

**An exploration of the role of the superior temporal gyrus in visual search
and spatial perception using TMS.**

Amanda Ellison*, Igor Schindler, Lara L. Pattison, A. David Milner.

Cognitive Neuroscience Research Unit
Wolfson Research Institute
University of Durham, Queen's Campus
Stockton-on-Tees
TS17 6BH
United Kingdom

* Corresponding Author:

amanda.ellison@durham.ac.uk

Phone: +44 (0)191 3340441

Fax: +44 (0)191 3340452

Running Title: **The role of STG lesions in neglect-like tasks**

Word count: 5,290

Summary

This study sought to investigate the recent claim by Karnath *et al.* (2001) that the crucial locus of neurological damage in neglect patients lies in the right superior temporal gyrus (STG), and not in the right posterior parietal cortex (PPC) as conventionally thought. Using Transcranial Magnetic Stimulation (TMS), we first tested the involvement of the right STG in a task commonly used in the diagnosis of neglect, the landmark task. No evidence was found for a critical involvement of the right STG in the processing of this task, though evidence was found for the involvement of the right PPC. In contrast, however, when we examined the effects of TMS on exploratory search, a double dissociation between right STG and right PPC was found. When the processing of conjunction items was required, involvement of the right PPC (and not STG) was found, in accordance with previous research (Ellison *et al.*, 2003). When difficult exploratory search through feature items was required however, the right STG (not PPC) was found to be involved. A hitherto unknown role for right STG in visual search tasks was thus uncovered. These data suggest that conclusions about the area of brain damage resulting in neglect-like symptoms are highly dependent on the task used to diagnose them, with lesions in right PPC leading to deficits on the landmark task and conjunction visual search, and lesions in right STG resulting in deficits in feature based serial exploratory search tasks.

Keywords: temporal cortex, spatial neglect, visual search, landmark task, TMS.

Abbreviations: STG= superior temporal gyrus; PPC= posterior parietal cortex; TMS= transcranial magnetic stimulation; rTMS= repetitive TMS; TPJ= temporo-parietal junction; MCA= middle cerebral artery

Introduction

The use of Transcranial Magnetic Stimulation (TMS) in the investigation of neurological deficits is not new (Walsh *et al.*, 1998, Pascual-Leone *et al.*, 1994). However, neuropsychology and TMS differ in how they approach solutions to the same problem, namely: “how does the normal brain work?” Neuropsychology identifies tasks that patients with particular lesions cannot do, and so attributes the processing of such tasks to the damaged area. The obvious drawback to such an approach is that brain lesions are often large and diffuse and the neuropsychologist is trying to make inferences about normal brain function using an abnormal preparation. Also, testing of such patients can occur many years after the causative neurological insult. One of the many strengths of the human brain is its ability to reorganise itself to regain functions lost (Robertson, 1999). Such an element of plasticity is an unknown in the inferences made about normal brain function following damage. TMS, on the other hand, approaches the same problem but from the opposite end of the experimental spectrum. By the introduction of a brief period of neural disorder in a localised area, the role of a discrete region of cortex in the processing of a concurrent task can be delineated. To this end, the symptomatic effects of lesions, the causes of which can only be postulated by neuropsychologists, can be investigated with respect to the normal functioning brain (see Walsh and Cowey, 2000 and Stewart *et al.*, 2001 for review).

It is within such a framework that the present study originated. The brain regions crucially associated with neglect have recently become a subject of intense dispute (Karnath and Himmelbach 2002a; Marshall *et al.*, 2002) as a result of a series of anatomical group studies. Based on studies of unselected middle cerebral artery (MCA) patients it has been generally found that the crucial cortical area most commonly associated with neglect is the inferior right posterior parietal lobe (IPL) and the temporo-parietal junction (TPJ) in particular (Leibovitch *et al.*, 1998; Mort *et al.*, 2003, Vallar and Perani 1986; Vallar 2001). However, a controversial paper by Karnath *et al.* (2001) suggested that the crucial locus of brain damage that causes neglect symptoms was not in the right posterior parietal cortex (PPC) at all, but in the middle of the right superior temporal gyrus (STG), Brodmann's area 42), well anterior to the TPJ. This conclusion was based on the analysis of lesion position in 25 non-hemianopic neglect patients. It has, therefore, been criticized as an artefact due to the exclusion of many typical neglect patients with associated visual field deficits, resulting in an anterior shift of the apparent lesion focus (Mort *et al.*, 2003). Indeed Mort *et al.*'s group study reconfirmed the traditional findings by including hemianopic neglect patients.

However, taken together, these results do not necessarily exclude each other: instead of supporting the idea of one single crucial cortical region associated with neglect, they rather suggest the possibility of (at least) two areas depending on the absence or presence of hemianopia as well as on the

functional definition of neglect by the screening tasks used. The latter argument becomes evident given that in Karnath *et al.*'s study the neglect screening was strongly biased towards tasks involving visual search (cancellation and scene copying), while excluding line bisection. In contrast Mort *et al.*'s patients were assessed in more traditional fashion with both line bisection and cancellation tasks. However a substantial number of these patients showed a double dissociation between line bisection and cancellation. It is now hotly debated whether the contrasting anatomical results reflect specific functional task demands involving different neuronal components in neglect or methodological differences in patient selection or lesion analysis (Mort *et al.*, 2004, Karnath *et al.*, 2004). As there is no definite answer, it would seem a potentially useful contribution to the debate for TMS studies to test the functional role of the right STG using line bisection as well as a visual search paradigm.

A perceptual version of the traditional line bisection paradigm is provided by the landmark task (in which the subject is asked make judgements about whether pre-bisected lines are bisected to the left or right of centre: (Milner *et al.*, 1992, 1993; Bisiach *et al.*, 1998). Biases in the landmark task, like those seen in the line bisection task, have often been taken to reflect distorted spatial perception in neglect patients (Milner *et al.*, 1998; Bisiach *et al.*, 1998). It has already been shown by Fierro *et al.* (2000) that it is possible to induce similar contralateral effects on the landmark task in healthy subjects using event-related repetitive-pulse TMS (rTMS) over right posterior parietal cortex (PPC).

This was further investigated by Bjoertomt *et al.* (2002), who found that the involvement of PPC in the task was restricted to near space. If, then, rTMS to the right STG results in similar neglect-like symptoms in the landmark task, clear support would be provided for Karnath *et al.*'s theory.

The other traditionally sensitive measure of neglect involves the use of cancellation tasks of various kinds, i.e. tasks involving the search for multiple targets in an array (see, e.g., Robertson and Marshall, 1993). It appears that bisection and cancellation tasks may tap different aspects of the neglect syndrome, given that they show mutual double dissociations among individual neglect patients (Halligan and Marshall, 1992), and correlate poorly together across the neglect population (Ferber and Karnath, 2001). A number of formal studies of search performance have been undertaken to explore the cancellation impairment (e.g. Karnath and Niemeier, 2002b; Behrmann *et al.*, 1997; Karnath *et al.*, 1998). In the light of this work, we carried out a second experiment in which we sought to test the involvement of the right STG in visual search tasks. Much is already known about the involvement of right PPC in such tasks, with current TMS evidence arguing strongly for its critical involvement being in the processing of conjunction items in space (Ellison *et al.*, 2003). On the other hand, other evidence (including from functional MRI) has suggested that the critical determinant of brain processing in visual search tasks lay along the dimension of the difficulty of search, and thus the attention required for its processing, and that this aspect involved right PPC (e.g. Nobre

et al., 2003). One of the problems with many previous discussions of visual search is that there has been a conflation between ‘difficult/easy’, ‘serial/parallel’ and ‘conjunction/feature’ search tasks. But in fact the search stimulus used (feature versus conjunction) is not 100% correlated with the search pattern required to find it. Specifically, one can construct the following four distinct search tasks: parallel (easy) feature, serial (hard) feature, parallel (easy) conjunction and serial (hard) conjunction. Thus, as Ellison *et al.* point out, it is possible to have feature search arrays that require a serial search and conjunction search arrays that only require parallel search (Treisman and Gelade, 1980). The literature on visual search in neglect has been beset to some degree with the same conflation. Using a serial search for a unique feature (inaccurately named a conjunction search to remain “consistent with literature” interchanging serial search with conjunction tasks), Behrmann *et al.* (2004) also agree that “the binary distinction between preattentive/featural and attentive/conjunction processing does not obviously hold” in neglect patients. Ellison *et al.* (2003) attempted to separate these different aspects of visual search with respect to the parietal cortex using rTMS. They showed that right PPC is involved in the processing of any search for conjunction items even if this search was extremely easy and parallel (< 5 ms per item). rTMS has therefore shown that the critical involvement of right PPC is in conjunction search in space, irrespective of difficulty. In contrast, rTMS of this region does not have any effect even on very difficult serial (50ms per item) feature search.

Therefore we would predict that the relative pattern of difficulty neglect patients have should be related lawfully to the anatomy of their damage.

In the present study we thus attempt a complementary approach to lesion studies, using TMS to investigate the functional involvement of the right STG in tasks related to the two traditional neglect paradigms. As an experimental comparison, and in order to replicate earlier studies, we have also examined the effects of TMS to the right PPC as well in each case.

Method

Subjects

Five healthy subjects, aged 21-36, with normal or corrected to normal vision (all right handed; 2 female, 3 male), participated in all tasks. Subjects gave their signed informed consent in accordance with Durham University Ethics Advisory Committee, and could leave the experiment at any point. Subject selection complied with current guidelines for rTMS research (Wassermann, 1998).

Stimuli

All stimuli were presented on a 320mm x 240mm monitor driven by a Pentium-4 PC programmed in E-Prime (Psychology Software Tools, Inc). Subjects were seated comfortably 57.5 cm away from the screen with the centre of the screen at pupil level. The subjects' head and trunk sagittal midline was aligned with the centre of the screen, and head position was controlled by a chinrest. Except for the light from the PC screen the room was darkened, and the stimuli were equiluminant at 120 cd/m².

Landmark Task

The landmark paradigm used in this experiment was a modified version of that used by Bjoertomt *et al.* (2002) original experiment. Each stimulus consisted of a symmetrically or asymmetrically bisected white horizontal line on a black background. The lines were of four different lengths ranging from 20° to 23°.

In one-third of trials the line was symmetrically bisected by a short vertical line (2° visual angle long). Both long and short lines were symmetrically bisected in order to eliminate length processing as a strategy. In the remainder of trials the line was asymmetrically bisected to make either the left or right side longer by either 1° or 2° of visual angle. All lines were 0.1° thick. The stimuli were always presented with the bisection mark at the head and body midline of the subject.

A central fixation cross appeared for 500ms followed by the appearance of the stimulus for 300ms, which was immediately followed by a mask ($30^\circ \times 30^\circ$), which then remained present until the subject responded. The mask consisted of a thick (0.2°) horizontal line and central vertical bar, which in combination always covered the previously displayed stimulus. Subjects were asked to respond in one of two ways, the first instruction being “Which was longer: Left or Right?”, and the second being “Which was shorter: Left or Right?” (see Figure 1). Each instruction was tested in separate blocks of trials with adequate practice given for each. Responses were made on a button box with the left button denoting left and the right button denoting right. Subjects were asked to respond as quickly as they could but not to sacrifice accuracy for speed. Inter-trial interval was 4000ms.

Figure 1 about here please

Visual Search Tasks

Three visual search tasks were used (see Figure 2). Two of the tasks (feature and conjunction) required serial search ($>10\text{ms/item}$) and constitute “hard” search tasks in terms of difficulty. The third task (feature) was a simple “pop-out” search with a parallel search function ($< 5\text{ms/item}$) and is termed “easy” search. The target could appear anywhere in the 8×6 array of virtual boxes on the screen.

In the feature tasks, the target was unique amongst distractors whereas in the conjunction task, both the orientation and colour of the target was shared amongst distractors. All items subtended $2^\circ \times 2^\circ$ visual angle and were presented against a black background. Subjects were asked to respond as quickly and as accurately as possible on a button box (left button for target-present, right button for target-absent) to indicate the presence or absence of the target. Each trial was preceded by a central fixation cross ($0.5^\circ \times 0.5^\circ$) for 500ms followed immediately by the stimulus array. There were 8 items in each array. In trials where the target was absent, an extra distractor was displayed to eliminate counting as a strategy. The target was present in 50% of trials, and there was never more than one target. The visual array remained present until response or for 1500ms, whichever was shorter, and the inter-trial interval was 4000ms.

Figure 2 about here please

The hard feature task required search for a white L shaped target amongst 180° rotated L shapes and 270° rotated L shapes. The easy feature task required search for a white slash (/), amongst white backslashes (\). The hard conjunction task required search for a red slash amongst red backslashes and green slashes (see Figure 2).

TMS

A Magstim™ Model 200 was used and stimulation was applied at 65% of the stimulator's maximum power. This level of stimulation is greater than the thresholds required to induce movement (over motor cortex) or the perception of phosphenes (over visual cortex).

Two sites of stimulation were used, right superior temporal gyrus, STG, and right posterior parietal cortex, PPC. The STG site (Brodmann's area 42, the main area of lesion overlap in Karnath *et al.*'s analysis) was located using frameless stereotaxy (BrainSight™, Rogue Research, Montreal, Canada) at the beginning of the session. This area is located approximately 1 cm posterior to vertex and 14cm lateral on the scalp (see Figure 3). The PPC site was identified by using a hunting procedure with the hard conjunction task, as described in Ashbridge *et al.* (1997) and used by Bjoertomt *et al.* (2002) in their investigation of the landmark task. This site lies posteriorly within the typical

area of parietal cortex damage causes neglect. In the hunting procedure, 10 trials of TMS are given to each site in a 3 x 3 grid (each point 1 cm apart, see Figure 3) around a central point 9 cm dorsal to the mastoid-inion and 6cm lateral. The “hotspot” for activation is denoted by a 100ms increase in reaction time over the trials in which no TMS was administered. This functionally localised position was then verified using BrainSight™ (see Figure 4) before the experimental procedure.

Figure 3 about here please

Figure 4 about here please

Right STG stimulation was applied using a small (50mm) ‘figure of 8’ coil placed tangential to the skull. Due to the likelihood of magnetic pulses in this area (just above the ear) causing superficial facial muscle twitches that might interfere with the processing of the visual task, the frequency used was 4 Hz for 500 ms. This resulted in 2 pulses per trial. Right PPC TMS was applied in the more conventional manner, with a 70 mm figure of 8 coil at 10 Hz for 500 ms, resulting in 5 pulses per trial. In the no-TMS condition, the TMS coil discharged the pulses near to, but directed away from, the subject’s head. Therefore, the audible effect of TMS was always present but without the accompanying pulse delivery to the cortex.

At each site, the train of pulses began at presentation of the visual stimulus (post-fixation). The landmark task was tested at each stimulation site in 8 blocks x 12 trials (alternate TMS and no-TMS blocks, randomised across subjects) for each instruction ('which is longer?' and 'which is shorter?'). Each visual search task was also tested in 8 x 12 trials at each stimulation site. The order of all tasks was randomised across subjects to preclude practice effects. Three testing sessions (one per week), lasting approximately 1.5 hrs, were required per subject, each of whom completed all tasks.

Results

Landmark task

Accuracy with asymmetrically bisected lines was always above 97% and there was no significant difference between error rates on TMS and no-TMS trials (3 factor [site of stimulation x line length x instruction] repeated measures ANOVA). TMS over either site had no significant effect on reaction time, whether lines were either asymmetrically or symmetrically bisected (3 factor [hemispace x instruction x TMS condition] repeated measures ANOVA).

The most illuminating results in this task relate to the pattern of subjects' responses when lines were centrally bisected. When TMS was applied to the PPC, subjects responded that the left side of the line was shorter in 20% more trials than without TMS ($t = 4.080$, $df = 4$, $p = 0.027$, paired t-test). When they were asked which side was longer, they responded that the right side was longer in 22% more TMS trials than in no-TMS trials ($t = 6.326$, $df = 4$, $p = 0.003$). Subjects therefore exhibited, with PPC TMS, a tendency to underestimate the leftward segment of the lines, as in contralateral neglect (see Figure 5).

In contrast, there were no significant differences in response patterns when TMS was applied over the right STG ($t = 0.214$, $df = 4$, $p = 0.841$, 'longer' condition; $t = 0.412$, $df = 4$, $p = 0.701$, 'shorter' condition) (see Figure 5).

Figure 5 about here please

Visual search

The visual search tasks displayed a clear contrast between the effects of TMS over STG and PPC on target-present reaction times. There was a significant main effect (3 factor [site of stimulation x task x TMS] repeated measures ANOVA) for task ($F_{(2,8)} = 32.772$, $p < 0.001$) and a significant interaction between the three factors ($F = 15.911$, $p = 0.002$). Post hoc Bonferroni tests revealed that TMS over STG had a significant effect on search reaction time for the target in the hard feature search task ($t = 8.039$, $df = 4$, $p = 0.001$) but not in the easy feature task ($t = 0.516$, $df = 4$, $p = 0.633$) or the hard conjunction task ($t = 0.228$, $df = 4$, $p = 0.831$). Conversely, TMS over the PPC had a significant effect on reaction time in the serial conjunction task ($t = 3.790$, $df = 4$, $p = 0.019$), but not in the hard feature task ($t = 1.186$, $df = 4$, $p = 0.301$), or the easy feature task ($t = 0.666$, $df = 4$, $p = 0.542$) (see Figure 6).

Figure 6 about here please

In a two factor [task x hemispace] repeated measures ANOVA (using TMS/no TMS scores) for each stimulation site separately, there was no significant difference between TMS effects for targets presented in left or right hemispace under either STG or PPC stimulation (STG: $F_{(1, 4)} = 0.196$, $p = 0.681$; PPC: $F_{(1,4)} = 0.026$, $p = 0.880$). Error rates in all visual search tasks were less than 2%

and there was no significant difference between error rates for TMS and no-TMS trials.

Discussion

Previous findings of contralesional neglect-like symptoms on the landmark task following TMS over right PPC (Fierro *et al.*, 2000; Bjoertomt *et al.*, 2002) were replicated in this study, which is also in line with recent fMRI data (Fink *et al.*, 2000, 2001). However, no such effect on the landmark task was found with TMS over right STG. This finding might seem to be inconsistent with Karnath *et al.* (2001)'s view that Brodmann's area 42 is the main locus of neurological damage underlying neglect.

However, as discussed in the introduction, neglect as a condition can be diagnosed in many ways, and neglect patients are known to be impaired in a variety of different tasks (see Bisiach and Vallar, 2000; Robertson and Marshall, 1993). In fact, the existence of double dissociations between tasks in neglect patients led Ferber and Karnath (2001), like Halligan and Marshall (1992) before them, to question neglect as a “meaningful theoretical entity”. These indications of the multifarious nature of neglect are borne out by the results of the present study, in which we found that a particular exploratory search task revealed an involvement of the right STG, but not the PPC. More specifically, we found involvement of the right STG in a difficult visual search for feature items, though not for conjunction items, nor for simple “pop-out” search.

It is clear that these visual search results cannot be explained by a generalised TMS effect, since the effects were modulated by task: i.e. stimulation at each site caused processing deficits in one visual search task but not in the other two. Effects cannot be explained by the difference in stimulation parameters between areas either. As previously mentioned, the position of right STG on the scalp necessitated a lower frequency of stimulation in order to minimise muscle twitch and eye blinks which would impede the subject's ability to perform the task. Of course, if we could not find effects using these lower stimulation parameters over right STG in any of our tasks, then we could not be sure that our stimulation of this site was sufficient to cause a disruptive effect on processing. In practice, however, 4Hz did allow us to induce clear task-specific disruption to processing in right STG, presumably at the critical time at which it is active in the processing of the task. It is clearly a possibility that if it were possible to stimulate right STG with 10Hz, these effects would be even stronger, as brain activity at the critical time would no doubt be disrupted to a more selective degree. However, the parameters we used were nonetheless sensitive enough to detect clear differential effects, thus allowing us to demonstrate an all important double dissociation in our results. It is very unlikely that a higher frequency of stimulation over right STG would "induce" hitherto uncovered effects in the landmark task, as no deficits in processing were observed at all with 4Hz stimulation which is sufficiently effective to reveal right STG involvement in other visual tasks. This view is supported by our pilot experiments which revealed that 4Hz stimulation over right PPC

replicated our results in the 10Hz stimulation condition, although the observed effects were not large enough to reach significance. Using 4Hz in the landmark task, subjects underestimated the length of the left line 18% more than without TMS (as opposed to an average 25% difference with 10Hz stimulation). In the search conditions, 4Hz TMS over PPC induced a 36.25ms increase in reaction time in the hard conjunction condition (c.f. 76.47ms increase with 10hz). Although it is possible to achieve significant increases in reaction time in our conjunction search task with single pulses delivered at 100ms post stimulus onset (Ashbridge *et al.*, 1997), presumably 4Hz stimulation does not cover this time frame as effectively as 10Hz would.

A common concern with TMS experiments is that the inferences made about the stimulated area's involvement in the processing of a task may be unfounded given the spread of current following a TMS pulse. Current does indeed spread to adjacent cortex and along neurological pathways (Ilmoniemi *et al.*, 1997). However, it is unlikely that this secondary activation is ever strong enough to cause disruption of cognitive processing in these areas (Nikulin *et al.*, 2003).

Also, effects cannot be explained by practice effects modulating performance in our visual search tasks. The order of the testing sessions was randomised across weeks to preclude any practice effects, which are typically quite strong for visual search tasks. The order of the tasks was randomised within each testing session and each testing session used a different site of stimulation.

However, even with such controls some differences (albeit non-significant) between no-TMS reaction times are evident. It is worth pointing out however that the final failsafe in this design is that no-TMS reaction times were taken on each testing day, therefore if subjects were faster on Day 2 for example, their TMS reaction times on that day were directly comparable with their no TMS reaction times collected in the same session.

Although it has been postulated from functional imaging (Hayakawa *et al.*, 2003) and neuropsychological (Humphreys *et al.*, 1992a, b) data that the temporal cortex is involved in feature search, this is the first demonstration of a critical involvement of the superior temporal gyrus in this kind of processing. It is notable also that the right STG is not involved in the processing of simple pop-out search; hence its involvement is not based on the presence of single-feature items *per se*. A more difficult spatial search is required. This is evidence that highly parallel feature search is processed earlier in the visual system than either of the sites we have studied. In contrast, Ellison *et al.* (2003) found that the right PPC was involved in the processing of conjunction items no matter how easy the search was.

It is therefore evident from our visual search results that right STG is involved in certain spatial aspects of visual processing. It is notable, however, that asymmetrical (i.e. contralesional hemispace) effects were not manifested for either the PPC or STG stimulation in the visual search tasks, although they

were in the landmark experiment. Aside from the obvious difference of lesion volume between neglect patients after MCA infarction and the more focal TMS-induced disturbances, this may be due to three reasons. The first reason could be the special characteristics of neglect itself. It has been shown that the failure of neglect patients to orient and respond to contralesional stimuli occurs not only with respect to egocentric-reference frames e.g. where left and right are defined with respect to the sagittal plane of the body or body parts (Hornak, 1992; Karnath, 1997; Karnath *et al.*, 1998) but also with respect to object-centred reference frames (Driver *et al.*, 1994; Tipper and Behrmann, 1996; Behrmann and Tipper, 1999). In the latter case left and right are defined by object features and consequently neglect can be observed independently of the object's location within egocentric space. In this context, our findings of absent lateralized reaction time effects despite higher overall latencies may suggest that we reproduced an object-centred deficit. That is, if each fixated object's processing were impaired, there would be the same degree of reaction-time deficit for targets appearing in both the left and right hemifields. This finding may be peculiar to TMS-induced effects, in mimicking a rather atypical form of neglect that is only sometimes present in patients (e.g. Driver, 1999). This theory could be tested by using the same stimuli but presenting them in a way so as not to allow eye movements (as in the landmark task). If we could demonstrate contralesional TMS effects in this case, it would provide support for an object-centred interpretation of our results.

The second reason stems from the irrefutable fact that following neurological insult, the brain is very efficient in reorganising itself (Robertson, 1999). In the normal brain, there is evidence that the right PPC has a dominant role in distributing spatial attention on both sides of visual space (Nobre *et al.*, 1997, Corbetta *et al.*, 1993). Following a lesion to the right PPC, the left PPC may by default take over such processing (cf. Luria, 1963) even though due to its limited abilities, only the contralateral hemispace can be processed (Corbetta *et al.*, 1993; but see Corbetta *et al.*, 1998). This would result in the common happenstance of left hemispatial neglect following a right hemisphere lesion in patients tested after their damage occurred (as first proposed by Heilman and Van Den Abell, 1980). Although patients may experience contralateral neglect even minutes after a stroke, perhaps those few minutes are crucial for the switch to left-hemisphere control. In contrast, the very brief stimulation period of TMS means that no such time window is available for the switch of control to occur.

The third possible reason why we did not uncover contralateral neglect in the visual search tasks may be a function of the decision demands of the task. The effects seen in the landmark task were contralateral and in this case the subject's response was explicitly based on spatial categories relevant in neglect i.e. "left" or "right". However, in our visual search tasks the response was "target-present" or "target-absent". It may be that the processing of a present or absent response requires more global processing, less spatially intensive than

the search required if the subject is asked to indicate which side of space the target appeared in (i.e. detection vs localisation). Requiring a left/right response would more closely resemble the directional nature of responses in clinical cancellation tasks, and might thereby reveal contralateral effects from TMS. In support of this idea, Behrmann *et al.* (1997) showed that patients with neglect have a deficient search pattern biased to the right hemispace. Such a search pattern may be sufficient to execute a target-present/target-absent search in both hemispaces, but contra-lesional effects may be seen in a left/right search. This can be easily tested using TMS.

In conclusion, we have found some support for Karnath *et al.*'s (2001) seminal claim for the importance of STG damage in the causation of neglect. We have demonstrated a critical involvement of right STG in a hard feature visual search task. Given the double dissociation we have found between task used and brain area stimulated, it is clear that the detection of neglect is likely to be highly dependent on the task used. Indeed our results show that the right PPC has a key role in processing of both the landmark and hard conjunction tasks. These findings are partially consistent with reports of an earlier lesion study in 21 neglect patients (Binder *et al.* 1992) showing that patients with lesions in the right temporo-parieto-occipital area are frequently impaired in cancellation as well as line bisection. In contrast, the maximal lesion overlap in patients who were only impaired in cancellation was found in pre-rolandic regions including the prefrontal cortex, insula and adjacent subcortical areas. One reason for this

latter result may be that in contrast to the search paradigms used in our study, the Mesulam cancellation task used by Binder *et al.* might have involved a spatial working memory component, which has been shown to be impaired in neglect patients with frontal lesions (Walker *et al.* 1998). The interesting question that arises from our results is what would be found in patients with different *posterior* lesions using the specific tasks used here. We would predict that patients with PPC lesions should be more likely to have deficits on the landmark task and in conjunction visual search, whereas those with right STG lesions should be more likely to have deficits in difficult exploratory single-feature search.

References

Ashbridge E, Walsh V, Cowey A. Temporal aspects of visual search studied by transcranial magnetic stimulation. *Neuropsychologia* 1997; 35: 1221-89.

Behrmann M, Tipper SP. Attention accesses multiple reference frames: evidence from visual neglect. *J Exp Psychol Hum Percept Perform* 1999; 25: 83-101.

Behrmann M, Ebert P, Black SE. Hemispatial neglect and visual search: a large scale analysis. *Cortex* 2004, 40, 247-263.

Behrmann M, Watt S, Black SE, Barton, JJS. Impaired visual search in patients with unilateral neglect: an oculographic analysis. *Neuropsychologia* 1997; 35: 1445-58.

Binder J, Marshall R, Lazar R, Benjamin J, Mohr JP. Distinct syndromes of hemineglect. *Arch Neurol* 1992; 49: 1187-94.

Bisiach E, Vallar G. Unilateral neglect in humans. In: Boller F, Grafman J, editors. *Handbook of neuropsychology*, Vol. 1. 2nd edn. Amsterdam: Elsevier; 2000. p. 459-502.

Bisiach E, Ricci R, Lualdi M, Colombo MR. Perceptual and response bias in unilateral neglect: two modified versions of the Milner landmark task. *Brain Cogn* 1998; 37: 369-86.

Bjoertomt O, Cowey A, Walsh V. Spatial neglect in near and far space investigated by repetitive transcranial magnetic stimulation. *Brain* 2002; 125: 2012-22.

Corbetta M, Miezin FM, Shulman GL, Petersen SE. A PET study of visuospatial attention. *J Neurosci* 1993; 13: 1202-26.

Corbetta M, Akbudak E, Conturo TE, Snyder AZ, Ollinger JM, Drury HA, *et al.* A common network of functional areas for attention and eye movements. *Neuron* 1998; 21: 761-73.

Driver, J. Object-based and egocentric visual neglect. In: Burgess N, Jeffery K, O'Keefe J, editors. *The hippocampal and parietal foundations of spatial cognition*. Oxford: Oxford University Press; 1999. p. 67-89.

Driver J, Baylis GC, Goodrich SJ, Rafal RD. Axis-based neglect of visual shapes. *Neuropsychologia* 1994; 32: 1353-65.

Ellison A, Rushworth MFS, Walsh V. Visual search and posterior parietal cortex: a visuomotor hypothesis. *Clin Neurophysiol* 2003; s56: 321-30.

Ferber S, Karnath HO. How to assess spatial-neglect – line bisection or cancellation tasks? *J Clin Neuropsychol* 2001; 23: 599-607.

Fierro B, Filippo B, Oliveri M, Piazza A, La Bua V, Buffa D, *et al.* Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. *Neuroreport* 2000; 11: 1519-21.

Fink GR, Marshall JC, Shah NJ, Weiss PH, Halligan PW, Gross-Ruyken M, *et al.* Line bisection judgements implicate right parietal cortex and cerebellum as assessed by fMRI. *Neurology* 2000; 54: 1324-31.

Fink GR, Marshall JC, Weiss PH, Zilles K. The neural basis of vertical and horizontal line bisection judgements: an fMRI study of normal volunteers. *Neuroimage* 2001; 14: 59-67.

Halligan PW, Marshall CJ. Left visuo-spatial neglect: a meaningless entity? *Cortex* 1992; 28: 525-35.

Hayakawa T, Miyauchi S, Fujimaki N, Kato M, Yagi A. Information flow related to visual search assessed during magnetoencephalography. *Brain Res Cogn Brain Res* 2003; 15: 285-95.

Heilman KM, Van Den Abell T. Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology* 1980; 30: 327-30.

Hornak, J. Ocular exploration in the dark by patients with visual neglect. *Neuropsychologia* 1992; 30: 547-52.

Humphreys GW, Riddoch MJ, Quinlan PT, Price CJ, Donnelly N. Parallel processing in visual agnosia. *Can J Psychol* 1992a; 46: 377-416.

Humphreys GW, Freeman TA, Muller HJ. Lesioning a connectionist model of visual search, selective effects on distractor grouping. *Can J Psychol* 1992b; 46: 417-27.

Karnath HO. Spatial orientation and the representation of space with parietal lobe lesions. *Philos Trans R Soc Lond B Biol Sci* 1997; 352: 1411-19.

Karnath HO, Ferber S, Himmelbach M. Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature* 2001; 411: 950-53.

Karnath HO, Fruhmann Berger M, Zopf R, Küker W. Using SPM normalization for lesion analysis in spatial neglect. *Brain* 2004; 127: E10.

Karnath HO, Himmelbach M. Strategies of lesion localisation. *Cortex* 2002a; 38: 258-60.

Karnath HO, Niemeier M. Task-dependent differences in the exploratory behaviour of patients with spatial neglect. *Neuropsychologia* 2002b; 40: 1577-85.

Karnath HO, Niemeier M, Dichgans J. Space exploration in neglect. *Brain* 1998; 121: 2357-67.

Leibovitch FS, Black SE, Caldwell CB, Ebert PL, Ehrlich LE, Szalai JP. Brain-behaviour correlations in hemispatial neglect using CT and SPECT: the Sunnybrook Stroke Study. *Neurology* 1998; 50: 901-8.

Luria AR. Restoration of function after brain injury. New York: Pergamon Press; 1963.

Marshall JC, Fink GR, Halligan PW, Vallar G. Spatial awareness: a function of the posterior parietal lobe? *Cortex* 2002; 38: 253-7.

Milner AD, Brechmann M, Pagliarini L. To halve and halve not: an analysis of line bisection judgements in normal subjects. *Neuropsychologia* 1992; 30: 515-26.

Milner AD, Harvey M, Roberts RC, Forster SV. Line bisection errors in visual neglect: misguided action or size distortion? *Neuropsychologia* 1993; 31: 39-49.

Milner AD, Harvey M, Pritchard CL. Visual size processing in spatial neglect. *Exp Brain Res* 1998; 123: 192-200.

Mort DJ, Malhotra P, Mannan SK, Rorden C, Pambakian A, Kennard C, Husain M. The anatomy of visual neglect. *Brain* 2003; 126: 1986-97.

Mort DJ, Malhotra P, Mannan SK, Pambakian A, Kennard C, Husain M. Reply to: Using SPM normalization for lesion analysis in spatial neglect. *Brain* 2004; 127: E11.

Nikulin VV, Kicic D, Kahkonen S, Ilmoniemi RJ. Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. *Eur J Neurosci.* 2003; 18:1206-12.

Nobre AC, Coull JT, Walsh V, Frith CD. Brain activations during visual search: contributions of search efficiency versus feature binding. *Neuroimage* 2003; 18: 91-103.

Nobre AC, Sebestyen GN, Gitelman DR, Mesulam MM, Frackowiak RSJ, Frith CD. Functional localisation of the system for visuospatial attention using positron emission tomography. *Brain* 1997; 120: 515-33.

Pascual-Leone A, Gomez-Tortosa E, Grafman J, Always D, Nichelli P, Hallett M. Induction of visual extinction by rapid-rate transcranial magnetic stimulation of parietal lobe. *Neurology* 1994; 44: 494-98.

Robertson IH. Cognitive rehabilitation: attention and neglect. *Trends Cogn Sci* 1999; 3: 385-93.

Robertson, IH, Marshall JC. *Unilateral Neglect: Clinical and Experimental Studies*. Hove, UK: Lawrence Erlbaum; 1993.

Stewart LM, Ellison A, Walsh V, Cowey A. The role of transcranial magnetic stimulation (TMS) in studies of vision, attention and cognition. *Acta Psychol (Amst)* 2001; 107: 275-91.

Tipper SP, Behrmann M. Object-centred not scene-based visual neglect. *Neuropsychol Rehab* 1996; 6: 19-25.

Treisman, AM & Gelade G. A feature-integration theory of attention. *Cognit Psychol* 1980; 12: 97-136.

Vallar G. Extrapersonal visual neglect and its neuroanatomy. *Neuroimage* 2001; 14: 52-8

Vallar G, Perani D. The anatomy of unilateral neglect after right-hemisphere stroke lesions: A clinical/CT-scan correlation study in man. *Neuropsychologia* 1986; 24: 609-22.

Walker R, Husain M, Hodgson TL, Harrison J, Kennard C. Saccadic eye movements and working memory deficits following damage to human prefrontal cortex. *Neuropsychologia* 1998; 36: 1141-59.

Walsh V, Cowey A. Transcranial magnetic stimulation and cognitive neuroscience. *Nat Rev Neurosci* 2000; 1: 73-79.

Walsh V, Ellison A, Battelli L, Cowey A. Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5. *Philos Trans R Soc Lond B Biol Sci* 1998; 265: 537-43.

Wasserman EM. Risk and safety of repetitive Transcranial Magnetic Stimulation: report and suggested guidelines from the International workshop on the safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol* 1998; 108: 1-16.

Figure Legends

Figure 1.

The Landmark Task arrays. Subjects were asked to decide which side of a bisected line was longer, or which was shorter. In one-third of trials lines were bisected centrally.

Figure 2.

The visual search tasks. In the 'easy feature' search the target was a white slash (/) amongst white backslashes (\). The 'hard feature' search was for a white L shape amongst rotated white L shapes. The 'hard conjunction' (orientation and colour) search target was a red slash (solid /) amongst red backslashes (solid \) and green slashes (broken /).

Figure 3.

The 3 x 3 grid used to functionally localise right PPC using the hard conjunction search task and the resultant position in each subject.

Figure 4.

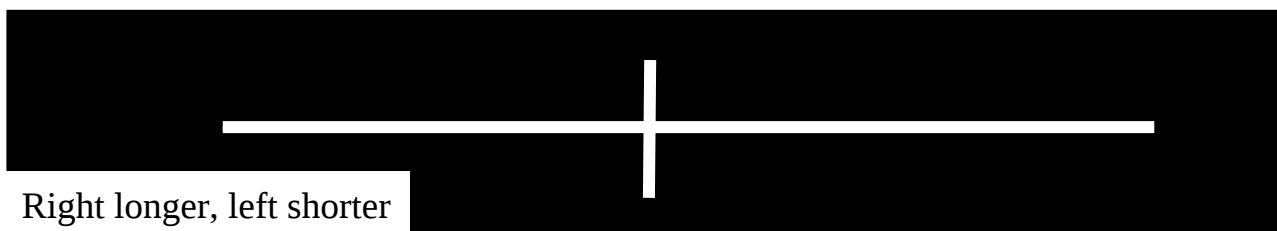
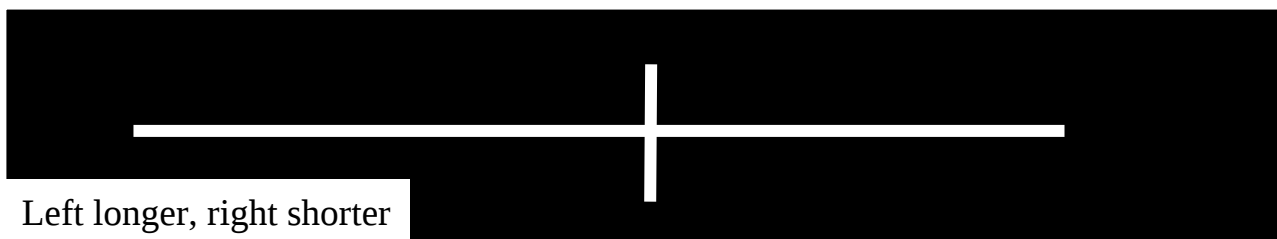
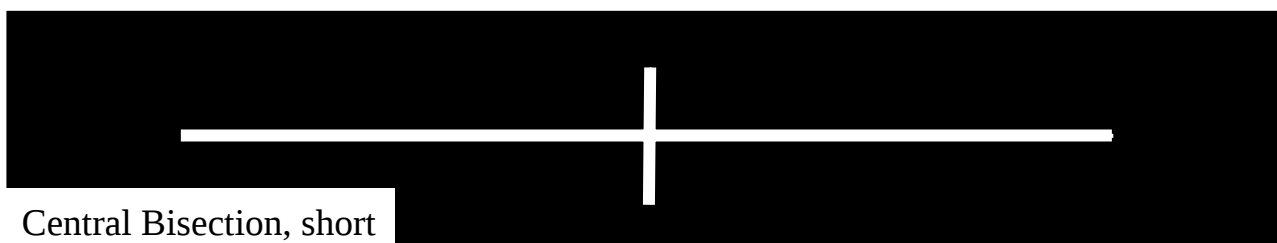
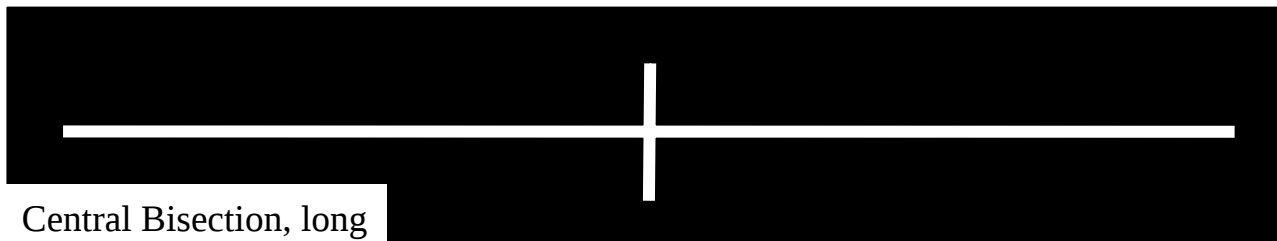
Stimulated areas were localised using each subjects' MRI scan co-registered to their skull co-ordinates using BrainSight™ software.

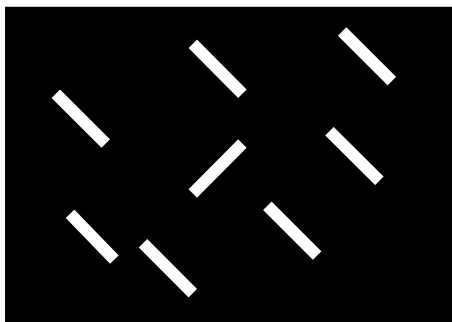
Figure 5.

Response patterns when the line was bisected in the landmark task. Only TMS over right PPC induces contralateral neglect-like effects.

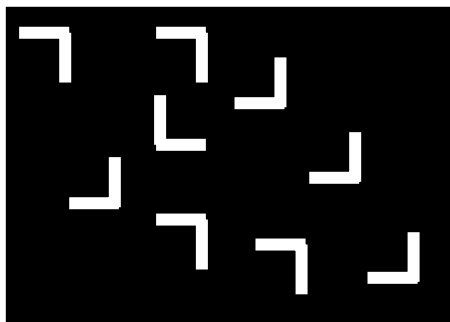
Figure 6.

Effect of TMS on reaction time in the visual search tasks. TMS over right STG causes a significant increase in reaction time in the hard feature search. TMS over right PPC causes a significant increase in reaction time in the hard conjunction search task.

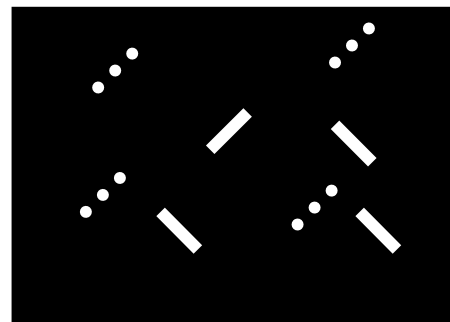




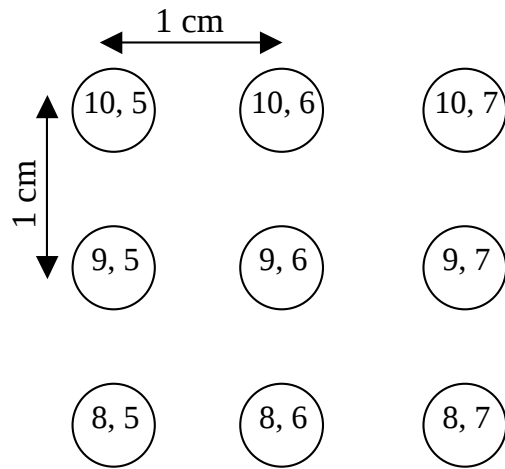
easy feature



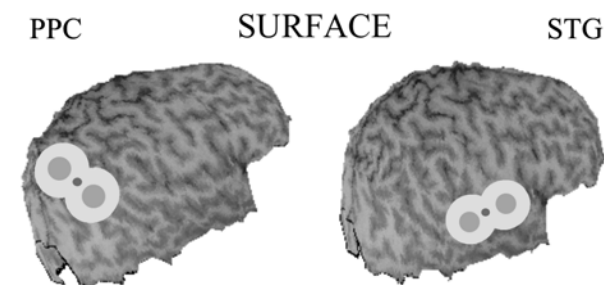
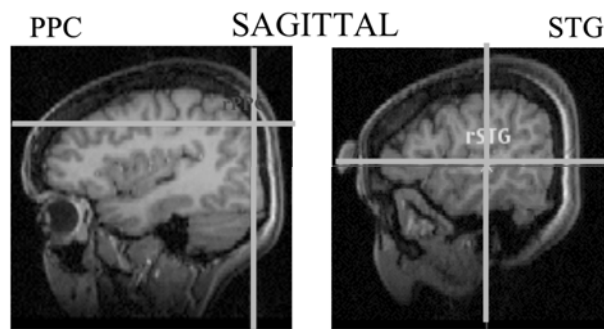
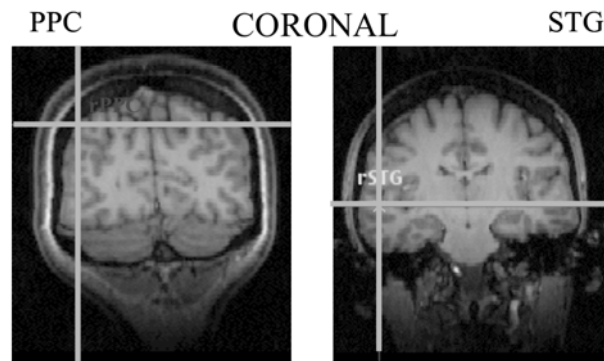
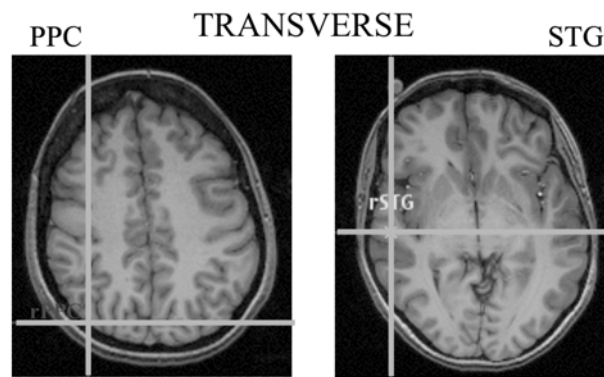
hard feature



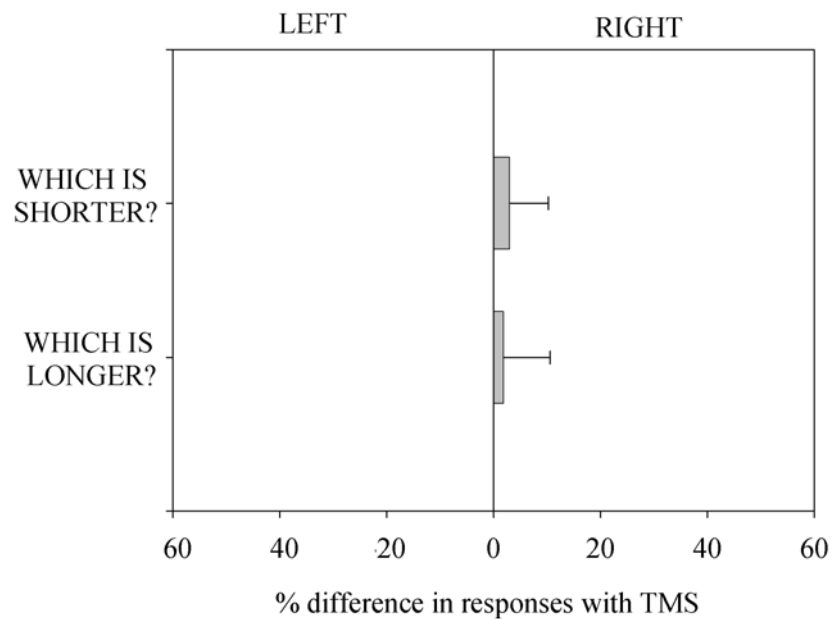
hard conjunction



subject	dorsal	lateral
1	9cm	6cm
2	9cm	6cm
3	8cm	5cm
4	9cm	7cm
5	9cm	6cm



Effect of rSTG TMS on % responses
in the landmark task with bisected lines



Effect of rPPC TMS on % responses
in the landmark task with bisected lines

