that the ideal placement of the bisection mark is an unsettled issue, analyses involving curve fitting procedures have been proposed to circumvent this problem (Toraldo et al., 2002, 2004). In any case, when reviewing the strength and weaknesses of the different tasks developed for assessing input and output-related tasks, Harvey (2004, p. 327) concluded that landmark tasks are "the most appropriate, thoroughly researched tool" for such assessments.

While patients with pure output-related neglect are impaired in reaching to the left-side of space they are thought to have relatively spared perceptual skills. Asking patients to judge their own bisections therefore offers a solution to shed light on the underlying impairment. Based on this reasoning, the first goal of the current study was to introduce a simple method of disentangling input- and output-related neglect. In traditional versions of the landmark task, the experimenter bisects the lines and then presents them to the patient. This may not be ideal because of the difficulties in determining which level of difficulty to use and because the lines are not related to the patient's actual motor behavior in space. Both these issues can be solved if the patients generate the stimuli themselves. Our new experimental paradigm first requires the patient to bisect a series of horizontal lines. Subsequently, the lines are presented again and the patient judges their own bisections (see **Figure 1**). By asking the patient to bisect a line and then judge that bisection, the task should allow us to disentangle input- and output-related neglect. Output-related impairments hamper the placement of the bisection mark at the intended location, but not the subsequent perceptual error judgment task. Accordingly, patients with output-related neglect were expected to recognize their own bisection errors. Patients with input-related neglect were expected to show a different pattern of results. Because their output is relatively spared, their manual bisections were expected to be subjectively accurate. Therefore, when judging the accuracy of their own bisections, they were expected to have much more difficulty.

Output-related neglect may not only affect the spatial scale of goal-directed movements but also the timing of these movements. That is, patients with output-related neglect may be impaired in initiating leftward movements (directional hypokinesia) and/or may be slowed in the execution of leftward movements (directional bradykinesia). Impairments in these temporal aspects of goal-directed movements were first observed in animal studies (Watson et al., 1978) and have subsequently been described in neglect patients (Heilman et al., 1985; Mattingley et al., 1992, 1994). Investigations of temporal impairments in movements are commonly investigated using simple reaction time paradigms where the initiation and response times for movements toward left- and right-sided targets are compared (Heilman et al., 1985; Mattingley et al., 1992; Husain et al., 2000; Buxbaum et al., 2004).

Although the neural processes underlying the timing of movement may be distinct from those involved in scaling the movement amplitude (Mattingley et al., 1992, 1994), the relationship between temporal and spatial characteristics of output-related neglect has received relatively little attention in the literature. The second goal of the study is to examine the behavioral relationship between the temporal and spatial aspects of output-related neglect. Specifically, the time required to perform leftward relative to rightward bisections is compared to the spatial deviations of leftward relative to rightward bisections. A correlation between these measures would imply that differentiating between the two subtypes of output-related neglect is not necessary. Conversely, independence of temporal and spatial biases implies that a fine-grained differentiation of what constitutes output-related neglect is needed.

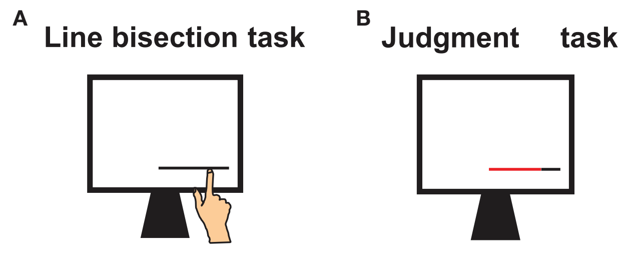


**FIGURE 1 | Tasks and procedure. (A)** Participants first performed a line bisection task in which they pointed to the lines' midpoint with their index finger. **(B)** Participants then judged their own bisection errors. Each line, divided into two colored segments at the locations where the participant previously placed the bisection mark, was then re-presented. Participants had to name the color of the longer line segment.

## MATERIALS AND METHODS

### PARTICIPANTS

Sixteen patients with left-sided spatial neglect after right brain damage (12 men, mean age 62 years, SD = 11 years, see **Table 1** for demographic and clinical details) participated in this study. Like our previous study, inclusion criteria were based on the presence of a right hemisphere lesion and signs of left-sided neglect for at least two out of five standard paper and pencil tests. Tests included line bisection, cancellation, figure copying, reading, and a figural fluency task (see Loetscher and Brugger, 2009 for details and cut-off criteria). Visual field deficits were assessed clinically by finger perimetry. Twenty healthy participants (11 men, mean age 61 years, SD = 14 years) matched for age and years of education served as controls. The study protocol was performed in accordance with the ethical standards laid down in the Declaration of Helsinki and all subjects gave written informed consent.

### APPARATUS AND PROCEDURE

Stimuli were presented on an Elo Entuitive 17' LCD desktop touch monitor (15,500 touchpoints/cm$^2$). The generation and sequencing of stimuli was controlled with Java Script programming. Participants were seated with their midsagittal plane aligned to the center of the touch screen. The viewing distance was roughly 560 mm; eye level was slightly above the vertical center of the screen. Eye and limb movements were not constrained.

The participants were first familiarized with the touch screen. They performed a pointing task, in which they pointed as accurately as possible to different illuminated circles on the screen. All participants were able to do so. After familiarization, the participants performed the line bisection task and subsequently the error judgment task (see **Figure 1**).

#### *Line bisection task*

In the line bisection task, participants pointed with their right index finger to the subjective middle of horizontal lines presented on the screen. The presentation of a line was triggered by pressing the space bar with the right index finger. After pointing to the subjective midpoint, the screen turned blank (white) and the space bar had to be pressed again to start the next trial. With this procedure a central starting point for each trial was assured.

In total, 18 black lines with a length of 160 mm were presented in a pseudo-randomized order either on the left, center or right side of the screen. There were six lines per side of presentation with the lines in the lateral conditions being shifted 40 mm to the left and right, respectively. The time period between pressing the space bar (elicitation of the line) and the touch response on the screen, as well as the horizontal coordinates of each fingertip were recorded. There were no time constraints for the response. The deviation of the these coordinates from the objective midpoint of the line were measured to the nearest millimeter—with right-sided errors scored as positive and left-sided errors as negative deviations.

**Table 1 | Demographic, clinical, and neuropsychological details of neglect patients with right brain damage.**

| Demographic and clinical data | | | | | | | Neglect tests | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient** | **Sex** | **Age** | **Lesion type** | **Lesion site** | **Days since stroke/surgery** | **Visual 1 field deficit** | **Figure copying** | **Bells task** | **LB dev%** | **Reading** | **Five-point Test** |
| 1 | m | 54 | Vascular | F, SC | 9 | Yes | 1 | 4 | 4.2 | No | Yes |
| 2 | m | 61 | Vascular | F, SC | 31 | Yes | 0 | 4 | 8.5 | No | No |
| 3 | w | 57 | Tumor | F,T | 4 | Yes | NA | 3 | 9.8 | NA | No |
| 4 | m | 59 | Tumor | T, P,SC | 8 | NA | 1 | −1 | 2.0 | NA | Yes |
| 5 | m | 66 | Tumor | T, P, SC | Pre-op | Yes | 4 | NA | 7.9 | NA | Yes |
| 6 | m | 60 | Vascular | T, P | 3 | No | 4 | 13 | 25.8 | NA | Yes |
| 7 | w | 79 | Tumor | T, P, Sc | 3 | Yes | NA | 6 | 67.1 | Yes | NA |
| 8 | w | 74 | Vascular | F, Sc | 6 | No | 4 | 10 | 9.9 | No | Yes |
| 9 | m | 60 | Tumor | F, T, 0 | Pre-op | Yes | 3 | 0 | 11.3 | No | Yes |
| 10 | m | 62 | Vascular | T, P | 2 | Yes | 4 | 0 | 70.6 | Yes | Yes |
| 11 | w | 36 | Vascular | F, P, Sc | 7 | No | 0 | 3 | 4.3 | No | Yes |
| 12 | m | 58 | Tumor | T, P, Sc | 52 | Yes | 0 | −2 | 26.5 | Yes | NA |
| 13 | m | 61 | Vascular | F, P | 3 | Yes | 1 | 0 | 13.1 | No | Yes |
| 14 | m | 79 | Tumor | P, T, Sc | Pre-op | Yes | 4 | NA | 31.9 | No | Yes |
| 15 | m | 60 | Vascular | F, T, P, 0, Sc | NA | No | 2 | 7 | 13.6 | Yes | Yes |
| 16 | m | 73 | Tumor | F, T, P, Sc | Pre-op | Yes | 0 | 3 | 8.9 | No | Yes |

*Lesion site: F = Frontal, T = Temporal, P = Parietal, O = Occipital, SC = Subcortical; Days since surgery/operation: number indicates days since stroke or operation, pre-op = preoperative.*

*Neglect tests: (A) Figure copying, scores range from 0 (no omissions) to 4 [several left-sided omissions, see Azouvi et al. (2002) for details], cut-off point >0; (B) "Bells task" (Gauthier et al., 1989), score gives number of left minus right-sided omissions, cut-off point >2; (C) LB dev% = Line Bisection deviation in % from true half, positive values denote rightward deviations, cut-off point > 6.5; (D) Reading, cut-off point > 0 left-sided omission; (E) five-point-test = figural fluency task (Regard et al., 1982), cut-off point > 0 omission of left-sided columns. Cut-off scores for the neglect tests A–D as defined in Azouvi et al. (2002); for test E as in Vuilleumier et al. (2004). Tests above cut-off-point are gray-colored. NA = Not available.*

#### *Error judgment task*

In the line judgment task, each of the previously bisected 18 lines were presented in sequence at the same location as the line bisection task. The lines were divided into two segments at the point where the participant previously placed the bisection mark. The left and right segments were colored red or black, respectively. In order to counterbalance the coloring of the lines, each line was presented twice, once with the left side colored black (right side red) and once with the left side red (right side black). The 36 lines were presented in a pseudo-randomized order and participants named the color of the longer line segment (forced choice design with no time constraints for response). The subject's task was to say which line segment was longer ("red" or "black") and verbal responses were recorded by the examiner. The percentage of correct judgments was the dependent variable.

## RESULTS

### LINE BISECTION TASK

Data were collapsed across the side presentation (left, center, right). As the data in the neglect group were not normally distributed (Shapiro–Wilk $p < 0.01$) non-parametric tests were applied. Wilcoxon signed-rank tests were used to determine whether the bisection biases were significantly different from zero. Patients with neglect bisected the lines too far to the right side (median 4.9 mm; $Z = 2.8$, $p < 0.006$), while healthy controls showed a leftward bias (median = −2.5 mm; $Z = 3.2$, $p < 0.002$). An independent-samples Mann–Whitney test demonstrated a significant difference between the neglect and control groups ($U = 37$, $Z = 3.9$, $p < 0.001$).

Subgroup analyses found no difference between patients with and without visual field deficits ($U = 18.0$, $Z = 0.5$, $p =$ n.s.) and patients with vascular and tumor etiology ($U = 32.0$, $Z < 0.01$, $p =$ n.s.).

### ERROR JUDGMENT TASK

Neglect patients (median correct judgments 72.2 %) were significantly worse in detecting their own bisection errors compared to the controls (median 93.5%; $U = 51.5$, $Z = 3.5$, $p < 0.001$). The standard deviation was more than four times larger in the neglect group (SD 25.2) compared to controls (SD 5.7), indicating considerable heterogeneity in the neglect population.

The number of correct judgments was not modulated by the presence of visual field deficits ($U = 20.5$, $Z = 0.2$, $p =$ n.s.), or lesion etiology ($U = 31.0$, $Z = 0.1$, $p =$ n.s.).

### DISENTANGLING INPUT AND OUTPUT-RELATED COMPONENTS

To extricate input- and output-related components, cut-off criteria for the line bisection and error judgment task were defined. For the line bisection task, Bayesian inferential statistics were used to determine the cut-off scores, which differentiated the controls from neglect patients (see Crawford and Garthwaite, 2007). Using this technique, deviations larger than 2.4 mm were classified as significantly different from controls (Bayesian $p < 0.05$).

For the error judgment task, cut-off scores were based on normative data collected in an unpublished pilot study with 71 healthy subjects. That study showed that the accuracy in error judgments depended on the magnitude of the bisection error. That is, larger errors were much easier to spot than smaller ones (see **Figure 2**). The varying degree of difficulty in judging errors was controlled by calculating the lower bound of a 95% confidence interval for the percentage of correct error judgments for each bisection deviation. The corresponding values were then fitted with a cumulative normal distribution function. This curve fitting procedure determined a cut-off score for the percentage of correct judgment as a function of bisection error. Judgment scores below the lower bound confidence curve were considered to reflect an input-related impairment.

Using the cut-off criteria outlined above, individual patient data were plotted in **Figure 3** to distinguish input and output-related components of spatial neglect. Inspection of **Figure 3** allows a number of conclusions to be drawn: (1) The bisection and judgment performance of four neglect patients was within normal limits; (2) three patients showed signs of neglect in the bisection task, but intact judgment abilities. These patients can be considered as suffering from output-related neglect; (3) nine patients were impaired in the bisection and judgment task. These patients can be considered as suffering predominantly, but not necessarily exclusively, from input-related neglect; (4) the performance of neglect patients is characterized by considerable heterogeneity compared to the rather homogenous performance of controls.

### RELATIONSHIP BETWEEN TEMPORAL AND SPATIAL BIASES IN LINE BISECTION

To investigate the relationship between temporal (time differences in bisecting left and right-sided lines) and spatial aspects (differences in deviation errors for left and right-sided lines) lateralization scores were calculated (Bryden and Sprott, 1981). The temporal lateralization score was calculated as the natural logarithm of the ratio "bisection times of lines presented on the left side divided by bisection times of lines presented on the right side." Positive values denote quicker responses to right-sided lines, negative values indicate an advantage for left-sided lines, and a value of zero denotes equal response times for left and right-sided lines. A spatial bias measure was calculated using an analogous procedure. As the logarithm has to be drawn from positive values, the use of deviation measures was not appropriate. Instead, the positions of the bisection mark as measured from the left end of the line were used. The spatial lateralization score was then calculated as the natural logarithm of the ratio "bisection position of lines presented on the right side divided by the bisection position of lines presented on the left side." Here, negative values denote that left-sided lines are bisected further to the right than right-sided lines (vice-versa for positive values).

The relationship between temporal and spatial aspects of neglect is plotted in **Figure 4**. The two aspects were uncorrelated in neglect patients ($r = -0.15$, $p =$ n.s.) and controls ($r = 0.12$, $p =$ n.s.).

## DISCUSSION

Common tests of neglect, such as line bisection and cancellation tasks, fail to provide information on the subtype of neglect that is present. The primary goal of the current study was to introduce a simple method that allows us to dissociate input- and output-related subtypes of neglect. This method required patients to bisect a series of horizontal lines (manual motor task) and then to judge their own bisections (visual perceptual task). In both of these tasks, typical signs of neglect emerged at a group level. That is, a rightward deviation in the line bisection task (Schenkenberg et al., 1980) and impairments in detecting horizontal length asymmetries in the perceptual judgment task (Milner et al., 1993). The results in the neglect group were also characterized by large standard deviations, signifying considerable heterogeneity in performance. Such an increased variability in performance has been

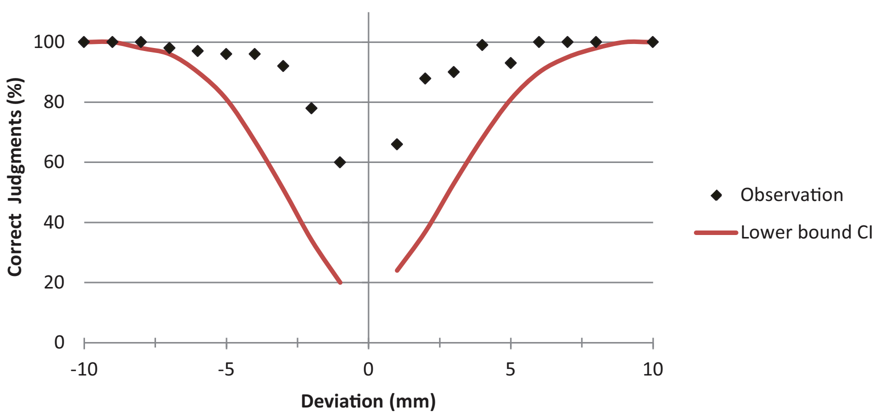


**FIGURE 2 | Dependency of correct judgment on deviation error.** The percentage of correct judgments is plotted as a function of bisection error. The graph shows the normative data of 71 healthy subjects (black dots) and the corresponding lower bound of the 95% confidence interval (red line). Judgment scores below the lower bound of the fitted confidence interval curve were considered as indicating impaired perceptual judgment abilities.

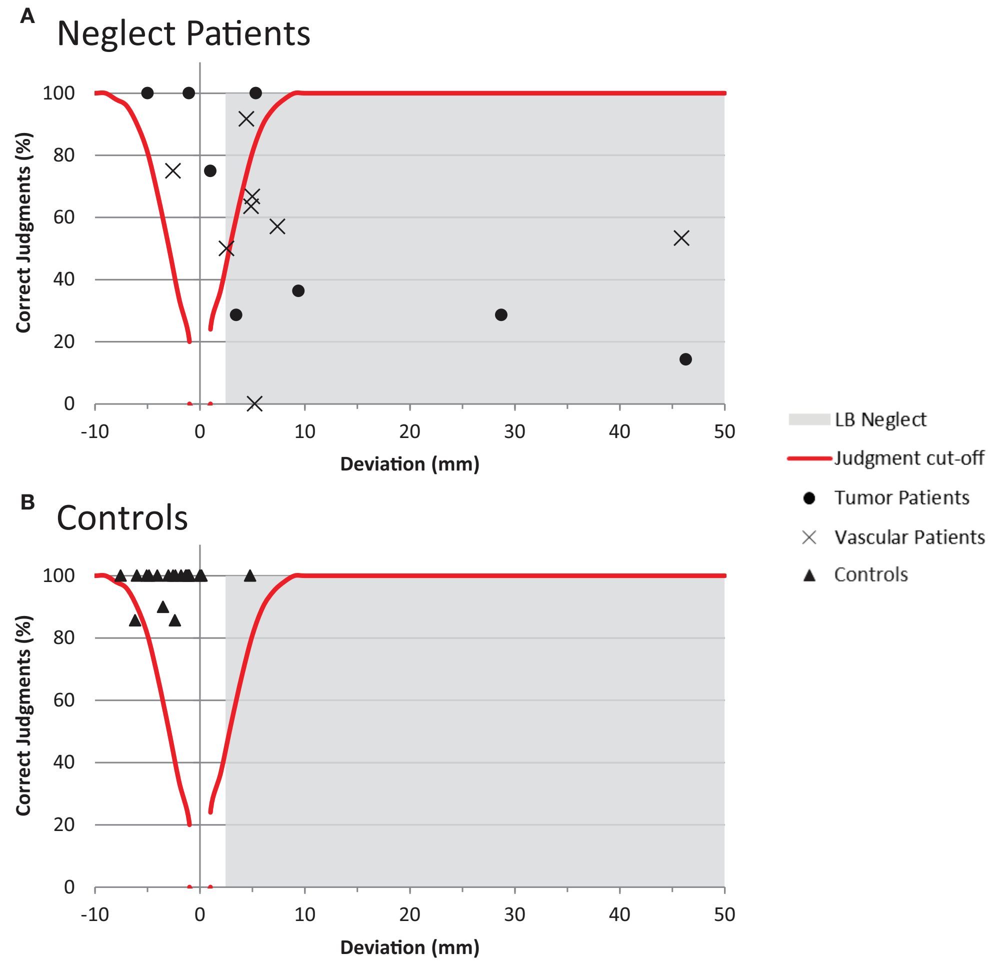


**FIGURE 3 | Disentangling input- and output-related neglect.** **(A)** Shows the performance of the individual patients in the line bisection and error judgment task (split by etiology). Bisection values in the gray colored area indicate the presence of neglect in the line bisection task. Error judgments below the red curve indicate impaired perceptual judgment abilities. See main text for indications of input or output-related neglect **(B)** Shows the corresponding performance of the control participants.

shown to be a valid marker of neglect (Marshall and Halligan, 1989; Bonato et al., 2008).

The extrication of input- and output-related subtypes was based on individual performances in the two tasks. With the emphasis being the identification of the predominant subtype, the 16 neglect patients could be classified in three distinct subgroups (see also **Figure 3**). The first group, comprising three patients, showed a rightward bias when bisecting lines, but no difficulties in recognizing the erroneous bisections when judging them. This pattern clearly corresponds to an output-related deficit, which is indicated by impairments in movements toward the left (resulting in rightward deviations) and intact spatial perceptual capabilities. The second group of nine patients demonstrated neglect in the bisection and the perception task. Intact spatial perception allows the patient to detect misplaced bisection marks. An inability to do so would therefore indicate a perceptual impairment. These patients were accordingly classified as suffering predominantly, but not necessarily exclusively, from an input-related deficit. The third group, comprising the remaining four patients, showed normal performances in the line bisection and judgment task and therefore could not be classified as having input- or output-related neglect. It should be noted, however, that an inability to isolate an input/output subtype in some patients is not necessarily due to a lack of test sensitivity. Indeed, input/output subtypes of neglect are just one dimension along which neglect patients can differ (Barrett et al., 2006). Furthermore, the inclusion criterion for neglect in the current study was based on signs of neglect in at least two out of five common paper and pencil tests. A rightward deviation for the line bisection task was therefore not a precondition for inclusion.

The current study revealed that patients with neglect were three times more likely to suffer from a predominantly input-related than from an output-related subtype. While this proportion gives some indication of the relative incidence of input- and output-related neglect, it should be borne in mind that the patient sample used in the current study was relatively small. The relative incidence of the different subtypes of neglect is further complicated by the different methods of assessment.

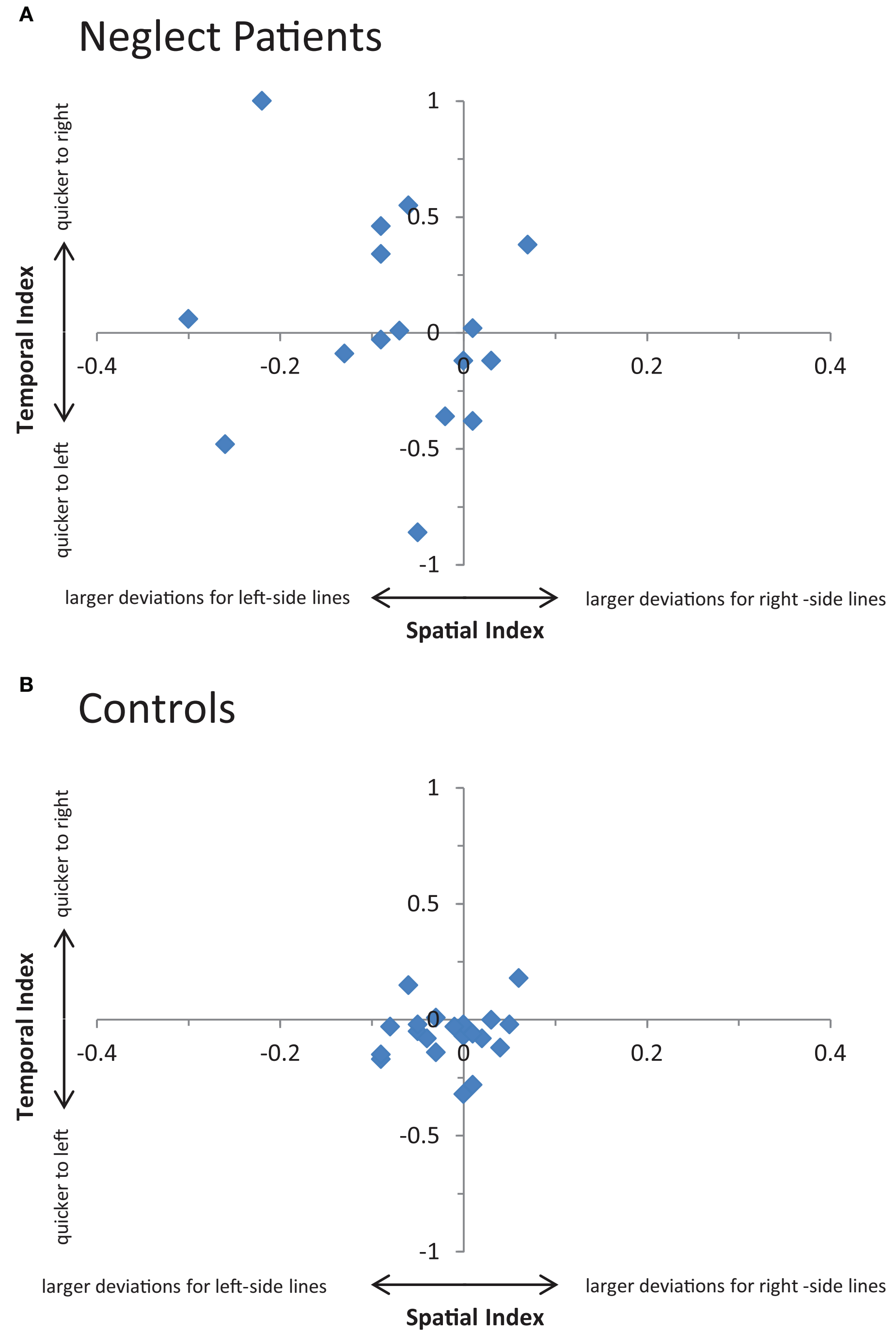


**FIGURE 4 | Relationship between temporal and spatial aspects of neglect. (A)** Shows 23 individual patients' temporal (i.e., time required to perform leftward relative to rightward 24 bisections) and spatial (i.e., deviations of leftward relative to rightward bisections) scores 25 in the line bisection task. See main text for details **(B)** Shows the corresponding 26 performance of the control participants.

For example, inconsistent classifications have been observed between the landmark and the pulley tests (Harvey et al., 2002) and line bisection and cancellation tests (Adair et al., 1998; Na et al., 1998). Bearing these points in mind, the relative proportion of the input/output subtypes observed in the current study should be treated with some caution. Nevertheless, the finding of more patients with input-related neglect is consistent with almost all previous studies assessing these subtypes in larger patient samples ($n > 40$, Mijovic, 1991; Buxbaum et al., 2004; Shimodozono et al., 2006; Sapir et al., 2007). The current results only stand in contrast to one large patient sample study ($n = 121$, Bisiach et al., 1998), which reported a higher proportion of output-related neglect for a landmark bisection task. In this case, however, the landmark stimuli were easy to discriminate, with a difference of at least 30 mm between the left and right segments of the line. Because of the easy perceptual nature of this task, it is likely that patients with mild or moderate input-related neglect were able to detect the difference—resulting in a low relative incidence of that form of neglect.

A secondary goal of the study was to compare spatial and temporal aspects of output-related neglect. Our results indicate that these aspects are independent. Impairments in the initiation and execution of leftward movements were not associated with a marked rightward deviation in the line bisection task. Despite the problems of drawing implications from null results, the findings suggest that a fine-grained differentiation of output-related neglect is required. That is, it is conceivable that temporal and spatial aspects constitute different neglect subtypes. The phenomenological differences could be based on distinct neural processes underlying the timing of movement and the scaling of the movement amplitude (Mattingley et al., 1992, 1994). If this holds true, then attempts to elucidate the anatomical substrates of output-related neglect should differentiate temporal and spatial measures. Neglecting this sort of differentiation might have contributed to the controversy regarding the role of the parietal lobe in motor neglect (as addressed, for example, in Carey, 1998; Husain et al., 1998). While many studies assessing motor impairments by spatial measures found a predominance of anterior impairments (e.g., Bisiach et al., 1990; Coslett et al., 1990; Nico, 1996; Na et al., 1998), it is noteworthy that the studies which found that posterior brain regions were associated with motor neglect applied temporal measurers (Mattingley et al., 1998; Husain et al., 2000;but see Sapir et al., 2007 for contradictory finding). It remains to be seen to what degree this discrepancy is related to the use of different measures. In any case, the independence of spatial and temporal measures observed in the current study clearly demonstrates that these aspects would deserve a more fine-grained analysis in the literature.

The results of the current have demonstrated the feasibility of our new method of dissociating input- and output-related neglect, which has some important advantages over previous methods. One advantage is that it does not involve conflicting visuo-motor movements. This is important as there are anecdotal reports of patients who refused to continue with incongruent movement tests because they found them too frustrating (Nico, 1996). Such task requirements have accordingly been criticized as being too confusing for patients with brain damage (Mattingley et al., 1998; Husain et al., 2000). In contrast, the current paradigm is straightforward and relatively easy—even for patients with severe forms of neglect. The current method also addresses some potential shortcomings of the landmark test, which is still considered to be one of the best tools for differentiating input- and output-related forms of neglect (Harvey, 2004). A major issue for the landmark test is the placement of the bisector and the subsequent difficulty of the task. Bisiach et al. (1998) proposed, for example, the use of stimuli in which the difference between the left and right segments of the line ranged from 30 to 150 mm. As discussed above, it is doubtful that these easy discriminations would identify subtle forms of perceptual neglect. The optimal transector placement might, in fact, depend on the severity of the patient's impairment. A second problem with the landmark task is that they are required to judge spatial relations, which are not derived from their motor behavior. Contrasting a patient's actual motor behavior with the subsequent judgment of this behavior seems to be a more intuitive and natural way to infer subtypes of neglect.

While the methods introduced in the study address some of the weaknesses of previous research, the study has some limitations on its own. First, the task does not necessarily provide a pure measure of output-related impairments. The manual line bisection task involves both motor and visual input components. It is therefore possible that the paradigm biased the findings toward input over output-related deficits (see Garza et al., 2008; Chen et al., 2011). It should also be noted that the bisection task and the visual perceptual task may differ with respect to the involvement of bottom-up (exogenous) and top-down (endogenous) processes. That is, judging the accuracy of bisected lines might have involved more top-down, endogenous orienting processes than the line bisection task. As deficits in endogenous and exogenous orienting can be dissociated in patients (Bartolomeo and Chokron, 2002; Sieroff et al., 2007; Loetscher et al., 2010), it is possible that differences in the processing demands of the tasks affected the results.

The assessment of neurological impairments and activities in everyday functions with scales such as the Barthel Index (Mahoney and Barthel, 1965) and the Catherine Bergego Scale (Azouvi et al., 2003) may have provided a better characterization of patients. A better functional characterization might have been important as there is some evidence, for example, that items of the Catherine Bergego Scale are better predictors of output- versus input-related neglect impairments than performance in standard neglect tests (Goedert et al., 2012). It is noteworthy that the patient characteristics that were assessed, such as lesion etiology and visual field deficits, yielded inconclusive results. While these characteristics did not affect task performances statistically, the sample of 16 neglect patients might simply have been too small to uncover any differences. Hemianopia, for example, has been shown to influence line bisection tasks (e.g., Doricchi and Angelelli, 1999; Doricchi et al., 2002) and this influence may vary depending on the time since stroke (Saj et al., 2012). Clearly, a sample of just four patients without visual field deficits, as in the current study, cannot address the modulating effect of hemianopia conclusively. Importantly, however, an exclusion of the four patients (three with input-related and one with output-related deficits) does not change the main results: there was still is a predominance of input- over output-related subtypes. The same predominance is also evident when considering patients with vascular etiology only (see **Figure 3**). The findings in the tumor group are somewhat different as three out of eight tumor patients performed within normal limits. However, when only considering patients affected by one of the two investigated subtypes, there was also a clear predominance of input (four patients) over output-related subtypes (one patient). To summarize, the current study has observed a predominance of input-related neglect across a variety of patient characteristics. While this predominance appears to be consistent, it should be borne in mind that broader conclusions are limited by the relatively small patient sample.

Although the heterogeneity of the sample probably added some noise to the data, including patients with different etiologies can also be seen as an advantage. Different methodological problems and confounds are associated with specific etiologies (Bartolomeo, 2011). Thus, studies combining a variety of etiologies, such as stroke and tumor data, might provide converging evidence on the widely distributed functional brain network that controls spatial attention.

While neglect patients typically exhibit an ipsilesional bias, some patients may show signs of a paradoxical contralesional bias (Robertson et al., 1994). What is more, ipsilesional and contralesional biases may be dissociated with respect to input- and output-related errors (Bisiach et al., 1990; Schwartz et al., 1999; Barrett and Burkholder, 2006). While potentially only a minority of patients would show such a dissociation, it should be acknowledged that the present method is not sensitive to uncover these patients.

Finally, it should be recognized that the assumption of a strict dichotomy between input and output-related aspects of neglect is likely to be a considerable oversimplification (Adair et al., 1998). Planning, executing, and visually guiding movements toward targets rely on continuous integration of sensory information. As a result, input and output-related processing streams will interact—resulting in a blurring of the boundaries between the processes (Mesulam, 1981, 1999). From a strictly theoretical perspective, therefore, it might be more accurate to describe the relationship between the two neglect subtypes along a continuum instead of a strict dichotomy. It is also likely that both types of deficit are present to varying degrees in an individual patient. The current method of analysis allows the determination of the predominant subtype only. While this determination might be useful in a clinical context (see below), it is worth considering refining the method and analysis in future studies to obtain continuous and mathematically independent measures of input versus output-related deficits. The methodological approach for analysing landmark task performance proposed by Toraldo and colleagues (2002, 2004) could serve as a template for improving the current task. The approach involves psychometric curve fitting procedures and illustrates nicely how mathematical modeling of behavior can help improving clinical measures.

From a clinical and rehabilitative perspective, however, the input/output dichotomy might be useful. There are suggestions, for example, that patients who present with a predominantly output-related subtype are more likely to have a chronic disability (Eskes and Barrett, 2009; Goedert et al., 2012) and input-related impairments seem especially amenable to recovery (Rengachary et al., 2011). Different treatment regimens may also affect input and output-related neglect differently. This idea has been examined for several interventions by one laboratory (e.g., with monocular patching: Barrett et al., 2001, 2004; Barrett and Burkholder, 2006; Chen et al., 2009). Intuitively, it seems plausible that perceptual-attentional impairments and deficiencies in spatial movements respond best to different treatment approaches. Rehabilitation procedures like attentional alerting, scanning training, or monocular patching may be more efficacious for input than output-related neglect. Conversely, procedures like limb activation therapy and dopaminergic medications may be more appropriate for the treatment of output-related neglect (see Barrett et al., 2006; Sapir et al., 2007 for comprehensive discussion of treatment rationales).

While the diagnosis of the subtypes of neglect is potentially important for subsequent treatment (Barrett et al., 2006; Bowen and Lincoln, 2007a), there are still a number of unanswered questions. Foremost amongst these is the issue of the stability of neglect subtypes over time. To our knowledge, only one study has addressed this issue (Hamilton et al., 2007). In that study, subtypes were assessed in 21 acute neglect patients at three different time points separated by at least one week. Eighteen of those patients (86%) showed significant variability in their performance on measures of neglect subtype. The authors claim that this inconsistency was not related to spontaneous recovery or practice effects. It is not clear, at present, whether the results are due to methodological limitations (e.g., insufficient sensitivity or specificity of the tests) or fluctuations in individual neglect behavior. If the latter proposition turns out to be correct, then this would have implications for the validity of tests of neglect subtypes and for the prognosis and treatment of those subtypes. The testing paradigm used in the current study may help to shed light on this issue.

## ACKNOWLEDGMENTS

We thank Enrique Wintsch, Nicole Kavan, and Pascale Sandmann for programming assistance and help in collecting normative data.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 15 February 2012; accepted: 29 May 2012; published online: 13 June 2012.*
*Citation: Loetscher T, Nicholls MER, Brodtmann A, Thomas NA and Brugger P (2012) Disentangling input and output-related components of spatial neglect. Front. Hum. Neurosci.* ***6****:176. doi: 10.3389/fnhum.2012.00176*

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 21 August 2012
doi: 10.3389/fnhum.2012.00232

# Speed impairs attending on the left: comparing attentional asymmetries for neglect patients in speeded and unspeeded cueing tasks

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Visuospatial neglect after stroke is often characterized by a disengage deficit on a cued orienting task, in which individuals are disproportionately slower to respond to targets presented on the contralesional side of space following an ispilesional cue as compared to the reverse. The purpose of this study was to investigate the generality of the finding of a disengage deficit on another measure of cued attention, the temporal order judgment (TOJ) task, that does not depend upon speeded manual responses. Individuals with right hemisphere stroke with and without spatial neglect and older healthy controls (OHC) were tested with both a speeded RT cueing task and an unspeeded TOJ-with-cuing task. All stroke patients evidenced a disengage deficit on the speeded RT cueing task, although the size and direction of the bias was not associated with the severity of neglect. In contrast, few neglect patients showed a disengage deficit on the TOJ task. This discrepancy suggests that the disengage deficit may be related to task demands, rather than solely due to impaired attentional mechanisms *per se*. Further, the results of our study show that the disengage deficit is neither necessary nor sufficient for neglect to manifest.

**Keywords: attention, spatial cueing, temporal order judgments, unilateral neglect**

## INTRODUCTION

Visuospatial neglect is a condition whereby people are deficient at attending to or noticing the contralesional side of space when the deficiency cannot be explained by primary sensory or motor deficits (Heilman and Valenstein, 1979). As such, neglect is often described as a cognitive disorder of attention (Bisiach et al., 1979; Posner and Petersen, 1990; Karnath et al., 2002b). The condition is more likely to manifest in people with right rather than left hemisphere lesions, and has been associated with lesions in a variety of brain regions and white matter networks, including anterior frontal lobe, the parietal lobe and tempo-parietal junction, superior temporal gyrus as well as subcortical areas (Mesulam, 1981; Vallar and Perani, 1986; Leibovitch et al., 1998; Vallar, 2001; Karnath et al., 2002a,b, 2004; Mort et al., 2003; Bartolomeo et al., 2007).

One of the most popular experimental paradigms for studying attention and neglect is the exogenous spatial cueing task developed by Posner and colleagues in the late 1970s (Posner, 1978, 1980; Posner et al., 1980). The task involves presenting participants with a central fixation flanked by two peripheral boxes. A cue is presented in one of the two peripheral locations, followed by a target presented in one of those locations; the cue may or may not predict the location of the target. When the time interval between the cue and the target is short (approximately 250 ms), participants are typically faster to respond to the target when it appears at the same location as the cue (a "valid" or "cued" trial) compared to when it appears at the opposite location (an "invalid" or "uncued" trial)—an effect referred to as facilitation (Posner and Cohen, 1984). The spatial cueing task has been exploited to examine various aspects of spatial attention and has allowed the description of several general attention-related effects (cf. Posner et al., 1985), as well as specific effects related to various neuropsychological and psychiatric disorders (cf. Maruff et al., 1995; Townsend et al., 1996).

Posner used the spatial cueing paradigm to help develop a model of orienting involving three distinct operations: attention first disengages from its current focus, it then shifts toward the new target location, and finally attention engages the new target (Posner et al., 1982, 1984). Posner and colleagues were the first to use the spatial cueing paradigm to investigate the effects of parietal lobe lesions and reported that after left or right parietal lobe damage, while individuals were able to benefit from cues provided on the same side as the target, they were disproportionately slower to respond to targets presented on the contralesional side of space following an ispilesional cue as compared to the reverse (Posner et al., 1982). Posner and others have characterized this pattern (increased cost for contralesional targets following ipsilesional cues) as a difficulty disengaging attention from the patient's "good" field in order to deal with a target presented to the "poor" field, and have thus christened the effect a *disengage deficit* (Posner et al., 1982; Rastelli et al., 2008).

Losier and Klein (2001)[1] conducted a meta-analysis of the literature dealing with the disengage deficit to reveal several important characteristics of the effect. As with neglect itself, the disengage deficit is greater in patients with right compared to left hemisphere damage. In patients with right hemisphere damage, the disengage deficit is greater using shorter cue-target onset asynchronies (CTOAs; i.e., less than 550 ms) compared to longer CTOAs (Losier and Klein, 2001). However, patients with left hemisphere damage tend to have a relatively stable disengage deficit across cue-target intervals. There is some evidence that patients with damage to one hemisphere who fail to show clinical signs of neglect can exhibit a disengage deficit; however, the disengage deficit is significantly larger in patients *with* neglect (cf. Posner et al., 1984). Additionally, the size of the disengage deficit is related to neglect severity, such that patients with more severe neglect tend to have larger disengage deficits (e.g., Baynes et al., 1986; Morrow and Ratcliff, 1988; Farah et al., 1989; D'Erme et al., 1994; Egly et al., 1994; Losier and Klein, 2001; Snyder and Chatterjee, 2006; Bonato et al., 2009; Schindler et al., 2009; Olk et al., 2010), although this relationship has not always been found (Posner et al., 1984; Sacher et al., 2004; Sieroff et al., 2007). This effect is amplified in right-hemisphere neglect patients compared to left-hemisphere neglect patients. Recently, Rastelli et al. (2008) have shown that the disengage deficit is greater when the cue remains on screen for the entire trial compared to when the cue is removed before the target appears, suggesting the disengage deficit is stronger for objects than it is for locations.

The current interpretation of the disengage deficit implies something general about the way that neglect manifests; once attention is captured by a cue in the good field, targets presented to the poor field have particular difficulty generating disengagement from this cue. However, to our knowledge, the effect has only been studied using variants of Posner's spatial cueing paradigm. If the disengage deficit is actually about attention, then it should generalize to other paradigms sensitive to attentional cueing. One candidate task for testing this hypothesis is the temporal order judgment (TOJ) paradigm. In a conventional TOJ task two stimuli are presented in rapid succession, e.g., one on the left and one on the right side. The order of side of first presentation, left or right, varies across trials, along with the interval, or stimulus onset asynchrony (SOA), between the stimulus onsets. To avoid response biases, participants can be asked to report which item was presented first using a stimulus characteristic (e.g., color or orientation) rather than stimulus location (Spence et al., 2001). Typically, left-first trials are coded with negative SOAs while right-first trials are coded with positive SOAs; the likelihood of reporting the item on the right as appearing first is calculated and plotted per SOA. The SOA at which the likelihood for reporting right-first is 50% is considered the point at which participants subjectively experience the two events as occurring at the same time. This SOA is referred to as the point of subjective simultaneity (PSS). Normal observers are usually very accurate, and under neutral conditions without cueing the PSS averages around 0, indicating no spatial asymmetry. Judgments in this task are also influenced by spatial cueing (Stelmach and Herdman, 1991; Shore et al., 2001), such that presenting a cue on either the left or right side prior to presenting the test stimuli can impact which item participants perceive as occurring first. This shift in the PSS is presumed to reflect a perceptual change due to the drawing of attention to the cued side, with corresponding earlier arrival at a temporal comparison stage (Stelmach and Herdman, 1991; Shore et al., 2001). The TOJ task has been used to reveal visual spatial attention asymmetries in individuals with extinction and/or spatial neglect, and a number of investigators have reported a shift in the PSS under neutral conditions without cueing such that the stimulus on the contralesional side must temporally lead the stimulus on the ipsilesional side in order for the two to be perceived as simultaneous (Rorden et al., 1997; Robertson et al., 1998; Baylis et al., 2002; Berberovic et al., 2004; Sinnett et al., 2007; but see Dove et al., 2007).

While Posner's speeded RT cueing task and the unspeeded TOJ-with-cueing task share similar characteristics in spatial cuing (e.g., Eskes et al., 2007) that suggest neglect patients will show a disengage deficit in both tasks, there are several differences and reported dissociations between the tasks which may impact the results (e.g., Neumann et al., 1993; Miller and Schwarz, 2006). TOJ tasks *can* require participants to make a speeded response (cf. Heath, 1984; Shore et al., 2001), but because the primary measure is related to accuracy and SOA rather than speed, this requirement is unnecessary and the authors know of no published reports in patients using a speeded TOJ task. In the speeded RT cueing task, the actions of attention are inferred by RTs, and so speeded responding cannot be avoided. **Table 1** summarizes the task characteristics for the TOJ and RT tasks.

Some evidence that the disengage deficit may not transfer to a TOJ task was hinted at in Di Pellegrino et al. (1997). Di Pellegrino et al. described a case study of a 65-year-old patient with neglect and extinction following a right-hemisphere stroke. The patient was asked to report the identity of two target letters presented asynchronously, one on either side of a central fixation. If the patient's neglect and extinction were due to a disengage deficit, one would expect that contralesional targets would be less likely to be identified correctly when an ipsilesional target was presented first compared to when the ipsilesional target was presented second in the pair. However, the researchers found that the patient was significantly worse at reporting a contralesional target if it was presented within 600 ms of the letter presented on the ipsilesional side of space, and that the deficit was similar in duration and magnitude irrespective of whether the contralesional target was present first or second in the pair.

**Table 1 | Summary comparison of the characteristics of the two experimental tasks.**

| Characteristic | RT task | TOJ task |
|---|---|---|
| Sensitive to spatial cueing | Yes | Yes |
| Speeded response required | Yes | No |
| Disengage deficit | Yes | ? |

[1] Losier and Klein's (2001) meta-analysis included studies that used both predictive and non-predictive cues. In the current study, we used non-predictive cues in both tasks; however, Losier and Klein found that the disengage deficit is robust with peripheral cues whether or not they are informative.

Di Pellegrino et al. explain these results in terms of a competitive model of selective attention, rather than a model that assumes a difficulty in disengaging from ipsilesional objects. In the competitive model, ipsilesional targets are assumed to have a higher weight in terms of capturing selective attention, such that even if they arrive 300–400 ms after a contralesional target they still manage to capture attentional resources and interrupt contralesional processing before contralesional target identity is determined.

The current paper explores whether the disengage deficit is observable in a TOJ-with-cueing task as well as in a speeded RT cueing task that are matched for stimuli and task decision. The goal is to determine whether, when the stimuli (cues and targets) and decision demands of the two task are relatively similar, the disengage deficit is a general phenomenon of neglect, or whether it is specific to the speeded RT cueing task. The TOJ task in the current experiment was conducted using an *unspeeded* response, while the RT task was conducted using standard *speeded* responses. If both tasks produce a disengage deficit, this similarity would provide converging evidence that neglect is a general problem of attentional orienting. However, if the TOJ task fails to produce a disengage deficit, then this difference would suggest that the effect has more to do with speeded responding than attention.

While most cases of neglect involve changes in processing of the contralesional side of space associated with an ipsilesional disengage deficit, there have been some reports of ipsilesional neglect (Kim et al., 1999). Patients with ipsilesional neglect might be expected to show a contralesional disengage deficit. To differentiate these two patterns, we will refer to the ipsilesional disengage deficit predicted by Posner et al. (1984) model of attention as a standard disengage deficit, and a contralesional disengage deficit as a paradoxical disengage deficit. In the current study, only patients with right hemisphere damage were tested and so their attentional deficits, if any, should appear on the left side of space. Therefore a standard (ipsilesional) disengage deficit would represent a rightward bias in attention, while a paradoxical (contralateral) disengage deficit would represent a leftward bias in attention.

It should be noted that both tasks in this study required participants to make a similarly demanding 2-choice, non-spatial discrimination. In the RT tasks participants decided as quickly as possible whether the target was red or blue while in the TOJ task participants decided, with no speed pressure, whether the first of two successively presented targets was red or blue. While the disengage deficit is typically studied using simple detection in the RT cueing task, cueing effects are also obtained in non-spatial discrimination (e.g., color discrimination) tasks in studies of visual orienting with control populations, beginning with Jonides and Irwin (1981). The target discrimination task has been suggested by several investigators for use in the TOJ task, specifically (Spence and Driver, 1994; Spence et al., 2001) to be necessary to avoid the possibility that early facilitation is simply the result of a criterion shift for responding to targets at the cued location (i.e., accepting less evidence from that location than the uncued one). False alarms on catch trials (trials without a target) cannot be used in a simple detection task to distinguish speed-accuracy trade-offs because the false alarms cannot be attributed to the cued or uncued location. Therefore, we have two rationales for our decision to use a color choice judgment for the RT task; (1) we wanted to equate stimulus-response demands with the TOJ task, and (2) we wanted the ability to look at errors in order to create an analogous measure for the disengage deficit.

## MATERIALS AND METHODS

### PARTICIPANTS

Individuals with a right hemisphere stroke were recruited for the stroke groups. Inclusion criteria included medically stable and normal or corrected-to-normal visual acuity. Exclusion criteria included other current psychiatric or neurological disorders, severe aphasia or dementia and color blindness. Individuals were assigned to either the neglect group (NEG) or right hemisphere control group (RHC) based on their performance on the Behavioral Inattention Test (BIT). The criterion for neglect was abnormal performance, as based on the standard clinical cut-off, on at least one subtest of the BIT (please see **Table A1** for the scores for each of the BIT subtests for each patient). This criterion for neglect was similar to that used by Sieroff et al. (2007) and adopted in order to increase the sensitivity of the BIT to the presence of neglect, as paper and pencil tests are often less sensitive to the presence of neglect in the post-acute or chronic phase (Friedrich and Margolin, 1993; Mattingley et al., 1994; Deouell et al., 2005; List et al., 2008; van Kessel et al., 2010; Bonato et al., 2012; reviewed in Bonato, 2012). Patients' stroke location was determined by clinical CT report. A summary of clinical, demographic and baseline data for participants in the NEG and RHC groups is presented in **Table 2**. We also included a control group, referred to as older healthy controls (OHC). These participants had no history of stroke, no signs of dementia, and no visual deficits.

### APPARATUS AND STIMULI

Each participant ran in both the RT task as well as the TOJ task. Stimuli were presented on an Apple iMac computer and were programmed using PsyScope Version 1.2.5. We used colored stimuli on a white background. A black fixation cross, measuring 1° × 1° of visual angle (VA), was presented in the center of the screen. Two box outlines in black, each measuring 4° × 4° VA, were positioned to the left and right of fixation offset from center by 4° to each box center. Cues consisted of a 45 ms change in box line-thickness (from one to four points) for one of the two boxes. A stimulus appeared in the center of each box and consisted of a red or blue pinwheel measuring 3° in diameter (see **Figure 1**). In the RT task, only one pinwheel was presented in one of the two boxes, while in the TOJ task one pinwheel was presented sequentially in each box.

### PROCEDURE

The following tasks were carried out in accordance with the Tri-Council Policy Statement (Canada) and with the approval of the Capital Health Research Ethics Board (formerly the Queen Elizabeth II Health Sciences Center Research Ethics Board). Informed consent was obtained from all the participants.

**Table 2 | Demographic and baseline neuropsychological assessment.**

| Subject code | Group | Stroke location | Time post-stroke (mos) | Age (years) | Gender | Dominant hand | Education (years) | Visual field deficit | Visual extinction | Judgment of line orientation | Elevator counting | BIT total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1047 | NEG | P | 25 | 48 | M | L | 12 | No | No | NA | NA | 141 |
| 1084 | NEG | F,T,P,O, cereb | 5 | 71 | M | R | 12 | Yes | N/A | 11 | 7 | 129 |
| 1085 | NEG | F, T, Ins | 4 | 75 | M | R | 11 | Yes | Yes | 11 | 3 | 130 |
| 1086 | NEG | F, T, BG | 3 | 38 | M | R | 10 | No | No | 12 | 0 | 135 |
| 1090 | NEG | F, T, Ins | 2 | 63 | M | R | 10 | Yes | Yes | 10 | 6 | 119 |
| 1157 | NEG | P | 3 | 61 | M | L | 17 | No | No | 12 | 4 | 136 |
| 1159 | NEG | T, Thal, IC | 2 | 48 | M | R | 22 | No | N/A | 12 | 7 | 100 |
| 1058 | RHC | NA | 2 | 79 | M | R | 12 | No | No | NA | NA | 141 |
| 1081 | RHC | F | 3 | 55 | M | R | 12 | No | No | 11 | 1 | 135 |
| 1082 | RHC | BG, Ins | 1 | 44 | F | R | 12 | No | No | 12 | 7 | 144 |
| 1087 | RHC | T | 3 | 70 | M | R | 14 | No | No | 12 | 7 | 138 |
| 1160 | RHC | F, P | 2 | 54 | M | R | 14 | No | No | 12 | 7 | 144 |
| 1162 | OHC | – | – | 61 | F | R | 17 | No | No | 11 | 7 | 146 |
| 1163 | OHC | – | – | 51 | F | R | 11 | No | No | 12 | 7 | 146 |
| 1164 | OHC | – | – | 37 | M | R | 24 | No | No | 12 | 7 | 146 |

*NA, Not available; NEG, neglect patient; RHC, right hemisphere control patient; OHC, older healthy control participant; F, frontal lobe; T, temporal lobe; P, parietal lobe; O, occipital lobe; cereb, cerebellum; Ins, insular gyrus; Thal, thalamus; IC, internal capsule; BG, basal ganglia.*

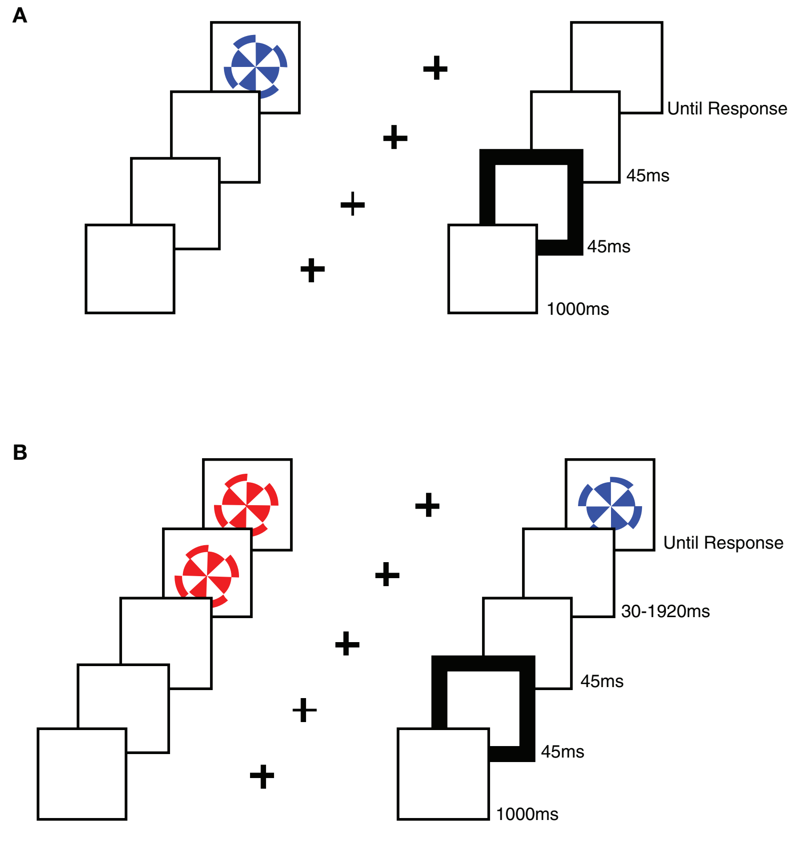


**FIGURE 1 | A schematic representation of the stimuli used in each task. (A)** An example sequence of stimuli in a RT task trial, showing a sequence from the uncued condition. **(B)** An example sequence of stimuli in a TOJ task trial, showing a sequence from the uncued, left-target condition.

### *Clinical tests*

Standard neuropsychological tests for attention were administered to each participant in addition to the experimental tasks including Judgment of Line Orientation (Benton et al., 1983), the Elevator Counting Task (from the Test of Everyday Attention, Robertson et al., 1996), and the behavioral inattention task (BIT; Stone et al., 1991). The results of these tests are summarized with the patient data in **Table 2**. Three participants were found to have visual field deficits using the confrontation method; of those three, two showed detection of left-sided items on an in-house computerized perimetry testing task. The third participant with visual field deficits scored normal on the TOJ task. Thus, no individual had a visual field deficit that interfered with testing.

### *RT and TOJ tasks*

Participants were seated 57 cm from the computer monitor and instructed to place their first two fingers of their right hand over the "2" and "8" keys of the number pad. The participants were instructed to fixate the central cross, which was on the screen for 1150 ms at the start of each trial. Fixation was visually monitored by the experimenter, and participants were reminded to remain fixated for the duration of the trial whenever they moved their eyes during a trial. A 45 ms cue was presented to one of the boxes (for left or right cue trials) or both boxes (for neutral cue trials) followed by the presentation of the pinwheel(s). Cues appeared at the same location as the target on 50% of trials, and at the opposite location on 50% of the trials.

In the RT task, only one target (a red or blue pinwheel) was presented in one of the peripheral boxes using a CTOA of 90 ms. The target remained visible until a response was made (see **Figure 1**). Participants ran in 120 trials. Participants were instructed to respond as fast as possible, without losing accuracy, pressing the "2" key if the target was red and the "8" key if the target was blue. Note that these keys were arranged one above the other on the number pad, and were therefore orthogonal to the dimension of spatial cueing (i.e., left vs. right).

In the TOJ task, the time interval between the onset of the cue and the onset of the first target pinwheel (CTOA) was fixed at 90 ms, while SOA between the first pinwheel and the second pinwheel varied, using the following intervals:−1920 ms, −960 ms, −480 ms, −240 ms, −120 ms, −60 ms, −30 ms, 30 ms, 60 ms, 120 ms, 240 ms, 480 ms, 960 ms, and 1920 ms, with negative SOAs indicating left-side first trials. Participants were asked to report the color of the first pinwheel (the target) presented following the cue *without time pressure*, and responses were recorded by pressing the "2" key if the target was red and the "8" key if the target was blue (a manual response was used in the TOJ task in order to better equate it with the RT task). Note that these keys were arranged one above the other on the number pad, and were therefore orthogonal to the dimension of spatial cueing (i.e., left vs. right). Both stimuli remained visible until a response was given. Participants ran in an average of 391 trials, and trials were distributed among the SOAs such that the smallest SOAs were sampled more often than the longest SOAs. The actual percentages used for the selection of SOA on each trial were 13.3% for +/−30 ms, 10% for +/−60 ms, 6.7% for +/−120 ms, +/−240 ms, and +/−480 ms, and 3.3% for +/−960 ms and +/−1920 ms. Although the number of trials per SOA condition varied slightly due to random sampling of SOA condition, on average the proportions achieved were very close to our intentions for both groups. Total trial number varied somewhat due to differences in fatigue level.

### METHODS OF ANALYSIS

In the RT task we used individual mean RTs to calculate two cueing effects (CE = uncued RT minus cued RT) for each participant, one for left-side targets and one for right-side targets. These CEs were then used to create a cueing asymmetry score for each participant. The formula for calculating cueing asymmetry scores is the same as that used to calculate the standard disengage deficit for patients with damage to the right hemisphere: $CE_{\text{left-side targets}}$ minus $CE_{\text{right-side targets}}$. Positive scores indicate a slower response to targets presented in the left side of space following a right side cue compared to the reverse. This pattern represents a rightward asymmetry, which is the same direction as the standard disengage deficit. Negative scores represent a leftward asymmetry (paradoxical disengage deficit).

We wanted to generate comparable cueing asymmetry scores for both the RT and TOJ tasks. While we have used PSS scores to determine whether there was a cueing effect in the TOJ task (see Eskes et al., 2007), the PSS cannot be coded in terms of the visual field of the target nor in terms of the location of the cue relative to the target, because targets are presented to both fields on every trial in a TOJ study. In order to calculate an analogous cueing asymmetry score for the TOJ task we defined TOJ trials based on "target" side, with a target side referring to the visual field of the item that was presented first. For example, all trials when the left item came up first (i.e., negative SOA trials) were defined as left-target trials. This allowed us to examine error rate as both a function of cueing (uncued vs. cued) and target location, just as in the RT task. We used individual mean error rates to calculate a CE (uncued error rate minus cued error rate) separately for left-side targets and right-side targets. If TOJs are affected in the expected direction by the cues (PSS shift) then errors will necessarily be lower when the cue is presented on the side of the first target (cued) than on the side of the second target (uncued). We then performed the standard cueing asymmetry score subtraction for patients with damage to the right hemisphere ($CE_{\text{left-side targets}}$ minus $CE_{\text{right-side targets}}$). Positive scores represent a rightward cueing asymmetry, which is in the same direction as the standard disengage deficit, while negative scores represent a leftward cueing asymmetry (paradoxical disengage deficit). For clarity, the meaning ascribed to the direction of these cueing asymmetry scores is congruent with the meaning ascribed to the direction of the cueing asymmetry scores in the RT task.

## RESULTS

### RT TASK RESULTS

We examined error rates and mean RTs for each participant and for the entire set of participants to confirm that each participant was competent at performing the task. One participant in the NEG group had an error rate more than 5 SD from the mean, so he was eliminated from further analysis. To ensure both tasks were easily compared, we also eliminated the same subject from the TOJ analysis described below. All other participants had mean error rates and mean RTs that were within 2 SD of the overall means. The average error rate was 4.2% (SD = 7.1, $n = 16$). A mixed effects ANOVA on errors including cue location and target location as the within-subject variables, and group as the between-subject variable revealed no significant main effects or interactions.

Trials on which participants made erroneous responses (4.2%) and trials on which the participant missed the target (1%) were eliminated from RT analyses. Trials on which RTs were greater than 2 SD above a participant's mean for each condition were considered outliers and were eliminated from subsequent analysis (1.5%). Trials on which RTs were less than 150 ms were also eliminated (0.02%). Mean RTs for the NEG group ($n = 7$), RHC group ($n = 5$), and OHC group ($n = 3$) were 1034 ms (SD = 2224), 1316 ms (SD = 2482), and 494 ms (SD = 194), respectively.

To ensure that the RT task was effective at producing a cueing effect, mean RTs were calculated by cueing condition collapsed over side. The overall mean for cued, neutral and uncued trials were 781 ms (SD = 510), 823 ms (SD = 587), and 876 ms (SD = 600), respectively (see left graph, **Figure 2**). A one-way ANOVA revealed a significant effect of cueing condition [$F(2, 28) = 5.91, p < 0.01$, MSE = 5753].

Individual mean RTs were then used to calculate cueing effects (CEs) and cueing asymmetry scores for left- and right-side targets for each participant (see section "*Methods of Analysis*", above). From these data, group averages were created. **Table 3** includes the descriptive statistics by group for left- and right-side target CEs and cueing asymmetry scores. **Figure 3** illustrates group means for the cueing asymmetry scores.

Because of the small number of participants in each group, we used non-parametric statistics to evaluate group differences in cueing asymmetry scores. While it appeared that the NEG group overall showed a rightward bias that was much greater than the OHC group, and that the RHC group showed a leftward bias, a Kruskal-Wallis one-way ANOVA revealed no significant difference in bias scores between the groups for the RT task ($H = 0.08$, $df = 2$, $p > 0.9$). To confirm that there was no difference between the stroke groups alone, we performed a Mann-Whitney U test on the mean bias scores for the NEG and RHC groups, also demonstrating no significant difference ($W = 25$, $n = 12$, $p > 0.6$).

Because the mean cueing asymmetry scores for the NEG group appeared different from the RHC and OHC in the hypothesized direction, and because of the large variability, we examined cueing asymmetry scores for each individual participant in both the NEG and RHC groups. **Figure 4** illustrates these individual cueing asymmetry scores, presented in order of their BIT Star Cancellation scores (indicated in the figures in italics). We also used the mean cueing asymmetry score +/−2 SD from the OHC group (indicated with dotted lines; 52 and 29, respectively) to determine which individual patients showed a right cueing asymmetry, indicative of a standard disengage deficit, or a left cueing asymmetry, suggesting a paradoxical disengage deficit. The graph reveals three interesting patterns:

1. All individuals in both stroke groups possessed cueing asymmetry scores that were +/−2 SD beyond the mean cueing asymmetry score of the OHC group, indicating that cuing effects for each patient were abnormal either on the left side *or* on the right side. That is, all patients in the RT task qualified for a disengage deficit label; however, they were almost equally likely to have a standard disengage deficit as they were to have a paradoxical disengage deficit.
2. Patients in the NEG group were no more likely than patients in the RHC group to have cueing asymmetry scores that put them in the range of a standard disengage deficit. In fact, more participants with neglect showed a paradoxical disengage

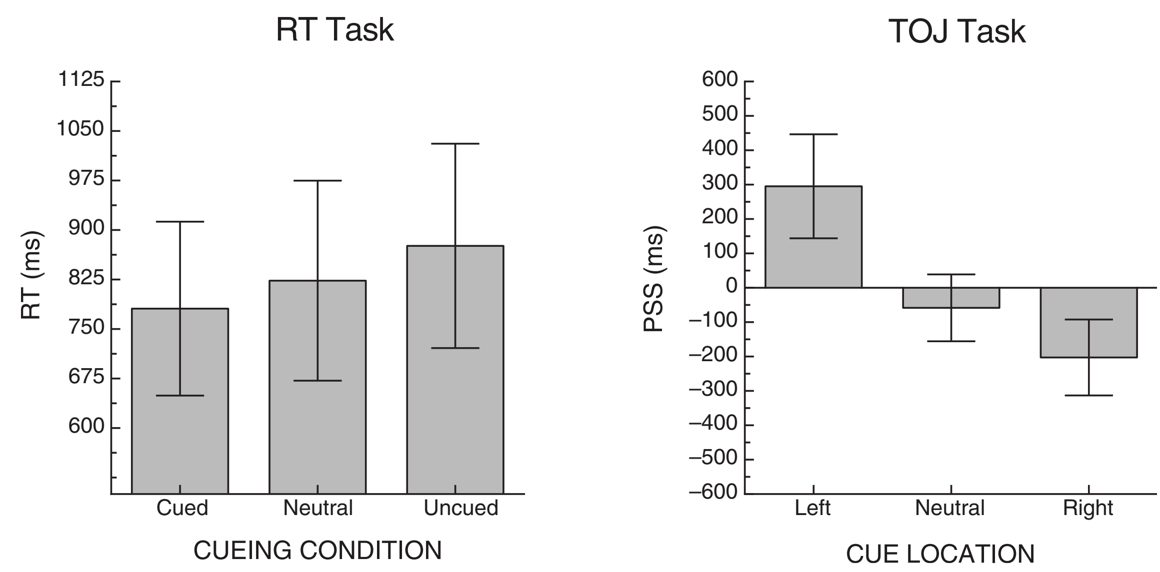


**FIGURE 2 | Mean cueing effects for each of the two tasks across all participants.** Error bars represent +/− the standard error of the mean for each condition.

**Table 3 | Means and SDs (in brackets) for each condition and task; means and SDs for the CEs and cueing asymmetry scores have been derived from subtractions for each individual participant.**

| | RT task[a] | | | TOJ task[b] | | |
|---|---|---|---|---|---|---|
| | **Neglect** | **RHC** | **OHC[c]** | **Neglect** | **RHC** | **OHC[c]** |
| **LEFT TARGETS** | | | | | | |
| Cued | 790 (197) | 1182 (1077) | 447 (30) | 0.35 (0.32) | 0.17 (0.06) | 0.08 (0.04) |
| Neutral | 768 (204) | 1189 (1046) | 512 (42) | 0.46 (0.30) | 0.30 (0.07) | 0.11 (0.08) |
| Uncued | 944 (385) | 1273 (1076) | 487 (37) | 0.54 (0.28) | 0.31 (0.08) | 0.28 (0.13) |
| CE | 154 (259) | 92 (106) | 39 (17) | 0.19 (0.20) | 0.14 (0.09) | 0.19 (0.13) |
| **RIGHT TARGETS** | | | | | | |
| Cued | 644 (166) | 963 (602) | 467 (40) | 0.17 (0.20) | 0.25 (0.15) | 0.08 (0.04) |
| Neutral | 714 (225) | 1092 (895) | 475 (30) | 0.19 (0.19) | 0.33 (0.13) | 0.28 (0.03) |
| Uncued | 685 (152) | 1108 (818) | 476 (47) | 0.36 (0.24) | 0.43 (0.15) | 0.37 (0.04) |
| CE | 42 (75) | 145 (227) | 9 (8) | 0.19 (0.25) | 0.18 (0.10) | 0.29 (0.04) |
| **CUEING ASYMMETRY SCORE** | | | | | | |
| | 112 (218) | −53 (264) | 30 (11) | 0.0 (0.15) | −0.03 (0.11) | −0.10 (0.11) |

[a] *Raw units are mean RTs.*
[b] *Raw units are proportion of errors.*
[c] *Older healthy controls.*

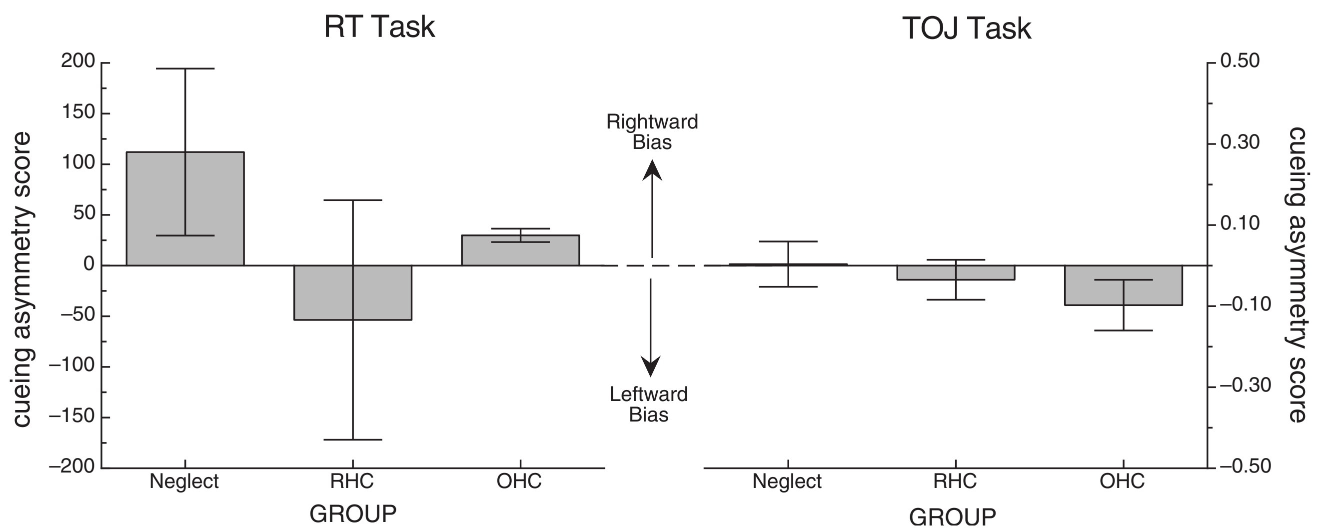


**FIGURE 3 | Mean cueing asymmetry score for each of the two tasks.** Error bars represent +/− the standard error of the mean for each group. In both cases, positive scores represent a rightward bias (the direction of the standard disengage deficit) and negative scores represent a leftward bias.

deficit than a standard disengage deficit, albeit the paradoxical disengage deficits were smaller in terms of the absolute scores.

3. We found no relationship between neglect scores as derived from the BIT Star Cancellation task and the overall cueing asymmetry score in the RT task ($r = 0.02$, $df = 10$, $p > 0.9$). This was also true for the total BIT scores ($r = 0.02$, $df = 10$, $p > 0.9$) and the center of cancellation scores on the line cancellation subtest (see Rorden and Karnath, 2010; $r = -0.02$, $df = 10$, $p > 0.9$). That is, patients with clinical left neglect (indicated by low BIT Star Cancellation scores) did not necessarily have cueing asymmetry scores indicative of a standard disengage deficit. This was true for individuals in both the NEG and RHC groups (see **Table 4** for the correlations and *p*-values comparing cueing asymmetry scores and scores from the BIT subtests and BIT subtest center of cancellation scores, using all of the stroke patients).

### TOJ TASK RESULTS

To ensure that the cues in the TOJ task were effective at producing cueing, we examined PSS. A positive PSS indicates that the right-target would have to be presented before the left-target in order for a participant to experience them as being presented simultaneously; with the numerical value indicating how much of a lead the right-target would need (in ms). Three PSS scores were calculated

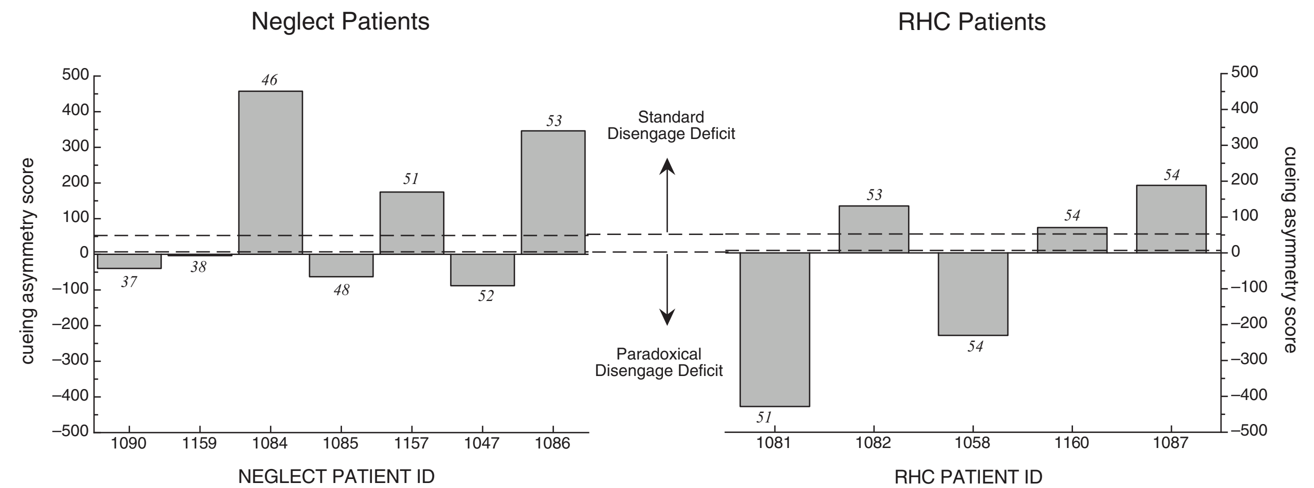


**FIGURE 4 | Cueing asymmetry scores for NEG (left graph) and RHC group (right graph) in the RT task.** Patients are represented in order of the BIT Star Cancellation scores, from lowest to highest (individual BIT Star Cancellation scores are listed above or below the individual bars). Cueing asymmetry scores above zero represent a rightward bias. Note that the *x*-axis spaces patients equidistantly, and does not represent the listed BIT Star Cancellation scores on an ordinal scale. See text for details.

**Table 4 | Pearson correlations for the subtests of the BIT with the cueing asymmetry scores for both the RT task and TOJ task, including patients from both the NEG and RHC groups.**

| BIT subtest | RT cueing asymmetry score | | TOJ cueing asymmetry score | |
|---|---|---|---|---|
| | Correlation | *p*-value | Correlation | *p*-value |
| Line cancellation | 0.06 | >0.8 | 0.07 | >0.8 |
| Line: CoC[a] | −0.06 | >0.8 | −0.07 | >0.7 |
| Letter cancellation | −0.01 | >0.9 | −0.11 | >0.7 |
| Letter: CoC[a] | −0.22 | >0.4 | 0.04 | >0.8 |
| Star cancellation | 0.01 | >0.9 | 0.04 | >0.8 |
| Star: CoC[a] | −0.05 | >0.8 | 0.24 | >0.3 |
| Line bisection | −0.23 | >0.4 | 0.14 | >0.6 |
| Leftmost line bisection[b] | −0.27 | >0.3 | −0.15 | >0.5 |
| Figure copying | −0.17 | >0.5 | 0.10 | >0.7 |
| Figure leftmost copy[b] | −0.43 | >0.1 | 0.03 | >0.9 |
| Drawing | −0.01 | >0.9 | 0.02 | >0.9 |
| Drawing leftmost item[b] | −0.42 | >0.1 | 0.33 | >0.2 |

[a] *CoC, center of cancellation scores; see Rorden and Karnath, 2010 for score calculation.*

[b] *BIT subtests that were not predisposed to calculating a center of cancellation score were rescored to evaluate the left-most components.*

per participant; one for trials on which a left cue was presented (left PSS), trials on which a neutral cue was presented (neutral PSS) and trials on which a right cue was presented (right PSS). Due to severe left neglect, we were unable to calculate reliable PSS scores for one neglect patient (ID 1159), so his data were excluded from the PSS cueing analysis. For the remaining participants, the mean PSS for these conditions was 295 ms (SD = 566), −58 ms (SD = 364), and −203 ms (SD = 413), respectively (see right graph, **Figure 2**). A one-way ANOVA revealed a significant effect of cue location [$F(2, 26) = 5.96$, $p < 0.01$, MSE = 154,041]. **Table 3** includes the descriptive statistics for left- and right-side target CEs based on error rates as well as the cueing asymmetry scores (see section "*Methods of Analysis*", above).

Just as in the RT task, we used non-parametric tests to evaluate group differences in cueing asymmetry scores for the TOJ task. A Kruskal-Wallis one-way ANOVA revealed no significant difference in cueing asymmetry scores between the groups ($H = 1.72$, $df = 2$, $p > 0.4$). To confirm that there was no significant difference among just the stroke groups, we performed a Mann-Whitney U test on mean cueing asymmetry scores for NEG and RHC groups, also demonstrating no significant difference ($W = 21$, $n = 12$, $p < 0.64$). **Figure 3** (right graph) illustrates group means for the cueing asymmetry scores for the TOJ task.

Because TOJ cueing asymmetry scores had a finite range (1 to −1), and because the mean cueing asymmetry scores for each group were relatively small in comparison to this range, we were not compelled to examine the individual cueing asymmetry scores. However, to be consistent with the analysis in the RT task, we plotted the individual scores for each patient group in **Figure 5** in order of their BIT Star Cancellation scores (indicated in italics). We again used the mean cueing asymmetry +/−2 SD from the OHC group (indicated with dotted lines; 0.12 and −0.31, respectively) to define a standard disengage deficit or a paradoxical disengage deficit. The graph reveals two interesting patterns:

1. Most individuals in both groups were within a normal range, as defined by the mean cueing asymmetry score of the OHC group +/−2 SD.
2. The two individuals with neglect whose cueing asymmetry scores were outside the normal range (OHC) and in the range of a standard disengage deficit did not have the most severe clinical neglect as determined by their BIT Star Cancellation

scores. Indeed, there was no overall relationship between cueing asymmetry scores for the TOJ task and any of the BIT subtests (correlations and *p*-values are listed in **Table 4**).

#### POST-HOC ANALYSES

To ensure the results were not due to a lack of counterbalancing the keys, we looked at responses as a function of response keys ("8" vs. "2"). For RT in the RT task, there was no main effect of key across all participants using a within-subject one-way ANOVA. There was also no interaction between key and participant group in a mixed ANOVA. This was also true for the TOJ task.

The correlation between the cueing asymmetry scores in two tasks, including all participants in all groups, was small and not significant ($r = 0.08$, $df = 13$, $p > 0.7$). We wanted to confirm that there was no relationship between cueing asymmetry scores in the RT task and TOJ task. To this end, we created two post-hoc groups of participants from the stroke population in our study: a Standard Disengage Deficit Group and a Paradoxical Disengage Deficit Group. These groups were chosen *based on each patient's cueing asymmetry score from the RT task only*. As one would expect, a Mann-Whitney U test revealed a significant effect of the post-hoc grouping on cueing asymmetry scores ($W = 36$, $n = 12$, $p < 0.01$). We then kept the groups the same to examine whether individuals who showed a standard disengage deficit in the RT task also show a standard disengage deficit (or even a bias in that direction) in the TOJ task. A Mann-Whitney U test revealed no significant difference between the post-hoc groups on cueing asymmetry scores in the TOJ task ($W = 20$, $n = 12$, $p > 0.8$). **Figure 6** illustrates the mean cueing asymmetry scores for these post-hoc groups for both tasks. The TOJ graph nicely illustrates that there appears to be no difference between groups. Indeed, neither the Standard Disengage Deficit Group nor the Paradoxical Disengage Deficit Group showed a cueing asymmetry score different from zero

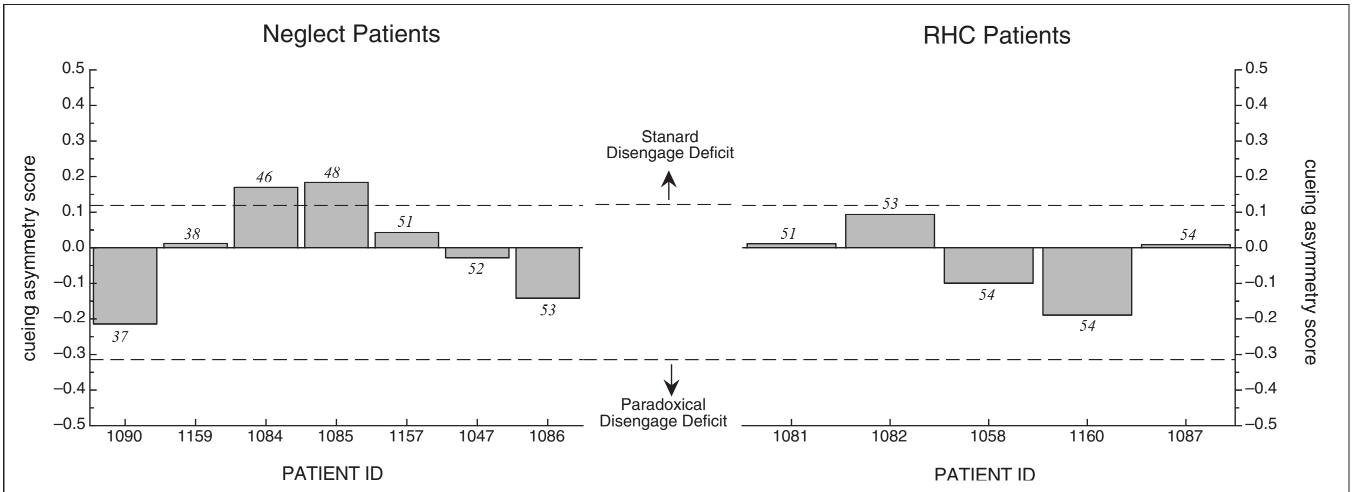


**FIGURE 5 | Cueing asymmetry scores in the TOJ task for Neglect patients (left graph) and RHC patients (right graph) plotted in order of each patient's BIT Star Cancellation score (see text for details).** Dotted lines represent +/− 2SD of mean OHC cueing asymmetry score.

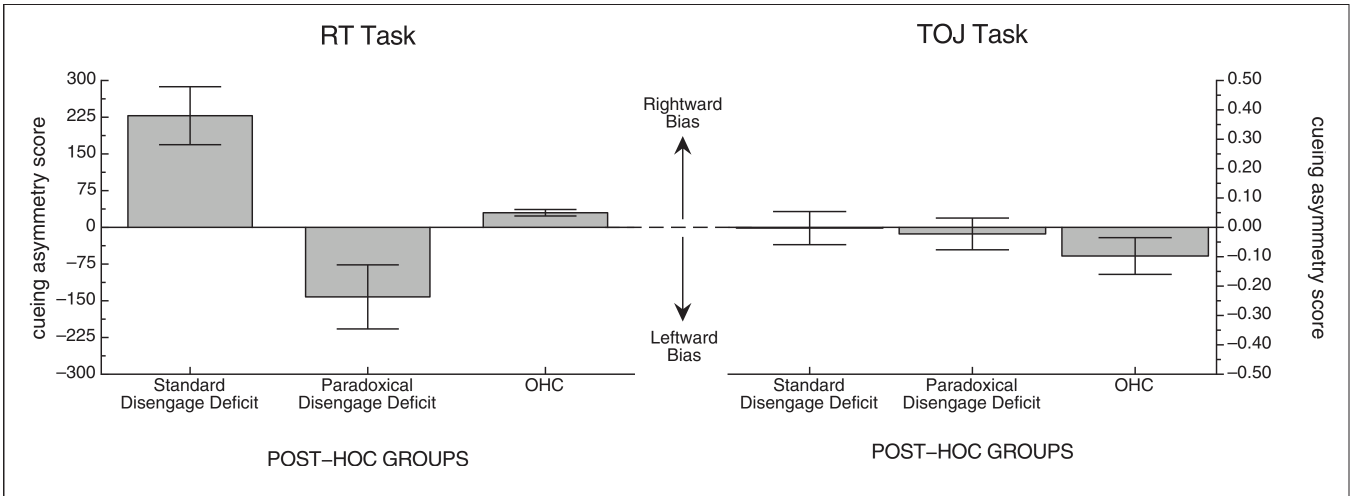


**FIGURE 6 | Mean cueing asymmetry scores in each task for the post-hoc groups.** OHC group is included for reference. See text for details.

($x = -0.003$, $df = 5$, $p > 0.9$, and $x = -0.02$, $df = 5$, $p > 0.6$, respectively). The OHC group is included in the figure for reference.

## DISCUSSION

In the current study we sought to examine whether the disengage deficit typically observed in an RT task in patients with unilateral neglect might also be observed in the same patients using a TOJ task with spatial cueing. To this end, we compared performance on a standard speeded RT cueing task to a TOJ-with-cueing task that were equated for stimuli and response choice discrimination. It should be noted that for both tasks the peripheral cues were uninformative. As noted by Losier and Klein (2001) when neglect patients are subjected to a typical spatial cuing paradigm, the disengage deficit in RT is robust when peripheral cues are used (whether or not these cues are informative) while the disengage deficit is small to absent following purely endogenous cuing (informative central arrow cues).

Performance on both tasks showed significant cueing effects as expected and validated the cueing manipulation. Across both tasks, however, there were three major surprising and noteworthy patterns of results:

1. Few stroke patients showed a disengage deficit in the TOJ task and cueing asymmetry scores in the TOJ task were not consistent with the cueing asymmetry scores in the RT task, either in a correlational analysis, or by post-hoc grouping.
2. In the RT task typically used to demonstrate a standard disengage deficit, stroke patients were almost equally likely to show a standard disengage deficit (indicative of a spatial bias in favor of the ipsilesional side of space) as they were to show a paradoxical disengage deficit (indicative of a spatial bias in favor of the contralesional size of space).
3. There was no relationship between the size and/or direction (i.e., whether it was standard or paradoxical) of the speeded disengage deficit and neglect severity. Indeed, patients who did not meet the criteria for clinical neglect (i.e., RHC) were just as likely to have a disengage deficit as patients who did meet the criteria for clinical neglect (i.e., NEG).

The cueing asymmetry scores in the two tasks were not consistent with each other, and indeed patients seemed to have very low cueing asymmetry scores in the TOJ task. This inconsistency would indicate that the disengage deficits evident in the RT task are a manifestation of the task demands rather than a general attentional state in patients with or without neglect. One possibility is that the differences in task demands elicited different mental sets; in the RT task the action system needed to be rapidly recruited, while in the TOJ task it did not.

Goodale and Milner (1992); Milner and Goodale (2008) proposed an influential model of vision that divides visual processing into two functional streams. The dorsal stream is involved in the use of vision for action; this stream controls detailed programming of online movements using bottom-up inputs from the retina to determine the specific parameters for movement. The ventral stream is involved with vision for identification; this stream enables the perception and identification of objects and their spatial relations. Knowing in advance that they would be required to execute a speeded motoric response in the RT task involving a key choice could have set the participants up to engage their dorsal stream. The cue may have provided an exogenous trigger for the initiation of a visually-guided motor plan, which would have to be inhibited in favor of a new plan triggered by the target. However, neglect patients often show motor perseveration—that is, a continuation of a behavior after a change in task demands (Kim et al., 1999). For example, neglect patients frequently mark individual stars repeatedly in the BIT star cancellation task, even while ignoring all of the stars in their neglected field. Engagement of the dorsal stream coupled with motor perseveration would preferentially impact reaction times in the RT task, but not accuracy in the TOJ task.

Another surprising finding, however, was that a direction of the patient's deficit in the RT task was not necessarily predicted by the location of their lesion or the side of space they were prone to neglect in standard tests of neglect. About half of the patients with right hemisphere damage, irrespective of whether they met the criteria for contralesional neglect or not, showed a disengage deficit in the RT task that was in *favor* of their contralesional side of space (i.e., demonstrating a paradoxical disengage deficit). The presence of a paradoxical disengage deficit as seen in our study has also been reported by others (e.g., Sacher et al., 2004 in their individual analyses). One reason for this pattern may be due to compensatory effects (Robertson et al., 1994; Dove et al., 2007). That is, patients who have contralesional neglect and are aware of their deficit may overcompensate for their spatial bias by making an effort to direct their attention leftward. Compensatory strategies for a task involving a time-pressured response coupled with motor perseveration might explain the paradoxical disengage deficits that were observed on some of the patients tested, although this compensation was not evident in the TOJ task. The role of compensatory strategies in neglect recovery and interaction with task demands has been highlighted in recent papers and reviews (e.g., Manly et al., 2002; Bonato et al., 2010; Bonato, 2012).

The fact that the standard disengage deficit was not consistent in the NEG group, and was also present in some of the RHC group is perhaps not surprising. Previous studies have shown that patients who have right hemisphere damage but who do not meet the criteria for clinical neglect might also have a standard disengage deficit, suggesting that some experimental tasks, including the Posner spatial cueing RT task that we used, might be more sensitive at detecting behavioral neglect than the standard clinical tests of neglect (Rengachary et al., 2009). In their meta-analysis, Losier and Klein (2001) found that the standard disengage deficit was significantly more severe in patients with neglect and, among those with neglect there was a significant correlation between neglect severity and the size of the disengage deficit. Neither of these patterns held up in our group of patients; however, this pattern is itself not entirely consistent in the literature. For example, Sieroff et al. (2007) found that there was no relationship between the magnitude of the disengage deficit and neglect severity in a group of patients defined in a similar way as our study. The lack of a group correlation between the disengage deficit and neglect severity, or the dissociation between the presence of a disengage deficit and neglect symptoms on clinical tests in individual patients has also been reported in several studies (e.g., Sacher et al., 2004; Olk et al., 2010; Bonato et al., 2012). Thus, further examination of what other variables may underlie the disengage deficit pattern appears warranted.

One explanation for our deviation from this pattern could be the variability of the data itself. The mean cueing asymmetry score for the NEG group was not significantly different from zero, and the only significant effects were found in the post-hoc groups, which is no surprise. What is noteworthy is that even when we grouped the patients according to whether they showed a standard disengage deficit in the RT task, they did not show a corresponding disengage deficit on TOJ task.

The performance of our patient participants on the RT task is more variable between-subject than the representative literature (cf., Losier and Klein, 2001), but there are several reasons that may explain this difference. First, we used relatively unrestricted inclusion criteria for our neglect patients and our individual analyses may have identified more variability than is normally included in small group studies. Second, researchers often report data in aggregate form, which may obscure individual differences among patients, and hide patients who lack the standard disengage deficit. We specifically examined the individual patients to determine how variable the disengage deficit was. We were surprised by the variability; however, we also felt that the extent and direction of the variability itself was interesting and important to report. Third, patient or methodological differences in the current study may have led to these findings. We chose to use a discrimination task in the cuing paradigm, in order to directly match the task requirements from the TOJ task. Since most cuing tasks use a detection response, this difference may have created some of the variability. Further investigation into the impact of type of task processing on the spatial cuing paradigm may help to resolve this issue. In any event, the disengage deficit has been regarded as a better test of neglect than the standard clinical tests, but if patients only show the effect under a very narrow range of conditions, the disengage deficit may not be an effective explanation or marker of neglect. Finally, and possibly most critically, the variability of performance among neglect patients in a spatial cueing paradigm may be under-reported due to a publication bias. Authors may shelve studies in which the patients are highly variable because the data don't conform to the author's theoretical framework, or may be rejected by reviewers because the data don't conform to the literature. However, every patient is providing valuable data, irrespective of one's theoretical framework. It is important that a literature represents the population it is studying, and in this case that population is highly variable.

Whatever the reason, the results of our study show that the disengage deficit is neither necessary nor sufficient to produce neglect. Not necessary because patients with left neglect might show no disengage deficit or a paradoxical disengage deficit; not sufficient because some patients without classic neglect as seen on paper and pencil tasks (i.e., RHC patients) show the standard disengage deficit. Our finding that the disengage deficit is not consistent across well-matched tasks (RT cuing vs. TOJ) also suggests that the disengage deficit is perhaps not the unifying explanation of neglect that some researchers hoped it would be (Adair and Barrett, 2008). In addition, our findings suggest that a better understanding of contributory factors that can influence visuo-spatial responding (e.g., non-spatial attention deficits, compensation strategies, and the role of task demands and manual responses) appears necessary to further advance theories of the basic mechanisms underlying spatial neglect.

## ACKNOWLEDGMENTS

This study was supported by a Canadian Institutes of Health Research operating grant (to Drs. Gail A. Eskes et al.). We thank Dr. David Shore for his helpful advice and support with the TOJ paradigm, Hilary Duncan for technical support and the Capital Health stroke teams for help with patient recruitment. Thanks also go to the patients and controls who volunteered their time for this project.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 26 January 2012; accepted: 21 July 2012; published online: 21 August 2012.*

*Citation: Dukewich KR, Eskes GA, Lawrence MA, MacIsaac M-B, Phillips SJ and Klein RM (2012) Speed impairs attending on the left: comparing attentional asymmetries for neglect patients in speeded and unspeeded cueing tasks. Front. Hum. Neurosci. **6**:232. doi: 10.3389/fnhum.2012.00232*

## APPENDIX

**Table A1 | Behavioral inattention task subtest scores.**

| Subject code | Group | Line cancellation (center of cancellation) | Letter cancellation (center of cancellation) | Star cancellation (center of cancellation) | Copying (only left errors) | Line bisection center of cancellation (left-most line only) | Drawing (only left errors) |
|---|---|---|---|---|---|---|---|
| 1047 | NEG | 36 (0.00) | 40 (0.00) | 49 (0.01) | 4 (4) | 0.07 (0.11) | 3 (3) |
| 1084 | NEG | 36 (0.00) | 37 (0.03) | 46 (0.05) | 3 (3) | −0.18 (−0.16) | 2 (–) |
| 1085 | NEG | 35 (0.00) | 39 (0.00) | 48 (0.02) | 2 (4) | 0.05 (0.26) | 1 (2) |
| 1086 | NEG | 36 (0.00) | 33 (−0.06) | 52 (0.01) | 3 (3) | 0.11 (0.15) | 3 (3) |
| 1090 | NEG | 36 (0.00) | 34 (0.15) | 37 (0.32) | 2 (2) | −0.06 (−0.04) | 1 (1) |
| 1157 | NEG | 36 (0.00) | 40 (0.00) | 51 (0.04) | 1 (1) | −0.10 (0.01) | 1 (1) |
| 1159 | NEG | 30 (0.19) | 22 (0.27) | 39 (0.17) | 2 (3) | 0.25 (0.48) | 3 (3) |
| 1058 | RHC | 36 (0.00) | 38 (0.00) | 54 (0.00) | 2 (4) | −0.10 (−0.08) | 3 (3) |
| 1081 | RHC | 36 (0.00) | 35 (0.06) | 51 (0.01) | 4 (4) | 0.05 (0.18) | 3 (3) |
| 1082 | RHC | 36 (0.00) | 40 (0.00) | 53 (0.00) | 3 (3) | −0.06 (0.02) | 3 (3) |
| 1087 | RHC | 36 (0.00) | 34 (0.02) | 54 (0.00) | 2 (3) | 0.04 (0.10) | 3 (3) |
| 1160 | RHC | 36 (0.00) | 38 (−0.05) | 54 (0.00) | 4 (4) | −0.02 (−0.07) | 3 (3) |
| 1162 | OHC | 36 (0.00) | 40 (0.00) | 54 (0.00) | 4 (4) | 0.00 (0.01) | 3 (3) |
| 1163 | OHC | 36 (0.00) | 40 (0.00) | 54 (0.00) | 4 (4) | 0.02 (0.05) | 3 (3) |
| 1164 | OHC | 36 (0.00) | 40 (0.00) | 54 (0.00) | 4 (4) | −0.01 (0.01) | 3 (3) |

*NEG, neglect patient; RHC, right hemisphere control patient; OHC, older healthy control participant.*

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 05 October 2012
doi: 10.3389/fnhum.2012.00267

# Extracting the mean size across the visual field in patients with mild, chronic unilateral neglect

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Previous studies suggest that normal vision pools information from groups of objects in a display to extract statistical summaries (e.g., mean size). Here we explored whether patients with mild, chronic left neglect were able to extract statistical summaries on the right and left sides of space in a typical manner. We tested four patients using a visual search task and varied the mean size of a group of circles within the display. On each trial, a single circle first appeared in the center of the screen (the target). This circle varied in size from trial to trial. Then a multi-item display appeared with circles of various sizes grouped together either on the left or right side of the display. The instructions were to search the circles and determine whether the target was present or not. The circles were always accompanied by a group of task-irrelevant triangles that appeared on the opposite side of the display. On half the trials, the mean size of the circles was the size of the target. On the other half the mean size was different from the target. The patients were not told that this was the case, and no explicit report of the statistics was required. The results showed that when the targets were absent patients produced more false alarms to the mean than non-mean size when the circles were on the left (neglected) side of the display. This finding demonstrates that statistical information was implicitly extracted from the left group of circles. However, summary statistics on the right side were not limited to the circles. Rather it appears that participants pooled the distractors with the target circles, yielding a skewed statistical summary on the right side. These findings are discussed as they relate to statistical summary processing, visual search and segregation of right and left items in patients with mild, chronic unilateral neglect.

**Keywords: statistical summary, unilateral neglect, attention, visual perception**

## INTRODUCTION

When we walk down a crowded street we encounter a scene rich with information. Typically, we form the impression that we have a full representation of our surroundings. However, due to limitations of the visual system, it is unlikely that we formulate a detailed representation of every object in the scene. Instead, we achieve an overall interpretation of the scene. One way that we formulate this "gist" is via statistical summary (see review, Alvarez, 2011). Within almost every visual scene, there are numerous redundancies, and we can gain a quick average summary of similar features in the environment by calculating statistical summaries. Statistical summary of similar sets of objects has been demonstrated in several areas of visual perception. For instance, Ariely (2001) and Chong and Treisman (2003) reported that subjects can judge the average size of circles in a visual display as well as the average size of items grouped together on the right or left side of a display. Similarly, Parkes et al. (2001) reports that subjects can determine the average orientation of items in the visual field. Others have shown that subjects can accurately judge the mean direction of motion (Williams and Sekuler, 1984) and speed (Watamaniuk and Duchon, 1992). More recent work has shown that statistical summary can occur over time as well (Haberman et al., 2009; Albrecht and Scholl, 2010). Statistical summary is used in countless ways and normally serves individuals well. We employ it not only to summarize characteristics of simplistic objects (i.e., geometric shapes), but also to obtain the average walking direction or higher-order face characteristics of a crowd (Haberman and Whitney, 2007; Sweeny et al., 2011; Yamanashi Leib et al., 2012).

In addition, summary statistics are dependent on accurate grouping of items within the visual field. For instance, if a sweet shop captures a person's attention while walking down a crowded street, statistical summary processes may extract the mean color and shape from the storefront display (brown and square). This information could help lead him/her to the conclusion that the store is selling chocolate as opposed to jelly beans. Simultaneously, the visual system may extract summary statistics from objects outside the focus of attention (i.e., the adjacent clothing store). Imagine if the shape and color of distractors (clothing) were averaged with the shape/color of the target (candy). The resulting summary statistics would be distorted. Fortunately, typical perceivers can successfully extract the mean from different groups of objects presented simultaneously. For instance, Chong and Treisman report that subjects can create separate ensemble statistics for groups of differently colored circles and/or circles that are clustered in different spatial locations (Chong and Treisman, 2003, 2005).

Statistical summary mechanisms benefit visual perception in typical populations—but could also potentially be advantageous for patients with attentional deficits. In explicit experimental tasks, unilateral neglect patients are impaired in attentional search on one side of space (Eglin et al., 1989; Behrmann et al., 1997; Esterman et al., 2000; Laeng et al., 2002; Pavlovskaya et al., 2002). Within daily life, these attentional impairments become evident as neglect patients may neglect to eat food from one side of the plate, forget to dress one side of their body, or fail to draw one side of an object (Husain and Rorden, 2003). Although attentional search is degraded, other perceptual mechanisms remain intact. For instance, organizational processes such as grouping or completion (Brooks et al., 2005) across the right and left sides of a display are relatively unimpaired. Additionally, many priming tasks indicate that neglect patients can be implicitly cued by stimuli presented on the left (neglected) side of space (Marshall and Halligan, 1988; McGlinchey-Berroth et al., 1993). We are interested in exploring whether statistical summary, a process that can occur implicitly (Ariely, 2001; Haberman and Whitney, 2007; De Fockert and Wolfenstein, 2009) is similarly spared in neglect patients. If statistical summary mechanisms are spared, this may allow patients to gain an implicit, unitized percept of their surroundings, despite the fact that attentional search mechanisms are degraded. Statistical summary confers multiple benefits to visual perception including: increased precision, information compression, and rapid updating of working memory (Alvarez, 2011; Brady et al., 2011). Such benefits could be especially useful to unilateral neglect patients, who receive limited benefits from explicit attentional search.

To explore this question, we designed an experiment that investigated whether patients with very mild chronic signs of neglect and psychophysical evidence of continued left sided attentional deficits extract statistical summary under implicit conditions. In brief, we presented a target circle centrally, then asked patients search for the target circle size within a multi-circle display with distractors. Importantly, on half the trials, the mean size of the circles was the size of the target. On the other half the mean size was different from the target. We predicted that if patients extract summary statistics, they will form a clear mental representation of the mean circle size within the search display. This mental representation should trigger patients to falsely report that the mean target size is present in the search display—even when it is absent. Thus, there will be an increase in false alarms when the searched target is the mean size of the display. This method of implicit mean detection has been successfully used in numerous statistical summary experiments (Ariely, 2001; Treisman, 2006; Haberman and Whitney, 2007; De Fockert and Wolfenstein, 2009). We adopted the task reported in Treisman, 2006 to accommodate unilateral neglect patients. Specifically, the multi-circle display was shown either on the left or the right side of the screen. It was always accompanied by a group of distractor triangles on the opposite side of the display. In this way, we could examine whether patients could reject these triangles in responding to the circular array. If they could, false alarms on the right and left should show the same pattern of results (i.e, more FAs to the mean than non-mean). However, if the distractors on the left were pooled with the circular array on the right, then the mean would be distorted and a different pattern of results could occur.

## MATERIALS AND METHODS

### PARTICIPANTS

We tested four patients with chronic unilateral left neglect (three males and one female). Three were mildly impaired on only the line bisection and cancellation task from the standard SCAN test for spatial neglect (McGlinchey-Berroth et al., 1996).

#### *Line bisection task*

The line bisection task involves showing the patient a horizontal line (centrally presented) on a piece of paper. Patients are asked to write a mark in the exact center of the line. Deviation from the right of center may indicate left neglect. Deviation is measured in centimeters.

#### *Cancellation tasks*

In the cancellation tasks, patients are presented with 16 letters, symbols, or lines scattered across a piece of paper. Symbols and letters are presented with distractors; lines are not presented with distractors. The patient is asked to cross out a target letter, symbol, or line. The patient is given unlimited time to complete the task and verbally indicates completion. Unilateral neglect patients often fail to cross out items on one side of the page because of impaired attention. The total number of missed items is summed, and items missed on both sides are excluded from the calculation. Our patients completed six cancellation tasks in total, each with 16 targets. One patient did not complete the SCAN and was referred to us by a rehabilitation specialist who noted neglect of left sided information. Diagnosis of unilateral neglect was made by an optometrist and confirmed by the psychophysical conjunction task that we administered prior to testing (reported in **Table 2**). Some patients took the SCAN during the acute stages of neglect (with scores ranging from 2–9 items missed in the cancellation task and deviations of 0.95–11.35 cm from center in the line bisection task) **Table 1** reports age, years post onset, and the scores from our patients most recent SCAN tasks. In order to investigate the role of attention in statistical summary processes we included patients that exhibited attentional biases in one hemifield.

**Table 1 | Patient age and SCAN scores are presented below.**

| | | | SCAN scores | |
|---|---|---|---|---|
| **Participant** | **Age** | **Onset prior to testing** | **Cancellation (No. of missed/16)** | **Line bisection (cm to right)** |
| UNP1 | 50 | 5 years | 3 | 1.40 |
| UNP2 | 68 | 3 years | 1 | 1.85 |
| UNP3 | 50 | 1 year | * | * |
| UNP4 | 77 | 1 year | 2 | 3.20 |

**This participant did not take the SCAN.*

At the same time, including patients with a moderate unilateral bias allowed the assessment and comparison of performance on both visual fields.

Previous studies have shown that patients who have minimal signs of neglect on paper and pencil tests, or have never been diagnosed with neglect, will still show significant signs of lateralized impairment during attentionally demanding computerized tests (e.g., List et al., 2008; Bonato et al., 2010, 2012). Thus, the main screening measure was based on a psychophysical task developed to test for chronic signs of neglect [described below (List et al., 2008)]. Note that all four patients were at least 1 year post at the time of testing. Radiological images of lesions for each patient are shown in **Figure 1**. (Slice regions are provided in **Figure A1**). Patient 1 had surgery for an aneurysm in the anterior communicating artery resulting in a relatively small anterior cingulated lesion. Vasospasm resulted in significant right orbitofrontal damage and smaller lacunars in the right lateral thalamus and deep inferior basal nucleus of Minert. The remaining patients all had infarct to the territory of the right middle cerebral artery. Patient 2′s lesion included frontal, parietal and occipital regions. Patient 3′s lesion included posterior frontal and anterior parietal regions. Patient 4′s lesions included parietal and temporal regions, extending into the temporal occipital junction. All patients were diagnosed with acute unilateral neglect shortly after being hospitalized. All patients gave informed consents approved by the Internal Review Board at the VA, Northern California Health Care System.

### PSYCHOPHYSICAL TESTING FOR CHRONIC NEGLECT

Each patient first completed a computerized conjunction search task designed to measure attentional search times (see Treisman and Gelade, 1980). This test was altered to detect symptoms of chronic attentional deficits in neglect using a psychophysical staircase procedure (List et al., 2008). In this task, patients view a screen of colored geometric shapes, and are asked to verbally respond whether there is a red square (target) among distractors.

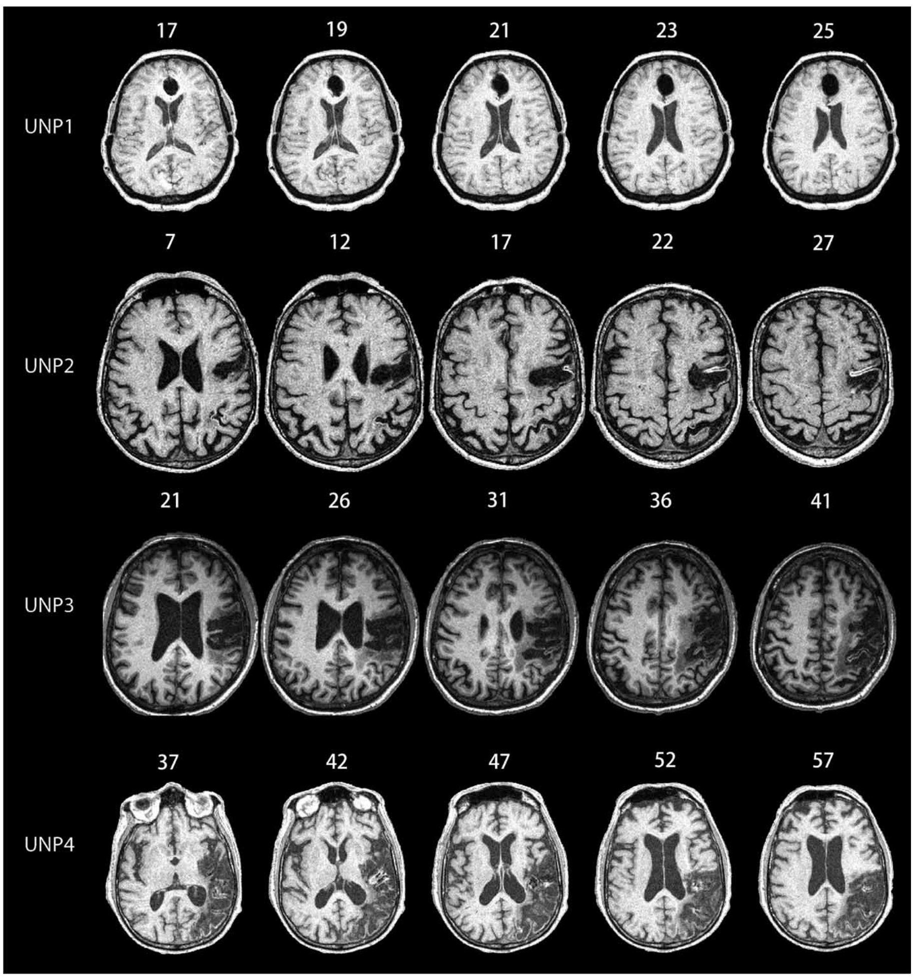


**FIGURE 1 | MRI scans for all of the unilateral neglect patients (UNPs) included in the study.** Numbers listed above each picture depict the MNI coordinates. UNP1 has lesions in the anterior cingulate, orbitofrontal, and thalamic regions. UNP2 has lesions in the frontal, parietal, and occipital regions. UNP3 has lesions in the posterior frontal and anterior parietal regions. UNP4 has lesions in the parietal regions and temporal regions, extending into the temporal-occipital junctions. We include a figure depicting slice regions for each participant in the Appendix, **Figure A1**.

The distractors include a combination of blue squares, red circles, and red/blue triangles. The target is randomly presented on either the left or right side of the display, and exposure times for each trial are adjusted according to participants' performance. In this adaptive staircase procedure, the display is initially presented for 2000 ms. Exposure time decreases when patients correctly identify the target and increases when patients incorrectly identify the target. The staircase is thresholded to produce 75% correct performance both on the left and right sides of the display. Consistent with chronic neglect measures (List et al., 2008), our patients required significantly longer viewing durations when the target was displayed on the left (mean = 826 ms) compared to the right (mean = 483.5 ms) side of the screen, $t_{(3)} = 4.175$, $p < 0.025$. See **Table 2** for individual response times in each hemifield.

### SIZE DISCRIMINATION TASK

Having established symptoms of unilateral attentional neglect in each participant, we proceeded to measure their size discrimination ability. This was important, as the task required in the statistical summary experiment is based on size judgments. During this task, the participant was shown a circle for 1000 ms in the middle of the screen followed by a second circle until response. We asked patients to report which of the two circles was bigger (by indicating "first" or "second"). Importantly, the circles sizes were identical to those used in the main experiment (see below). There were 20 trials in total. All patients accurately discriminated circle size with a performance of 90% or above.

### STATISTICAL SUMMARY PROCEDURE

Subsequently, each patient participated in the main statistical summary portion of the experiment. Each trial began with fixation (500 ms). Next, we showed the patient a single target circle in the center of the screen for 500 ms that varied in size from trial to trial. This was followed immediately by a search display containing a group of circles on one side and a group of task-irrelevant triangles on the other. The patients were instructed to ignore the triangles and to indicate whether the target size was present or absent in the group of circles. Patients verbalized "yes" for target size present or "no" for target size absent. The examiner keyed in each response on an external keyboard. Importantly, half of the targets matched the mean size of the circles group within the search display, whereas half did not. **Figure 2** depicts a schematic example of a target circle (on the left panel in the figure), which was randomly chosen from eight possible sizes with equal probability (diameter 0.98°, 1.12°, 1.26°, 1.29°, 1.40°, 1.47°, 1.66° and 1.84°). **Figure 2** also depicts a schematic search display (circles on the right side in the figure) containing 12 circles presented on either the left or right side of the display. Each circle in the display was randomly selected between 0.60° and 2.72° with two constraints. First, their mean size had to match with the pre-defined mean size of the display in the half of trials and they did not match in the other half. Second, neighboring sizes of the target (both mean and non-mean sizes) should have the same distance from the target. This method of choosing sizes was adapted from Treisman (2006) in a study of normal statistical size processing. The triangles were similar in size to the largest circle but their location was jittered between trials. Resolution of the screen was 1024 × 768 with a 60 Hz refresh rate. On half the trials the target size was present, whereas in the remaining half, target size was absent. The exposure of the search display began at 1000 ms, as determined by the size discrimination procedure and was staircased to produce 70% correct performance across all conditions on average. Successful performance on two trials decreased display exposure by 66.67 ms, whereas unsuccessful performance on one trial increased display duration for 66.67 ms. The number of trials varied slightly, as we deleted trials if the patient was inattentive or made eye movements (mean no. of trials = 125, range = 117–128). Thus, on average there were 62 targets present and 62 target absent trials: 31 on the left and 31 on the right. Fifteen of each was the mean and 15 were the non-mean size.

Prior to the experiment, practice trials were given until subjects indicated they were comfortable with the task/instructions (but no less than 10 trials). All practice trials included feedback. Incorrect answers were followed by a brief high-pitched tone, whereas correct answers were followed by an absence of sound. There was no feedback in the experimental trials.

**Table 2 | This table shows the exposure duration needed for patients to detect targets displayed the left or the right side of the screen.**

| | Threshold display times (ms) | |
|---|---|---|
| **Participant** | **Left target** | **Right target** |
| UNP1 | 388 | 182 |
| UNP2 | 620 | 404 |
| UNP3 | 704 | 154 |
| UNP4 | 1592 | 1194 |

## RESULTS

### HITS RATES

We calculated the hit rate for mean and non-mean trials for each participant in each hemifield. Hit rate performance was then subjected to a 2 × 2 ANOVA for the group as a whole with the following factors: Hemifield (Right and Left) and Target Statistic (Mean and Non-Mean). There was a significant main effect of Hemifield [$F_{(1,\ 3)} = 54.857$, $p = 0.005$, $\eta p^2 = 0.948$], with patients performing better on the right side compared to the left side. There were no other main effects or interactions that even approached significant levels. We formally assessed whether hemifield differences were significant for each participant by using a bootstrapping technique (200 iterations per participant). Each bootstrapped sample is permuted to simulate variations that may occur over a greater number of trials (see Efron, 1986). We compared the distribution of bootstrapped samples using the Kolmogorov-Smirnov test (Kolmogorov, 1933; Smirnov, 1948). This non-parametric test evaluates whether boot sample mean distributions for two conditions are from the same continuous distribution or whether the samples are from two different continuous distributions. All k statistics show that participants' hit performance was significantly better for detecting targets on the right compared to the left right side (UNP1, $k = 0.99$, $p < 0.001$; UNP2, $k = 0.88$, $p < 0.001$; UNP3, $k = 0.85$, $p < 0.001$; UNP4, $k = 0.76$, $p < 0.0001$). See **Figure 3**.

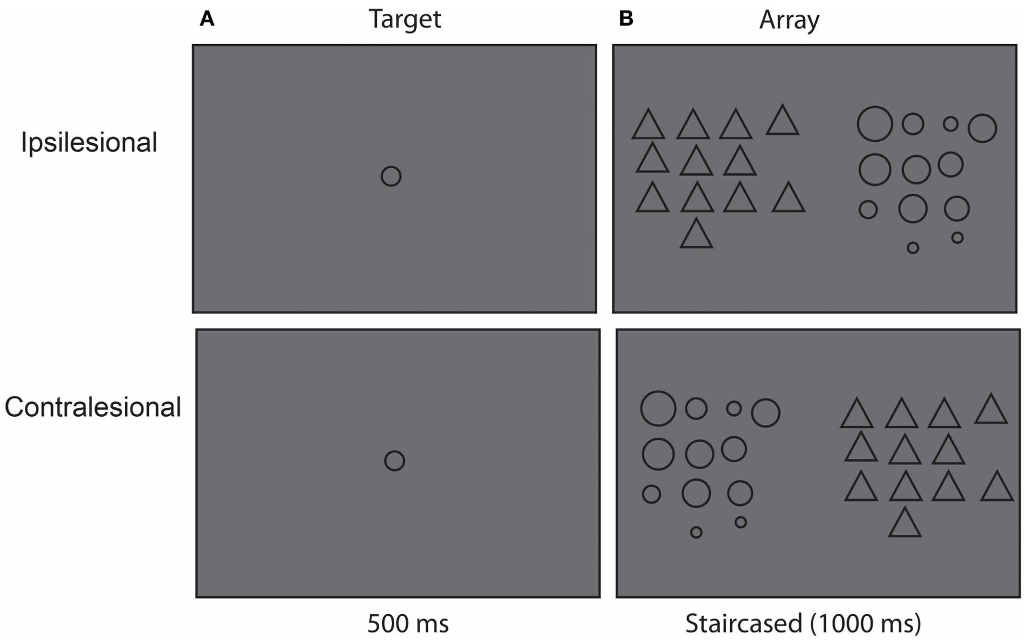


**FIGURE 2 | Experimental procedure. (A)** First patients viewed a target circle and were asked to remember its size. **(B)** Next, patients viewed a display of 12 circles and distractor triangles. The position of the circles and triangles varied between trials, such that sometimes the circle were presented on the right side and the triangles were presented on the left side and vise versa.

### FALSE ALARM RATES

We calculated the false alarm rates for mean and non-mean trials for each participant in each hemifield. The 2 × 2 ANOVA on the group as a whole showed a significant interaction between Hemifield and Target Size, [$F_{(1,\ 3)} = 13.252$ $p = 0.036$ $\eta p^2 = 0.815$] but no significant overall main effects. Motivated by this interaction, we then examined each patient's data with the same bootstrapping method as described above. 3 of the 4 patients showed greater false alarms to the mean compared to the non-mean on the left side with 1 having very few false alarms and reversing (UNP1, $k = 0.71$, $p < 0.0001$; UNP2, $k = 0.77$ $p < 0.0001$; UNP3, $k = 0.84$, $p < 0.0001$; UNP4, $k = 0.61$, $p < 0.0001$). Conversely all four patients showed greater false alarms for the non-mean compared to the mean on the right side (UNP1, $k = 0.47$, $p < 0.0001$; UNP2, $k = 0.45$, $p < 0.0001$; UNP3, $k = 0.75$, $p < 0.0001$; UNP4, $k = 0.27$, $p < 0.0006$). **Figure 4** shows the false alarm rate for each patient.

## DISCUSSION

### VISUAL SEARCH

Consistent with the neglect literature and visual search, patients' performance (as measured by hit rates) was worse on the left than the right side. All patients exhibited this pattern with hit rates on the left close to chance levels, consistent with unilateral neglect (see **Figure 3**). Each patient saw the search display for a different amount of time, as our goal was to keep the accuracy rate across the whole display as close to 70% as possible. We did this using the staircase method to adjust the duration of the search display throughout the experiment. The main question regarding visual search was whether performance differed between the right and left sides, and this was the case. When the left target was present, hit rates on the left hovered around chance performance (i.e., we were able to induce severe left neglect at these short stimulus presentations), while on the right it was well above chance performance. The difference in search between the two sides is consistent with fast and more efficient attentional deployment on the right compared to the left side of the display. This pattern is also consistent with left hemi-extinction, the less dramatic cousin to left unilateral neglect. When items occur on both sides of a display, left items are more likely to be missed. Since every trial had a group of irrelevant triangles opposite the circles, both sides were always filled with stimulation. As intended, these triangles appear to have attracted attention when they were on the right side (Eglin et al., 1989).

### STATISTICAL SUMMARY

However, the processes governing extraction of statistical summary appears to differ from those governing individuation of an object in search. Although this distinction has been proposed before in the literature with typical observers (Ariely, 2001; Chong and Treisman, 2003; Haberman and Whitney, 2007), there is no strong evidence for it in neglect patients. The present results demonstrate dissociation between performance measures for visual search and those for statistical summary. These can be seen most robustly in the false alarm rates on the left and right sides. When the target was absent most of the patients were more likely to say it was present when the average of the circle was the mean than when it was the non-mean. The opposite was true when the circles were on the right for all four patients (more false alarms to the non-mean than mean). If we consider the display

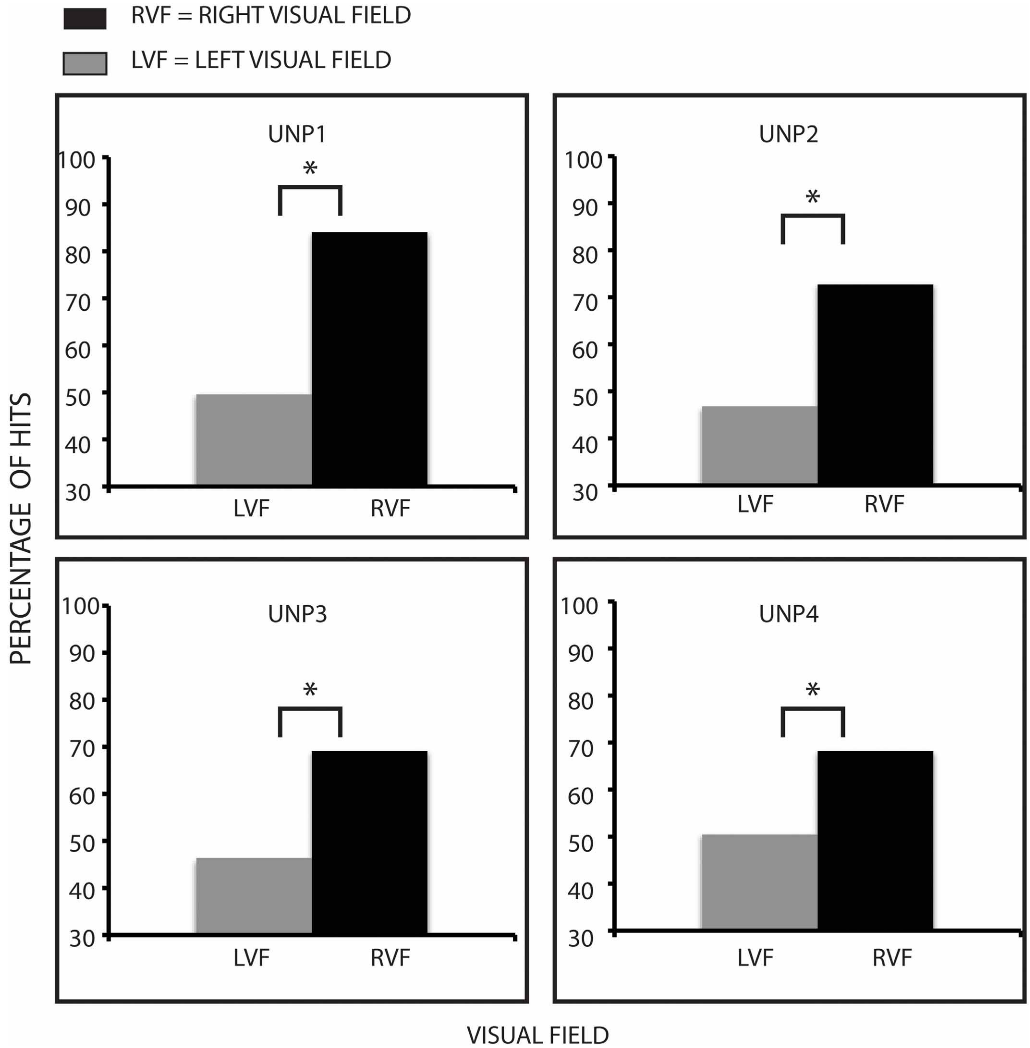


**FIGURE 3 | Hit rate patterns for participants.** Hits rates are lower on the left side compared to the right side, indicating that neglect patients have difficulty performing visual search. *Denotes statistical significance of at least $p < 0.05$.

as a whole, the reasons for this pattern become clearer. Recall that during every trial, distractor triangles must be discounted in order for participants to form a statistical summary, consistent with the target size. If the triangles are not rejected, they will contribute to the estimate of the mean size—and skew the statistical summary. Returning to the scenario presented in the introduction, the neglect patients may be "pooling the clothes in the adjacent store window with the candy."

## DISTRACTORS

This hypothesis is consistent with previous work on unilateral neglect suggesting that information presented on the neglected side is inappropriately filtered. For instance Kim (1997) used a negative priming paradigm in which two letters overlapped. One letter was the target (e.g., the red one), while the other letter was the non-target or distractor. Negative priming is indicated by a slower response to a distractor letter when it appears as a target on a subsequent trial. Results in patients with unilateral neglect demonstrated that negative priming is normal when displays are on the right side, but positive priming appears when displays are on the left side, indicating that the distractor letter was not inhibited. If this is the case, distractors in a statistical summary test may significantly impact extraction of the mean. Specifically, if information on the neglected left side is improperly filtered, the presence of distractors should compromise statistical summary on the right side of the display—and this is what we found.

**Figures 3** and **4** together suggest that statistical encoding took place implicitly even though controlled (explicit) attentional search of the left side was reduced. On the right side, the pattern of results did not support statistical processing. Indeed, the pattern of FAs was reversed (more FAs when the target was non-mean). We performed non-parametric tests on the right side to further statistically examine these results. Again, all patients showed a significantly greater effect to the non-mean on the right side. This skewed pattern of FAs indicates that statistical processing in the

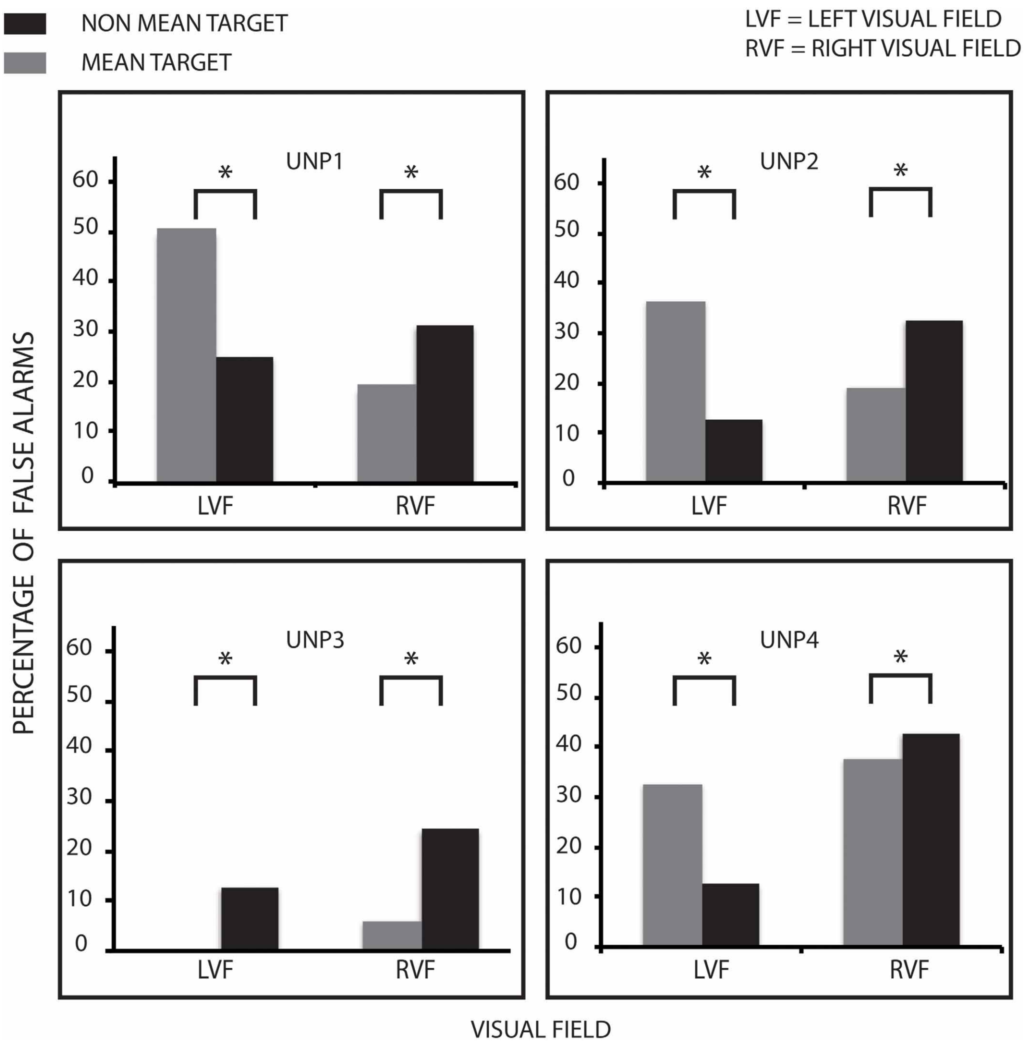


**FIGURE 4 | False alarm rates for participants.** False alarm rates are higher to the mean compared to the non-mean target on the left (neglected) side, mirroring the expected performance for neurologically intact participants. However, false alarm rates on the right (non-neglected) side exhibit the opposite pattern. *Denotes statistical significance of at least $p < 0.05$.

right hemifield was disrupted. One interpretation of this result is that distractors could be rejected from the summary statistic when presented on the right side but not when presented on the left side.

## IMPACT OF DISTRACTORS

In order to further explore whether distractors presented on the left side are "encroaching" into the target pool (and thereby resulting in an erroneous statistical summary), we compared how distractor size affected performance when search display circles were smaller or larger. Importantly, distractor triangles are always the same size (the base of the triangle was similar in size to the largest circle diameter). However, circles within the search display varied in size, rendering distractors either more or less close to the circles mean size. This allowed us to observe whether the pattern of false alarms was affected by the distractors. The false alarm pattern presented in **Figure 5** provides provisional support that subjects included distractors into their judgment of the mean—when distractors were presented on the left side. Data from all participants are concatenated to increase the number of trials evaluated (as each participant saw only eight trials with small circles and eight trials with large circles). When distractors and display were different in size (**Figure 5B**), the pattern of false alarms is distorted (more false alarms to the non-mean compared to the mean). However, when distractors and display were similar in size (**Figure 5A**) the distorted pattern decreased. This is a small but not unexpected difference (given the small difference in mean size), and this would be the expected pattern if the triangles on the left were pooled with the circles displayed on the right.

## SUMMARY

Previous research indicates that unilateral neglect causes widespread disruption in attention, visual working memory, and spatial representation (Husain and Rorden, 2003; Malhotra et al.,

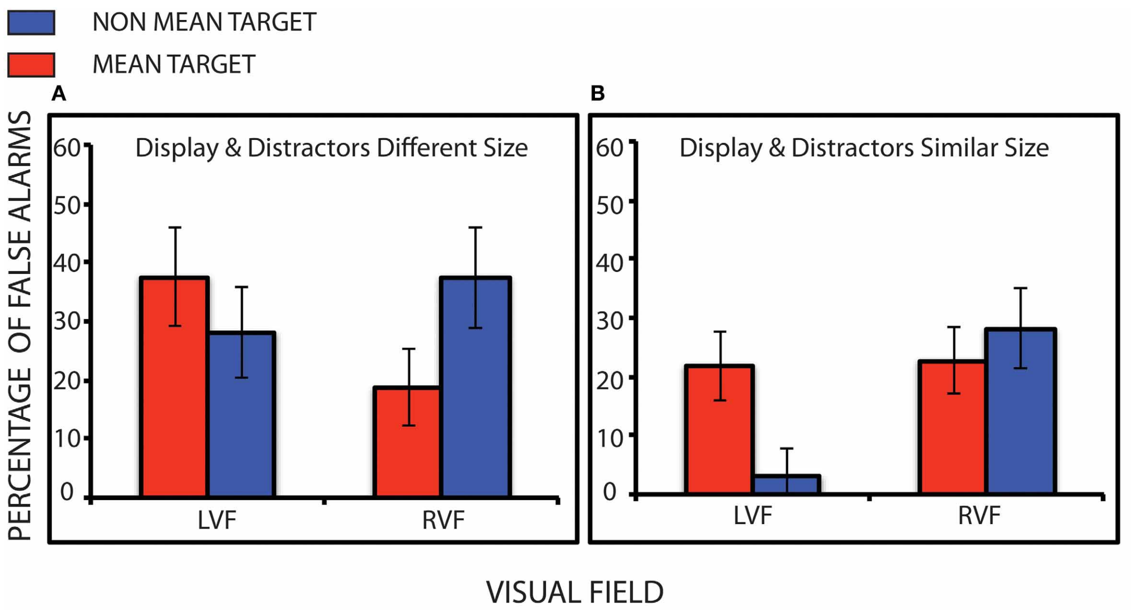


**FIGURE 5 | False alarm rates for patients during trials when distractor and display were very different in size (A) and trials when distractor and display were more similar in size (B).** Error bars represent the standard deviation of the bootstrapped samples. Note: In no case were the distractors and targets the same size. In panel **(A)**, differences between false alarms to the mean and non-mean on the right side are large (and mirror the original findings), suggesting that distractors are influencing statistical coding. Whereas, in panel **(B)**, there is minimal difference between the mean and non-mean targets on the right side, suggesting that distractors are minimally impacting statistical coding.

2005). These impairments negatively impact daily functioning in everyday life, resulting in problems with navigation, driving, reading, etc. While much is known about the disruptions in controlled attention and visual search, the role of statistical summary has only begun to be tested (Pavlovskaya et al., 2010, 2011). Here we tested patients who had recovered from clinical signs of neglect but continued to show neglect of the left side in a visual search paradigm and when display times were limited. There is some evidence from studies of patients with the neuropsychological diagnosis of Balint's syndrome that statistical summaries may be calculated from unattended information in the visual field (Riddoch and Humphreys, 1987; Demeyere and Humphreys, 2007; Demeyere et al., 2008). However, to our knowledge this is the first study to explore how the extraction of statistical summary may be affected by distractors in bilateral, grouped displays. This is a particularly relevant question because statistical summary in the real-world rarely, if ever, occurs without distractors.

Our results show that patients with chronic neglect (as measured psychophysically) successfully segregated distractors on the right when targets were on the left side. They showed the expected pattern of statistical summary on the left—despite the fact that these patients allocated limited attention to this side (i.e., were at chance explicitly detecting the target). This result supports and expands Pavlovskaya et al.'s findings (2010, 2011), which suggested that neglected items contribute to explicit statistical summary estimates. Moreover, both findings reinforce Alvarez and Oliva's previous work with healthy normal participants, showing that statistical summary occurs even with reduced attention (Alvarez and Oliva, 2009; Joo et al., 2009; Haberman and Whitney, 2011) but extend this work by showing that statistical summary can be successfully performed by patients with unilateral attentional deficits. However, on the right side, patients showed more false alarms to targets that were the mean size compared to targets that were the non-mean size. One interpretation of this result is that neglect patients pooled distractors on the left side with targets on the right side causing the resulting statistical summary to be based on the display as a whole and thus distorted.

## FUTURE DIRECTIONS

These results imply that within real-world settings, neglect patients' ability to statistically summarize different sets of objects may be compromised. Future studies should further investigate whether altering the distractor features reduces the negative impact upon the statistical code in the right hemifield. For instance, our distractors, while different in shape, shared similar outline/filler color with the targets. It is possible that increasing the contrast in target outline/filler compared to distractor outline/filler will reduce pooling of targets and distractors. Further exploration of how distractor/target congruency interacts with statistical summary may yield a greater understanding of the neglect phenomenon and potentially contribute to rehabilitative programs.

Interestingly, the different pattern of performance between hits and false alarms suggests that statistical summary processes are distinct from object individuation. When the target was present, the patients exhibited the expected pattern of performance during visual search (poor performance on the left/better performance on the right). Whereas, when the target was absent, statistical coding dominates. This pattern reinforces previous research showing that object individuation operates independently from statistical summary mechanisms. For instance, neurologically intact participants can perform at chance when asked to individuate objects, yet, are still remarkably accurate in statistically summarizing across objects (Ariely, 2001; Haberman and Whitney, 2007; De Fockert and Wolfenstein, 2009; Haberman et al., 2009; Alvarez, 2011). Additionally Haberman and Whitney (2011), using change blindness paradigms, demonstrate that statistical summary occurs independent of change localization. We reinforce and extend these findings by showing that when object individuation does occur, it is distinct from statistical summary performance.

Our findings also raise interesting questions about how attention influences statistical summaries within normal populations. Chong and Treisman (2005) found that neurologically intact participants can successfully segregate items into different groups to produce separate statistical codes. However, they also found that the individual group averages were nonetheless affected by the overall average of both groups. Further studies should explore how distractors interact with the formulation of the statistical code, and specifically how reduced attention affects the filtering of distractors. Under impoverished attentional conditions (e.g., divided attention, peripheral viewing), can normal perceivers successfully segregate distractors?

## CONCLUSION

In conclusion, fundamental statistical summary abilities on the left side remained intact in patients who presented with unilateral neglect that had substantially abated but continued to be robust on psychophysical tests. Under conditions that amplify neglect, the patients did summarize the statistics in a display. However, within the real-world, where targets and distractors are equally present within the visual environment, it is important to be able to pool information within different sets. We show for the first time that patients' with left sided attentional deficits, while not interrupting the averaging process *per se*, nonetheless alter summary statistics on the right side. Abnormal statistical coding may substantially affect patient functioning, as statistical summary operates on many levels of visual processing integral to daily life. Research has shown that it contributes to low-level processing (simple shapes), high level processing (faces and other complex stimuli), and visual working memory (Alvarez, 2011). Our work here, with chronic unilateral neglect patients, indicates that distractors encroach into summary coding of target displays, and the statistical summary fails to reflect veridical statistics of the target group. Such distortions may adversely affect the visual analyses of complex scenes in the real-world for such patients.

## ACKNOWLEDGMENTS

We would like to thank Amy Liu for assisting in data analysis. This research was supported by the Veterans' Administration and the National Institutes of Health Grant EY- 016975-05 (Lynn Robertson) and the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2011-0030097, Sang C. Chong). Lynn Robertson also has a VA appointment in VA Clinical Sciences Research Service, Department of Veterans Affairs Medical Center, Martinez, CA. She is a Senior Research Career Scientist.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 21 February 2012; accepted: 10 September 2012; published online: 05 October 2012.*

*Citation: Yamanashi Leib A, Landau AN, Baek Y, Chong SC and Robertson L (2012) Extracting the mean size across the visual field in patients with mild, chronic unilateral neglect. Front. Hum. Neurosci.* ***6****:267. doi: 10.3389/fnhum.2012.00267*

## APPENDIX

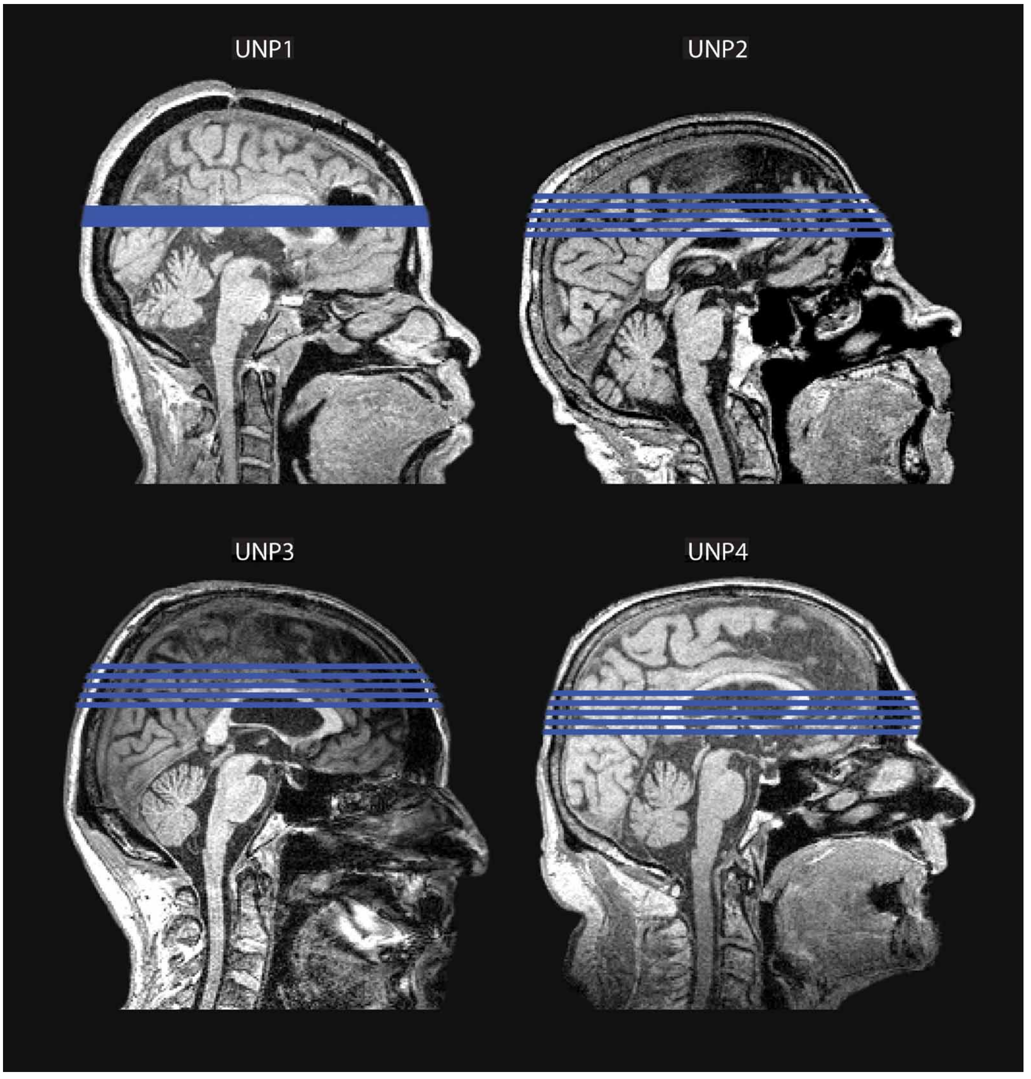


**FIGURE A1 | This figure shows the slice regions (in blue) for all four unilateral neglect patients.**

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 22 June 2012
doi: 10.3389/fnhum.2012.00188

# Limb activation ameliorates body-related deficits in spatial neglect

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Many neglect patients show deficits in the mental representation of their contralesional body side or body parts, termed personal neglect. These deficits include impairments in identifying body parts on schematic drawings of human bodies. Limb activation and alertness cues have been shown to modulate neglect transiently, and are effective treatments for several symptoms of the neglect syndrome. Here, we tested on eight patients with right-hemispheric stroke and left-sided spatial neglect whether these two techniques modulate deficits in the mental representation of hands, assessed with a hand-test in which the subjects had to decide whether a depicted schematic hand belongs to the left or right side of the human body. The results showed that neglect patients made marginally significant ($p = 0.065$) more errors in left-hand-decisions than right-hand-decisions, indicating a neglect-specific disorder. Moreover, we found that left-sided limb activation but not non-lateralized alertness cueing (a loud noise immediately before patients made their perceptual decision) significantly reduced misidentifications for depicted left hands as compared to baseline. No effect of any intervention was observed on error rates for depicted right hands. We conclude that the amelioration of the performance in the hand task is modulated by the activation of the body schema or other body representations through left-sided limb activation.

**Keywords: personal neglect, body schema, representational neglect, body representational neglect, limb activation, phasic alerting, treatment, rehabilitation**

## INTRODUCTION

Neglect as a failure to report, respond, or orient to contralesional stimuli (Heilman et al., 2000) may affect extrapersonal or personal space. Many of these patients fail to use or recognize the contralesional side of their body, an impairment which is termed personal neglect (Adair et al., 1995) or body representational neglect (Glocker et al., 2006). Personal neglect is frequently observed after lesions of the right hemisphere, but also after left hemispheric lesions (Groh-Bordin et al., 2009). The incidence is estimated to be up to about 45% in right hemispheric damaged patients, depending on the study and the used assessment instrument (Bisiach et al., 1986; Zoccolotti and Judica, 1991; Bowen et al., 2005; Groh-Bordin et al., 2009; Baas et al., 2011).

Personal neglect has been considered to be the origin of, or to be closely associated with, several neglect related impairments, including unilateral premotor deficits (Heilman et al., 1985), the misrepresentation of extrapersonal space (Bisiach, 1993; Umilta, 1995), and the disruption of the body-centered reference system (Karnath, 1994). However, although extrapersonal and personal impairments are often observed together as a symptom cluster in neglect patients, some studies using tests developed to assess personal neglect specifically like the Fluff-Test (Cocchini et al., 2001) the Vest Test (Glocker et al., 2006), or the Comb-and-Razor-Test (Beschin and Robertson, 1997; McIntosh et al., 2000) have found evidence of a double dissociation of these symptoms, both on the behavioral and anatomical level (Bisiach et al., 1986; Zoccolotti and Judica, 1991; Bowen et al., 2005; Committeri et al., 2007; Baas et al., 2011). Therefore, personal neglect seems to be only one aspect of the multifactorial heterogenous neglect syndrome that has been shown to occur in several sensory modalities and may also include motor neglect.

Disorders associated with body representational neglect include impairments of identifying body parts on schematic drawings of human bodies. As a possible origin of these impairments, some authors (Coslett, 1998; Baas et al., 2011) suggested an impaired mental body schema, respectively, a reduced access to this schema, which can be understood as a three-dimensional, dynamic representation of the spatial and biomechanical features of the own body (Coslett, 1998; Gallagher, 1998). Some authors postulate this mechanism to be responsible for the cortical representation of the trunk surface (Berlucchi and Aglioti, 1997) and peripersonal space (Graziano and Gross, 1998), whereas Cardinali et al. (2009) pointed out that peripersonal space and the body schema might be tightly related but distinct concepts with different sensory inputs (vision, audition, and touch vs. proprioception, kinesthetic, and touch), functional properties (defensive movements and voluntary actions vs. unconscious body knowledge for action), and neural mechanisms (parieto-frontal bimodal neurons vs. prefrontal and parietal cortex). Furthermore, other authors distinguish these space and action-related concepts from a semantic and lexical representation of the body (body part names, functions, and relations with objects), termed body image (Coslett et al., 2002; Schwoebel and Coslett, 2005). Even if the psychological validity of the concept "body schema" and the number of different body representations can be debated (Bisiach, 1993; Cardinali et al., 2009), there are several studies that support this concept (as defined above) with evidence (McCloskey, 1978; Lackner, 1988; Iriki et al., 1996; Maravita et al., 2003; Mussap and Salton, 2006). Moreover, the debates about the psychological validity of this concept may have in part been provoked by the inconsistent use of the term "body schema" in different studies (Poeck and Orgass, 1971; Gallagher, 1998; for a recent view on this topic see Berlucchi and Aglioti, 2010). For example, both body representational neglect and apraxia (Schwoebel et al., 2004) after left-hemispheric lesions are based on the concept of a body schema. Both disorders are associated with impaired knowledge about body parts, their position in space, and their spatial relationship. However, Groh-Bordin et al. (2009) found that the two disorders form a double dissociation at the behavioral and anatomical level.

Several studies indicated that healthy subjects use their own body schema to decide whether a depicted body part belongs to the left or the right side of the body (Cooper and Shepard, 1975; Sekiyama, 1982; Parsons, 1987a,b, 1994). For example, Parsons (1994) showed that the actual observer's own position affects the speed with which the observer can decide whether a depicted rotated hand (the palm or the back of a hand) is a left or a right hand. In his study, the subjects' reaction times for the left or right hand judgments were similar to the time the participants needed for a real movement of their own hand into the requested position. Therefore, it can be concluded that humans make those left-right judgments of displayed hands by mentally rotating the representation of their own hands (Cooper and Shepard, 1975; Sekiyama, 1982; Parsons, 1987b). Interestingly, Coslett (1998) found that patients with personal neglect are impaired in identifying depicted left-sided body parts. The patients were asked to name photographs of left or right hands. They labeled the right hand drawings more reliably than those of the left hand. In contrast, control patients without neglect did not name the left hands with a reduced reliability. Coslett (1998) concluded, that the impairment of patients with body neglect in identifying left hands is related to a disturbed schema of the left half of the body. In a recent study Baas et al. (2011) replicated this finding. Furthermore, judging errors for left hands were the best predictor of personal neglect compared to other variables like extrapersonal neglect, somatosensory or motor impairments, or deficits in the representation of the left-sided extrapersonal space. The results of Coslett (1998) and Baas et al. (2011) can be explained by the findings of Parsons et al. (Parsons and Fox, 1998; Parsons et al., 1998) according to which sensorimotor representations of the body or body parts are controlled by areas in the hemisphere contralateral to the limb. Therefore, it is plausible that lesions of these brain areas affect the mental simulation of movements that are associated with the correct identification of left or right hands. In summary, it can be hypothesized that the disruption of, or a reduced access to the actual representation of the own body features, the body schema, is responsible for the impairment of patients with body neglect in identifying left hands.

Based on different explanations of the neglect syndrome, several treatments have been developed and evaluated in the last decades (for review see Kerkhoff, 2003; Kerkhoff and Schenk, 2012). Most of them aim to modulate the rightward bias in spatial attention and exploration of neglect patients by providing additional sensory or motor input. One of these bottom-up treatments is limb activation. During limb activation, the patient is asked to make limb movements with their contralesional arm while performing spatial tasks. These movements reduce neglect symptoms, including motor impairments (Robertson et al., 2002), visual and sensory neglect (Robertson and North, 1993), and motor extinction (Robertson and North, 1994). Robertson and North (Robertson and North, 1992, 1993) favor the *active* movement of limbs to be the critical factor that alleviates neglect symptoms. Unfortunately, as many stroke patients suffer from paresis of the contralesional limbs or the whole contralesional side of the body, active limb activation is no appropriate treatment for a large group of patients. However, a few studies have shown that *passive* limb movements can improve neglect signs as well (Ladavas et al., 1997; Frassinetti et al., 2001; Harding and Riddoch, 2009). Several studies have shown that specifically the position of the left hand (which has to be placed in the left hemispace) rather than the active movement seems to be the critical factor to ameliorate neglect symptoms in the peri-personal space (Halligan et al., 1991; Robertson and North, 1993; Ladavas et al., 1997; Frassinetti et al., 2001). Therefore, the effects of passive as well as of active limb activation on neglect can be traced back to the additional (sensory) proprioceptive input which the limb movement provides.

Several attentional systems can be affected in neglect (Van Vleet et al., 2011). In addition to the pathological rightward bias in *spatial* attention, neglect patients often show an impaired *non-spatial* tonic alertness which is associated with large lesions of the right hemisphere including frontal areas (Wilkins et al., 1987; Pardo et al., 1991; Whitehead, 1991; Shallice et al., 2008). Several studies provided evidence supporting the idea that both attentional systems are closely linked and that impairments in tonic alertness may enhance the spatial bias of neglect patients to the right (Posner, 1993; Robertson et al., 1995, 1997, 1998; Sturm et al., 2006). Consequently, it is plausible that central alerting cues may alleviate spatial neglect. Robertson et al. (1998) examined this theory by having their patients make temporal order judgments whereby a left-sided, visually presented bar was preceded or followed by a similar bar presented on the right side. Neglect patients tend to perceive the right-sided stimuli first even when this stimulus was in fact preceded by the stimulus on their left side. Robertson and colleagues (1998) found that presenting a loud (centrally presented) noise just before patients take their decision will reduce this spatial bias.

In summary, there is ample evidence showing that limb activation and phasic alerting modulate a variety of visual or sensory deficits in patients with left-sided neglect. But what about deficits that are associated with body neglect? Studies evaluating effects of limb activation or alertness cueing on body neglect related symptoms, such as a disturbed body schema, are not available to the best of our knowledge, although body neglect is not an infrequent phenomenon after brain damage (Glocker et al., 2006). In the present study, we examined whether these two treatments have the potential to modulate the disturbed body schema of patients with personal neglect.

## MATERIALS AND METHODS

### PATIENTS

Eight patients (Mean age = 61.1 years; SD = 12.1) with right-hemispheric stroke and moderate to severe left-sided visual neglect (assessed with four conventional neglect screening tests, namely paragraph reading test, horizontal line-bisection, number cancellation and drawing figures; for details see Utz et al., 2011) were included. All patients also showed moderate to severe left-sided body neglect (see **Table 1**), assessed with the standardized vest test (see Glocker et al., 2006; Groh-Bordin et al., 2009). This test requires the blindfolded patient to search for 24 objects (12 on either trunk side) placed in pockets on the front side of a vest she/he wears, using his/her ipsilesional hand. The subject is required to search as quickly as possible for all objects and handle them to the experimenter. Normative values are available from 25 healthy subjects performing the test with their right hand, and 25 healthy subjects performing the test with their left hand (Glocker et al., 2006).

The mean interval from stroke to testing was 9.8 weeks (SD = 5.7). All subjects had a decimal visual acuity of at least 0.70 (20/30 Snellen equivalent) for the near viewing distance of 0.4 m (see **Table 1** for clinical and demographic details). Brain lesions were confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) scans, and lesioned areas were mapped onto a standard MRI template using MRIcro software (Rorden and Brett, 2000). **Figure 2** shows lesion maps of six of the patients. From two patients (Pt. 4 and 8) radiological images were no longer available for lesion mapping. All participants were informed of the experimental protocol which was conducted in accordance with the Declaration of Helsinki II and gave their written informed consent prior to their participation in the study. The study was approved by the ethics committee of the Ludwigs-Maximilian-Universität, München/Germany, Project Nr. 352-09 in November 2009.

### HAND TEST

The hand-test used in the present study was developed based on the studies of Cooper and Shepard (1975); Parsons (1994); Coslett (1998). The stimuli included 24 schematic line drawings of the palm or the back of left or right human hands (see **Figure 1**). The stimuli (only one at a time) were presented centrally on a 15′ computer screen in randomized order. The patients were asked to decide whether the drawing depicted a left or a right human hand and they were instructed to imagine their own hand to facilitate the identification of the drawings. The response time was not limited. To rule out visual comparisons of the own and the depicted hands, the hands of the patients were covered with a black blanket. The patients' verbal responses were recorded by one examiner. No feedback of their performance was given to the patient in any of the experimental conditions.

### LIMB ACTIVATION AND ALERTNESS CUEING

The patients sat in front of the computer screen with their eyes aligned with the center of the screen. For the passive-limb-activation intervention we adopted the protocol from the study of Frassinetti et al. (2001). During the assessment period the lower left arm of the patient was continuously stretched and flexed passively by an examiner up to a 45° angle and with a frequency of about 1.5 movements per second. The palm of the hand was

**Table 1 | Clinical and demographic data of the eight patients with left visual neglect after a single vascular lesion of the right hemisphere.**

| Patient | Age, sex | Etiology | Localization | Weeks post lesion | Body neglect (omissions L-R side) | Reading omissions | Figure copy | Line bisection | Number cancellation |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 60, M | MCI, ACI | FL, TL, PL | 13 | 12/7 | − | − | − | − |
| 2 | 60, W | MCI | Th | 7 | 8/1 | + | + | − | − |
| 3 | 81, W | MCI | FL, TL, PL | 11 | 12/7 | − | − | + | − |
| 4 | 68, W | MCI | * | 4 | 10/4 | − | − | − | − |
| 5 | 52, W | MCI | BG, FL | 7 | 8/5 | − | + | − | − |
| 6 | 65, W | MCI | * | 23 | 7/5 | − | − | − | − |
| 7 | 64, M | MCI | BG, TL, PL | 5 | 4/4 | − | − | − | − |
| 8 | 39, M | MCI | BG | 8 | 9/8 | − | − | − | − |
| Mean | 61.1 years | | | 9.8 weeks | 8/8 − 7/8* impaired | 7/8 impaired | 6/8 impaired | 7/8 impaired | 8/8 impaired |

*Abbreviations: MCI, middle cerebral artery infarction; ACI, anterior cerebral artery infarction; BG, basal ganglia; Th, Thalamus; FL, Frontal Lobe; TL, Temporal Lobe; PL, Parietal Lobe; *, No imaging available. Neglect screening tests: −, impaired; +, normal performance. Reading omissions: Paragraph reading of a 150 word reading test (normal cutoff max two omissions). Figure copy: Left sided omissions or distortions. Line bisection: normal cutoff max 5 mm deviation to the right. Number cancellation: normal cutoff: max two omissions on the left side (for details see Utz et al., 2011). Body neglect test: Vest test (see Glocker et al., 2006), cutoff scores: max three omissions for left/right side (from 12 targets on each trunk side); *Eight from eight patients were impaired for the left vest test side, seven from eight patients were impaired for the right vest side, but with a less marked impairment.*

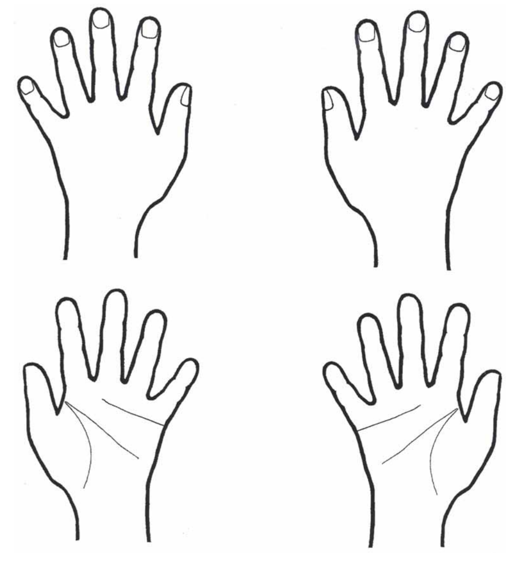

**FIGURE 1 | Examples of hand stimuli.** The schematic drawing could depict the palm or the back of a left or a right hand. Hands were shown as single stimulus (see Materials and Methods).

oriented toward the patient. The elbow of the arm rested on the table in front of the patient on the left side of space, the upper arm, and the trunk forming an angel of about 35–55°. As noted above, the moving left arm was covered with a black blanket and the right arm rested without any movement and invisible for the patient under the table on his right leg. The limb activation began 5 min before the hand-test task.

For the alertness-cueing intervention we adopted the protocol from the study by Robertson et al. (1998). The alertness cue (2200 Hz, 65–80 dB, 350 ms duration) was presented 1000 ms before the presentation of every visual stimulus via an external loudspeaker which was connected to the PC used for the visual stimulus presentation. To prevent spatial cueing the acoustic cue was presented from a central position relative to the observer's body midline in 0.80 m distance.

The patients were instructed to identify immediately after the presentation of the visual stimulus whether the picture represented a left or a right hand.

All experimental conditions were implemented in a randomized order to rule out sequence or test adaptation effects. The visual neglect tests were assessed at the beginning of the first and at the end of the second session. The whole experiment was realized within one week in two sessions of about one hour each.

## RESULTS

A $T$-test for repeated measurements (one-tailed) revealed a marginally significant difference between left- and right-hand-judgments in the baseline measurement [$T_{(7)} = 1.710$; $p = 0.065$]. An ANOVA for repeated measurements with the factors Treatment (Baseline, Limb Activation, Alertness Cueing) and Hand-Side (schematic pictures of left or right hands) revealed a significant effect of Treatment [$F_{(2,\ 14)} = 3.951$; $p = 0.044$, $\eta_p^2 = 0.361$] and a marginally significant effect of Hand-Side [$F_{(1,\ 7)} = 5.029$; $p = 0.060$; $\eta_p^2 = 0.418$]. The Treatment × Hand-Side interaction [$F_{(2,\ 14)} = 1.047$; $p = 0.377$; $\eta_p^2 = 0.130$] was not significant. Subsequent $T$-Tests for repeated measurements were computed for a more specific examination of the treatment effects for each hand-side separately. For left hands the analysis (one tailed) revealed a significant reduction in decision errors for Limb Activation [$T_{(7)} = 2.200$; $p = 0.032$; $d = 0.77$], but not for Alertness Cueing [$T_{(7)} = 0.659$; $p = 0.265$; $d = 0.23$] compared to the Baseline. There was also a significant difference between the two treatments Limb Activation and Alertness Cueing [$T_{(7)} = -2.570$; $p = 0.037$; $d = 0.91$; two-tailed]. For the right side, $T$-Tests revealed no significant differences between any of the conditions. Results are depicted in **Figure 3**.

$T$-Tests for repeated measurements revealed no significant differences between the first and the second assessment of the visual neglect paragraph reading test [left-sided word omissions; $T_{(7)} = 1.24$; $p = 0.25$], horizontal line-bisection deviation [$T_{(7)} = -0.16$; $p = 0.89$] and number cancellation [left-sided omissions; $T_{(7)} = -0.89$; $p = 0.40$].

## DISCUSSION

In this study, we examined to which extent limb activation and alertness cueing can modulate signs of personal neglect assessed with a schematic hand discrimination task (left vs. right hand judgment). Unfortunately, there was only a marginal significant higher error rate for the identification of *left* hands as contrasted to depicted right hands. However, as the $p$-value (0.065) is close to the significance level of $p = 0.05$ our finding can cautiously be interpreted in line with the findings of Coslett (1998) and Baas et al. (2011) that neglect patients show a deficit in the identification of left hands related to their disorder. Several studies support the theory that subjects use their own body schema to identify depicted body parts, specifically hands. Therefore, the deficit of the participating patients in identifying left hands can be interpreted in favor of an impaired left-sided body schema (Coslett, 1998) for the left body side or in terms of a reduced access to this body representation of their left side. Another possible explanation is that patients with personal neglect principally could use their (unimpaired) body schema for hand identifications and simply do not use it because of their attentional neglect for the left side. Alternatively, it may be also hypothesized that this effect could be due to activation of other body representations beyond the body schema, i.e., body image, or motor imagery. This might explain why the body schema—which is typically conceived as an "unconscious" body representation—was modulated although our patients were explicitly (hence consciously) instructed to imagine their hands during the experiment.

Even if the effect of Hand-Side was only marginally significant and there was no significant interaction of Hand-Side × Treatment observable, we think that three significant effects are noteworthy because they possibly indicate an advantage of limb activation over alertness cueing in manipulating the disturbed identification of left hands in neglect. First, there was a significant main effect of Treatment indicating that the identification of depicted hands can be manipulated. Second, subsequent

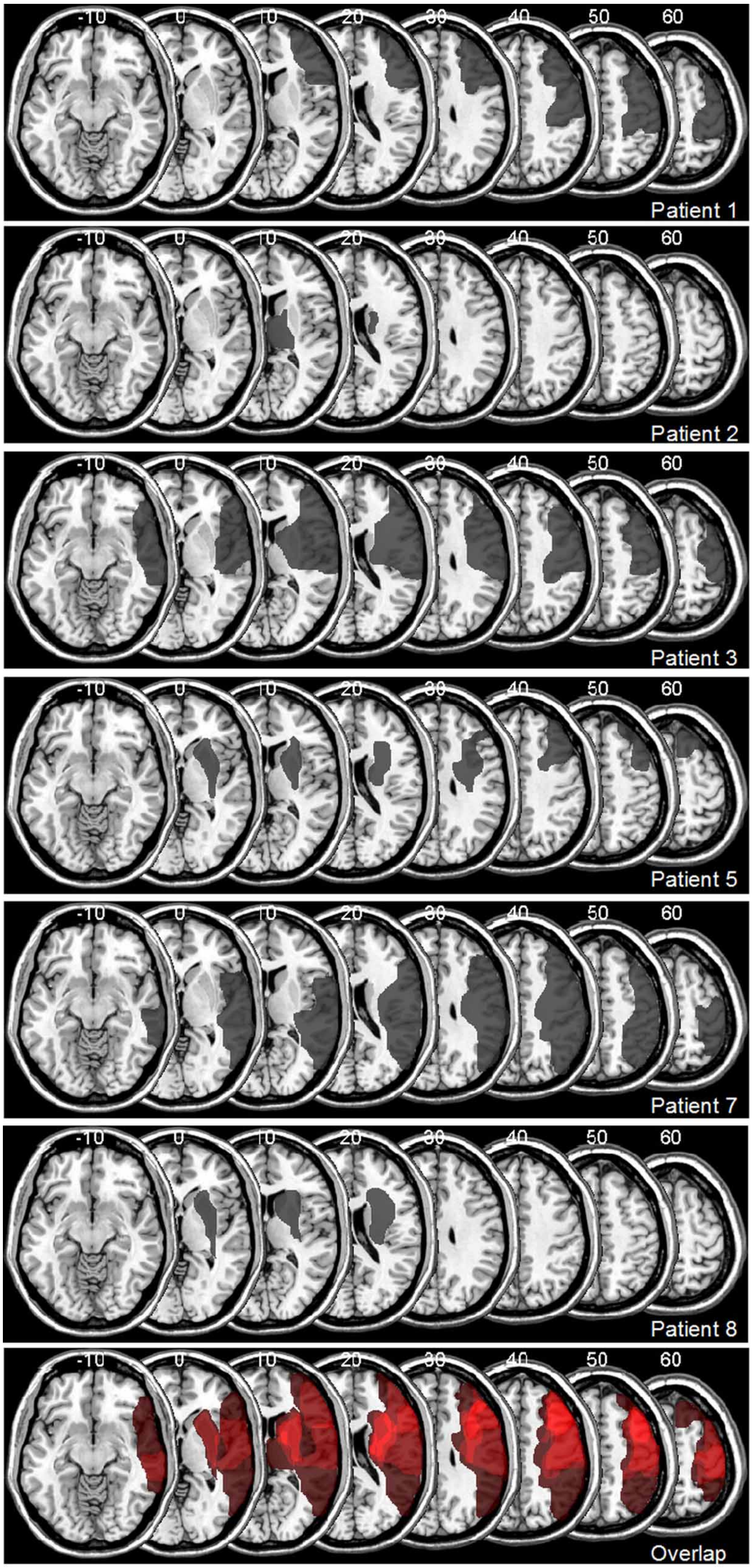


**FIGURE 2 | Lesion Maps for 6 out of 8 Patients with Visuospatial Neglect, Plotted onto a Normal Template Brain Using MRIcro Software (Rorden and Brett, 2000).** Affected areas (translucent gray) are plotted onto axial slices, with numbers indicating *Z*-coordinates in Talairach space.

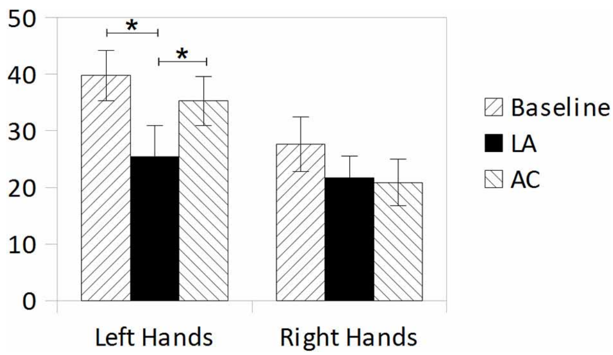


**FIGURE 3 | Mean error rates (%) in the hands-test during Baseline, Limb Activation, and Alertness conditions for depicted left hands (left bars) and depicted right hands (right bars).** Error bars indicate standard errors of the mean (SEM).

analyses examining that effect revealed a significant reduction of misidentifications of left hands only during limb activation and no reduction during alertness cueing (both compared to the baseline). Third, there was a significant difference between limb activation and alertness cueing reflecting a greater reduction of misidentifications during limb activation. Therefore, it cautiously can be concluded that limb activation possibly has an advantage over alertness cueing in manipulating the disturbed identification of left hands in neglect patients. On the one hand, this result suggests that the body schema for left-sided body parts can be activated, at least in part, and therefore appears to be basically intact and accessible rather than completely destroyed. On the other hand, the results indicate that this activation has to be specifically *body-related*. An unspecific elevation of non-spatial alertness appears to be insufficient to alleviate the impairments in body representation observed in our small sample. However, as our results are not unambiguous and the lack of significance of the Treatment × Hand-Side interaction possibly is due to the small statistical power of our small sample, these hypotheses require further evaluation in subsequent studies with larger sample size.

These results would not only be of theoretical interest, but potentially also of clinical relevance. Passive limb activation has been found to decrease different neglect symptoms, particularly visual neglect (Ladavas et al., 1997; Frassinetti et al., 2001; Harding and Riddoch, 2009). Here we have shown that this treatment *transiently* modulates also the body schema which is disturbed in representational personal neglect. Currently we do not know whether it is also possible to obtain longer-lasting effects. Therefore, we will have to leave it to future research to determine whether limb-activation can be used as a treatment for personal neglect.

## LIMITATIONS OF THE STUDY

While the present results suggest—in our view—an interesting modulation of body-related deficits in patients with visual and body-neglect using limb-activation, there are several limitations. First, the sample size was limited. Second, no non-neglecting control group with right-hemisphere damage was included, thus, we do not know whether the observed manipulations are specific to neglect or would occur in other subjects (patients or healthy controls) as well. Moreover, the statistical analysis showed only a marginally significant effect of Hand-Side (close but beyond $p = 0.05$) and a non-significant Treatment × Hand-Side interaction. Finally, the precise mechanisms by which the typically unconscious body schema can be activated by an explicit (and hence initially conscious) instruction to imagine the own hands requires clarification in subsequent studies. Nevertheless, we believe that these admittedly preliminary results—which to our knowledge are the first on the modulation of this type of body-related deficits in spatial neglect—might stimulate interesting subsequent research. Furthermore, it might be interesting to evaluate whether such limb-activation effects might also be present in non-neglecting subjects, i.e., healthy subjects, or other clinical populations with body-related deficits, but without stroke.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 14 December 2011; accepted: 07 June 2012; published online: 22 June 2012.*

*Citation: Reinhart S, Schmidt L, Kuhn C, Rosenthal A, Schenk T, Keller I and Kerkhoff G (2012) Limb activation ameliorates body-related deficits in spatial neglect. Front. Hum. Neurosci.* ***6****:188. doi: 10.3389/fnhum.2012.00188*

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 05 June 2012
doi: 10.3389/fnhum.2012.00154

# Bisecting real and fake body parts: effects of prism adaptation after right brain damage

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The representation of body parts holds a special status in the brain, due to their prototypical shape and the contribution of multisensory (visual and somatosensory-proprioceptive) information. In a previous study (Sposito et al., 2010), we showed that patients with left unilateral spatial neglect exhibit a rightward bias in setting the midpoint of their left forearm, which becomes larger when bisecting a cylindrical object comparable in size. This body part advantage, found also in control participants, suggests partly different processes for computing the extent of body parts and objects. In this study we tested 16 right-brain-damaged patients, and 10 unimpaired participants, on a manual bisection task of their own (real) left forearm, or a size-matched fake forearm. We then explored the effects of adaptation to rightward displacing prism exposure, which brings about leftward aftereffects. We found that all participants showed prism adaptation (PA) and aftereffects, with right-brain-damaged patients exhibiting a reduction of the rightward bias for both real and fake forearm, with no overall differences between them. Second, correlation analyses highlighted the role of visual and proprioceptive information for the metrics of body parts. Third, single-patient analyses showed dissociations between real and fake forearm bisections, and the effects of PA, as well as a more frequent impairment with fake body parts. In sum, the rightward bias shown by right-brain-damaged patients in bisecting body parts is reduced by prism exposure, as other components of the neglect syndrome; discrete spatial representations for real and fake body parts, for which visual and proprioceptive codes play different roles, are likely to exist. Multisensory information seems to render self bodily segments more resistant to the disruption brought about by right-hemisphere injury.

**Keywords: prismatic adaptation, space coding, body representation, multisensory, unilateral spatial neglect**

## INTRODUCTION

After an unilateral brain damage patients may show an altered representation of the space contralateral to the damaged hemisphere, that produces the neuropsychological syndrome of unilateral spatial neglect (USN). USN is more frequent and severe after damage to the right cerebral hemisphere, and involves the left portion of egocentric space in right-handed patients (Vallar, 1998; Bisiach and Vallar, 2000; Heilman et al., 2003; Husain, 2008; Vallar and Bolognini, in press). Basically, patients with USN show an inability to report sensory events occurring in the left side of space, contralateral to the side of the lesion (contralesional), and to perform actions in that portion of space. The deficit is dissociated from primary sensory and motor disorders, may be modality-specific, and conscious awareness may be more or less completely lost for the contralesional side of space. Patients with USN may show a variety of selective patterns of impairment, suggesting the existence of multiple spatial representations for different sectors of physical and imaginal space (Vallar and Bolognini, in press), and for specific stimuli, such as letter strings (Vallar et al., 2010). Particularly, USN may concern near extra-personal space or the body (Bisiach et al., 1986a; Guariglia and Antonucci, 1992; Committeri et al., 2007; Vallar and Maravita, 2009). These dissociations suggest that the internal representation of the space around us, far from being unitary, includes a number of discrete, though related, components, with partly different neural correlates (Rizzolatti et al., 1997; Vallar, 1998).

One hallmark of the syndrome of left USN is a rightward deviation error in the task of bisecting a horizontal line (Schenkenberg et al., 1980; Bisiach et al., 1983; Vallar et al., 2000; but see Karnath and Rorden, 2012, for the view that a line bisection bias is not a core manifestation of USN). The line bisection task is a standard, simple test, widely used for the clinical diagnosis and the experimental investigation of USN. This task has been typically employed to explore the spatial representation, particularly the lateral extent, of extra-personal objects, most frequently segments (Schenkenberg et al., 1980; Bisiach et al., 1983; Halligan and Marshall, 1994; Vallar et al., 2000). Recently, we used this task to explore the spatial metrics of body parts in right-brain-damaged patients with left USN, and in neurologically unimpaired participants (Sposito et al., 2010). Particularly, we demonstrated that USN patients show a rightward bisection bias for both their own left forearm and a three-dimensional extra-corporeal object comparable in size (i.e., a plastic cylinder), as compared to control participants. However, analyses of group performance showed that the bisection error is minor for the forearm, in both USN patients (with a reduction of the rightward bias), and in neurologically unimpaired participants. Yet, single-patient analyses also reveal that in USN patients the rightward bias can be significantly more severe either in cylinder than in forearm bisection (the prevailing pattern, as indicated by the above mentioned group analysis), or, vice versa, in forearm bisection. This double dissociation suggests the existence of independent representations for extra-personal objects and body parts, likely supported by discrete spatial processes (Sposito et al., 2010).

In the same study we also performed a second experiment in neurologically unimpaired participants, investigating the mechanisms underlying the body part (forearm) advantage, using a fake forearm as the object, instead of the cylinder. No advantage for the real, as compared to the fake, forearm was found in the bisection task, suggesting that real and fake body parts share a common spatial representation, primarily based on a visuo-spatial code (Sposito et al., 2010).

The present study further explored the spatial representation of real and fake body parts in right-brain-damaged patients, with and without USN, and in neurologically unimpaired participants. The aim was twofold. First, we looked for putative differences in real vs. fake forearm bisection biases in right-brain-damaged patients, to explore the hypothesis (Sposito et al., 2010) that the involved representation is based upon a visuo-spatial coding of the metrics of body parts, with therefore no differences between real and fake forearm bisections. Second, we assessed the effects of prism adaptation (PA) on the bisection of (real and fake) body parts. Basically, PA consists in a short period of adaptive pointing toward targets optically displaced by prisms (Redding et al., 2005). As far as left USN is concerned, patients' exposure to prisms displacing the visual scene rightward, after adaptation through a visuo-spatial pointing task, brings about a leftward displacement in pointing ("aftereffects," occurring subsequent to prism removal), and an improvement of many manifestations of USN (Redding et al., 2005; Rode et al., 2006a). The mechanisms whereby PA operates are complex and debated (Rossetti et al., 1999; Redding et al., 2005). In USN patients adaptation to rightward displacing prisms may operate by restoring the egocentric reference frame, pathologically distorted rightward, and bringing previously neglected space into awareness. The manifestations of USN temporarily alleviated by PA include visual (Rossetti et al., 1998; Farnè et al., 2002; Vallar et al., 2006), haptic/somatosensory (McIntosh et al., 2002; Maravita et al., 2003a), auditory (Jacquin-Courtois et al., 2010), and representational (Rode and Perenin, 1994; Rossetti et al., 2004) deficits. We predicted that if real and fake body parts share a similar visuo-spatial representation, PA is expected to modulate their bisection bias in a similar way.

## MATERIALS AND METHODS

### PARTICIPANTS

Participants were recruited from the inpatient population of the IRCCS Istituto Auxologico Italiano (Milano, Italy). All participants gave their informed consent to participate in the study. The protocol was carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302: 1194), and it was approved by the ethical committee of the IRCCS Istituto Auxologico Italiano.

Participants in the study included: 10 right-handed healthy subjects (i.e., Control Group, four males and six females; mean age: 56, range: 36–83; educational level: 9, range: 5–13), with no history or evidence of neurological disease; 16 right-handed right-hemisphere-damaged patients (i.e., RHD Group, 5 males and 11 females; mean age: 60, range: 30–97; educational level: 12, range: 5–19). For the patients' groups, inclusion criteria were the presence of a right hemispheric lesion. All patients had no evidence of previous neurological disease or psychiatric disorders.

Contralesional motor, somatosensory, and visual field deficits, including extinction to tactile and visual stimuli, were assessed by a standard neurological examination; for each function tested (i.e., visual, somatosensory, and motor), the score range was: 3 = maximum deficit; 0 = unimpaired performance (Bisiach and Faglioni, 1974). Anosognosia for neurological deficits was assessed by the standard interview of Bisiach et al. (1986b), which provides scores ranging from 0 (no anosognosia) to 3 (maximum deficit).

Position sense disorders were assessed by using the test developed by Vallar et al. (1993). The patient's contralesional (left) forearm was placed on the bottom of a black box, which prevented patients from viewing the tested forearm. The upper limb was placed extended on a table, and the forearm was moved passively by the examiner to four different positions: straight ahead, 30°, 60°, and 90° adducted, with respect to the arm, toward the patient's trunk. In each trial, the starting point was a position with the forearm straight ahead; the forearm was repeatedly adducted and abducted before the intended position was reached. Patients received instructions to look in front of them while the examiner moved their arm to the intended position, and to communicate the perceived position of the arm, by pointing to the corresponding silhouette on the cover of the box. There were 40 trials (10 per position), in a random-fixed order. The score was the number of errors, i.e., a reported position of the forearm different from the actual position (error range: 0–40). The control participants' average error was 0.087 (range 0–2; Vallar et al., 1993).

The demographical and clinical details of each patient are reported in **Table 1**.

### BASELINE NEUROPSYCHOLOGICAL ASSESSMENT FOR EXTRA-PERSONAL AND PERSONAL USN

#### *Cancelation tasks: letter, bell, star*

In the Letter task (Diller and Weinberg, 1977) the score was the number of "H" letter targets crossed out by each participant (53 on the left-hand side and 51 on the right-hand side of the sheet). Neurologically unimpaired participants made a mean of 0.13 (0.12%, SD ±0.45, range 0–4) omission errors out of 104 targets, with the maximum difference between omissions on the two sides of the sheet being two targets (Vallar et al., 1994). In the Bell task (Gauthier et al., 1989), the score was the number of "bell" targets crossed out by each participant (18 on the left-hand side, and 17 on the right-hand side of the sheet). Neurologically unimpaired participants made a mean of 0.47 (1.3%, SD ±0.83, range 0–4) omission errors out of 35 targets, with the maximum difference between omissions on the two sides of the sheet being four targets (Vallar et al., 1994). In the Star task (Wilson et al., 1987) the score

**Table 1 | Demographical and neurological data.**

| | | Length of illness (days) | Etiology | Age/gender | Neurological examination | | | Anosognosia | | | Position sense |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | V | SS | M | V | SS | M | |
| N– | P1 | 17 | T + H | 41/F | – | – | + | – | – | – | 0 |
| N– | P2 | 15 | T | 55/M | – | – | – | – | – | – | 1 |
| N– | P3 | 58 | A + H | 63/F | NA | NA | NA | NA | NA | NA | 0 |
| N– | P4 | 15 | I | 43/F | – | E | + | – | – | – | 2 |
| N– | P5 | 38 | I | 52/F | – | – | + | – | – | – | NA |
| N– | P6 | 33 | I | 53/M | – | E | + | – | – | – | 3 |
| N– | P7 | 30 | I | 66/F | – | E | + | – | – | – | 0 |
| N– | P8 | 32 | I | 78/F | E | ++ | ++ | – | + | + | 7 |
| N– | P9 | 17 | H | 57/F | – | E | ++ | – | – | – | 6 |
| N+ | P10 | 47 | I + H | 97/F | ++ | + | ++ | ++ | ++ | ++ | NA |
| N+ | P11 | 128 | H | 73/F | ++ | + | ++ | + | + | ++ | 11 |
| N+ | P12 | 32 | I + H | 51/F | ++ | ++ | ++ | + | + | + | 10 |
| N+ | P13 | 26 | I | 60/M | ++ | – | ++ | ++ | – | – | 7 |
| N+ | P14 | 547 | T | 30/M | ++ | ++ | ++ | – | – | – | 12 |
| N+ | P15 | 40 | H +T | 70/F | ++ | ++ | ++ | + | + | – | NA |
| N+ | P16 | 23 | TBI | 60/M | ++ | ++ | ++ | – | – | – | 19 |

*Etiology: I/H/A/T/TBI, ischemic/hemorrhagic/aneurysm/tumor/traumatic brain injury. Neurological examination: M/SS/V, motor/somatosensory/visual half-field deficits contralateral to the damaged hemisphere. Anosognosia: M/SS/V, for motor/somatosensory/visual half-field deficits. e, extinction to double simultaneous stimulation (for visual and somatosensory deficits); ++/+, severe/moderate deficit; –, no deficit; NA, not available. Position sense: n° errors out of 40 trials. N–, patients without USN; N+, patients with USN.*

was the number of small "star" targets crossed out by each participant (30 on the left-hand side and 26 on the right-hand side). Ten neurologically unimpaired participants (mean age: 72.2, SD: 5.27, range: 67–82; mean years of schooling 9.2, SD: 6.21, range: 3–18) scored 0.5 average omissions (0.9%, SD: ±0.7, range: 0–2), with the maximum difference between omission errors on the two sides of the sheet being one target (Fortis et al., 2010).

### *Line bisection*

The patients' task was to mark with a pencil the midpoint of six horizontal black lines (two 10 cm, two 15 cm, and two 25 cm in length, all 2 mm in width), presented in a random-fixed order. Each line was printed in the center of an A4 sheet, aligned with the midsagittal plane of the participant's body. The length of the left-hand side of the line (i.e., from the left end of the line to the participant's mark) was measured to the nearest millimeter. A deviation score (percentage deviation) was then computed by means of the following formula: measured left half minus objective left half)/objective left half × 100 (Rode et al., 2006b; Sposito et al., 2010). This transformation yields positive numbers for rightward deviations, and negative numbers for leftward deviations. Control data for this version of the line bisection test were available from 65 neurologically unimpaired participants (mean age: 72.2, range: 65–83; educational level: 9.5, range: 5–18). The mean percentage of bisection error of the control group was −1.21% (SD ±3.48, range: −16.2 to +6.2%; Fortis et al., 2010).

### *Five-element complex drawing (Gainotti et al., 1972)*

The patients' task was to copy a complex five-element figure: from left to right, two trees, a house, and two pine trees. Each element was scored 2 (flawless copy), 1.5 (partial omission of the left-hand side of an element), 1 (complete omission of the left-hand side of an element), 0.5 (complete omission of the left-hand side of an element, together with partial omission of the right-hand side of the same element), or 0 (no drawing, or no recognizable element). The total score ranged from 0 to 10. According to normative data from 148 neurologically unimpaired participants (age: range 40–79; education: range 5–13 years of schooling) a score lower than 10 indicated a defective performance (Fortis et al., 2010).

### *Sentence reading (Pizzamiglio et al., 1992)*

Patients were asked to read six sentences. The score was the number of correctly read sentences (range 0–6). Ten control participants (see above, star cancelation) made no neglect-like errors, and 0.3 (5%, SD ±0.64, range 0–2) other errors (Fortis et al., 2010).

### *Personal neglect test (Fortis et al., 2010)*

In this test patients were asked to reach six left-sided body parts (ear, shoulder, elbow, wrist, waist, knee), using their right hand. Each response was scored 0 (no movement), 1 (search without reaching), 2 (reaching with hesitation and search), or 3 (immediate reaching), with a 0–18 score range. Ten control participants (see above, star cancelation) made no errors (Fortis et al., 2010).

The patients' performance in each test is reported in **Table 2**. A pathological score in at least three tests was considered as an index of USN (see Fortis et al., 2010, for such a criterion); using this criterion, 7 out of 16 RHD patients showed USN (i.e., from patient P10 to patient P16).

**Table 2 | Assessment for visuo-spatial neglect.**

| | Line bisection (%) | Bell cancelation | | Letter cancelation | | tar cancelation | | Drawing (out of 10) | Reading (out of 6) | Personal neglect (out of 18) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | L (out of 18) | R (out of 17) | L (out 53) | R (out of 51) | L (out of 30) | R (out of 26) | | | |
| P1 | −1 | 1 | 3 | 1 | 0 | 0 | 0 | 10 | 6 | 18 |
| P2 | −9 | 1 | 0 | 0 | 0 | NA | NA | 10 | NA | 18 |
| P3 | −3.4 | 1 | 0 | NA | NA | NA | NA | 10 | 6 | 18 |
| P4 | 2.2 | 1 | 0 | 0 | 0 | 0 | 0 | 10 | 6 | 18 |
| P5 | −4.2 | 1 | 1 | 0 | 0 | 0 | 0 | 10 | 6 | 18 |
| P6 | −2 | 4 | 0 | 2 | 3 | 0 | 0 | 10 | 6 | NA |
| P7 | +5.2 | 4 | 0 | 0 | 3 | 1 | 0 | 10 | 6 | 18 |
| P8 | −3 | 2 | 4 | 2 | 4 | 0 | 2 | 9.5* | 6 | 18 |
| P9 | −0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 9.5* | 6 | 18 |
| P10 | +24.6* | 18* | 16* | 53* | 49* | 30* | 19* | 1* | 0* | 16* |
| P11 | +9* | 2 | 1 | 19* | 12* | 15* | 0* | 10 | 6 | 17* |
| P12 | +6.2* | 1 | 0 | 50* | 8* | 11* | 0* | 9* | 6 | 17* |
| P13 | +77.8* | 18* | 3* | 53* | 35* | 30* | 15* | 4* | 0* | 18 |
| P14 | +16* | 18* | 8* | 20* | 0* | 30* | 7* | 10 | 3* | 18 |
| P15 | +83.2* | 18* | 13* | 53* | 47* | 30* | 18* | 2* | 0* | 14* |
| P16 | +70* | 18* | 12* | 53* | 40* | 30* | 18* | 1.5* | 0* | 16* |

*Line bisection: percent deviation error (−/+, leftward/rightward). Cancellation tests: number of targets omitted in the left- and right-hand sides of the sheet (L/R), out of total targets. Asterisks: defective score, indicating left USN. Drawing, reading, and personal neglect tests: patient's score/maximum possible score (see text for details). NA, not available.*

## LESION DATA

**Figure 1** shows the mapping of the brain lesions for the 14 out of the 16 RHD patients, for whom the original brain scan was available. Lesions were mapped using the software MRIcro (Rorden and Brett, 2000). We reconstructed the region of interest (ROI) to define the location and the size of the lesion for each patient by using a Template Technique, that is, by manually drawing the lesion on the standard template from the Montreal Neurological Institute. ROIs were created by mapping the regions on each and every 2D slice of a 3D volume.

## EXPERIMENTAL PROCEDURE

### *Body bisection task*

Participants sat on a chair and were presented with a stimulus in front of them which could be either their own left forearm (real forearm condition) or a left fake forearm (fake forearm condition), placed at a distance of about 20 cm from the participant, with the objective midpoint aligned with their midsagittal plane. The fake forearm was a realistic, custom-made reproduction of a human male or female arm made by a scenic studio, and its length was broadly matched to that of a real forearm, as measured between the proximal and distal extremities of the ulnar bone (real forearm, controls = 23.6 cm ± 1.9; Patients = 23 cm ± 1.9; fake forearm = 24/22 cm, for a male/female forearm, respectively). During the bisection tasks, patients wore a black mantle; in the real forearm condition, each participant slid off the forearm from two side holes made in the mantle, so that only the forearm remained visible, while the hand and the arm above the elbow remained covered by the mantle; in the same way, in the fake forearm condition, only the fake forearm was out of the mantle (see **Figure 2A**). In both conditions, the right and the left extremities of the forearm were marked by black tags, and were clearly indicated to each participant prior to each block of trials.

Participants rested their right index finger touching their body midline at the level of the sternum. In each trial, they were required to point with their right index finger to the perceived midpoint of each stimulus, considering the black tags as its right and left endpoints. Each pointing was performed once, with no time constraints and no corrections allowed. After each trial, the distance between the left side of the stimulus and the participant's pointing was measured to the nearest millimeter. The participant was then required to put the index finger back to the starting position, before the following trial. The bisection task, comprising both real and fake forearm conditions, was given to participants in two sessions, namely before and after a 10-min application of 10° right-shifting prismatic lenses during pointing (see below, PA). Stimulus condition was blocked in an ABAB (BABA) design, with each block comprising 12 trials for each stimulus condition (i.e., two blocks were administered before PA, and two blocks after PA). In sum, there were a total of 48 trials, 24 for each stimulus condition (i.e., 24 Real forearm bisections, and 24 Fake forearm bisections), 24 (12 Real, and 12 Fake) before and 24 after PA. The order of the Real and Fake conditions was randomized across participants. A percent deviation score was calculated for both conditions with the formula used for the line bisection test.

### *Prism adaptation*

The procedure of Frassinetti et al. (2002), and of Fortis et al. (2010) was used. Each participant was seated in front of a table. A wooden box (height 30 cm, depth 34 cm at the center, and 18 cm at the two

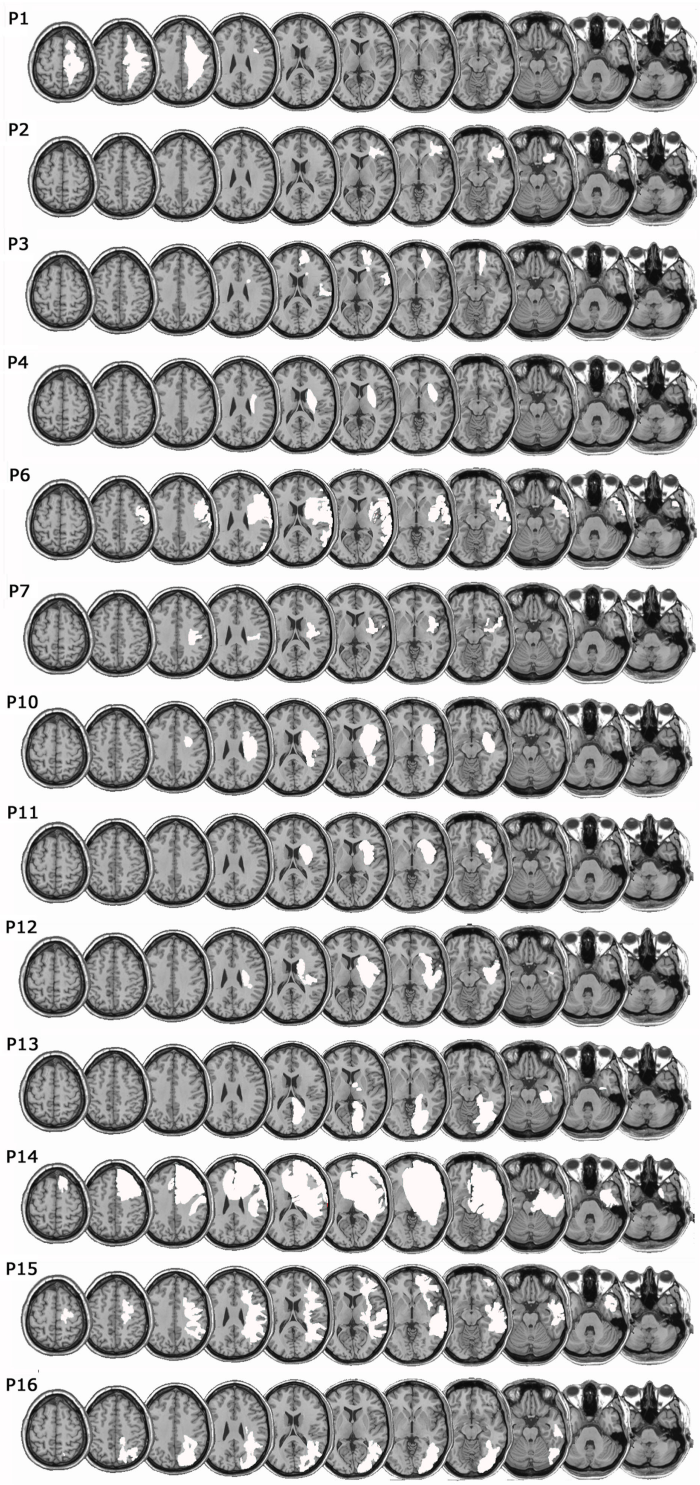


**FIGURE 1 | Lesion mapping.** Lesions were mapped onto a standard template (Montreal Neurological Institute) using the software MRIcro (Rorden and Brett, 2000). White areas represent the extension of the lesion of each patient.

sides, width 72 cm) was placed in front of him or her. The box was open on the side facing the participant ("proximal"), and on the opposite side ("distal"), facing the experimenter. On the experimenter's side (distal), the box could be made either open ("visible pointing"), or closed by a removable plexiglas ("invisible pointing" condition). In the visible pointing condition, the

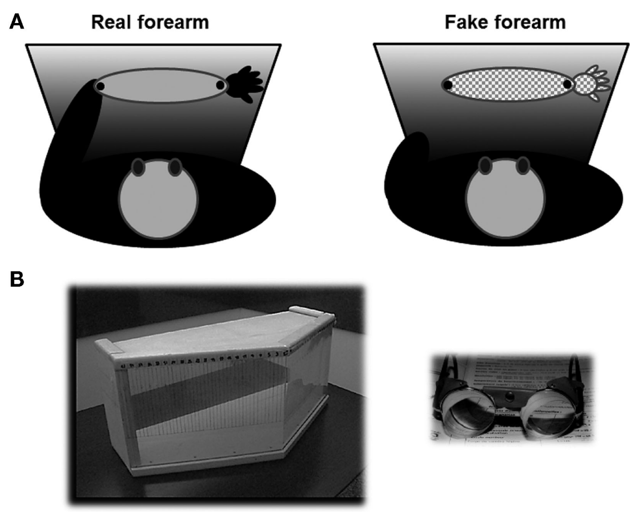


**FIGURE 2 | (A)** Schematic bird's eye view of the experimental setting for the real (left, light gray) and fake (right, pattern) forearm. Participants wore a black mantle, and they could see only their real forearm, which lay outside of two side holes of the mantle, or the fake forearm; black dots limited the extent of the real/fake forearm considered for the bisection task. **(B)** On the left, the box used for prism adaptation by repeated pointing trials, closed by the removable plexiglas, seen from the examiner's side (Fortis et al., 2010). Marks for the recording of the patients' pointing errors are shown. On the right, the prismatic goggles inducing a 10° shift of the visual field to the right.

participant's index finger came out of the box's open distal side, becoming visible to the participant. A visual target (a pen) was presented manually by the experimenter at the distal edge of the top face of the box (see **Figure 2B**). The visual target was presented randomly in one of three possible positions: central, straight ahead in front of the participant (0°), lateral to the left (–21°) or to the right (+21°) of the participant's body midline. The distal edge of the top face of the box was graduated (in degrees), so that the experimenter measured the patients' pointing accuracy, namely the distance between their finger and the target, measured in degrees. A positive score denoted a rightward displacement with respect to the position of the target, a negative score a leftward displacement.

Participants were asked to keep their right hand, ipsilateral to the side of the lesion (ipsilesional) for right-brain-damaged patients, on their chest, at the level of the sternum (hand starting position) and to point with their right index finger toward the pen, at a fast but comfortable speed. The movement of the participant's pointing arm was executed below the top face of the wooden box, so that they could not see the arm's trajectory. Once the experimenter had recorded the patient's pointing performance, the patient retrieved the arm and prepared for the successive trial. The pointing task was performed in three experimental conditions: Pre-exposure, Exposure, and Post-exposure.

***Pre-exposure condition.*** In this condition, immediately before wearing the prismatic goggles, participants were required to point with their index finger toward 60 targets presented randomly in one of the above mentioned three possible positions (20 targets at the center, 20 at −21° and 20 at +21°). Participants performed the first block of trials (30) with visible pointing, and the second block with invisible pointing.

***Exposure condition.*** Participants wore prismatic goggles (Optique Peter, Lyon, France), fitted with wide-field, prismatic lenses, inducing a 10° shift of the visual field to the right. Participants were asked to point with their right index finger to 90 targets presented in a random-fixed order in each of the three possible positions (30 targets at the center, 30 at −21°, and 30 at +21°). The pointing movement was hidden below the top face of the box, apart from its final part, where the index finger emerged beyond the distal edge of the top face of the box (visible pointing).

***Post-exposure condition.*** Immediately after prism removal, participants were required to point to 30 targets (10 targets at the center, 10 at −21°, and 10 at +21°) in a random-fixed order. As in the pre-exposure condition, pointing was invisible.

### STATISTICAL ANALYSES

To assess the presence and amount of the aftereffects following PA, we compared the participants' pointing error in the pre-exposure and post-exposure conditions by a repeated-measures analysis of variance (ANOVA) with Group as a between-subjects factor (Control, RHD), and two within-subjects factors: Session (pre-exposure, post-exposure), and Target position (left, center, and right). The dependent measure in this analysis was the mean displacement (expressed as degrees of visual angle) of the participants' invisible pointing responses.

We also analyzed the visible pointing responses in the pre-exposure condition via a repeated-measures ANOVA with Group as a between-subjects factor, and Target Location as a within-subjects factor.

Second, we assessed the effect of PA on the participants' performance in the body bisection task; the mean percentage of deviation errors was analyzed by a repeated-measures ANOVA with Group (Control, RHD) as a between-subjects factor, and two within-subjects factors: Stimulus (real forearm and fake forearm), and Session (pre-exposure and post-exposure).

Moreover, in order to control for a possible effect of the lesion size in determining the body bisection pattern and the PA effect in RHD patients, we carried out an analysis of covariance (ANCOVA) on the RHD patients' mean bisection error with Stimulus and Session as within-subjects factor, and Lesion size (mean volume of the lesion = 90 cc, range = 40–25 cc) as covariate (the covariate was mean centered prior to the analyses).

For every analysis, we calculated the partial Eta Squared ($p\eta^2$), which measures the proportion of the total variance that is attributable to a main factor or to an interaction (Cohen, 1973), and whenever necessary pairwise comparisons were conducted with the Newman–Keuls test. The level of significance was always set at 0.05.

To assess for the presence of any significant defective performance in individual RBD patients, we compared the deviation errors in the real and fake forearm conditions (considering the data before PA, i.e., the pre-exposure session) of each patient, with those of healthy participants. The comparison was performed by *t*-tests following the procedure of Crawford and Garthwaite (2005). Following the same procedure, we also compared the effects of PA on real and fake forearm bisections (i.e., the difference between the percent scores in the pre-exposure and post-exposure sessions) in each patient, with those of healthy control participants. Furthermore, following the Revised Standardized Difference Test (Crawford and Garthwaite, 2005), we compared in each patient the difference between real and fake forearm bisections in the pre-exposure condition, as well as between the effects of PA in the two bisection conditions, with the same differences in the neurologically healthy participants.

Finally, for right-brain-damaged patients, Pearson's correlation analyses were performed between the bisection error in the real and fake forearm conditions and the following variables: scores in the forearm proprioceptive test, in the standardized neurological exam (visual, tactile, and motor deficits), and in the clinical tests assessing USN.

## RESULTS

### AFTEREFFECTS

As **Figure 3A** shows, aftereffects (as indexed by the difference between the pointing errors during invisible pointing, before and after PA) took place after prism removal in controls and RHD patients. The ANOVA showed a significant main effect of Session [$F(1,24) = 37.52$; $P < 0.001$, $p\eta^2 = 0.99$], with a larger leftward deviation (i.e., aftereffects) in the post-exposure (−2.1°), as compared to the pre-exposure session (−0.36°). The main effect of Target location was significant [$F(2,48) = 13.39$; $P < 0.0001$, $p\eta^2 = 0.86$]: invisible pointing deviations to left target stimuli (−0.82°) differed from central (−1.22°, $P < 0.01$) and right (−1.65°, $P < 0.01$) target stimuli; pointing to central and right target stimuli were different too ($P < 0.02$). Other main effects and interactions were not significant: Group [$F(1,24) = 0.39$; $P = 0.5$, $p\eta^2 = 0.02$], Group by Session [$F(1,24) = 0.26$; $P = 0.6$, $p\eta^2 = 0.01$], Group by Target location [$F(2,48) = 2.11$; $P = 0.1$,

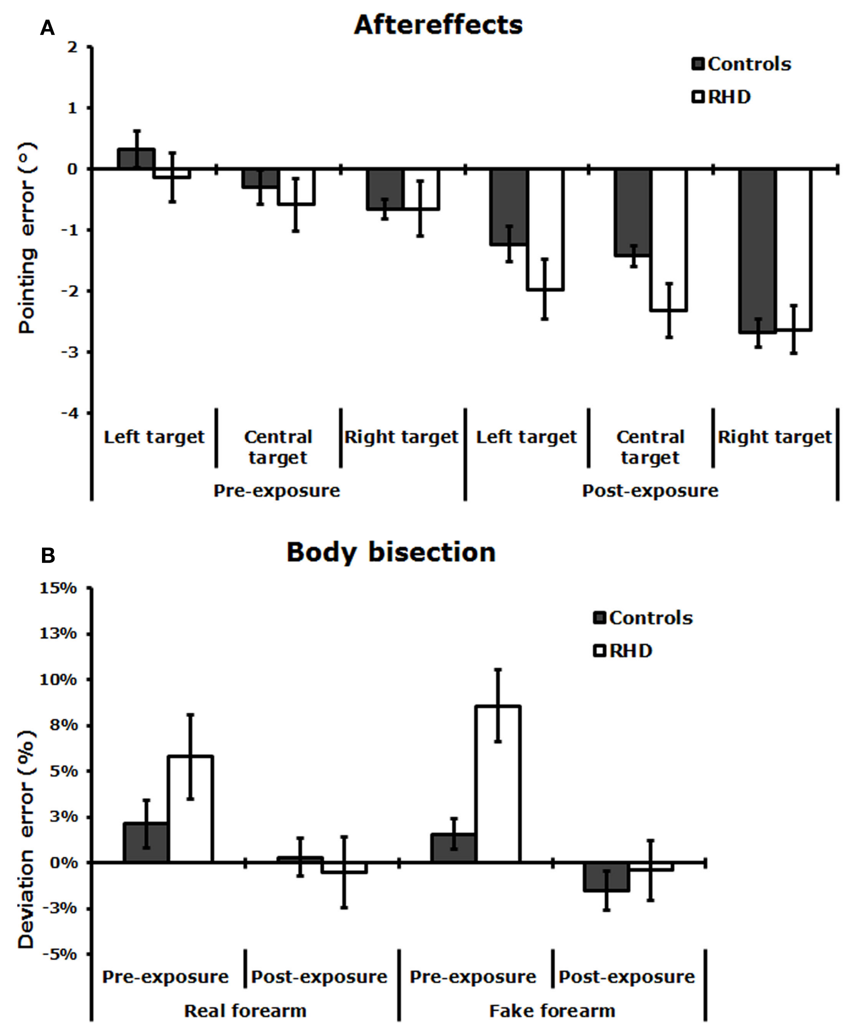


**FIGURE 3 | (A)** Aftereffects: Invisible condition. Mean pointing error (in degrees of visual angle, ±SE) in the pre-exposure and post-exposure sessions, made by neurologically unimpaired control participants, and RHD patients. **(B)** Mean percent deviation error (±SE) made by control participants and RHD patients, by stimulus condition (real and fake forearm), before and after PA.

$p\eta^2 = 0.08$], Session by Target location [$F(2,48) = 2.29$; $P = 0.1$, $p\eta^2 = 0.09$], Group by Session by Target location [$F(2,48) = 0.73$; $P = 0.5$, $p\eta^2 = 0.03$]. The lack of significant interactions involving the Group main factor indicates that the size of the aftereffects was comparable across the two groups, as well as the pointing deviations to different target locations.

The analysis of visible pointing responses in the pre-exposure condition showed a significant effect of Target location [$F(2,48) = 5.02$; $P < 0.01$, $p\eta^2 = 0.2$]: visible pointing deviations to left target stimuli (1.58°) differed from central (1.12°, $P < 0.01$), and right (0.99°, $P < 0.01$) target stimuli; pointings to central and right target stimuli did not differ ($P = 0.4$). Other main effects and interactions were not significant: Group [$F(1,24) = 3.12$; $P = 0.07$, $p\eta^2 = 0.2$], and Group by Target location [$F(2,48) = 0.07$; $P = 0.9$, $p\eta^2 = 0.01$]. These findings suggest that both controls and RHD patients were equally accurate in pointing to visual targets in a baseline (with no prisms) condition.

### EFFECTS OF PRISM ADAPTATION ON BODY BISECTION

**Figure 3B** shows that, in the Pre-exposure session, each group made a deviation error toward the right side in both the real and the fake forearm conditions, with a slightly more accurate performance in the real than in the fake forearm condition in RHD patients. RHD patients produced a larger rightward bisection error than neurologically unimpaired control overall. In the Post-exposure session, in both stimulus conditions the rightward bias diminished in all groups, with a greater effect emerging in RHD patients. The ANOVA revealed a significant main effect of exposure Session [$F(1,24) = 21.38$; $P < 0.0001$, $p\eta^2 = 0.47$], showing that both in controls and RHD patients there was a reduction of the rightward error in the estimation of the subjective midpoint of the real and fake forearms in the Post-exposure session (−0.51%, $P < 0.001$), as compared to the Pre-exposure session (5.13%). The significant Group by Session interaction [$F(2,24) = 5.67$; $P < 0.02$, $p\eta^2 = 0.37$] showed that PA diminished the rightward bias in RHD patients only, in either stimulus condition (pre-exposure = +7.19% vs. post-exposure = −0.45%, $P < 0.001$), with no PA effects in control participants (pre-exposure = +1.85% vs. post-exposure = −0.6%, $P = 0.3$). RHD patients differed from control participants only in the pre-exposure session ($P < 0.05$), but not in the post-exposure session ($P = 0.9$). The main effect of Group [$F(1,24) = 1.76$; $P = 0.2$, $p\eta^2 = 0.07$], and of Stimulus [$F(1,24) = 0.02$; $P = 0.9$, $p\eta^2 = 0.01$], and the Group by Stimulus [$F(2,24) = 1.69$; $P = 0.2$, $p\eta^2 = 0.07$], Session by Stimulus [$F(1,24) = 1.81$; $P = 0.2$, $p\eta^2 = 0.07$], and Group by Session by Stimulus [$F(2,24) = 0.23$; $P = 0.6$, $p\eta^2 = 0.01$] interactions were not significant.

The ANCOVA showed that the main effect of the covariate Lesion size, [$F(1,11) = 2.38$; $P = 0.2$, $p\eta^2 = 0.18$] failed to reach significance. Moreover, Lesion size did not significantly interact with the main effects of Session [$F(1,11) = 0.04$; $P = 0.8$, $p\eta^2 = 0.01$], and of Stimulus [$F(1,11) = 0.12$; $P = 0.7$, $p\eta^2 = 0.01$], as well as with the Session by Stimulus [$F(1,11) = 1.08$; $P = 0.3$, $p\eta^2 = 0.09$] interaction. Importantly, the main effect of Session was still significant [$F(1,11) = 14.89$, $P = 0.01$, $p\eta^2 = 0.58$]. Hence, lesion size did not influence the performance of RHD patients.

Pearson's correlation analysis between the bisection error in the real and in the fake forearm conditions, for both the pre-exposure and the post-exposure sessions were also performed. In healthy participants, there was no significant correlation between real and fake forearm bisections both in the pre-exposure session ($r = 0.42$, $P = 0.2$), and in the post-exposure session ($r = 0.11$, $P = 0.7$). Instead, in RHD patients, there was a positive correlation between the bisection error in the real and in the fake forearm conditions in the pre-exposure ($r = 0.72$, $P < 0.01$), but not in the post-exposure session ($r = 0.42$, $P = 0.1$). Moreover, the amount of the aftereffects (post-exposure minus pre-exposure pointing error) was not correlated with the amount of shift in the body bisection task (post-exposure minus pre-exposure deviation error) both in controls (real forearm, $r = -0.14$, $P = 0.7$; fake forearm, $r = -0.63$, $P = 0.06$), and in RHD patients (real forearm, $r = -0.12$, $P = 0.7$; fake forearm, $r = 0.17$, $P = 0.5$). It may be noted that in controls a negative correlation between the size of the aftereffects and the bisection error for the fake stimulus approached significance.

### COMPARISON BETWEEN PATIENTS AND CONTROLS

As shown by **Figure 4A**, before PA, 10 out of 16 RHD patients showed some degree of difference in the amount of error in one or both bisection conditions, as compared to controls. In particular, five patients had a significantly defective performance only in the fake forearm condition, showing a rightward error: P2 = +12% of deviation error, $t(9) = 3.18$, $P < 0.01$; P5 = +11% of deviation error, $t(9) = 2.86$, $P < 0.01$; P6 = +11% of deviation error, $t(9) = 2.86$, $P < 0.01$; P15 = +11%, $t(9) = 2.86$, $P < 0.01$; P16 = +13%, $t(9) = 3.49$, $P < 0.01$. Instead, the performances of P8, P10, P11, P12, and P14 were defective for both the real and the fake forearm bisections: P8 = real, −7%, $t(9) = -2.15$, $P < 0.03$, fake, +11%, $t(9) = 2.86$, $P < 0.01$; P10 = real, +28%, $t(9) = 6.19$, $P < 0.01$, fake, +22%, $t(9) = 6.36$, $P < 0.01$; P11 = real, +17%, $t(9) = 3.58$, $P < 0.01$, fake, +19%, $t(9) = 5.4$, $P < 0.01$; P12 = real, +14%, $t(9) = 2.86$, $P < 0.01$, fake, +9%, $t(9) = 2.22$, $P < 0.02$; P14 = real, +16%, $t(9) = 3.37$, $P < 0.01$, fake, +19%, $t(9) = 5.4$, $P < 0.01$. P5 and P8 also showed a significant difference between the two bisection conditions, with a greater rightward error for the fake forearm: P5 = +11%, $t(9) = 2.77$, $P < 0.02$; P8 = +18%, $t(9) = 4.09$, $P < 0.01$.

We also compared the performance of patients with or without USN in the two bisection conditions (real forearm vs. fake forearm) via an ANOVA with Group, as a between-subjects factor, and Stimulus, as a within-subjects factor; the dependent measure was the mean deviation error before PA. Only the factor Group was significant [$F(1,14) = 8.15$; $P < 0.01$, $p\eta^2 = 0.92$]: patients with USN showed a larger rightward bisection error (+12%) in both the real and the fake forearm conditions, as compared to patients without USN (+3%). Other effects were not significant: Stimulus [$F(1,14) = 2.38$; $P = 0.1$, $p\eta^2 = 0.15$], Group by Stimulus interaction [$F(1,14) = 0.94$; $P = 0.4$, $p\eta^2 = 0.03$].

With respect to the effects of PA on bisection performance (i.e., the difference in the deviation errors between the post-exposure and the pre-exposure sessions, see **Figure 4B**), six RHD patients differed from controls in the fake forearm, showing a greater leftward error: P2 = −13%, $t(9) = -3.18$, $P < 0.01$, P8 = −21%,

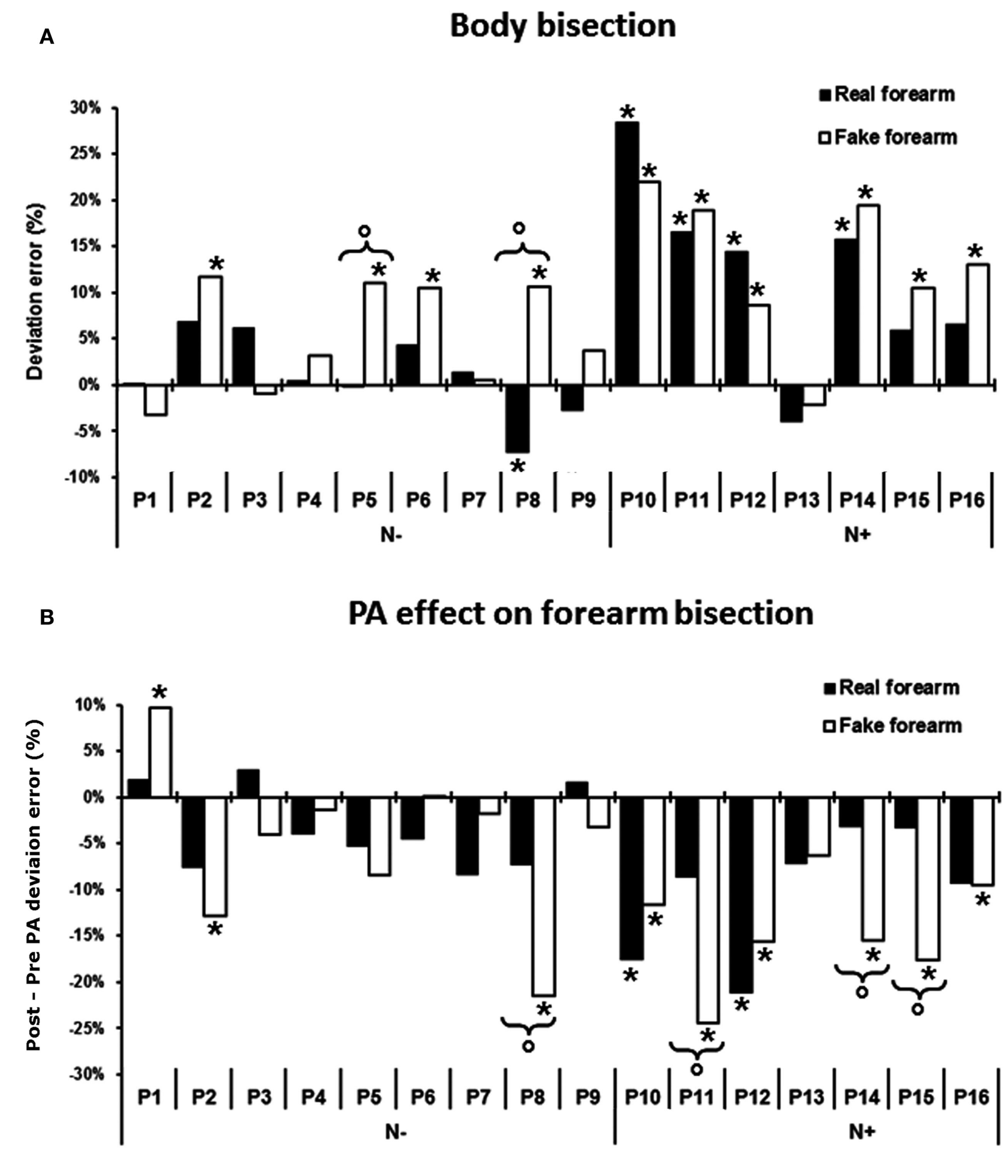


**FIGURE 4 | (A)** Pre-exposure condition: mean percent deviation error by stimulus condition in each of the 16 RHD patients. **(B)** Effects of PA on forearm bisection, i.e., difference in the deviation error between post-exposure and pre-exposure to prisms (post minus pre PA), for the real and the fake forearm conditions in each of the 16 patients. A negative score indicates a leftward, PA-induced, net effect, a positive score a rightward effect. Asterisk: significant difference between each patient's score and the mean score of the control group for each stimulus condition. Circles and brackets: significant difference between fake and real forearm bisection in the individual patient, as compared to the same average difference in the control group. N−, patients without USN; N+, patients with USN.

$t(9) = -5.72$, $P < 0.01$, P11 = −24%, $t(9) = -6.67$, $P < 0.01$; P14 = −16%, $t(9) = -4.13$, $P < 0.01$; P15 = −18%, $t(9) = -4.77$, $P < 0.01$; P16 = −9%, $t(9) = -1.9$, $P < 0.04$. P1 did not show the typical leftward aftereffects, exhibiting instead a significant rightward deviation in fake forearm bisection after prism removal [+10%, $t(9) = 4.13$, $P < 0.01$]. Two patients showed significantly larger effects of PA in both the real and fake forearm bisections, which did not differ ($P > 0.1$): P10 = real forearm, −18%, $t(9) = -3.81$, $P < 0.01$, fake forearm, −12%, $t(9) = -2.86$, $P < 0.01$; P12 = real forearm, −21%, $t(9) = -4.53$, $P < 0.01$, fake forearm, −16%, $t(9) = -4.13$, $P < 0.01$. A significant difference between the aftereffects in the two forearm conditions was found in four patients, with a greater leftward shift for the fake forearm: P8 = 14%, $t(9) = 2.85$, $P < 0.02$; P11 = −16%, $t(9) = 3.14$, $P < 0.01$; P14 = −12%, $t(9) = 2.45$, $P < 0.04$; P15 = −14%, $t(9) = 2.84$, $P < 0.02$.

An ANOVA with Group (patients with vs. without USN) and Stimulus (real forearm vs. fake forearm) as main factors, run on the difference in the deviation error between post-exposure and pre-exposure to PA (post-PA minus pre-PA), showed a significant effect only of the factor Group [$F(1,14) = 9.22$; $P < 0.01$, $p\eta^2 = 0.85$]: patients with USN showed a larger PA-induced leftward bias

(−12%), as compared to patients without USN (−4%). Other effects were not significant: Stimulus [$F(1,14) = 1.86$; $P = 0.2$, $p\eta^2 = 0.12$], Group by Stimulus interaction [$F(1,14) = 0.48$; $P = 0.5$, $p\eta^2 = 0.02$].

### CORRELATIONS BETWEEN FOREARM BISECTION AND CLINICAL SCORES IN RHD PATIENTS

As reported in **Tables 3** and **4**, in RHD patients, only two significant correlations were found: the amount of visual deficit was positively correlated with the amount of the deviation error in both the real ($r = 0.76$, $P < 0.01$) and the fake ($r = 0.77$, $P < 0.01$) forearm conditions. Instead, the amount of proprioceptive deficit (i.e., position sense) was positively correlated with bisection performance in the fake forearm ($r = 0.64$, $P < 0.01$), but not in the real forearm ($r = 0.41$, $P = 0.2$) condition. No other significant correlations between performances in the experimental task and clinical scores were found.

## DISCUSSION

Two main results emerge from this study. First, in RHD patients, with and without USN, and in neurologically healthy participants, bisection performance is overall similar for one's own forearm and for the fake forearm, as shown by the group analyses. As expected in a bisection task (see, e.g., Mancini et al., 2011, for a line bisection study comparing the performances of RHD patients with and without USN), RHD patients with USN make greater rightward errors in either stimulus conditions (i.e., real and fake forearm), than those committed by RHD patients without USN. These results are qualified by the single-patient analyses, which show that, as compared to healthy controls, 6 out of the 16 RHD patients (namely, P2, P5, P6, P8; P15, and P16, see **Figure 4A**) exhibit a pathological rightward bisection error only for the fake forearm, being statistically unimpaired for the real forearm (except for patient P8 who shows a defective performance also with the real forearm, but with a leftward bisection bias). Two patients (P5 and P8) show a significant difference between the real and the fake forearm bisections, with a greater rightward error in the fake forearm condition. As found in our previous study (Sposito et al., 2010), the forearm bisection deficit was unrelated to personal neglect (see **Table 1**).

The second finding is that all participants show PA and aftereffects. Overall, PA diminishes the rightward bisection bias in RHD patients in both real and fake forearm conditions, with no significant effects in control participants. The PA-induced leftward

**Table 3 | Correlation matrix between the bisection performances of RHD patients in the real and the fake forearm conditions, pre- and post-PA, and the demographic, neurological, anosognosia, and position sense (left forearm) scores.**

| | Age | Length of illness | Neurological examination | | | Anosognosia | | | Position sense |
|---|---|---|---|---|---|---|---|---|---|
| | | | V | SS | M | V | SS | M | |
| Real forearm bisection (pre-exposure) | $r = 0.28$<br>$P = 0.4$ | $r = 0.36$<br>$P = 0.2$ | $r = 0.76$*<br>$P < 0.01$* | $r = 0.42$<br>$P = 0.2$ | $r = 0.14$<br>$P = 0.6$ | $r = 0.39$<br>$P = 0.2$ | $r = 0.32$<br>$P = 0.3$ | $r = 0.41$<br>$P = 0.2$ | $r = 0.41$<br>$P = 0.2$ |
| Fake forearm Bisection (pre-exposure) | $r = 0.35$<br>$P = 0.2$ | $r = 0.47$<br>$P = 0.1$ | $r = 0.77$*<br>$P < 0.01$* | $r = 0.47$<br>$P = 0.1$ | $r = 0.16$<br>$P = 0.7$ | $r = 0.11$<br>$P = 0.7$ | $r = 0.46$<br>$P = 0.1$ | $r = 0.48$<br>$P = 0.09$ | $r = 0.64$<br>$P = 0.01$* |
| Real forearm Bisection (post-exposure) | $r = -0.02$<br>$P = 0.9$ | $r = 0.45$<br>$P = 0.07$ | $r = 0.52$<br>$P = 0.06$ | $r = 0.09$<br>$P = 0.8$ | $r = 0.09$<br>$P = 0.8$ | $r = 0.13$<br>$P = 0.7$ | $r = 0.03$<br>$P = 0.9$ | $r = 0.03$<br>$P = 0.9$ | $r = 0.04$<br>$P = 0.9$ |
| Fake forearm Bisection (post-exposure) | $r = -0.14$<br>$P = 0.7$ | $r = 0.18$<br>$P = 0.6$ | $r = 0.07$<br>$P = 0.9$ | $r = 0.02$<br>$P = 0.7$ | $r = -0.06$<br>$P = 0.8$ | $r = -0.05$<br>$P = 0.8$ | $r = -0.1$<br>$P = 0.6$ | $r = -0.17$<br>$P = 0.5$ | $r = -0.09$<br>$P = 0.8$ |

*Asterisk: significant correlation.*

**Table 4 | Correlation matrix between the bisection performances of RHD patients in the real and the fake forearm conditions, pre- and post-PA, and neuropsychological scores.**

| | Line bisection | Cancelation | | | Drawing | Reading | Personal neglect |
|---|---|---|---|---|---|---|---|
| | | Bell | Letter | Star | | | |
| Real forearm bisection (pre-exposure) | $r = -0.03$<br>$P = 0.9$ | $r = -0.44$<br>$P = 0.2$ | $r = -0.48$<br>$P = 0.1$ | $r = -0.45$<br>$P = 0.1$ | $r = -0.31$<br>$P = 0.3$ | $r = -0.31$<br>$P = 0.3$ | $r = -0.42$<br>$P = 0.2$ |
| Fake forearm bisection (pre-exposure) | $r = -0.02$<br>$P = 0.9$ | $r = -0.43$<br>$P = 0.2$ | $r = -0.29$<br>$P = 0.3$ | $r = -0.45$<br>$P = 0.3$ | $r = -0.36$<br>$P = 0.5$ | $r = -0.21$<br>$P = 0.5$ | $r = -0.38$<br>$P = 0.2$ |
| Real forearm bisection (post-exposure) | $r = -0.02$<br>$P = 0.9$ | $r = -0.39$<br>$P = 0.2$ | $r = -0.18$<br>$P = 0.6$ | $r = -0.45$<br>$P = 0.3$ | $r = -0.31$<br>$P = 0.7$ | $r = -0.11$<br>$P = 0.5$ | $r = -0.31$<br>$P = 0.3$ |
| Fake forearm bisection (post-exposure) | $r = -0.21$<br>$P = 0.5$ | $r = -0.23$<br>$P = 0.5$ | $r = 0.05$<br>$P = 0.8$ | $r = -0.05$<br>$P = 0.8$ | $r = -0.11$<br>$P = 0.7$ | $r = -0.11$<br>$P = 0.7$ | $r = 0.05$<br>$P = 0.9$ |

*No significant correlations were found.*

bias in the real and fake conditions is greater in patients with USN, than in patients without USN. Moreover, analyses of the individual patients' performance, compared to healthy controls, show that, in 6 out of 16 RHD patients (P2, P8, P11, P14–16), PA reduces the rightward bisection bias in the fake forearm condition only. Furthermore, four patients (P8, P11, P14, and P15) show a significant difference between the effects of PA in the two stimulus conditions, namely: a greater increase of the PA-induced leftward bias for fake forearm bisection. Finally, in two RHD patients with USN (P10 and P12) PA brought about the leftward bias in both forearm conditions.

### REAL AND FAKE FOREARM BISECTION

The overall lack of differences between the biases for the real and the fake forearm bisection tasks in right-brain-damaged and healthy participants shown by the group analysis, and the similarities of the effects of PA on the two types of stimuli, suggest that, at least as the present bisection paradigm is concerned, a shared spatial representation of real and fake body parts is available. The vision of a body part, as a highly specific and familiar object, may activate its prototypical standard representation, including spatial information about its length, thus allowing a comparable bisection performance for one's own forearm, and for a fake forearm, likely based on a visual analysis of the stimulus. The crucial role of visual inputs is supported by the significant correlation between the bisection performances in the two conditions, and the presence of a visual half-field deficit: the greater is the visual impairment, the larger is the bisection error in both real and fake forearm conditions. This finding is also consistent with the evidence that RHD patients with left USN and hemianopia make a greater rightward error in line bisection than USN patients without hemianopia (D'Erme et al., 1987; Doricchi and Angelelli, 1999; Daini et al., 2002). Notably, however, in RHD patients line bisection performance does not correlate with real and fake forearm bisection, in line with the recent previous evidence that different spatial processes are involved in the representation of extent, as assessed by bisection, of bodily and extra-personal objects (Sposito et al., 2010). Also fake and real forearm bisection performances do not correlate in healthy control participants, suggesting at least partly independent underlying processes, although caution is in order, since this conclusion is based on a negative finding. Interestingly, a significant correlation between the bisection performances in fake and real forearm conditions was found in RHD patients before, but not after, PA: this finding is likely to reflect the rightward-USN related bias shown by RHD patients, which affects both forearm types. The rightward error may however be differentially modulated by PA, according to forearm type, with effects confined to and greater in the fake forearm, as shown by the individual patients' analyses.

Importantly, we also found in RHD patients that an impaired position sense was related to the amount of deviation in fake, but not in real, forearm bisection. There is an important bodily illusion that might be relevant to explain why proprioceptive deficits are related to the ability of coding the spatial extension of the fake forearm. Visual capture of limb position is the phenomenon of perceiving the felt position of a limb to occupy the illusorily seen position when other sensory cues, such as proprioceptive inputs, are in conflict (Giummarra et al., 2008). Proprioceptive input regarding the positions of body parts can drift them from their actual position when they are hidden from view (as it occurs in our experimental task; Gross and Melzack, 1978; Giummarra et al., 2008). An important example of this effect is the rubber hand illusion (RHI). The RHI is evoked when the participant watches a rubber hand being stroked, while their own unseen hand is stroked in synchrony. This results in feeling ownership over the rubber hand, and induces a relocation of the perceived position of one's unseen own hand toward that of the rubber hand (Botvinick and Cohen, 1998). However, the rubber hand produces no such modulatory effect when placed in an anatomically implausible posture, that is totally inconsistent with the real hands' actual posture. Thus, while purely visual information (i.e., the sight of a fake forearm) can dominate slightly discrepant proprioception (as in the case of the fake forearm, placed, as in our experiment, in a plausible position), a proprioceptive deficit may reduce the impact of vision when the visual information about the position of body parts is inconsistent with proprioception, and with the representation of the body schema. This multisensory, body-related mechanism may explain the similar performances in real and fake forearm bisections: under normal conditions, as in neurologically unimpaired controls (see also Sposito et al., 2010), the sight of a fake forearm in a possible anatomical location for the real forearm determines a visual capture effect of limb position; as a consequence, the fake forearm is processed as the participant's own real forearm, for the purpose of bisection. A different scenario emerges when position sense is impaired by brain damage: the visual capture of the fake forearm is compromised, as the disrupted proprioceptive input regarding the position of the real forearm cannot be drifted to the location of the fake forearm. Now, since the fake forearm is no longer processed as the real forearm, belonging to the participant's own body, the fake forearm ceases to benefit from a multisensory (visual-proprioceptive) code, that, in its proprioceptive component, is putatively crucial for real body parts, but is not available to fake body parts [unless there is embodiment of the fake forearm, see Giummarra et al., 2008]. Under these conditions, the fake forearm is now encoded as a mere extra-personal object, and becomes more susceptible to the spatial disruption brought about by damage to the right hemisphere, in line with previous evidence (Sposito et al., 2010).

This finding supports the idea that, although the visual appearance of the fake forearm as a body part may ensure, *per se,* a better spatial analysis as compared to a neutral object (Sposito et al., 2010), the proprioceptive input always plays a role in the spatial analysis of bodily related visual information.

The dissociations found in RHD patients further indicate that the metrics of real and fake body parts are supported by discrete spatial processes, that may be selectively disrupted by a brain lesion. As shown in **Figure 4A**, even some patients without USN show a selective impairment for fake, but not for real, forearm bisection (P2, P5, P6, and P8, the last patient, however, exhibits a leftward bias, namely no right USN, with the real forearm). Also, two patients with USN (P15, P16) are impaired in the fake forearm condition only, and an opposite dissociation is not found, suggesting that the representation of the length of self-body parts is more reliable and resistant to the spatial disruption induced by a damage to the right hemisphere (see also Sposito et al., 2010).

Our findings are also in line with a dyadic model of body representation proposed in the literature, since the seminal studies of Bonnier (1905, see also Vallar and Rode, 2009), and Head and Holmes (1911; see for reviews: Berlucchi and Aglioti, 1997; Vallar and Papagno, 2003; Maravita, 2006; De Vignemont, 2010). A distinction has been drawn between a Body Schema, mainly constructed on somatosensory-proprioceptive and tactile information, which serves the guidance of actions, and a Body Image, which relies mainly on visual and tactile information, and mainly serves perception. Neuropsychological evidence shows that the Body Schema is actually dissociable from the Body Image. For instance, patients with USN are generally still able to perform non-conscious and automatic movements with neglected body parts, hence showing an intact Body Schema. Rather, the personal or bodily manifestations of USN appear to result from distortions of the Body Image, particularly affecting the conscious awareness of parts of the body (Sirigu et al., 1991; Gallagher and Cole, 1995; Coslett, 1998; Coslett et al., 2002; Gallagher, 2005; Maravita, 2006; De Vignemont, 2010; Preston and Newport, 2011). In this context, one may speculate that the Body Schema plays a pivotal role in the multisensory analysis of the metric of real body parts, whereas the visuo-spatial coding of fake body parts is a process pertaining to the impaired Body Image. The significant correlation between the severity of the proprioceptive deficit and that of the bisection error for the fake forearm suggests that, under unimpaired conditions, an object such as a fake body part may be processed as a real body part, namely as a part of the Body Schema, through computations involving position sense.

With respect to the neural correlates of deficits of real and fake forearm bisection, the limited number of patients, the different etiologies of the lesions, and the fact that some lesion images were not available for mapping, prevent definite conclusions. It may be cautiously noted, however, that the damage of the four RHD patients (P10, P11, P12, and P14) showing an impairment in the two bisection conditions is anterior-subcortical, affecting frontal areas, the insular cortex and subcortical structures including the putamen (see **Figure 1**). The frontal premotor cortex (PMC) and the putamen are known to instantiate a multisensory representation of peripersonal space. This representation is body part-centered, and it integrates visual, somatosensory, and proprioceptive information regarding stimulus location relative to the body (Graziano and Gross, 1993, 1995; Graziano et al., 1994; Maravita et al., 2003b). Moreover, in healthy humans, the experimental manipulation of ownership of individual body parts or of the whole body is associated with activity in PMC, the intraparietal sulcus (IPS), and the putamen (Ehrsson et al., 2004; Petkova et al., 2011). Finally, the insula has been definitely implicated in neurological disorders including anosognosia for hemiplegia, the sense of body ownership, the sense of agency and out-of-the-body experiences (Karnath et al., 2005; Baier and Karnath, 2008; Craig, 2009; Vallar and Ronchi, 2009; Berlucchi and Aglioti, 2010). Therefore, a damage to this network might disrupt the multisensory coding of the spatial extension of self-body parts, and the visual capture effect for fake body parts.

On the other hand, neuroimaging data suggest the existence of a posterior network concerned with a predominately visual representation of body parts; this network might play a crucial role in the selective deficit for fake forearm bisection, with spared real forearm. Indeed, the lateral occipito-temporal cortex includes a category-specific cortical region, the extrastriate body area (i.e., EBA), which responds in a selective manner to the visual presentation of real or stylized images of human body parts belonging to the participant or to someone else (Downing et al., 2001, 2006; Chan et al., 2004). Patients with posterior lesions including either the left or the right EBA are impaired in the visual processing of bodily forms, but not of bodily actions, while patients with anterior brain lesions, including either the left or the right ventral PMC, show an opposite pattern of deficits (Moro et al., 2008). Moreover, in humans, the lateral occipital cortex and the posterior part of the IPS (i.e., adjoining the transverse occipital sulcus) represent the hand-centered space in a predominantly visual manner, regardless of whether the hand is real or illusory, and with no relevant contribution of proprioceptive information about hand position (Makin et al., 2007). Instead, the anterior part of the IPS uses proprioceptive multisensory information in representing peri-hand space (Bolognini and Maravita, 2007, 2011; Makin et al., 2007). It may be noted that the one patient (P16) with a mainly posterior (temporo-occipito-parietal, see **Figure 1**) lesion is significantly impaired in the fake condition only, as compared with control participants. Also anterior lesions, however, may bring about this pattern of deficit (P2).

### PA AND AFTEREFFECTS

All participants showed aftereffects after PA, as assessed by the invisible pointing task, and the size of the aftereffects (i.e., the difference between pre- and post-PA invisible pointing performance) was comparable in the RHD and control participants. A recent study (Sarri et al., 2008), using a visual open loop pointing task (broadly comparable to our invisible pointing task), found that the error of patients with USN was comparable to that of neurologically unimpaired participants; crucially, the size of the aftereffects was comparable in patients with USN and in controls. A different pattern emerges when a dependent variable which has been considered an index of the neglect syndrome is used, namely the subjective straight ahead (Jeannerod and Biguer, 1987; Karnath, 1994, 1997; but see Farnè et al., 1998). Neglect patients show a larger rightward shift of the subjective straight ahead, assessed with participants being blindfolded, and greater effects of PA on this variable, as compared to healthy participants (Rossetti et al., 1998; Sarri et al., 2008). These findings may be interpreted as an indication that the disproportionate rightward shift of the subjective straight ahead is a pathological manifestation of USN, though it is not systematically found (Chokron and Bartolomeo, 1997; Farnè et al., 1998; Chokron, 2003); accordingly, in USN patients the effects of PA may be larger than in unimpaired participants (Sarri et al., 2008). With respect to line bisection performance, several studies (e.g., Colent et al., 2000; Berberovic and Mattingley, 2003; Michel et al., 2003; Fortis et al., 2011) have found a small neglect-like rightward bias on line bisection and Landmark tasks in normal participants following exposure to leftward, but not rightward, optical displacement; in patients with USN some studies show a reduction of the rightward bias (e.g., Rossetti et al., 1998; Pisella et al., 2002; Redding et al., 2005, for review), others do not (e.g., Luauté et al., 2006; Nys et al., 2008; Fortis et al., 2010). In the present study, PA diminishes the rightward bisection bias only in RHD patients in both stimulus conditions (real and fake forearm, with no effects in control participants, supporting the view that these deficits are manifestations of the neglect syndrome brought about by right brain damage (Sposito et al., 2010). This is further supported by the comparison between patients with and without USN, which shows a greater PA effect on both the fake forearm and real forearm bisections in USN patients. On the other hand, the amount of the aftereffects is not correlated with the amount of shift in the real and fake bisection tasks both in controls, and in RHD patients. Notably, the present study, unlike the abovementioned previous reports (Rossetti et al., 1998; Sarri et al., 2008) included also RHD patients without USN, in addition to the patients with USN and the healthy participants.

Overall, these novel results demonstrate that in RHD patients PA affects the metric representation of the body, as indexed by forearm bisection performance, supporting the view that their rightward bias in real and fake forearm bisection is a manifestation of the left USN syndrome caused by the right hemispheric damage. Finally, the analysis of the performances of individual patients (showing in a number of patients effects on fake body bisection, and not on real body bisection) supports the view that the representations and processing of these two types of objects are, at least in part, independent.

## ACKNOWLEDGMENTS

This work was supported in part by MIUR and FAR grants from the University of Milano-Bicocca to Nadia Bolognini, Angelo Maravita, and Giuseppe Vallar, and by a Ricerca Corrente Grant from the IRCCS Italian Institute for Auxology to Giuseppe Vallar. We are grateful to Dr. Roberta Ronchi, PhD, for her assistance in patients' selection and lesion mapping.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 27 January 2012; accepted: 16 May 2012; published online: 05 June 2012.*

*Citation: Bolognini N, Casanova D, Maravita A and Vallar G (2012) Bisecting real and fake body parts: effects of prism adaptation after right brain damage. Front. Hum. Neurosci. **6**:154. doi: 10.3389/fnhum.2012.00154*

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 17 July 2012
doi: 10.3389/fnhum.2012.00210

# Talking to the senses: modulation of tactile extinction through hypnotic suggestion

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Following brain damage, typically of the right hemisphere, patients can show reduced awareness of sensory events occurring in the space contralateral to the brain damage. The present work shows that a hypnotic suggestion can temporarily reduce tactile extinction to double bilateral stimulation, i.e., a loss of contralesional stimuli when these are presented together with ipsilesional ones. Patient EB showed an improved detection of contralesional targets after a single 20-min hypnosis session, during which specific suggestions were delivered with the aim of increasing her insight into somatosensory perception on both sides of the body. Simple overt attention orienting toward the contralesional side, or a hypnotic induction procedure not accompanied by specifically aimed suggestions, were not effective in modulating extinction. The present result is the first systematic evidence that hypnosis can temporarily improve a neuropsychological condition, namely Extinction, and may open the way for the use of this technique as a fruitful rehabilitative tool for brain-damaged patients affected by neuropsychological deficits.

**Keywords: hypnosis, neuropsychology, brain-damage, tactile extinction, rehabilitation**

## INTRODUCTION

Brain damage can deeply alter conscious perception of sensory events. A striking example of this is extinction to double simultaneous stimulation, whereby patients can detect unilateral stimuli on both sides of space, but fail to detect stimuli delivered to the side contralateral to the damaged hemisphere [more often left-sided stimuli following a right hemispheric lesion (Vallar et al., 1994a)], when these are delivered together with simultaneous ipsilesional ones (Bender, 1945; Bender and Diamond, 1975; Vallar and Maravita, 2009). Extinction is believed to originate from an abnormal competition for attentional resources between stimuli on opposite sides, which would cause the loss of the contralesional, "weaker," stimulus on bilateral presentations (Driver et al., 1997). A striking aspect of extinction is that, by definition, the deficit cannot be fully explained by a primary sensory loss (although this often co-exists), as shown by the correct detection of unilateral contralesional stimuli and by the evidence for various degree of implicit processing of the unreported targets (Maravita, 1997; Berti et al., 1999). The core deficit of these patients, therefore, would be at a higher level of perceptual processing, where sensory stimuli escape conscious detection after a certain degree of sensory analysis.

Extinction usually accompanies, or follows the more complex syndrome of Unilateral Spatial Neglect (USN), although it is dissociable from it (Cocchini et al., 1999). USN a complex, multicomponential syndrome in which patients fail to report bodily or extrapersonal stimuli delivered to the side contralateral to the damaged hemisphere (typically left-sided stimuli following a right hemispheric lesion), even if delivered in isolation (Heilman et al., 2003; Husain, 2008; Vallar and Maravita, 2009).

A clinically relevant feature of USN and extinction is that patients are typically unaware of their neuropsychological deficit (as well as of other co-existing primary sensory and motor deficits) a condition named anosognosia (Vallar and Ronchi, 2006). USN (Di Monaco et al., 2011), anosognosia (Gialanella et al., 2005) and to some extent even extinction (Rose et al., 1994) are regarded as negative predictors of outcome in brain-damaged patients with sensorimotor deficits. In particular, anosognosia seems to have a pervasive negative influence on the functional recovery after stroke (Gialanella et al., 2005) since it significantly limits the active participation of patients to any rehabilitation training. For this reason there is a strong need for a better understanding of these deficits and to find novel approaches by which residual sensory processing can be made available to awareness, even in patients who do not fully acknowledge their deficits and, therefore, are not likely to adopt explicit strategies to improve. Following these principles, many approaches have been proposed to date, such as vestibular stimulation (Cappa et al., 1987), neck muscle vibration (Karnath et al., 1993), TMS (Fierro et al., 2006), prism adaptation (Rossetti et al., 1998; Maravita et al., 2003), and limb crossing (Smania and Aglioti, 1995). These techniques have proved effective in producing short- or long-lasting improvements of USN and extinction in a "bottom up" fashion, i.e., without requiring the patient to adopt any explicit strategy.

In the present work hypnotic suggestion was used as a novel approach to modulate sensory extinction, and in particular tactile extinction. This technique is nowadays regarded as an important tool for studying sensory and cognitive brain functions (Oakley and Halligan, 2009; Raz, 2011) given its efficacy in modulating several electrophysiological and neurofunctional indexes (Rainville et al., 1997; De Pascalis, 1999; Maquet et al., 1999;

Cojan et al., 2009), perceptual-cognitive effects (Szechtman et al., 1998; Kosslyn et al., 2000; Raz et al., 2007; Cohen Kadosh et al., 2009; Cojan et al., 2009; Casiglia et al., 2010; Priftis et al., 2011), clinical conditions (Oakley et al., 2002) or even simulating neurological or psychiatric conditions (Halligan et al., 2000; Blakemore et al., 2003).

During hypnosis, participants experience a peculiar condition (also indicated as "state of trance"), which is induced by the hypnotist through specific verbalizations. The nature of the "trance" state is still a matter of discussion. Researchers have found different physiological markers which would characterize the patient in hypnosis, including specific patterns of functional brain activations and deactivations (Maquet et al., 1999), changes in electrical cortical activity (De Pascalis and Penna, 1990) or increased activity in the anterior areas of the "default mode" network in highly susceptible individuals (McGeown et al., 2009). In the clinical practice, the hypnotic state is believed to help the patients accepting suggestions oriented at modifying their behavior not only while in hypnosis but, critically, even once the trance state is over (Erickson, 1980). In the present work we applied (although non-rigidly, as shown in the Methods section) a mainly indirect approach for delivering hypnotic suggestions, in line with the theoretical view outlined by Milton Erikson and currently used by many clinical psychotherapists (Erickson, 1980). This approach typically avoids proposing directive suggestions or the adoption of explicit behavior to the patient, but makes use of metaphoric statements or verbal descriptions that help patients building up insight into their deficit and stimulate the discovery of their own strategies for recovery (Williams, 1983; Matthews, 2000; Maudoux et al., 2007; Ross et al., 2007). Using this approach in hypnosis seemed an ideal way to improve neuropsychological deficits that typically escape the patient's awareness, such as extinction. In the present study we specifically targeted tactile extinction, with the aim of testing whether this deficit could be positively modulated by a single session of hypnosis in a right brain-damaged patient. The rationale of the hypnotic suggestions was that of guiding the patient towards a reduction of competition between the ipsilesional and the contralesional stimuli, following the idea of limited attentional capacity in these patients (Driver et al., 1997). While the rationale of this hypnotic approach was decided before meeting the patient, the details of the suggestions and the specific verbalization useful to reach that aim were decided online, following the imaginative contents produced by the patient during hypnosis.

## CASE DESCRIPTION

EB is a lively and cooperative 58 year-old, right-handed woman. Two years previous to testing she suffered a large ischemic stroke involving the insular, frontal and temporal regions of the right hemisphere (see **Figure 1**). Sensory and motor functions were briefly assessed through the standardized neurological examination by Bisiach et al. (1986). With this test both functions are examined according to a three-point scale ranging from score 0 (absence of deficit) to score 3 (maximum deficit). At the time of testing EB presented with left spastic hemiparesis (score 2 for the lower and 3 for the upper limb) and left hemianopia (score 3 for both quadrants). She also presented with USN and tactile extinction, as described below.

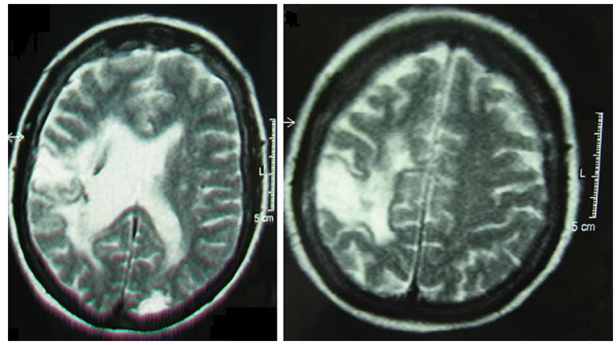


**FIGURE 1 | Magnetic Resonance images of EB's brain lesion.** Following the radiological convention, the right hemisphere is on the left side of the image.

### ASSESSMENT OF TACTILE SENSITIVITY AND USN

Tactile sensation and extinction were tested in the baseline assessment and in the experimental evaluations by computer-controlled devices (Foreman & Co., UK) producing single silent and invisible touches of 100 ms duration. The stimulators were taped on the distal pad of the forefinger of each hand while EB rested the hands on her lap and fixated a central mark placed on the table in front of her. Each testing session comprised the following stimulus types: 12 unilateral left, 12 unilateral right and 24 bilateral, plus 12 catch trials (no stimulation), for a total of 60 trials, delivered in random order within a single session. After each trial the examiner verbally prompted the patient to report the presence and the side of any perceived stimulus, recorded EB's response and started the following trial.

USN was formally tested in the baseline assessment and the experimental sessions, through common standardized tests, namely letter cancellation (Diller and Weinberg, 1977), star cancellation (Wilson et al., 1987), figure and shape copying test (Wilson et al., 1987), and sentence reading test (Pizzamiglio et al., 1990)[1].

[1]In the letter cancellation test (Diller and Weinberg, 1977) the patient was asked to mark all the "H" letters presented among other distracter letters and aligned in six horizontal lines. The score was the number of targets crossed out (53 on the left, and 51 on the right side of the sheet in total). The maximum difference between omission errors on the two sides of the sheet is two targets in neurologically unimpaired observers (Vallar et al., 1994b). In the star cancellation task the patient had to cancel star targets and ignore distracters (Wilson et al., 1987); the score was the number of correct targets crossed out (30 on the left, and 26 on the right-hand side in total). Ten comparable neurologically unimpaired participants tested in a previous experiment (Fortis et al., 2010) scored 0.5 omissions on average (SD 0.7, range 0–2), with the maximum difference between omission errors on the two sides of the sheet being one target. In the figure and shape copying test (Wilson et al., 1987), the score was given following a 0–4 range, based on the completeness of each drawn figure. The cut-off score for this test is 3. In the line bisection test the patient was requested to mark the midpoint of three 204-mm lines drawn on a single sheet of paper. The score range is 3–9, calculated on the amount of deviation from the objective center for each line, with a cut-off score of 7 (Wilson et al., 1987). In the sentence reading test patient was requested to read six sentences in Italian, consecutively presented in separate sheets of paper (score: 1 for each sentence read without omissions; score range: 0–6). Normal observers make no errors in this test (Pizzamiglio et al., 1990).

# METHODS

## EXPERIMENTAL DESIGN

The patient was tested in accordance with the guidelines of the Declaration of Helsinki, in eight sessions distributed over three days during a three-week period. Although the main focus of the hypnotic intervention was extinction, in all sessions EB was tested for tactile extinction and USN, apart from the last session when she was tested for extinction only. The patient was informed of the experimental procedure and that we planned to use hypnosis in order to improve her condition, in particular her perceptual functions, without explaining in full details the experimental design, in order not to influence her performance in the testing sessions. A full debriefing was given to EB at the end of the last experimental session.

The first day (day 1) comprised a first baseline testing of USN and extinction, plus an identical delayed baseline, that was performed after a 20-min interval occupied by an unstructured interview. The delayed baseline was performed in order to check for test–retest reliability of extinction and USN in a sequence comparable to that of the critical experimental sessions with hypnosis (see below). Furthermore, a third session was performed after EB was instructed to voluntarily orient her attention toward the left hand. This manipulation was introduced in order to compare the effect of a simple explicit attention-orienting strategy with the critical hypnosis suggestion. On the second day of testing (14 days after day 1), EB was tested before and after a preliminary hypnotic training (named Hypnosis-1) where she could familiarize with the induction of hypnosis, but without receiving any specific suggestion targeting extinction. On the third testing day (seven days after day 2) two further evaluations were performed, separated by the critical hypnotic induction (Hypnosis-2) specifically aimed at improving extinction, plus a further follow-up testing (Post-hypnosis-2 delayed), performed after 45 min in order to test for any delayed effect.

The number of correct responses in the different conditions was compared using planned Chi-squared tests.

## DESCRIPTION OF THE HYPNOTIC INDUCTIONS

### *First induction (Hypnosis-1)*

This first hypnosis session had the following aims: collecting the clinical history and establishing a good therapeutic rapport with the patient and explaining to EB the principles of hypnosis, with explicit reference to this technique, and the aims of the procedure. Furthermore, in this experimental session the hypnotic induction was performed without any specific suggestion directed at influencing EB's sensory processing, but only as a training for reaching a good state of hypnosis and as a control for any unspecific effect of the hypnotic state on extinction.

A simple progressive relaxation technique, i.e., backward counting, was used by the hypnotist (one of the authors, Mario Cigada). This was meant to facilitate the hypnotic induction, also given that EB appeared very distractible and manifested some difficulty in paying attention to the hypnotist's voice. After some relaxation was obtained, the hypnotist asked the patient to imagine herself in a pleasant place and describe what she imagined. EB referred that it was difficult for her to try and visualize anything, and her level of relaxation was waxing and waning for some time, with frequent interruptions of the hypnotic induction procedure, in which the patient started talking to the hypnotist about her clinical condition. The relaxation procedure was repeated a few times, since EB appeared more focused on the words of the hypnotist. At this stage, EB was able to relax quite easily and spontaneously recollected a trip to Athens occurred 30 years before, describing many images and details. The patient appeared to reach a good level of trance, as suggested by some overt behavioral signs, such as spontaneous eye closing, reduced loudness and tone of the voice, reduced facial expressions, absence of unrequested voluntary movements, decreased breath frequency and muscular relaxation that included the upper and lower limb on the plegic side[2]. In particular we observed a visible reduction of spasticity on the left hand as a consequence of muscular relaxation. This was of much surprise for the patient's daughter, who was present during the hypnosis session, since a reduction of the left hand spasticity was usually very difficult to obtain. After about 15 min, the hypnosis was terminated and the patient showed a sudden change of trunk posture and successive postural adjustments on the wheelchair, eye opening and gaze re-orienting, all suggesting that she was out of the hypnotic state.

### *Second induction (Hypnosis-2)*

The aim of the second experimental session was to influence the contralesional tactile extinction by specific suggestions during the hypnotic state.

The hypnotist started by using the same progressive relaxation technique (backward counting) used in the previous hypnotic session, in order to reach a state of concentration and relaxation. Again the procedure was initially quite effortful for the patient and required a few minutes to be effective. The trance was progressively deepened by the recall of several pleasant sensations experienced spontaneously by the patient in the previous session. After EB seemed to have reached a trance state, as suggested by similar behavioral signs of as those described above (including, again, visible muscular relaxation with reduced spasticity), the patient spontaneously recalled a car trip to the seaside. EB described the landscape that she imagined to see through the car window. A suggestion was then given that "the windscreen is misted over and that she can try and make left-sided images brighter by cleaning it." After a while the imaginary trip took EB over a bridge on the Po River (located in the North of Italy). The patient became quite emotional at this memory and her level

[2]The deepness of the hypnotic trance was systematically assessed using a custom-made questionnaire. The questionnaire is divided in two sections: the first comprises direct questions that are asked to the subject immediately after hypnosis to quantify his/her experience, the second is a check list in which a number of behavioural signs, observed in the participant during the trance state, are scored. Although this tool is not meant to score the hypnotic susceptibility but to qualify the actual experience of hypnosis, the scores at this questionnaire have been found to show some degree of correlation with the Stanford Hypnotic Susceptibility Scale ($r = 0.47$; $p < 0.01$) (data presented at the XI National Meeting of the "AMISI"—Italian Medical Association for the Study of Hypnosis-1998 Firenze "Quarant'anni di ipnosi in Italia:presente e futuro" G. Mosconi ed.). EB reached a score of 43% (a percent score relative to the maximum possible score) for the Hypnosis-1 and 46% for the Hypnosis-2 sessions. Such scores indicate that the patient reached a good, albeit not deep, hypnotic state.

of concentration decreased. After EB was again relaxed, she was invited to "imagine to dip both hands into the river's fresh water and try and experience how pleasant is to play with the sensations coming from both hands, for example, by reducing the sensitivity of the right hand and increasing that of the left hand." The patient found this exercise pleasant and easy to perform. The sensory manipulation was suggested a few times and it was also suggested that she "could keeping on playing with the sensitivity from the hands as if she was performing a physical training, in order to get stronger and feeling better, and that she could learn this pleasant exercise and repeat it from time to time in her daily life." The rationale of this statement was to favor EB's insight into tactile experience from both hands, by suggesting a positive association between somatosensory imagery and physical health, with the final aim of an improvement of extinction. The suggestion that this exercise could be repeated in the future as a sort of healthy training was aimed at anchoring EB's experience in hypnosis with her daily life, in order to help her favoring a process of self-healing.

The patient suddenly started crying, while recollecting her mother, who died a few years before and who joined the patient during that trip to the river. After she felt calmer, EB's somatosensory imagery was again stimulated by inviting the patient to "visualize her body walking around, and to concentrate on the somatosensory sensations coming from the movement of the left and right sides of the body." After EB has concentrated on this task for a while, describing sensation of touch, pressure, and temperature coming from her body, she was asked to slowly end her imaginary, and hypnosis was terminated. Again EB showed clear signs of sudden, spontaneous postural and attentional re-orienting. This session of hypnosis lasted around 20 min.

## RESULTS

### BASELINE TESTING OF EXTINCTION AND USN (TABLES 1, 2)

When tested for tactile extinction EB showed perfect detection of right-handed stimuli, reduced sensitivity on the left-handed stimuli (8 out of 12 correctly perceived) and 100% extinction of the left touches on bilateral stimulations (**Table 1**). There were only occasional responses to catch trials, always consisting in the false perception of unilateral left touches. Furthermore, clear signs of USN were present in all tests (**Table 2**). EB was deeply unaware of her defective performance in extinction and neglect testing. Although she had a good awareness of her motor deficits, she generally attributed any other deficit of the daily life, i.e., neglecting objects on the left side, bumping into doorways or impaired reading abilities, to fatigue and impaired vision.

### EFFECTS OF HYPNOSIS ON TACTILE EXTINCTION AND USN (TABLES 1, 2)

When tested for extinction (**Table 1**), EB showed a fluctuation in the performance on left unilateral trials across all sessions. On the other hand, there was a very clear and reliable pattern for the double bilateral stimulations: In the first two baseline sessions the left stimulus was never detected. Similarly, in the third session, when EB was instructed to orient her attention toward the left side, there was a non-significant increase of correct perception of bilateral trials (1/24 correct), but also an increase in false alarms (8/12) [CHI2(1) = 0,980, $p = 0.3$ and CHI2(1) = 2.5; $p = 0.1$, respectively]. This pattern suggests the adoption of an overall less conservative criterion in reporting left targets, following the attentional shift. Even the first hypnotic induction (Hypnosis-1) produced no effect on extinction. By contrast, after the second (specific) hypnotic session (Hypnosis-2) the perception of left touches on bilateral trials critically improved (8/24 stimuli correctly reported post-hypnosis vs. 0 pre-hypnosis, CHI2 (1) = 5,4; $p < 0.05$), with no difference in false alarms (100% correct) (**Table 1**). The improvement was still observed in the delayed post-hypnosis testing (6/24 stimuli correctly reported, CHI2 (1) = 4.5, $p < 0.05$). Also the response to left unilateral trials showed a marginally significant improvement in both the immediate and delayed post-hypnotic testing sessions (100% correct for both sessions vs. 9/12 correct before hypnosis, CHI2 (1) = 3.4, $p = 0.06$).

At odds with extinction, which showed remarkably stable results before the critical Hypnosis-2 session, the scores on most tests for USN showed a progressive improvement going from the first to the last repetition of the neuropsychological assessment (**Table 2**). More specifically, in the sentence reading test, some improvement was present in the baseline testing, in the unspecific hypnosis session, but not in the critical Hypnosis-2 session. In the figure and shape copying task, the amount of improvement in the critical Hypnosis-2 session was the same as in the baseline. The star cancellation was the only test showing some improvement in the Hypnosis-2 session, although some improvement was also found in the baseline test, while letter cancellation actually showed a worsening after hypnosis. Finally the line bisection showed no effect in the Hypnosis-2 session. Overall, the improvement found from the first baseline to the pre-Hypnosis-2 session was in most cases comparable, or superior, to that found following the critical Hypnosis-2 session and is likely due to unspecific learning effects, caused by the numerous repetitions of the testing battery. Due to this general pattern, and to the main target of the experimental procedure, which was extinction, USN scores were not further analyzed.

**Table 1 | Testing for extinction.**

| Day of testing | Session | Left | Right | Bilateral | Catch |
|---|---|---|---|---|---|
| 1 | First baseline | 67 | 100 | 0 | 67 |
| 1 | Delayed baseline | 75 | 100 | 0 | 100 |
| 1 | Endogenous attention shift | 83 | 100 | 4 | 33 |
| 2 | Pre-Hypnosis-1 | 83 | 100 | 0 | 100 |
| 2 | Post-hypnosis-1 | 83 | 100 | 0 | 92 |
| 3 | Pre-hypnosis-2 | 75 | 100 | 0 | 100 |
| 3 | Post-hypnosys-2 | 100 | 100 | 33 | 100 |
| 3 | Post-hypnosys-2 delayed | 100 | 100 | 25 | 100 |

*Percent of correct responses to unilateral and bilateral trials in the different testing sessions. Errors on bilateral trials always consisted of the omission of the left-sided stimulus. Errors on catch trials always consisted of the false report of a left-sided stimulation.*

**Table 2 | Neuropsychological evaluation of USN.**

| Session | Sentence reading (correct) | Figure and shape copying (score) | Star cancellation (left/right omissions) | Letter cancellation (left/right omissions) | Line bisection (score) |
|---|---|---|---|---|---|
| First baseline | 2* | 1* | 23/2* | 26/6* | 3* |
| Delayed baseline | 3* | 2* | 20/1* | 22/5* | 3* |
| Endogenous attention shift | 4* | 2* | 18/3* | 19/6* | 4* |
| Pre-hypnosis-1 | 3* | 2* | 19/0* | 14/8* | 6* |
| Post-hypnosis-1 | 4* | 2* | 18/0* | 10/1* | 6* |
| Pre-hypnosis-2 | 5* | 1* | 20/6* | 12/6* | 7 |
| Post-hypnosis2 | 5* | 2* | 12/0* | 14/2* | 7 |

*Scores on the neuropsychological tests for USN in the different experimental conditions (see text for the scoring procedures and the asterisk indicates abnormal performance.*

## DISCUSSION

The present case shows that hypnotic suggestion can positively affect a post-stroke, chronic neuropsychological deficit, namely tactile extinction. Within the imaginative context based on the patient's spontaneous recalls of a pleasant situation during the hypnotic trance, it was suggested to EB to try and modulate ("play with," as stated by the hypnotist) any somatosensory sensations coming from the right and left sides of the body, in the situation she was visualizing. In particular it was suggested to try and reduce the weight of right sided afferences, and increase that of left-sided ones. This suggestion was inspired by the theoretical notion that extinction consists of an ipsilesional bias in the competitive selection that the brain normally operates in the presence of multiple stimuli (Duncan, 1980, 1984; Bundesen, 1990). Due to this biased competition, even when stimuli are equally salient, the one presented ipsilesionally would be more likely perceived than the contralesional one (Driver et al., 1997). Accordingly, the suggestion of decreasing the weight of the ipsilesional stimulus and increasing that of the contralesional one was aimed at reducing stimulus competition, thus improving extinction. Such a specific content of the hypnotic verbalizations may also explain the selective effect of the procedure for tactile extinction, as compared to USN, in the critical Hypnosis-2 session.

The same increased contralesional processing would explain the improved perception of unilateral left stimuli, consistent with the idea that part of the contralesional somatosensory deficit occurring in right brain-damaged patients is not due to a primary sensory deficit but to impaired awareness (Sterzi et al., 1993).

Critically, hypnotic suggestion showed a stronger effect than the mere orienting of endogenous spatial attention towards the affected side without hypnosis. Indeed, as famously shown by Raz and colleagues (Raz et al., 2007; Raz and Campbell, 2011), hypnotic suggestion can strongly modulate attentional processes, including the performance on automatic attentional interference tasks, such as the Stroop effect, that would be typically refractory to any attentional effort made to override them. Our result is also in line with recent findings by Priftis et al. (2011) who showed that post-hypnotic suggestion can induce a neglect-like behavior in the response time to lateralized targets in healthy participants. Critically, in the same participants, the effect was much weaker following a mere condition of endogenous attentional orienting than in the case of post-hypnotic suggestion.

One main reason for the stronger effect of hypnotic suggestion over simple attention orienting in our patient could be that EB was unaware of her neuropsychological deficit, as typically observed in these patients (Vallar and Ronchi, 2006). This usually makes rehabilitation procedures based upon "bottom-up" or automatic mechanisms more effective than those based on explicit strategies that are typically aimed at increasing leftward attentional orienting in neglect and extinction (see Maravita et al., 2003; Fortis et al., 2010). In this view, hypnosis may represent an optimal strategy for the rehabilitation of deficits involving some degree of unawareness and anosognosia.

Noteworthy, the improvement of extinction found in EB occurred without the necessity for EB to adopt any overt strategy to overcome her sensory deficit, out of hypnosis. In order to explain how this was possible, it is useful to mention that experimental evidence showed that in patients with tactile extinction contralesional stimuli, although ignored during bilateral stimulations, can be nonetheless processed to some extent by the sensory systems, which can be completely unaffected by the lesion, even if the patient is not aware of them—an occurrence typically referred as implicit processing (Maravita, 1997; Berti et al., 1999). This evidence is in favor of the idea that somatosensory extinction corresponds to a deficit of higher level sensory processing, whereby sensory stimuli are processed only unconsciously, critically failing to reach the patient's awareness. In this view it is intriguing to think that any implicit information could be a precious anchor to try and improve the patient's performance. Through the critical verbalization given in trance of "playing" with the sensations coming from both hands, the patient was likely enabled to improve her awareness over residual tactile input coming from her left side, thus experiencing those inputs differently and opening the way to a better perception of left-sided stimuli even in the context of bilateral stimulations. This is unlikely to be due to increased endogenous attentional orienting toward the left side, given that an overt orienting of attention to the left was ineffective. One intriguing possibility is that the positive sensation imagined by the patient in the pleasant situation she visualized, may have acted as positive rewarding experience. Recent findings show that rewards can significantly bias attentional selection and learning (Della Libera and Chelazzi, 2006, 2009; Della Libera et al., 2011); in our case they could have increased the competitive weight of the contralesional stimulus, thus allowing them to reach awareness even during bilateral presentations.

It is important to say that the successful use of mainly indirect suggestions in the present case, which was given to the clinical experience of the hypnotist (MC) and the aforementioned theoretical issues, does not exclude that a more directive approach or an explicit post-hypnotic suggestion (e.g., suggesting to shift attention to the left) could be also successful. In fact, in the current literature, more directive hypnotic instructions have been typically used to bias behavior (see review in Oakley and Halligan, 2009). On one side it has to be said that, although the approach used in the present paper is not as directive as, for example, an overt suggestion of anesthesia (Rainville et al., 1997), or of attention modulation (Raz et al., 2007), it contains clear suggestions to guide the patient visual and sensory imagery, as well as suggestions to use these same imagined experiences in the daily life as a sort of healthy training exercise. In fact, the experimental approach used in the present work was not to use a "strict Ericksonian" approach (whose theoretical foundations are still a matter of discussion, Barber, 2000; Matthews, 2000; Peter and Revenstorf, 2000) in contrast with a "directive" one, although this approach is fruitfully used by many clinicians. By contrast, we think that indirect suggestions, post hypnotic commands and direct suggestions could be usefully compared, or even mixed, in the search of a successful rehabilitative approach.

Furthermore, although we think that using hypnosis in an imaginative context is surely a useful and promising approach, it remains possible that successful neuropsychological interventions in extinction patients may take advantage of visuomotor or haptic imagery, even without hypnotic suggestion (see related work on USN patients by Smania et al., 1997).

In order to assess the effectiveness of hypnosis, a critical question is clearly to assess the level of any "trance" state reached by the patient during the hypnosis session. In the present case we used an observational method, in which overt behavioral signs were taken as clues that a trance state was reached (see footnote 2). Of course, other variables could be taken into account, such as the level of hypnotic and non-hypnotic suggestibility of the patient (see discussion in Oakley and Halligan, 2011). In particular, the level of non-hypnotic suggestibility refers to the level of response to imaginative suggestions given out of hypnosis, while hypnotic suggestibility refers to the response to a suggestion while in hypnosis (Braffman and Kirsch, 1999). The level of non-hypnotic suggestibility has been found to correlate principally to response expectancy but also to other personality factors such as absorption, fantasy proneness and motivation (Braffman and Kirsch, 1999).

The results of the present paper are in line with growing evidence that hypnosis is a valuable tool to investigate neurocognitive functions, and with the recent suggestion that hypnosis could be used to improve different neuropsychological conditions such as USN (Oakley and Halligan, 2009; Priftis et al., 2011). To the best of our knowledge this work shows the first systematic evidence for the effect of hypnotic suggestion on a documented neuropsychological deficit in a brain-damaged patient. Although our experiment was aimed at testing any effect of hypnosis following a single experimental session and not as a long-lasting rehabilitative training, it opens the way to the possibility of a novel rehabilitative approach to neuropsychological disorders, in analogy to what already reported for other post-stroke deficits treated with hypnosis (Holroyd and Hill, 1989; Diamond et al., 2006). In particular, in future case studies a multiple-session approach could be used, which would favor the gradual implementation of specific suggestions tailored on the patient's needs and imaginative abilities, with the aim of training the patient to increase awareness of sensory events in order to obtain long-lasting improvements.

Noteworthy, in the present case, beside the specific improvement of extinction, the hypnotic procedure was effective in favoring attentional focusing and imagery in an otherwise emotional and distractible patient, as well as inducing deep muscular relaxation and reduction of spasticity in the plegic hand. It is therefore conceivable that hypnosis could exert beneficial effects not only by affecting the neuropsychological deficit and improving specific symptoms, but also by increasing the patient's compliance and motivation towards standard rehabilitation procedures targeting different sensory-motor functions.

## ACKNOWLEDGMENTS

We thank EB for her precious collaboration, Emanuela Bricolo for help in revising the paper and the reviewers for their insightful suggestions. Preliminary data were presented at the XIV national meeting of the "AMISI"—Italian Medical Association for the Study of Hypnosis September 2008, Milano, Italy. The authors also wish to thank the Frontiers Research Foundation for financial support.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 23 February 2012; accepted: 27 June 2012; published online: 17 July 2012.*

*Citation: Maravita A, Cigada M and Posteraro L (2012) Talking to the senses: modulation of tactile extinction through hypnotic suggestion. Front. Hum. Neurosci.* ***6****:210. doi: 10.3389/fnhum.2012.00210*

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 25 July 2012
doi: 10.3389/fnhum.2012.00217

# Visual and spatial modulation of tactile extinction: behavioural and electrophysiological evidence

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Crossing the hands over the midline reduces left tactile extinction to double simultaneous stimulation in right-brain-damaged patients, suggesting that spatial attentional biases toward the ipsilesional (right) side of space contribute to the patients' contralesional (left) deficit. We investigated (1) whether the position of the left hand, and its vision, affected processing speed of tactile stimuli, and (2) the electrophysiological underpinnings of the effect of hand position. (1) Four right-brain-damaged patients with spatial neglect and contralesional left tactile extinction or somatosensory deficits, and eight neurologically unimpaired participants, performed a speeded detection task on single taps delivered on their left index finger. In patients, placing the left hand in the right (heteronymous) hemi-space resulted in faster reaction times (RTs) to tactile stimuli, compared to placing that hand in the left (homonymous) hemi-space, particularly when the hand was visible. By contrast, in controls placing the left hand in the heteronymous hemi-space increased RTs. (2) Somatosensory event-related potentials (ERPs) were recorded from one patient and two controls in response to the stimulation of the left hand, placed in the two spatial positions. In the patient, the somatosensory P70, N140, and N250 components were enhanced when the left hand was placed in the heteronymous hemi-space, whereas in controls these components were not modulated by hand position. The novel findings are that in patients placing the left hand in the right, ipsilesional hemi-space yields a *temporal advantage* in processing tactile stimuli, and this effect may rely on a modulation of stimulus processing taking place as early as in the primary somatosensory cortex, as indexed by evoked potentials. Furthermore, vision enhances tactile processing specifically when the left hand is placed in the hemi-space toward which the patients' attentional biases are pathologically directed, namely rightwards.

**Keywords: attention, ERPs, hand crossing, multisensory, space, tactile extinction**

## INTRODUCTION

Perception of sensory stimuli (e.g., tactile, visual) can be impaired following unilateral brain damage. Patients with unilateral hemispheric damage may fail to report stimuli contralateral to the side of the lesion (contralesional) due to primary sensory deficits (hemianaesthesia, hemianopia; Ropper and Samuels, 2009), or to higher-order disorders of spatial attention and representation such as unilateral spatial neglect (USN; Kooistra and Heilman, 1989; Vallar et al., 1991a,b). USN is a complex neuropsychological disorder, more frequent and severe after damage to the right cerebral hemisphere, whereby patients fail to report stimuli presented in the contralesional side of space, and to explore that portion of space (Bisiach and Vallar, 2000; Halligan et al., 2003; Heilman et al., 2003; Husain, 2008). The distinction between the primary sensory and the higher-order components underlying the defective perception of tactile and visual contralesional single stimuli may be made through electrophysiological methods (Vallar et al., 1991a,b; Angelelli et al., 1996), which show evidence of preserved primary sensory processing in these patients. The role of USN-related pathological mechanisms in bringing about deficits of somatosensory and visual perception of single stimuli delivered in the contralesional side of space and the body is also suggested by the clinical finding that somatosensory and visual half-field deficits are more frequent after right than after left hemispheric lesions (Sterzi et al., 1993). This hemispheric asymmetry cannot be readily accounted for in terms of primary sensory deficits, suggesting instead a higher-order impairment related to the right side of the lesion, and to deficits of spatial representation and attention (Vallar, 1998). The USN-related component of the somatosensory deficits of right-brain-damaged patients, which results in a defective report of somatosensory stimuli delivered to the left side of the body, has been termed "somatosensory hemineglect" (Vallar, 1998). Patients with unilateral hemispheric lesions may also fail to report the contralesional tactile or visual stimulus only when an ipsilesional stimulus is presented at the same time. This deficit (extinction to double simultaneous stimulation, see reviews in Bisiach and Vallar, 2000; Driver and Vuilleumier, 2001; Heilman et al., 2003) is, as USN, more closely associated with right rather than with left brain damage, but may occur independently of USN signs such as the defective exploration of peripersonal space (e.g., Vallar et al., 1994; Vossel et al., 2011). Extinction has been interpreted as a deficit of the orientation of spatial attention (with an ipsilesional bias): it manifests under conditions of bilateral stimulation, in which the ipsilesional and contralesional stimuli undergo an exaggerate competition for spatial attentional resources (Driver et al., 1997), with the ipsilesional stimulus exerting a disproportionate attraction of attention (Bisiach and Vallar, 2000; Driver and Vuilleumier, 2001; Heilman et al., 2003). Sensory extinction may occur both within and between sensory modalities (Brozzoli et al., 2006).

As for the tactile domain, a further indication of a spatial, rather than purely sensory, component of the somatosensory deficits of right-brain-damaged patients has been provided by the finding that irrigating the left external ear canal with cold water, or the right canal with warm water (caloric vestibular stimulation) temporarily ameliorates somatosensory deficits and extinction to double simultaneous stimulation in right-brain-damaged patients (Vallar et al., 1990, 1993; Bottini et al., 2005). The finding that caloric stimulation improves many aspects of the USN syndrome (Vallar et al., 1997) concurs with the abovementioned evidence to suggest that somatosensory deficits may have non-sensory components, related to the impairment of the spatial representations of corporeal space, contributing to the perceptual awareness of tactile stimuli (Gallace and Spence, 2007; Vallar, 2007).

Finally, a converging source of evidence comes from studies that have manipulated the reference frames in which stimuli are encoded, through the posture of the participants' hands (Moscovitch and Behrmann, 1994; Smania and Aglioti, 1995; Aglioti et al., 1999; Bartolomeo et al., 2004) or knees (Bartolomeo et al., 2004), with the aim of disentangling the relative contribution of the somatotopic and higher-order spatial reference frames in modulating the somatosensory deficit caused by unilateral brain damage. Brain-damaged patients with tactile extinction fail to report somatosensory stimuli delivered to the contralesional side of either wrist, when both sides of the wrist are simultaneously stimulated, regardless of whether the patients' hands are positioned palm up or palm down (Moscovitch and Behrmann, 1994): namely, irrespective of hand posture, patients extinguish the left-sided stimulus, with reference to the spatial, not to the sensory (somatotopic), coordinate frames. Similarly, the ability of right-brain-damaged patients to detect left-sided stimuli (both single and associated with a simultaneous right-sided touch) improves when their hands are crossed over the mid-sagittal plane of the body, so that the left hand is placed in the right-hand side of egocentric space (ipsilesional) and vice versa for the right hand (Smania and Aglioti, 1995; Aglioti et al., 1999; Moro et al., 2004). Such improvement appears to be reduced under high attentional load conditions, namely when patients are required to monitor several body sites (i.e., cheeks, hands, and knees) for tactile detection (Bartolomeo et al., 2004). Furthermore, when the right hand of right-brain-damaged patients with left tactile extinction is placed in the left side of space, detection performance worsens, although the size of the effect appears minor compared to that found for the left, contralesional hand placed in the right side of space, as discussed above (Aglioti et al., 1999). Altogether, these results are important as they suggest that higher-order, spatial impairments contribute to somatosensory deficits and tactile extinction of right-brain-damaged patients.

As in the abovementioned studies participants were blindfolded, the contribution of viewing the stimulated hand to these somatosensory disorders remains unexplored. Spatial frames of reference are dominated by vision (Shore et al., 2002; Eimer, 2004; Röder et al., 2004), which is the most accurate sensory modality for spatial perception in humans (Rock and Victor, 1964; Eimer, 2004). Furthermore, crossmodal links between vision and touch (Botvinick and Cohen, 1998; Tipper et al., 1998; Taylor-Clarke et al., 2002; Maravita et al., 2003; Fiorio and Haggard, 2005; Serino et al., 2007), and between vision and proprioception (van Beers et al., 1996, 1999; Botvinick and Cohen, 1998; Graziano, 1999; Lloyd et al., 2003; Maravita et al., 2003) have been extensively shown, including the critical role of vision in determining limb position (van Beers et al., 1996), in localizing tactile sensations (Botvinick and Cohen, 1998; Graziano, 1999), and in attentional selection (Sambo et al., 2009). Accordingly, the prediction can be made that non-informative vision of the stimulated hand may modulate spatial effects on tactile detection in right-brain-damaged patients with USN and tactile extinction or somatosensory deficits.

In this study, performed in right-brain-damaged patients with USN and tactile extinction or somatosensory deficits, we tested (1) whether the position of the left hand in space, and the vision of that hand, affected the processing speed of tactile stimuli, and (2) the electrophysiological underpinnings of the effect of hand position. We specifically tested our hypotheses in this kind of patients since previous studies show that only right-brain-damaged patients with tactile extinction or somatosensory deficits, but not right-brain-damaged patients without tactile extinction or left-brain-damaged patients, are more accurate in reporting stimuli delivered to the left hand when their hands are crossed over the midline compared to when their hands are uncrossed: critically, under these conditions, the improvement is found for stimuli delivered to the left hand, which is placed in the right (heteronymous) side of space (Smania and Aglioti, 1995; Aglioti et al., 1999). We hypothesized that in right-brain-damaged patients with these deficits, latencies to unilateral touches delivered to the left hand are shorter when that hand is placed in the right ("heteronymous"), ipsilesional side of space, compared to the left ("homonymous"), contralesional side of space, with reference to the mid-sagittal plane of the body, particularly when the hand is visible (Experiment 1). Furthermore, by recording somatosensory event-related potentials (ERPs) we addressed the question of which stages of somatosensory processing are modulated by the spatial position of the left hand. To this aim, in one right-brain-damaged patient with tactile extinction and in two age-matched neurologically unimpaired control participants, we compared ERPs elicited by tactile stimuli delivered to the left hand placed in the heteronymous or homonymous sides of space (Experiment 2).

## EXPERIMENT 1: SIMPLE REACTION TIME

### METHODS

#### *Participants*

Four right-brain-damaged patients with left tactile extinction or somatosensory deficits (see details on the computerized somatosensory testing below) and USN (mean age: 62 years, see **Tables 1** and **2**), and eight age-matched, neurologically unimpaired control participants (mean age: 64.5 years, range: 31–87; mean years of education: 10.25, range: 3–17) entered in this study. Three patients were recruited from the Neuropsychological Laboratory of the IRCCS Istituto Auxologico Italiano, Milano, Italy, and one from the Rehabilitation Unit, Ospedale "C. Poma," Bozzolo, Mantova, Italy. All patients, and the control participants, gave their informed consent to the study. All patients, and the control participants, were right-handed. Patients had no history or evidence of previous neurological or psychiatric disorders. The patients' demographic, neurological, and neuropsychological characteristics are summarized in **Tables 1** and **2**. Motor, somatosensory, and visual half-field deficit were assessed by a standard neurological exam (Bisiach and Faglioni, 1974). **Figure 1** shows the lesion maps of the four right-brain-damaged patients who took part in Experiment 1. Patient #1, who also participated in Experiment 2, presented with a cortical-subcortical lesion affecting the basal ganglia (putamen and caudate nuclei), the temporal cortex, the rolandic operculum and, marginally, the parietal (post-central, supramarginal, and angular gyri) and inferior frontal cortices; the subcortical white matter was also extensively involved. Patient #2 had a surgical evacuation of an intracerebral hematoma and the lesion involved the frontal and temporal cortices, the basal ganglia, partially the insula and the white matter underneath the parietal and temporal cortices. Patient #3 had an extensive lesion, including the frontal (superior, middle, and inferior portions), parietal (post-central, angular, supramarginal, inferior, and superior regions), and temporal (superior, middle, and inferior portions) cortices, as well as the insula, the basal ganglia, and the subcortical white matter. The lesion of patient #4 involved the temporal cortex (superior, middle, and inferior portions), the frontal inferior regions, the parietal cortex (post-central, angular, supramarginal portions), the insula, the putamen, and the subcortical white matter.

#### *Neuropsychological assessment*

USN was assessed using the following tests:

1. *Line cancellation* (Albert, 1973). The scores were the numbers of line targets crossed out by each participant (11 on the left-hand side and 10 on the right-hand side of the sheet). Marks such as lines, crosses, or dots systematically placed in the close proximity of each line were considered as correct cancellations. Neurologically unimpaired participants have a flawless performance on this task.
2. *Letter cancellation* (Diller et al., 1974). The patients' task was to cross out all of 104 H letters (53 in the left-hand side and 51 in the right-hand-side of the sheet), printed on an A3 sheet,

**Table 1 | Demographic and neurological characteristics of four right-brain-damaged, right-handed patients.**

| Patient | Sex/age | Schooling (years) | Aetiology/lesion site | Duration of disease (months) | Neurological deficits | | |
|---|---|---|---|---|---|---|---|
| | | | | | M | SS | VF |
| 1 | M/77 | illiterate | I/BG/pvwm | 14 | 1 | 2 | 2 |
| 2 | M/36 | 9 | #/H/BG/FT | 12 | 1 | 0 | 0 |
| 3 | M/76 | 17 | I/FTP/pvwm | 11 | 1 | e | e |
| 4 | M/69 | 7 | I/FTP | 1 | 3 | 3 | 3 |

*I/H, infarction, hemorrhage; #, surgical evacuation of an intracerebral hematoma; clamp of the middle cerebral artery. F, T, P, frontal, temporal, parietal cortico-subcortical damage; BG, basal ganglia; pvwm, periventricular white matter. Neurological impairment (M, motor; SS, somatosensory; VF, visual half-field): 1 (mild), 2 (moderate), 3 (severe) impairment, 0 (no deficit); e, extinction to double simultaneous stimulation.*

**Table 2 | Neuropsychological assessment scores.**

| Patient | Target cancellation | | | | | | Line bisection (%) | Drawings | | | Personal neglect | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Line | | Letter | | Bell | | | Complex | Daisy | Clock | L | | R |
| | L | R | L | R | L | R | | | | | | | |
| 1 | 0/11 | 0/10 | 9/53* | 2/51 | 2/18 | 0/17 | +14,2* | 9/10* | 2/2 | 10/12 | 0/3[b] | 13/15[f] | 8/9[f] |
| 2 | 7/11* | 0/10 | 3/53 | 0/51 | 10/18* | 4/17* | +11,2* | 5/10* | 1/2* | 3/12* | 0/3[b] | 15/15[f] | 9/9[f] |
| 3 | 4/11* | 0/10 | 53/53* | 28/51* | 18/18* | 11/17* | +11,6* | 5/10* | 2/2 | 8/12* | 0/3[b] | 18/18[e] | n/a |
| 4 | n/a | n/a | 42/53* | 12/51* | 18/18* | 9/17* | +16,8* | 7/10* | 1.5/2 | 3/12* | 0/3[b] | 18/18[e] | n/a |

*Target cancellation: left-sided (L) and right-sided (R) omissions/number of targets; Line bisection, percent rightward deviation error; Drawings and Personal neglect: patient's score/maximum possible score (see text for details); n/a, not available or not applicable; [b], Bisiach's personal neglect test; [e], extension of Bisiach's personal neglect test; [f], Fluff test; *, defective performance.*

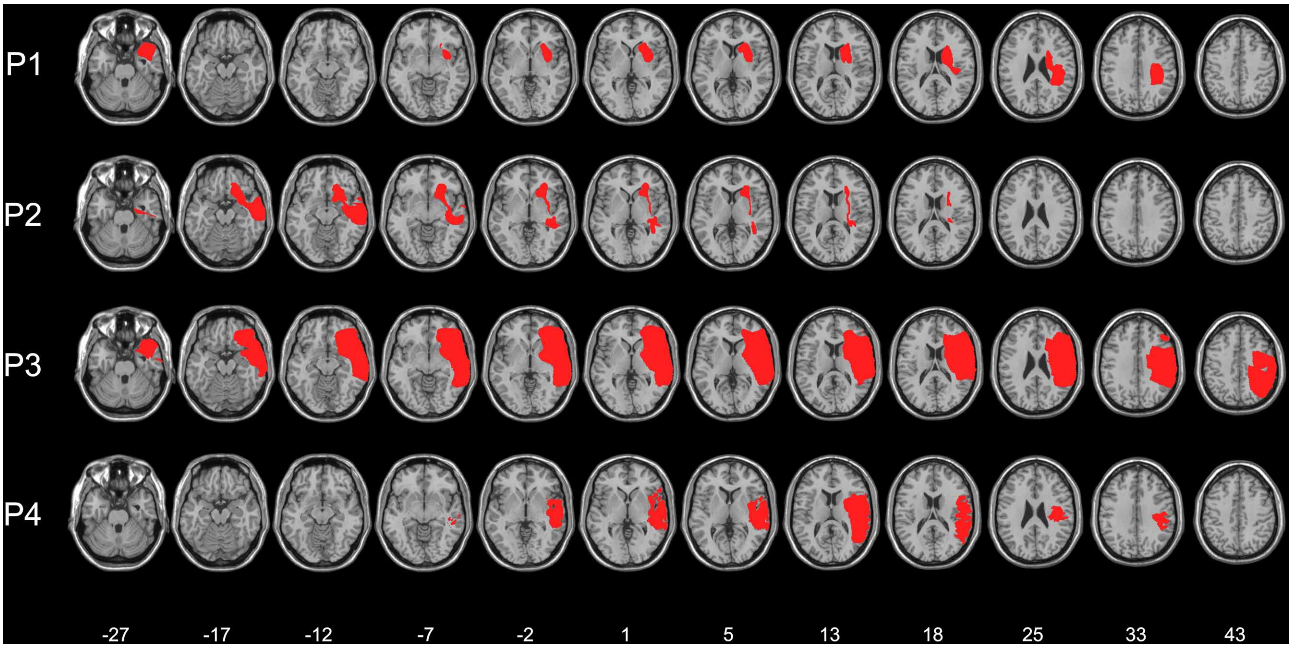


**FIGURE 1 | Lesion maps of the four right-brain-damaged patients (see text for details).** Each individual lesion was superimposed onto a standard brain format conforming to stereotactic space. Montreal Neurological Institute (MNI) Z-coordinates of each transverse section are shown.

together with other distractor letters. Neurologically unimpaired participants made a mean of 0.13 (0.12%, *SD* ± 0.45, range 0–4) omission errors out of 104 targets, with the maximum difference between omissions on the two sides of the sheet being two targets (Vallar et al., 1994).

3. *Bell cancellation* (Gauthier et al., 1989). The score was the number of "bell" targets crossed out by each participant (18 on the left-hand side and 17 on the right-hand side of the sheet). Neurologically unimpaired participants made a mean of 0.47 (1.3%, SD ± 0.83, range 0–4) omission errors out of 35 targets, with the maximum difference between omissions on the two sides of the sheet being four targets (Vallar et al., 1994).
4. *Line bisection*. The patients' task was to mark with a pencil the midpoint of six horizontal black lines (two 10 cm, two 15 cm, and two 25 cm in length, all 2 mm in width), presented in a random fixed order. Each line was printed in the center of an A4 sheet, aligned with the mid-sagittal plane of the participant's body. The length of the left-hand side of the line (i.e., from the left end of the line to the subject's mark) was measured to the nearest mm. That measurement was converted to a standardized score (percent deviation): measured left half minus objective half/objective half × 100 (Rode et al., 2006). This transformation yields positive numbers for marks placed to the right of the physical center, and negative numbers for marks placed to the left of it. The mean percent deviation score of 65 neurologically unimpaired participants, matched for age (mean 72.2, SD ± 5.16, range 65–83), and years of education (mean 9.5, SD ± 4.48, range 5–18), was 1.21% (SD ± 3.48, range −16.2 to +6.2%; Fortis et al., 2010).
5. *Five-element complex drawing* (Gainotti et al., 1972). The patients' task was to copy a complex five-element figure comprising, from left to right, two trees, a house, and two pine trees. Each element was scored 2 (flawless copy), 1.5 (partial omission of the left-hand side of an element), 1 (complete omission of the left-hand side of an element), 0.5 (complete omission of the left-hand side of an element, together with partial omission of the right-hand side of the same element), or 0 (no drawing, or no recognizable element). The horizontal ground line was not considered for scoring. The total score ranged from 0 to 10. The mean score of 148 neurologically unimpaired participants (mean age = 61.89, SD ± 11.95, range 40–89) was 9.89 (SD ± 0.23, range 9.5–10). Accordingly, a score lower than 9.5 indicated a defective performance (Mancini et al., 2011).
6. *Daisy drawing*. The patients' task was to copy a line drawing of a daisy. Scores ranged from 0 to 2 and were calculated as follows: 2 (flawless copy), 1.5 (partial omission of the left-hand side of the daisy), 1 (complete omission of the left-hand side of the daisy), 0.5 (complete omission of the left-hand side of the daisy, and partial omission of the right-hand side of the daisy), 0 (no drawing, or no recognizable element). The mean omission score of 148 neurologically unimpaired participants (mean age = 61.89, SD ± 11.95, range 40–89) was 1.99 (SD ± 0.12, range 1–2). Accordingly, the presence of a partial or complete omission of the left-hand side of the daisy (score lower than 1.5) was considered as indicative of left USN (Mancini et al., 2011).
7. *Clock drawing from memory*. The patients' task was to draw from memory the hours of a clock in a circular quadrant (diameter 12 cm), printed on an A4 sheet. Scores ranged from 0 to 12 and were calculated as follows: 1 (for each element in the correct position), 0 (for each omission or translocation

of an element from one side to the other; elements "12" and "6" were scored as translocated when displaced in the right- or left-hand side quadrants). The mean score of 148 neurologically unimpaired participants (mean age = 61.89, SD ± 11.95, range 40–89) was 11.55 (SD ± 1.17, range 0–6). Accordingly, a score lower than 9 indicated a defective performance (Mancini et al., 2011). Furthermore, neurologically unimpaired participants made no translocations.

8. *Personal neglect* (Bisiach et al., 1986). The patients' task was to reach the contralesional hand with the ipsilesional hand (score range: 3 = maximum deficit, 0 = unimpaired performance). Two additional tests were also used: the Fluff test (Cocchini et al., 2001) in patients #1 and #2, and an extension of the personal neglect test (Bisiach et al., 1986; Fortis et al., 2010) in patients #3 and #4. In the Fluff test, the patients' task was to remove, with the right ipsilesional arm, 24 circle targets attached to the patients' clothes with velcro strap. The targets were located on the right-hand side (nine: three on the torso, three on the thigh, and three on leg) and on the left-hand side (15: three on the arm, three on the forearm, three on the torso, three on the thigh, and three on the leg) of the participants' body with respect to the midline. The number of collected items on both sides was scored (range 0–15 on the left, 0–9 on the right side of the body), for a total maximum score of 24. A score lower than 13 on the left-hand side of the body indicates defective performance (Cocchini et al., 2001). In the extension of the personal neglect test (Bisiach et al., 1986; Fortis et al., 2010), the patients' task was to reach six left-sided body parts (ear, shoulder, elbow, wrist, waist, knee), using their right hand. Each response was scored 0 (no movement), 1 (search without reaching), 2 (reaching with hesitation and search), or 3 (immediate reaching), with a 0–18 score range. Ten control participants made no errors (Fortis et al., 2010).

### Tactile perception

The patients' ability to report single and double somatosensory stimuli was assessed by a computer-driven test (E-Prime, www.eprime2.eu). This consisted of 60 stimuli, with 20 tactile stimuli being delivered to the left hand, 20 to the right hand, and 20 bilaterally, in a random fixed order. Tactile stimuli were delivered using 12 V solenoids (www.heijo.com), driving a metal rod with a blunt conical tip that contacted the top segment of the index finger for 200 ms. Participants fixated a cross drawn on a paper sheet placed on the table where they rested their left arm; the fixation cross was aligned with the mid-sagittal plane of the participants' body, at a distance of about 50 cm. Participants received instructions to report verbally the occurrence and side of each delivered tactile stimulus (i.e., left-sided, right-sided, or bilateral). Patients were considered to show left-sided extinction when over 80% of unilateral left-sided tactile stimuli were reported correctly, and the left-sided stimulus of a bilateral stimulation was not reported in more than 30% of trials. The patients' performance is shown in **Table 3**. Three out of four patients showed left tactile extinction, while patient #4 missed 85% of the unilateral left-sided stimuli. Errors on bilateral trials always (100%) consisted of left-sided omissions. All control participants performed at ceiling with both unilateral and bilateral stimuli. It is noteworthy that the computerized procedure used here to assess extinction was more sensitive than the standard manual confrontation task. In particular, patient #2, who exhibited no deficit of tactile perception at the standard neurological examination, showed 100% extinction at the computerized test.

**Table 3 | Percent correct responses ("right-sided", "left-sided", or "bilateral") to computerized tactile stimuli.**

| Stimulation | Right-sided | Left-sided | Bilateral |
|---|---|---|---|
| Patient 1 | 90% | 95% | 10% |
| Patient 2 | 100% | 85% | 0% |
| Patient 3 | 100% | 85% | 0% |
| Patient 4 | 85% | 15% | 0% |
| Control group (average) | 100% | 100% | 100% |

### Experimental study

A speeded tactile detection task was administered, consisting of eight experimental blocks, each including 40 trials. Tactile stimuli were delivered to the participants' left index finger in 30 trials per block. The remaining 10 were "catch trials" in which no stimulation was given. Tactile stimuli were delivered using a 12 V solenoid (see above), and consisted of single taps lasting for 200 ms. In alternating blocks, the participants' left hand was placed either in the left ("homonymous") contralesional hemi-space, or in the right ("heteronymous") ipsilesional hemi-space, with the vision of the left hand being either available or prevented. The right hand was always held along the body and hidden from view (see **Figure 2**). Participants performed four experimental conditions: "homonymous-seen", "homonymous-unseen", "heteronymous-seen", and "heteronymous-unseen". Two blocks were performed for each condition in an ABCDDCBA order ("homonymous-seen", "homonymous-unseen", "heteronymous-seen", and "heteronymous-unseen", then the reverse) for half of the participants, and the reversed order for the other half of the participants. A wooden box (70 × 35 × 10 cm) covered the participant's hands in the two "unseen" conditions. A central, squared aperture (side 15 cm) in the box allowed participants to see the fixation cross (see above). Participants were instructed to fixate the cross throughout each block, and make a vocal response ("one") as quickly as possible whenever a tactile stimulus was detected. Vocal reaction times (RTs) were recorded by a voice key. Participants were allowed 2000 ms to respond after the stimulus presentation. Then the experimenter entered the participants' response ("1" when participants said "one," and "0" for no response), and pressed a key on the computer keyboard for the next trial after checking for fixation, and ensuring that the participant was ready to proceed. Due to his low accuracy in the detection task, patient #4 completed two sessions of eight blocks each (i.e., 16 blocks in total), to provide enough trials for RTs analysis.

### Statistical analysis

A repeated-measures ANOVA was performed in patients and control participants on the mean vocal RTs to tactile stimuli delivered to the left hand, with Hemi-space (two levels: "homonymous"

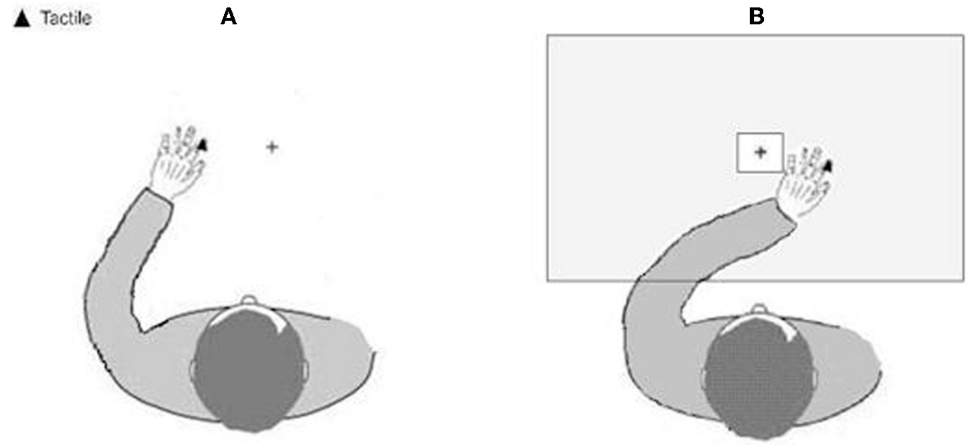


**FIGURE 2 | Schematic representation of the experimental setup showing the position of the left hand. (A)** in the left-hand side of space (homonymous), and **(B)** in the right-hand side of space (heteronymous). Tactile stimuli were applied to the tip of the participants' left index finger.

vs. "heteronymous") and Vision (two levels: "seen" vs. "unseen") as within-subjects factors, and Group (two levels: "patients" vs. "controls") as a between-subjects factor. Follow-up comparisons (*t*-tests and ANOVAs) were performed to explore significant two-way and three-way interactions.

## RESULTS

Patients #1, #2, and #3 and control participants missed on average less than 1% of tactile stimuli (range 0–2.2%). Patient #4 missed 44% of the stimuli in the "heteronymous-seen" condition, 46% in the "heteronymous-unseen" condition, 65% in the "homonymous-seen" condition, and 77% in the "homonymous-unseen" condition. The average false alarm rate for all participants (patients and controls) was 1.2% (range 0.3–2.4%). For each participant, trials in which the RTs exceeded ± 3 SD from the participant's average RTs were discarded. This procedure led to the removal of 2.3% of the trials overall. As shown in **Figure 3**, all patients were faster at responding to tactile stimuli in the "heteronymous" compared to the "homonymous" conditions. Moreover, all patients responded faster in the "heteronymous-seen" compared to "heteronymous-unseen" trials, while three out of four patients were slower in the "homonymous-seen" compared to the "homonymous-unseen" trials. On average, control participants were faster to respond to tactile stimuli under "homonymous" conditions, and showed a small advantage from seeing their left hand only in the "heteronymous" trials.

A repeated-measures ANOVA performed in patients and control participants on the mean vocal RTs to tactile stimuli delivered to the left hand revealed no main effect of Group [$F_{(1,\ 10)} = 2.45$, $p = 0.24$], indicating that, overall, patients' RTs were not significantly different from those of age-matched control participants. A main effect of Hemi-space was found [$F_{(1,\ 10)} = 5.56$, $p = 0.043$, $\eta^2 = 0.46$], with faster RTs to tactile stimuli on "heteronymous" ($M = 481$, $SD = \pm 168$ ms) than on "homonymous" ($M = 513$ ms, $SD = \pm 182$ ms) trials overall. The main effect of Vision [$F_{(1,\ 10)} = 8.17$, $p = 0.022$, $\eta^2 = 0.57$] was significant, indicating that participants were faster at responding to tactile stimuli when their hand was visible ($M = 486$, SD = $\pm 187$ vs. $M = 509$, SD = $\pm 200$ ms). The Group by Hemi-space interaction was significant [$F_{(1,\ 10)} = 31.91$, $p = 0.001$, $\eta^2 = 0.76$], indicating that the response latencies in the patients were shorter for the "heteronymous" ($M = 489$, SD = $\pm 202$ ms) than for the "homonymous" ($M = 585$, SD = $\pm 209$ ms) trials, while control participants showed a reversed pattern ($M = 474$, SD = $\pm 88$ ms for "heteronymous" vs. 431, SD = $\pm 76$ ms for "homonymous" trials).

Follow-up ANOVAs were performed separately for the patients and the controls group, with the factors Hemi-space and Vision. These analyses revealed the presence of a significant main effect of Hemi-space on RTs in both groups [$F_{(1,\ 3)} = 16.43$, $p = 0.013$, $\eta^2 = 0.62$ in the patients; and $F_{(1,\ 7)} = 11.27$, $p = 0.017$, $\eta^2 = 0.60$ in the controls]. The opposite effects shown by the two groups (see above) confirm that control participants were significantly faster in the "homonymous" compared to the "heteronymous" trials, consistent with the literature (e.g., Yamamoto and Kitazawa, 2001), while the overall faster response in the "heteronymous" than "homonymous" trials found in the previous analysis was due to the large advantage of the patients in the former condition. A Hemi-space by Vision interaction was found in the patients' ANOVA [$F_{(1,\ 3)} = 6.13$, $p = 0.04$, $\eta^2 = 0.51$], but not in the controls' ANOVA [$F_{(1,\ 7)} = 2.33$, $p = 0.27$]. Post-hoc t-tests in the patients, revealed significantly faster responses for the "heteronymous-seen" compared to the "heteronymous-unseen" trials [$t_{(3)} = 4.78$, $p = 0.007$], whereas the difference between "homonymous-seen" and "homonymous-unseen" trials was not significant [$t_{(3)} = 1.78$, $p = 0.23$][1].

[1]Because of the more severe symptoms and the more acute stage of the illness of patient #4 compared to the other patients (see **Tables 1** and **2**), an additional ANOVA was conducted in the patients, with the factors Hemi-space and Vision, without including patient #4. A similar pattern of results was found in this analysis, with a main effect of Hemi-space [$F(1, 2) = 18.64$, $p = 0.048$] and a Hemi-space by Vision interaction [$F(1, 2) = 19.35$, $p = 0.046$].

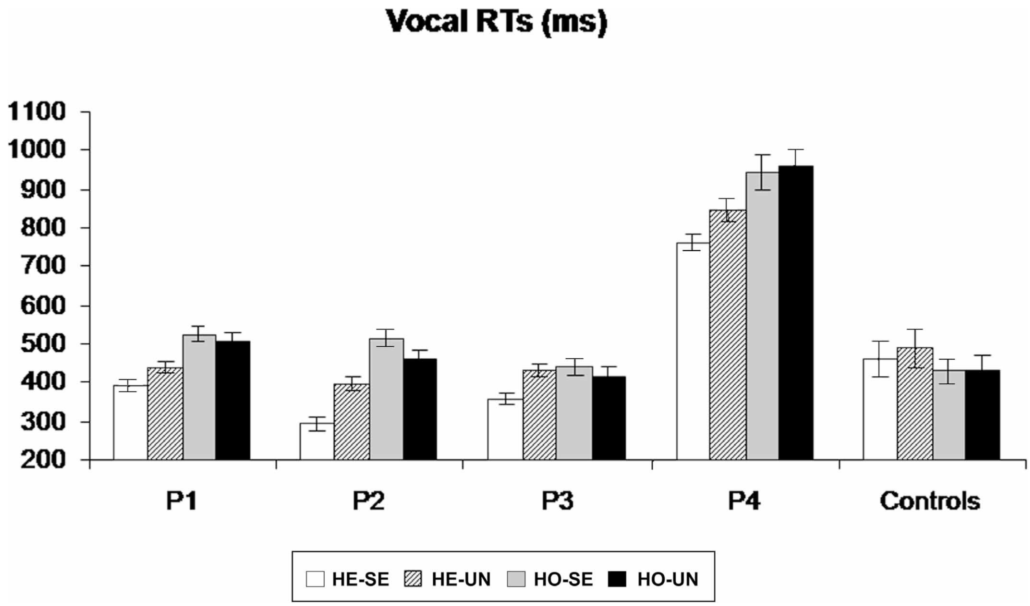


**FIGURE 3 | Mean (and standard errors) vocal RTs to left-sided tactile stimuli for patients P1–P4, and for the control group, in the four experimental conditions, obtained by manipulating the hemi-space where the hand was placed (Homonymous/Heteronymous: HO/HE), and the vision of the left, stimulated hand (Seen/Unseen: SE/UN).**

## EXPERIMENT 2: SOMATOSENSORY EVENT-RELATED POTENTIALS

### METHODS

#### *Participants*

Somatosensory event-related brain potentials (ERPs) were recorded from patient #1 (see **Table 1**), and from two neurologically unimpaired age-matched male controls (Control #1, 78 year-old; Control #2, 80 year-old), who did not take part in Experiment 1. All participants gave written informed consent.

#### *Experimental procedure*

The general experimental set-up and procedures were similar to those of Experiment 1, with the following differences. First, vision of the left hand was available in all trials. Thus, participants performed the task under two experimental conditions, i.e., with the left hand placed in the left ("homonymous") vs. the right ("heteronymous") hemi-space (see Experiment 1), in alternating blocks. Second, in order to increase the number of critical left stimuli for the purpose of statistical analysis, a greater number of trials was given. Patient #1 was tested in two sessions, separated by 8 days. The two control participants completed one single experimental session. Each session consisted of eight blocks with 50 trials per block, including 40 left-sided touches and 10 "catch trials" (absent stimulation).

#### *EEG recording and data analysis*

EEG was recorded with Ag-AgCl electrodes from 28 scalp electrodes (midline electrodes: Cz, Pz, POz, Oz; electrodes over the right hemisphere: Fp2, F4, F8, C4, T8, TP8, Cp4, P4, P8, PO4, PO8, O2, and the homologous electrode sites over the left hemisphere). Horizontal electrooculogram (HEOG) was recorded bipolarly from the outer canthi of both eyes. Electrode impedance was kept below 5 kΩ. EEG and EOG were sampled with a 500 Hz digitization rate. EEG and EOG were epoched off-line into 450 ms periods, starting 100 ms before and ending 350 ms after the onset of tactile stimulation. Trials with eye blinks and movement-related artefacts (EEG waveforms exceeding $\pm 80\,\mu V$ relative to baseline), measured at any recording sites within 350 ms after stimulus onset, were excluded from analysis. ERP waveforms were averaged relative to a 100 ms pre-stimulus baseline, separately for "homonymous" and "heteronymous" trials. The total number of trials contributing to the resulting average waveforms (collapsed across the two sessions) for patient #1 was 201 for "homonymous" and 189 for "heteronymous" trials. For statistical analysis each of the two sessions of the patient was further subdivided into two sub-sessions for a total of four sub-sessions for each experimental condition ("homonymous" vs. "heteronymous"). The mean number of trials contributing to the average ERPs for each sub-session was 62.75 (range: 54–78; for a similar statistical method see Marzi et al., 2000; Eimer et al., 2002). For the controls' data, each participant's session was subdivided into two sub-sessions, producing a total of four sub-sessions for each of the two left hand positions for the two participants. The mean amplitudes of early- and mid-latency somatosensory ERP components (P70[2] and N140) were computed within analysis windows centered on the peak latency of these components. As the N140 component was somewhat delayed in both control participants compared to the N140 component observed in patient #1 (see **Figures 4** and **5A,B**), two distinct time windows were computed for this component centered on the peak of the N140

[2]The P70 component may correspond to the P45 component observed in young neurologically unimpaired participants (e.g., Allison et al., 1992; Eimer and Forster, 2003a), here slightly delayed as in Eimer et al. (2002).

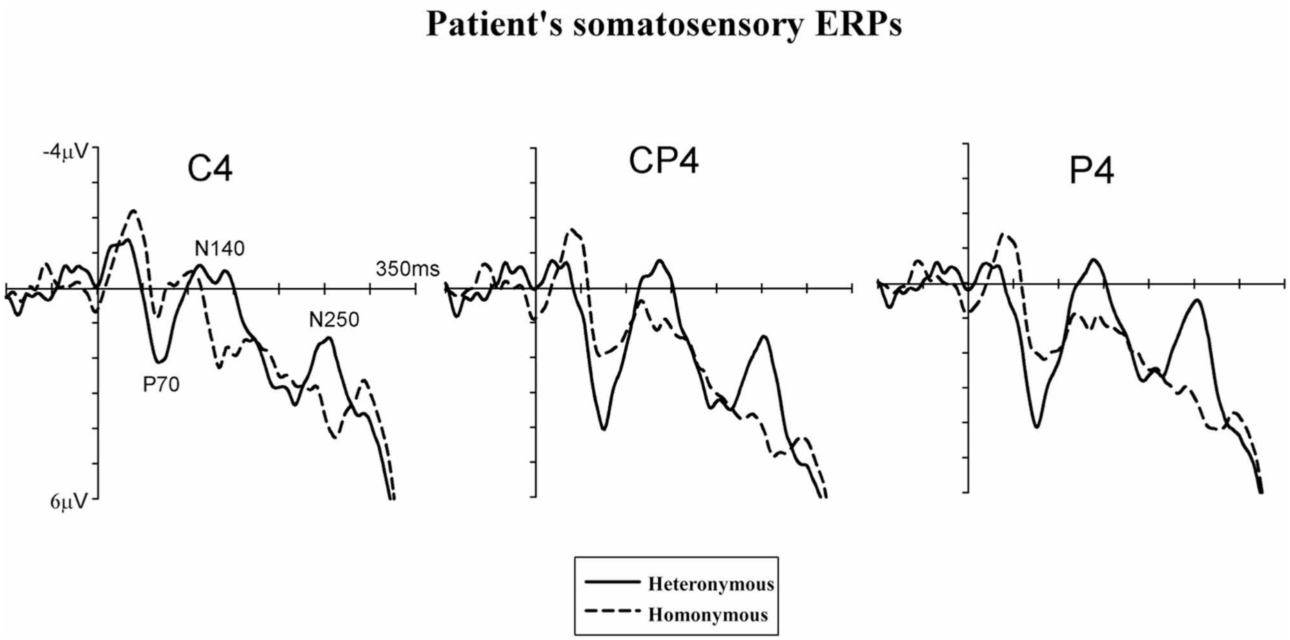


**FIGURE 4 | Somatosensory ERP waveforms of patient #1.** Tactile stimuli were delivered to the left hand while this hand was placed in the right, heteronymous hemi-space (*solid lines*) and in the left, homonymous hemi-space (*dashed lines*). ERPs are shown in the 350-ms interval following stimulus onset for centro-parietal electrodes (C4, CP4, and P4) contralateral to the site of the tactile stimulation (i.e., over the right, damaged, hemisphere).

in the patient (N140p) and on the peak of the N140 in the controls (N140c). In addition, in order to investigate longer-latency effects of Hemi-space, the mean amplitudes were also computed within the analysis window centered on the peak latency of the patient's N250 component (N250p). This component was absent in the ERP waveforms of both control participants, who showed a "sustained negativity" beyond 220 ms post-stimulus. Thus, mean amplitude values were computed for the following post-stimulus latency windows in all participants: 55–90 ms post-stimulus (P70), 105–155 ms post-stimulus (N140p), 150–195 ms post-stimulus (N140c), 235–270 ms post-stimulus (N250p), and 220–350 ms post-stimulus. Analyses of ERP data were restricted to centro-parietal electrodes contralateral to the side of stimulation where somatosensory ERP components are maximal (Goff et al., 1978). Separate repeated-measures ANOVAs were conducted on mean amplitudes for the P70, N140p, N140c, and N250p components, and for the 220–350 ms post-stimulus measurement window with the factors Hemi-space (two levels: "homonymous" vs. "heteronymous") and Electrode site (three levels: C4 vs. CP4 vs. P4) as within-subjects factors, and Group (two levels: patient's blocks vs. controls' blocks) as a between-subjects factor.

## RESULTS

**Figure 4** displays somatosensory ERPs recorded from patient #1 in response to left tactile stimuli delivered when the left (contralesional) hand was placed in the right, "heteronymous" (*solid line*) and the left, "homonymous" (*dashed line*) hemi-space. As can be seen from these waveforms, left tactile stimuli elicited a positive-going deflection peaking at about 70 ms after onset of the stimulus (i.e., somatosensory P70 component) followed by two negative deflections with a latency of about 140 ms (i.e., overlapping with the somatosensory N140 component), and 250 ms (i.e., overlapping with the somatosensory N250 component). As shown in **Figure 4**, tactile stimuli elicited enhanced P70, N140, and N250 amplitudes when the left hand was placed in the right hemi-space ("heteronymous" trials), compared to when the hand was held in the left hemi-space ("homonymous" trials). Similarly to the somatosensory ERPs recorded from one right-brain-damaged patient in a previous study (Eimer et al., 2002), somatosensory N80 and P100 components that are typically evoked by tactile stimuli in neurologically unimpaired participants (e.g., Michie et al., 1987; Taylor-Clarke et al., 2002; Eimer and Forster, 2003a) were not apparent in the patient's waveforms. Conversely, these components were present in the ERP waveforms of both control participants, following the P70 component (see **Figures 5A,B**). Importantly, **Figure 5** suggests that in control participants none of the short- and mid-latency somatosensory components was modulated by the spatial position of the stimulated hand. In particular, the observation of the ERP responses suggests that in control #1 these components were not modulated by the hemi-space within which the hand was placed, while in control #2 the amplitude of the somatosensory N140 was, if anything, slightly larger for tactile stimuli delivered in the "homonymous" compared to "heteronymous" condition. This pattern is the reverse of that shown by the patient. In addition, at later time intervals a sustained negativity was evident in the waveforms of the control participants for tactile stimuli delivered

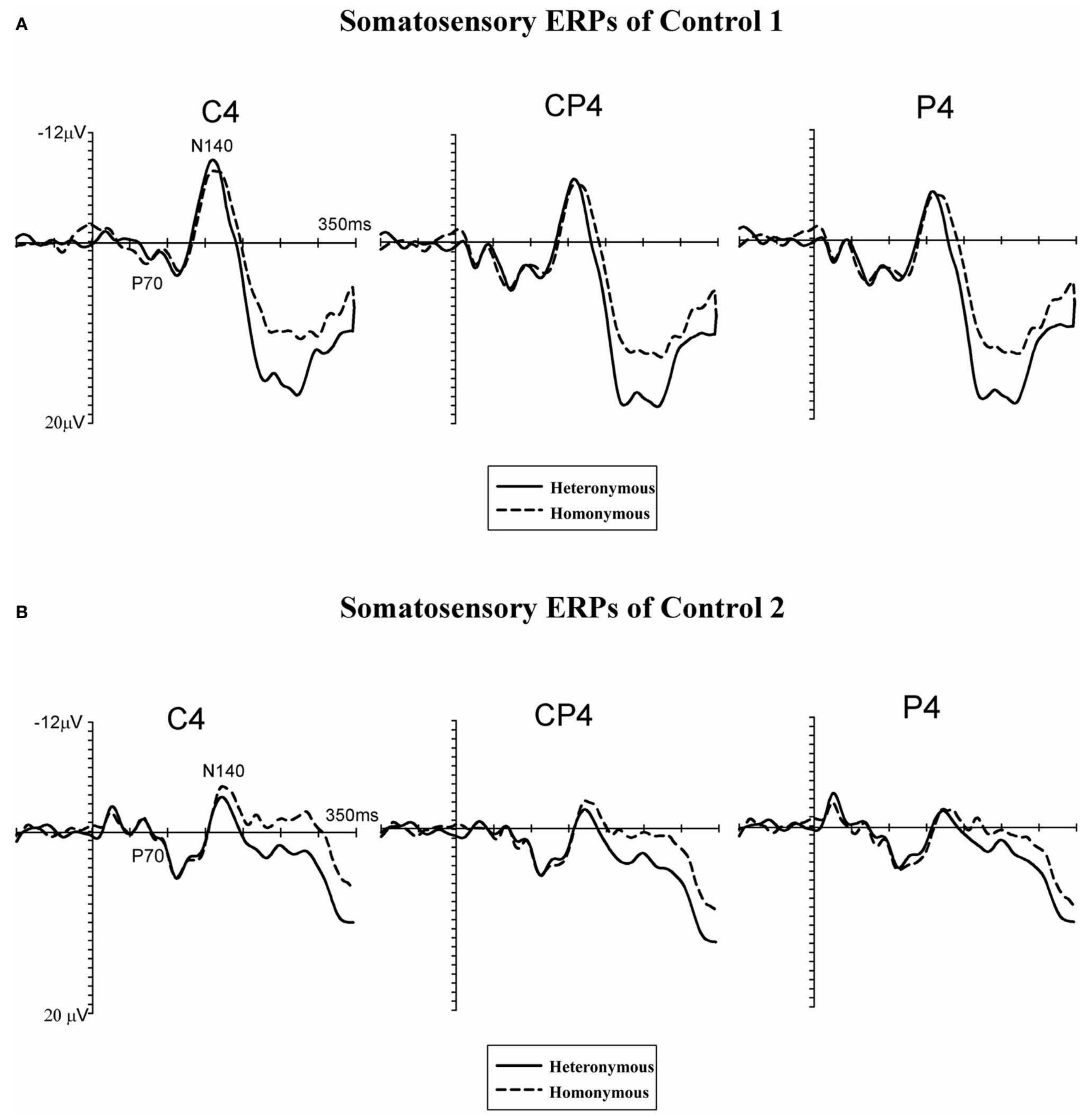


**FIGURE 5 | Grand-averaged somatosensory ERP waveforms of two neurologically unimpaired participants (A,B).** Tactile stimuli were delivered to the left hand while this hand was placed in the right, heteronymous hemi-space (*solid lines*) and in the left, homonymous hemi-space (*dashed lines*). ERPs are shown in the 350-ms interval following stimulus onset for centro-parietal electrodes (C4, CP4, and P4) contralateral to the site of the tactile stimulation (i.e., over the right hemisphere).

when the left hand was placed in the "homonymous" compared to the "heteronymous" hemi-space, revealing a pattern opposite to that that shown in the patient's waveforms at a similar time interval.

Repeated-measures ANOVAs, performed on the somatosensory ERPs of the patient's and the controls' blocks, revealed a main effect of Group in the P70 [$F_{(1, 6)} = 6.12$, $p = 0.041$, $\eta^2 = 0.47$] and N140c [$F_{(1, 6)} = 36.23$, $p = 0.001$, $\eta^2 = 0.80$] time windows, but not in the N140p [$F_{(1, 6)} = 1.61$, $p = 0.23$], N250 [$F_{(1, 6)} = 1.97$, $p = 0.19$], and 220–350 ms [$F_{(1, 6)} = 1.49$, $p = 0.26$] windows, indicating that the amplitude of the ERPs in the P70 and N140c time intervals was greater in the blocks recorded from control participants compared to those recorded from the patient. The main effects of Hemi-space and Electrode side were not significant in any of the time intervals tested (all $F$s $< 1$). The Group by Hemi-space interaction was significant in all time intervals tested except for the N140c interval [P70: $F_{(1,\ 6)} = 7.15$, $p = 0.038$, $\eta^2 = 0.52$; N140p: $F_{(1,\ 6)} = 11.27$, $p = 0.019$, $\eta^2 = 0.61$; N140c: $F_{(1,\ 6)} = 3.31$, $p = 0.32$, $\eta^2 = 0.41$; N250p: $F_{(1,\ 6)} = 18.08$, $p = 0.006$, $\eta^2 = 0.73$; 220–350 ms interval: $F_{(1,\ 6)} = 10.87$, $p = 0.021$, $\eta^2 = 0.69$]. The two-way interaction between Hemi-space and Electrode site and the three-way interaction between Group, Hemi-space, and Electrode site were not significant for any of the time windows tested (all $F$s $< 1$).

Follow-up ANOVAs were performed separately in the patient's and the controls' blocks for each of the time intervals to test the Group by Hemi-space interaction, with the factors Hemi-space and Electrode site. In the patient's blocks, a nearly significant effect of Hemi-space was found in the P70 [$F_{(1,\ 3)} = 5.85$, $p = 0.052$, $\eta^2 = 0.43$]. The effect was significant in the N140p [$F_{(1,\ 3)} = 6.70$, $p = 0.041$, $\eta^2 = 0.50$], and in the N250p [$F_{(1,\ 3)} = 9.25$, $p = 0.024$, $\eta^2 = 0.60$] time windows, reflecting greater amplitudes of ERPs elicited by tactile stimuli in "heteronymous" compared to "homonymous" trials. In the latency range of the N140c component, and in the subsequent 220–350 ms post-stimulus interval, there was no main effect of Hemi-space [N140c: $F_{(1,\ 3)} = 2.18$, $p = 0.16$; 220–350 ms interval: $F_{(1,\ 3)} = 2.98$, $p = 0.13$]. There was a significant main effect of Electrode site in the P70 time window [$F_{(1,\ 3)} = 6.29$, $p = 0.042$, $\eta^2 = 0.53$], but not in any of the other intervals tested (all $F$s $< 1$), indicating that the P70 component was overall smaller at the C4 electrode site compared to the other two electrode sites. The two-way interaction between Hemi-space and Electrode site was not significant for any of the time windows tested (all $F$s $< 1$). In the control participants, the same analyses did not show any main effect of Hemi-space for short- and mid-latency ERP components [P70: $F_{(1,\ 3)} = 0.29$, $p = 0.43$; N140p: $F_{(1,\ 3)} = 0.78$, $p = 0.33$; N140c: $F_{(1,\ 3)} = 1.66$, $p = 0.23$], indicating that no reliable differences in amplitudes were present at these latencies between ERPs elicited by tactile stimuli delivered when the left hand was placed in the "homonymous" vs. the "heteronymous" hemi-space. Similarly, in the latency range of the patient's N250 component (i.e., N250p) there was no main effect of Hemi-space [$F_{(1,\ 3)} = 1.08$, $p = 0.28$]. By contrast, a sustained negativity was elicited beyond 220 ms (i.e., 220–350 ms post-stimulus) by tactile stimuli in "homonymous" compared to "heteronymous" trials, resulting in a main effect of Hemi-space [$F_{(1,\ 3)} = 6.10$, $p = 0.042$, $\eta^2 = 0.52$]. The main effect of Electrode site and the two-way interaction between Hemi-space and Electrode site were not significant for any of the time windows tested (all $F$s $< 1$).

## DISCUSSION

All four right-brain-damaged patients were faster at responding to tactile stimuli delivered to their left hand when this hand was held in the right ipsilesional hemi-space. This finding confirms and extends previous observations showing that right-brain-damaged patients are more *accurate* in detecting left-sided tactile stimuli (under conditions of single and double stimulations) when their hands are crossed over the midline, so that the left hand is placed in the right ("heteronymous") side of space, and vice-versa for the right hand (Smania and Aglioti, 1995; Aglioti et al., 1999; Moro et al., 2004). These results also add to previous evidence suggesting a crucial role for higher-order spatial and attentional factors, not only for sensory factors, in accounting for the somatosensory deficits exhibited by patients with tactile extinction and neglect (Vallar et al., 1990, 1997, 1993; Moscovitch and Behrmann, 1994; Vaishnavi et al., 2001; Gallace and Spence, 2007; Vallar, 2007). Processing of tactile stimuli by right-brain-damaged patients with extinction to double simultaneous stimulation may be slower for single unilateral stimulation, with increased latencies for stimuli presented in the left-hand side of space, compared to the right-hand side, under anatomical (uncrossed) hands posture (Eimer et al., 2002). A novel finding of the present study is that placing the left hand in the right-hand side of space yields a *temporal advantage* in the processing of tactile stimuli, compared to conditions in which that hand is held in the left-hand side of space. This pattern of results is in line with the view that conscious sensation of touch involves egocentric reference frames (Vallar, 1997, 1999), and tallies with a model proposed by Kitazawa (2002; based on data from neurologically unimpaired participants), which maintains that conscious sensation of touch is localized in space, namely at the location where the stimulated body part lies (in egocentric reference frames) before it is localized to the skin (in somatotopic reference frames; see also Azañón and Soto-Faraco, 2008).

Furthermore, we found that the temporal advantage given by placing the hand in the heteronymous side of space is significantly greater when patients are able to see their stimulated hand. In previous studies that manipulated hand position in order to investigate the role of somatosensory and spatial reference frames in tactile processing, right-brain-damaged patients (and so control participants) were blindfolded, as in a standard neurological examination of tactile sensation (Ropper and Samuels, 2009). Accordingly, both visuo-spatial information and vision of the hands were absent. Since in the present study visuo-spatial information was always available (that is, participants kept their eyes open throughout the experiment), our findings specifically suggest that seeing the left hand when placed in the right, ipsilesional side of space further facilitates processing of contralesional tactile stimuli in right-brain-damaged patients (see also Sambo et al., 2009). By contrast, vision of the left hand does not improve tactile detection when this hand lies in the left, "neglected" side of space. In fact, a perusal of the data from individual patients shows a decrease in performance (i.e., longer response latencies) in patients #1, #2, and #3 when vision is allowed and the left hand is held in the left hemi-space. Critically, while patient #1 presents with a left visual field defect, patient #2 has no left hemianopia, and patients #3 only shows visual extinction to double simultaneous stimulation. In right-brain-damaged-patients vision may further bias attentional resources toward the ipsilesional (right) side of space, reducing processing efficiency in the contralesional (left) side of space. The finding that USN symptoms may be more severe when vision is available, compared to conditions in which only tactile inputs are available (Gainotti, 2010; Mancini et al., 2011), is largely in line with these conclusions.

"Visual enhancement of touch," that is, the facilitation of tactile processing by viewing the body, is observed specifically in difficult spatial discrimination tasks, but not in easier non-spatial task, in healthy participants (Press et al., 2004). Press and colleagues suggest that vision of the body improves tactile perception by enhancing the spatial representation of the body surface, which, in turn, may improve the signal-to-noise ratio for tactile processing. While in neurologically unimpaired participants this mechanism would be beneficial only under difficult task conditions, involving spatial discrimination (Press et al., 2004; Cardini et al., 2012), in right-brain-damaged patients with somatosensory deficits viewing the body may help tactile detection, possibly by recruiting a higher proportion of neurons, or increasing synchrony of neural firing, in response to the stimulation (McLeod et al., 1998). Such mechanisms are similar to those that have been proposed to be involved in spatial attention. Crucially, in our study the advantage shown by right-brain-damaged patients under viewing conditions occurs specifically when the left hand is placed in the right hemi-space, thus suggesting that viewing the body could further boost the advantage of placing the hand in the non-neglected (attended) hemi-space. Recently, two studies have specifically investigated the reciprocal effects of vision of a body location and attention to that location, in healthy volunteers. These studies have shown that these two effects may interact in such a way that visual information about the body facilitates spatial attentional selection of tactile input (Sambo et al., 2009; Michael et al., 2012) by enhancing activity within the somatosensory cortex. Here we provide the first evidence in patients with spatio-attentional deficits that vision enhances tactile processing specifically when the hand is placed in the hemi-space toward which attentional biases are directed (i.e., the right hemi-space, in right-brain-damaged patients with USN and tactile extinction or somatosensory deficits). We propose that, when the left hand is placed in the homonymous left hemi-space, contralateral to the patients' lesion, the representation of this side of space, which is mainly supported by the right (damaged, in right-brain-damaged patients) hemisphere (Bisiach and Vallar, 2000; Mesulam, 2002), fails to be, or is weakly, activated. Conversely, when the left hand is placed in the heteronymous right side of space, the representation of this side of space, mainly supported by the left (intact) hemisphere, may be activated, resulting in a higher processing speed of tactile stimuli applied to the left hand. Such space-based representations are controlled by fronto-parietal networks, that are also involved in multisensory integration between inputs from different modalities (e.g., touch, vision, and proprioception), and in the control of spatial attention (Mesulam, 2002; Maravita et al., 2003; Silver and Kastner, 2009; Vallar and Maravita, 2009).

In contrast with the pattern found in right-brain-damaged patients, control participants exhibit a disadvantage when their left hand is placed in the heteronymous hemi-space: their responses are significantly slower when the left hand is placed in the right, compared to the left, side of space. In a similar vein, previous studies in neurologically unimpaired participants show a reduction in perceived intensity and electrophysiological responses to somatosensory stimuli (Gallace et al., 2011), as well as a decrease in performance in temporal discrimination judgments (Yamamoto and Kitazawa, 2001; Shore et al., 2002), under crossed hands posture. In addition, in the present study the effect of vision of the stimulated hand on tactile detection is marginal and not significant in neurologically unimpaired participants, possibly because we did not use a difficult spatial tactile discrimination task (see Press et al., 2004).

In line with the behavioral results obtained in the patients' group, in one right-brain-damaged patient (#1) placing the left hand in the heteronymous side of space modulates somatosensory processing, as reflected by the enhancement of early- (i.e., P70) and mid-latency ERP (i.e., N140) components, as well as of a longer-latency component (i.e., N250), for left tactile stimuli delivered when the left hand is placed in the right hemi-space, compared to the left, "neglected," side of space. According to intra-cranial recordings and MEG studies (Hari et al., 1984; Allison et al., 1992; Frot and Mauguière, 1999), somatosensory ERP components elicited within 100 ms, such as the P70, originate within SI, and the somatosensory N140 component originates in SII. The present results therefore suggest that holding the left hand in the "intact," right-hand side of space may enhance neural activity in the primary somatosensory regions, which, in turn, facilitates detection of tactile stimuli delivered to that hand. In sum, spatial and attentional factors related to the position of the hand affect sensory cortical responses in patient #1. Previous studies in young neurologically unimpaired participants have also shown that spatial attention enhances the amplitude of short-latency somatosensory ERP and MEG components, starting as early as 40–50 ms after stimulus onset (Michie et al., 1987; Mima et al., 1998; Eimer and Forster, 2003a; Schubert et al., 2008). Residual activity has been observed in the SI and SII regions of the somatosensory cortex of the right hemisphere in patients with tactile extinction, during unilateral left, as well as bilateral, tactile stimulation (see Eimer et al., 2002 for an ERP study; and Remy et al., 1999 for a PET study). Such a residual processing may be boosted by placing the left hand in the "intact" right-hand side of space, allowing a more effective conscious elaboration of the sensory stimulus.

The present finding that the spatial position of the hand can modulate neural responses in early somatosensory areas is also in line with an fMRI study in a right-brain-damaged patient with mild left USN and left tactile extinction. In this study (Valenza et al., 2004), neural activity in the primary and secondary somatosensory areas was decreased when the patient's right ipsilesional hand was placed in the left (contralesional) side of space, as compared to when the hand was held in the right ipsilesional side of space (i.e., a manipulation opposite to the one used in the present study). Interestingly, fMRI responses were reduced under bilateral as well as unilateral tactile stimulation of the right hand in a crossed position (i.e., in the left-hand side of space). Behaviorally, however, the detection of touches to the right hand in a crossed position was dramatically reduced only when a simultaneous stimulation of the right elbow (placed in the right-hand side of space) was given. At the neural level, the results from Valenza et al.'s study (2004) suggest that the spatial position of body parts can modulate the strength of activation of early somatosensory areas also in response to single tactile stimulations, similarly to the results of the present study.

In addition to the modulation of early ERP components, enhancement of the patient's ERPs to tactile stimuli when the left hand was placed in the right, compared to the left, hemi-space is also present at later time intervals (i.e., around 250 ms after onset of the tactile stimuli, corresponding to the somatosensory N250 component). Such long-latency modulations are likely to stem from regions within the premotor frontal-posterior parietal network which are thought to be involved in the control of spatial attention (Mesulam, 1981; Corbetta et al., 1993; Gitelman et al., 1999; Hopfinger et al., 2000) and the spatial representation of the body (Schwoebel and Coslett, 2005; Tsakiris et al., 2007). In agreement with this view, greater activations of the posterior parietal cortex and of the middle frontal gyri were reported in the abovementioned fMRI study (Valenza et al., 2004) when the patient's right hand was held in the ipsilesional side of space (uncrossed position), compared to when it was placed in the left, contralesional side of space (crossed position). The increased processing of bodily stimuli through the integration of somatosensory, proprioceptive, and visual inputs from the stimulated body part (Rorden et al., 1999; Maravita et al., 2003; Vallar and Maravita, 2009) may also contribute to improve the patient's performance when the contralesional hand is crossed over the midline, so that the somatosensory input from that hand is made spatially coincident with the vision of the hand in the ipsilesional, intact visual field.

Unlike in patient #1, early somatosensory components in age-matched controls are not modulated by the spatial position of the left hand. However, a difference between ERPs in response to tactile stimuli emerged at later stages of processing, with a sustained negativity starting from about 220 ms after stimulus onset for stimuli delivered when the left hand was placed in the left, compared to the right, hemi-space, opposite to the pattern found in the patient. In previous ERP studies performed in healthy participants a sustained negativity was elicited at corresponding latencies by tactile stimuli presented at attended, compared to unattended, locations, indicating facilitation of processing for attended stimuli (Michie et al., 1987; Eimer and Forster, 2003a,b; Forster and Eimer, 2005). Our finding that, in neurologically unimpaired participants, tactile stimuli delivered to the left hand in the "homonymous" trials elicit an enhanced sustained negativity, compared to the "heteronymous" trials, may indicate increased attention allocated to the left hand when this is held in the left hemi-space (i.e., when the somatotopic and the spatial frames of reference overlap), compared to when that hand is placed in the right, heteronymous side of space. This is in line with the evidence that, in healthy participants, crossing the hands over the midline disrupts tactile-spatial selection processes, possibly because of the conflict between anatomical and external, visually defined spatial reference frames for coding body locations (Eimer et al., 2001; Heed and Röder, 2010).

It is important to note some limitations of this study. First, we investigated a limited number of patients. Therefore, although the present results provide insights into the effect of postural displacement and visual control of limbs on tactile processing in right-brain-damaged patients with USN and tactile extinction or somatosensory deficits, additional studies are needed to further qualify such effects and to understand the possible applications of these manipulations to clinical practice, for both the assessment and the treatment of tactile extinction and somatosensory deficits. Second, in this study we manipulated the spatial position and vision of the left hand but not of the right hand. Previous studies have shown that placing the right hand (Smania and Aglioti, 1995; Aglioti et al., 1999; Bartolomeo et al., 2004) or the right knee (Bartolomeo et al., 2004) in the left side of space slightly impairs tactile detection. However, such impairment is relatively small, and only occurs for double, but not single, stimulation conditions. Therefore, we may predict that, using our paradigm where only single tactile stimuli are delivered, especially in order to obtain clearer ERP data, no or minor effects would be found when manipulating the position of the right hand. Finally, in this study the performance of right-brain-damaged patients with tactile extinction was compared with that of age-matched unimpaired participants, but not with that of right-brain-damaged patients without tactile extinction or left-brain-damaged patients. Although it would be interesting to assess the performance of these participants, it is worth noting that Aglioti et al. (1999) showed that, unlike right-brain-damaged with somatosensory deficits and tactile extinction, right-brain-damaged patients without tactile extinction, as well as left-brain-damaged patients, are more accurate in reporting tactile stimuli when their hands are in the homonymous compared to the heteronymous position, that is, they perform similarly to neurologically unimpaired participants.

In sum, and keeping the abovementioned limitations in mind, the present behavioral and ERP results show that in right-brain-damaged patients with left USN and tactile extinction or somatosensory deficits, moving the left hand to the ipsilesional right-hand side of space improves somatosensory processing, possibly allocating more attentional resources to the tactile stimuli. The effects start from the very early stages of stimulus processing (putatively, in SI and SII), as indexed by an enhancement of early- and mid-latency somatosensory components (P70, N140) when the left hand is held in the heteronymous, compared to the homonymous, hemi-space. These findings may have clinical applications, not only for assessment but also for training to help recovery. Indeed, placing the left hand in the right, ipsilesional side of space may help differentiate primary somatosensory deficits from tactile extinction or USN in patients with right brain damage (e.g., Aglioti et al., 1999; Maravita, 2008). Secondly, the rehabilitation of somatosensory USN (Vallar, 1998) may be aided both by training the contralesional (left) hand while it lies in the right side of space, where the effect of any tactile stimulation may be enhanced, and by viewing the hand.

## ACKNOWLEDGMENTS

The authors wish to thank Prof. Marcello Gallucci for his statistical advice, and Dr. Elena Olgiati for her help with the neuropsychological data of patient #4. This research was supported by a PRIN 2007 grant to Giuseppe Vallar and Angelo Maravita. The electrophysiological study was performed by equipment funded by a Grandi Attrezzature Grant 2005 of the University of Milano-Bicocca to Giuseppe Vallar.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 15 February 2012; accepted: 04 July 2012; published online: 25 July 2012.*
*Citation: Sambo CF, Vallar G, Fortis P, Ronchi R, Posteraro L, Forster B and Maravita A (2012) Visual and spatial modulation of tactile extinction: behavioural and electrophysiological evidence. Front. Hum. Neurosci.* ***6****:217. doi: 10.3389/fnhum.2012.00217*