

Role of right posterior parietal cortex in maintaining attention to spatial locations over time

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Recent models of human posterior parietal cortex (PPC) have variously emphasized its role in spatial perception, visuomotor control or directing attention. However, neuroimaging and lesion studies also suggest that the right PPC might play a special role in maintaining an alert state. Previously, assessments of right-hemisphere patients with hemispatial neglect have revealed significant overall deficits on vigilance tasks, but to date there has been no demonstration of a deterioration of performance over time—a vigilance decrement—considered by some to be a key index of a deficit in maintaining attention. Moreover, sustained attention deficits in neglect have not specifically been related to PPC lesions, and it remains unclear whether they interact with spatial impairments in this syndrome. Here we examined the ability of right-hemisphere patients with neglect to maintain attention, comparing them to stroke controls and healthy individuals. We found evidence of an overall deficit in sustaining attention associated with PPC lesions, even for a simple detection task with stimuli presented centrally. In a second experiment, we demonstrated a vigilance decrement in neglect patients specifically only when they were required to maintain attention to spatial locations, but not verbal material. Lesioned voxels in the right PPC spanning a region between the intraparietal sulcus and inferior parietal lobe were significantly associated with this deficit. Finally, we compared performance on a task that required attention to be maintained either to visual patterns or spatial locations, matched for task difficulty. Again, we found a vigilance decrement but only when attention had to be maintained on spatial information. We conclude that sustaining attention to spatial locations is a critical function of the human right PPC which needs to be incorporated into models of normal parietal function as well as those of the clinical syndrome of hemispatial neglect.

Keywords: sustained attention; vigilance; neglect; attention; spatial memory

Abbreviations: IPL = inferior parietal lobe; IPS = intraparietal sulcus; PPC = posterior parietal cortex; SPL = superior parietal lobe; SWM = spatial working memory; TPJ = temporo-parietal junction

Introduction

Current views of the human posterior parietal cortex (PPC) have been dominated by three highly influential research themes: spatial perception, vision-for-action and visuospatial attention. Experiments in monkeys first led Ungerleider and Mishkin to propose that the parietal cortex is part of a dorsal visual stream involved in the perception of space, whereas temporal regions form part of a ventral stream, crucial in their view for object recognition (Ungerleider and Mishkin, 1982). According to Milner and Goodale, however, the dorsal visual pathway to PPC is responsible for real-time guidance of limb or eye movements towards a target—*vision-for-action*—while the ventral stream is involved in vision-for-perception (Milner and Goodale, 1995). In their scheme, the superior parietal lobe (SPL) in humans is part of the dorsal pathway, whereas the inferior parietal lobe (IPL) is postulated to be involved in 'high-level' representations that are reliant on information from the ventral stream. A more recent model separates the parietal lobe into a dorso-dorsal system and dorso-ventral system (involving SPL and IPL, respectively), with the former taking part in controlling action 'online' and the latter involved in action understanding and spatial perception (Rizzolatti and Matelli, 2003).

In contrast to these proposals for the visual pathways from occipital cortex, Corbetta and Shulman's highly influential model has focused on the role of fronto-parietal networks in visuospatial attention (Corbetta and Shulman, 2002). Data from functional imaging experiments in healthy humans underpin their proposal that SPL and intraparietal sulcus (IPS) are involved in the deployment of attention and response selection, whereas more inferior regions, in particular the temporo-parietal junction (TPJ), may be part of a ventral attentional network acting as a neural 'circuit-breaker', allowing attention to be re-deployed to unexpected salient or novel events (Corbetta and Shulman, 2002).

Although there is now considerable evidence for PPC involvement in all three of these functions—spatial perception, vision-for-action and visuospatial attention—one area of research that has tended to receive little interest is that of sustained attention (Robertson and Garavan, 2004). In their seminal review, Posner and Petersen pointed out that there was an emerging body of evidence which supported a role in humans for right parietal and frontal regions in maintaining an alert state (Posner and Petersen, 1990). Although the terms sustained attention, alertness and vigilance have been used in slightly different ways, one useful proposal has been to consider these functions as part of a system controlling the intensity of attention, rather than its selectivity (Posner and Boies, 1971; van Zomeran and Brouwer, 1994).

Several functional imaging studies in healthy humans now support the concept of a parietal role in some of the intensity aspects of attention (Pardo et al., 1991; Johannsen et al., 1997; Coull and Frith, 1998; Hager et al., 1998; Sturm et al., 1999; Adler et al., 2001; Vandenberghe et al., 2001; Lawrence et al., 2003; Manly et al., 2003; Foucher et al., 2004; Kelley et al., 2008; Luks et al., 2008). Moreover, focal resections of the PPC (Rueckert and Grafman, 1998) as well as right frontal areas (Wilkins et al., 1987; Rueckert and Grafman, 1996) lead to deficits in sustaining attention. Despite these findings, there have been few attempts

to integrate intensity aspects of attention into current models of PPC function. An exception has been the recent proposal that while parts of the SPL and IPS are involved in spatial aspects of attention, working memory and directing limb or eye movements, other regions within the right IPL and IPS in humans may have crucial roles in sustaining attention as well as detecting salient, novel events (Husain and Nachev, 2007).

The clinical syndrome that is most often associated with strokes involving the right PPC in humans is that of hemispatial neglect (Heilman et al., 1983; Vallar and Perani, 1986; Mort et al., 2003), although this is controversial (Karnath et al., 2001; Hillis et al., 2005). Interestingly, deficits in spatial representation (Bisiach and Luzzatti, 1978), action control (Heilman et al., 1985; Mattingley et al., 1998; Husain et al., 2000) and visuospatial attention (Riddoch and Humphreys, 1983; Posner et al., 1984; Morrow and Ratcliff, 1988; Friedrich et al., 1998; Duncan et al., 1999; Bartolomeo and Chokron, 2002) have all been invoked as mechanisms underlying this disorder, echoing developments in models of normal PPC function. Although it is now established that neglect patients may also suffer from deficits in sustaining attention (Heilman et al., 1978; Hjaltason et al., 1996; Robertson et al., 1997; Samuelsson et al., 1998; Maguire and Ogden, 2002; Buxbaum et al., 2004; Farne et al., 2004) and benefit from alerting cues (Robertson et al., 1998), three important issues need to be resolved.

First, there has been no clear mapping of sustained attention deficits in neglect to the PPC; such deficits might, for example, be secondary to right frontal damage (Husain and Kennard, 1996). Second, studies that have examined the ability to maintain attention have shown an *overall* deficit in neglect patients compared to stroke controls. However, none of them have to date demonstrated a *vigilance decrement* over time. Some authors consider an impairment of sustained attention is best demonstrated through decline in performance over the duration of a task (See et al., 1995; Whyte et al., 1995; Parasuraman et al., 1998). For it could be argued that initial poor performance, which continues to be maintained at a similar level throughout a task, simply indexes a difficulty due to the specific cognitive demands of that task, rather than one of sustaining attention on it. However, many investigators contend that overall poor performance throughout a task might also be indicative of a deficit. It is possible, for example, that vigilance declines very rapidly at the beginning of the task and this might be missed by averaging over an epoch.

Third, it remains unclear whether deficits in maintaining attention might interact with spatial deficits in the neglect syndrome. Most investigators now consider neglect to be a multi-component disorder (Mesulam, 1999; Driver and Vuilleumier, 2001; Robertson, 2001; Husain and Rorden, 2003; Buxbaum et al., 2004; Hillis et al., 2005; Milner and McIntosh, 2005; Bartolomeo, 2007), but one key question that remains to be resolved is how such components interact. Some recent studies in healthy individuals have examined the relationship between sustained attention and either spatial awareness or spatial working memory (Caggiano and Parasuraman, 2004; Manly et al., 2005) but there has been no similar investigation in the neglect syndrome.

Here we attempt to investigate deficits of sustained attention and its interaction with spatial impairments in right-hemisphere neglect patients using a set of novel visual tasks. We were particularly interested to assess whether there is deterioration of performance over time—a vigilance decrement—since this is considered a critical index of sustained attention by some investigators. A crucial aspect of our paradigms is that stimuli were presented sequentially, either at central fixation or in the vertical meridian, without competing distractors. Such displays minimize the problem that items might not be encoded well in left space because of inattention of those items, which is known to be exacerbated by right-sided distractors. In fact a recent study (Molenberghs *et al.*, 2008) has shown even in healthy subjects that when attention needs to be paid to stimuli on the horizontal axis, activations within the IPS are different compared to stimuli presented in the vertical axis. Moreover, patients with lesions involving the same location within the right IPS are more impaired at detecting contralesional targets in the presence of ipsilesional distractors when these are on the horizontal axis.

In our study, by mapping performance deficits to lesion location, we hoped to elucidate the neuroanatomical basis for deficits of sustained attention and its interaction with spatial impairments in our neglect population. Our findings have important implications for understanding the normal role of the right PPC. They demonstrate that sustaining attention to spatial locations is a critical function that should be incorporated in any comprehensive model of human parietal cortex, as well as the syndrome of neglect.

Experiment 1: Simple sustained attention

The aim of Experiment 1 was to examine sustained attention in neglect patients using a simple visual task with minimal working memory requirements. Our objective was first to examine the ability to maintain attention without concurrently deploying another so-called 'executive' function—working memory (Caggiano and Parasuraman, 2004). Participants were presented with only target ('go') stimuli during the task so there was no requirement to remember or distinguish between target and non-target stimulus identities. Moreover, there was no requirement to withhold responses to any ('no go') stimuli (Manly *et al.*, 2003; Buxbaum *et al.*, 2004).

The optimum frequency of event presentation with which to demonstrate a deficit in sustained attention is unclear. However, several studies in patient groups without neglect have shown that impairment is more likely to be demonstrated at slower presentation rates (Wilkins *et al.*, 1987; Rueckert and Grafman, 1996, 1998). Designs with variable interstimulus intervals have also been successful in eliciting impairments in both healthy and brain-damaged individuals (See *et al.*, 1995; Robertson *et al.*, 1997; Parasuraman *et al.*, 1998; Samuelsson *et al.*, 1998). Thus the basic visual test of sustained attention we developed had relatively low frequency target presentations with variable interstimulus intervals. The task lasted ~8 min, sufficient time

in which to show an *overall* deficit in neglect patients on an auditory task (Hjaltason *et al.*, 1996).

Methods

All subjects gave written consent according to the Declaration of Helsinki. Patients were recruited from three stroke units in London with the study being approved by hospital research ethics committees.

Subjects

All patients who participated had been admitted to hospital with acute right-hemispheric stroke, details of which are shown in Table 1. Eight patients with neglect (mean age 59.6 years, SEM 8.6; mean time since stroke 281 days, SEM 258.6) and eight control stroke patients without neglect (mean age 58.6 years, SEM 7.37; mean time since stroke 23 days, SEM 8.1) were tested. Screening tests for neglect included Mesulam shape cancellation (Mesulam, 1985), BIT star cancellation and copying drawings (Wilson *et al.*, 1987), line bisection, reporting objects around the room (Stone and Greenwood, 1991), pointing to body parts, comb and razor test for personal neglect (McIntosh *et al.*, 2000) and clock drawing. Patients were recruited only if they were able to report centrally presented stimuli. Two individuals with neglect were excluded from the study because they could not do this reliably, and were therefore unable to perform the task. Crucially, none of the control stroke patients showed signs of neglect when tested within 1 week of stroke, so it is very unlikely that any members of this group were patients who had recovered from neglect.

Elderly healthy controls [mean age 72.9 years, (SEM 2.86), $n=8$] included patient relatives and other volunteers. None had any history of neurological disease. Each participant was also tested on the Mesulam shape cancellation and BIT star cancellation tasks, as well as bisecting three separate eighteen cm lines, immediately before taking part in the experiment (Table 1). Healthy elderly control subjects showed no signs of neglect on any of these three tests.

Brain lesions were imaged by clinical CT or MRI and plotted using MRICro software (<http://www.psychology.nottingham.ac.uk/staff/cr1/micro.html>) and a graphics tablet (WACOM Intuos A6). A T1 weighted template consisting of 12 axial slices were used to demarcate the lesions for neglect (Fig. 1) and non-neglect control patients (Fig. 2).

Behavioural task

The task was developed using E-Prime software (Psychology Tools Inc.) Participants were tested using a laptop computer (Toshiba Satellite Pro XP 22), seated at a distance of ~50 cm from the laptop screen (display 28.5 × 21.5 cm). At varying intervals, a target consisting of a central black circle (8-mm diameter) on a uniform grey background (Fig. 3A) was presented and the subjects' task was to respond as quickly as possible by pressing the central button on a response box (PST Serial Response Box, Psychology Tools Inc.). The circle remained on the screen for 1 s and interstimulus intervals were multiples of 1 s (pseudorandom variation), up to a maximum of 7 s. Stimuli (100) were presented over a total period of ~8 min. Reaction times and numbers of correct responses were recorded via the response box. Responses >1 s were not used for analysis as it would be difficult to be confident these were genuine responses to targets. Patients' eye movements were monitored clinically by the experimenter throughout the experiment, to ensure that individuals did not gaze rightwards of stimulus presentation. All subjects had a brief practice session before beginning the task.

Table 1 Stroke patients with Neglect (N1–N8) and without Neglect (C1–C8) who took part in Experiments 1 and 2

	Age (Years)	Time since stroke (Days)	MES (L)	MES (R)	BIT (L)	BIT (R)	Line bisection (cm)	Primary visual deficit	Lesion volume (cm ³)	Total errors (EXPT 1)
N1	95	20	16	23	16	22	0.8	HH	14.4	7
N2	36	38	26	28	26	27	0	NIL	83.4	4
N3	23	23	11	20	19	22	0.7	NIL	34.5	0
N4	44	3	15	30	25	27	0.5	NIL	35.3	16
N5	63	36	15	29	19	26	1.7	NIL	172	23
N6	83	22	2	25	12	25	1.1	NIL	61.4	2
N7	73	2091	29	29	25	25	2.7	NIL	94.5	6
N8	60	13	6	18	0	23	2.6	NIL	7.5	16
MEAN	59.6	22.5 ^a	15.0	25.3	17.8	24.6	1.3	–	62.9	9.3
C1	61	65	30	30	27	27	0	NIL	35.2	0
C2	78	13	30	30	27	27	0	NIL	19.0	0
C3	63	9	30	30	27	27	–0.1	HH	7.1	0
C4	24	6	30	30	27	27	–0.2	NIL	43.8	0
C5	64	51	30	30	27	27	0.2	NIL	13.3	0
C6	76	18	17	18	23	22	0.4	NIL	2.7	0
C7	74	19	26	28	27	27	–1.0	NIL	25	8
C8	29	2	29	29	27	27	0	NIL	8	1
MEAN	58.6	22.9	27.8	28.1	26.5	26.4	–0.1	–	19.3	1.1

^a Median instead of mean.

Mes (L), Mes (R): Scores out of 30 on the left and right sides of the Mesulam shape cancellation task. BIT (L), BIT (R): Scores out of 27 on the left and right sides of the BIT star cancellation. Line Bisection: Mean deviation (+ve=Rightward) on attempted bisection of three separate 18 cm centrally located horizontal Lines. Primary visual deficit: HH=Homonymous Hemianopia; NIL=No visual deficit was found to confrontation. None of our patients or control subjects had any visual deficits that were unrelated to stroke or that were not corrected with spectacles.

Results

The duration of the task was separated into ten successive epochs, each lasting 50 s. Both omissions in responding to targets and reaction times were analysed overall, and across each of these 10 time epochs.

Errors

Figure 3B shows the number of errors made by each group during the basic visual sustained attention task and the number of errors made by each individual patient is displayed in Table 1. As error data were not normally distributed, a non-parametric Kruskal–Wallis analysis was employed to assess whether there was a difference between the three groups. This revealed a significant effect for subject group ($\chi^2(2)=10.9$, $P<0.05$) with the neglect group making more errors than either the right-hemisphere stroke control group or the elderly control subjects (Fig. 3B). Overall, neglect patients made a mean of 9.13 omissions out of a possible total of 100, whereas for the stroke control and healthy control group the corresponding values were 0.75 and 0.38, respectively.

There was no significant difference between the two control groups and no interaction between group and epoch, indicating that no group showed a decrement over time. Thus although neglect patients were impaired *overall* at performing the task, this impairment did *not* worsen over time. In other words, there was no vigilance decrement over time on this task but neglect patients were impaired throughout the task compared to the other control groups.

Reaction time

A mixed design ANOVA was performed for reaction times with epoch as the within-subject variable and group as the between-subject factor. As Mauchly's test of sphericity was significant, a Greenhouse–Geisser correction (for possible inequality of variance and covariance) was performed, and no significant effect for epoch was found. There was also no significant effect for group indicating that neglect patients were not significantly impaired compared to the two control groups with respect to reaction time on the trials in which they responded. There was also no significant interaction between group and epoch, demonstrating again that there was no evidence of a selective decrement on the task for any group. Finally, reaction time *variance*, which has been used to index sustained attention in attention deficit hyperactivity disorder (Klein *et al.*, 2006; Johnson *et al.*, 2007), was not significantly greater in the neglect group compared to the stroke controls or elderly controls.

Correlation between total errors and measures of spatial bias

There was no significant correlation (Pearson's correlation coefficient) between the number of errors made by neglect patients and their total scores or degrees of lateralized bias on three standard tests of spatial neglect (Mesulam shape cancellation, BIT star cancellation, bisection of 3×18 cm lines). Degree of lateralized bias on cancellation tasks was calculated by dividing the difference between scores on the right and left sides of each array by the total number of targets found.

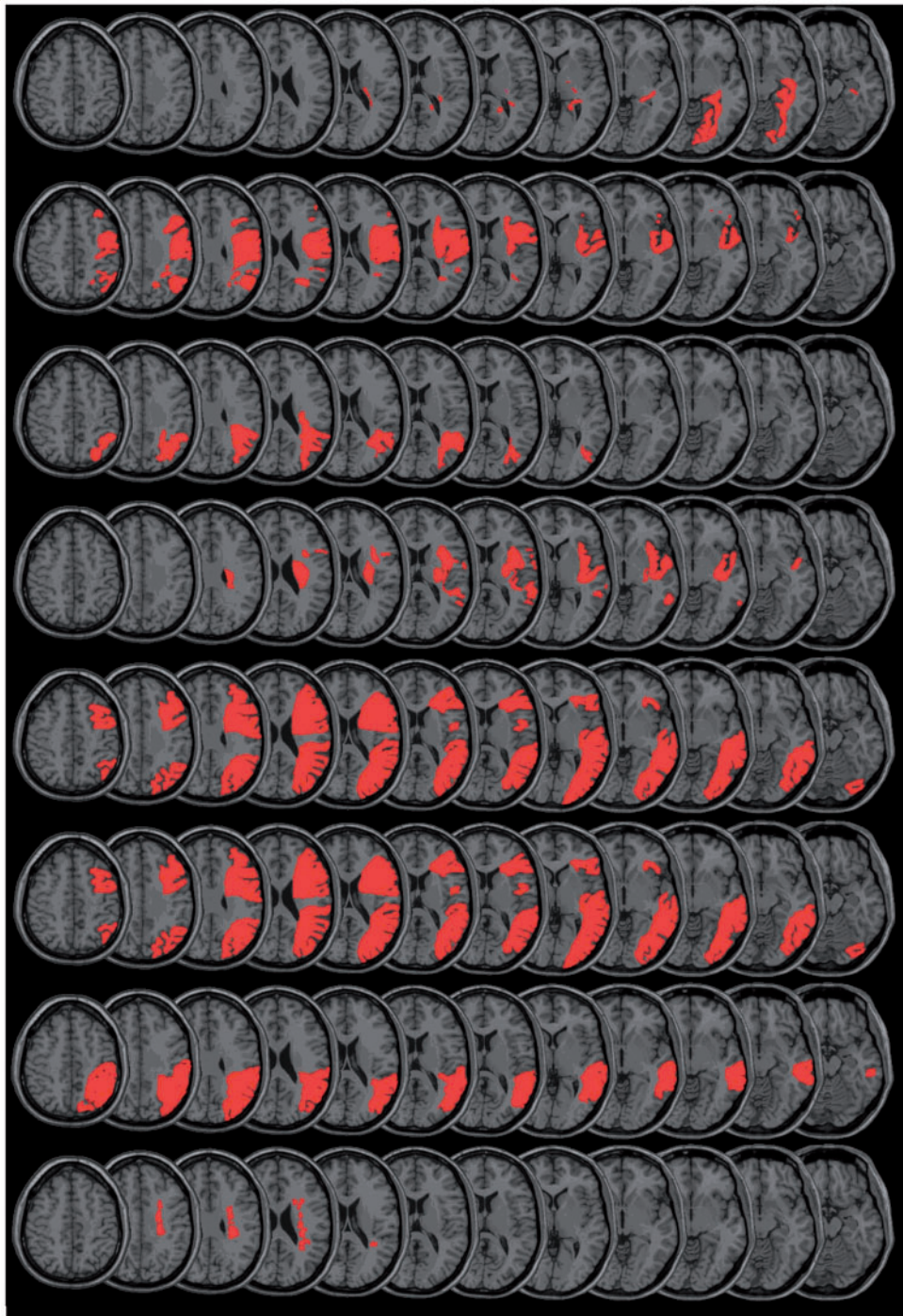


Figure 1 Lesions of neglect patients (N1–N8).

Relation to lesion volume and location

The lesion volumes of all the patients who participated in the experiment are presented in Table 1. As in previous lesion studies of stroke patients, individuals with neglect had much larger lesion volumes than patients without neglect (mean 62.9 cm^3 versus 19.3 cm^3), although it should be noted that the largest lesion in the right-hemisphere control stroke group (43.8 cm^3) was much larger than the smallest lesion in the neglect group (7.5 cm^3).

No significant correlation (Pearson's correlation coefficient) was found between lesion volume and neglect severity (as measured by number of targets found on the right side of the Mesulam cancellation array minus the number found on the left). In addition, there was no significant correlation between the total number of errors made on the sustained attention task and lesion volume within the neglect group. The lack of a statistically significant relationship between lesion volume and neglect, or

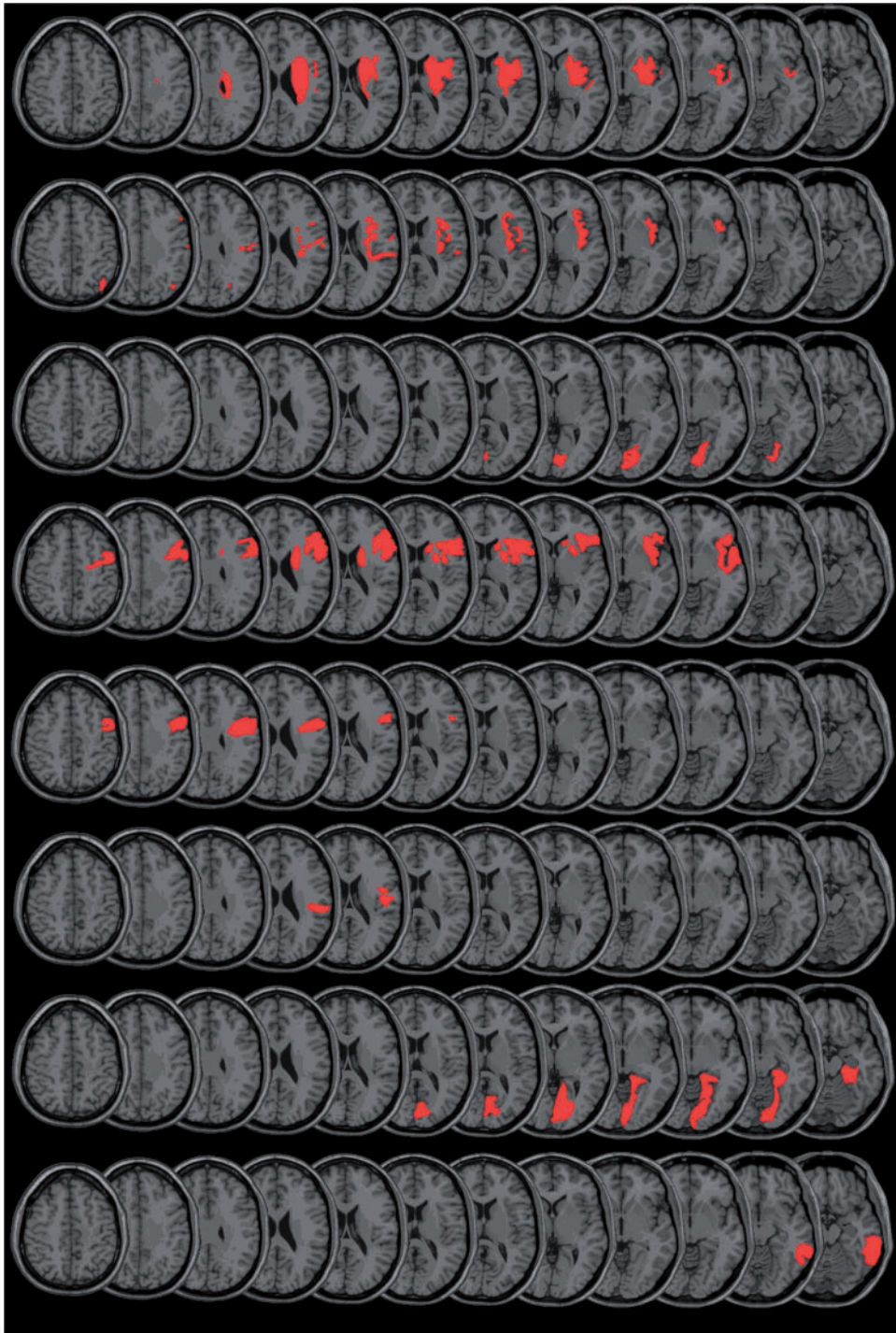


Figure 2 Lesions of non-neglect control stroke patients (C1–C8).

lesion volume and task performance, suggests that lesion volume was unlikely to be as important as lesion location in contributing to impaired performance. Moreover, although small group size can make the absence of a correlation difficult to interpret, it should be noted that patients with large lesions (e.g. N2, N7, C4) could perform the task relatively well, making only a small number of errors, whereas patients with smaller lesions (e.g. N8) made

substantially more errors (Table 1). This further supports the proposal that lesion anatomy, rather than volume, is most likely to be the crucial determinant of impairment on the task.

Figure 4 shows the lesion overlap analysis. Strokes involving either right middle cerebral or posterior cerebral artery territories occurred in both groups, as arterial territory was not used as a selection criterion. The red, orange and yellow areas in Fig. 4C

indicate those regions that were damaged in patients with neglect *and* also undamaged in patients without neglect. The purple and blue areas signify regions damaged in the non-neglect group but not in the neglect group. Two foci (indicated in yellow) were maximally damaged in patients with neglect but not in any of the control subjects. These both lay in the white matter deep to the temporoparietal junction (Talairach coordinates of centres: 52, –42, 17 and 39, –40, 24).

Discussion

Overall, patients with neglect were impaired compared to both control stroke patients as well as healthy elderly control subjects, when required to respond to a simple centrally presented visual stimulus. However, they did not demonstrate a performance decrement on the task. This finding is consistent with previous

studies of sustained attention in neglect, which also showed *overall* deficits but, as in this experiment, did not report vigilance decrements (Heilman *et al.*, 1978; Hjaltason *et al.*, 1996; Robertson *et al.*, 1997; Samuelsson *et al.*, 1998; Maguire and Ogden, 2002; Buxbaum *et al.*, 2004; Farne *et al.*, 2004). An alternative way to examine deficits of sustained attention is to index variability—or fluctuations—in reaction time (Klein *et al.*, 2006; Johnson *et al.*, 2007) but this was not significantly greater in neglect patients on this task either.

We designed the current task to have minimal visual processing and working memory demands, so subjects did not have to discriminate between stimuli and were not subjected to multiple simultaneous competing stimuli (Duncan *et al.*, 1999). Furthermore, because stimuli were presented at only one location, there was no need to make eye movements or spatial shifts of attention to perform the task accurately. Thus our detection task was designed to be as simple as possible so that errors would be unlikely to be attributable to deficits in visual processing, perception, working memory or neglect *per se*. Nevertheless, to make a stronger case for a deficit of sustained attention in neglect patients it would be important to demonstrate more than simply an overall deficit in performance.

Experiment 2: Sustaining attention to spatial locations or letter identity

Those visual studies that have demonstrated premature vigilance decrements in brain-damaged patients—but without neglect—have been conducted using discrimination paradigms that required

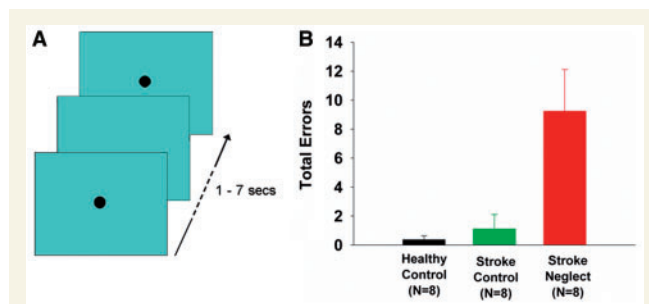


Figure 3 'Basic' sustained attention task. (A) Subjects responded by pressing a button each time a black circle appeared on the screen. The circles were presented irregularly and the task lasted ~8 min. (B) Errors made by each group on the 'basic' sustained attention task.

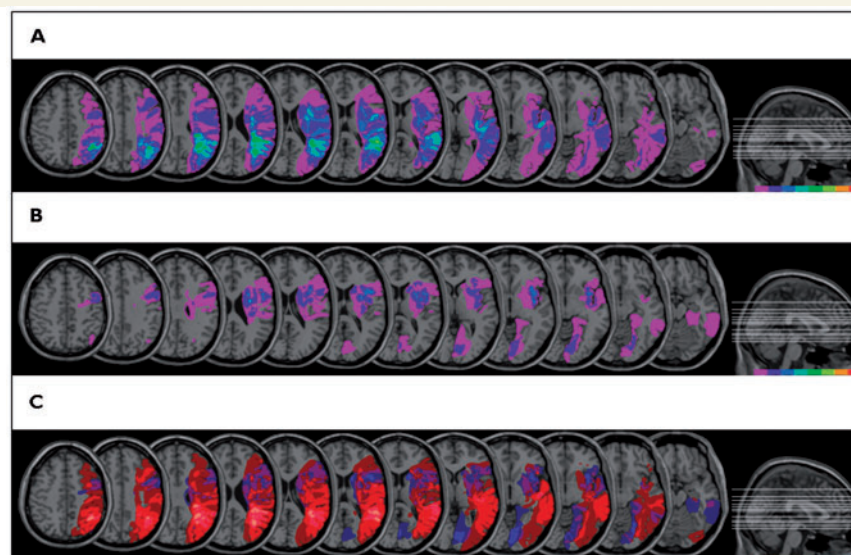


Figure 4 Lesion overlaps and subtractions for patients. (A) Right-hemisphere patients with neglect. (B) Right-hemisphere control patients without neglect. (C) Lesions of neglect patients minus those of control patients. The bright red areas indicate those regions most damaged in those patients with neglect and that were undamaged in those patients without neglect. The blue areas signify regions damaged in the non-neglect group but not in the neglect group.

responses to targets as well as withholding of responses to non-target stimuli (Whyte *et al.*, 1995; Rueckert and Grafman, 1998; Manly *et al.*, 2003). The current detection task had no such requirement, perhaps making it less likely that a vigilance decrement would be found. To further assess this, a second visual paradigm was developed, where subjects were required to respond to targets and withhold responses to non-targets. Two versions of the task were used, one requiring responses to spatial targets and the other to non-spatial targets, allowing us to examine whether neglect patients manifest a selective spatial deficit in the maintenance of attention *over time*.

To investigate whether there is an interaction between deficits of spatial and vigilant attention, an explicit spatial component was incorporated, although crucially this was *not* spatially lateralized (i.e. displayed left to right across the screen). In this paradigm, subjects were required to respond when targets appeared in previously specified locations on the vertical meridian. The use of sequential stimulus presentation on the vertical meridian helped to avoid the possibility that neglect patients would simply not perceive or encode stimuli that were presented contralesionally, on their neglected side, a factor that is exacerbated by concurrent ipsilesional distractors (Molenberghs *et al.*, 2008).

As neglect patients have oculomotor deficits (Girotti *et al.*, 1983; Walker and Findlay, 1996; Behrmann *et al.*, 2001) and have also been shown to have impairments in shifting attention from one item in space to another (Posner *et al.*, 1984; Bartolomeo and Chokron, 2002; Vandenberghe *et al.*, 2005) they might be impaired on a task where targets were displayed in different locations, whether or not it was spatially lateralized. The patients in the current study were therefore also tested with a control, non-spatial task that employed *identical* stimuli and locations to the spatial task, so the requirement for accurate eye movements and shifts of attention were matched. For both spatial and non-spatial versions of the task we used letter stimuli.

The key difference was that the non-spatial task required attention to be directed to the identity of the letters rather than their locations, whereas the spatial task required subjects to attend to the locations of letters, regardless of their identity. Thus any difference in performance between the tasks would not be due to the requirement for attending to several different locations over time, but rather to the need to maintain attention towards spatial rather than non-spatial attributes of the stimuli. Stimuli were presented successively rather than simultaneously. Because parietal patients are known to have a reduced capacity for attending to multiple simultaneously presented stimuli, even in the ipsilesional hemifield (Duncan *et al.*, 1999; Vuilleumier and Rafal, 2000), the presence of only one stimulus in the display at any one time eliminated the possibility that targets might be missed because of any competing non-target stimuli.

Methods

Subjects

Participants were identical to those who took part in Experiment 1 (see Table 1 for details and Figs 1 and 2 for lesion anatomy).

Behavioural task

The task was developed using E-Prime software (Psychology Tools Inc.) Participants were tested using a laptop computer (Toshiba Satellite Pro XP 22), seated at a distance of ~50cm from the laptop screen (display 28.5 × 21.5 cm). During both spatial and non-spatial versions of the task subjects were presented with a sequence of black letters (consisting of 'A', 'B', 'C', 'D' or 'E', each ~15 × 15 mm) on a uniform grey background at one of five positions along the vertical meridian of the screen (Fig. 5). Participants were asked to respond as quickly as possible by pressing the central button on a response box when they saw one of two predefined target stimuli. Stimuli were presented every 2 s, remaining on the screen for 1 s. Two hundred-fifty stimuli (targets and non-targets) were presented in total over a total period of ~8 min, with 100 target stimuli shown during that time period. Reaction times (for button presses made within 1 s after stimulus onset) and numbers of correct responses were recorded.

For the spatial task, patients were initially shown the five possible locations on the vertical meridian where stimuli might appear, with

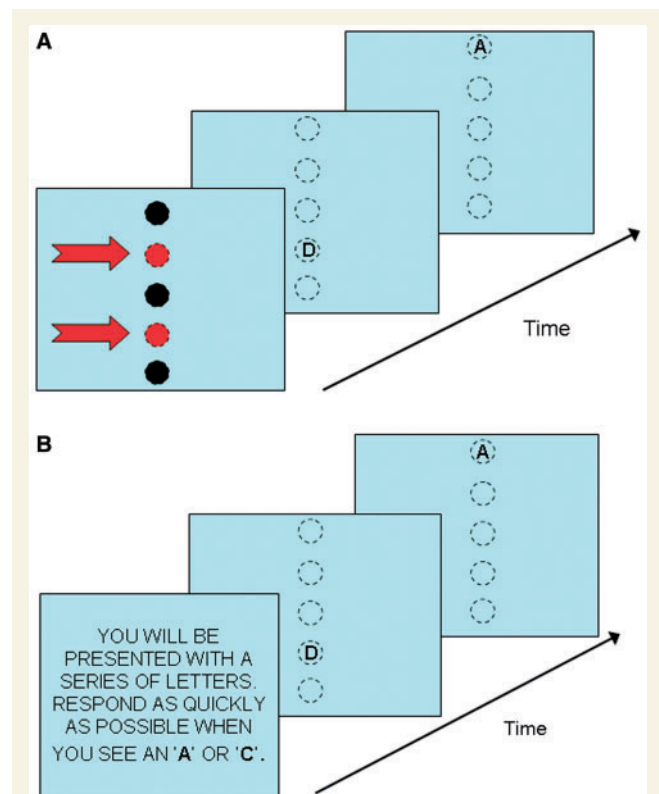


Figure 5 Spatial and non-spatial (verbal) tasks in Experiment 2. **(A)** In the spatial task, subjects were asked to respond whenever a letter was presented at either of the two predefined locations (indicated by red arrows in this figure, but not displayed during the actual experiment). The first test display shows a letter appearing at one of the target locations; the second display shows a letter at a non-target location. Broken-line circles indicate potential target positions; targets were displayed on a blank screen and there were no target markers. **(B)** In the non-spatial task, subjects responded whenever the letter 'A' or 'C' was presented regardless of their spatial location. The second test display shows a target stimulus; the first display shows a non-target.

one location above and one location below the horizontal meridian being designated target locations (Fig. 5A). They were asked to respond as quickly as possible when any letter appeared in either of those two locations. As in the letter task, targets appeared on a blank grey screen, with no placeholders for target locations. The same set of letter stimuli were used in the non-spatial control task (Fig. 5B), but in this condition subjects were instructed to press the button on the response box as quickly as possible if they saw an 'A' or a 'C', *regardless of its position* on the screen. When subjects felt that they had understood the instructions and had a brief practice session, they were asked to press the central button on the response box and the testing session began.

Results

Errors

A mixed design ANOVA was completed for errors with epoch and task as within subject factors (Fig. 6). There was a significant effect of group [$F(2,21)=21.58$, $P<0.001$], with the neglect group making more errors than right-hemisphere stroke patients without neglect (*Post hoc* Tukey's HSD test, $P<0.001$). There was also a significant effect of task [$F(1,21)=38.95$, $P<0.001$], with all groups making more errors on the spatial than the non-spatial task. Neglect patients were not significantly worse than the two control groups on the non-spatial task (One way ANOVA, [$F(2,21)=2.24$, $P=0.133$]). In addition, there was also a significant interaction between task and group [$F(2,21)=17.67$, $P<0.001$] but no significant interaction for epoch versus group.

Critically, there was a significant three way interaction between task, group and epoch [$F(18,189)=27.9$, $P=0.04$], Mauchly's test of sphericity positive; Greenhouse–Geisser correction. Figure 6A shows that patients with neglect made far more errors than the control groups throughout the spatial task. Not only did they make more errors at the beginning of the task but also the number of errors that they made increased substantially *with time* on the spatial task, reflected by the statistically significant three-way interaction. Note that the decline in performance did not begin instantaneously but commenced 3–4 min after starting the task.

Thus neglect patients showed a *decrement* in sustained attention during the task. They showed no such decrement when performing the non-spatial version of the task, which required attention to identical stimuli but responses to letters rather than spatial targets. Neither control group showed a decrement with respect to reaction times or errors in either the spatial or the non-spatial variant of the task. An almost identical number of total responses was made by neglect patients (786) compared to stroke controls without neglect (787) (see Supplementary material, Table S2). However, with increasing time on task, although the number of correct responses and omissions made by the neglect group remained relatively stable, the level of commission errors increased substantially after the fourth epoch (Supplementary material, Fig. S1).

Individual performances are given in the Supplementary material (Table S1). Note that two patients in the neglect group (N2 and N4) were not impaired on the spatial task, when compared with individuals in the stroke control group.

Signal detection theory and vigilance decrement

To assess the nature of any decrement that might have occurred on either task variant, signal detection analysis was performed (Green and Swets, 1966). In particular, the sensitivity (d') of each group to spatial signals was calculated. This index represents the ability to differentiate signals from non-signals, with a d' of 0 representing chance performance. This was to assess whether the decrement observed in neglect patients was due to a genuine sensitivity decrement over time, or whether it represented an increase in the response criterion with sensitivity remaining stable. That is, subjects may have been adopting a more conservative response strategy as the task continued, causing a change in performance that was not necessarily secondary to any change in sensitivity to target stimuli (Whyte *et al.*, 1995; Parasuraman *et al.*, 1998). Such a sensitivity decrement appears to be associated with a genuine loss in the ability to discriminate targets from non-targets (See *et al.*, 1995).

Figure 6C shows on a log scale the sensitivity (d') during each epoch for the neglect and stroke control groups while performing the spatial variant of the sustained attention task. The sensitivity of

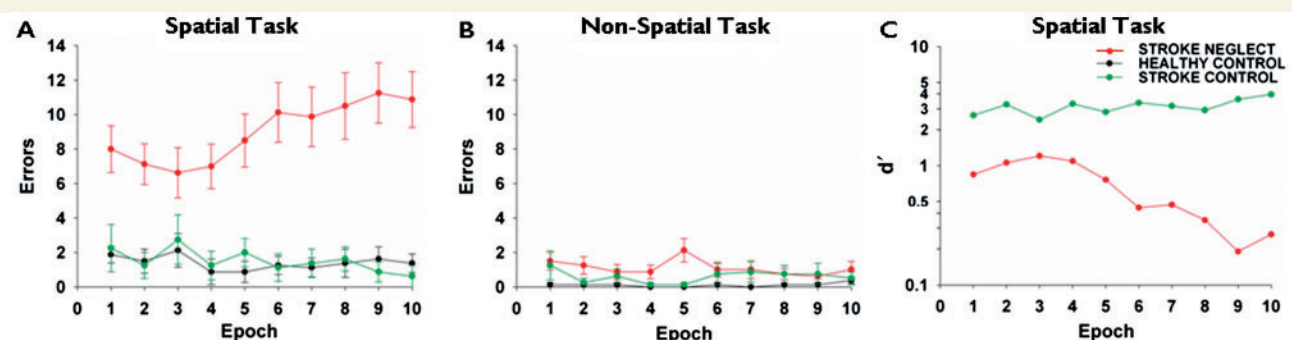


Figure 6 Performance over time on spatial and non-spatial tasks. (A) Errors over time epoch on spatial task (Error bars=SEM). Total time= ~ 8 min. (B) Errors over time on non-spatial task (Error bars=SEM). Total time= ~ 8 min. (C) Sensitivity of target detection (d') across time on the spatial task. Neglect patients begin with lower target sensitivity than control patients, and this decreases substantially after the fourth epoch. Note log scale.

the control stroke patients was higher throughout the task and showed no decrease with increasing time. In contrast, the neglect group showed a marked decline in sensitivity from the end of the third epoch. Thus the decrement observed in neglect patients on the spatial task does not seem to be secondary to the adoption of a different response bias by these patients. Instead, it appears to reflect a genuine decline in sensitivity to spatial stimuli with increasing time on task.

Reaction time

A mixed design ANOVA of reaction times was conducted with epoch and task as within subjects factors (only seven neglect patients were included in this analysis as there were no correct responses in some epochs for one subject). There was a significant effect of task [$F(1,20)=34.7$, $P<0.001$] with the spatial variant being associated with longer reaction times than the non-spatial (letter) task (See Supplementary material, Fig. S2). Thus, the spatial paradigm may have been more difficult than its verbal counterpart, an issue we address in Experiment 3. There was no effect for epoch and no significant interaction. Finally, although reaction times were generally longer for the neglect group, the difference failed to reach statistical significance. There was no statistically significant difference between the reaction times for commission errors (false alarms) and correct responses in the neglect group (Mann–Whitney, $P=0.940$). In addition, reaction times for commission errors remained stable over the duration of the task (See Supplementary material, Fig. S3).

No significant correlations were found between any of the standard measures of neglect (Mesulam Shape cancellation, BIT star cancellation or line bisection) and performance on either the spatial and non-spatial sustained attention tasks (where performance indices were total errors, omissions, commissions and decline in any of these parameters over the duration of the task). There was also no significant correlation between performance on spatial and non-spatial versions of the tasks (total errors, omissions and commissions).

Altitudinal neglect

To assess whether performance was equivalent for superior and inferior targets (whether there was any evidence of altitudinal neglect), we conducted an analysis of error rate for targets above and below the horizontal meridian. Performance was equivalent for superior versus inferior targets [Paired t -test

($P=0.918$)] suggesting that results were not influenced by any altitudinal neglect or field defect.

Anatomy of interaction between spatial and vigilant attention

The lesion overlaps of neglect and non-neglect patients are identical to those shown for Experiment 1 in Fig. 4. However, lesion overlap maps such as these do not differentiate between loci of damage associated with abnormal behavioural performance and those areas most likely to be damaged by vascular insult simply because they receive the same arterial supply as areas that are critical for the behaviour under consideration.

To investigate further the precise brain regions damaged in patients who show a performance decrement over time on the spatial task, therefore, we performed a permuted Brunner–Munzel rank order analysis, which is now part of MRICron software (www.micron.com/mricron). This analysis does not depend upon any *a priori* division of patients into neglect and non-neglect groups. It takes the behavioural data from all patients and asks which voxels, when lesioned, are associated with that behavioural characteristic. Therefore, this test provides a relatively assumption-free measure of whether or not damage at each voxel is associated with a particular deficit (Rorden *et al.*, 2007). The Brunner–Munzel test has also been found to be robust in the face of violations of normality and is considered the statistic of choice for studies such as this one.

For the purposes of this analysis we indexed our behavioural measure of interest—decrement in performance over time on the spatial task—by subtracting the number of errors in first half of task from errors in the second half of the task, for each subject. Brunner–Munzel analysis revealed an extremely highly significant association between decline in performance on the spatial task and lesioned voxels which span a region from IPS (most dorsal MNI coordinates: $-51, -49, 48$) to TPJ (Fig. 7).

Discussion

The results of Experiment 2 demonstrated that neglect patients were impaired at maintaining attention over time on the spatial task, an effect associated with lesioned voxels in the right PPC. However, their performance on this task was also generally worse than on the non-spatial task. It could be argued, therefore, that the decrement observed on the spatial task might not have been

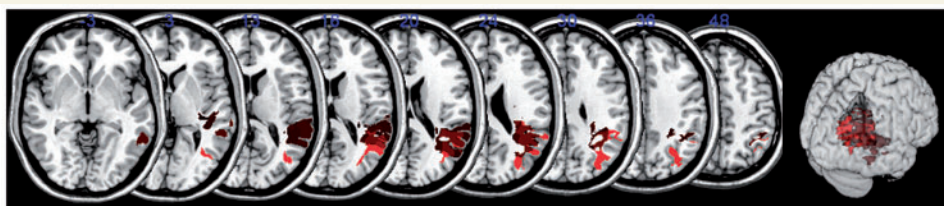


Figure 7 Neuroanatomical correlates of interaction between Spatial and Sustained Attention. Dark areas indicate voxels with weaker association with decrement on spatial Task ($2.20 < Z < 6.0$) and areas in red show voxels that had strong association ($Z > 15$) with decline in performance on the spatial task.

due to a particular problem with maintaining attention over time to *spatial* aspects of the stimuli, but instead to an impairment of sustaining attention over time whilst performing a more taxing task. If the spatial task required greater effort and cognitive resources for neglect patients, it may have led to a premature worsening of performance because vigilance tends to decline during high demand tasks, even when stimuli are identical (Smit *et al.*, 2004). Thus the observed decline in sustained attention may have resulted from the interaction between task difficulty and prolonged performance rather than any particular impairment of *spatial* sustained attention. We therefore designed a new, more demanding experiment such that control subjects made a similar numbers of initial errors on *both* spatial and non-spatial variants of the task.

Experiment 3: Sustaining attention to spatial locations or pattern identity

In this task, subjects now sustained attention either to spatial locations or the identity of patterns in stimuli. If performance on this more difficult non-spatial task were to be associated with a decline in performance in control participants, then it would be likely that the decrement observed in Experiment 2 in neglect patients was primarily due to the increased cognitive resources demanded by a spatial task. On the other hand, if neglect patients were to show a decline in performance only on the spatial task and healthy individuals show no such decrement on either spatial or non-spatial task, then the specific interaction between responding to spatial targets and maintaining attention on task in patients with neglect would be unique.

Methods

Subjects

Eight patients with neglect (mean age 53.5 years, mean time since stroke: 466 days) were tested, including two involved in the previous

experiments (Table 2). Fourteen elderly healthy controls (mean age 67.6 years) were also studied. None had any history of neurological disease. Screening tests for neglect included Mesulam shape cancellation (Mesulam, 1985), BIT star cancellation and copying drawings (Wilson *et al.*, 1987), line bisection, reporting objects around the room (Stone and Greenwood, 1991), pointing to body parts, comb and razor test for personal neglect (McIntosh *et al.*, 2000) and clock drawing. Healthy elderly control subjects showed no signs of neglect on BIT star cancellation, Mesulam shape cancellation or line bisection tasks.

Behavioural task

Task conditions were identical to those in Experiment 2, but instead of being presented with a sequence of black letters participants were shown a series of separate *pattern stimuli* (15 × 15 mm) at the same five vertical locations on the laptop screen. As in Experiment 2, they were asked to respond to individual locations on the spatial variant of the task, whereas they were now asked to respond to two (out of a possible 5) patterns on the non-spatial task (Fig. 8A).

Results

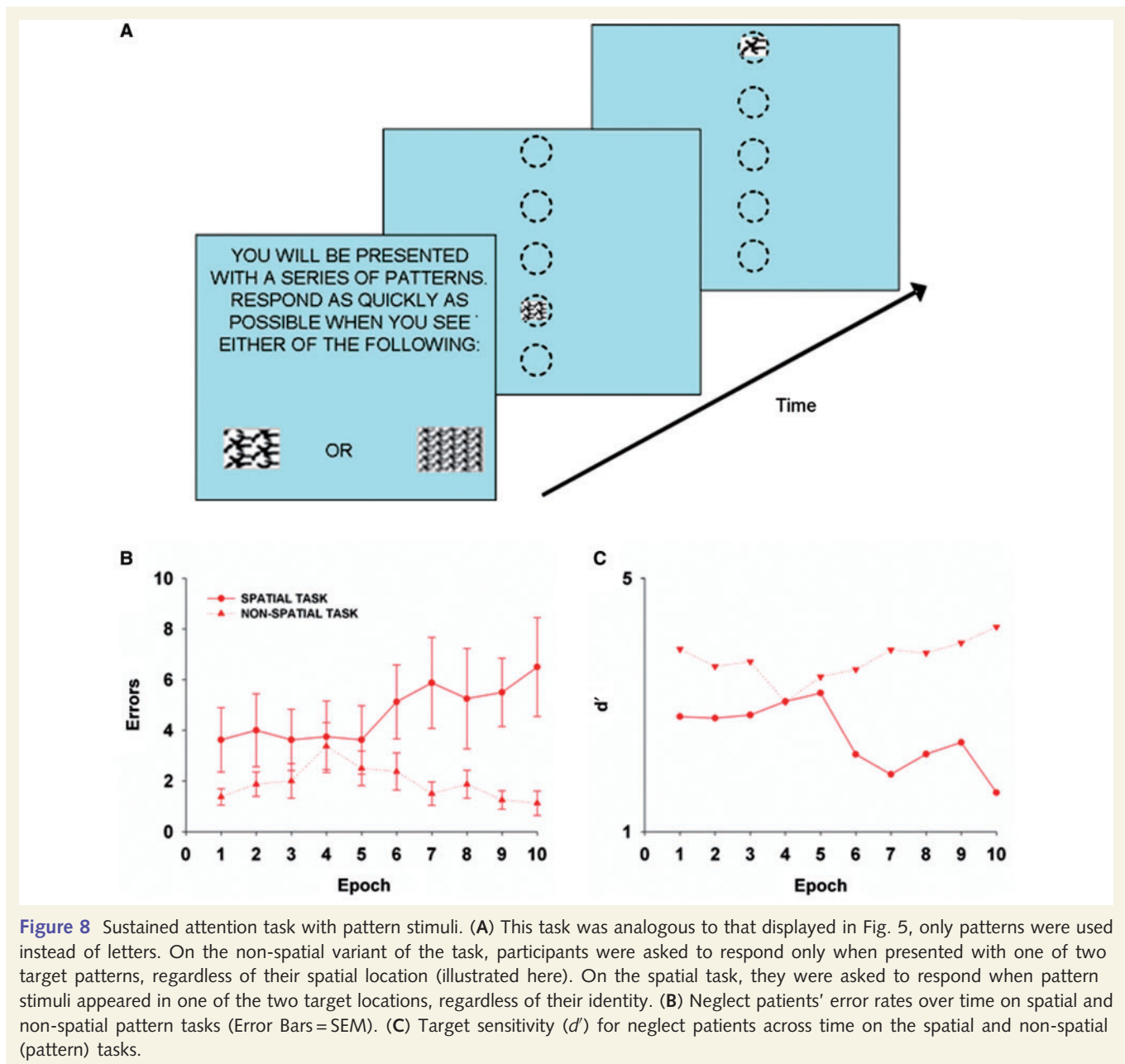
Unlike Experiment 2, where letters were used, healthy elderly control subjects did *not* perform significantly worse on the spatial variant of the task compared to the non-spatial (pattern) variant [paired *t*, $P > 0.05$; Mean errors on spatial task = 2.21 (SD 2.36, 95% CI 0.85–3.58) and mean errors on non-spatial task = 6.36 (SD 9.26, 95% CI 1.01–11.7)]. If anything, the non-spatial task might have been a little harder than the spatial one, although not significantly so.

A mixed design ANOVA on the error data revealed a significant interaction between task and group [$F(1,20) = 9.40$, $P = 0.006$] such that neglect patients performed worse on the spatial task than the pattern task (see Supplementary material, Table S3 for details of individual patients' performance). Crucially, there was also a significant three-way interaction between epoch, group and task [$F(9,180) = 15.3$, $P = 0.048$] with neglect patients showing a decline in performance between the first half of the experiment and the second half, specifically only for the spatial task (Fig. 8B).

Table 2 Stroke patients with Neglect (N1–N8) who took part in Experiment 3

	Age (Years)	Time since stroke (Days)	MES (L)	MES (R)	BIT (L)	BIT (R)	Line bisection (cm)	Primary visual deficit
N1	70	31	4	25	4	23	2.9	NIL
N2	74	2700	29	29	25	25	2.7	NIL
N3	23	60	8	20	22	19	1.0	NIL
N4	67	900	7	30	12	23	0	NIL
N5	40	3	25	25	27	27	0.5	NIL
N6	36	6	30	30	20	27	0.7	NIL
N7	60	21	19	23	15	16	2	NIL
N8	59	14	0	14	17	20	1.0	NIL
MEAN	53.5	466.9	15.3	24.5	17.8	22.5	1.4	NIL

Mes (L), Mes (R): Scores out of 30 on the left and right sides of the Mesulam shape cancellation task. BIT (L), BIT (R): Scores out of 27 on the left and right sides of the BIT star cancellation. Line Bisection: Mean deviation (+ve = Rightward) on attempted bisection of three separate 18 cm centrally located horizontal Lines. Primary visual deficit: HH = Homonymous Hemianopia; NIL = No visual deficit was found to confrontation.



Neglect patients did not make significantly more errors in the first half of the spatial task than they did in the first half of the non-spatial task (t -test, $P=0.247$). Thus the pattern task was, *initially*, equivalent in difficulty as the spatial task for both neglect patients and healthy elderly controls. However, neglect patients were significantly worse in the second half of the spatial task (Paired t -test: $t=2.58$, df 7, $P=0.037$). Thus initial difficulty levels were comparable, but neglect patients again manifested a vigilance decrement only on the spatial task. Note that although the non-spatial task was now much harder than in Experiment 2, there was still no evidence of a decrement in performance within the 8-min duration of this task.

Importantly, the decline in performance on the spatial task was again associated with a decrease in sensitivity (d') (Fig. 8C). Thus, the effect was not simply attributable to an alteration

in response bias but appeared to be a genuine decrement in sensitivity. The equivalence of the spatial tasks in Experiments 2 and 3 is demonstrated in Supplementary Fig. S4, which displays the fraction of total errors across time for the neglect group on both spatial tasks. Patients with neglect had very similar temporal patterns of decrement in both experiments, providing further evidence for the close correspondence of the two spatial tasks, across experiments. Analysis of the reaction time data did not reveal any significant main effects of task, epoch or their interaction.

Discussion

The results of the experiments described here provide evidence for a deficit in the ability to maintain attention to even simple visual

stimuli presented centrally in the neglect syndrome (Experiment 1; Fig. 3). However, as in previous studies of neglect patients, performance on this simple task did not decline over time. A *vigilance decrement* was found specifically when neglect patients were required to maintain attention to spatial locations, but not to letter identity (Experiment 2; Fig. 6). In a final experiment, which equated task difficulty between spatial and non-spatial material (pattern identity) we again found a specific vigilance decrement when patients with neglect were required to sustain attention to spatial locations but not to non-spatial features (Experiment 3; Fig. 8). Interrogation of the lesion anatomy across neglect and non-neglect patients, demonstrated that the impairment in maintaining vigilance to spatial information, was associated with damage to cortical voxels between the right IPS and IPL and the underlying white matter (Fig. 7).

These findings reveal a highly specific interaction between deficits in spatial processes and sustained attention in the neglect syndrome, associated with a clear anatomical locus in the right PPC. Neglect patients have previously been found to be impaired when responding to simple stimuli (usually auditory), but these tasks sometimes involved additional cognitive components, in particular working memory and/or response inhibition (Heilman *et al.*, 1978; Hjaltason *et al.*, 1996; Robertson *et al.*, 1997; Samuelsson *et al.*, 1998; Maguire and Ogden, 2002; Buxbaum *et al.*, 2004; Farne *et al.*, 2004). The simple visual task described in Experiment 1 had no such requirements. Even though these processes were not required for accurate task completion, our patients with neglect were still impaired overall when compared to stroke patients with right-hemisphere damage and healthy elderly volunteers.

However, it might be argued that poor performance which continues to be maintained at a similar level throughout a task indexes difficulty due to the specific cognitive demands of that task, rather than one of sustaining attention on it. In studies of healthy individuals and non-stroke patients, vigilance decrements have often been used as a key measure of a decline in sustained attention (Whyte *et al.*, 1995; Rueckert and Grafman, 1996, 1998; Parasuraman *et al.*, 1998). In the current series of experiments, patients with neglect did manifest a decrement in sensitivity over time on task, but only on the spatial variants of the tasks in Experiments 2 and 3.

Might such a deterioration in performance be due simply to impairments in spatial memory? Neglect patients have previously been shown to have deficits in spatial working memory (SWM), which might have contributed to poor performance in both experiments here. This impairment has been found to be present on both spatially lateralized (Pisella *et al.*, 2004; Mannan *et al.*, 2005) and non-lateralized tasks (Malhotra *et al.*, 2005; Ferber and Danckert, 2006). However, it should be noted that the working memory demands of the tasks in Experiments 2 and 3 were low, because subjects needed to keep only two spatial targets online to perform the task accurately. Furthermore, target identities remained static throughout the duration of the task, minimizing requirements for manipulation of information, and similar paradigms have in fact been employed as control (or '0-back') tasks in working memory studies. However, it is still possible that neglect patients were simply unable to hold an online

representations of both spatial targets, as the right posterior cortical regions that were damaged in these patients have been associated with poor maintenance of spatial information (De Renzi and Nichelli, 1975) and some individuals with neglect may only be able to hold information about one location at any one time (Malhotra *et al.*, 2005). Moreover, patients might have been unable to accurately localize spatial stimuli (DiPellegrino and De Renzi, 1995) leading to higher error rates.

Deficits of SWM in neglect have been demonstrated over seconds (Pisella *et al.*, 2004; Malhotra *et al.*, 2005; Mannan *et al.*, 2005) whereas sensitivity in the current task did not decrease until over 3 mins had passed (Figs. 6 and 8). Therefore, SWM deficits could indeed have been responsible for the *initial* poor performance of patients with neglect on the spatial sustained attention task. However, these impairments alone would not account for the substantial *decline* in performance of the neglect group, associated with a decrease in sensitivity to spatial targets, which occurred approximately half way through each task. Thus, the initial poor performance of the neglect group when performing the spatial tasks (Fig. 6A) might in part be due to an impairment of SWM. Failure to sustain attention to spatial information is indexed by the performance decrement (including target sensitivity) which was not observed until approximately halfway (~4 min) into *both* the spatial tasks in Experiments 2 and 3 (Supplementary Fig. S4).

We propose that an interaction between weak spatial target representation (including SWM) and the need to maintain attention towards spatial stimuli is likely to have led to the selective vigilance decrement on the spatial tasks in both experiments. It is likely that the spatial requirements of the tasks in Experiments 2 and 3 were particularly demanding for patients with neglect and posterior parietal damage, leading to the observed time-on-task decline in both experiments. This is consistent with studies of healthy individuals which have shown that increased working memory load can interact with the ability to sustain attention, resulting in premature vigilance decrements (Parasuraman, 1979; Caggiano and Parasuraman, 2004).

Why should there be such an interaction between spatial processes and sustained attention? It might be that the deficit that characterizes neglect is an impairment in a unitary mechanism that involves maintaining attention to spatial locations. Alternatively, the functional interaction might result from the proximity of cognitive modules in the PPC that are involved *separately* in spatial functions and sustaining attention. This would be more consistent with suggestions that neglect is a multi-component syndrome with different patients being affected by different combinations of deficit (Mattingley *et al.*, 1998; Mesulam, 1999; Driver and Vuilleumier, 2001; Robertson, 2001; Husain and Rorden, 2003; Buxbaum *et al.*, 2004; Hillis *et al.*, 2005; Milner and McIntosh, 2005; Hillis, 2006; Bartolomeo, 2007). Such a view is supported by our finding that not all neglect patients showed a deficit in sustaining attention to spatial locations. Patients N2 and N4 did not have a deficit in sustaining attention on the spatial task in Experiment 2 (see Supplementary material, Table S1). Damage to the right posterior parietal cortex appears to impair the ability to sustain attention to spatial locations; many patients with neglect will have such a deficit because their lesions involve this region,

but some individuals will not demonstrate such an impairment even though they have clinical signs of neglect.

Recently, it has been proposed that while sub-regions within the SPL and IPS are involved in spatial aspects of attention, working memory and directing limb or eye movements, other regions within the right IPL and IPS may have key roles in sustaining attention as well as detecting salient, novel events (Husain and Rorden, 2003; Husain and Nachev, 2007). Thus, according to this scheme, there is a dorso–ventral gradient across the right PPC with predominantly spatial functions associated with the SPL and predominantly non-spatial functions associated with the IPL, and some IPS regions subserving both. In the current study, decrement in performance on the spatial vigilance task was strongly associated with damage to the IPL, extending dorsally to the IPS and medially to involve the underlying white matter (Fig. 7). The result is in keeping with the model since the lesioned voxels associated with this specific deficit span regions associated with both spatial functions and sustained attention. Damage to white matter tracts may also serve to disconnect these parietal areas from frontal regions (Doricchi and Tomaiuolo, 2003; Thiebaut de Schotten *et al.*, 2005; He *et al.*, 2007) which play a functional contribution to these processes (Husain and Nachev, 2007). Recent investigations with diffusion tensor imaging have demonstrated that the IPL is connected to the lateral prefrontal cortex by the human homologue of the third branch of the Superior Longitudinal Fasciculus (Thiebaut de Schotten *et al.*, 2005, 2008; Bartolomeo *et al.*, 2008). As the right prefrontal cortex has also been demonstrated to be involved in the ability to sustain attention (Wilkins *et al.*, 1987), the selective vigilance decrement that we have found for spatial information may perhaps be related to the right PFC being disconnected from cortical parietal modules that are involved in coding spatial locations.

An interaction between sustained attention and spatial performance has also been demonstrated recently by the effects of guanfacine on a small set of neglect patients (Malhotra *et al.*, 2006). Improvements in spatial search following the administration of this noradrenergic agonist may have been due to its positive effects in prolonging time-on-task. Some recent studies in healthy individuals have also revealed interactions between sustained attention and spatial awareness or spatial working memory (Caggiano and Parasuraman, 2004; Manly *et al.*, 2005).

Two important issues remain to be determined in future investigations. First, how does the deficit in sustaining attention to spatial locations contribute to the severity or presentation of neglect? In the current study, we found no significant correlations with performance on our tasks and simple bedside clinical measures of neglect. It is possible that such clinical neglect measures might not always be sensitive indices. Alternatively, the lack of such a finding might be due to the influence of other contributing variables or components of the neglect syndrome. Deficits of sustaining attention to spatial locations might have differing effects on neglect severity, depending upon interactions with other cognitive components of neglect, which we know to be variable across patients (Buxbaum *et al.*, 2004). This issue is really part of the larger question of how the many component deficits

identified in the neglect syndrome might impact on each other to define the clinical presentation of the disorder—a challenge for any future study.

Second is the deficit of maintaining attention to spatial locations really unitary disorder or due to two different processes (globally sustaining attention and holding a representation of spatial locations) subserved by regions that lie close to each other in the PPC? This is a difficult question to answer. One potential solution would be to investigate patients with highly focal lesions of the right PPC, who need not have neglect. If dissociations as well as associations between sustaining attention and memory for spatial locations can be found, related systematically to lesions of different parts of the PPC, this would provide a strong case for two separate processes. However, such focal lesions are rare so an alternative possibility is to examine interactions between these two processes in functional imaging studies with healthy individuals. To the best of our knowledge, no such investigation has been performed. The results would have important implications for competing models of human PPC function.

To date, most proposals regarding parietal function have focused on other functions such as spatial vision, vision-for-action or action understanding (Ungerleider and Haxby, 1994; Milner and Goodale, 1995; Rizzolatti and Matelli, 2003). Alternatively, they have considered sustained attention findings (Posner and Petersen, 1990), but most recently from the perspective of a general role in detecting behaviourally relevant salient stimuli (Corbetta and Shulman, 2002; Corbetta *et al.*, 2005). While we also acknowledge an important role for the IPL in detecting salient information (Husain and Nachev, 2007), we argue that sustained attention and its articulation with spatial functions are crucial aspects of PPC function that need to be considered separately if we are to have a better understanding of the neglect syndrome and the normal functions of the PPC.

Supplementary material

Supplementary material is available at *Brain* online.

Acknowledgements

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