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Spatial working memory deficit in unilateral neglect

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Abstract

Based on the similarity of brain areas lesioned in neglect and those activated by spatial working memory (WM) tasks in normals, we hypothesized that neglect may involve spatial WM impairments. A left neglect patient with right inferior frontal and basal ganglia damage performed cancellation tasks, making either highly visible marks (to provide a reminder of visited items), or invisible marks (so only spatial WM could represent cancelled items). Invisible marks led to repeated cancellations for targets that differed only in location, but not for targets with memorable unique identities, suggesting a deficit of *spatial* WM, with non-spatial WM spared. Neglect was greater for cancellation with invisible marks, consistent with a role for deficient spatial WM in cancellation deficits, but contrary to account solely in terms of attention capture by salient visible marks made in ipsilesional space.

Keywords: Attention; Cancellation; Neglect; Spatial working memory

1. Introduction

Unilateral visual neglect is a marked impairment in the ability to detect or respond to information contralateral to the side of brain damage. Most theories of neglect explain it as a deficit in visuospatial attention, characterized by a failure to direct attention contralesionally and/or an ipsilesional attentional bias [15,18,22]. Here, we test whether deficits in neglect may also extend to spatial working memory (WM).

Our hypothesis was based on several related observations. First, recent functional imaging studies of spatial WM [8,9,14,21] in normals observed a right-lateralized network of activations that closely resembles the areas typically involved in neglect [18,30] (e.g. right posterior parietal and lateral prefrontal cortex). It has been argued that such areas may be important for the temporary storage of spatial information [8–10,14,21]. Findings of spatial WM-related activity in parietal and frontal cells have also been reported in monkeys [2,11]. The similarity of neural substrates implicated in neglect and spatial WM suggests that neglect may be associated with spatial WM deficits.

Second, behavioral studies of memory function indicate that attention is critical for the formation of explicit memory traces [25,29]. Recent evidence suggests that shifts of spatial attention may be involved in the maintenance of information in spatial WM [27], acting as a rehearsal mechanism [4]. Such a dependence of spatial WM on spatial attention also implies that neglect, commonly interpreted as an attentional impairment, may additionally involve deficits in spatial WM.

Third, many standard tests of neglect (e.g. visual search, cancellation, drawing, copying a figure, or comparing two figures) involve an overlooked spatial WM component. In visual search, for example, spatial WM may be required to store locations of already visited items and thus prevent their repetitive rechecking. A deficit in spatial WM could increase perseverative refixations that may exacerbate the bias towards ipsilesional space. Such perseverative saccades have been documented in frontal and parietal patients [34]. In a typical cancellation test [1,19], neglect patients are asked to cancel (cross out) all relevant items. Although cancellation marks in principle provide a permanent reminder of visited items, when made faintly with pencil, these

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marks are rarely salient in peripheral vision. Hence, patients may need to refoveate items to see whether they have been cancelled, if that information can no longer be stored in spatial WM. More salient marks might then actually *reduce* neglect by providing a highly visible reminder of which items have already been visited.

This prediction contrasts with the perceptual salience hypothesis for neglect [17], which suggests that visible marks initially made in ipsilesional space may *increase* patients' bias towards that side. Patients cancel fewer items when they draw over them than when they erase them, which has been attibuted to the salience of initial marks on the ipsilesional side capturing attention, making it harder to move search into contralesional space [17]. However, erasing ipsilesional items not only decreases their salience, but also obviates the need to keep track of the cancelled items. Improved performance when erasing might therefore reflect a reduced spatial WM load, not just reduced salience in ipsilesional space.

Here, we tested whether spatial WM deficits can be present in neglect, contrasting this hypothesis with the account in terms of the salience of initial marks. Our left neglect patient was tested on cancellation tasks, with instructions to cancel each target *once only* while ignoring distractors. In one version ('visible' cancellation), he cancelled targets with a thick marker that made very salient red marks, serving as a permanent, highly visible reminder of which items had been cancelled. In the 'invisible' version, he cancelled targets using the same pen, but now with the cap on that pen, making his marks invisible to him (although recorded with carbon paper onto a sheet underneath). Thus, spatial WM load was increased in the invisible test: in the absence of visible marks, previously cancelled items can only be represented as visited locations within spatial WM.

The hypothesis of deficient spatial WM in neglect makes three predictions. First, consider what should happen when the patient is asked to cancel identical targets (Os) that differ only in location. If spatial WM deficits are present in neglect, the patient may repeatedly cancel the same items (presumably, on the ipsilesional side) when using invisible marks, because they cannot be stored as already cancelled in spatial WM. That is, there should be more *re-cancellation* errors with invisible than with visible marks.

Second, if re-cancellation errors reflect a specifically *spatial* WM deficit, they should be frequent for targets differing only in location (the Os), but not for memorable objects that differ in shape (and name), as well as location. For such objects, the patient should be able to remember that a particular object has already been marked on the basis of *non-spatial* (object or verbal) WM, which should prevent re-cancellations. Conversely, if WM in general is impaired, *re-cancellation* should be equally common for objects and Os.

Third, if the spatial WM deficit exacerbates neglect, there should be more neglect (i.e. a greater difference between proportion of items cancelled in right versus left space) for invisible than visible cancellation. The ipsilesional bias should be more pronounced in the invisible task because cancelled items on that side remain potential targets if they cannot be represented in spatial WM as already cancelled. This prediction contrasts directly with the perceptual salience hypothesis [17], which suggests that neglect is exacerbated by patients' initial visible marks in ipsilesional space. The salience hypothesis makes the opposite prediction: highly visible red marks made on the ipsilesional side should make that region more perceptually salient, increasing neglect relative to invisible marks.

2. Materials and methods

2.1. Patient

S.R. was 59-years-old when he suffered an infarct of the right inferior frontal cortex and basal ganglia (as assessed from CT scan performed 4 days after infarction). His lesion thus affected several components of the right-lateralized network that is activated in normals for spatial working memory tasks [8,9,14,21], while sparing other parts of the network structurally (e.g. parietal cortex and the supplementary motor area). The patient's stroke induced left hemiplegia and left visuospatial neglect. When tested 6 weeks after infarction, the patient scored 28/40 and 35/54 on the letter- and star-cancellation tests, respectively, of the BIT battery [32], and 21/60 on Mesulam's shape cancellation test [19], with all omissions on the left. The present experiment was run 3 weeks later (i.e. 9 weeks after infarction) in two sessions, 2 days apart. S.R. participated with informed consent.

2.2. Stimuli and design

Each sheet (A3 paper, 42 cm × 30 cm) was composed of 24 identical Os and 24 different drawings of common objects [28], all printed in black (Fig. 1). The Os and objects were intermingled in eight 'pseudocolumns' (i.e. with stimuli in each pseudocolumn scattered to appear randomly distributed across the page), with three Os and three objects in each pseudocolumn. Two counterbalancing sets of eight sheets each were created. In Set I, each sheet used a different set of 24 objects. Objects and Os were distributed randomly within each pseudocolumn. In Set II, each sheet was rearranged in two ways. First, those objects appearing on the left in Set I occurred on the right in Set II (with objects in the leftmost column now in the rightmost column, those in the second left column now in the second right, etc.). Second, the positions of Os and objects within each pseudocolumn were switched, such that locations occupied by objects in Set I were occupied by Os in Set II, and vice versa. This counterbalanced for the specific locations of Os and objects, plus the memorability of objects used in the two halves of each sheet.

The crossed factors were: cancellation condition (visible/invisible marks), stimuli to be cancelled (objects/Os), and sheet side, with data for left and right halves scored separately for each sheet. Visible and invisible cancellation was performed on identical sheets across different trials, and scores for left and right halves were obtained from the same sheet on one trial, so condition and side were treated as repeated measures. The random variable was trials.

2.3. Procedure

S.R. completed 32 trials in total (16 per session), with eight trials per cell. A red marker was used for visible cancellation, while invisible cancellation was performed using the same pen, but with the cap on, so that the invisible marks were recorded only via carbon paper. S.R. cancelled with his right hand.

Set I sheets were used in the first session, and Set II in the second. This reduced any potential proactive interference in memory for cancelled objects (i.e. sheets with the same objects occurred only twice per session, once for visible and once for invisible cancellation). In each session, trials were presented in a pseudorandom order with the constraint that for trials using the same sheets, half occurred as visible first and then as invisible, and vice versa for the other half.

Before each trial, S.R. was instructed to cancel all relevant items (i.e. just objects or just Os), marking each *once only*. To ensure that he paid attention to object identity, S.R. was asked to name the objects when cancelling them; to control for this additional verbal requirement, he named successive letters of the alphabet while cancelling Os. S.R. cancelled items by crossing them (i.e. using two marks for each cancellation), so a re-cancellation was scored for any additional cross (an extra single line was scored as 0.5 re-cancellation).

3. Results

3.1. Re-cancellations

S.R. made frequent re-cancellation errors for the

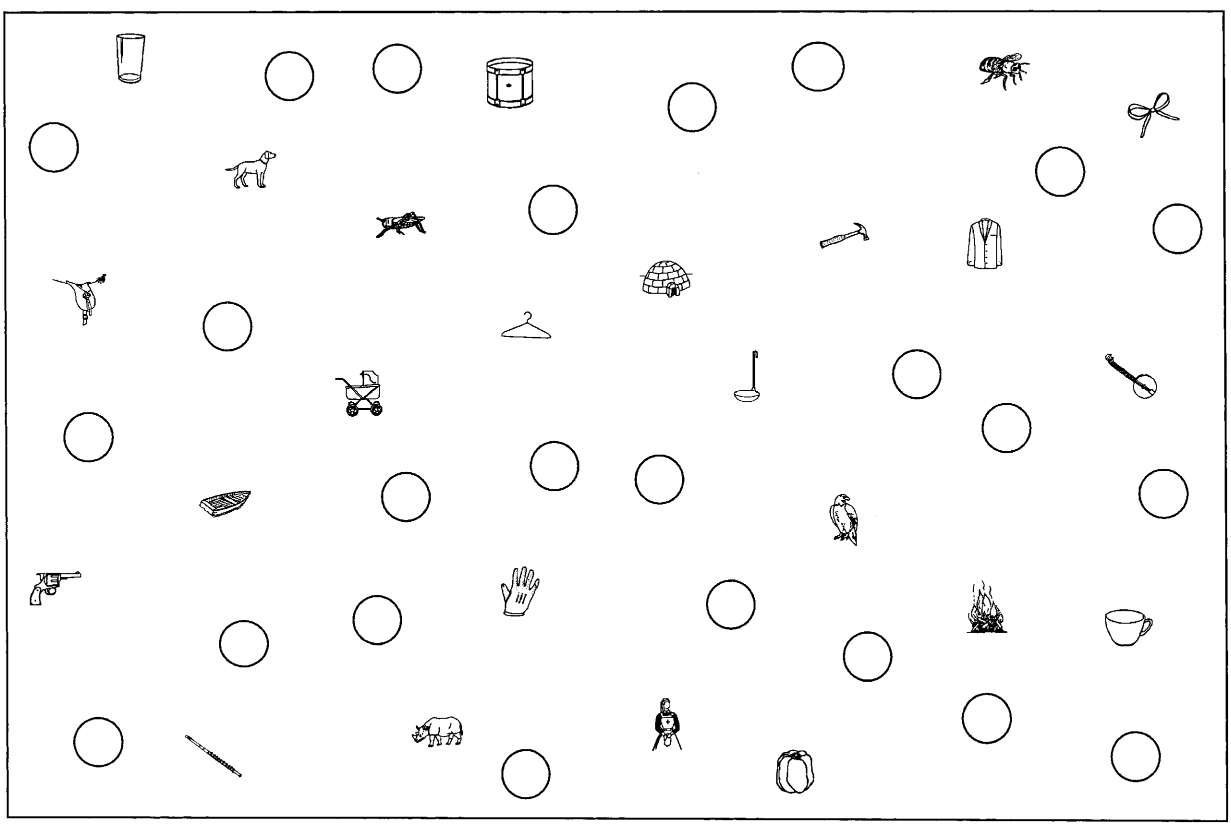

Fig. 1. Sample stimulus sheet, illustrating the intermingling of Os and objects, with each object having a unique identity.

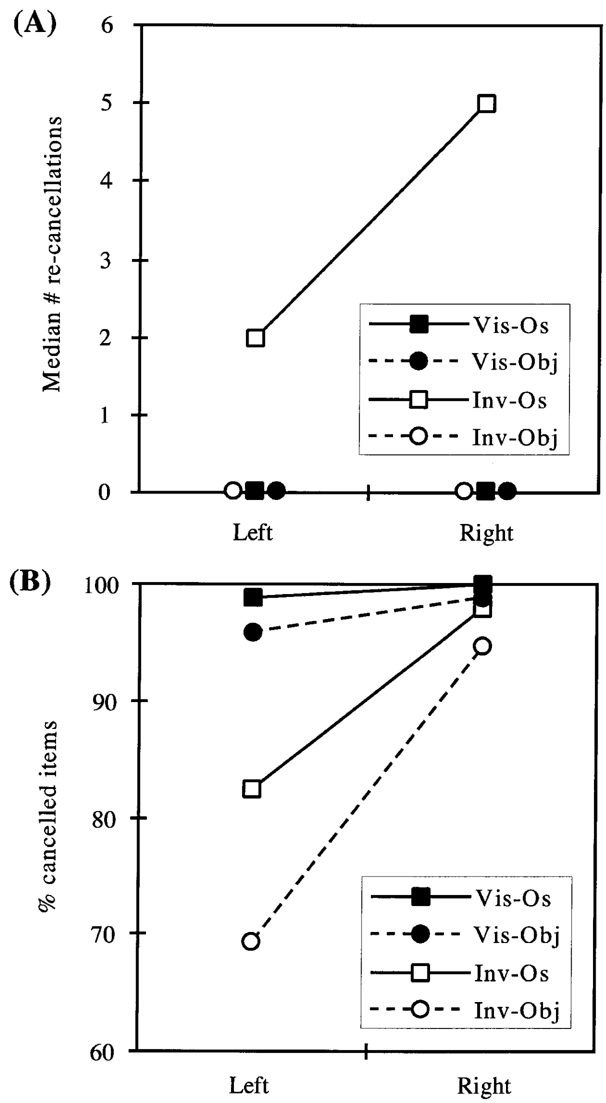

Fig. 2. Patient's performance for visible and invisible cancellation of objects or Os. (A) Re-cancellation errors. (B) Cancellation scores. Abbreviations: Vis: visible marks; Inv: invisible marks; Obj: objects.

invisible-O condition only (Fig. 2a). Because variance for re-cancellations was not homogenous across conditions, non-parametric statistics were used.

The difference in re-cancellations for invisible versus visible conditions was greater for Os (median difference = 7.25/sheet) than for objects (median difference = 0.5/sheet; Wilcoxon rank-sum test: $W_{\text{obj}} = 36$, $W_{\text{Os}} = 91$, N1 = N2 = 8, $P = 0.0001$). Within the invisible task, re-cancellations were also more common for Os (median = 7.25/sheet) than objects (median = 0.5/sheet), which was also significant (same statistics as above; the visible task produced zero re-cancellations).

Re-cancellations in the invisible-O task were more frequent on the right than on the left (median difference = 4.5; Wilcoxon matched-pairs signed-ranks test: $T^+ = 26$, $n = 7$, $P = 0.02$; one tie dropped [26]). However, this could simply reflect the fact that re-cancellations are inevitably more likely on the side where more items were cancelled. To take this into account, we compared the *ratio* of re-cancellations to cancellations on each side. The difference remained significant ($T^+ = 31$, $n = 8$, $P < 0.04$, with median ratios of 0.18 vs. 0.30 for left and right halves, respectively; median difference = 0.24). Thus, the distribution of re-cancellation errors showed a non-trivial ipsilesional bias. The invisible-*object* task, for which re-cancellations were very rare, showed no such difference between the right (median = 0) versus left half [median = 0; $T^+ = 4$, $n = 4$, $P > 0.4$; 4 ties (all scores of 0) dropped [26]].

3.2. Cancellation

For cancellation scores (which provide the standard measure of neglect), any marked item was scored as such *regardless* of the number of marks (re-cancellations) upon it. The cancellation scores were analyzed with ANOVA. As shown in Fig. 2b, S.R. cancelled more items with visible (98%) than with invisible marks (86%) overall [$F(1,14) = 18.2$, $P < 0.005$], and more on the right (98%) than on the left [87%; $F(1,14) = 16.6$, $P < 0.005$]. Critically, the interaction of condition by side was also significant [$F(1,14) = 7.4$, $P < 0.02$], showing stronger neglect of the left side for invisible cancellation (96% right vs. 76% left) than visible cancellation (99% right vs. 97% left). Thus, neglect was exacerbated by invisible marks, as we predicted. Indeed, S.R. no longer showed neglect on visible cancellation [simple effect of side: $F(1,14) = 2.1$, $P > 0.15$], but did still show it on invisible cancellation [simple effect: $F(1,14) = 11.6$, $P < 0.005$].

The triple interaction was not significant [$F(1,14) < 1$], indicating that the stronger neglect for invisible than for visible cancellation was similar for objects and Os.

4. Discussion

We tested whether visuospatial neglect is associated with an impairment in spatial WM and, if so, whether this can exacerbate neglect. Our left neglect patient performed modified cancellation tasks. Spatial WM load was manipulated by whether his marks were visible, thus providing a permanent reminder of visited items, or invisible, so that only spatial WM could represent items as already cancelled. As predicted, when his marks were invisible, S.R. made frequent re-cancellation errors for the Os (which differed only in location), suggesting that his spatial WM could not retain the locations of items that had been cancelled. These re-cancellations were virtually eliminated when cancelling different common objects with memorable identities, suggesting that non-spatial (i.e. object or verbal) memory was intact and could prevent re-cancellations. This result suggests that the many re-cancellations in the invisible-O task reflect an impairment of specifically *spatial* WM, not a general deficit of WM.

Importantly, left neglect (i.e. the failure to cancel items on the left but not the right side) was significantly stronger in the new invisible condition than for visible cancellation. This occurred even though the visible red marks were highly salient. It suggests that the failure to cancel left items on the contralesional side in this patient cannot be explained solely by the perceptual salience of items that have been visibly marked on the ipsilesional side, which has previously been argued to lock neglect patients' attention onto that side [17]. Our study suggests that highly visible marks on the right may actually *help* direct the patient's search to the left, by indicating that the items on the right have already been cancelled. Invisible cancellation can evidently provide a more sensitive measure of neglect than visible cancellation.

Indeed, at the time of this experiment, the patient's neglect was no longer detectable when cancelling with the visible red marks. This contrasts with his poor performance 3 weeks earlier on standard cancellation tasks (where 'visible' but faint pencil marks are made; see Section 1 and the patient description in Section 2). While this apparent improvement might indicate partial recovery, our spatial WM hypothesis suggests another possibility. Standard cancellation tasks, performed with faint pencil marks, may include a substantial spatial WM component. Because such marks are barely visible in peripheral vision, patients may need to refixate an item to determine whether it has already been cancelled, when visited locations can no longer be stored in spatial WM. Our new invisible-cancellation conditon could be considered as an extreme form of 'faint' marking, with absolutely no visible reminder of what has been cancelled, thus maximizing the spatial WM requirements. The presence of reliable neglect in the invisible task for S.R. in our experiment, despite his virtually perfect performance using highly visible red marks within the very same sessions, demonstrates that the new 'invisible' test may have useful clinical applications, particularly in testing for residual neglect during recovery and rehabilitation.

Although this patient had left-sided neglect, his re-cancellations in the invisible-O task were primarily made for items on the right side, suggesting poor memory for visited locations even on the *ipsilesional* side of space. Accordingly, we would not suggest that the spatial working memory deficit on its own produces contralesional neglect; this may initially stem from a pathological bias in visual attention following the unilateral lesion, as traditionally argued [15,18,22]. Our proposal is instead that a spatial WM deficit *across all positions* may *exacerbate* neglect, by rendering the patient unable to remember that particular ipsilesional locations (to which attention was initially drawn) have already been visited. Previous functional imaging studies of spatial WM [8,9,14,21] show that a right-lateralized network of brain areas, similar to those typically damaged in neglect (and including the areas affected in our patient), is normally involved in maintaining locations in WM, including locations falling on the ipsilateral right side of space. Similarly, recent data indicate that unilateral frontal excisions can induce spatial WM deficits that affect both hemifields [23]. Our patient's performance, with re-cancellation errors occurring more frequently on the ipsilesional side, is thus likely due to combined deficits: an initial attentional bias towards right-sided stimuli, exacerbated by a spatial WM deficit that leads to recursive search of those same stimuli. Although patients with frontal lesions but no neglect might also have deficient spatial WM, lateralization of re-cancellation errors, as observed in our patient, may require the combination of the two deficits.

The stronger neglect that we observed for invisible than visible cancellation did not differ for objects versus Os. Thus, the virtual elimination of re-cancellations when memorable objects served as targets did not help to reduce neglect in the invisible task. This may be due to re-fixations [34] of invisibly marked objects on the right. The objects were small (about 2–3°) and so would typically have to be re-fixated before becoming identifiable as a particular item that had already been (invisibly) cancelled. Hence, their identity could aid memory only *after* re-fixation. Re-cancellations might therefore be reduced as observed here, yet with eye movement patterns in visual search (and thus neglect) remaining similar for objects and Os.

It was not possible to measure eye movements for patient S.R., but the expected pattern of results was observed in a subsequent study [12,13] of a neglect patient with a focal right inferior-parietal lesion (see case report in [24]). This patient showed an abnormally high rate of re-fixations on right items (see also [34]), which did not differ for objects versus Os. Like the present patient S.R., he treated previously visited right items as new discoveries when they were Os but not when re-fixating objects whose distinct identities could be remembered non-spatially. In addition to confirming the expected pattern of eye-movements, this subsequent study [13] shows that the present spatial WM deficit can be found in parietal neglect patients, as well as for frontal/subcortical cases like S.R. Moreover, the parietal patient did not perform any verbal task during his search tasks (unlike the present object-naming, or alphabet-reciting), thus confirming that the latter secondary tasks are not essential for our result. Note also that secondary verbal tasks typically show little interference with spatial tasks [5].

Another recent single-case study described a right frontal patient who, although largely recovered from neglect on standard (visible) cancellation tests, continued to show deficits on spatial WM tasks and memory-guided saccades [31]. Our results agree well with these observations, and further indicate that neglect in right frontal patients can be accompanied by a specifically *spatial* WM impairment, with non-spatial WM preserved. Moreover, our findings are consistent with the emerging notion of some functional and anatomical overlap between networks mediating spatial attention and spatial WM [3]. While tasks in both domains commonly activate similar regions of dorsolateral prefrontal and parietal cortex [6,8,9,14,16,21,33], they can also produce activations in more inferior prefrontal areas [7,9,20,21] such as those damaged in our patient.

In summary, neglect can be stronger with invisible than with highly visible cancellation marks. This suggests that a deficit in spatial WM contributes to neglect in cancellation and argues against any account solely in terms of attention capture by salient visible marks when initially placed on the right [17]. Taxing spatial WM, by removing the visible reminders of which items have already been cancelled, increases neglect and produces frequent re-cancellation errors for targets that can only be distinguished from each other by their location.

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