IMPAIRED SPATIAL WORKING MEMORY: ONE COMPONENT OF THE VISUAL NEGLECT SYNDROME?

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ABSTRACT

Both impaired spatial working memory (SWM) and unilateral neglect may follow damage to the right parietal lobe. We propose that impaired SWM can exacerbate visual neglect, due to failures in remembering locations that have already been searched. When combined with an attentional bias to the ipsilesional right side, such a SWM impairment should induce recursive search of ipsilesional locations. Here we studied a left neglect patient with a right temporoparietal haemorrhage. On a nonlateralised, purely vertical SWM task, he was impaired in retaining spatial locations.

In a visual search task, his eye position was monitored while his spatial memory was probed. He recursively searched through right stimuli, re-fixating previously inspected items, and critically treated them as if they were new discoveries, consistent with the SWM deficit. When his recovery was tracked over several months, his SWM deficit and left neglect showed concurrent improvements. We argue that impaired SWM may be one important component of the visual neglect syndrome.

Key words: spatial working memory, hemispatial neglect, parietal, stroke

INTRODUCTION

Visual neglect is a common disabling disorder following stroke (Stone et al.,1992). Although it may occur after damage to either cerebral hemisphere, neglect is most severe and enduring following right hemisphere strokes, particularly those involving the inferior parietal lobe (Vallar, 1993, 2001; De Renzi, 1982; Heilman et al., 2003). Lesions elsewhere within the perisylvian zone, including inferior frontal and superior temporal cortex, have also been associated with the condition, as have subcortical strokes involving the thalamus and basal ganglia (Vallar, 2001). Patients with such right hemisphere lesions tend to orient ipsilesionally towards the right, often ignoring contralesional objects to their left. For example, on bedside cancellation tests that require search for multiple targets, they typically commence searching from the right, finding targets on that side, but often failing to find those located towards the left. Moreover, many patients repeatedly re-examine locations on the right, at the expense of stimuli to the left, even when given unlimited time (Husain et al., 2001; Chedru et al., 1973; Behrmann et al., 1997).

Such behaviour by right hemisphere neglect patients has been attributed to a bias in visual attention towards the right (Kinsbourne, 1993; Ladavas et al., 1990; Gainotti et al., 1991; Smania et al., 1998), 'magnetic attraction' to stimuli on the right (De Renzi et al., 1989), difficulty in disengaging from items on the right to shift leftwards (Posner et al., 1984) and/or distortions in where search is centred (Karnath, 1997). Proposed deficits of this kind may help to explain the

evident lateral biases that patients manifest on bedside tests, as well as in everyday life. However, the neglect syndrome is increasingly considered to have many components, including some that do not only affect stimuli or responses towards one side of space (Robertson, 2001; Husain and Rorden, 2003). For example, the time course of attentive visual processing can be abnormally prolonged, even for a stream of stimuli presented only at central fixation (Husain et al., 1997). Moreover, some patients with neglect are impaired at sustaining attention to central auditory tones (Robertson et al., 1997).

The multi-component nature of the neglect syndrome is perhaps unsurprising given the wide range of lesion sites associated with the condition (Mesulam, 1999; Bisiach and Vallar, 2000; Heilman et al., 2003). Depending upon the location and extent of brain damage, different combinations of deficit may be present in different patients. For example, a visual attention bias may combine with different types of motor impairment in neglect patients with parietal or frontal lesions (Husain et al., 2000). Moreover, impairments that previously have been described in the context of patients *without* neglect may also contribute to the neglect syndrome. For example, non-neglect patients can be impaired on (nonspatial) sustained-attention tasks (Rueckart and Grafman, 1996; 1998). As mentioned above, a similar nonspatial deficit is also present in some patients with neglect, whose lesions may encroach into similar areas. When combined with biases towards one side of space, such a deficit may serve to exacerbate the severity of neglect. A similar argument has been made for the bias towards local

scales of visual detail associated with damage to the right temporo-parietal junction, which may also exacerbate a bias towards one side of space when conjointly present (Robertson et al., 1988; Halligan and Marshall, 1994).

We have recently proposed (Wojciulik et al., 2001; Husain et al., 2001; Driver and Husain, 2002) that a deficit in SWM (specifically, in keeping track of previously examined locations, across saccades) may also contribute to the neglect syndrome. If so, this would forge a link between two areas of neuropsychology (neglect and SWM) in which De Renzi made many seminal contributions (eg. De Renzi and Nichelli, 1975; De Renzi et al., 1977, 1989; De Renzi, 1982). While others have proposed the involvement of certain spatial working memory impairments in 'representational' or imaginal aspects of neglect (Beschin et al., 1997; Ellis et al, 1996), our hypothesis is directed instead towards explaining the visual-search behaviour of neglect patients. Specifically we have suggested that a failure to keep track of searched locations, when combined with a bias to direct attention rightward, should lead to repeated returns to locations on the right that have already been examined, thus exacerbating the spatial bias so that search fails to progress towards the left.

As one initial test of our hypothesis (Wojciulik et al., 2001; Driver and Husain, 2002) we examined in detail the visual search of a right-parietal patient with left neglect (Husain et al., 2001). He performed a multi-target visual search task (that did not require any visible marks to be made, but merely unseen button-presses), while we tracked his eye movements and simultaneously probed his memory for searched locations. As in other studies of search and scan-paths in neglect (Chedru et al., 1973; Behrmann et al., 1997), we found that the patient recursively re-examined stimuli on the right, neglecting stimuli to the left even when given unlimited time (self-terminated search). The critical new result was that, when re-examining a previously inspected target on the right, he often failed to recall that he had searched that location before, mistakenly treating re-fixated targets as new discoveries, at a pathological rate. We proposed (Husain et al., 2001; Driver and Husain, 2002) that such a trans-saccadic SWM deficit may exacerbate the spatial bias to the right, explaining why search not only typically begins on that side, but also typically returns recursively to items there, thus failing to proceed leftward and producing enduring neglect for left stimuli even when given unlimited time.

One important aspect of this hypothesis is that (as with the sustained-attention deficits mentioned earlier, or the bias towards local detail), the specific SWM deficit we have proposed need not apply to only one side of space, and yet could still exacerbate any neglect for the left side. In principle, the SWM deficit could apply to both sides, and might also be apparent with non-lateralised displays. The role of

such a SWM deficit in neglect would be to exacerbate the attentional bias towards the ipsilesional side, by leading the patient to treat old items there as new discoveries, thus preventing them from proceeding onto truly new items on the contralesional side that have yet to be inspected.

Although many factors (e.g. ipsilesional bias, 'magnetic attraction' of ipsilesional stimuli, or difficulties in disengaging attention) might in principle serve to keep attention towards the right, recent studies show that in fact neglect patients typically make as many leftward as rightward saccades during search (Niemeier and Karnath, 2000; Husain et al., 2001). Thus, search can in fact move in a leftward direction from rightward items, but tends then to return (Husain et al., 2001) to the latter items. The SWM deficit we have proposed could explain why these returns arise, and in particular why neglect patients typically do not realise that they are then covering old ground while missing new ground on the left. If locations on the right are recursively re-examined as if being searched for the first time, stimuli to the left will continue to be neglected.

The search-and-click method we developed (Husain et al., 2001; Driver and Husain, 2002) to examine the role of SWM in pathological search by neglect patients incorporated a SWM measure (did the patient remember that the currently fixated target had previously been found?) within a search task. A different approach to the possible involvement of SWM deficits would be to index any such deficits in an entirely separate task from the measure of neglect or of pathological search.

Pioneering studies by De Renzi, addressing SWM in patients *without* neglect, used the Corsi blocks procedure. In this, subjects observe the examiner tap out a spatial sequence on a set of nine blocks distributed irregularly on a 20cm by 25cm board, and are then required to tap out the same spatial sequence themselves. Non-neglect patients with damage to posterior cerebral regions – particularly of the right hemisphere - are impaired at retaining spatial locations on this test (De Renzi and Nichelli, 1975; De Renzi et al., 1977). However, the traditional Corsi task is unsuitable for assessing SWM in patients with neglect, as performance could be impaired because of a deficit in perceiving or attending to locations in contralesional (neglected) space, rather than due to poor spatial memory *per se*.

One way to overcome this problem would be a task in which the locations to be encoded are not spatially lateralised, but are arranged in a purely vertical array instead. Such a test may allow us to examine whether an *unlateralised* SWM deficit might contribute to the neglect syndrome. Here, we applied this logic to a neglect patient with a right posterior haemorrhage using a new vertical analogue of the traditional Corsi task, developed specifically to test SWM in unilateral neglect. We found that the neglect patient is indeed significantly impaired at
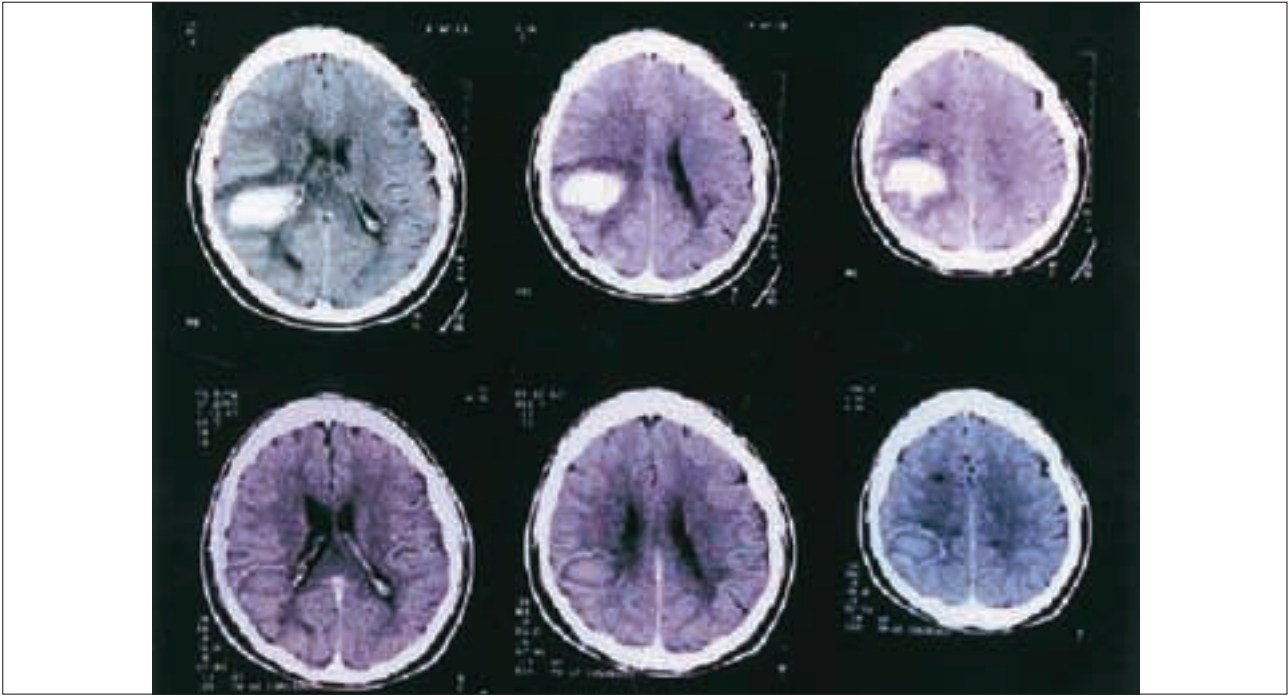
Fig. 1 – *Top row: CT scan of patient BI soon after admission demonstrating a haematoma involving the right inferior parietal lobe (including intraparietal sulcus) and superior temporal gyrus, with surrounding oedema and mass effect. Bottom row: CT scan two months after admission, showing that the mass effect had resolved, leaving an area of mixed attenuation in the right parietal and temporal regions.*

retaining locations on this vertical SWM task. Moreover, when tested on our recently developed (Husain et al., 2001) search-and-click eye-tracking procedure (which embeds a very different SWM measure within an otherwise conventional visual-search task), he recursively examined stimuli on the right, and critically failed to recall that he had searched those locations before, mistaking them for new discoveries at a pathological rate. Finally, during extended follow-up, we found that the patient's SWM impairment on the purely-vertical task improved over several months, following a similar pattern to improvement in his left spatial neglect.

CASE HISTORY

Patient BI was a 59 year old right-handed man who presented with a two week history of impaired vision to his left, difficulty with depth perception, unsteadiness and frontal headache. He had first noticed problems whilst working behind a charity stall when he found it difficult to reach accurately for prizes. He blamed this on a lack of depth perception. Subsequently he noticed he was bumping into objects to his left.

Relatives observed that he had to hold onto furniture whilst walking around the house and that he seemed to have slight weakness of his left side.

On examination, he was noted to hold his left arm in a flexed posture. He tended to look towards his right. Visual field testing with a 5 mm red hatpin (four trials in each quadrant) revealed a left inferior quadrantanopia. Within the superior left quadrant his

responses to smaller stimuli were variable, but he could count fingers. If two fingers were simultaneously presented *very briefly* within this quadrant, he always (four out of four trials) demonstrated extinction of the leftmost stimulus, even though he could detect it when presented alone. Examination of the limbs demonstrated a left pronator drift, normal tone and coordination, and minimal weakness in the left arm. Fine finger movements of the left hand were slow. Deep tendon reflexes were normal and symmetrical in the upper limbs, but were brisker in the left leg than on the right. Plantar reflexes were flexor bilaterally. Sensory examination of the limbs revealed reduced joint position sense in the left hand and left tactile extinction.

BI was assessed on standard neuropsychological tests for visuospatial neglect (Mesulam, 1985; Wilson et al., 1987). His score on the Mesulam shape cancellation task was 13/60 (scoring 0 on the left side of the page and 13 on the right). On the BIT (Behavioural Inattention Test (Thames Valley, Bury St Edmunds, UK)) star cancellation test he scored 13/54, again finding targets only on the right. His score on the BIT figure and shape copying task was 2/4, and he exhibited a mean rightward deviation of 3.2 cm when asked to bisect three separate 18 cm lines. When asked to name 10 objects on the ward, he reported only objects located to his right. When asked to show how he would comb or shave he groomed only the right side of his face.

Computed tomographic (CT) scanning on admission revealed a high attenuation region (consistent with a recent haematoma) involving the right inferior parietal lobe (including intraparietal
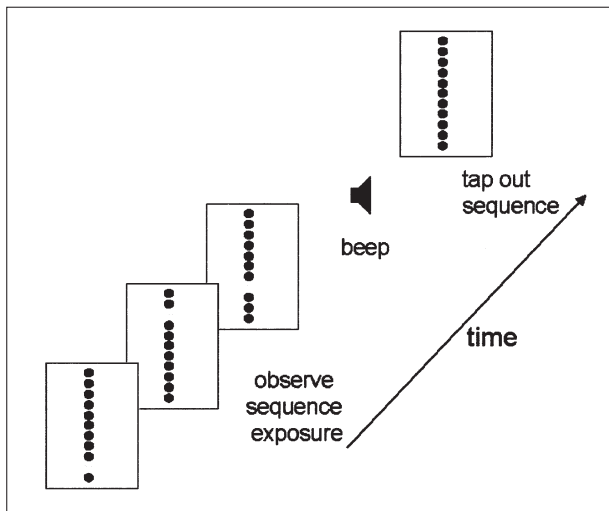
Fig. 2 – *Example of a sequence length of 3 on the vertical spatial working memory task. Subject is exposed to a sequence of 3 vertical arrays, each containing a purple circle in a different position. Following the auditory beep, they tap out the sequence from memory onto the black vertical array presented on the touchscreen.*

sulcus) and superior temporal gyrus, with surrounding oedema and mass effect (Figure 1; top row). In addition there was a small area of low attenuation, consistent with a small old lacunar infarct, in the right frontal white matter. Two months later, the mass effect associated with the acute haemorrhage had resolved, leaving an area of mixed attenuation in the right parietal and temporal region (Figure 1, bottom row).

VERTICAL SPATIAL WORKING MEMORY

We used a computerised task in which the locations to be encoded were not spatially lateralised. This vertical SWM task was programmed using E-Prime software (Psychology Tools Inc.) and presented on a touchscreen (NEC Multisync LCD 2010X) which was 31.5 cm wide and 39.5 cm tall. Participants viewed the screen from approximately 50 cm. To start each trial, they pressed a button on a keypad. They were asked to keep their right index finger on the button until they heard an auditory beep. A vertical array of eleven black circles, each 2 cm in diameter and separated by 1.6 cm, was then presented along the vertical meridian of the touchscreen (Figure 2). Every two seconds one of the circles was highlighted (the extreme locations at top or bottom were never selected for this) by being displayed in a purple colour.

No circle was highlighted twice during a sequence. Sequence lengths varied between 1-5 spatial locations (purple circles) to be remembered. Immediately after viewing a sequence, subjects were presented with the vertical array of eleven circles (now all black again), and a beep which was their cue to tap out on the touchscreen the sequence they recalled. Subjects were instructed to touch each

circle that had been highlighted, and to do so in the correct order. Just as in the traditional (lateralised) Corsi task (Milner, 1971; De Renzi and Nichelli, 1975; De Renzi et al., 1977), they were free to move their eyes throughout the experiment.

Before starting the experiment, participants were given a demonstration of how to tap out varying sequence lengths and had three practice trials each with sequence lengths of n = 1 and n = 2. In the experiment, there were five sequences at each sequence length. The level of difficulty was increased incrementally from sequence lengths of 1 through to 5. In total, each participant thus viewed and reported 25 sequences. We scored performance by giving one point for each location recalled correctly in a sequence. Thus, one point was given for pressing the correct target at a sequence length of one, and five points for correctly pressing all targets in the correct order for a sequence length of five. The maximum score was therefore 75 [(5 × 1) + (5 × 2) + (5 × 3) + (5 × 4) + (5 × 5)].

The neglect patient BI, three age-matched volunteers, and three age-matched stroke patients without neglect (10-18 days following stroke) or any visual field defect were tested on this task (Table 1). All subjects were noted to follow the sequence by moving their eyes, gazing at each location as it was highlighted. Each participant was also tested on the Mesulam shape cancellation, BIT star cancellation, as well as on line bisection, immediately beforehand. As expected, none of the control patients or healthy subjects showed any neglect . BI was severely impaired on the vertical SWM task, scoring only 16 out of 75, more than 3 SDs below the mean for control age-matched stroke patients who obtained a mean score of 39.3 (SE 4.2; 95% confidence intervals: 21.3 – 57.3). By comparison, healthy elderly controls (mean age 58, range 56 to 62) performed much better than either BI or the control stroke patients, with a mean score of 67 (SE 1.5; 95% confidence intervals: 60.4 – 73.6). Thus, in addition to his spatial neglect, BI demonstrated a deficit on the non-lateralised test of (vertical) SWM, which exceeded that for the non-neglect control patients.

To examine whether his SWM deficit might contribute to his left-sided neglect, we next tracked his eye movements while probing his memory for previously inspected locations during visual search, using the search-and-click eye-tracking procedure recently introduced by Husain et al. (2001).

SPATIAL WORKING MEMORY DURING VISUAL SEARCH

We used our recently developed multi-target search task, in which participants are asked to look for target letter Ts embedded among distractor letter Ls (full details in Husain et al., 2001) making a button-press only when fixating a newly discovered

TABLE 1

Patient details and lesion sites for control stroke patients and patient BI. Results of standard neuropsychological tests for spatial neglect and results for vertical SWM task. Mesulam Left and Mesulam Right denote correct cancellations on the left and right side of the cancellation display respectively (with a maximum possible score of 30 on each side). BIT star Left and BIT star Right denote correct cancellations on the left and right side of the cancellation display respectively (with a maximum possible score of 27 on each side). Deviation on line bisection denotes mean deviation on bisection of 3 separate horizontal 18cm lines.

|	Age	Day since CVA	Vertical SWM Score	Lesion site	Mesulam Left	Mesulam Right	BIT star Left	BIT star Right	Deviation on Line Bisection
Control Stroke Patients *(Vertical Spatial Memory)*									
1	59	18	31	R posterior frontal infarct	30	30	27	27	< 0.5 cm
2	64	10	43	R corona radiata infarct	30	30	27	27	< 0.5 cm
3	64	11	44	R external capsule and R corona radiata infarct	26	24	26	26	< 0.5 cm
MEAN	62	13	39						
SD	2.9	4.4	7.2						
SE	1.7	2.5	4.1						
Control Stroke Patients *(Search task)*									
1	58	26	–	R subcortical MCA infarct	30	30	27	27	< 0.5 cm
2	55	55	–	R posterior frontal infarct	30	30	27	27	< 0.5 cm
3	73	46	–	R internal capsule infarct	29	30	27	27	< 0.5 cm
MEAN	62	42							
SD	9.6	14.8							
SE	5.6	8.6							
Patient BI									
BI 1	57	15	16		0	13	0	13	3.2 cm Rightward
BI 2		41	24		17	22	21	23	< 0.5 cm
BI 3		120	33		26	26	25	26	< 0.5 cm
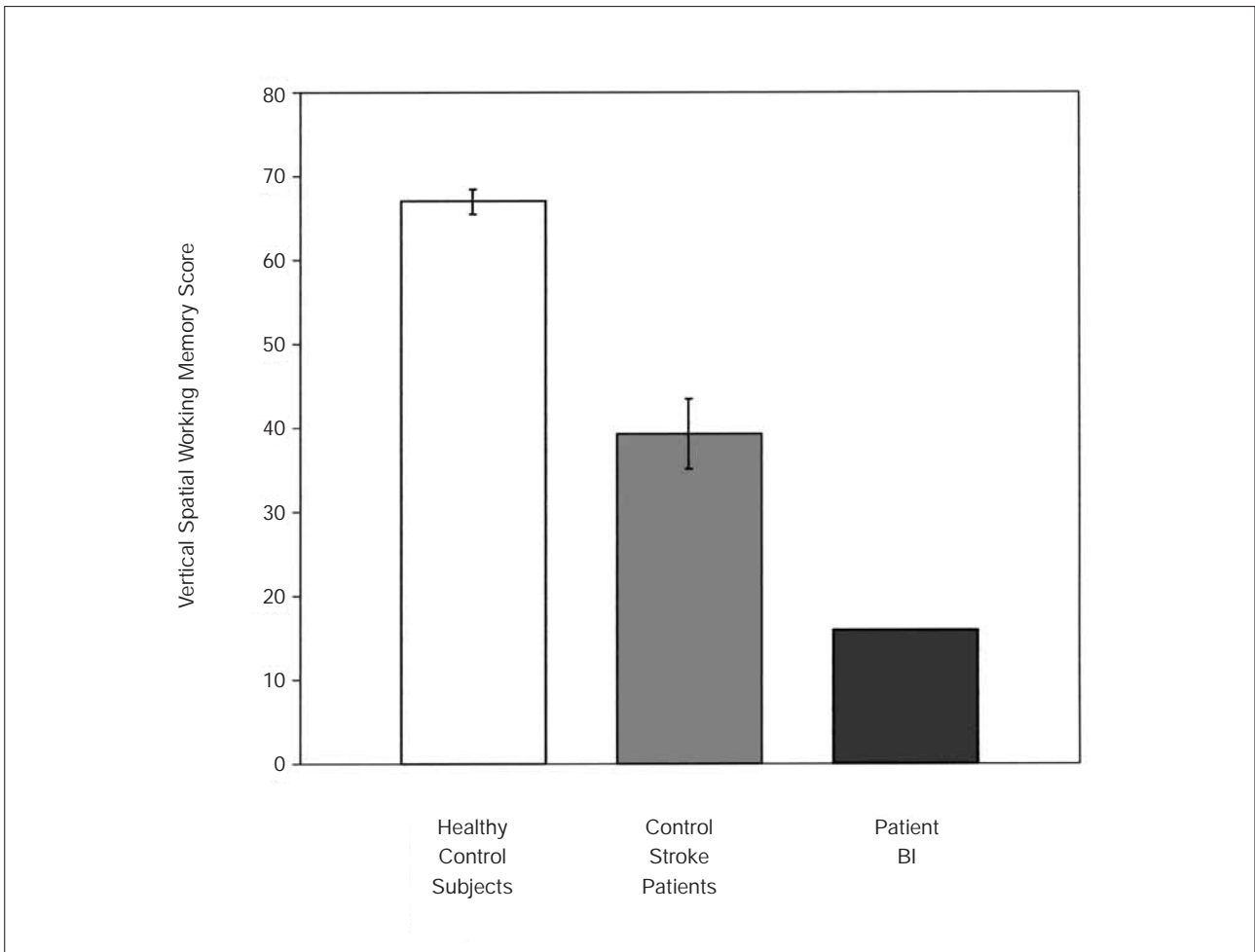
Fig. 3 – *Comparison of Patient BI with 3 age matched healthy control subjects and three stroke patients matched for age and time elapsed since stroke on the vertical spatial working memory task. Patient BI's score is more than 3 SDs below the mean for the stroke patients, who in turn perform worse than healthy age-matched controls. Error bars represent the standard error of the mean.*

target. Critically, button-presses must be withheld when re-fixating a previously discovered target. Failures to do this thus indicate a failure to retain the locations of previously inspected items, across saccades. Stimuli were presented on an SVGA monitor (29°x22°) and viewed from a distance of 57cm. Each search array consisted of a virtual 9x7 grid, with each cell of the grid containing a single 1° element – either a letter T (the target) or a letter L (distractor). Each element's position within a cell was jittered, with 19 targets and 44 distractors randomly distributed over the virtual grid, and the number of targets in each half of the display (left vs right) balanced across trials. The T-targets were always upright but the L-shaped distractors could appear in any of 4 orientations. Eye movements were recorded using a video-based pupil tracker with a temporal resolution of 4ms (EyeLink; Sensorimotoric Systems GmbH). Each trial was initiated by the experimenter and began with a central fixation cross for 1s, then the search display. Analysis of eye movements was performed off-line, after the experiment.

Participants were instructed that while looking at any target, they should click a response-button held in the right hand *only if they considered this target to be a new discovery* (i.e. a target they had not clicked on before). Clicking the response-button did not change the display (i.e. unlike standard cancellation tests, but like search in real life, no visible mark was made on a detected target). Subjects were reminded, throughout testing, to click on each target found once only. Any later re-click on a previously-found target thus indicates a failure to retain the fact that this target had already been discovered, providing our

measure of SWM during search. Each search was terminated when the subject indicated verbally that they felt they had found all the targets in the display. Each subject searched a minimum of 7 displays. Eye movements were analysed off-line using custom software. An automatic algorithm was used to extract saccades (saccade onset defined as eye speed rising above $25° \text{ s}^{-1}$ for two or more samples and a criterion of minimum fixation duration of 60ms).

Blinks were eliminated from the trace by visual inspection, and saccade and fixation delineation checked visually in the record. A fixation was assigned to a display item if its mean position fell within one degree. Two or more consecutive fixations on the same item were re-scored as a single extended fixation. A re-fixation was scored only when at least one fixation on another item intervened. Button-clicks were assigned to an item if eye-position at the time of the click was within 2 degrees of that item. A reclick on an item required at least one fixation between successive clicks.

Percentage *re-fixation rates* were calculated by dividing the total number of re-fixations made during a trial by the total number of targets fixated during that trial and multiplying the ratio by 100. Percentage *re-click rates* were calculated by dividing the total number of re-clicks by the total number of targets fixated and initially clicked upon, and multiplying the ratio by 100.

The performance of patient BI was compared to normative data obtained from three non-neglect patient control subjects matched for age and time since stroke (see Table I). On this search task, patient BI demonstrated neglect of targets to the left,
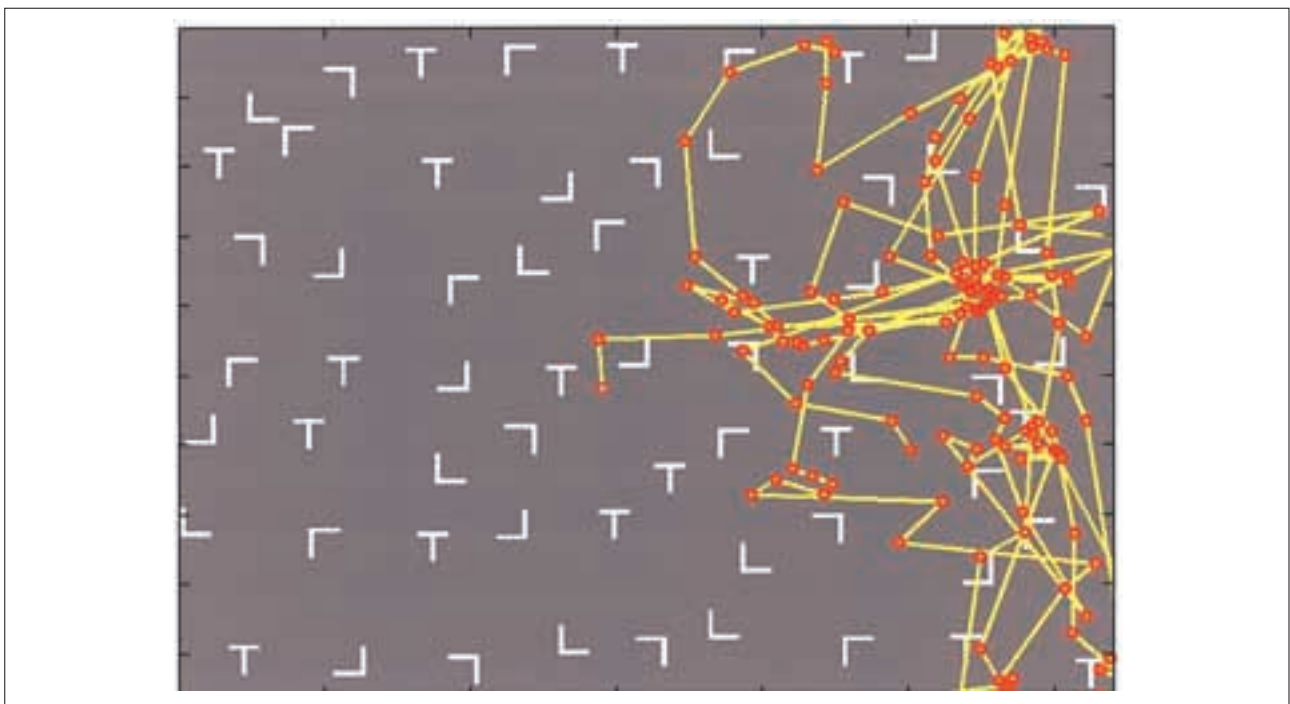

Fig. 4 – *Display showing BI's eye movements during visual search for Ts amongst Ls. He shows repeated refixations of items on the right, neglecting targets on the left. During search, he repeatedly re-clicked on right targets, indicating that he was mistakenly treating these as new discoveries.*

missing, on average, 67% of targets (SD = 9), all on the left (Figure 4a). In addition, he recursively re-fixated targets on the right with a mean refixation rate of 117% (cf. control patients' mean 52%; SD = 34%). Critically, he also re-clicked on targets at an abnormally high rate of 64%, compared to patient control mean re-click rates of only 13% (upper 95% confidence limit = 35%). Thus, on this search task BI not only neglected stimuli on the left, but also failed to retain the locations of targets he had already inspected on the right, mistakenly treating them as new discoveries at a pathologically high rate, as revealed by our re-click measure of SWM. The median interval between clicking on a target and re-clicking on it (expressed as the number of intervening eye movements) was 38.5 saccades, suggesting that his pathologically high re-click cannot be due to compulsively perseverative button-pressing, nor to a failure to direct his gaze away from a target. Instead, his performance suggests some impairment in the ability to retain, over intervening saccades, locations that have been previously fixated and clicked.

RECOVERY OF VERTICAL SPATIAL WORKING MEMORY AND LEFT-SIDED NEGLECT OVER TIME

We were able to assess BI again at later points, 41 and 120 days after his stroke. On both these occasions, his neglect had become less severe, as demonstrated by higher scores on both Mesulam-shape and BIT-star cancellation tasks, plus no significant deviation on line bisection (Table 1). On both visits, we were able to test him also on the vertical SWM task. His performance on this also showed parallel improvement during this period. Compared to his initial score of 16/75, he obtained scores of 24 and 33 on Days 41 and 120 post-stroke respectively. Figure 5 tracks his performance, demonstrating analogous improvements in both neglect (as measured by cancellation) and in vertical SWM performance. This is consistent with some relationship between the severity of any SWM deficit, and the severity of neglect (see also Husain et al. 2001) for evidence for some relationship between these when manipulating search difficulty within one patient; and Husain et al. (2002) for evidence of some relationship between re-click deficits and neglect severity across different patients).

DISCUSSION

The neglect syndrome is increasingly considered to have multiple components, with different patients suffering from different combinations of component deficits (Husain and Rorden, 2003). We have proposed that deficits of spatial working memory (SWM) may be one
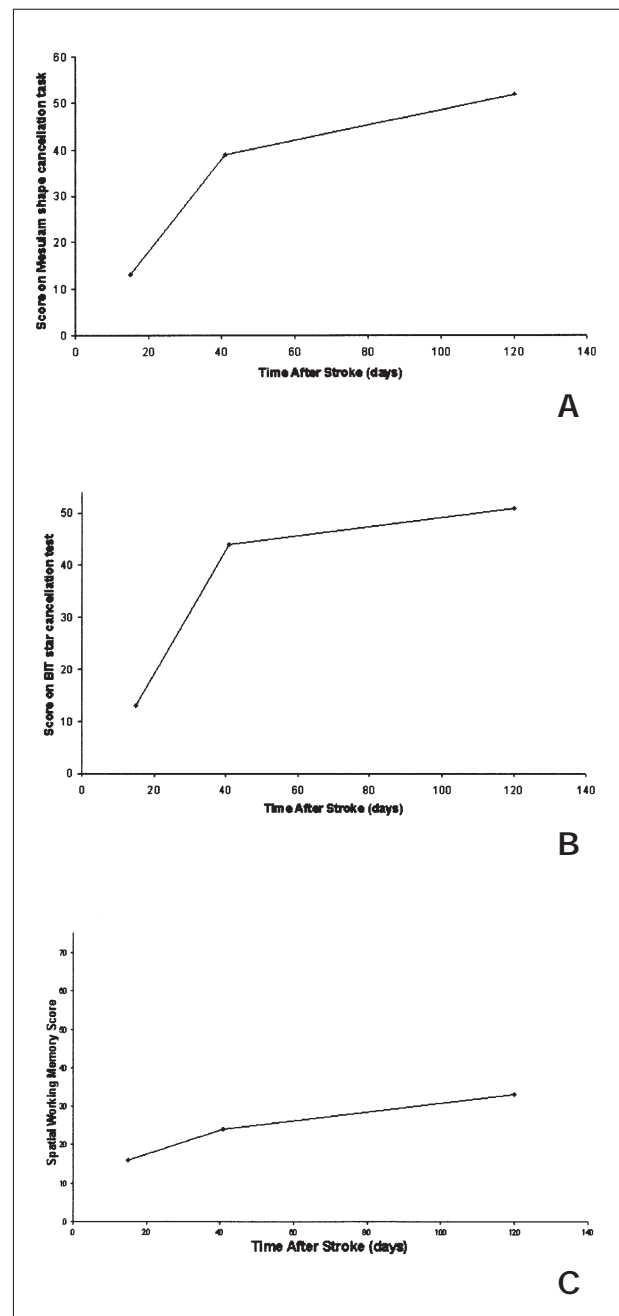

Fig. 5 – *The results of Patient BI displayed as a percentage of the maximum possible score on the Mesulam shape cancellation task (a), the BIT star cancellation task (b), and the vertical spatial working memory task (c) at 15, 41 and 120 days post stroke. Patient BI shows an increasing improvement in standard cancellation tasks and spatial working memory over this period.*

important component (see also Ellis et al., 1996; Beschin et al., 1997). Specifically, we proposed a role for a deficit in retaining previously searched locations across saccades (Husain et al., 2001; Wojciulik et al., 2001; Driver and Husain, 2002). When combined with a lateralized spatial bias to direct attention towards ipsilesional stimuli, such a SWM deficit should lead to recursive search of ipsilesional space, at the expense of contralesional stimuli which would continue to be neglected, even when given unlimited time.

Conventional SWM tasks such as the Corsi blocks are not suitable for testing neglect patients, who may perform poorly simply because they are impaired at perceiving stimuli in contralesional space, rather than because they have a deficit in spatial memory *per se*. We therefore developed a task in which the locations are arranged in a non-spatially lateralised array. We examined a patient with neglect following right temporoparietal haemorrhage and showed that he was impaired in retaining spatial locations on this task. In addition, on a spatially lateralised multitarget search task he recursively refixated stimuli on the right and, critically, often failed to remember that he had searched these locations before, as demonstrated by his abnormally high re-click rate. The use of lateralised stimuli in our search task does not confound measurement of SWM across saccades, because it is precisely the stimuli which are *not* neglected that reveal the SWM deficit. It has previously been shown that central attentional resources are involved in working memory tasks (Salway and Logie, 1995), and such resources may be affected in spatial neglect (Husain and Rorden, 2003; Robertson, 2001). It is possible that impairments in central attentional resources contributed to patient BI's performance on our SWM and search tasks.

We hypothesize that the SWM impairment, when combined with a rightward attentional bias, leads to re-examination of stimuli on the right (which are repeatedly mistaken for new discoveries), at the expense of stimuli on the left. This predicts that the severity of neglect should reduce if SWM improves, since locations to the right that have been searched before should then be revisited less frequently, thus allowing search to progress leftwards. Consistent with this hypothesis, we found that, over time, both the patient's left-sided neglect and his SWM deficit improved in parallel.

Of course, the data presented in the current study pertain to only a single case. In a recent investigation (Husain et al., 2002) we applied both our search-and-click and vertical SWM methods to groups of stroke patients with and without neglect.

Importantly, we found that the extent of any SWM impairment correlated with the severity of neglect for left stimuli, both within the search task itself, and also for neglect severity on standard clinical tasks. This impairment did not appear to be accompanied by a deficit in non-SWM, as neglect patients did not show a significant difference in digit span when compared to non-neglect right hemisphere patients.

We must emphasise that we are *not* proposing that a SWM deficit is the primary or sole cause of neglect. Rather, we suggest that it may increase the severity of the syndrome, by exacerbating the effect of spatial bias. The results of our vertical SWM study demonstrate a deficit that is not localised to the neglected side of space. Moreover,

the pathological re-clicks in our search task actually arose for items in right-sided locations, that were not neglected.

The pioneering studies of De Renzi and his colleagues originally demonstrated that patients with posterior lesions, particularly of the right hemisphere, have impaired SWM, as assessed on the Corsi blocks. In those studies, patients with neglect were specifically excluded and the critical location associated with the SWM deficit could not be established definitively, because of the lack of precise imaging techniques.

Warrington and James used tests of dot enumeration and counting, which may also require SWM, and found that patients with lesions involving the right parietal lobe were particularly impaired (Warrington and James, 1967). In more recent years, functional imaging has demonstrated a predominantly right-lateralised network, involving both posterior parietal and lateral frontal cortex, when healthy volunteers perform a variety of SWM tasks, including saccades to remembered positions (Heide et al., 2001; Owen, 1997).

Both right posterior parietal and lateral frontal regions have been implicated in spatial neglect as well as in SWM. However, some forms of impaired SWM can be dissociated from spatial neglect, as demonstrated in the group studies of De Renzi, as well as in some single-case reports (Hanley et al., 1991; Walker et al., 1998). It is possible that the critical factor determining whether a lateral spatial bias in attention is *associated* with a SWM deficit is the location of the lesion.

Functional imaging studies suggest some fractionation of function within different regions of both posterior parietal and lateral frontal cortex (Owen, 1997; Fletcher and Henson, 2001; Culham and Kanwisher, 2001; Corbetta and Shulman, 2002), although some authors contend that active maintenance of remembered locations may be mediated by shifts of spatial attention to those locations (Smyth and Scholey, 1996; Awh et al., 2000). Damage to particular sub-regions within these areas may lead to SWM deficits without neglect; while other sub-regions may need to be damaged to cause the spatial bias towards one side that is so evident in neglect.

Lesions that span both sub-regions might lead to a combined spatial bias plus SWM deficit, which on our account would exacerbate the impact of the spatial bias, and thus lead to more severe neglect.

We suggest that the SWM deficit present in some neglect patients may be due specifically to a failure in updating spatial representations across saccades. Patients with lesions involving right parietal cortex exhibit difficulties in retaining target locations across eye movements, in double-step saccade tasks (Duhamel et al., 1992b; Heide et al., 1995). A recent functional imaging study in healthy volunteers performing a related triple-step saccade

task demonstrated a critical trans-saccadic spatial updating role for a region within the right intraparietal sulcus (Heide et al., 2001), an area that was also affected in the present patient, and which was an area of common damage in many of the patients showing pathological re-click rates in our recent group study (Husain et al., 2001). This region in humans may correspond to area LIP in monkeys. Neurons there encode memory for stimulus location in tasks that require saccades to remembered positions (Colby and Goldberg, 1999; Mazzoni et al., 1996), and some studies suggest that LIP has a specific role in updating spatial representations across saccades (Duhamel et al., 1992a).

Even if one accepts that some neglect patients may also have a SWM deficit, it could be argued that such a failure to remember previously searched locations is unlikely to contribute to performance on tasks such as cancellation, since these require visible marks to be made on targets that are found, permanently indicating that these have already been inspected. However, cancellation tasks often involve placing relatively faint marks which may not be seen in peripheral vision, particularly if neglect patients have a local spatial bias (Robertson et al., 1988; Halligan and Marshall, 1994), or a restricted field of view (Husain and Kennard, 1997). Thus, memory for searched locations may be critical to prevent gaze from returning to rightward locations, even if they have been marked before, as the marks might not be visible until gaze returns to them. Consistent with this proposal, we have demonstrated in a detailed case study (Wojciulik et al., 2001), as well as in a group study of twenty-three patients (see Driver and Husain, 2002 for preliminary data), that neglect is more severe when cancellation is performed using invisible marks, compared to salient red marks (Wojciulik et al., 2001).

In summary, this study demonstrates the co-existence of a SWM deficit in a patient with spatial neglect. The spatial memory deficit is demonstrable on both a vertical SWM task and during search of laterally extended displays. We propose that the SWM deficit may be a specific failure to update representations of stimulus locations across saccades. Such an impairment may exacerbate the spatial bias in neglect, contributing to recursive search of ipsilesional locations, at the expense of stimuli in contralesional space.

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