LOST IN SPACE – THE FATE OF MEMORY REPRESENTATIONS FOR NON-NEGLECTED STIMULI

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ABSTRACT

Typically, spatial neglect after right-hemisphere brain damage is defined as a failure to orient towards or attend to stimuli located towards the contralesional, in this case the left, side of space. Here, we report that neglect patients have difficulty maintaining the spatial locations of vertically arranged stimuli on the right side of space. This indicates that neglect is associated with a severe deficit in the maintenance of spatial information even on the ipsilesional “good” side.

KEY WORDS: Spatial neglect, attention, spatial working memory, awareness

INTRODUCTION

Only recently have non-attentional deficits been examined in neglect patients. For example, two single-case studies and one group study have demonstrated impairments to working memory functions in neglect (Wojciulik, Husain, Clark & Driver, 2001; Husain, Mannan, Hodgson, Wojciulik, Driver & Kennard, 2001; Mannan, Mort, Hodgson, Driver, Kennard & Husain, 2005). The authors used visual search paradigms and found that neglect patients repeatedly revisited previously explored locations as if they were treating these 'old' locations as 'new.' Pisella and co-workers (2004) also used a visual search paradigm but asked patients to report changes in previously determined stimulus attributes (location, shape or colour). They found that neglect patients with parietal lesions were impaired in detecting location changes relative to colour or shape changes. Even though these findings indicate a spatial working memory deficit in these patients, they remain open to several alternate interpretations. First, it is unclear whether the revisiting behaviour is due to a working memory problem per se or a problem related to eye movement programming or saccadic remapping (Duhamel, Colby & Goldberg,1992; Colby & Goldberg, 1999; Pisella & Mattingley, 2004): whenever the eye moves, the locations of objects must be updated with respect to the new eye position. Given that the displays used extended across the horizontal axis, these tasks required the planning and execution of several horizontal eye movements. Accordingly, it is possible that the results were confounded by potential deficits of saccadic remapping along the horizontal axis rather than, or in addition to, a deficit of working memory.

More importantly, the horizontal arrangement of targets may have led to competition between target locations at encoding. Given that neglect patients have a severe deficit in allocating attention toward contralesional stimuli, independent of memory load, this type of display is problematic: when stimuli on the left side compete with stimuli on the right, it is likely that the right-side stimuli will be represented as more salient. Therefore, the aim of this study was to disambiguate working memory processes from lateral biases leading to competition between target locations either at encoding or retrieval. Accordingly, all stimuli were arranged *vertically* and were presented on the right side only.

PATIENTS AND METHODS

Four neglect patients were compared to ten age-matched neurologically healthy controls (HC) and four right-brain damaged (RBD) patients without neglect. Neglect was assessed using two cancellation tasks, figure copying and line bisection (see Table 1). Written informed consent was obtained from all patients and controls. The study was approved by the relevant hospital and institutional ethics review boards. All patients (neglect and RBD) were tested at least three months post stroke.

For all experiments, patients and controls sat in front of a computer screen at a viewing distance of 57 cm, and the head and body axis were aligned. At the beginning of each trial of the spatial working memory task, participants fixated on a red central fixation cross (see Figure 1A; fixation cross depicted in black). Once the participant fixated, the trial was initiated by the experimenter and the fixation

cross changed to green (depicted in grey in Fig. 1A), indicating that the trial had commenced. After one second, three target squares were presented two degrees to the right of the fixation cross. The squares each subtended 1.5 degrees in visual angle and were vertically arranged with a minimum separation of 2 degrees between squares. Squares could appear in any of six different vertical locations.

In any given trial, three squares were presented simultaneously for two seconds. Initially, we asked patients to maintain central fixation for the duration of the trial but all neglect patients were either unable to maintain central fixation as soon as a stimulus was presented on the right side or they performed so poorly with central fixation that we then decided to encourage all participants to make eye movements to all locations. This means that our task involved eye movements and thus saccadic remapping; however, the important remapping processes occurred along the vertical axis. To the best of our knowledge no studies as of yet have demonstrated a vertical saccadic remapping problem in neglect patients. For practice purposes, the patients were also encouraged to count the squares during the initial trials. Only patients who detected all three squares reliably were included in this study. After two seconds, the three squares disappeared, and subjects were asked to keep the location of these squares in mind over a three second delay period. After this 3-s delay, a circle was presented in one of the six possible locations along the same vertical column (i.e., at the same horizontal position) as the squares and the participant had to indicate whether or not the location of this circle matched the location of any of

the three previously presented squares. The circle remained on the screen until a verbal response was made. Then, the experimenter advanced the program to the next trial. A total of 120 trials was completed by all participants in up to two sessions. In 50% of all trials the circle occupied a location previously occupied by a square. All participants were allowed to rest at any time. We also administered a task assessing verbal working memory in which we presented three single-digit numbers as targets instead of squares (numbers subtended 1.5 degrees of visual angle and were presented for 2s using the same locations occupied by squares in the spatial working memory task). After the 3-s delay an old or new number was presented and subjects had to indicate verbally whether it was old or new. Accordingly, on each trial participants had to keep three different numbers in mind to compare these with the upcoming probe (see Fig. 1A). NP3 was not tested on this task due to time constraints prior to that patient returning home some distance away. However, she (like all other neglect patients) was tested on a low level perceptual control task comprising an additional 120 trials in which the squares and the circle were presented at the same time. This task has been introduced by Jonides and colleagues (1993) in a functional imaging context to keep the actual stimuli (squares and circles) and the stimulus locations constant for both the experimental and control tasks.

We were able to analyze the lesions of three neglect patients and three right-brain damaged control patients according to the following protocol: the three stroke patients without neglect had digital 3D T1-weighted MRI (TR/TE, 35/5 msec, flip angle 35°, voxel dimension 0.86x0.86x1.2 mm, matrix 256x192). The

three patients with neglect had CT scan films with a slice thickness of 5 mm, which were transferred to digital 3D images using an in-house 2Dto3D protocol.

All lesions were traced manually on axial T1 MRI or CT scans on a slice-by-slice basis, which was conducted using ANALYZE AVW™ Software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). Lesions in T1-weighted MRI and CT scans were defined as the hypointense or hypodense stroke compared to its surrounding parenchyma. We then transformed individual brain scans to a template MRI scan from the Montreal Neurological Institute (http://www.bic.mni.mcgill.ca/cgi/icbm_view), which is based on 27 repeated Colin T1-weighted MRI scans, normalized to Talairach space. The brain tissue was extracted from the skull either by using the Brain Extraction Tool software package or by manual segmentation to avoid removing lesioned tissue to allow for more accurate co-registration of the patients' brain scans with the template brain scan. The actual transformation was a two-step process using Automatic Image Registration version 5.2.5 software (AIR; http://bishopw.loni.ucla.edu/AIR5): first, we ran a spatial normalization protocol including a linear 12-parameter affine transformation (including aligning scans to ACPC aligned Talairach space), and then we used a non-linear fourth order parameter warping model to make scans fit best to the template. The resulting images had a voxel size of 1mm × 1mm × 1mm. Visual inspection of the raw images and the transformed lesion maps suggested good correspondence between individual and template scans.

Using the transformed lesion maps, we estimated the proportion of each Brodmann area or anatomical region involved in each patient's lesion, using the single-subject Colin template in MRIcro (http://people.cas.sc.edu/rorden/). To superimpose the individual brain lesions, the same MRIcro software was used (Rorden & Brett, 2000).

RESULTS

Responses were analyzed according to the number of hits and the number of false alarms. For the spatial working memory task, a response was scored as a 'hit' when the participant correctly indicated that the circle was presented in the same location as any of the three squares. A response was scored as a 'false alarm' when the participant indicated that the circle's location matched one of the locations of the target squares even though it had been presented at a new location. In the verbal task, a 'hit' classified the correct identification of a number probe as one of the preceding target numbers, while a 'false alarm' classified the identification of the number probe as old when it was in fact new. In all cases, an accuracy score was calculated by subtracting the percentage of false alarms from the percentage of hits.

Neurologically-intact healthy participants and right-brain damaged control patients performed well on the spatial working memory task, reaching mean accuracy scores of 79% (SD = 8.7) and 89% (SD = 6.1), respectively (see Fig. 1B). We calculated the 95% confidence interval for both control groups and the lower boundaries were 72.5% for our neurologically healthy subjects and 79.4%

for our right-brain damaged patients. In stark contrast to these performances, all four neglect patients performed poorly on the spatial working memory task. They reached individual accuracy scores of NP1 = 44% (hits: 51%, false alarms: 7%), NP2 = 10% (hits: 40%, false alarms: 30%), NP3 = 43% (hits: 51%, false alarms: 8%) and NP4 = 38% (hits: 51%, false alarms: 13%) which were all well below the lower limits of the 95% confidence intervals for both control groups (see Fig. 1B). However, neglect patients performed no worse than controls on the verbal working memory task (all neglect patients = 100% each, RBD = 98%, SD = 4.3), indicating that they can maintain verbal material over the 3-s delay period. While these high scores may be related to a ceiling effect, the important point to note is that this task employs exactly the same delay length and spatial layout of the target and probe stimuli as does the spatial working memory task. Furthermore, the verbal task required the online maintenance of the identities of three different stimuli. But in contrast to the poor performance on the spatial task, the patients performed perfectly when verbal material had to be maintained over the same retention interval indicating that the working memory deficit was restricted to the spatial domain. Furthermore, all patients performed well on the perceptual control task indicating that patients were not impaired at making simple spatial comparisons (average accuracy scores NP = 97%, SD = 2.38; RBD = 100%, SD = .85; HC = 99%, SD = 1.63).

We also analyzed lesion locations in our patients. Figure 2 shows the lesions of the right-brain damaged control patients without neglect and the lesions of the neglect patients superimposed on a template brain. The lesions are

colour-coded such that each colour represents the lesion of one patient.

The commonly lesioned areas in our RBD patients were the precentral gyrus, the frontal operculum, the insula, the postcentral gyrus, the suparmarginal gyrus, the transverse temporal gyrus, the superior temporal gyrus and the middle temporal gyrus. The commonly lesioned areas in our neglect patients were the rolandic operculum, the insula, the postcentral gyrus, the supramarginal gyrus, the caudate, the putamen, the globus pallidus, the transverse temporal gyrus, the superior temporal gyrus and the middle temporal gyrus.

DISCUSSION

Our results suggest that patients with neglect suffer from a severe deficit in maintaining a limited amount of spatial information over a brief period of time. A similar result has recently been reported by Malhotra and co-workers (2005). We believe that our findings go beyond this initial report in that we found the spatial working memory deficit even on the ipsilesional side and our paradigm employs a purely spatial format. Stimulus locations in the Malhotra et al. (2005) study could have been encoded with respect to the locations of the other elements on the screen. This is certainly not the case in our task given that only the three relevant items were presented during encoding and the probe was presented in isolation. Furthermore, our control tasks clearly demonstrated that the deficit observed in our patients is not due to a failure to perceive the stimuli correctly. Our control experiments have shown that perceptual matching and

identification processes at the same spatial locations were intact. While our experimental set-up cannot rule out localization threshold problems it is unlikely that they confounded the results. The locations differed in terms of the vertical dimension and all neglect patients were able to describe the locations verbally. Furthermore, we asked our patients after the experiment how sure they were about their judgements, and all of them felt very sure about their decisions and they never had the impression that the probe was positioned just 'slightly off' with respect to the target locations. Also, we do not believe that the poor performance on our spatial working memory task was related to a potential problem in saccadic remapping. The stimuli in our SWM task were arranged vertically and the probe presented after the delay was presented at the same horizontal location as the preceding stimuli. Therefore, any eye movements towards target or probe stimuli would be mainly along the vertical axis - a direction of movement typically unaffected in neglect. We hypothesise that the spatial working memory deficit in neglect is related to rapid forgetting of spatial information. To that end, it would be interesting to test the time course of decay by varying the retention interval. It is important to note that in all previous work exploring a spatial working memory deficit in neglect, this aspect can not be controlled for due to the constraints of the visual search paradigms used. While our paradigm clearly allows for testing spatial working memory performance without any horizontal biases, future studies should use verbal working memory tasks that also incorporate a spatial component. This means that subjects should be presented with the to-be-remembered numbers during encoding but should be informed

about the nature of the task only at the end of the delay period. In other words, subjects will maintain both object location and identity information over the delay period and will then be probed either with respect to location ("is this number presented in an old or new location") or with respect to identity ("is this an old or new number"). This means that the input at encoding can be held constant and the modality (verbal versus spatial) will be relevant only at retrieval.

At first blush, the spatial working memory deficit reported here may appear similar to problems related to ipsilateral inattention (Albert, 1973; Weintraub & Mesulam, 1987) or the geometry of space perception on the ipsilesional side (Halligan & Marshall, 1991). We believe that our control tasks show that neglect patients can attend to the tested locations and can process stimulus information provided at those locations. Their deficient performance is only revealed when we test for spatial memory after a delay period. Accordingly, the deficit is not one of sensory processing of identities or locations per se but rather of maintaining the spatial information over a short delay period.

We believe that this spatial working memory deficit alone is insufficient to result in neglect: patients with prefrontal lesions but without neglect show a similar impairment (Kessels, Postma, Wijnalda & de Haan, 2000) and our neglect patients showed this deficit on the "good," ipsilesional side. Instead, we would suggest that while the spatial working memory deficit may be necessary for the characteristic lack of awareness to occur, it must be accompanied by a deficit in disengaging attention from the ipsilesional side (Posner, Walker, Friedrich & Rafal, 1984; Morrow & Ratcliff, 1988; Robertson & Eglin, 1993) to result in the

full-blown neglect syndrome. Further, we believe that the spatial working memory deficit is not limited to potential sub-groups within the neglect population. Neglect patients were included in our study based on performance on typical neglect tests, not on lesion location. As a result, the lesion sites of our patients are rather heterogeneous. Interestingly, lesion reconstruction revealed that the caudate and putamen were lesioned in all neglect patients but not in all right-brain damaged patients without neglect. While this observation is interesting in the context of a recent finding implicating the caudate and putamen as the sub-cortical substrates of neglect (Karnath, Himmelbach & Rorden, 2002) we do not believe that these regions are causal for the observed spatial working memory deficit. Two of our right-brain damaged control patients also showed lesions to these areas but performed no worse than healthy controls on the SWM task. Accordingly, we believe that the defining feature of the SWM deficit we observe here seems to be unrelated to a specific lesion site; rather it seems to be highly related to the presence or absence of neglect – a speculation that obviously needs to be confirmed in a larger sample size.

To summarize, neglect patients show spatially lateralized deficits in their daily-life activities and on bedside tests of drawing, figure copying and visual search which are usually interpreted as impairments of spatially directed attentional and/or motor processes. Here we show that neglect also involves a deficit of spatial working memory – even on the ipsilesional side. While our neglect patients were able to attend to the probed locations and process stimulus identity information provided at those locations, they were unable to maintain

spatial information over a short delay period. Working memory enables us to hold in our mind's eye a limited amount of information available for access by other cognitive faculties. The ability to transfer external events into working memory and maintain them there is likely to be crucial for consciously representing an ever-changing environment. Any impairment in such processes combined with a deficit in attentional orienting that favours the ipsilesional side and prevents patients from attending towards the contralesional side should lead to a lateralized loss of awareness.

ACKNOWLEDGEMENTS

We thank our patients for participating in this research. Stephen Emrich helped with collecting data from control subjects. We also thank Sandra E. Black and Fuqiang Gao for their help with the lesion analysis. This research was supported by grants from the Natural Sciences and Engineering Research Council of Canada awarded to both authors.

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FIGURE LEGEND

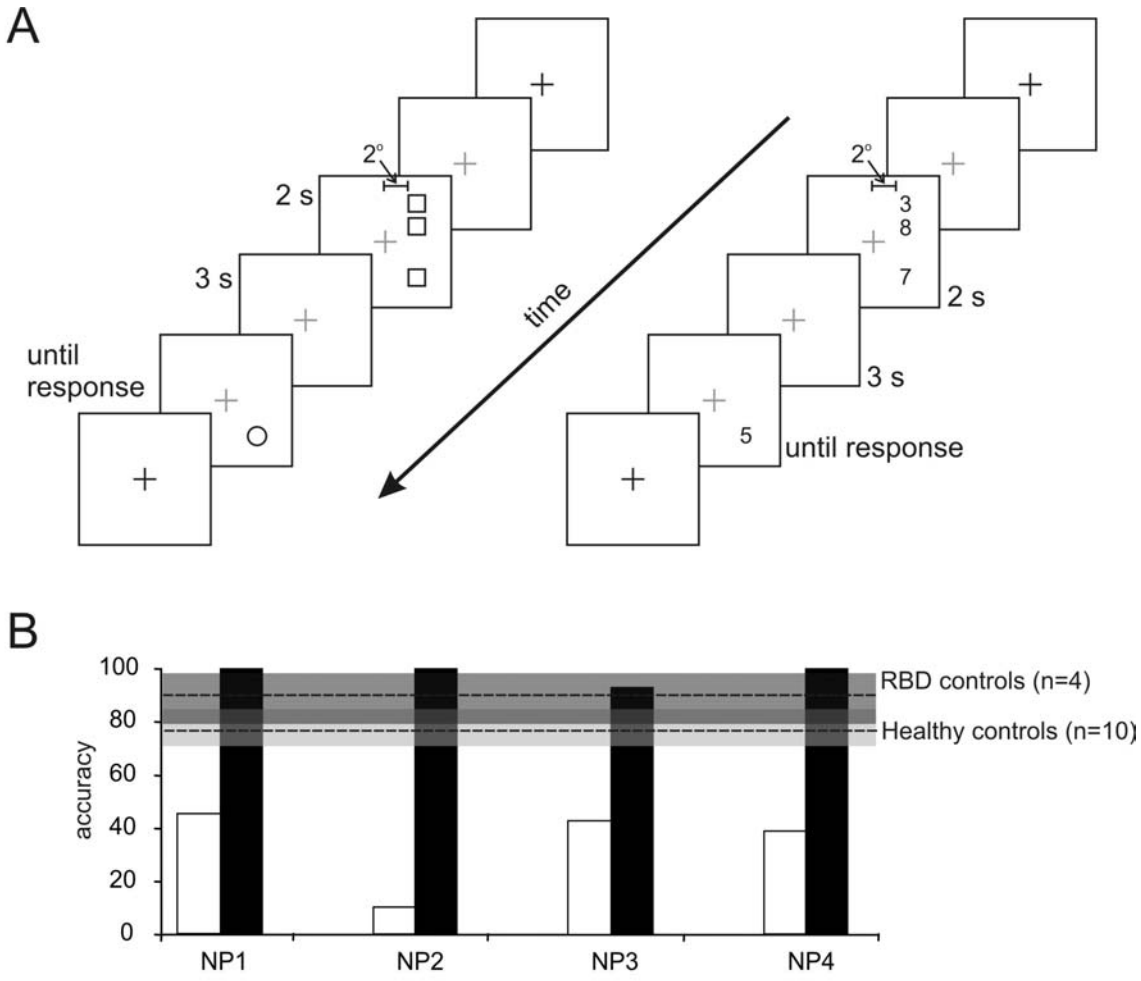
Figure 1: **(A)** Spatial working memory task and verbal control condition. On the left is a schematic representation of the spatial working memory (SWM) task; on the right is a schematic of the verbal control task. SWM task: trials began with a fixation cross after which three targets were presented for 2 seconds. This was followed by a 3-s delay after which a circle appeared (probe). The patient had to indicate whether or not the circle was presented at one of the locations in which a target had previously been presented (in this case the correct answer is yes). Verbal working memory control task: three single-digit numbers were presented for two seconds and participants were asked to maintain the identity of those numbers over the following 3-s delay period. Participants had to indicate whether the probe was an old (previously presented) or new number. **(B)** Accuracy scores. The dotted lines represent the average accuracy scores achieved by right-brain damaged (RBD) control patients (n=4) and by neurologically healthy subjects (n=10) on the spatial working memory task. The light grey shaded area indicates the 95% confidence interval for the SWM task for age-matched healthy controls; the dark grey shaded area indicates the 95% confidence interval for RBD patients. All neglect patients performed well below the 95% confidence interval for both control groups on the SWM task (white bars; black bars represent performance on the verbal working memory control task; note that NP3 did not complete this task; instead her performance on the perceptual control task is given).

Figure 2: Lesion plots. We used the MRIcro software package to superimpose individual brain lesions on a template brain scan, see Methods section for details. Lesions are colour-coded so that each colour represents the lesion of one patient. Images of NP4 and RBD4 were not available to us.

Table 1: Demographic and clinical data for all neglect patients. All patients suffered a right hemisphere stroke at least 3 months before testing. Letter cancellation: Patients had to find 60 (30 on each side) target letters 'A' randomly dispersed among distractors. The data presented is the percentage of omissions. Bells test: Seven columns of images of objects, each containing five bells and 40 distractors, are presented on a sheet of paper. The patient is asked to cross out all bells. Percentage omissions for the three leftmost and three rightmost columns are given. For both cancellation tasks a high score reflects a high number of omissions. Line bisection: a percentage of rightward deviation was calculated by measuring the deviation of the bisection mark from the true centre, dividing this measure by the total line length, and multiplying this quotient by 100. Figure copying: a "+" indicates that clear signs of neglect were present; * indicates that the patient showed visuo-constructional deficits.

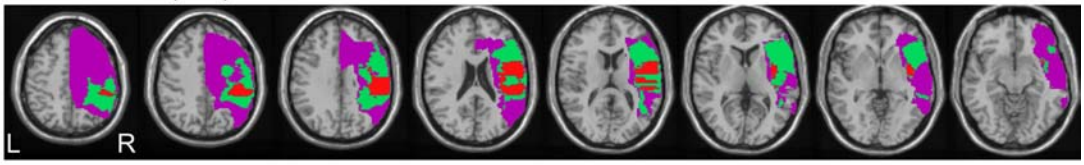
Table 1: Demographic and clinical data for all neglect patients.

	Age (years)	Sex	Letter cancellation (% omissions)		Bells test (% omissions)		Line bisection (% dev.)	copying
			left	right	left	right		
NP1	55	m	90	14	56	18	3.95	+
NP2	55	m	43	36	33	29	5.9	*
NP3	68	f	40	20	33	35	5.1	+
NP4	78	m	97	7	100	6	7.2	+

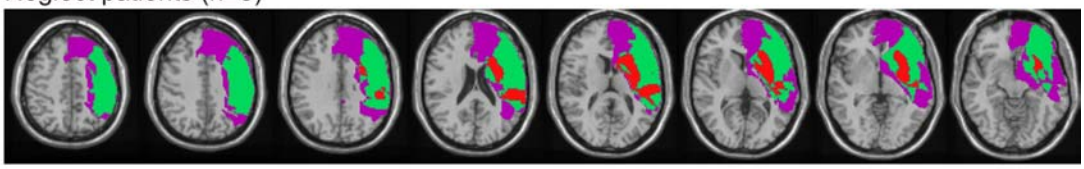


Ferber and Danckert, Fig. 1

RBD controls (n=3)



Neglect patients (n=3)



Ferber and Danckert, Fig. 2