Spatial working memory capacity in unilateral neglect

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Summary

It has been proposed recently that a deficit in keeping track of spatial locations may contribute to the severity of unilateral neglect in some right hemisphere stroke patients. However, performance on traditional spatial working memory (SWM) tasks (e.g. Corsi blocks) might be confounded by failure to encode leftward locations, rather than a true deficit of maintaining locations in SWM. Here we introduced new procedures for circumventing this to measure SWM capacity in neglect. In a first experiment, 20 right hemisphere stroke patients (10 with and 10 without neglect) were tested on a computerized vertical variant of the Corsi task. Sequences of spatial locations in a vertical column were displayed and participants had to tap out the remembered sequence on a touchscreen. Patients with left neglect were impaired on this vertical SWM task compared with all control groups. However, poor performance on this task (as for Corsi blocks) might involve impaired memory for stimulus sequence, or poor visuomotor control of manual responding, rather than reduced SWM capacity *per se*. A second experiment therefore employed a purer measure of vertical SWM. After the displayed sequence, a single location was now probed visually, with observers judging verbally (yes/no) if it had been in the preceding sequence. Hence order no longer mattered, and no spatial motor response was required. Again, the neglect group was impaired relative to all others, now with very little overlap between the performances of individual neglect patients versus individuals in control groups. Poor performance on the second task, which provides a purer measure of SWM capacity, correlated with severity of left neglect on cancellation tasks (but not on line bisection), consistent with recent proposals that SWM deficits can exacerbate left neglect on visual search tasks when present conjointly. Lesion anatomy indicated that neglect patients with a SWM deficit were most likely to have damage to parietal white matter, plus, in the second experiment, to the insula also. These findings demonstrate that an impairment in SWM capacity can contribute to the neglect syndrome in patients with stroke involving regions within the right parietal lobe and insula.

Introduction

Contemporary views of the neglect syndrome consider it to be a heterogeneous condition, consistent with the variety of anatomical sites that are often disrupted in such patients (Halligan and Marshall, 1994; Mesulam, 1999; Heilman and Watson, 2001; Vallar, 2001; Husain and Rorden, 2003; Harvey, 2004; Parton *et al*., 2004; Pia *et al*., 2004). Different combinations of underlying deficit are present in different patients with the syndrome (Buxbaum *et al*., 2004), with potential mechanisms including an intrinsic rightward bias in visual attention (Gainotti *et al*., 1972; Kinsbourne, 1993; Bartolomeo and Chokron, 2002), a magnetic attraction towards stimuli on the right (De Renzi *et al*., 1989), difficulty in disengaging attention to shift it leftwards (Posner *et al*., 1984; Friedrich *et al*., 1998), impaired motor responses towards the left

(Heilman *et al*., 1985; Mattingley *et al*., 1998) and deficits in mentally representing leftward space (Bisiach *et al*., 1979). These proposed deficits may all help to explain the striking lateral spatial bias towards the ipsilesional—and away from the contralesional—side that neglect patients demonstrate in everyday life and on bedside clinical tests.

However, in addition to such spatially lateralized mechanisms (i.e. affecting one side of space differently from the other), it is increasingly recognized that some patients' neglect may be exacerbated by deficits that may not be spatially lateralized. For example, right hemisphere neglect patients may also be impaired in their ability to sustain attention to centrally presented auditory or visual stimuli (Robertson *et al*., 1997, 1998; Buxbaum *et al*., 2004); and display an abnormal time course for visual attention even at central fixation (Husain *et al*., 1997). Furthermore, some of their deficits in visual processing can even be apparent on the ipsilesional side (Duncan *et al*., 1999; Battelli *et al*., 2001, 2003). The classical florid presentation of neglect after major right hemisphere stroke may thus involve both spatially lateralized and non-spatially lateralized deficits (Robertson, 2001), with the latter potentially exacerbating the spatial biases towards one side (Husain and Rorden, 2003).

One recent proposal (Husain *et al*., 2001; Wojciulik *et al*., 2001) suggests that a deficit in keeping track of spatial locations (i.e. in aspects of 'spatial working memory', or SWM) may contribute to neglect. Thus neglect patients who have SWM deficits in addition to lateralized biases in attention could forget they had already searched rightwards locations and so return there, leading to recursive search on the right and hence more left neglect. To date, support for this proposal has come primarily from variations on standard search or cancellation tasks (Husain *et al*., 2001; Wojciulik *et al*., 2001; Sprenger *et al*., 2002; Mannan *et al*., 2005). One recent investigation (Pisella *et al*., 2004) has used a very different (change detection) task to assess SWM and reported working memory deficits in judgements for spatial location, but not for colour or shape, in right parietal neglect patients. Importantly, therefore, the SWM impairment in these patients is unlikely to be due to a generalized visual attention deficit.

However, although these previous studies provide strong evidence for a SWM deficit in some neglect patients, they have not measured SWM capacity directly using the traditional clinical method, i.e. the Corsi blocks [one study has employed other techniques to measure capacity in a representational neglect patient (Beschin *et al*., 1997)]. This Corsi method, developed from Knox's cube tapping test for intelligence, requires subjects to observe and replicate the sequence of spatial locations tapped out by the examiner. Damage to posterior right hemisphere regions classically has been associated with SWM impairments on the Corsi blocks (De Renzi *et al*., 1977), but patients with neglect were specifically excluded because any neglect of leftward items might have trivially led to poor performance, rather than reflecting a deficit in SWM *per se*. What is needed therefore is an analogue of the Corsi blocks that can be implemented in neglect patients without contamination by any perceptual, attentional or motor biases which may disadvantage stimuli towards the contralesional left side.

Here we introduce two procedures designed specifically for assessing SWM capacity in neglect, while circumventing the above problems. In a first experiment, we used a strictly vertical version of the traditional Corsi block method. Patients and controls were shown a sequence of locations but now in a columnar array, using a computer-controlled touchscreen, and were then asked to tap out the series of locations they had been shown on the touchscreen. Testing SWM specifically for locations along the vertical meridian should prevent neglect of leftward items from contaminating performance [note that we also tested whether any 'altitudinal' neglect (Làdavas *et al*., 1994; Rapcsak *et al*., 1988) might contribute to our results]. In this way, we eliminated the lateral aspect of the conventional Corsi blocks task, analogous to the way Gainotti and colleagues first minimized the influence of neglect on their version of Raven's matrices (Gainotti *et al*., 1986).

However, good performance on our task still requires, as in the traditional Corsi procedure, intact memory not only for locations but also for stimulus sequence (see Pickering *et al*., 2001), plus the production of appropriate visually guided spatial responses with the hand. Any deficits in these aspects for stroke patients might therefore also contribute to performance. Accordingly, in a second experiment, we developed a far 'purer' measure of vertical SWM, which importantly did not require memory for sequence, nor any spatial manual responding. In this task, after being shown the locations to be remembered, just a single location was probed visually. The patients had to make a yes/no verbal response about whether this location had been shown in the previous sequence, now regardless of stimulus sequence.

For both our tasks, the SWM hypothesis outlined above makes a clear prediction: right hemisphere patients with left neglect, and lesions involving posterior parietal cortex, should be impaired in retaining spatial locations even on vertical SWM tests. Moreover, if such SWM deficits can contribute to spatial neglect when combined with any lateral biases, patients with worse SWM should also show stronger left neglect. The first task has been reported previously in a study of a single patient with neglect (Malhotra *et al*., 2004).

Methods

All subjects gave written consent according to the Declaration of Helsinki. Patients with stroke were recruited from the Stroke Unit at Charing Cross Hospital and Acute Brain Injury Unit, National Hospital for Neurology and Neurosurgery. The study was approved by the hospital research ethics committees.

Experiment 1: computerized vertical Corsi on touchscreen
Subjects

All patients (10 with and 10 without neglect) had been admitted with acute right hemispheric stroke (see Table 1

Table 1 *Neglect and non-neglect stroke patients participating in experiment 1*

	Age (years)	Time since stroke (days)	L (Mes) (max = 30)	R (Mes) (max = 30)	Mes total (max = 60)	L (BIT) (max = 27)	R (BIT) (max = 27)	BIT total (max = 54)	Line bisection (cm)	Lesion volume (cm³)
Neglect patients										
1	64	192	18	18	36	24	27	51	1.7	96.4
2	62	75	17	16	33	18	23	41	0	44.6
3	57	15	0	13	13	0	13	13	3.2	18.4
4	73	10	1	21	22	23	27	50	0	10.8
5	67	84	16	27	43	22	25	47	2.5	28.4
6	86	74	*	*	*	19	20	39	1.6	43.4
7	76	23	0	5	5	17	24	41	1.8	12
8	56	6	0	12	12	8	17	25	1.4	17.9
9	23	27	26	29	55	26	26	52	0	96.9
10	64	128	0	9	9	2	18	20	−0.5	201.7
Mean	62.8	63.4	8.7	16.7	25.3	15.9	22	37.9	1.17	57
SD	16.7	60.4	10.4	8.0	17.3	9.3	4.8	13.9	1.2	60
SE	5.6	20.1	3.5	2.7	5.8	2.9	1.5	4.4	0.4	19.0
Stroke controls										
1	71	10	30	30	60	27	27	54	0	4.5
2	91	18	30	30	60	27	27	54	0	6.5
3	75	168	30	30	60	26	27	53	−1.1	8.9
4	68	79	28	28	56	26	27	53	0	12.8
5	63	8	27	26	53	25	21	46	0.9	28.2
6	67	60	30	30	60	27	27	54	0	2.65
7	56	114	30	30	60	27	27	54	−1.5	10.5
8	62	93	30	30	60	27	27	54	0	11.9
9	70	11	26	24	50	26	26	52	0	0.65
10	56	141	30	30	60	27	27	54	−0.9	11.5
Mean	69.2	70.2	29.1	28.8	57.9	26.5	26.3	52.8	−0.26	9.8
SD	10.2	58.6	1.5	2.1	3.7	0.7	1.9	2.5	0.7	7.7
SE	3.2	18.5	0.5	0.7	1.2	0.2	0.6	0.8	0.2	2.4

L = left; R = right; Mes = Mesulam shape cancellation test; BIT = star cancellation test of the BIT battery; line bisection = mean deviation from true centre to the right (positive) or to the left (negative) on three 18 cm lines.
*Mesulam shape cancellation just prior to the experiment was not available for one patient.

for details). Screening for neglect was first implemented within 1 week of stroke, including Mesulam shape cancellation (Mesulam, 1985); behavioural inattention test (BIT) star cancellation and copying of drawings (Wilson *et al.*, 1987); line bisection (18 cm lines); reporting objects around the room (Stone and Greenwood, 1991); and the comb/razor test (Beschin and Robertson, 1997). Importantly, none of the control stroke patients showed any signs of neglect when tested within 1 week of stroke, so this group does not include recovered neglect patients. Elderly healthy controls (*n* = 10; mean age 69.2 years, SE 3.2) included patients' relatives and other volunteers. None had any history of neurological disease, and they were also tested on the Mesulam shape cancellation and BIT star cancellation tasks, as well as bisecting three separate 18 cm lines, immediately before taking part in the experiment (Table 1). For completeness, we also tested young control subjects (*n* = 10; mean age 31.5 years, SE 1.1) who were all medically fit university graduates without any history of neurological disease.

Brain lesions in stroke patients were imaged by CT or MRI and plotted using MRICro software (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html) using a graphics tablet (WACOM Intuos A6). A T1-weighted template consisting of 12 axial slices was used to demarcate the lesions for neglect (Fig. 1) and non-neglect control patients (Fig. 2), and lesion volumes computed using MRICro software tools. Consistent with previous studies, lesions of neglect patients were larger than those of non-neglect controls (Table 1) but, as we discuss below, lesion volume was not the critical factor associated with poor SWM performance. Lesion location associated with SWM impairments is also considered below, but note that the main purpose of the present experiment was behavioural assessment of any SWM deficit in neglect patients compared with controls; initial anatomical findings are presented here for completeness.

Behavioural task

A vertical computerized test of SWM was developed using E-Prime software (Psychology Tools Inc.) and presented on a touchscreen (NEC Multisync LCD 2010X; 31.5 × 39.5 cm), viewed from ~50 cm. Each trial began with the subject pressing a button on a central keypad. Following a tone, a vertical array of 11 black discs (2 cm diameter; separation 1.6 cm) was then presented on the vertical meridian of the screen. Every 2 s, one of the discs was highlighted in purple to indicate that
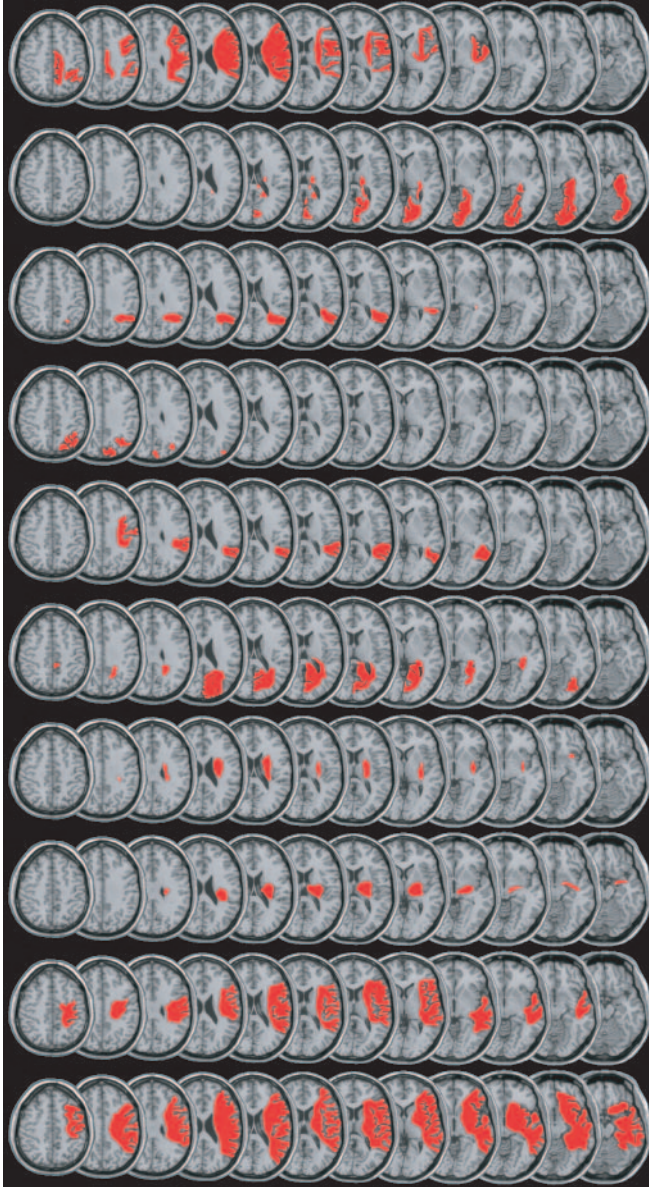
Fig. 1 Lesions of neglect patients participating in Experiment 1. The order of cases is the same as in the upper half of Table 1.
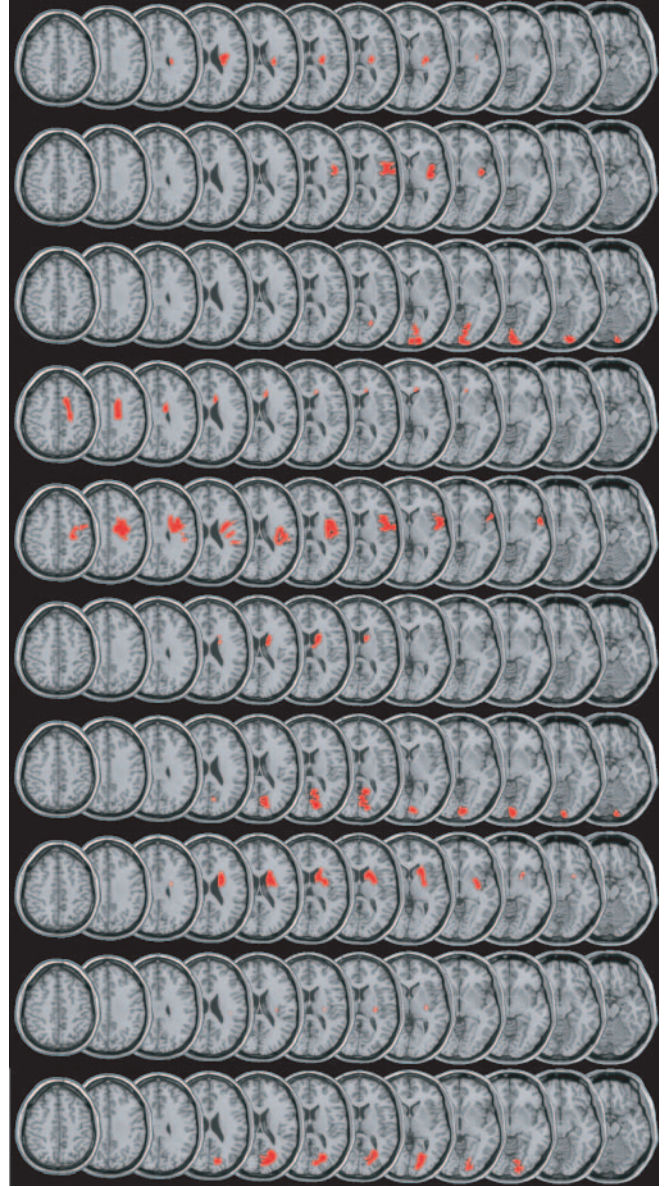
Fig. 2 Lesions of stroke patients without neglect participating in Experiment 1. The order of cases is the same as in the lower half of Table 1.

this was a location to be remembered (Fig. 3). Discs occupying the extreme top or bottom of the array were never selected, and no disc was highlighted twice during a sequence.

Sequence lengths varied between one and five locations (i.e. 1–5 different purple discs). Immediately after a sequence was presented, all discs became black again, and a tone signalled that the subject should tap out the sequence using the right index finger (Fig. 3). Subjects were instructed to touch each disc that had been highlighted in the correct order, in free vision. Two patients (one with and one without neglect) were unable to localize a single target immediately after it had been highlighted and were excluded from the study. The remaining 10 neglect and 10 non-neglect patients reported here were all able accurately to point to single targets.

Before starting the experiment, participants had three practice trials each with sequence lengths of one and two. Subjects were then tested with five sequences at each sequence length, with the level of difficulty increased incrementally from sequence lengths of 1–5. The number of correct responses was recorded, with the maximum overall score being 75, i.e. $(5 \times 1) + (5 \times 2) + (5 \times 3) + (5 \times 4) + (5 \times 5)$. A traditional 'spatial span' score analogous to digit span was also obtained by taking the longest sequence length at which subjects correctly completed correctly more than half of the five sequences. Note that, in principle, it is possible for overall score and spatial span to dissociate. Hence, both methods of analysis were used here, although as it turned out both yielded similar results.
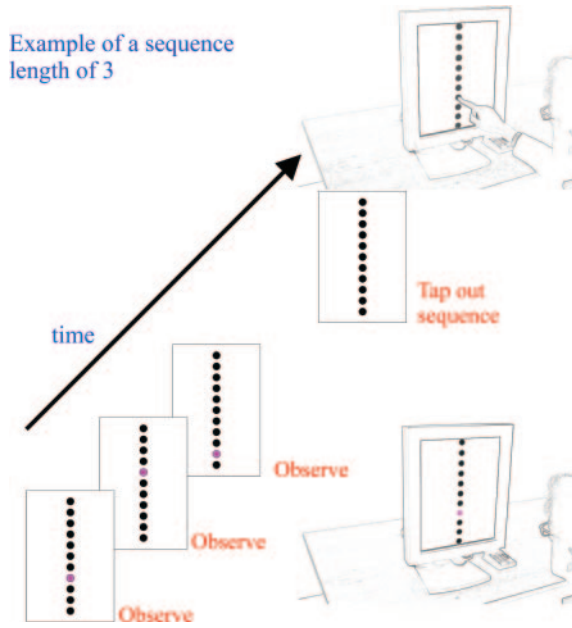
Fig. 3 Protocol used in Experiment 1. Observers viewed a sequence of locations (purple discs), each shown in turn, embedded in a vertical array of black discs. In this case, an example of a sequence of three locations to be remembered is shown. After the locations had been displayed, observers were required to tap out the remembered sequence on the black discs displayed on the touchscreen.

Results of Experiment 1

Analysis of the performance of the different groups (Fig. 4A) revealed a significant effect of subject group on totals of correct responses (overall score) in a one-way analysis of variance (ANOVA) [$F(3,36) = 11.88$, $P < 0.001$]. This was attributable to the neglect patients who were significantly impaired compared with all other groups ($P < 0.01$; *post hoc* Tukey's HSD test), with no significant differences between the three control groups. Neglect patients had a mean score of 27.6 (SE 4.3) out of 75, compared with a mean of 48.8 (SE 12.4) obtained by non-neglect stroke patients. Note, however, that some neglect patients actually scored as well as control subjects; conversely, two non-neglect stroke patients, both with right lateral frontal lesions (cases 2 and 5), scored poorly (Fig. 4A).

A one-way ANOVA on spatial span scores also showed a significant effect of subject group [$F(3,35) = 7.75$, $P < 0.01$], again attributable to significant differences between the neglect patient group and all other control groups ($P < 0.02$; *post hoc* Tukey's HSD test). Again there were no significant differences between the three control groups (Fig. 4B). Neglect patients, as a group, had a mean spatial span of just 1.3, so although they were able to localize and accurately point to a single stimulated location, they encountered great difficulty with longer sequences. (Note also that all the neglect patients we included were able to localize single locations in the upper and lower halves of the array equally well, so there was no evidence of altitudinal neglect on this task.)
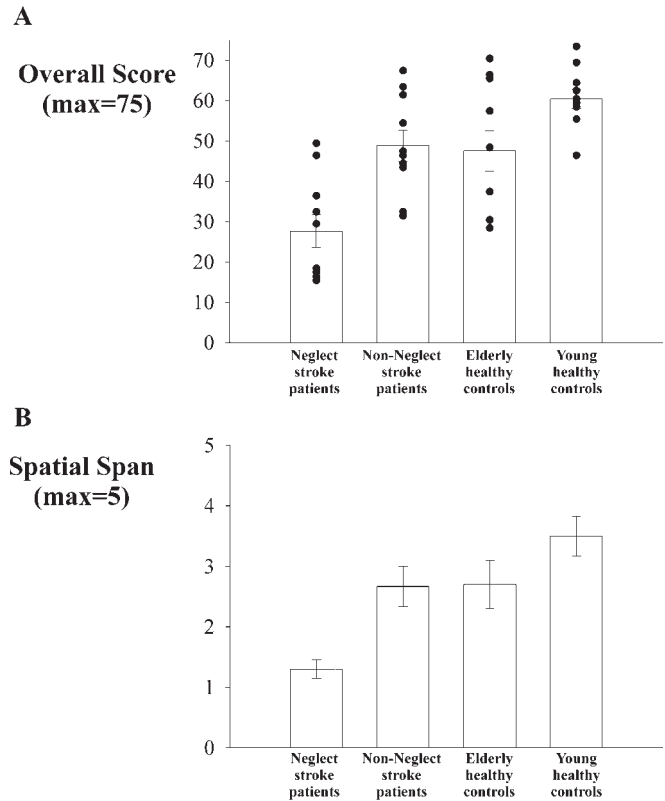

Fig. 4 (**A**) Overall scores on the vertical task used in Experiment 1, where the maximum score was 75. As a group, neglect patients were worse than all other groups, but some individual neglect patients did perform as well as non-neglect patients or elderly healthy control subjects. (**B**) Spatial span scores on the vertical task used in Experiment 1 show a similar pattern to overall scores (maximum span = 5).

In contrast, control stroke patients had a mean span of 2.6, although two of the control stroke patients (again cases 2 and 5) had a very low span of just 1.

We assessed correlations for neglect patients between vertical Corsi overall score and standard, spatially lateralized, tests of neglect (cancellation and line bisection). There were no significant correlations between vertical SWM score and overall or lateralized performance [given by (right – left)/total number of targets cancelled] on the Mesulam shape cancellation task, BIT star cancellation or line bisection task. There was also no significant correlation between SWM score and lesion volume.

Anatomy of vertical Corsi SWM deficit in the neglect patients

To assess whether lesion location distinguishes between patients within the neglect group who performed poorly on this SWM task versus those who did well, we divided neglect patients into two subgroups. The lesions of the five neglect
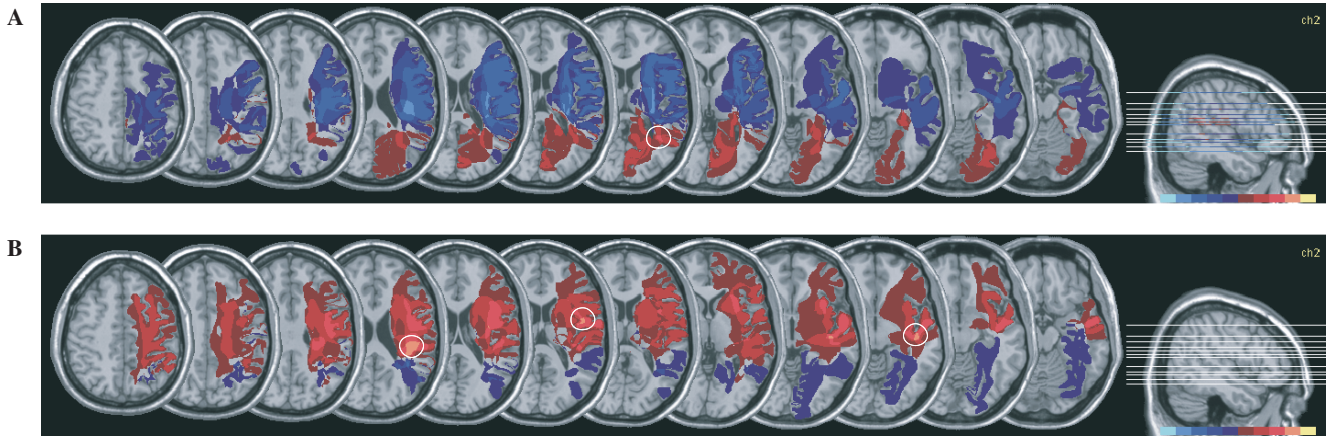
A

B

Fig. 5 (**A**) The lesion site associated with worst performance on Experiment 1 within the neglect group of patients is located in the white matter of the parietal lobe. Regions that are damaged in the five neglect patients with worst SWM performance and spared in the five neglect patients with best SWM performance are shown in red to orange; whereas regions in blue denote areas affected in patients with best SWM performance but spared in patients with poor SWM performance. (**B**) Lesion sites associated with worst performance on the vertical SWM task used in Experiment 2, obtained by a similar subtraction of best five from worst five neglect patients. For this group of neglect patients locations in the parietal white matter and insula were found to be associated with worst SWM performance. Note that frontal regions were far more likely to be implicated by the 'purer' SWM task used in Experiment 2 (orange-red colours) compared to Experiment 1.

patients who showed the best performance on the vertical Corsi (scores >28 out of 75) were subtracted from the five with the worst performance (scores <19 out of 75) using MRICro software. The region of maximum overlap in the neglect group with worst SWM performance, which also was not involved in the group with better SWM, was located in white matter deep to the temporo-parietal junction (Fig. 5A, centroid Talairach coordinates 35, −53, 15). Note that this location is not simply the maximum overlap lesion zone for all the neglect patients (the Talairach coordinates of the centroid for that lie in the parietal lobe at 36, −39, 17). Rather the location identified in Fig. 5A represents the area which when damaged appears to be particularly associated with impaired SWM in the neglect patients we tested.

Experiment 2: vertical SWM with single location probed with verbal forced choice

To perform well on our vertical Corsi task (Experiment 1), subjects were required to encode not only spatial locations but also stimulus sequence, and further had to make spatially accurate manual responses in a sequence. Although this is also true for the standard clinical Corsi blocks, performing well on such a test clearly requires far more than just the ability to retain individual locations. Although in Experiment 1 we excluded two patients who were unable to reach accurately, this procedure does not completely exclude the possibility that some errors made by participants might have been due to inaccurate manual responses or sequencing. Accordingly, Experiment 2 was designed to provide a 'purer' measure of SWM, and to remove the possibility of errors being due to misreaching or a failure to encode stimulus sequence. Subjects observed a vertical sequence of locations, as previously, but their memory for spatial locations was now assessed by

highlighting just a single location, and requiring a forced choice verbal yes/no decision about whether this probe location had been one of those shown. Finally, to ensure that any deficit on this SWM task was indeed due to a spatial impairment, rather than a more general deficit in all aspects of working memory, we also now measured patients' digit spans as a test of verbal working memory, to investigate any association between poor performance on the vertical SWM task and ability to recall digit sequences.

Subjects

The majority of neglect patients (*n* = 9 out of 10) in this experiment were different from those in Experiment 1; only one was involved in both experiments. Six of the control stroke patients had participated in the previous experiment. Healthy elderly (*n* = 10, mean age 65.5 years, SE 2.7) and young (*n* = 10, mean age 31.0 years, SE 0.99) control subjects were also tested. Patients without neglect had again all been screened for neglect within 1 week of symptom onset, with none found for them.

Tests for neglect were administered immediately before participation in the experiment (Table 2). Patients were also now tested with the digit span section of the Wechsler Adult Intelligence Scale (WAIS). Each subject was asked to repeat two sequences of numbers at each sequence length, and was assigned a digit span as the greatest sequence length at which they could correctly recall at least one of the two sequences. Lesion locations were plotted, as previously, for neglect (Fig. 6) and non-neglect (Fig. 7) stroke patients.

Behavioural task

A second computerized task, developed using E-Prime software (Psychology Tools Inc.), was presented on a

Table 2 *Neglect and non-neglect stroke patients participating in Experiment 2*

	Age (years)	Time since stroke (days)	L (Mes) (max = 30)	R (Mes) (max = 30)	Mes total (max = 60)	L (BIT) (max = 27)	R (BIT) (max = 27)	BIT total (max = 54)	Line bisection (cm)	Lesion volume (cm^3)
Neglect patients										
1	64	60	2	24	26	12	23	35	*	5.3
2	68	257	28	30	58	22	25	47	2.5	28.4
3	71	40	4	13	17	08	12	20	0.9	77.1
4	83	17	20	28	48	25	26	51	0.6	40.1
5	68	38	0	14	14	8	21	29	1.3	163.4
6	53	14	0	3	3	0	10	10	1.5	34.2
7	54	17	0	6	6	2	19	21	0	31.9
8	67	16	26	30	56	26	26	52	0	29.3
9	66	24	22	30	52	27	26	53	<0.5	15.3
10	69	24	24	30	54	27	27	54	1.0	7
Mean	66.3	50.7	12.6	20.8	33.4	15.7	21.5	37.2	0.9	43.2
SD	8.49	73.91	12.3	10.8	22.3	10.8	6.1	16.4	0.8	46.8
SE	2.68	23.38	3.9	3.4	7.1	3.4	1.9	5.2	0.3	14.8
Stroke controls										
1	64	11	26	24	50	26	26	52	<0.5	0.7
2	42	3	29	28	57	26	26	52	<0.5	11.9
3	26	30	30	29	59	27	27	54	−1.1	8.9
4	67	40	29	29	58	27	27	54	−0.5	10.5
5	77	61	26	25	51	26	25	51	−0.8	11.5
6	63	9	30	30	60	27	27	54	1	2.7
7	68	20	30	30	60	27	27	54	<0.5	31.2
8	76	10	29	30	59	27	27	54	<0.5	7.6
9	68	7	29	28	57	27	26	53	0.6	1.9
10	65	7	29	30	59	26	26	52	<0.5	0.5
Mean	61.6	19.8	28.7	28.3	57	26.6	26.4	53	−0.1	8.7
SD	15.7	18.6	1.5	2.2	3.6	0.5	0.7	1.2	0.6	9.1
SE	5.0	5.9	0.5	0.7	1.1	0.2	0.2	0.4	0.2	2.9

L = left; R = right; Mes = Mesulam shape cancellation test; BIT = star cancellation test of the BIT battery; line bisection = mean deviation from true centre to the right (positive) or to the left (negative) on three 18 cm lines.
*Line bisection just prior to the experiment was not available for one patient.

28.5 × 21.5 cm screen (Toshiba Satellite Pro: Trident Cyberblade XP 22), viewed from ∼50 cm. Each trial began with a vertical array of 10 black discs (1.5 cm diameter; separation 0.4 cm). A central fixation cross separated the top and bottom five discs. As in the first experiment, during each trial, a sequence of discs was highlighted one at a time in purple, with sequence lengths varied between one and five locations. Each disc was highlighted for 1 s. No circle was highlighted twice during a sequence and all locations (except extreme top or bottom) were equally likely to be part of the sequence. Immediately after a sequence, subjects were shown a random dot mask (for 1 s), followed by the vertical array of discs again, now with a single highlighted location plus a tone which was their cue to give a verbal 'yes'/'no' response. There was a 50% probability on each trial that the location being probed had been part of the preceding sequence. The yes/no response was entered via a keypad by the experimenter. Subjects received immediate feedback on the screen as to whether their answer was correct.

Before starting the experiment, participants were given a demonstration of sequence lengths 1–5, and were shown a correct ('yes') and incorrect ('no') trial at each sequence length. Testing then began, with the level of difficulty increased in blocks from sequence lengths of 1–5 (20 trials at each level). In total, each participant reported on 100 sequences, giving a maximum score of 100. In addition, the probability of a correct response was also plotted against sequence length, where 0.5 is chance performance.

Results of Experiment 2

Neglect patients were less able to recall spatial locations than right hemisphere individuals in any of the three control groups (Table 3; Fig. 8). Note that in this 'purer' measure of SWM, there was now scarcely any overlap between performance for individuals in the neglect group and those in the other groups. The neglect group's performance at spatial sequences of >1 location fell sharply, with performance barely above chance at sequence lengths >3 (Fig. 8B). In comparison, the three control groups all performed much better even for longer sequence lengths, demonstrating far better ability to retain spatial locations.

A mixed measures ANOVA examining the four groups and spatial sequence length showed significant effects for group and for sequence [$F(3,36) = 25.7$, $P < 0.001$ and $F(4,144) = 37.7$, $P < 0.001$, respectively]. Although subjects
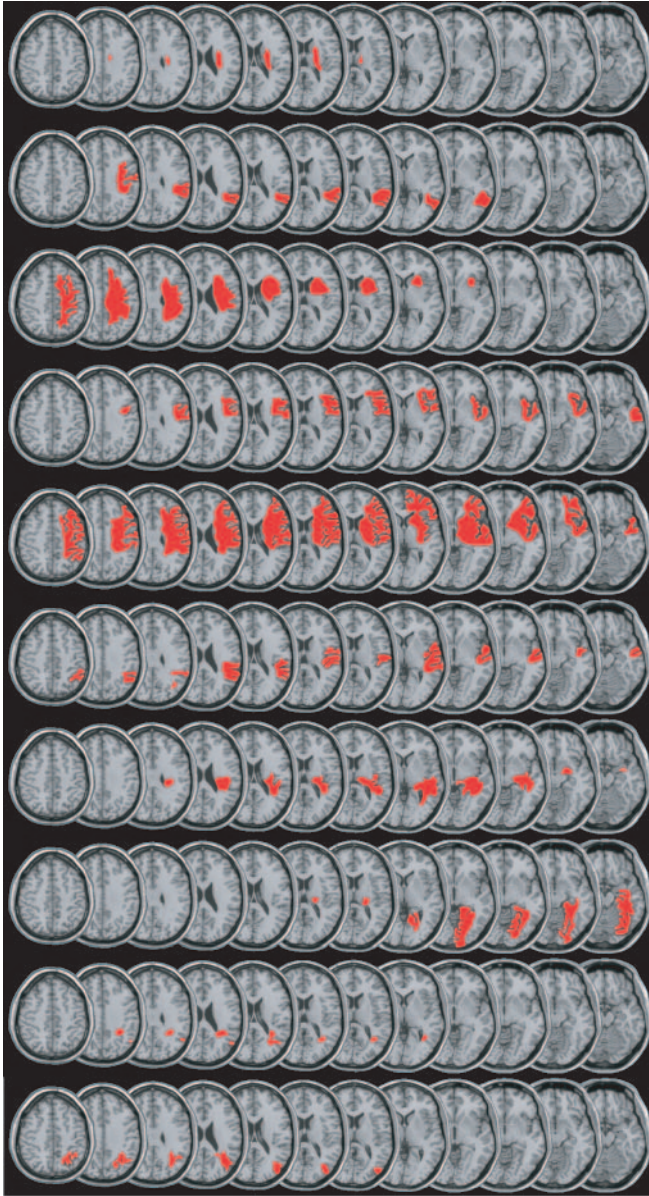
Fig. 6 Lesions of neglect patients participating in Experiment 2. The order of cases is the same as in the upper half of Table 2.

Fig. 7 Lesions of stroke patients without neglect participating in Experiment 2. The order of cases is the same as in the lower half of Table 2.

were required to report only whether the probed location had been part of the sequence, note that with sequences of >1, stimulus order effects might nevertheless contaminate their response. However, this would apply to all groups. The neglect group's performance was significantly worse than that of all three control groups ($P < 0.01$; Tukey's HSD test). There was no significant difference between the stroke patients without neglect and both sets of healthy volunteers, although there was a trend for young control subjects to perform best. Note also that the neglect patients' performance was not attributable to altitudinal neglect for lower versus upper stimuli; a one-way ANOVA for their responses to single stimuli presented above versus below the fixation cross revealed no significant difference [$F(2,198) = 2.016$, NS].
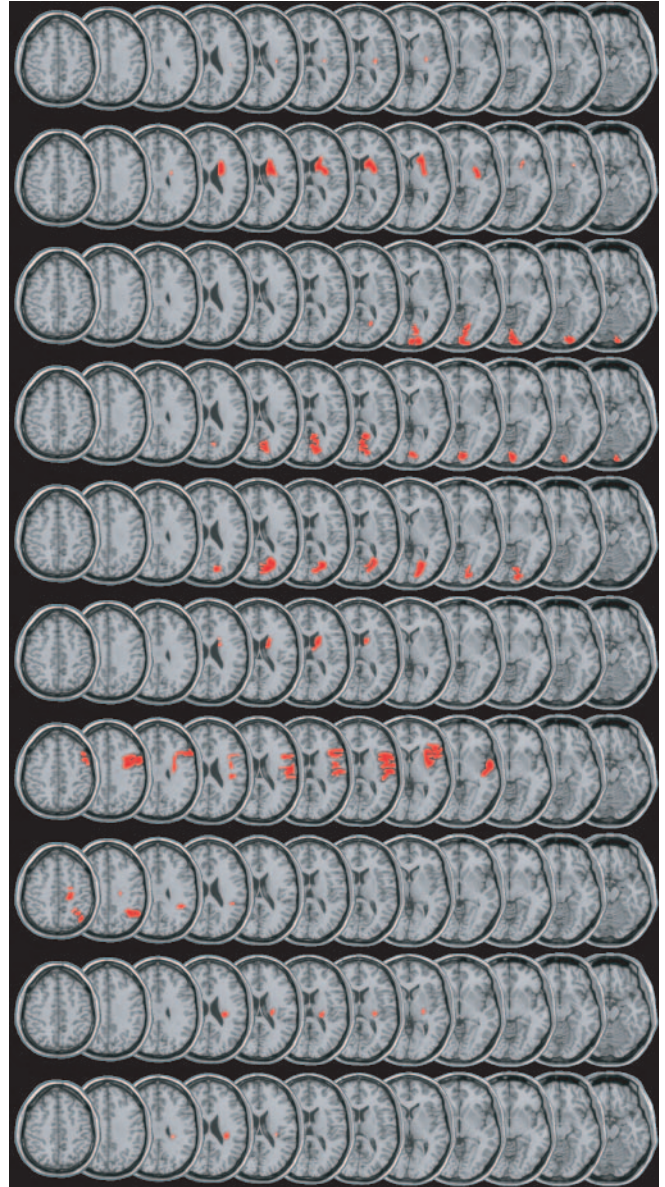
Correlation analyses were performed for neglect patients' scores on cancellation tasks and line bisection, against vertical SWM score out of 100. Unlike Experiment 1, a significant positive correlation was found between vertical SWM score and total number of targets cancelled on the BIT star [$r(9) = 0.74$, $P < 0.05$] and Mesulam shape [$r(9) = 0.79$, $P < 0.01$] cancellation tasks; see Fig. 9. However, there was no significant correlation with deviation on line bisection. As total scores on cancellation tasks do not necessarily give a measure of lateralized bias towards the right, we also examined a spatially lateralized score [(right − left)/total number of targets cancelled]. Significant negative correlations were found between these values and the vertical SWM score for the Mesulam shape cancellation [$r(9) = –0.69$, $P < 0.05$]

Table 3 *Performance in experiment 2 given as a function of sequence length to be remembered for all groups*

Subject group	Total score (max = 100)	Proportion of correct responses at each sequence length				
		1	2	3	4	5
Neglect patients						
Mean	66.9	0.865	0.67	0.665	0.57	0.575
SD	11.6	0.1	0.2	0.1	0.1	0.1
SE	3.66	0.04	0.07	0.04	0.04	0.04
Stroke controls						
Mean	89.1	0.995	0.94	0.905	0.825	0.79
SD	6.87	0.01	0.07	0.09	0.136	0.120
SE	2.17	0.01	0.022	0.03	0.04	0.03
Elderly controls						
Mean	89.6	89.6	0.96	0.87	0.855	0.8
SD	6.95	0.02	0.05	0.11	0.12	0.13
SE	2.20	0.01	0.02	0.04	0.04	0.04
Young controls						
Mean	95.29	0.995	0.995	0.97	0.905	0.895
SD	3.76	0.02	0.02	0.06	0.08	0.09
SE	1.18	0.01	0.01	0.02	0.03	0.03

On this two alternative forced-choice task, a value of 0.5 represents performance at chance level.

and BIT star cancellation tests [$r(9) = -0.69$, $P < 0.05$], demonstrating an association between degree of lateral bias on these cancellation tasks and vertical SWM impairment. Importantly, there was no significant correlation between lesion volume in neglect patients and their SWM score, so the relationship between neglect and SWM impairment cannot be attributed to the extent of brain damage. Nor was there a significant correlation between SWM score and patient age or time since stroke.

Verbal working memory span

Verbal working memory was also assessed to control for the possibility that the impaired SWM observed in the neglect patients might reflect some non-specific deficit in all aspects of working memory, rather than SWM in particular. However, the mean digit span of the neglect patients was a respectable 6.3, compared with 7.2 for non-neglect stroke patients, 6.8 for elderly healthy controls and 7.3 for young healthy controls. ANOVA showed no effect of group. Thus, neglect patients did not demonstrate a generalized impairment of working memory, but instead showed a specific deficit in retaining spatial locations. Digit span and vertical SWM score did not correlate significantly in the stroke patients either. The data from the digit span control task thus indicate that verbal working memory cannot explain the effects observed in neglect patients for vertical SWM.

Anatomy of the SWM deficit in the probed vertical task

The lesions of the five neglect patients who showed the best performance were subtracted from those of the five patients with the worst performance using MRICro software. This identified two major regions of maximum overlap in the neglect group with worst SWM performance, which also

were not involved in the group with better SWM. The first was located in the parietal white matter deep to the supramarginal gyrus (Fig. 5B; centroid Talairach coordinates 35, −30, 24, quite close to the locus identified in Experiment 1 which was 35, −53, 15). The second region involved the insula, including two foci (Fig. 5B; centred at Talairach coordinates 44, −12, 16 and 43, −19, −4). Both these areas were affected in four of the patients with poor SWM and none of the neglect patients in the better SWM group. Note that, as in Experiment 1, these locations were not simply the maximum overlap lesion zones for all the neglect patients. Indeed, as in Experiment 1, there was only one maximum focus for lesion overlap of the entire neglect group which was located in the parietal lobe (Talairach coordinates 37, −39, 24; cf. 36, −39, 17 in the first experiment). The locations identified in Fig. 5B are thus candidate areas which when damaged appear to be particularly associated with impaired SWM in the neglect patients we tested using our second 'purer' measure of SWM.

Discussion

Taken together, the results of the two experiments reported here demonstrate that as a group, right hemisphere patients with left neglect have impaired SWM capacity even on purely vertical tasks. The results cannot be accounted for by spatially lateralized impairments since all stimuli were presented on the vertical meridian. Nor can they be explained by any 'altitudinal' neglect (Rapcsak *et al.*, 1988; Làdavas *et al.*, 1994), since we found no significant differences for stimuli presented in the superior versus inferior visual space. Moreover, it is unlikely that the pattern of SWM impairment we have found is due to poor perceptual spatial localization *per se*. In Experiment 1 (our vertical computerized touchscreen analogue of the traditional Corsi blocks task), all of the neglect patients who were studied had a spatial span of at
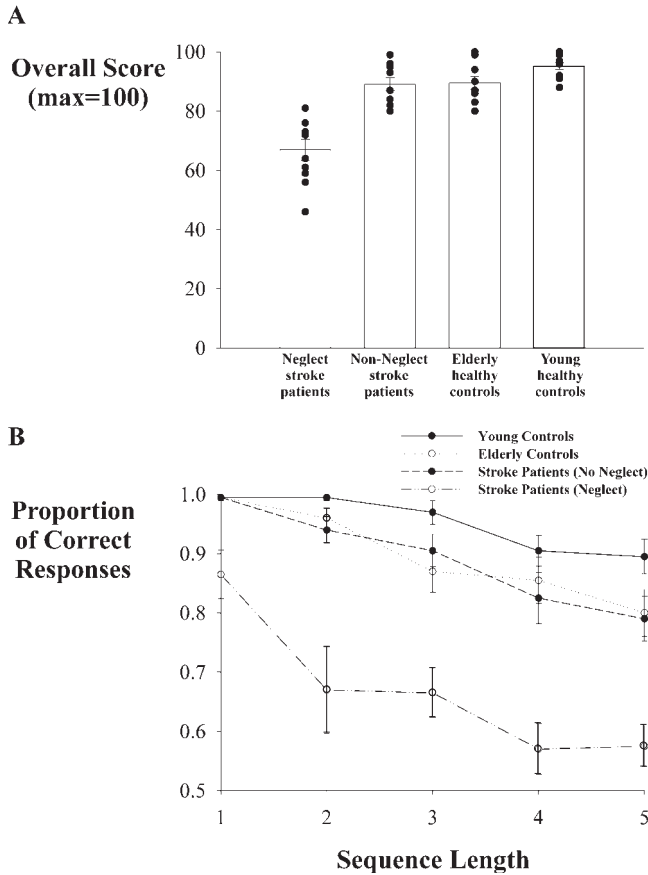
A

Overall Score (max=100)

B

Proportion of Correct Responses

- ● Young Controls
- ○ Elderly Controls
- ● Stroke Patients (No Neglect)
- ○ Stroke Patients (Neglect)

Sequence Length

Fig. 8 **(A)** Scores on the vertical task used in Experiment 2, where maximum score was 100. Neglect patients were worse than all other groups. **(B)** Performance in Experiment 2 as a function of the sequence length to be remembered. Note that chance performance is 0.5 in this two-alternative forced choice task.

Fig. 9 Plot of score on Mesulam cancellation task (max = 60) against overall vertical SWM score in Experiment 2 (max = 100).

least one, and therefore could respond accurately to a single location, ruling out deficits in spatial sensory encoding. Analogously, in experiment 2 (which no longer required memory for stimulus sequence, nor any manual response), the mean performance for correctly reporting single locations was significantly greater than chance for the neglect group. However, in both experiments, the performance of the neglect patients was significantly impaired relative to controls for the longer spatial sequences, consistent with a SWM deficit.

On the second task, which provides a purer measure of SWM (not confounded by memory for stimulus sequence or manual responding), there was also a significant correlation between neglect severity on cancellation tasks and SWM impairment (Fig. 9). Note that there was no significant correlation with line bisection performance, consistent with the proposal that SWM impairments may affect visual search behaviour, but not all aspects of the neglect syndrome (see also Mannan *et al.*, 2005).

The poor performance of the neglect patients on the vertical SWM task is unlikely to reflect a generalized deficit in working memory. In contrast to their significantly impaired SWM
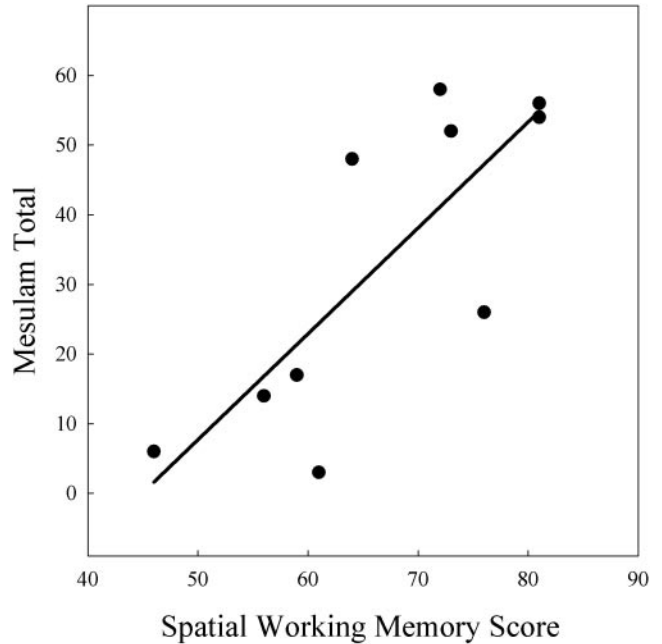
performance, their verbal working memory (digit span) was intact. It might still be argued that a dissociation between verbal and SWM would not be unexpected given the association of verbal working memory functions with posterior left hemisphere regions (Vallar and Shallice, 1990). However, our analysis demonstrates also that lesion volume within the right hemisphere does not correlate with SWM impairment in neglect patients, again arguing against a non-specific general deficit. Although the number of patients is relatively small, it should be noted that in Experiment 2 there was a significant correlation for the same small number of individuals when comparing neglect severity on cancellation with SWM performance (Fig. 9).

Prior to the experiments reported here, there has been no direct measurement of SWM capacity using the Corsi blocks in visual neglect patients. Indeed, patients with neglect traditionally have been excluded from studies using the standard Corsi method (De Renzi *et al.*, 1977) precisely because performance might be contaminated by failures to encode leftward locations, rather than a true deficit of maintaining locations in SWM. One recent study (Pisella *et al.*, 2004) has used a change detection task to assess SWM in neglect. In that study, neglect patients with parietal lesions were specifically impaired in detecting location changes but not in judgements for colour or shape change, again arguing against a generalized deficit as an explanation for the SWM impairment found in some neglect patients.

In our study, damage to the right parietal and insula region was implicated in SWM deficits within the neglect group (Fig. 5). Previous neuropsychological studies of non-neglect patients have identified similar regions as critical substrates for SWM performance (De Renzi *et al.*, 1977; Owen *et al.*,

1990; Walker *et al*., 1998), consistent with the results of functional imaging studies in healthy individuals (Owen, 1997; D'Esposito *et al*., 1998; Awh and Jonides, 2001). Importantly, lesions to these brain areas are also often associated with the neglect syndrome, which was part of the original rationale for our hypothesis that SWM might be disrupted in some neglect patients (Husain *et al*., 2001; Wojciulik *et al*., 2001).

The findings presented here are consistent with proposals that a SWM deficit in keeping track of spatial locations may contribute to the severity of leftward neglect in some right hemisphere stroke patients (Driver and Husain, 2002), even if the SWM deficit does not specifically affect just leftward locations. Others have suggested that impairments to some aspects of SWM might contribute to 'representational' features of neglect (Ellis *et al*., 1996; Beschin *et al*., 1997). Here we have been concerned with possible contributions of SWM deficits to standard visuospatial aspects of neglect, specifically to visual search behaviour on cancellation tasks. However, our findings nevertheless support the 'representational' hypothesis in so far as they demonstrate that deficits in the neglect syndrome need not be strictly perceptual, but may also exist in spatial memory. Future studies might profitably study how SWM capacity deficits on tasks such as ours relate to performance on traditional, and more recent, measures of representational neglect (Denis *et al*., 2002; Della Sala *et al*., 2004).

Classically, deficits in SWM have been considered to be dissociable from neglect (De Renzi, 1982). The correlations found here between experimental SWM deficit and neglect severity on cancellation measures suggest that SWM deficits and neglect may interact when conjointly present, so that an SWM deficit can exacerbate any co-existing lateral bias towards the right. When combined with a rightward attentional bias, a SWM deficit might lead to recursive search of rightward locations at the expense of those to the left (because a patient with impaired SWM would not remember that rightward locations had already been searched), hence exacerbating neglect of leftward stimuli (Husain *et al*., 2001; Wojciulik *et al*., 2001). We would not claim that the SWM deficit identified here directly causes neglect on its own. Rather it is a deficit that may interact with any lateral spatial biases (e.g. in attention) towards the right, to exacerbate neglect (Husain and Rorden, 2003).

According to our proposal, a deficit in SWM would not be expected in all neglect patients, but it would be anticipated to occur in those who have damage to critical areas in the right parietal and frontal lobe that support SWM performance. Conversely, it would be expected that some non-neglect patients might also show SWM impairment if their lesions involved such areas, but did not induce any lateral biases. The current results are consistent with this general perspective. First, while neglect patients as a group show SWM deficits, some individuals had SWM performance within the normal range (especially in Experiment 1; there was much less overlap between groups on the 'purer' SWM measure in

Experiment 2). Secondly, lesion locations associated with the poorest SWM performance among neglect patients were in right parietal white matter and, in the second experiment, also the right insula. Damage to both these sites would be consistent with deafferentation and/or loss of cortical regions known to support SWM based on functional neuroimaging evidence (Owen, 1997; D'Esposito *et al*., 1998; Awh and Jonides, 2001). Finally, in Experiment 1, two non-neglect cases (both with right frontal involvement) performed within the impaired range, indicating that SWM deficits can dissociate from neglect in some cases (at least on the more complex vertical Corsi task which requires manual responding and sequencing), while still being associated with more severe neglect in those patients who show neglect.

Further investigations using the SWM measures we have developed here should shed more light on the underlying functional anatomy. For present purposes, the most important aspect of our study is the demonstration that neglect patients can show SWM deficits even on purely vertical tasks, which relate nevertheless to the severity of their left neglect as measured clinically, indicating a functional relationship. Although SWM deficits alone may not cause neglect (and can dissociate from it in some individual cases), when present conjointly with lateral biases towards the contralesional side, they may exacerbate neglect and contribute to its clinical manifestation.

Acknowledgements

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