Dissociable components of spatial neglect associated with frontal and parietal lesions

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ABSTRACT

Spatial neglect is a complex neuropsychological disorder, in which patients fail to detect and respond to contralesional stimuli. Recent studies suggest that these symptoms may reflect a combination of different component deficits, associated with different lesion substrates. Thus, damage to right lateral prefrontal and inferior parietal regions produce different degrees of left neglect on cancellation and line bisection tasks, respectively. Here we tested for dissociable behaviors across two tasks designed to assess distinct cognitive processes possibly mediating such components, in 14 patients with right focal lesion in either the frontal or parietal lobe. In the "distractor filtering" task, patients had to respond to a visual target presented centrally, with or without a lateralized distractor. Only frontal-lesioned patients showed a marked slowing of reaction times when a central target appeared with a simultaneous right distractor (compared to center and left distractor). In the "spatial coding" task, patients had to detect a target among successive visual stimuli presented horizontally with three sequence conditions (regular/predictive or irregular/non-predictive). Only parietal-lesioned patients were unable to benefit from the predictability of the target position, with similar reaction times across all sequence conditions. By contrast, frontal patients showed faster reaction times on trials with a regular succession of stimuli (compared to random order). Taken together, these results suggest that frontal damage may contribute to left inattention by disrupting top-down control and resistance to distractors on the ipsilesional side, whereas parietal damage may disrupt the maintenance of stable locations in space across gaze shifts or time. This further supports the notion that left neglect may arise as a combined breakdown or impaired connectivity between frontal and parietal mechanisms involved (respectively) in the selective control and memory storage components of spatial attention.

1. Introduction

Spatial neglect is defined as a failure to perceive, orient to, and report stimuli appearing on the side opposite to a unilateral brain lesion (Heilman and Valenstein, 1979). These symptoms are imputed to disturbances in mechanisms controlling attention and space representations, but the exact underlying cognitive processes and neural circuits remain incompletely resolved (Bartolomeo et al., 2012; Karnath, 1988; Vuilleumier, 2013).

On the one hand, neglect may arise following damage to several different brain regions, most often involving the right inferior parietal cortex (Mort et al., 2003), but also frontal (Damasio et al., 1980) or even temporal cortex (Karnath et al., 2001), as well as subcortical areas in basal ganglia and thalamus (Karnath et al., 2002) or white-matter tracts interconnecting these regions (Doricchi et al., 2008). This anatomical diversity points to the key role of distributed networks mediating spatial attention and awareness, which are typically damaged in neglect patients (Bartolomeo et al., 2012; Corbetta et al., 2005a; Corbetta et al., 2005b; Mesulam, 1999). On the other hand, several dissociations have been observed between neglect symptoms that may be present in some tasks but not others in some patients (Halligan and Marshall, 1991; Vuilleumier, 2013), indicating heterogeneity and partly separable features in clinical manifestations. This has led to the view that spatial neglect might constitute a multi-componential syndrome resulting from the combination and interaction of distinct deficits, possibly associated with different neural substrates.

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In keeping with the latter view, a study by Verdon et al. (Verdon et al., 2010) used a factorial analysis approach to identify distinct dimensions of spatial neglect based on the performance of a large group of patients (n = 80) across a series of standard clinical tests. Results suggested that neglect symptoms tend to cluster along three main components. These included a perceptual-spatial component accounting for neglect in line bisection, text reading, and drawing; a motor-exploratory component accounting for neglect in visual cancellation and drawing; and an object-based component accounting for allocentric neglect affecting single word or single object perception regardless of position in egocentric space. Remarkably, voxel-wise lesion-symptom mapping indicated that the first perceptual-spatial component correlated with damage to parietal areas, whereas the second motor-exploratory component correlated with dorsolateral prefrontal damage, and the third object-based component with temporal damage (Saj et al., 2011; Vaessen et al., 2016). These distinct components accord with other factorial analyses of neglect symptoms as derived from similar tests (Kinsella and Ford, 1980; Saj et al., 2011; Verdon et al., 2010), and with previous studies reporting frequent dissociations between cancellation and line bisection tasks in patients with frontal vs parietal lesions, respectively (Molenberghs and Sale, 2011; Verdon et al., 2010). However, the exact cognitive operations sub-serving the different spatial tasks encompassed in each of these neglect components still remain to be determined.

A traditional view to explain anatomical differences across distinct neglect symptoms is to refer to a dissociable role for parietal areas in perceptual components of neglect and for frontal areas in motor-exploratory components of neglect (Mesulam, 1999). However, directional motor neglect is also associated with parietal damage, rather than frontal damage only (Mattingley et al., 1998). Alternatively, parietal and frontal involvement might differentially affect the maintenance of spatial locations and the control of selectivity in attention processes, respectively (Verdon et al., 2010; Vuilleumier, 2013). This could account for the association of deficits in line bisection and text reading deficits in the same parietal factor but deficits in search with a distinct frontal factor in lesion mapping analyses (Verdon et al., 2010; Saj et al., 2011, Molenbergh and Sale, 2011; Woodbridge et al., 2012). Parietal areas are involved in spatial working memory processes (Mackey et al., 2016) allowing for the representation of specific locations in space (across different sensory modalities), a capability that has found to be impaired in neglect patients (Malhotra et al., 2005). Instead frontal areas seem more critically implicated in top-down executive control according to behavioral goals (Jurado and Rosselli, 2007), and their damage may lead to a form of neglect triggered by the presence of right-side distractors. These distinct facets of spatial neglect have been highlighted by several recent studies, but typically studied separately and not systematically related to different anatomical substrates. (Husain and Kennard, 1997).

1.1. Deficits in working memory and spatial neglect

Some authors (Ellis et al., 1996; Malhotra et al., 2005, 2004; Della Sala et al., 2010) proposed that deficits in visuo-spatial working memory (WM) may be closely linked to spatial asymmetries in the behavior of many neglect patients during classic cancellation tasks. Accordingly, working memory deficits could result in abnormal search behavior that lead patients to repeatedly orient to and mark targets already explored. Such deficits are observed only in spatial but not verbal WM, and do not depend on the horizontal layout of targets as they also occur for to-be-remembered locations along a vertical version of the Corsi span task (Kessels et al., 2008). Another study of visual search reported that neglect patients show no performance cost when targets swap locations over time as compared with targets remaining at fixed locations, especially in the left visual field, suggesting that their search operates without keeping track of the location of the previously explored stimuli (Kristjánsson and Vuilleumier, 2010).

In parallel, abundant neuroimaging work (e.g. D'Esposito et al., 1999; Petrides, 2000; Postle et al., 2003) has pointed to a key role of a distributed parieto-frontal network in the WM process that allows storing and manipulating spatial information across time and distracting events. In this perspective, posterior parietal regions may store the spatial representations of a stimulus, perhaps in different coordinates systems (e.g. gaze or body centered), while prefrontal regions would be in charge of executive control controlling the encoding and use of stored information. A major role of posterior parietal areas in spatial WM is also compatible with numerous studies of selective spatial attention, where the location of an expected target is held in memory before target appearance, which usually recruits areas around the intraparietal areas (IPS) in a spatiotopic manner (Corbetta et al., 2005b; Jerde and Curtis, 2013)

1.2. Deficits in visual remapping and spatial neglect

An impairment in the encoding and maintenance of spatial locations in WM has also been attributed to impaired remapping of visual locations across eye movements (Pisella and Mattingley, 2004), a deficit found to be more severe in right-brain damaged patients with neglect than those without (Vuilleumier et al., 2007). Accordingly, part of the neglect symptoms could be explained by a unilateral loss in spatial remapping mechanisms, normally responsible for constructing a stable representation of the visual environment despite ongoing changes in retinal inputs. Moreover, some authors (Danckert and Ferber, 2006) suggest that spatial working memory and spatial remapping processes might be partly independent of each other. In any case, the neural substrates of spatial remapping that allow for a maintenance of stable spatial representations have also been linked to posterior parietal areas (Colby et al., 1995). While primary visual areas hold a retinotopic map of the visual environment, constantly renewed at each new ocular fixation, parietal neurons combine visual inputs with eye position signals in order to code for spatial locations in a head or body-centered coordinates (Driver and Pouget, 2000). In addition to the lateral intraparietal sulcus (Andersen and Zipser, 1988; Gnadt and Andersen, 1988; Goldberg and Bruce, 1990), however, other neuro-anatomical studies on spatial remapping suggest an involvement of the frontal oculomotor fields (Goldberg and Bruce, 1990), or the superior colliculus (Goldberg and Bruce, 1990; Mays and Sparks, 1980) in the remapping process.

Lesion studies in human patients also highlighted remapping deficits after parietal lobe damage (Ansuini et al., 2006; Molenberghs et al., 2007), particularly in paradigms using a double-step saccadic paradigm (Duhamel et al., 1992; Heide et al., 1995).

Based on these findings, Pisella and Mattingley (Pisella and Mattingley, 2004) suggested that remapping deficits in parietal patients should preferentially occur when they make a saccade across the midline after encoding an object's location in one visual hemifield (left or right). According to this view, after right parietal damage, an internal saliency map of previously attended or to-be-remembered locations would be erased over the whole visual field following a leftward saccade, whereas a rightward saccade would erase only the left part of the visual field within the saliency map. Other findings suggest that remapping deficit arise for information in either visual fields whenever a saccade is made to another location more toward the right side, rather than more toward the left side (Vuilleumier et al., 2007). In any case, spatial remapping deficit have been proposed to account for some manifestations of spatial neglect (e.g. the tendency to revisit previously explored locations) that are also thought to rely on WM abilities (Husain et al., 2001), but this deficit may in principle also occur without a full neglect syndrome (Heide et al., 1995). Interestingly, a recent study reported deficits in remapping visual information across saccades in patients with constructional apraxia following right hemisphere stroke (Russell et al., 2010).

1.3. Selective attention in frontal lobe and neglect

Another component associated with both selective attention and working memory is the ability to resist to interference by distracting information, typically associated with frontal rather than parietal functions (Duecker et al., 2013). Spatial neglect symptoms after frontal lesions might be particularly sensitive to such interference. A seminal case study (Husain and Kennard, 1997) described a patient with focal right frontal lobe damage in whom left spatial neglect on various cancellation tasks was dependent on the amount of concurrent distractors - a pattern not observed in other patients with parietal lesions. In the context of spatial WM, dorsolateral prefrontal areas are involved in executive and manipulation components allowing the maintenance and use of task-relevant information, respectively across time delays and sensory distraction (Collette and Van der Linden, 2002). Thus, while a deficit in spatial working memory may contribute to spatial neglect (Danckert and Ferber, 2006; Husain et al., 2001; Malhotra et al., 2005, 2004; Milner and McIntosh, 2005), it remains to be determined whether different components are affected depending on lesion site.

Here, we specifically sought to dissect parietal and frontal mechanisms of spatial cognition that may contribute to the major neglect components previously identified in lesion mapping studies (Verdon et al., 2010; Chechlacz et al., 2012a, 2012b, 2012c), using two novel tasks specifically designed to probe for processes mediating spatial WM and interference control. We hypothesized that the "perceptual" parietal component associated with neglect in both line bisection and text reading tasks might reflect their common reliance on spatial processes allowing the creation of a stable spatial representation of visual locations across gaze shifts, through WM or remapping processes (tested in exp. 2); whereas the "exploratory" fontal component associated with neglect in search (and to a lesser extent drawing) might instead implicate executive attentional processes allowing for the filtering of distractor information (tested in exp. 1).

2. Experiment 1: Distractor filtering task

2.1. Methods

2.1.1. Patients

Seven patients (mean age 61 ± 21, range 34–94) with focal lesions in the right frontal lobe (Fig. 1a) were tested and compared to seven patients (mean age 68 ± 12, range 51–84) with lesions in the right parietal lobe (Fig. 1b). All patients had a first right-hemisphere stroke, haemorrhagic or ischemic, demonstrated by MRI or CT scan. Patients were recruited consecutively among stroke patients admitted to the Neurology Department, University Hospital of Geneva. Neglect and other neuropsychological deficits were assessed using a standard battery of clinical tests (Rousseaux et al., 2001; Verdon et al., 2010; Saj et al., 2011). All patients had normal hearing function in both ears according to their clinical history and neurological examination during the clinical workup. The presence of neglect (see Table 1) was diagnosed on the basis of their pathological performance in at least two of three standardized test, with global severity quantified by averaging scores across these tests, including the Bells Cancellation task (Gauthier et al., 1989), Figure Copy (Gainotti et al., 1970), and Line Bisection (Schenkenber et al., 1980). All patients were also examined using a routine battery of clinical neuropsychological tests, including mini-mental state examination, to exclude dementia and any other major cognitive disorder that would impact on task performance and collaboration. Monocular visual acuity was > 7/10 in all cases. A full hemianopia was diagnosed by manual testing and Goldman perimetry in 2 patients from the parietal group. Motor deficits were evaluated with the FMA score.

In addition, patients were compared with five control subjects free of cerebral disease (mean age: 69.0 ± 12.5 years) who were recruited among the hospital staff. Age and education level were not significantly different among the three groups ($p > .05$). Moreover, the two patients groups were similar in age ($F(4,40) = 2.08$; $p = .11$), education level ($F(4,40) = .48$; $p = .99$), and delay since stroke ($F(3,27) = 1.04$; $p = .38$). All participants gave informed consent according to the local ethics rules of the University Hospital of Geneva.

For each patient, brain lesions were demonstrated by clinical MRI scans and reconstructed on axial slices using MRIcro (Rorden and Brett, 2000), according to previously described methods (Russell et al., 2010; Verdon et al., 2010; Vuilleumier et al., 2008). Lesioned areas were transformed to a three-dimensional region of interest (ROI) corresponding to the lesion volume, and normalized to a standard brain template using MRIcro. The normalized lesion ROIs were then superimposed on a T1 MRI template in order to determine the maximal overlap of lesions (Fig. 1). Based on their anatomical stroke location, each patient was assigned to either the parietal or the frontal damage group. Lesion analysis with MRIcro clearly demonstrated different overlap distribution in each group (Fig. 1).

2.1.2. Procedure

The objective of the Distractor Filtering task (Fig. 2a) was to test for the ability of patients to focus selective attention on relevant visual targets in the presence of irrelevant distractors (on either side of space), and during different attentional load conditions. This allowed us to determine whether frontal and parietal patients show different behavioral performance as a function of attentional demands and laterality of distractors. Patients were placed in front of a computer screen where a geometric color figure could appear at three possible locations (center, right, left), selected from a set of 20 different figures. These figures could be a circle (blue, green, yellow, or red), a square (blue, green, yellow or red), a diamond (blue, green, yellow or red), a triangle (blue, green, yellow or red), but also a blue parallelogram, green star, yellow trapeze, or red pentagon. The task included two variants that differed in their attentional load: either low load (easy), with only one possible target (F1 condition: red circle), or high load (difficult), with four possible targets (F4 condition: red circle, blue square, green diamond, yellow triangle). The other shapes were always distractors. The patient had to respond by pressing a key (with their right hand) as fast and accurately as possible when they detected a target at the central location, but withhold responses otherwise (go-nogo task). There were four conditions of presentation: only the central target, the central target with a peripheral distractor (50% right and 50% left), a central distractor with a peripheral target (50% right and 50% left), or a distractor alone in the center. The patient had to press the response key in the first two conditions of presentation (central target alone or central target with distractor in the periphery), but not in the last two conditions (distractor in center with or without a peripheral target).

Each task condition (Fig. 2a) was given in two stages: a practice phase and a test phase, with presentation of the stimulus display for a fixed duration of 600 and intertrial interval of 1800 ms (20 trials).

This task allowed us to probe selective attention in frontal and parietal patients along several dimensions. First, by comparing response times (RTs) to central targets across conditions, we could test not only for the impact of concurrent stimulus competition, but also any difference between right vs left distractors. Based on Husain and Kennard (1997), we expected that distracting effects due to exaggerated exogenous orienting might be larger in frontal than parietal patients and larger with right than left distractors. Conversely, more severe perceptual extinction might lead to smaller RT cost with left distractors in parietal than frontal patients. In addition, based on Lavie and Robertson (2001), we expected that greater load on WM during the F4 vs F1 condition would reduce executive control and exacerbate these distracting effects in frontal more than parietal patients. Alternatively, load effects might also be sensitive to parietal damage by recruiting non-spatial WM processes (e.g. see Pillay et al., 2016). Finally, commission errors on trials with peripheral target stimuli could probe for any tendency to respond inappropriately to target regardless of their

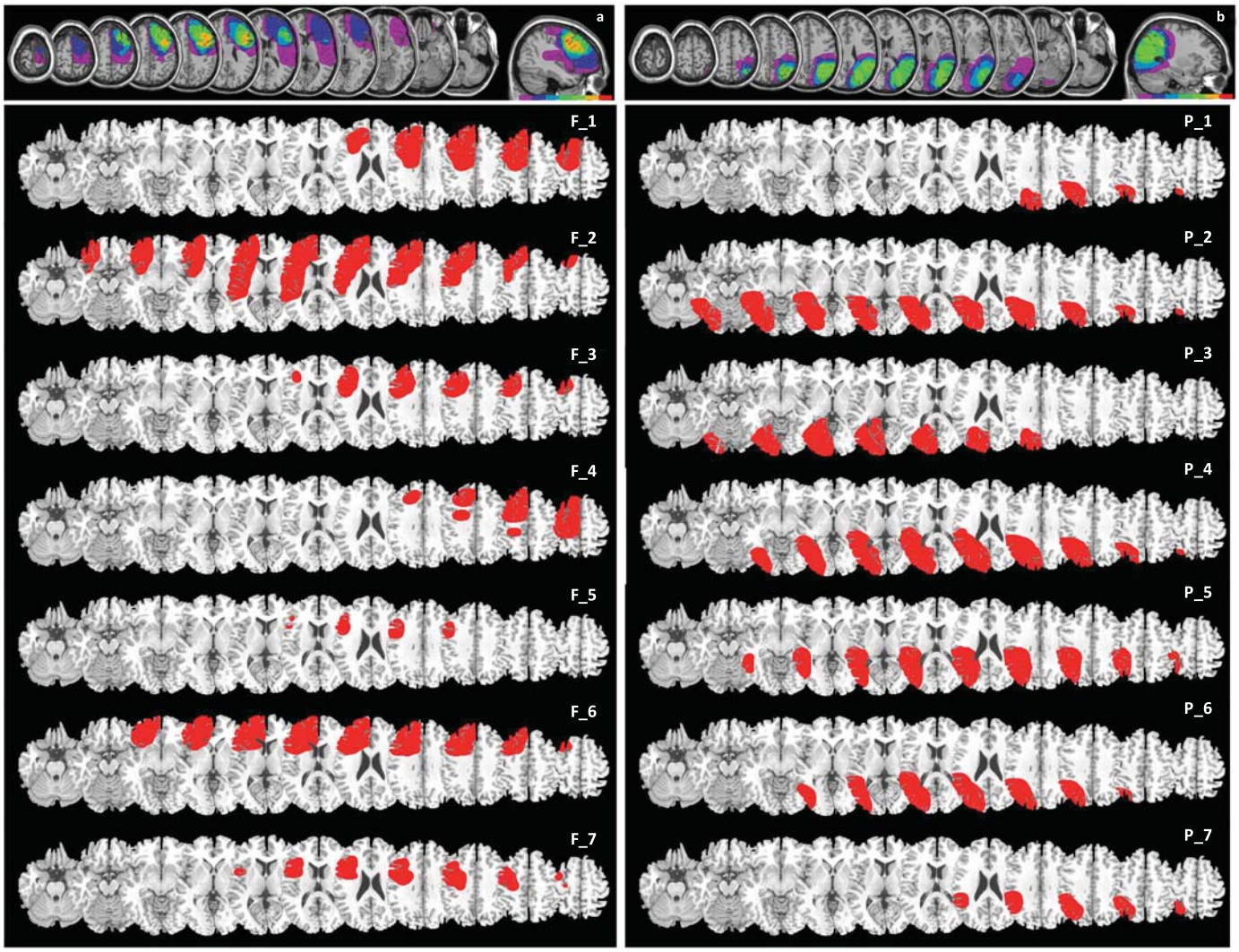

Fig. 1. Lesion overlaps of all patients. (a) Frontal patient group, (b) Parietal patient group.

Table 1
Demographic and clinical data of patients.

Group	Patient	Age	Sex	Day since stroke	Aetiology	FMA score	Visual field	Neglect severity	Bells cancellation			Line bisection (%)	Scene copy
									left	center	right		
Parietal	P_1	74	F	15	Isch	< 84	H-	+ + +	9	3	0	54.2	2
	P_2	69	F	27	Isch	95	H+ +	+ +	4	3	0	51.24	4
	P_3	76	M	33	Hem	98	H-	+ +	5	2	0	48.56	2
	P_4	51	M	17	Isch	< 84	H+ +	+ + +	8	1	0	35.12	4
	P_5	53	F	18	Isch	86	H-	+ +	6	4	2	18.52	1
	P_6	84	F	34	Isch	99	H-	+ + +	7	4	1	41.78	4
	P_7	68	M	10	Isch	< 84	H+	+ + +	12	4	4	72.25	4
Frontal	F_1	52	F	36	Isch	95	H-	+ + +	13	4	6	50.89	3
	F_2	49	F	23	Hem	< 84	H-	+ +	6	3	2	16.02	1
	F_3	46	M	33	Isch	99	H-	+ +	3	4	2	15.21	2
	F_4	94	F	24	Hem	99	H-	+ + +	15	5	8	26.25	2
	F_5	78	F	34	Hem	< 84	H-	+ +	7	4	2	12.13	0
	F_6	34	M	15	Isch	86	H-	+ +	15	5	6	51.21	0
	F_7	67	M	14	Isch	< 84	H-	+ + +	15	5	9	21.28	3

Aetiology - H, haemorragic; I, ischemic. FMA - Fugl-Meyer assessment. Visual field - H- no visual field defect, H+ partial visual field defect (peripheral or quadrantanopia), H+ + severe visual field defect (severe hemianopia). Bell cancellation - Number of omitted bells in the left (/15), central (/5) and right (/15) parts of the test sheet; cut-off score: > 3 on the left side. Line Bisection - Mean error in percentage of maximal possible error; cut-off score: > 11%. Scene copy - The scene includes four distinct elements from the left to the right of the sheet. Performance is coded from 0 (no omission) to 4 (severe omissions on the contralateral side); cut-off score: > 0. Neglect severity - (+) performance pathological in one of three standardized test; (+ +) 2/3; (+ + +) 3/3.

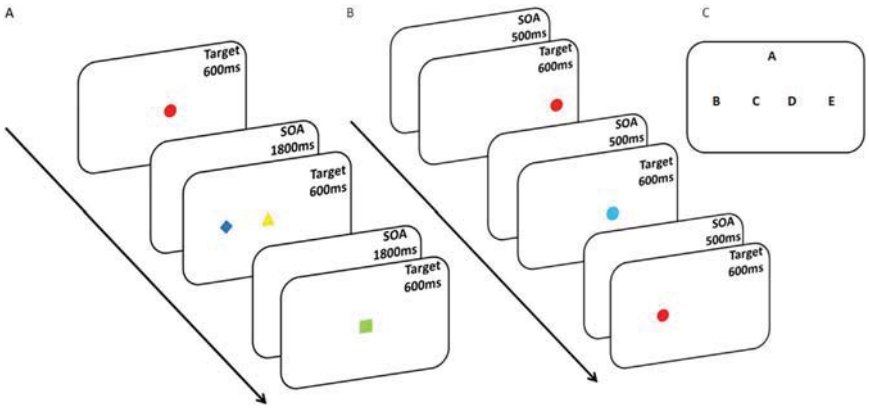

Fig. 2. Experimental paradigms illustrating (a) the distractor filtering task; (b) spatial coding task; (c) spatial positions during the spatial coding task.

spatial location, or more particularly when they appeared in the RVF, as observed for revisiting behavior during cancellation tasks in frontal more often than parietal patients (Wojciulik et al., 2001).

ANOVAs on reaction times from 'go' trials and commission error rates on 'no-go' trials were performed using the software Statistica. These analyses used the variables Group (Parietal, Frontal, Control), task load (F1, F4), and Target or Distractor condition (central target alone, left distractor, and right distractor for RTs; central, left-sided, and right-side target for commission errors). Post hoc analyses used the Newman–Keuls test. The alpha risk was fixed at $P < .05$.

3. Results

On average, correct responses were made on 66% of the "go" trials with central targets for frontal patients, 88% for parietal patients, and 95% for control participants, while responses were correctly withheld on, respectively, 72%, 69%, and 92% of the "no-go" trials.

The ANOVA of RTs to central targets showed significant main effects of group ($F(2, 16) = 6{,}6941$, $p = ,00772$), task load (high or low, $F(1,16) = 15.52$, $p < .01$), and distractor condition (none, right, or left, $F(2,24) = 13.23$, $p < .01$), as well as an interaction between Group and distractor condition ($F(4, 32) = 12{,}288$, $p < .01$). Other main effects and interactions were not significant. These results indicate a different performance profile between groups according to distractor position, but not task load (Fig. 3).

Indeed, Parietal patients showed no reliable difference between the condition where the target appeared alone and those where the target appeared with a distractor on the left or right side ($p > .05$, for the F1 and F4 tasks). Further, reaction times did not differ between left or right distractors when directly compared ($p > .05$, respectively). However, these patients showed a clear effect of task load, with longer RTs in the F4 vs F1 condition on trials with 'target alone' ($p = .01$), 'distractor to the right' ($p = .03$), and marginally also 'distractor to the left' ($p = .06$).

In contrast, for Frontal patients, in both task load conditions (F1 and F4), RTs were significantly slower when the central target was flanked by a distractor on the right side relative to when it appeared alone ($p < .001$ for task F1, $p = .008$ for task F4) or with a distractor on the left side ($p = .004$ and .03, respectively). However, like parietal patients, there was no difference between central targets presented alone or presented with a left distractor (p = ns). In addition, although RTs were numerically slower in the F4 than in the F1 load condition overall (mean 564 vs 489), this difference was only marginally significant for trials with a target alone ($p = .12$), but not with a left (p = ns) or right distractor (p = ns).

In comparison, for Controls, we found any significant difference in all the conditions. Finally, the parietal group is slower than both frontal and control groups.

These results reveal a striking dissociation between frontal and parietal patients in the control of selective attention, with only the former showing a consistent cost in reaction times for a visual target presented at central fixation when it is accompanied by a distractor on the ipsilesional/right side, with no such effect when the a distractor is presented on the left side (Fig. 3). On the other hand, although task load effects were significant in parietal but not frontal patients when inspecting each condition separately, this difference was not supported by a formal group x load interaction overall.

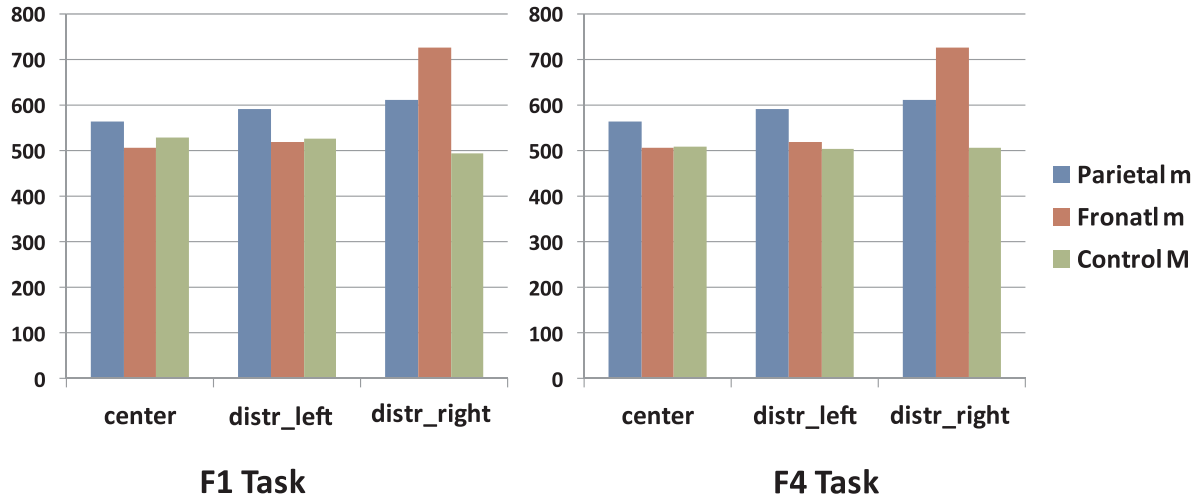

Fig. 3. Mean of reaction time for Frontal and Parietal patients in the low (F1) and high (F4) attentional load of the Filtering task.

4. Experiment 2: Spatial coding task

4.1. Methods

4.1.1. Patients

This second task was given to the same patients and healthy controls as above, on the same day but in pseudo-randomized counterbalanced order.

4.1.2. Procedure

The Spatial Coding task tested for the ability of patients to encode locations in space in a stable manner over time and thus return to them efficiently across shifts in eye movements, as supposedly subserved by remapping mechanisms (Vuilleumier et al., 2007). Similar to experiment 1, this task used a "go/no-go" design in order to assess reaction times to pre-defined targets presented at different spatial locations. The task consisted in a succession of colored dots appearing each in turn on a computer screen. The dot was blue in two thirds of trials, and red in one third. When a red dot appeared, the patient had to press the answer key as quickly as possible (but withhold responding to blue dots). On each trial, the first dot was always blue and presented on a central top position (see Fig. 2b), followed by a sequence of four dots presented at one of four horizontal (equidistant) spatial positions aligned along a virtual row on the screen, below the initial dot (Fig. 2c). This sequence (top then horizontal succession) was repeated for successive 5 cycles on each trial.

There were three conditions according to the sequence of dot presentation along the horizontal axis: clockwise condition (CW), where dots appeared from the right to the left of the horizontal row; counterclockwise condition (CCW), where dots appeared from left to right; and random order condition (RO), where the four dots appeared without a systematic sequence. In other words, in the CCW condition, following the initial central dot at the top position (A), the four horizontal dots appeared one after the other at positions B, C, D, and E along the virtual row, and then reappeared again 4 other times in the same order (5 cycles in total, Fig. 2c). In the CW condition, the four horizontal dots appeared one after the other but in a reverse sequence at positions E, D, C, and B, and then reappeared again in the same order. Finally, in the Random condition, the dots appeared each in turn but randomly at one of the four spatial positions and never jumped to a nearby location (e.g. B, D, C, and E). All trials in each of these three experimental conditions included a continuous series of 5 cycles with a similar sequence. Thus, in regular sequences, the location of the next upcoming dot could be predicted and attended before appearance. Hence, if spatial locations could be stored in memory and remapped across eye movement, target detection should be facilitated over time (i.e., across successive cycles) in the CW and CWW conditions (but not in the Random condition).

Dots were presented for 600 ms each and separated by a SOA of 500 ms. The red (go) and blue (no-go) dots were distributed pseudo-randomly among the horizontally aligned positions with the overall proportion corresponding to each color (respectively red 33.3% and blue 66.6%), with at least one red target appearing at each cycle. This resulted in a total of 40 'no-go' 20 'go' stimuli across the 5 cycles of each trial. There were 60 trials in each of the three experimental conditions (CCW, CW, and RO). The total duration of this task was about 20 min.

Critically, this paradigm allowed us not only to probe shifts of spatial attention when target location can be predicted from memory across successive visual events (sequential order), relative to unpredictable (random order), but also to compare such effects when the next predicted location is to the left or to the right of current fixation (CCW vs CW order). An intact ability to hold and remap spatial locations across successive gaze shifts should lead to successful anticipation of the next upcoming stimulus and speed up responses to the (red) target dot on go trials. Given previous research on spatial remapping (Pissella and Mattingley, 2007; Vuilleumier et al., 2007) and working memory in neglect (Husain et al., 2001; Wojciulik et al., 2001), as well as anatomical dissociations between different neglect components in patients (Verdon et al., 2010), we hypothesized that such ability might be more severely compromised after parietal than frontal lesions. Further, a total inability to code and/or remap visual locations across successive gaze shifts (e.g. see Pissella and Mattingley, 2007; Wojciulik et al., 2001) would predict no benefit for both the CCW and CW sequences relative to the Random condition, whereas a selective inability to remap and predict locations leftward from current fixation (e.g. see Vuilleumier et al., 2007) would predict a deficit in the CCW sequence alone (or vice versa in the CW sequence alone for a selective rightward remapping deficit).

To analyze these data, we first conducted ANOVAs of RTs on the "go" trials (red dot) and of commission error rates on the 'no-go' trials, using the software Statistica. These analyses used the factors Group (Parietal, Frontal, Control), Condition (CW, CCW, RAND), and Cycle (Cycle 1; 2; 3; 4; 5). Post hoc analyses used the Newman–Keuls test. The alpha risk was fixed at $P < .05$.

5. Results

Targets were correctly detected in 71%, 78%, and 97% of trials for Frontal patients, Parietal patients, and healthy controls, respectively, while commission errors were observed in 20%, 33%, and 3% of trials, respectively. The ANOVA of RTs a function of the number of cycles in the sequence of each trial (1–5, independent variable) showed significant main effects of group ($F(2, 16) = 2910$, $p = .033$), sequence condition (CCW, CW, or Random, $F(2,28) = 4.72$, $p = .015$), and cycle (cycle 1; 2; 3, 4; or 5, $F(4,48) = 2.97$, $p = .028$), as well as an interaction of Group*Cycle*CDT ($F(16, 128) = ,87061$, $p = .020$). Other main effects and interactions were not significant.

Post hoc comparisons showed that the parietal group was generally slower than both the frontal and control groups ($p = .01$). RTs were also generally slower in the RAND than predictable conditions ($p = .01$) and on the first than fifth cycles ($p = .01$). More critically for our predictions parietal patients were significantly different from the other two groups for the CW condition (Parietal vs. Frontal; $p = .01$; Parietal vs. Control; $p < .01$; Frontal vs. Control; $p = .35$; Fig. 4a). In the CCW condition, however, parietal patients were worse than controls but did not significantly differ from frontal patients overall (Parietal vs. Frontal; $p = .16$; Parietal vs. Control; $p = .04$; Frontal vs. Control; $p = .29$), although a progressive improvement of RTs was seen in the frontal like in the control group but not in parietal patients (Fig. 4b). There were no group differences for sequences in the RAND condition (Parietal vs. Frontal; $p = .33$; Parietal vs. Control; $p = .15$; Frontal vs. Control; $p = .32$; Fig. 4c).

These data suggest that parietal patients were unable to learn and benefit from predictability of the next target location over successive cycles (see Fig. 4). This was further demonstrated by analyses assessing the repetition cycle effects in each group separately. Indeed, to test for progressive learning of the dot locations across successive attention shifts in each group and condition, we also ran a linear regression analysis of RTs on correct "go" trials as a function of the number of cycles in the sequence ($1-5$), for each group and condition. Frontal patients showed a consistent decrease of RTs over time (negative regression slope) with the CW and CCW sequences ($R^2 = .976$ and $R^2 = .936$, respectively, $p < .01$), but not with the random sequence ($R^2 < .01$, $p = .72$). Healthy controls showed a similar pattern ($R^2 < .01$, $p = .89$ for CW, CWW, and RAND, respectively). In sharp contrast, parietal patients showed no significant slope in any of the three conditions (all $R^2 < .07$, $p > .25$).

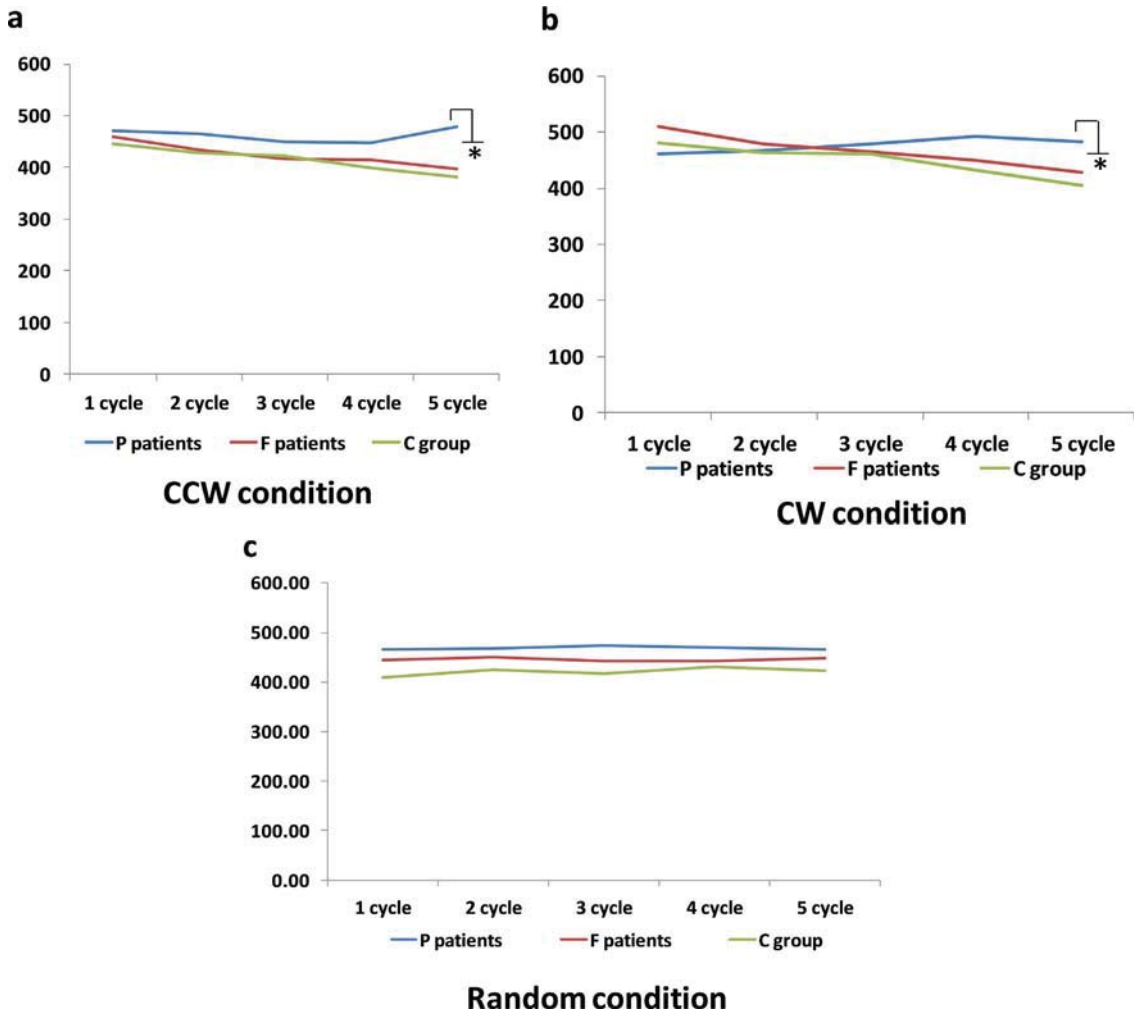

Fig. 4. Reaction times for correct target detection during 5 successive cycles of each trial, for Frontal and Parietal patients in the different sequence conditions: (a) counterclockwise (CCW), (b) clockwise (CW) and (c) random.

6. General discussion

6.1. Frontal neglect and resistance to distractors

In this study we designed two novel tasks that specifically aimed at probing distinct components of spatial attention possibly contributing to left neglect in right-brain damaged patients. The Distractor Filtering task allowed us to test for putative neglect components sensitive to frontal lesions, previously found to affect performance on search tasks but not line bisection (Verdon et al., 2011; Binder et al., 1992). Based on a seminal observation by Husain and Kennard (Husain and Kennard, 1997), we probed for a role of prefrontal areas in controlling the selectivity of visual processing as a function of the presence of distractors and their laterality (i.e., in ipsilesional space), but also task load, all factors that may contribute to exacerbate left spatial neglect during difficult search tasks with multiple competing stimuli (e.g., typical cancellation tests). In accordance with our assumptions, we found a striking dissociation between deficits in this task after frontal and parietal damage.

Parietal patients showed no difference in detection RTs when a central target appeared alone and when it appeared with a distractor on the left. Thus, neither the presence nor the laterality of distractors had any effect on selective attention performance for central targets in these patients. This pattern occurred even though parietal patients showed a general trend towards greater difficulty (larger slowing in reaction times) in the high-load F4 condition compared to the low-load F1 condition, suggesting that the task per se was not generally easier for them compared to frontal patients.

In sharp contrast, the ability to filter distractors out was significantly compromised by focal lesion in prefrontal regions. Indeed, frontal patients showed a distinctive "distractor laterality" effect, in both attentional load conditions (F1 and F4), with slower reaction times when the target was flanked by a distractor on the right side as compared to when it appeared alone or flanked by a distractor on the left side. However, frontal patients showed no significant worsening in performance between the F1 and F4 conditions, indicating that such lesions do not reduce the ability to mobilize more attentional resources and maintain more targets in working memory. These findings reveal that lateral frontal damage may not only disproportionally disturb the ability to manage (resist to) distractors, but also act in a spatially specific manner according to distractor laterality – with greater impact when they appear on the right/ipsilesional side.

Our results converge with the view that "frontal forms" of spatial neglect may be particularly dependent on distracting inputs and therefore predominate in multi-item visual search tasks (Husain and Kennard, 1997). More generally, they accord with a theoretical framework (Collette and Van der Linden, 2002) according to which the ability to deal with distractor load is primarily subtended by the frontal (control and manipulation) components of working memory. Thus, our new data add support to recent studies suggesting an important involvement of working memory deficit in spatial neglect (Danckert and Ferber, 2006; Husain et al., 2001; Malhotra et al., 2005, 2004; Milner

and McIntosh, 2005), but also go beyond previous work by demonstrating such deficit after frontal lesions may primarily reflect a deficit in the executive component of spatial working memory. At the neurophysiological level, these deficits might reflect a loss of top-down signals from frontal areas onto low-level perceptual systems, which serve to boost the amplitude and selectivity of neuronal responses to goal-relevant information while suppressing the response to irrelevant information (Chee et al., 2011; Lupiáñez et al., 2001). The laterality effects could be accounted for by ipsilateral direct projections from prefrontal cortex to extrastriate visual areas (Barcelo and Knight, 2007; Voytek et al., 2010).

We surmise that this executive attentional component mediated by frontal areas is particularly critical for efficient visual search during cancellation tasks with multiple distractors (e.g., bells cancellation, stars cancellation), which are widely used to assess neglect in brain-damaged patients (Verdon et al., 2010). In turn this would indicate that the "exploratory" biases previously attributed to a frontal component of left neglect (Verdon et al., 2010; Binder et al., 1992; Chechlacz et al., 2012a, 2012b, 2012c) might result from reduced filtering of right-side distractors and pathological capture of attention by the latter, instead of (or in addition to) a simple "motor" or "intentional" deficit in attentional behavior (Bisiach et al., 2004).

6.2. Parietal neglect and spatial remapping

Our second task was designed to assess the ability of patients to encode visual locations and hold them in memory across short time intervals with intervening eye movements, a process necessary to form a stable map of space. Such stable representations should allow more efficient shifts of attention to previously seen locations as compared with new or unexpected locations. Detailed studies of cancellation tasks in neglect suggest that patients with parietal lesions may have difficulties in remembering locations explored during search, such that they often revisit already cancelled targets (Husain et al., 2001) and show no performance cost when distractors and targets swap locations (Kristjánsson and Vuilleumier, 2010). We therefore hypothesized that impaired encoding of spatial locations into WM might be a crucial feature of the neglect component associated with parietal lesions (Verdon et al., 2010), unlike sensitivity to distractors associated with frontal lesions. Thus, in the Spatial Coding task, parietal patients were expected to be unable to benefit from conditions where they could predict the location of a target, whereas frontal patients should still be able to store locations in WM.

Our results confirmed this hypothesis. Indeed, when targets appeared in a predictable sequence along horizontal space, frontal patients showed faster responses in regular compared to random sequences (like controls), denoting a progressive improvement of detection across time (i.e., during the last vs first cycle of dots, with a significant linear correlation of detection RTs over repetitions). On the contrary, parietal patients demonstrated stable detection RTs across time and sequences, regardless of the predictability of stimulus location. Moreover, this lack of anticipatory attention to predictable locations was similar for stimuli appearing in a right-to-left (CCW) or left-to-right (CW) sequence, indicating it could not be explained only by slower attention shifts toward the contralesional side. This pattern supports the view that parietal lesions could disturb the ability to store and maintain spatial locations in order to allocate selective attention in space, and thus anticipate or return to behaviorally relevant stimuli at these locations.

More generally, our data also shed new lights on two alternative views in the literature regarding the implementation of storage in spatial WM. For some authors (e.g., Malhotra et al., 2005; Malhotra et al., 2004), a deficit in spatial WM might occur after parietal lesions that do not affect the executive component of WM (i.e. central executive). But for others (e.g. (Petrides, 2000), both storage and manipulation in WM are subtended by frontal regions, with the first process related to inferior frontal cortex and the second mediated by the dorsolateral parts. Here, we clearly observed a distinctive impact of parietal vs frontal lesions on a simple form of visuo-spatial storage in working memory.

In addition, these findings converge with the proposition from Pisella and Mattingley (Pisella and Mattingley, 2004) that a deficit in spatial remapping processes following a parietal lesion might underlie several manifestations of neglect. According to these authors, spatial remapping mechanisms are responsible for constructing a stable representation of the visual environment by storing and updating locations across body movements. Indeed, the retinotopic map of the visual environment is constantly renewed at each new ocular fixation, and the representation of space constancy requires specific mechanisms that integrate retinotopic visual inputs maps over time and "remap" them as a function of changes in gaze direction. Such remapping processes have been observed in neurons of different brain regions, particularly in parietal cortex (Colby et al., 1995). (Ansuini et al., 2006; Molenberghs et al., 2007).

This difference according to the direction of stimulus appearance may further reflect the effect of spatial neglect, with slower orienting or disengaging of attention towards targets on the contralesional side. However, importantly, an inability to anticipate target locations even in the CCW sequences (left-to-right) might accord with the suggestion of Pisella and Mattingley (Pisella and Mattingley, 2004) that spatial remapping deficits in neglect may operate across the entire visual fields. Another previous behavioral study in neglect patients (Vuilleumier et al., 2007) also reported that deficits in remembering visual locations may affect both visual hemifields when patients make a gaze shift further to the right, because such shift requires remapping of the remembered location to the left/contralesional space in gaze-centered coordinates.

Taken together, our results provide new evidence that losses in spatial representations that are held in WM and dynamically formed/updated through remapping processes constitute a critical dimension of neglect after parietal lesion, but not frontal lesion. We surmise that this component may at least partly underpin the "perceptual" component of neglect previously associated by factorial analysis and lesion mapping studies to parietal lobe damage (Binder et al., 1992; Verdon et al., 2010; Vaessen et al., 2016), and thus account for the shared contribution of this parietal component to deficits in line bisection and text reading (Verdon et al., 2010), in addition to impaired search paths and "revisiting" during cancellation tasks (Husain et al., 2001). Indeed, deficient encoding of spatial locations in WM may particularly hinder the ability to encode the position of line endpoints during bisection and return to the beginning of text lines during reading. Further studies are needed to better characterize these spatial WM processes and their neural substrates. Given growing realization that spatial neglect reflects a disruption between frontal and parietal areas across the two hemispheres which subtend selective attention and spatial awareness (e.g. Doricchi et al., 2008; Doricchi and Tomaiuolo, 2003; Karnath et al., 2009; Thiebaut de Schotten et al., 2005; Urbanski et al., 2008; Verdon et al., 2010), it is likely that lesion extension to white-matter projections within and between hemispheres (Vaessen et al., 2016; Urbanski et al., 2008) might play an important role in the deficit in working memory.

7. Conclusion

We designed two different tasks in order to tap into two specific components of spatial neglect (i.e., frontal and parietal) that were previously identified by a combination of factorial analysis and lesion mapping (Verdon et al., 2010). While the tasks differed in several respects and cannot be directly compared, the dissociated pattern of performance in our a priori defined groups of patients (one impaired in the first but not second task, and vice versa) strongly supports the idea that distinct cognitive processes are recruited by these two tasks and

thus affected by distinct lesion sites (in frontal and parietal lobe). Our results indicate that frontal lesions disturb the ability to filter right-sided distractors during selective attention, a common aspect of spatial neglect behavior, which appeared to arise independently of the task load. This frontal neglect component could reflect executive processes in working memory, which remain intact after parietal damage. Conversely, we also show that parietal lesions disturb the ability to learn and use spatial information in order to predict the location of a future visual stimulus. This parietal component of neglect may prevent creating a stable spatial representation across time intervals and reflect an impairment of storage or remapping processes in WM.

We note however that these deficits may not be linked to lesion affecting only cortical areas in frontal and parietal lobes, but damage to white matter tracts within these lobes could also contribute to the hypothesized functional components. Thus, the perceptual-scanning component of neglect may at least partly reflect an interruption of both interhemispheric and intrahemispheric fibers, including the forceps major from splenium and superior longitudinal fasciculus, respectively (Bartolomeo et al., 2007; Vaessen et al., 2016), perhaps due to the unique position of lesions in parietal WM at the crossroad of these two pathways. Likewise, an interruption of cortico-subcortical connections between frontal cortex and superior colliculus as well as cortico-cortical connections between frontal and parietal areas might contribute to the working memory component of neglect (Hillis et al., 2002; Rorden et al., 2012; Saj et al., 2012; Verdon et al., 2010).

Altogether, these novel findings add to the recent hypothesis that spatial neglect is a multi-component syndrome (Driver et al., 2004; Vuilleumier, 2007; Chechlacz et al., 2012a, 2012b, 2012c), and further strengthen the links between different anatomo-functional sub-components of spatial neglect (Verdon et al., 2010) with different features of working memory (manipulation versus storage). Given ongoing debates whether spatial remapping and spatial working memory functions are independent of each other or not (Danckert and Ferber, 2006), future research should focus on the possible commonalities or distinctions between these processes.

At the clinical level, our results confirm the importance of testing multiple behavioral dimensions when examining spatial neglect. Moreover, clinical tasks commonly used to assess neglect might usefully be re-evaluated in the light of new neuro-cognitive hypotheses, including the role of distinct working memory components in the syndrome of spatial neglect. New clinical tools focusing on spatial WM abilities could be employed not only to refine clinical assessment and mechanistic understanding of the syndrome, but also to extend and improve current rehabilitation techniques.

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