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Task-related modulation of visual neglect in cancellation tasks

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Abstract

Unilateral neglect involves deficits of spatial exploration and awareness that do not always affect a fixed portion of extrapersonal space, but may vary with current stimulation and possibly with task demands. Here, we assessed any 'top-down', task-related influences on visual neglect, with novel experimental variants of the cancellation test. Many different versions of the cancellation test are used clinically, and can differ in the extent of neglect revealed, though the exact factors determining this are not fully understood. Few cancellation studies have isolated the influence of top-down factors, as typically the stimuli are changed also when comparing different tests. Within each of three cancellation studies here, we manipulated task factors, while keeping visual displays identical across conditions to equate purely bottom-up factors. Our results show that top-down task-demands can significantly modulate neglect as revealed by cancellation on the same displays. Varying the target/non-target discrimination required for identical displays has a significant impact. Varying the judgement required can also have an impact on neglect even when all items are targets, so that non-targets no longer need filtering out. Requiring local versus global aspects of shape to be judged for the same displays also has a substantial impact, but the nature of discrimination required by the task still matters even when local/global level is held constant (e.g. for different colour discriminations on the same stimuli). Finally, an exploratory analysis of lesions among our neglect patients suggested that top-down task-related influences on neglect, as revealed by the new cancellation experiments here, might potentially depend on right superior temporal gyrus surviving the lesion.

Keywords

visual neglect; cancellation; spatial attention; top-down; stroke; spatial exploration

Introduction

Cancellation tests have long been used in neuropsychological assessment, as a bedside measure of spatial exploration and awareness, and as a simple diagnostic measure for unilateral spatial neglect (e.g. Albert, 1973; Gauthier, Dehault & Joanette, 1989; Halligan, Wilson & Cockburn, 1990; Weintraub & Mesulam, 1985). Cancellation is often administered as a paper-and-pencil test, assessing ability to search visually for targets and mark with a pen all such target items within the array, under free vision. In most clinical cancellation tasks, patients typically have to locate and manually 'cancel' (i.e. mark)

multiple targets in a display, with performance assessed primarily in terms of omissions, i.e. missed targets. Patients presenting with unilateral spatial neglect, most commonly after right-hemisphere lesions, typically perform poorly in these tasks, omitting to cancel targets on the contralesional (usually left) side of the page (Albert, 1973). Moreover, unlike healthy controls who often start from the top left, patients with left neglect often start from the top right of the cancellation page (Chatterjee, Mennemeier & Heilman, 1992; Gauthier, Dehaut, & Joannette, 1989; Mark & Heilman, 1997).

Cancellation tests are widely used in clinical practice, and are increasingly regarded as the most sensitive paper-and-pencil measure for assessment of spatial neglect, in terms of relation to real-life deficits (Azouvi *et al.*, 2002; Ferber & Karnath, 2001). Azouvi *et al.* (2002) tested 206 subacute right-hemisphere stroke patients and concluded that, among several paper-and-pencil tests, omissions in the Bells cancellation test (Figure 1C) was the most sensitive screening measure. Ferber and Karnath (2001) compared line bisection and cancellation, and reported that whereas line bisection missed 40% of the putative neglect cases identified by clinical observation in daily routines cancellation tests missed only 6%.

Despite their wide use, striking differences in sensitivity may also exist *between* different versions of the cancellation tests (e.g. see Figure 1 for an illustration of dramatically different outcomes with the same patient on three different versions of the cancellation task), for reasons that have not yet been fully characterised. The simplest version of cancellation introduced by Albert (1973) comprising short lines randomly placed on a sheet of paper, all of which should be cancelled, has been reported as relatively insensitive (in detecting mild/moderate neglect), compared to more complex versions of the cancellation test such as the Star (Halligan, Wilson & Cockburn, 1990), Bells (Gauthier, Dehaut & Joannette, 1989), Mesulam (Weintraub & Mesulam, 1985) and others; see Figure 1. The Star, Bells and Mesulam versions notably comprise target items embedded among many distractors that are similar in visual appearance (see also Ferber & Karnath, 2001; Vanier *et al.*, 1990).

The different extent of omissions in different versions of the cancellation test illustrates that neglect does not invariably affect just a fixed portion of space, but may vary with the current situation due to stimulus and/or task-related factors. But the exact determining factors remain incompletely understood for cancellation measures. Each version of the cancellation test in common clinical use typically differs in numerous respects from others, rather than just in one factor. Although there has been some recent growth in more experimental studies, examining which particular factors might affect cancellation performance by neglect patients (e.g. see Aglioti, *et al.*, 1997; Bottini & Toraldo, 2003; Chatterjee, Mennemeier & Heilman, 1992; Gauthier, Dehaut & Joannette, 1989; Husain & Kennard, 1997; Kaplan *et al.*, 1991; Manly, *et al.*, 2002; Mark, Kooistra & Heilman, 1988; Mennemeier *et al.*, 1998; Parton *et al.*, 2006; Rapcsak *et al.*, 1989; Robertson & North, 1993), typically most of these studies have altered some aspect of the bottom-up stimulus display, rather than just top-down task requirements, across different conditions; or may have unwittingly involved some subtle stimulus change when varying the task (see below). Hence, the issue of whether *purely* task-related factors can impact on cancellation performance by neglect patients remains largely unresolved, as explained further in our brief summary of the literature here.

Numerous studies investigated potential display/stimulus factors in relation to cancellation tests. Several reported that *presence of distractors* can induce more neglect in cancellation (e.g. Gauthier, Dehaut & Joannette, 1989; Husain & Kennard, 1997; Rapcsak *et al.*, 1989) and also that more neglect may be revealed when the *similarity between targets and non-targets* increases (e.g. Rapcsak *et al.*, 1989; see also Duncan & Humphreys, 1989, for effects on normal search performance). *Target salience* has also been considered important. Using a texture-segmentation paradigm, with single-feature or feature-conjunction cancellation

tasks, Aglioti *et al.*, (1997) reported that neglect patients made disproportionately more omission errors in a demanding conjunction task than an easier feature task, as compared to healthy controls, left-hemisphere patients and right-hemisphere patients without neglect. This was taken to suggest that performance of neglect patients may be particularly impaired when serial search is required, as induced by increased target-distractor similarity (see also Mennemeier, Morris & Heilman, 2004). Further stimulus-related factors known to affect neglect performance in cancellation include: the absolute number of targets (Chatterjee, Mennemeier & Heilman, 1992; Mennemeier *et al.*, 1998); the ratio of targets and distractors (Kaplan *et al.*, 1991); the similarity between different kinds of distractors (Riddoch & Humphreys, 1987) and the spatial structure of the display (Weintraub & Mesulam, 1988).

We note that in all the studies considered above, the experimental manipulations involved changes in the displays between different conditions. Adding distractors, making targets and non-targets more physically similar, or decreasing target saliency, for example, changes not only the task-related discrimination-requirement between conditions, but also the actual displays themselves, thus making it unclear whether the observed effects in these studies reflect the changed display appearance, the changed task requirements, or both. Task effects per se, in the absence of any stimulus change whatsoever, were not isolated in these studies.

Some studies, albeit fewer, have explicitly sought to investigate effects of *task* manipulation on cancellation by neglect patients, producing several interesting results. But even these can be hard to interpret as pure task effects, when the visual displays also differ between the tasks used. For instance, Mark, Kooistra and Heilman (1988) and Parton *et al.* (2006) found that having neglect patients erase rather than cross-out targets can lead to improvements in performance. This has been attributed to erasure of ipsilesional targets making it easier for patients to “disengage” their attention (Posner *et al.*, 1984) from those ipsilesional items that might otherwise have captured their attention. But note that the eraser manipulation not only changes the task but also changes the physical display, with found targets being physically removed, thus allowing a potential bottom-up explanation for the ‘task’ effect reported. It has also been reported recently that neglect can be exacerbated by “invisible” cancellation (Wojciulik *et al.*, 2001; 2004; Parton *et al.*, 2006), where cancellation is recorded with carbon paper, or via a touch-screen, to leave no visible marks. Once again, however, this visible/invisible task manipulation also changes the seen physical display (i.e. now with marks visible or not).

The only existing cancellation study to our knowledge that has manipulated task in an entirely pure way, keeping stimulus displays exactly equivalent across all conditions, was a single-case study by Mennemeier, Morris and Heilman (2004). In a baseline condition, the patient was asked to cross-out all items corresponding to a single specific numeral (e.g. all 3s, or instead all 4s, etc) in displays containing multiple one-digit and two-digit numerals. In a more demanding condition, the patient was given the same displays but now asked to select and cancel all multiples of a given number (e.g. to cross-out not only all 3s, but also then all 6s, 9s, 12s etc), which led to more omissions. Thus Mennemeier *et al.* showed that neglect in cancellation can sometimes be exacerbated even when the displays are kept identical, by changing the target criteria for cancellation (albeit in their case via the rather complex means of adding a substantial cognitive load related to mental arithmetic (for the multiples), while also now requiring visually heterogeneous targets to be found (i.e. not just the 3s, but also 6s and 9s etc), thus making it unclear exactly which aspect of the top-down, task-related change was critical).

This overview of previous cancellation studies indicates that, rather surprisingly, the majority of previous studies seeking to investigate any task influences on neglect performance in cancellation may often have inadvertently confounded top-down (task) with

bottom-up (stimulus) factors, in the sense of changing both aspects together. It thus remains rather unclear whether neglect in cancellation can be modulated by top-down, task-related factors (and if so, by exactly which aspects), when all stimulation remains identical. In the three studies described below we sought to isolate the possible role of several top-down, task-related influences on neglect in new experimental variants of cancellation. A key aspect of our approach was that, within each study, we now compared different tasks *always under identical stimulus-display conditions*, to hold purely bottom-up factors constant. In Experiment 1, we tested whether manipulating the task demand of target/non-target discrimination can affect the neglect observed during cancellation of exactly the same physical displays. In Experiment 2, all items were now targets, with the task-related judgment again being manipulated, but now without any requirement to distinguish targets from non-targets. Experiment 3 assessed whether shifting the task from a more 'global' to a more 'local' level of discrimination is particularly detrimental for neglect; or whether the top-down discrimination difficulty is all that matters even when applying at the same spatial scale (here, for different colour discriminations).

Processes such as selective attention, cognitive load, or 'local' versus 'global' discrimination, have often been previously suggested to play potential roles in the manifestation of neglect (e.g. see Driver, Vuilleumier & Husain, 2004; Karnath, Milner & Vallar, 2002, for illustrative reviews). But our aim here was to validate previous claims about the potential influences of such factors on neglect and cancellation, when by design eliminating any role for purely bottom-up influences (i.e. differences in stimulus displays) that may have affected some of the prior neglect studies on such issues. Overall, the results of our three new experiments clearly show that varying top-down visual-task demands, while keeping stimuli identical, can substantially modulate the extent of neglect revealed by cancellation-like measures. Finally, we also present an initial exploratory investigation of the possible lesions potentially associated with an impact of such task factors on neglect.

Experiment 1

This initial study sought to investigate whether manipulating the visual task demand of the target/non-target discrimination required (without changing the displays) would affect the neglect observed in cancellation. Using the same visual displays we asked patients to perform two tasks likely to differ in the demand on serial/focused attention (Treisman & Gelade, 1980; Treisman & Souther, 1985). We predicted more neglect in the task placing more demand on visual attention, even though our displays comprised perfectly equivalent stimuli across conditions. Although this prediction for increased neglect in the more demanding task, relative to the less demanding task, seems straightforward, we stress once again that the role of top-down, task-related visual-attention factors (as manipulated here) has surprisingly not been isolated before for cancellation, as previous cancellation studies typically confounded bottom-up with task-related factors (the single-case study by Mennemeier *et al.*, 2004 is the sole exception, but as noted above it used a rather complex task-manipulation, and this finding has not been validated across patients). The task-related issue of visual-attention demand during cancellation was thus isolated here for the first time and tested in a substantial group of neglect patients.

Method

Subjects—A consecutive series of 17 patients with spatial neglect participated. All had fairly typical lesions and symptoms for right-hemisphere stroke patients exhibiting aspects of left neglect (see below). On clinical examination all were alert and well-oriented in time and space. Potential neglect patients were initially identified in terms of presence of right-hemisphere cerebrovascular incidents, as revealed by CT or MRI scans. They were then

screened for neglect with a battery of standard paper-and-pencil tests. Patients were selected for further study on the basis of impaired performance in at least two standard tests for neglect, including cancellation, line bisection, figure copying, drawing from memory, word reading and chimeric object naming. A diagnosis of neglect was given if two of the following six criteria were met: minimum of 30% omissions on the left side of the page for either Star (Halligan, Wilson & Cockburn, 1994), Bells (Gauthier, Dehaut & Joanne, 1989), or Mesulam (Weintraub & Mesulam, 1985) cancellation; minimum average rightward deviation of 12% or more in a 5-item line (18cm) bisection task (Halligan *et al.*, 1990); omission of left sided elements in the BIT figure copying test (Wilson, Cockburn & Halligan, 1987); omission of left sided elements in a 'drawing from memory' test for a clock and a daisy; a minimum of 30% errors (omissions or mis-readings) for the left side of words in a 20-item word reading test; or a minimum of 30% leftward errors in a 20-item chimeric object naming test (e.g. Buxbaum & Coslett, 1994; Sarri *et al.*, 2006). Any patients exhibiting severe language, alertness or psychiatric problems were excluded. All patients gave informed consent to participate in accord with local ethics. See Table 1 for individual patient summaries and Figure 2 for an overlap of the lesion maps of the patients whose scans were available to us (n=14).

Stimuli—Importantly, the stimulus displays were always equivalent across conditions (see Figure 3A). The displays always comprised 30 circles (12mm diameter), plus 30 crosses orientated diagonally (X's, with diagonal of 12mm), arranged on a sheet of A4 paper. Half the circles were complete, the other half had a small arc (2mm) removed at their bottom. Similarly, half the crosses were complete and half had a small gap in the centre. Each cancellation sheet thus contained 60 items in total and each sheet could be divided into six 'columns', each column containing five circles and five crosses, five items in each column having a gap and five without a gap. The exact position of the individual items was pseudorandomly arranged within each column, in four different variations that were counterbalanced across task conditions. The four different cancellation sheets were also then reversed in mirror image left-right, to provide eight cancellation sheets in total, with equivalent stimuli on left and right sides. Importantly, these eight sheets were fully counterbalanced across the critical task conditions, see below.

Procedure—Patients sat at a table in front of the experimenter. Cancellation sheets were presented one at a time, directly in front of the patients, aligned with their mid-sagittal axis. Patients were given two tasks to perform using the same displays, in the task orders ABBABAAB or BAABABBA. In the 'shape' task, patients were instructed to mark all the circles in the array (*or* all the crosses, see below), irrespective of the presence or absence of a gap. In the 'gap' task, patients were asked to mark all the items in the array containing a gap (*or* all the items *not* containing a gap, see below), regardless of the shape of the items (circle or cross). Each patient completed four cancellation sheets per task. In half (i.e. two sheets) of the trials for the 'shape' task, patients were asked to cancel the circles; and in the other half the crosses. Similarly in half of the trials in the 'gap' task they were asked to cancel the items with the gap and in the other half the items without the gap. The order of target-type cancellation within task was counterbalanced between patients. For all subconditions, the total number of targets to be cancelled on each page was always 30 (half the total number of items in the array); 15 on the left and 15 on the right side of the page. Overall performance was thus rated in terms of omissions out of a total number of 120 (60 targets on the left and 60 on the right for each task, when adding the cancelled items from all four sheets per task) for each patient. The data were also scored by column. No time limits were set, but each cancellation trial terminated when patients reported they had fully completed that sheet. Termination time was recorded and later analysed to assess whether observed effects could be discounted as speed-accuracy trade-offs.

Results

Patients made no errors of commission at all in the 'shape' task and few commissions in the 'gap' task (mean 1.31% of total number of cancellations in that condition, $sd=1.91$), showing importantly that all could discriminate between the different types of items, could switch between response sets, and understood all the tasks.

Overall, the results revealed clear exacerbation of neglect in the 'gap' task (see Figure 3B) relative to the 'shape' task. We implemented a repeated-measure ANOVA, with factors of task and page-side. As expected, patients made significantly more omissions towards the contralesional side of each page (main effect of page-side: $F(1,16)=52.2$, $p<0.01$). Specifically, patients cancelled on average (when pooling over tasks) 79.8% of targets on the right versus 44.5% on the left of the page. More importantly, performance was better in the 'shape' than 'gap' task ($F(1,16)=92.2$, $p<0.01$). On average patients cancelled 74.7% (89.6/120) of targets in the 'shape' task ($sd=22.4\%$), with performance strikingly reduced to 49.6% (59.5/120) in the 'gap' task ($sd=21.2\%$). This difference was significant within both the left ($t(16)=7.5$, $p<0.01$) and right ($t(16)=5.5$, $p<0.01$) side of the page. But there was also a significant interaction between task and page-side ($F(1,16)=4.9$, $p=0.042$), as gap versus shape task had more impact for the contralesional side of the page.

On a case-by-case basis, 15 out of 17 patients showed a significant decrease of performance in the 'gap' compared to 'shape' tasks, as revealed by chi-square (for each patient $p<0.006$, except for cases N8 and N11 for whom this difference did not reach an individually significant level). Individual patient results and statistical values can be found in Table 2.

Overall, the time required to complete a single cancellation sheet in the 'gap' task (mean=2.57 mins, $sd=1.49$) was longer than in the 'shape' task (mean=1.93 mins, $sd=0.53$), confirming the greater difficulty, but thereby ruling out mere speed-accuracy trade-offs as an explanation for increased omissions in the gap task.

Discussion

The results of Experiment 1 clearly indicate that the extent of neglect in cancellation can be modulated by top-down, task-related factors, specifically here by the visual-attention demands of target/non-target discrimination required for exactly the same displays. Apart from the one single-case study of Mennemeier et al (2004), who used a rather complex task manipulation, this is the only demonstration to our knowledge that just changing the task requirements in cancellation, while holding purely bottom-up factors strictly constant, can dramatically change the extent of the spatial exploration deficit exhibited by neglect patients. Our results validate previous suggestions (e.g. Eglin, Robertson & Knight, 1991; Riddoch & Humphreys, 1987) for a role of attentional demands (likely to be inducing slower and more serial search) in modulating neglect, now confirming this for cancellation in a situation where displays were held constant across our task manipulation. But there are at least two top-down aspects to consider for our tasks so far; a) selection of an item as a target from among non-targets, and b) subsequent discrimination and cancellation of a selected target. From this perspective, a low versus high discrimination requirement for the currently judged target (i.e. aspect b) might determine the extent of processing resources that remain for contralesional space (e.g. see Vuilleumier & Driver, 2007). This could in principle provide a further interpretation for the results of Experiment 1; that is, not only the greater task difficulty of selecting targets from among distractors, but also (or instead) the difficulty of the discrimination performed on each individual item once selected, might have led to more neglect in the gap task than the shape task.

Experiment 2

To address this issue, in Experiment 2 we again varied the task demand of the discrimination required, but now made *all* of the items targets, that each had to be judged in turn, thus eliminating the need to select targets from among non-targets. The critical change in procedure here was thus that task instructions now required patients to make a discrimination judgement for *every single item* in the display in turn, thereby eliminating the need to select between targets and non-targets, allowing us to isolate any effects of task-defined discrimination difficulty for each individual item. If such selection of targets from among non-target items in a display is the sole ‘top-down’ task factor determining neglect performance in cancellation, then we should no longer find any difference between the two conditions here, since such selection from among non-targets was no longer required. If, however, the demands of the task-defined discrimination required for each target item is crucial, we may still find more omissions towards the contralesional side of the page in the higher demand condition.

Method

Subjects—Thirteen stroke patients with left neglect participated in this new experiment (cases N1, N2, N3, N4, N5, N6, N7, N8, N9, N10, N11, N15, 17); see Experiment 1 for patient selection criteria and Table 1 for individual patients' clinical details. All 13 patients had also previously participated in Experiment 1, with a minimum of a 1-day interval between the two experiments.

Stimuli—The stimulus displays used in this experiment were as for those used in Experiment 1 (see Figure 3A), and most importantly were still equivalent across the two conditions compared here within Experiment 2.

Procedure—The procedure was similar to Experiment 1, but critically with task instructions now differing. The patients were again given two tasks to perform on the same displays, in the order ABBABAAB or BAABABBA. In both tasks patients were now instructed to point at (with the ‘wrong’ end of a pen, i.e. that made no marks) and fixate each item in the array in turn, and to make an explicit verbal judgement about every single one while pointing at it. In the new ‘shape’ task, the patients judged whether each item in turn was a circle or a cross (i.e. had to say aloud either “circle” or “cross” to indicate the shape of the item currently pointed at). In the new ‘gap’ task, the patients were instructed to indicate instead whether each successively pointed-at item contained a gap or not (i.e. to say aloud “gap” or “no-gap” to indicate the nature of the item currently pointed at). Thus in both conditions patients no longer had to select targets from among task-irrelevant non-targets, as every item in the display was now by definition always a target requiring pointing at and judging. The patients were free to start anywhere in the array and to proceed in any direction they wanted. There were no time-limits set. The patients gave their responses verbally, which were then marked by the experimenter on a separate identical sheet, unseen by the patient, next to each corresponding item. Patients thus no longer made any visible cancellations on the paper and therefore there were no explicit marks to indicate which locations had been visited already (see Wojciulik *et al.*, 2001; 2004). But the more important point is that the physical displays, the pointing requirements, and the number of items that should be judged to give 100% performance, were exactly equivalent across the two conditions compared within Experiment 2. Thus, all that we now varied (in a top-down, task-related manner) was the type of discrimination required on each target item, either a shape or gap judgement.

Results

Patients made no discrimination errors at all for the items that were pointed at in the 'shape' task and rarely erred in the 'gap' task (mean error rate per total number of pointed-at items was only 3.6%, $sd=2.73$), showing that all patients could discriminate between the different types of target and that all understood the new tasks.

The mean group results are shown in Figure 4. The main effect of side ($F(1,12)=26.1$, $p<0.01$) was significant as expected, with more omissions on the left overall (52% of items on the left were not found, versus 27% on the right). More importantly, the main effect of task on omissions was also significant, with patients successfully pointing at and judging an average of 65% (155/240; $sd=25\%$) items in the new 'shape' task as compared to 55% (132/240; $sd=25.5\%$) in the new 'gap' task ($F(1,12)=11.0$, $p<0.01$). The interaction between task and left versus right side of the page did not reach full significance ($F(1,12)=2.5$, $p=0.138$), but a significant interaction was found ($F(1,12)=4.4$, $p=0.05$) when considering just the extreme leftmost versus the rightmost column of the array.

On a case-by-case level, the task manipulation had an individually significant effect in 7 out of 13 patients tested here (although note that none showed a significantly opposite effect), and was thus a less robust effect than in Experiment 1 (see Discussion). The results from Experiment 2 for individual patients can be seen in Table 3.

An analysis of the mean time required for completion of a single page showed that patients tended to be somewhat slower at completing the new 'gap' task (mean=2.01 mins, $sd=0.90$) than the 'shape' task (mean=1.54 mins, $sd=0.69$), ruling out mere speed-accuracy trade-offs as an explanation for omissions.

Overall the results of Experiment 2 indicate that the task-related discrimination required for each selected target might indeed partly contribute to the difference between gap and shape tasks that had already been observed in Experiment 1. However, as can be seen in Figure 5 (plotted here for the 13 patients participating in both Experiments 1 and 2), the overall effect of task (i.e. total number of items responded to in the lower demand 'shape' condition, minus those responded to in the higher demand 'gap' condition) was on average twice as big in Experiment 1 than 2 (for the common patients in those two studies), suggesting that discrimination demands for a currently selected and fixated target cannot fully explain the entire task effect seen in Experiment 1. There was a mean 25% increase in omissions for Experiment 1 in its 'gap' versus 'shape' task, compared with a smaller increase of only 10% respectively in Experiment 2 ($F(1,12)=19.7$, $p=0.001$), even though (when averaged across tasks) patients responded to the same proportion of targets in both experiments (total number of targets found in Experiment 1 was 58%, while this was 60% for Experiment 2). Moreover, the task manipulation significantly affected individual performance in 15 out of 17 patients for Experiment 1 (11 out of 13 for the subgroup of patients who participated in both experiments), but for only 7 out of 13 patients for Experiment 2. Finally, the patient-by-patient size of the task effect in Experiment 1 did not correlate with that found in Experiment 2 for the common patients ($r(11)=.331$, $p=0.269$), further suggesting that the task manipulations in these experiments affected performance for this group of patients in a somewhat different way. By contrast, individual performance in the two 'shape' tasks did correlate significantly between Experiments 1 and 2 ($r(11)=.793$, $p=0.001$), suggesting that the lack of correlation between the two experiments for the task effects (i.e. shape versus gap difference) was not simply due to lack of power.

Discussion

Experiment 2 revealed more neglect in the new gap task as compared to the new shape task. This indicates that neglect can be exacerbated when the top-down, task-related visual

discrimination required for each found target involves a more demanding judgement; and that this can still arise to some extent even when targets do not need to be selected from among non-targets. The present results may accord with recent findings showing that increasing attentional load at central fixation can decrease or even eliminate processing of other stimuli presented peripherally, that would have otherwise been processed under conditions of lower attentional demand at fixation (e.g. see Lavie, 2005; Schwartz *et al.*, 2005); and also showing that this effect may be lateralised in patients with right temporo-parietal lesions, with the contralesional side of space being affected disproportionately under conditions of high load (see Russell, Malhotra & Husain, 2004; Vuilleumier & Driver, 2007). Our results may extend such findings to the domain of search and cancellation tasks, in suggesting that increased attentional load for the currently selected target may further reduce the ability to find the next target towards the contralesional space and thereby exacerbate neglect (see General Discussion). However, the task-related effect in Experiment 2 was significantly less pronounced than for Experiment 1 (and a smaller proportion of patients was individually affected significantly by the manipulation of Experiment 2), indicating that having to select targets from among non-targets (as in Experiment 1) is also of particular importance for cancellation performance in neglect. This concurs with previous suggestions that the presence of distracting non-targets can exacerbate neglect (e.g. Gauthier, Dehaut & Joannette, 1989; Husain & Kennard, 1997; Rapcsak *et al.*, 1989), but now validates this point while holding stimulus displays constant.

Experiment 3

Both Experiments 1 and 2 demonstrated that increased task demands on visual attention demand led to more neglect, when the task required discrimination to be based on a more 'local' feature (gap presence/absence), as compared to a more 'global' feature (cross/circle shape) of the stimuli. It has been long hypothesised in the neuropsychological literature that unilateral brain damage, particularly involving the right temporo-parietal junction (TPJ), can lead to some deficits in processing more 'global' levels of representations relative to more 'local' levels (e.g. see Lamb, Robertson, & Knight, 1990; Robertson, Lamb & Knight, 1988). The right TPJ will of course often be implicated in many neglect patients' lesions, and so local biases may contribute to and potentially exacerbate their syndrome (Doricchi & Incoccia, 1998; Lux *et al.*, 2006; Marshall & Halligan, 1994, 1995). From this perspective, the results of the present Experiments 1 and 2 might reflect a difference between top-down, task-related attention being directed to more global ('shape') or more local ('gap') levels of discrimination. In our final experiment, we again sought to manipulate the top-down, task-related discrimination for equivalent cancellation displays, but now without varying the spatial scale of the required discrimination (colour was now judged, instead of shape or shape-detail). If global versus local levels of shape representation are the only critical factor, then we should presumably find no effect of the colour-discrimination demand in Experiment 3, since the spatial scale per se of the stimuli that had to be judged remained equivalent for the two new task conditions. However, if the task-related demand of the required discrimination remains important, even when the spatial scale of the judgement is no longer varied, then we might still find exacerbation of neglect when more demanding colour discriminations are required on the same stimuli.

Method

Subjects—Nine stroke patients with left neglect participated in the following experiment (N7, N9, N10, N11, N12, N13, N14, N15 & N17). All nine patients had also participated in Experiment 1, with a minimum interval of at least 1 day between experimental sessions (for those patients - N7, N9, N10, N11, N15, 17- who also participated in Experiment 2 there was likewise a minimum interval of 1 day between testing sessions for Experiment 2 and

Experiment 3). See Table 1 for individual patients' clinical details and Experiment 1 for patient selection criteria.

Stimuli—The stimulus displays in this experiment were very similar in concept to those in the preceding experiments, but the different target types were now defined by task instructions in terms of colour rather than shape. The actual stimulus displays were again always equivalent across the conditions compared *within* Experiment 3. They now comprised 60 stars; 30 red and the other 30 green. Half the red stars were coloured in a bright shade of red and the other half in a darker shade of red. Similarly, half the green stars were in a bright shade of green and the other half in a darker shade of green (see Figure 6A). The specific colours were selected so that, on inspection by normal observers, the perceptual difference between dark versus bright red stars appeared approximately comparable to that for dark versus bright green stars, when printed on paper. But note that in any case such discriminatory aspects were fully counterbalanced in our design for the patients (see below). The dark and bright colours were all highly visible against the white background on each page. Each cancellation sheet again contained 60 items in total, arranged on a sheet of A4 paper with each sheet divided into six 'columns', each column now always containing five red and five green stars, five of these same ten items being of bright colour and five being of dark colour. The exact position of the individual items was again pseudorandomly arranged within each column, in four different variations and was counterbalanced across task conditions. The four different cancellation sheets were then reversed in mirror image left-right, in order to provide eight cancellation sheets in total. These were fully counterbalanced across conditions, so that the stimulus displays were equivalent across the two tasks, to hold purely bottom-up factors constant.

Procedure—Again, there were two task conditions. In the 'colour' condition, patients were instructed to mark all the red stars in the array (*or* all the green stars, see below), irrespective of the light or dark shade of that colour. In the 'shade' condition, patients were asked instead to mark all the bright items in the array (*or* all the dark items, see below), regardless of the actual colour of the items (red or green). Each patient completed four cancellation sheets per condition. The eight cancellation sheets in total were given in ABBABAAB or BAABABBA task orders. In half (i.e. two sheets) of the trials for the colour task, patients were asked to cancel the red stars and in the other half the green stars. Similarly in half of the trials for the shade task they were asked to cancel the brighter stars and in the other half of trials the darker stars. The order of target-type cancellation within task was counterbalanced between patients. The total number of targets in each page - for both conditions- was 30 per sheet (half of the total number of items in the array); 15 on the left and 15 on the right. Performance was again scored in terms of omissions out of a total number of 60 targets on the left and 60 on the right for each condition (adding the cancelled items from all four sheets) for each patient. The data were also scored by column. No time limits were set, but termination time was recorded as before.

Results

Patients made almost no commission errors in the 'colour' task (mean error rate: 0.34% of total number of cancelled items, $sd=0.7$) and few errors in the 'shade' task (mean error rate: 4.09%, $sd=3.85$), showing that all could discriminate between the different types of items and that all understood the tasks.

The group results for omissions are shown in Figure 6B. Patients made significantly more omissions towards the left as expected (main effect of page side, $F(1,8)=42.7$, $p<0.01$; also a main effect of column, $F(5,40)=30.9$, $p<0.01$), with 85% of targets cancelled on the right side and 43.4% on the left. More importantly, they also made more omissions in the 'shade'

than 'colour' task (main effect of task: $F(1,8)=9.3$, $p=0.016$), cancelling on average 71% of targets in the latter (mean 84.6/120, $sd=21.8\%$), but only 58% in the former (mean 69.22/120, $sd=23.4\%$). There was a marginal interaction of task with page side ($F(1,8)=32.1$, $p=0.082$), due to a larger task effect for the left side.

Although when considering all patients together there was an overall effect of shade versus colour tasks, when considering each patient on a case-by case basis only four out of nine patients showed an individually significant decrease of performance in the shade condition compared to the colour condition on chi square (although none showed the opposite pattern). For individual patient results and statistics see Table 4.

Finally, the mean time for completion of a single cancellation sheet in the 'shade' task (mean=2.02 mins, $sd=1.39$) was longer than in the 'colour' task (mean=1.27 mins, $sd=0.57$), demonstrating that overall it took patients more time to cancel less items in the former and thus the task effect seen here can not be due to a mere speed-accuracy trade-off.

These results indicate that the demand of the task-related discrimination required can have some impact on omissions in cancellation, even when global versus local level of shape representation is no longer of any relevance to the required discriminations. However, the present task effect, while significant for the group, seems relatively small compared to Experiment 1. As can be seen in Figure 7 (plotted here for the 9 patients participating in both Experiments 1 and 3), the overall task effect in Experiment 1 (total number of items cancelled in that 'shape' condition versus those cancelled in the more demanding 'gap' condition) was almost twice as big (1.7 times) the task effect observed in Experiment 3 (total number of items cancelled in the colour versus shade condition), suggesting that our manipulation of shape discrimination in Experiment 1 was more detrimental to neglect than our manipulation of colour discrimination in Experiment 3. Specifically, we found a 23% increase of omissions in Experiment 1 for the more demanding 'gap' condition as compared to the 'shape' condition (for those patients commonly participating in both Experiments 1 and 3); but only a 13% increase of omissions for the higher demand condition within Experiment 3 ($F(1,8)=5.5$, $p=0.047$). This difference between these two experiments arose even though, when averaging across the two task conditions within each experiment, the patients cancelled approximately the same number of targets in both experiments (total percentage of targets cancelled was 70% in Experiment 1, 77% in Experiment 3). On an individual level the task manipulation in Experiment 1 significantly affected performance in 15 out of 17 patients (and 8 out of 9 for the subgroup of patients participating in both Experiments 1 and 3), but only in 4 out of 9 patients for Experiment 3.

Although differing in magnitude, the effect observed in Experiments 1 and 3 appears to have affected performance for both those experiments in a similar *spatial* manner, as we found here no three-way interaction between Experiment 1 versus 3, left versus right side of page, and the task effect ($F(1,8)=0.01$, $p=.926$), indicating a similar spatial distribution of task effects in the Experiments 1 and 3. Moreover, we also found that the size of the task effect demonstrated by individual patients correlated between Experiments 1 and 3 ($\rho(7)=.672$, $p=0.047$) when considering the contralesional side of the page that was most affected by task. This further suggests that the two task manipulations (of Experiments 1 and 3) affected performance for the common patients in a similar way, even though the local/global manipulation in Experiment 1 has produced a much bigger effect.

Discussion

The results of Experiment 3 indicate that the top-down, task-related demand of the required discrimination can affect the extent of neglect observed in cancellation, even when the spatial scale of the required judgement is no longer varied (unlike the global/local aspects of

shape that were considered in Experiment 1), with instead just a subtle or unsubtle colour discrimination being required for the same displays. Across the group of nine patients overall, more omissions and thus more neglect was observed for the more demanding colour discrimination. On the one hand, these results confirm and extend the observations of Experiment 1, in showing that task-related discrimination requirements can be a critical determinant of the extent of neglect observed on cancellation measures. On the other hand, the task effect was much bigger in Experiment 1 than in Experiment 3 (and was individually significant for more patients in Experiment 1), indicating that requiring top-down, task-related attention to be directed to more local aspects of shape (as in the gap task of Experiment 1) may indeed be particularly detrimental for neglect (consistent with several previous suggestions (e.g. Doricchi & Incoccia, 1998; Lux *et al.*, 2006; Marshall & Halligan, 1994, 1995), but now validated in cancellation while varying the task performed on constant stimulus displays). It cannot be argued that the 'gap' discrimination in Experiment 1 was simply harder than the subtle shade discrimination in Experiment 3, because in fact the commission-error rates for the two tasks point in the opposite direction, with the mean error rate in the shade task (mean=4.09%) tending to be higher than that in the gap task (mean=1.31%), indicating that if anything patients found the shade task intrinsically more difficult than the gap task.

Brain regions potentially associated with top-down modulation of neglect in cancellation

Lesion data were available for 14 of the 17 right hemisphere damaged patients with neglect who participated in our experiments (MRI scans for 8 patients and CT scans for 6 patients; we were unable to obtain scans for patients N13, N14 and N16, due to clinical constraints; see Figure 2 for an overlap of the reconstructed lesions). We provide an exploratory analysis of these lesion data in relation to our experimental effects here for completeness only, as they will require extension and corroboration in a larger group of neglect patients in future work. Moreover, examining left-hemisphere cases would be important for ascertaining any hemispheric-specificity of the possible anatomy underlying task effects upon cancellation in neglect. Left hemisphere cases were not considered here, as we had specifically sampled right-hemisphere cases for neglect, since clinical neglect is much more common after right-hemisphere damage and given that enduring neglect is relatively rare in most left-hemisphere patients, making its modulation harder to study for large groups of such patients. Importantly we acknowledge that new lesion data will always have the potential to overturn existing anatomical hypotheses.

The extent and location of each patient's lesion was defined and visualized using the MRIcro software package (Rorden & Brett, 2000; www.mricro.com). For each patient, the area of damage was determined by detailed visual inspection of the digital brain image, for every single slice, by a clinical neurologist, who was blind to the design, hypotheses and results of our behavioural experiments. Lesions were drawn manually on 12 axial slices of a T1-weighted template MRI scan from the Montreal Neurological Institute (www.bic.mni.mcgill.ca/cgi/icbm_view), corresponding to the 12 different MNI Z-coordinates of -16, -11, -6, -3, 3, 13, 16, 20, 24, 30, 36 and 48 mm, using the identical or closest matching transverse slices for each individual. Combining all slices produced a 3D lesion volume for each patient.

For initial anatomical analysis, we then employed the recently developed voxel-based lesion-mapping approach (Bates *et al.*, 2003), as implemented in several other recent patient studies (e.g. Committeri *et al.*, 2006; Saygin, 2007), using the MRIcron software (Rorden, Karnath & Bonilha, 2007; see <http://www.sph.sc.edu/comd/rorden/mricron/>). This approach has the potential advantage of allowing lesions to be related to behavioural performance,

with the latter considered as a continuous measure, rather than pre-categorising the patients into dichotomous groups with an all-or-none approach to behavior, as in traditional subtraction and overlap approaches (see Karnath, Ferber, & Himmelbach, 2001; Mort *et al.*, 2003). Thus the voxel-based lesion-mapping approach can potentially exploit the richness of continuous behavioral measures. We implemented the voxel-based lesion-mapping statistical approach to our patients' lesions, in relation to the behavioural scores in our experiments. For each of our three separate experiments (which yielded independently obtained behavioral scores), we made voxel-based maps of the Brunner-Munzel non-parametric statistic, a rank order test that is essentially assumption free (Brunner & Munzel, 2000; see Rorden, Bonilha & Nichols, 2007, for the advantages of this statistic), comparing the task effect as a function of the lesion in a voxelwise manner. We controlled for multiple comparisons using the False Discovery Rate (FDR) correction. All the results presented here survived an FDR cut-off threshold of $p < 0.01$. Since lesions of areas involved in producing top-down influences would be expected to reduce such an influence, we mapped in a voxelwise manner those regions within the patients' lesions that were significantly associated (as shown in red within Figure 8) with reduced modulation of neglect by our task manipulations.

The statistical map produced for Experiment 1 ($n=14$; see top row of Figure 8) revealed several cortical and subcortical brain areas statistically associated with reduced neglect modulation by task demand, including superior temporal gyrus ($z=7.89$, MNI peak co-ordinates: $-57, -41, 16$; $-18, -2, -3$; $z=3.71, -59, -34, 13$; $-66, -23, 3$) and underlying white matter ($z=3.71$, MNI co-ordinates: $-50, -31, 3$); thalamus ($z=13.4$, MNI co-ordinates: $-16, -1, 13$; $-14, -4, 3$; $z=4.34$, MNI co-ordinates: $-9, -7, 16$), putamen ($z=13.4$, MNI co-ordinates: $-22, -5, -6$; $-18, -2, -3$), globus pallidus ($z=4.34$, MNI co-ordinates: $-27, 9, -3$), white matter underlying the inferior parietal gyrus ($z=4.31$, MNI co-ordinates: $-42, -39, 20$) plus the middle temporal gyrus and underlying white matter ($z=4.08$, MNI co-ordinates: $-54, -31, -16$; $z=3.08$, MNI co-ordinates: $-56, -21, -6$; $-54, -38, -11$). The statistical map for Experiment 2 ($n=13$; see middle row of Figure 8) likewise implicated several regions in reduced neglect modulation by task demand, including once again white matter underlying the superior temporal gyrus ($z=19.17$, MNI co-ordinates: $-35, -33, 3$; $z=16.9$, MNI co-ordinates: $-34, -38, 16$; $-34, -33, 13$; $z=4.25$, MNI co-ordinates: $-33, -23, -3$), thalamus ($z=5$, MNI co-ordinates: $-13, -18, 16$), putamen ($z=3.88$, MNI co-ordinates: $-23, -3, 3$), globus pallidus ($z=3.88$, MNI co-ordinates: $-23, -1, 3$), plus now also the caudate nucleus ($z=19.17$, MNI co-ordinates: $-13, -1, 20$; $z=3.5$, MNI co-ordinates: $-20, -19, 24$). Finally, the statistical map for Experiment 3 ($n=7$; see bottom row of Figure 8) again highlighted white matter underlying the superior temporal gyrus ($z=4.47$, MNI co-ordinates: $-30, -43, 16$; $-43, -44, 16$; $-45, -44, 13$) and the middle temporal gyrus ($z=5.19$, MNI co-ordinates: $-44, -22, -11$; $z=4.47$, MNI co-ordinates: $-43, -54, 3$; $-4, -44, -3$).

There was thus quite good agreement between the statistical anatomical maps for the three separate experiments, despite the independently obtained behavioural scores for each, and the differing number of patients that underwent each study. In particular, we note that voxel-based lesion mapping highlighted the posterior end of the superior temporal gyrus (STG) and underlying white matter, across all 3 experiments, as being statistically associated with reduced effects of task manipulation on neglect. The consistence of this particular outcome is further underlined by the fact that we observed a very similar anatomical pattern when taking the simpler (but less statistical) lesion subtraction approach (e.g. Mort *et al.*, 2003), splitting patients in two subgroups for each experiment, and then contrasting those patients with a task-effect size lower than the median score against those patients with a task-effect size higher than the median. The highlighted STG region was implicated in the lesions of *all* patients who showed an effect size below the median score for each experiment.

Lesion volume alone was not sufficient to explain the size of our task effects. For instance, within Experiment 1, which had the most patients, there was no relation between lesion size overall and the size of the task effect ($\rho(12) = -0.377$, $p = 0.2$).

When assessing the lesion data for the reverse association (i.e. any brain regions that when damaged specifically lead to increased modulation of neglect by our task manipulations across the three experiments), there were no consistent findings. Instead, the anatomical consistency and significance, as presented above, concerned regions which when damaged tended to reduce the impact of the task manipulation.

General Discussion

Overall, our experiments reveal that top-down, task-related factors can dramatically modulate neglect performance in cancellation, with increasing demands on visual attention adversely affecting exploration towards the contralesional side, even when all purely bottom up factors (the visual displays) are kept constant, which was a key aspect of our designs here. Neglect for the left side of space may thus be significantly reduced or increased, depending entirely on the aspects of the same display that a patient is required to attend to and judge as determined by the task goals. Apart from the single-case study of Mennemeier, Morris and Heilman (2004) that had manipulated mental arithmetic, to our knowledge this is the only demonstration that just changing the task requirements in a cancellation task, while the display remains identical, can dramatically change the extent of the spatial exploration deficit exhibited by neglect patients. Moreover we showed this for a sizeable group of neglect patients here for the first time.

Experiment 1 manipulated target/non-target discrimination for the same displays, by requiring judgements either of overall shape or of a local detail. The extent of neglect in cancellation was dramatically modulated by the demand of the task-defined discrimination for constant displays. Two further experiments attempted to shed light on possible mechanisms underlying this.

Experiment 2 further indicated that increasing the demand of the task-related discrimination required for the same array items can exacerbate neglect, even when there was no longer any need for discrimination between targets and task-irrelevant non-targets, as all items in the display were now targets. This indicates that increasing the discrimination demands for separating targets from task-irrelevant non-targets is not always a necessary condition for neglect exacerbation in cancellation. Increasing the task-defined demand just for the discrimination performed on each found target can also impair patients' ability to search further into the contralesional left side. This new cancellation finding may accord with other recent findings (e.g. Russell, Malhotra & Husain, 2004; see also Robertson & Frasca, 1992) showing that an increase of attentional load for currently fixated items (as for each found, pointed-at and judged target in Experiment 2 here) in patients with right temporo-parietal lesions, who may suffer from capacity limits, may lead to shrinkage of their available peripheral visual field, and perhaps disproportionately so for the contralesional side (see also Lavie, 1995; 2005; Schwartz *et al.*, 2005 for related but non-lateralised findings of attentional load at current fixation on peripheral vision in normals). Moreover, recent emerging fMRI data in neglect patients (see Vuilleumier & Driver, 2007) indicate that visual responses even in early visual cortex may be significantly diminished, or even eliminated, for stimuli to the left (contralesional side) but not right (ipsilesional) of current fixation, under high task-demand at fixation in neglect patients, despite these early cortical visual responses remaining preserved and symmetrical for both visual hemifields under lower-demand at fixation in the same neglect cases. Hence less demanding discriminations at current fixation may lead to less neglect. Another way of thinking about this, which need not

be mutually exclusive, may be that rather general capacity limits in neglect (e.g. see Husain & Rorden, 2003) can lead to more pronounced deficits for contralesional than ipsilesional stimuli (relative to current fixation), if general capacity is exhausted by the high demand task, with this being superimposed upon a pre-existing left-right gradient that favours the right side, as often proposed to apply in neglect patients (e.g. see Driver, Vuilleumier & Husain, 2004). While to some extent we are speculating here in terms of potential underlying mechanisms in relation to other recent findings, a particularly solid empirical point emerged unequivocally from our three new cancellation experiments here, namely that neglect in cancellation can be strongly modulated by task-demand for exactly the same visual displays.

But more specifically, distinct influences of attentional demand for currently fixated targets (as implied by Experiment 2) or for target /non-target discrimination (as shown in Experiment 1) may exist for neglect performance in cancellation, as revealed by the direct comparison between Experiments 1 and 2 here. Although performance in both experiments was affected by increasing the demand of the task (requiring attention in both experiments to be directed to a local detail of the stimuli rather than their global shape, for the same displays), this effect was much bigger in Experiment 1, affected a higher proportion of cases in that study, and did not correlate with the task impact in Experiment 2, suggesting that increased attentional demand for discriminating *between* target and distracting non-targets (as additionally required in Experiment 1 only) may indeed be particularly detrimental for neglect. This validates previous suggestions that the presence of distractors embedded among targets can substantially exacerbate neglect (e.g. Husain & Kennard, 1997), but now shows this while holding stimulus displays constant, unlike previous cancellation studies on the topic.

Experiment 3 sought to determine whether the exacerbation of neglect observed by task in Experiments 1 and 2 may reflect increased attentional demands per se, or be more specific to judging 'local' versus 'global' aspects of shape in particular. Our third experiment revealed that increasing the task-defined discrimination demand, but now without altering the spatial scale of the features to be judged (as both tasks now required judgements to be based on colour, rather than on shape at different spatial scales), still had a significant impact on cancellation omissions. On the other hand, a direct comparison between Experiments 1 and 3 suggested that while increased task-defined visual discrimination demand can have a general impact on neglect (as found across all our experiments), this impact can be significantly larger when patients are required to judge more 'local' as opposed to 'global' shape features (as for Experiment 1, and 2). This would accord with a bias towards local details, as often observed after right-hemisphere damage (e.g. Lamb, Robertson & Knight, 1990; Robertson, Lamb & Knight, 1988) interacting with neglect to produce an exacerbation of the symptoms. This particular aspect of our new task-effects validates previous suggestions (Marshall & Halligan, 1994, 1995) that judgements requiring discrimination at a more 'local' level of shape may be particularly detrimental for neglect; but now does so for cancellation, and while holding displays constant within each experiment.

Our results clearly show that, in all three experiments, the more demanding task-defined visual discriminations (for the same stimulus displays) led to more neglect. A referee raised the intriguing question of whether this entails that the actual internal spatial bias of the patients takes on a steeper spatial gradient in the more demanding tasks; or whether instead the same fixed internal spatial gradient (bias) induced by the unilateral lesion can lead to more or less spatial neglect becoming evident behaviorally, when interacting with different discrimination demands. From a practical point of view, on either theoretical possibility the degree of neglect will still depend on task-related factors, even when holding the stimulus displays constant, as we have shown. One conceivable way to approach the theoretically-

intriguing issue about internal spatial gradients further, in future research as the referee suggested, may be to consider a modified version of Experiment 2, in which some of the target-defining features are common to both tasks (due to some target heterogeneity within the more demanding task, so that some of its targets are identical to those in the lower-demand task, while others differ). One might then measure separately the spatial bias manifest for the common targets, versus for the distinct ones, to determine if the common targets reveal the same or a different spatial gradient across the different tasks.

Turning to anatomical considerations, we performed an initial exploratory voxel-based lesion mapping analysis (see Figure 8), in order to reveal any areas potentially associated with an impact of top-down task-related factors on neglect in cancellation. This highlighted the posterior end of the right superior temporal gyrus (STG) and underlying white matter as a candidate region potentially associated with *reduced* modulation of neglect following top-down task manipulations, when damaged. While several further cortical and subcortical areas appear potentially implicated in this respect for single experiments, the right STG and underlying white matter were notable for being systematically implicated statistically, across all three separate analyses, for each experiment. Lesions here were consistently associated with a reduced impact of task modulation. Interestingly, a recent study by Grandjean *et al.*, (2008) on modulation of auditory neglect, also found the superior temporal cortex to be involved in patients showing reduced neglect modulation (in their situation by emotional factors). Our own anatomical results should be considered preliminary, and not central to our main conclusions. The anatomy will need refining in further work. Inclusion of patients with left hemisphere lesions in future studies might also help to clarify further whether task-related modulation of neglect is right-lateralized in particular. For the time being our present results only afford us some preliminary observations limited to the right hemisphere (see Figure 8), but even these preliminary results, implicating right STG and underlying white matter, seem of potential interest for several reasons. First, Karnath and colleagues (2001, 2004) originally proposed that the right STG may constitute a critical region for the neglect syndrome. The new evidence produced here indicates that damage to it may eliminate or reduce some top-down, task-related influences. Other anatomical approaches to neglect have emphasized possible functional disconnection and disruption between cortical areas, again implicating the right STG but now as part of a normal ‘ventral’ attentional network, whose structural or functional disruption may be of particular importance to the neglect syndrome (e.g. see Corbetta *et al.* 2005, He *et al.*, 2006). The right STG has also recently been implicated in normal visual search and exploration (Himmelbach, Erb & Karnath, 2006) and transient disruption of this area in normals has been reported to produce deficits of visual search and exploration (Ellison *et al.*, 2004; Gharabaghi *et al.*, 2006). Finally, the right temporo-parietal junction more generally, but still including right STG, has been associated with scene representation at a more ‘global’ level (Weissman & Woldorff; 2005; Yamaguchi, Yamagata & Kobayashi, 2000) and lesions in this general area, as mentioned earlier, have long been thought to contribute to ‘local’ biases (e.g. Lamb, Robertson, & Knight, 1990; Robertson, Lamb & Knight, 1988).

In conclusion, our three new experiments show that top-down, task-related factors can modulate neglect significantly in cancellation tasks, with increasing task-demands on visual attention adversely affecting spatial exploration, even when all purely bottom-up factors (here the visual displays) are kept constant within each experiment. Overall we have demonstrated several task-related factors that can influence neglect performance in cancellation, including the demand of discriminating targets from non-targets; the particular judgements that must be made for each target when found; and the spatial scale on which the judgement is based. Neglect was most exacerbated when considerable selective attention was required to select targets and filter-out non-targets in the array; when the required judgement for each target was also demanding; and when this had to be based on a local

level of detail. This validates several previous suggestions, while doing so with an approach that kept purely bottom-up stimulus factors strictly constant across our comparisons, while studying these issues for variants on cancellation procedures in particular. In highlighting some of the key task-related factors affecting neglect in cancellation, the present results should hopefully prove useful in developing simple yet more sensitive cancellation tests for clinical use in the future.

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Figure 1. Example of performance of one neglect patient (case N13) in three different cancellation tests that are commonly used in clinical practice, demonstrating a clear difference in test sensitivity, with a remarkable increase of omissions in tests **B** (Weintraub and Mesulam's shape cancellation test, 1985) and **C** (The Bells test; Gauthier, Dehaut, & Joanne, 1989), as compared to **A** (Star Cancellation test; Halligan, Wilson & Cockburn, 1990).

Figure 2.

Lesion overlap map summarising the degree of involvement for each voxel in the lesions of neglect patients participating in Experiment 1 (all patients, except for cases N13, N14 and N16 for which there were no available scans, $n=14$). The range of the colour scale derives from the absolute number of patient lesions involved in each voxel. The map is presented as 2D axial renderings on the MNI 'representative' brain, in descending steps. 12 axial slices are shown that correspond to Z-coordinates 48, 36, 30, 24, 20, 16, 13, 3, -3, -6, -11 and -16 of the MNI space. The region of maximal overlap in this group of patients (illustrated above in yellow), appears to be in the area of the right putamen and internal capsule, as found in some previous neglect studies, though not all. These lesion data are presented here solely for descriptive purposes.

Figure 3.

A) Example display from Experiment 1. **B)** Mean percentage of cancelled items per condition in Experiment 1. Numbers on the y-axis indicate mean percentage of cancelled targets (total number of targets per column across sheets is 20) and numbers on the x-axis indicate columns of the cancellation page (with 1 being the leftmost column and 6 being the rightmost column). Note more neglect omissions in gap task.

Figure 4.

Mean percentage of items 'pointed at' and explicitly judged, per column and condition, in Experiment 2. Numbers on the y-axis indicate the mean percentage of targets found (total number of targets per column across sheets is 40) and numbers on the x-axis indicate columns of the cancellation page (with 1 being the leftmost column and 6 being the rightmost column).

Figure 5.

Mean percentage of items found for the 'shape' and 'gap' conditions in Experiments 1 and 2, for the 13 patients that participated in both experiments. Numbers on the x-axis indicate columns of the cancellation page (with 1 being the leftmost column and 6 being the rightmost column).

Figure 6.

A) Example display from Experiment 3. **B)** Mean percentage of items cancelled by all patients in the colour and shade tasks of Experiment 3. Numbers on the y-axis indicate the mean percentage of cancelled targets (total number of targets per column across sheets is 20) and numbers on the x-axis indicate columns of the cancellation page (with 1 being the leftmost column and 6 being the rightmost column).

Figure 7.

Mean percentage of cancelled items for the 'shape' and 'gap' tasks of Experiment 1 and for the 'colour' and 'shade' tasks of Experiment 3, for the 9 patients that participated in both experiments. Numbers on the y-axis indicate percentage of cancelled items and numbers on the x-axis indicate columns of the cancellation page (with 1 being the leftmost column and 6 being the rightmost column).

Figure 8.

Voxel based lesion statistical maps revealing areas (in red) associated statistically with reduced task effect for each experiment, with Experiment 1 shown in upper row, then Experiment 2, then Experiment 3 in lower row. The maps are presented as axial renderings on the MNI 'representative' brain, in descending steps of 12 slices corresponding to z-coordinates 48, 36, 30, 24, 20, 16, 13 and 3, -3, -11, -16 of the MNI space. The areas shown here survived a FDR cutoff threshold of $p=0.01$. See text for further statistical details.

Table 1

Individual patient details and scores. Notes: Line

bis= % of average rightward deviation (negative numbers indicate a trend for deviation towards the left), Chim obj= % of the left side of chimeric objects identified out of 20, Chim faces= % of faces with smiling side on the right chosen as 'happier' out of 20, Post stroke= months post stroke at time of testing, Hemianopia: assessed by confrontation.

Patient	Sex	Age	Cancellation	Line Bis. %	Chim Obj. %	Post- stroke	Hemia nopia	Lesion site and pathology
N1	F	60	L: 3/27 R: 18/27 (Star)	46	0	1	Yes	R parieto-occipital infarct (PCA/MCA 'watershed')
N2	M	59	L: 0/17 R: 15/17 (Bells)	-12	100	19	No	R fronto-parietal infarct
N3	M	64	L: 12/27 R: 24/27 (Star)	13	0	1	Yes	R ICH involving external capsule and claustrum
N4	F	64	L: 0/27 R: 13/27 (Star)	61	n/a	2	No	R MCA infarct, extending to frontal cortex and including basal ganglia
N5	F	74	L: 9/27 R: 20/27 (Star)	40	10	1	Yes	R parieto-occipital infarct (PCA/MCA 'watershed')
N6	F	57	L: 5/27 R: 24/27 (Star)	23	0	1<	No	R MCA infarct, involving frontal lobe, basal ganglia and insular cortex
N7	F	59	L: 0/30 R: 28/30 (Mes.)	54	0	17	Yes	R infarct in the MCA territory with extension into the sylvian fissure
N8	M	51	L: 0/27 R: 8/27 (Star)	68	0	7	Yes	R parietal-temporal lobectomy following SDH
N9	M	67	L: 0/27 R: 12/27 (Star)	85	0	1<	No	R MCA infarct involving the temporo-parietal junction
N10	M	41	L: 3/30 R: 30/30 (Mes.)	1.4	40	9	No	R MCA infarct involving inferior parietal and frontal lobes
N11	M	51	L: 0/27 R: 10/27 (Star)	9	0	12	Yes	R ICH in the MCA territory, involving parietal and frontal lobes
N12	M	72	L: 13/30 R: 20/30 (Mes.)	-8	61	171	No	R infarct involving temporal and inferior frontal lobes
N13	M	69	L: 0/27 R: 22/27 (Star)	12	31	18	Yes	R MCA infarct, with possible later extension
N14	M	56	L: 5/17 R: 17/17 (Bells)	-7	94	4	No	R ACA infarct
N15	M	52	L: 0/27 R: 13/27 (Star)	34	0	6	Yes	R ganglionic ICH extending into insular cortex
N16	M	46	L: 8/30 R: 29/30 (Mes.)	2	13	6	Yes	R ganglionic ICH
N17	F	23	L: 11/30	39	50	5	Yes	R large MCA infarct

Patient	Sex	Age	Cancellation	Line Bis. %	Chim Obj. %	Post- stroke	Hemia nopia	Lesion site and pathology
R: 28/30 (Mes.)								

Table 2

Percentages of total number of cancelled targets in the 'shape' and 'gap' tasks of Experiment 1, plus statistical value of difference between the two conditions (*p*) for each individual patient.

Patient	Total %		<i>p</i>
	Shape	Gap	
N1	75	29	0.000 **
N2	89	73	0.002 **
N3	91	65	0.000 **
N4	80	47	0.000 **
N5	96	70	0.000 **
N6	89	62	0.000 **
N7	67	39	0.000 **
N8	27	18	0.122
N9	36	14	0.000 **
N10	80	57	0.000 **
N11	38	33	0.345
N12	93	82	0.006 **
N13	73	33	0.000 **
N14	96	77	0.000 **
N15	57	27	0.000 **
N16	93	57	0.000 **
N17	90	62	0.000 **

Table 3

Percentages of total number of cancelled targets in the 'shape' and 'gap' tasks of Experiment 2, plus statistical value of difference between the two conditions (*p*) for each individual patient.

Patient	Total %		<i>p</i>
	Shape	Gap	
N1	49	28	0.000 **
N2	93	85	0.009 **
N3	89	83	0.049 *
N4	92	89	0.348
N5	85	61	0.000 **
N6	72	49	0.000 **
N7	78	85	0.062
N8	24	23	0.746
N9	60	58	0.507
N10	69	57	0.006 **
N11	15	10	0.134
N15	50	50	1.000
N17	64	38	0.000 **

Table 4

Percentages of total number of cancelled targets in the 'colour' and 'shade' tasks of Experiment 3, plus statistical value of difference between the two conditions (p) for each individual patient.

Patient	Total %		<i>p</i>
	Colour	Shade	
N7	85	75	0.075 *
N9	74	71	0.665
N10	63	48	0.027 *
N11	45	28	0.011 *
N12	92	86	0.220
N13	75	43	0.000 **
N14	93	91	0.634
N15	28	31	0.777
N17	80	47	0.000 **