Understanding the neural basis of hemispatial neglect symptoms: an investigation in normal subjects

Pattison, Lara

Pattison, Lara (2005) *Understanding the neural basis of hemispatial neglect symptoms: an investigation in normal subjects*, Durham theses, Durham University. Available at Durham E-Theses Online: http://etheses.dur.ac.uk/2253/

Understanding the neural basis of hemispatial neglect symptoms: an investigation in normal subjects

Lara Pattison

MSc 2005

Durham University

Department of Psychology

Acknowledgements

I would like to thank my two supervisors; Professor David Milner and Dr. Rob McIntosh for their guidance and expertise with the thesis. A special thank you to Dr. Amanda Ellison for her encouragement and solid support throughout-you've been a wonderful colleague and friend when I needed it most.

A big thanks must also go to my friends in the Psychology Department who have made it a fun and thoroughly enjoyable place to work.

Last but not least, thank you to my mum, dad and friends for always being at the end of the phone when needed.

INDEX

Page

Abstract

Chapter 1: Introduction

Chapter 2: The role of superior temporal gyrus lesions in neglect-like symptoms: An investigation using transcranial magnetic stimulation.

Understanding the neural basis of hemispatial neglect symptoms: an investigation in normal subjects

Abstract

This thesis 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. In chapter 2, 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. In both cases, however, the deficit was present bilaterally across the search array, in contrast to the search deficits seen in patients with visual neglect, which are typically greater on the contralesional side. In chapter 3 we sought to determine whether it might be possible to induce such contralateral search deficits, using variations on the previous tasks. Experiment 1 required subjects to report the location of the search target (left or right) on each trial. We now found a significant deficit in contralateral search when TMS was applied to the PPC region. Experiment 2 used smaller, structured stimulus arrays, presented briefly to eliminate eye movements and to direct the target item to either the left or right hemisphere. This task was unaffected by TMS applied to either of the two sites. Experiment 3 presented similar small arrays for a longer duration, in either left, central, or right visual space. We found a contralateral within-array ('object-based') deficit when TMS was applied to the STG, whether the array was presented in the left or right hemispace, when a left/right response was required. There was, however, no relative 'hemispatial' deficit when the array was located on the contralateral left side. These results may indicate separate specializations for 'spatial' versus 'within-object' search in the two brain regions studied and are discussed in terms of the neglect and visual search literatures.

CHAPTER 1

INTRODUCTION

1.1 Neglect: The syndrome

Neglect can be an impairment to detect, refer, orient or respond to stimuli presented contralaterally to a cerebral lesion, without any impairment in sensory-motor elementary functions. Many forms of neglect have been described. The underlying mechanism involved in neglect may involve deficits in attention, intention or representation. The distribution of neglect may be personal or spatial. These forms of neglect (attentional, intentional, representational, either spatially or personally distributed) are not mutually exclusive and a patient may have one or more forms of neglect. A patient with extreme neglect may deny that the involved limbs are his/her own or may fail to shave or dress the neglected side. This is known as personal neglect (Kolb and Whishaw, 1996). As the experiments accounted in this thesis concern spatial neglect, a greater consideration of this distribution will be afforded.

1.1.1 Spatial neglect

Spatial neglect can be seen when a patient is asked to perform a variety of visual tasks in space. For example, when asked to bisect a line, they commonly make their mark toward the ipsilesional side of the line. When asked to cancel or cross out stimuli distributed across a page they can fail to cross out lines on the side of the page that is opposite their hemispheric injury. These patients appear to be neglecting a portion of contralateral space and this effect can be seen in a variety of other tasks including; figure copying, drawing from memory, reading and writing tasks. Hence it is most commonly termed unilateral spatial neglect. Spatial neglect is not restricted to the visual modality but occurs in tactile and auditory modalities as well (De Renzi *et al.* 1970; Chedru, 1976). The deficit may even impair their ability to plan contralesional eye movements or manual movements (Behrmann and Meegan. 1998; Behrmann *et al.* 2001).

Spatial neglect may occur in three reference frames: egocentric (body-centred), allocentric (environmentally centred), and allocentric (object-centred). Evidence for coding with respect to the trunk is strong. The midline of the trunk (body-centred reference frame) plays a fundamental role in dividing space into left and right (Karnath *et al.* 1991, 1993, 1996; Chokron and Imbert (1993); and Beschin *et al.* (1997)). In the study by Karnath *et al.* (1991), there was significant amelioration of neglect when the trunk was rotated to the left compared with the baseline condition, however, surprisingly, rotating the trunk to the right did not exacerbate the neglect. Evidence with regard to the role of limb co-ordinates in neglect is controversial. In a tactile study, Bisiach *et al.* (1985) found that manipulating the placement of the right limb had no effect on performance in neglect. However, a more recent study has shown that there is an involvement of limb co-ordinates in neglect but that this involves the spatial position of the limbs in relation to each other (Aglioti *et al.* 1998).

Most research on allocentric reference frames has focused on a reference frame defined with respect to the midline of individual objects in a scene (object-centred) or a reference frame with respect to the midline of a visual scene or environment (environmentally centred). To derive an environment-centred frame, computations regarding gravitational forces, visual input to define landmarks with respect to gravity and information to provide a sense of the body's posture in relation to gravity are required. In recent years, a large body of evidence has accumulated suggesting that spatial position may be coded with respect to the midline of an object. Patients may fail to report information appearing to the left of the object midline, even when this information is located to the right of the midline of the viewer and/or the environment (Driver and Halligan, 1991;Behrmann and Tipper, 1994).

1.2 Mechanisms of unilateral spatial neglect.

It was once believed that neglect in humans was a sensory deficit. Battersby *et al.* (1956) thought that decreased sensory input superimposed on a background of decreased mental function resulted in neglect. Eidelberg and Schwartz (1971) regarded neglect as a passive phenomenon due to quantitative asymmetrical sensory input to the two hemispheres. Evidence against the visual-sensory argument increased as it became apparent that patients may have neglect in different modalities as well (Ladavas and Pavani 1998). Also, neglect can occur quite independently of the existence of hemianopia. Evidence that neglect is a hemispatial deficit was uncovered by Heilman and Valenstein (1979). They asked patients to identify a letter at either the left or right end of a line before bisecting the line. Even when patients were required to look left in order to ensure they had seen the entire line, performance was significantly better when the line was placed in the right hemispace than when it was in the left hemispace. Thus neglect is a hemispatial deficit rather than a hemifield or hemianopic defect. Several mechanisms have been put forward to account for this hemispatial deficit, including deficits in attention, intention and representation.

1.2.1 The attentional hypothesis

Attentional neglect is an unawareness of contralesional stimuli and can include: hemi-inattention, allesthesia, allochiria, anosognosia (with/without somatoparaphrenia or misoplegia), and anos-diaphoria and sensory extinction. There have been at least five attentional hypotheses proposed to explain neglect but they are not necessarily mutually exclusive:

1/ spatial unawareness. This is the result of a patient failing to act in left hemispace because they are unaware of stimuli in left hemispace, shown by patients ignoring targets on the left of a cancellation task because they are unaware of them.

2/ Ipsilesional spatial attentional bias. When one hemisphere is injured, the other becomes hyperactive and attention is biased contralaterally and one is unaware of stimuli in the contralesional hemispace (Kinsbourne, 1970).

3/ Extinction of simultaneous stimuli. When stimuli are presented simultaneously to both left and right hemispace, patients with left neglect will only report having seen the stimulus in right hemispace, however when the stimuli are shown alone to either left or right hemispace the patient can identify both (Anton, 1899; Poppelreuter, 1917).

4/ Inability to disengage from ipsilesional stimuli. Posner (1984) suggested that patients neglect contralesional space because they cannot disengage from ipsilesional space.

5/ Reduced vigilance. Patients may become inattentive to stimuli because they have a rapid loss of vigilance. This can be seen when asking a patient to alternately cancel targets on the left and right of the array. This results in overcoming the right-sided bias but instead of ignoring stimuli on the left the patient ignores stimuli in the centre (Chatterjee, 1992).

1.2.2 The motor intentional hypothesis

Intentional neglect is a failure to act in contralesional space and can include: hemiakinesia, directional hypokinesia, motor impersistence and motor extinction.This theory states that while patients may be aware of stimuli in contralateral hemispace, they still fail to act on these stimuli. There are four forms of intentional deficits.

1/ Hemispatial akinesia. This is a failure to act in contralesional hemispace as shown when asking blindfolded patients to search a maze for a target, they failed to explore the left side of the maze (De Renzi *et al.* 1970).

2/ Directional hypokinesia. Asking patients to close their eyes can identify this. If when they re-open their eyes, they are automatically deviated to the right (gaze bias) then there is an ipsilesional spatial intentional bias (Heilman, 1983a). This is usually defined in terms of limb movements (Heilman et al., 1985).

3/ Motor perseveration. This is an inability for patients to disengage from ipsilesional space and a prime example of this is in cancellation tasks. When performing the cancellation task approximately 40 % of subjects repeatedly cancel the same target (Na *et al.* 1999).

4/ Directional impersistance. This is the intentional equivalent of defective vigilance and can be seen when patients fail to persist in searching for left targets in a cancellation task (Kertesz *et al.* 1985).

1.2.3 Representational hypothesis

Spatial neglect patients may find it difficult to recall perceived stimuli presented in contralesional hemispace. They may also show impairments in recalling stimuli learned before the neurological insult. Evidence of this is shown by the inability of some patients to describe from memory the details of a side of a room that is opposite to a brain lesion (Denny-Brown and Banker, 1954). Bisiach and Luzzati (1978) asked two patients to recall details of a square in Milan. When asked to recall details from one perspective, they neglected details on the left side of the square. However, when asked to recall details from the opposite perspective, the patients found problems recalling details on the left side of the perspective (which were on the right side from the first perspective). Findings like these suggest that neglect patients can have a deficit in body- centred hemispatial memory or imagery.

An organism has to be selective in the stimuli they choose to process, as the capacity to process information in the human brain is limited. Attention is directed in a top-down manner, except for stimuli that will be attended regardless of their significance such as bright lights, moving objects etc. Therefore the selection process is largely directed by representations and knowledge. In order to perform a spatial task, the target has to be represented independent of its location in space and a representation of the environment is also needed. The fact that neglect patients ignore stimuli on the left cannot be attributed to a loss of the representation of the target (as seen in cancellation tasks where patients are able to detect stimuli on the right). Attention may not be directed to left space because the patient has no knowledge of space (representations in the right hemisphere are destroyed and this is where the knowledge of left space is stored). This can be applied in the same way to mental representations that direct action. Therefore, both attentional and intentional deficits can be induced by a deficit in representation.

1.3 Neural basis of spatial neglect

The incidence of spatial neglect is not clearly shown in the literature. While Denes *et al.* (1982) reported a 17 % rate of occurrence of unilateral spatial neglect in right cerebrovascular accident patients (CVA); Stone et al. (1993) reported that 80 % of right CVA patients demonstrated unilateral spatial neglect. Since the early studies of neglect patients conducted by Brain (1941), it was thought that unilateral visual spatial neglect was largely a manifestation of right hemisphere damage. It is now widely acknowledged that left neglect after a right hemisphere stroke is the most common (Stone *et al.* 1993; Bowen *et al.* 1999; Colombo *et al.* 1982). It is possible however to find patients with right neglect after a left hemisphere stroke (Dronkers and Knight, 1988) and right neglect after a right hemisphere stroke (Robertson et al., 1994). Neuropsychological testing has shown that left neglect is more severe than right neglect (Denes *et al.* 1982) and severity of neglect increases with lesion size (Levine *et al.* 1986).

1.3.1. Neuropsychology

A large body of work regarding the anatomy underlying spatial neglect has been explained from studies involving hemispatial neglect patients. While studying the pattern of deficits in hemispatial neglect patients leads us to certain conclusions about the functions of damaged tissue, this approach has limitations. Brain lesions are often large and widespread, locations of lesions are not systematic and it is not known what the patients' attentional baseline was before the onset of impairment. Due to the disruption of neural connections, damage to one brain area can affect the functions of another. In addition, testing of such patients may occur many years after the causative neurological insult, so that often considerable compensatory rewiring may have occurred. Complementary techniques such as neuroimaging, electrophysiological techniques and disruptive techniques are useful in that they investigate a regions function in the normal processing of tasks.

1.3.2 Methods used to investigate neural processing

Recording techniques

Neuroimaging

The history of modern brain imaging began in the 1970s with computed tomography (CT) and proceeded at a rapid rate throughout the rest of the twentieth century.
The activity of any given area of the brain entails a change in the local cerebral blood flow. This increase can be detected by the method of Positron Emission Tomography (PET). The technique is based on the introduction of a radioactive tracer that is carried by the blood to the most active areas of the brain and is detected as they decay. Although the spatial resolution of the brain scans obtained are low (~8mm), the technique is however able to show active regions of the cerebral cortex and can therefore differentiate the parts of the cortex that are active in certain conditions; in other words, it is a powerful tool for functional localisation in the cerebral cortex. One of the most successful applications of PET was the mapping of the extent and topographical disposition of the primary visual cortex in the human brain (Fox *et al.*, 1986). It can show all cerebral areas which are active at any given time during a scan. It can therefore analyse the entire system or subsystem in the cerebral cortex.

Magnetic resonance imaging (MRI) is based on manipulation of magnetic fields and application of radio waves, which then emit radio signals. Atoms are first aligned by a strong static magnetic field, then knocked out of alignment by a radiofrequency pulse, and then allowed to realign. The fluctuating field created as the atoms relax to the aligned state is the signal that is measured. Standard MRI can give a high-resolution static 3-D image of the brain, but in addition the technology can be used to measure the functional activity of the brain. Early functional MRI used an injected contrast agent, more recent methods use the magnetic properties of the blood itself as a tracer, and therefore are entirely non-invasive. The spatial and temporal resolution of fMRI are limited by the dynamics of the blood; blood flow changes over seconds in response to neural activity, and these changes extend into nearby tissue. In practice, fMRI has a spatial resolution of 1 mm and a temporal resolution of approximately 1 s, which is adequate to distinguish among psychologically meaningful differences in brain activity (Aguirre, 2003).

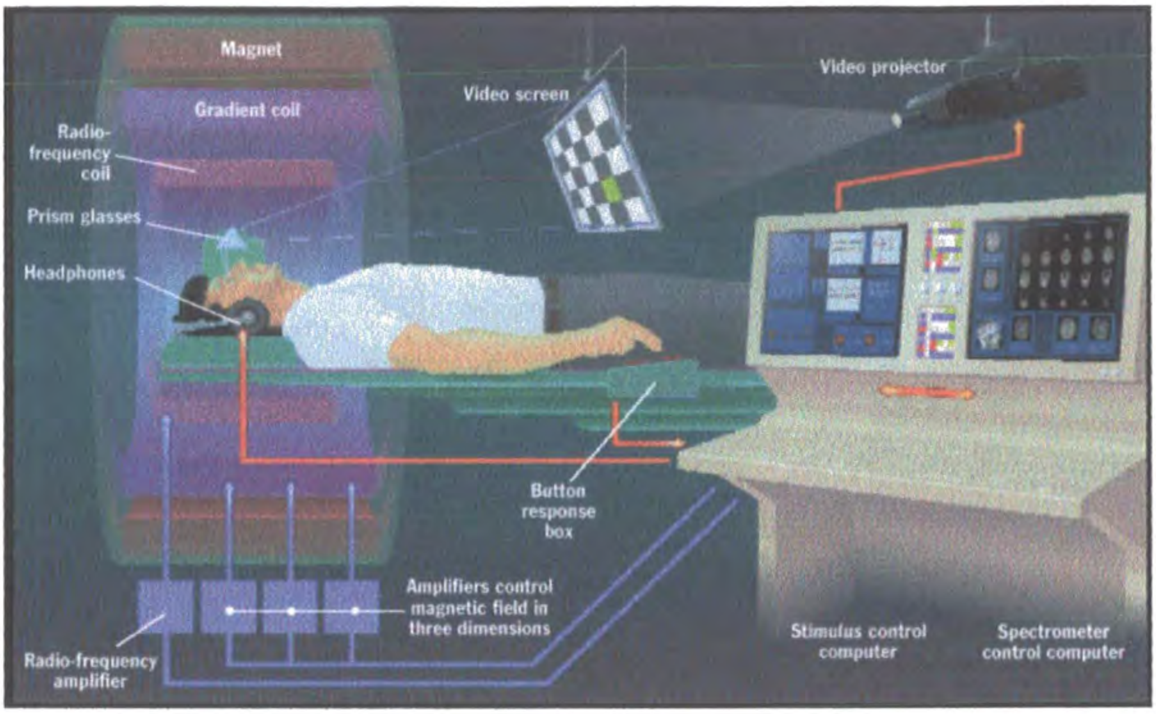


Figure 1.1: fMRI set-up. Only the head is placed in the magnetic field to maintain uniformity. The three orthogonal weak magnets are adjusted to make the magnetic field as homogeneous as possible.

Electrophysiological techniques

The electrical activity of the brain can be recorded from scalp electrodes by the technique commonly called the electroencephalogram or EEG. In an experimental refinement of this method, a stimulus is presented, and the electrical activity following it is recorded. If many trials are averaged together, only the electrical activity that is produced by the stimulus remains. This electrical activity produced by the stimulus is called the event-related potential (ERP). Recording of event-related potentials from the scalp of humans is one method for obtaining detailed information about the duration and sequence of activity.

Disruptive techniques

Transcranial magnetic stimulation (TMS)

TMS is a relatively new method for the non-invasive stimulation of nervous tissue. Magnetic stimulation causes neurons to become depolarised and fire action potentials. If this occurs in motor cortex, it will cause the corresponding part of the body to move. If the primary visual cortex is stimulated it will cause the appearance of phosphenes (flickers of light) in the visual field (Meyer *et al.*, 1991). Stimulation of secondary cortex leads to disruption in function, as the already depolarised neurons cannot respond to the visual or motor stimulus. Therefore, TMS can be used to transiently create ‘virtual’ neuropsychological patients by safely and reversibly disrupting the function of a selected brain area.

The scientific basis of TMS is Faraday’s property of electromagnetic induction in which current flowing in a primary circuit (the magnetic coil) would cause an electrical current to flow in a nearby secondary circuit (nervous tissue). It has been known since the work of Galvani and Volta in the 1790’s that neuromuscular tissue could be stimulated by externally applying electrical current but it was another one hundred years before D’Arsonaval used time-varying magnetic fields to report the phenomenon of magnetophosphenes, observed by participants with their heads placed in such a field (see figure 1.2). Silvanus P. Thompson continued working on the properties of this phenomenon in 1910, exposing volunteers’ heads to peak fields of 140 mT at frequencies of 50 Hz (see figure 1.3)

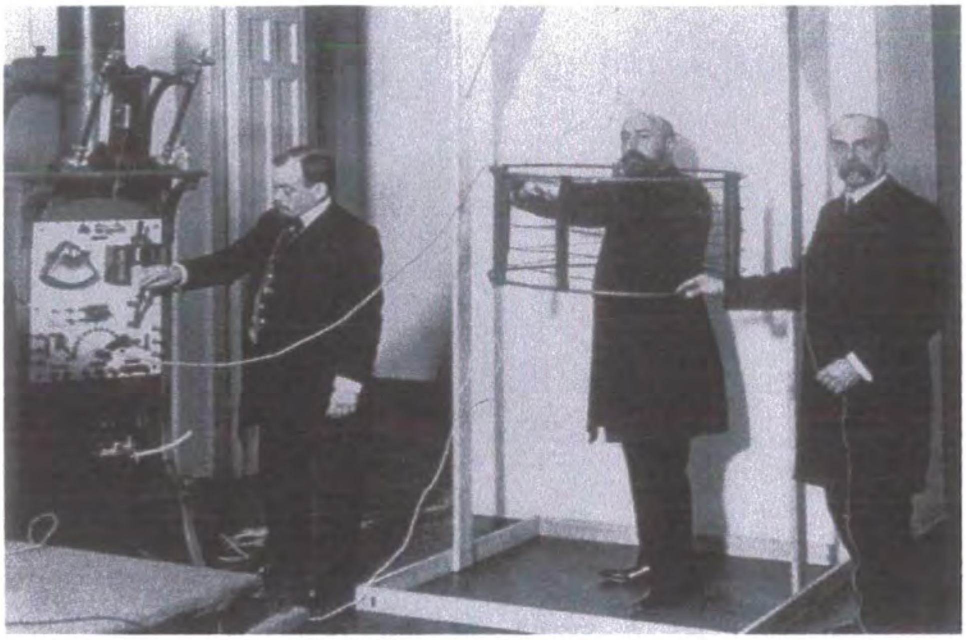


Figure 1.2: D'Arsonval performs painless stimulation of the nervous system by electromagnetic induction.

Figure 1.3: Silvanus P. Thompson attempting to electromagnetically stimulate his brain in 1910.

The use of TMS, in the investigation of the visual cortex was pioneered by Amassian *et al.* (1989), who showed that a subjects' performance was impaired when a magnetic pulse was administered to the visual cortex between 60 and 140 ms after the onset of the visual stimulus thus creating a temporary functional lesion. Since then, a number of studies have used both single pulse and repetitive pulse TMS to investigate neurological deficits (Pascuale-Leone *et al.*, 1994; Walsh *et al.*, 1998; Pourtois *et al.*, 2001). The advantage of TMS is that it is a safe way of producing focal, transient neural disorder in a localised area during the performance of cognitive tasks. Because the effects are reversible and instantaneous, the role of a particular brain function in a particular behavioural task can be established without the possibility of neural compensation occurring. Another advantage of TMS is that it has the spatial resolution of fMRI and the temporal resolution of EEG (see figure 1.4).

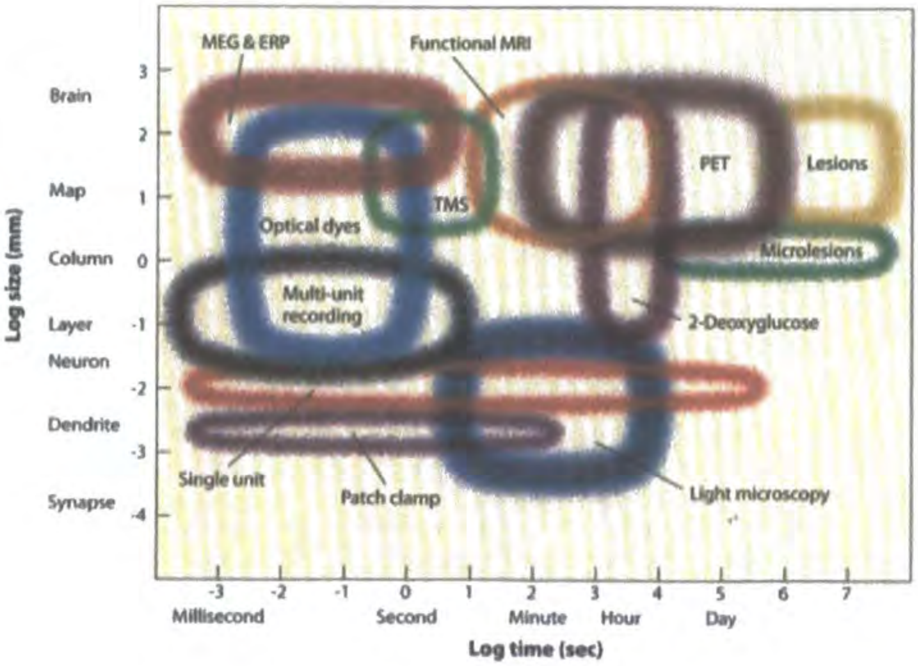


Figure 1.4: A comparison between TMS and other techniques

Functional connectivity and excitability of neuronal tissue are key in defining and understanding how the central nervous system works and TMS helps us better understand how the brain is organised in the normal functioning brain and in various diseases. Using Brainsight, we have the ability to co-register the subjects MRI scans with their scalp co-ordinates in order to locate the exact region of interest. Brainsight-frameless is a stereotactic image guidance system that facilitates the positioning of transcranial magnetic stimulator coils over a subject's brain. It can display the coil and targets (derived from MRI images) on anatomical MR images, providing an interactive navigational guide for coil positioning (see figure 5a). Figure 5b shows the TMS set-up.

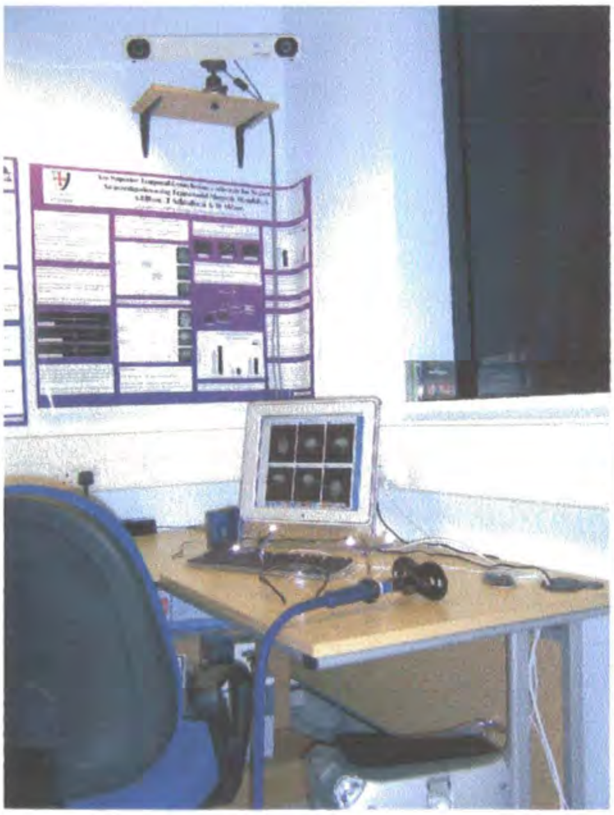


Figure 1.5a: Brainsight

Figure 1.5b: Magstim model 200. Trigger pulses from the coil initiate brief magnetic pulses

1.3.3 Spatial neglect: A parietal syndrome?

Traditionally, hemispatial neglect was referred to as a 'parietal syndrome' (Heilman *et al.* 1970; Heilman and Valenstein 1972; Vallar and Perani, 1986). Neglect-causing lesions have been reported in many different parts of the posterior parietal lobe. Based on studies of unselected middle cerebral artery (MCA) patients, the crucial cortical area most commonly associated with neglect is the inferior right posterior parietal lobe and in particular the temporo-parietal junction (TPJ) (Vallar and Perani, 1986; Leibovitch *et al.* 1998; Vallar, 2001; Mort *et al.* 2003). Clinical studies using patients with cortical lesions suggest that the posterior parietal cortex (PPC) is involved in the representation of visual space (Bisiach and Luzzatti 1978; De Renzi 1982;Vallar 2001). After a stroke that involves the PPC, the conception of space completely alters for a patient. This may result in the contralateral half of visual space shrinking and the ipsilateral side of space dilating. Even if an object can still be clearly recognised, its location in the field of view can appear distorted (Milner, 1987).

Perhaps the most used method for diagnosing the presence and severity of spatial neglect in patients is the line bisection task. Line bisection is a simple task in which the patient is asked to mark where they believe the centre of a horizontal line to be (see figure 1.6). Patients with PPC lesions bisect horizontal lines to the right of centre (Heilman, 1983). This has been attributed to patients perceiving linear extents in the left half of egocentric space as shorter than equivalent extents in the right half of space (Milner *et al.* 1993; Milner and Harvey, 1995).

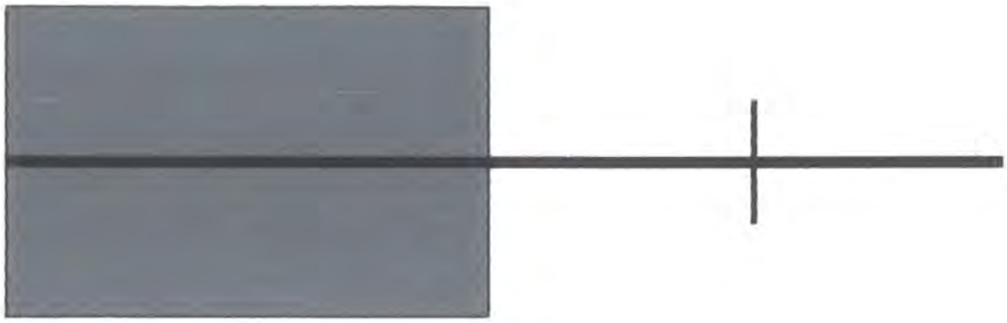


Figure 1.6: Shows the line bisection task. The grey portion represents the section neglected by the patient.

An ERP study in normal participants showed right hemisphere lateral occipital, inferior parietal and superior parietal areas were generators of activity in the line bisection task (Foxe *et al.* 2003). The latency of stimulus processing and contributions from parvocellular and magnocellular inputs were manipulated. It was shown that the line bisection effect systematically tracks the latency of the N1 component, which is considered a temporal marker for object processing in the ventral stream, suggesting this task involves an object-based form of visuospatial attention (Foxe *et al.* 2003). Fink *et al.* 2003 induced distortion of the egocentric reference frame through galvanic vestibular stimulation (GVS) while performing allocentric visuospatial judgements (line bisection) to investigate the neural mechanisms behind GVS and spatial frame reference computation using fMRI. Activation of the right posterior parietal and ventral premotor cortex reflects the increased processing demands when compensating for the distorted egocentric spatial reference frame while maintaining accurate performance during the allocentric spatial task. These results suggest that the right posterior parietal cortex and right ventral pre-motor areas are involved in the computation of spatial reference frames.

A perceptual version of the traditional line bisection paradigm is provided by the landmark task. Here, a subject is asked to make judgements about whether pre-bisected lines are bisected to the right or left 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 (Bisiach *et al.* 1998; Milner *et al.* 1998). Imaging studies with normal participants have shown increased neural activity in inferior parietal lobes when performing the landmark task (Fink *et al.* 2002). In healthy subjects, transient disruption of right PPC by repetitive transcranial magnetic stimulation (rTMS) provokes impairment on the landmark task, similarly to that found in structural lesions to that area (Fierro *et al.* 2000; Bjoertomt *et al.* 2002). Likewise, left posterior parietal TMS stimulation in left neglect patients ameliorated contralesional visuospatial neglect when performing the landmark task (Brighina *et al.* 2003).

Chiba *et al.* (2005) used a verbal and manual line bisection task as a new method of dissociating sensory attentional and motor intentional aspects in unilateral neglect patients. They found that patients with a large rightward bias in the verbal task but not in the manual task had impaired sensory attentional functions, rather than motor intentional functions. This supports the hyper rightward attention theory (Kinsbourne, 1970) and the impaired shifting attention theory (Posner *et al.*, 1987). Patients with large bisection errors in the manual task but not the verbal task had damage to motor intentional functions, rather than sensory attentional functions. This supports the directional hypokinesis hypothesis in which patients have an inability to make arm movements into left space while still able to attend stimuli in their left hemifield (Heilman and Valenstein, 1979). Some patients showed increased rightward deviation in both the verbal and manual tasks, indicating the co-existence of both attentional and intentional deficits in the same patient. They found that 10 out of the 12 patients with motor-intentional neglect had lesions to the pre-rolandic and subcortical areas, consistent with previous literature (Bisiach *et al.* 1990). Seven out of 11 of the patients with sensory attentional neglect had lesions to the post-rolandic areas, also consistent with previous literature (Mesulam, 1981). However 4 out of the 11 subjects did not show attentional neglect, despite having post-rolandic lesions and 2 out of the 12 patients with pre-rolandic lesions did not show motor-intentional neglect. The dichotomy therefore holds in the broad sense but there are exceptions.

It is thought, on the basis of fMRI studies that the inferior parietal lobe is responsible for the focalizing and fixating of attention (Vandenberghe *et al.* 2001). A traditional method of testing this ability in neglect patients is the cancellation task. Cancellation tasks are most commonly administered as pencil and paper tests that are used to assess ability to visually search for an identifiable target and to either cancel or circle all such target items in an array. They may be as simple as bisecting lines on a page (Albert, 1973) or they may include simple symbols such as the star cancellation task (as shown in figure 1.7), or they may involve more complex arrays such as the Bells Test (Gauthier *et al.* 1989). Scoring of cancellation tests is commonly based on the error scores (both omissions ('misses') and commissions ('false alarms')), the time taken to complete the task or the region in which most errors were made.

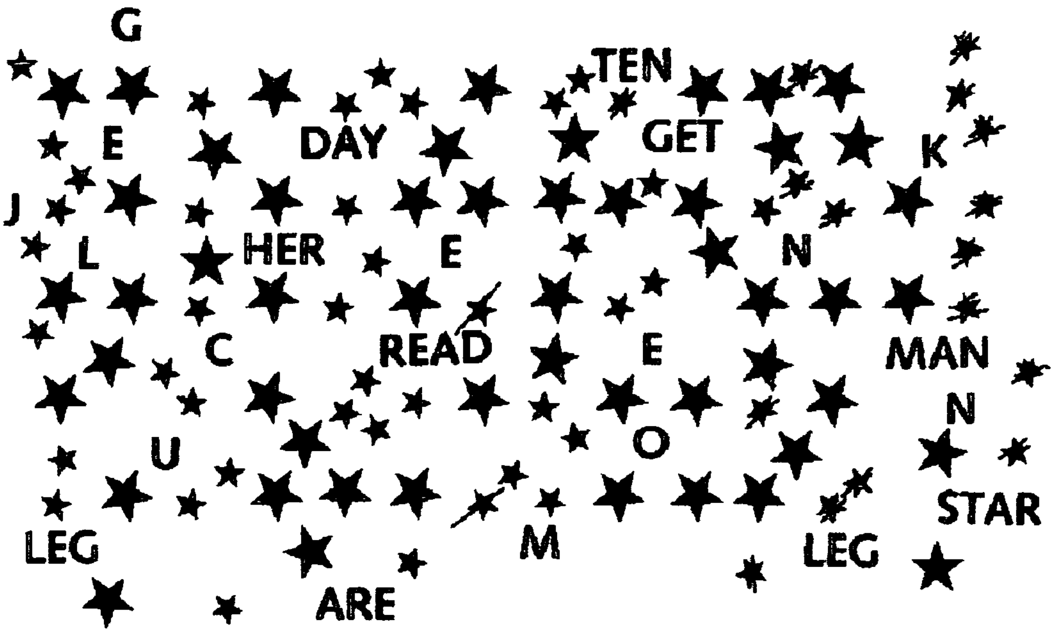
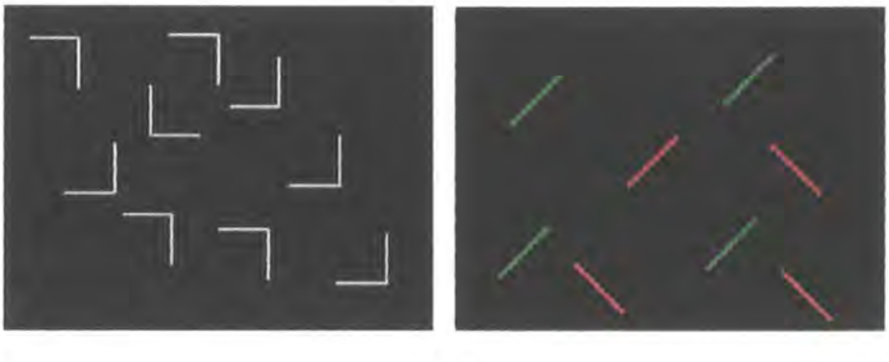


Figure 1.7: Star cancellation. The two marked central stars are cancelled by the experimenter, as an example for the patient. Here, the patient only cancels stars on the right hand side of the page.

Patients with spatial neglect often fail to cancel targets following a recognizable pattern, they move from target to target erratically (Gauthier *et al.* 1989), show a strong tendency to start their cancellation performance on the right (Jalas *et al.* 2002), and have a tendency to ignore targets in left hemispace and repeatedly cancel targets in the right hemispace. Neglect patients explore and cancel targets further into their contralateral side when there are fewer visual stimuli (Chatterjee *et al.* 1999).The extent of disorganisation during cancellation tasks can depend on the extent to which the targets themselves are spatially organised (Weintraub and Mesulam, 1988). Mannan *et al.* (2005) found that damage including the intra-parietal sulcus or right inferior frontal lobe tends to result in re-examining previously searched locations in a visual search task unlike damage to occipito-temporal lesions. Probability of re-examining items increased with time since first discovering it in intraparietal sulcus patients whereas for frontal patients it was independent of time. A new variant of the cancellation task in which invisible marks were made revealed neglect of contralesional targets was more pronounced with invisible marks and stronger neglect of contralesional targets correlated with more re-visits to ipsilesional targets for making additional invisible marks upon them (Wojciulik *et al.* 2004). This suggests that demands on spatial working memory (which is required to keep track of previously found items only when marked invisibly) can exacerbate spatial neglect due to failures in remembering locations that have already been searched (Malhotra *et al.* 2004). When spatial working memory deficits are found in neglect patients damage is seen in the right parietal lobe and insula (Malhotra *et al.* 2005). Visuo-spatial working memory can also provide a framework for interpreting aspects of representational neglect, with or without personal neglect (Beschin *et al.* 1997).

Another way to investigate the lesioned brains ability to focalise and fixate attention is the use of visual search tasks. These paradigms have been used extensively to characterize hemispatial neglect. Feature Integration theory was created to explain how we do the task of visual search. Visual search involves individuals searching for a pre-defined target in a display containing multiple items. One can construct the following four distinct search tasks: 1/ Parallel (easy) feature; 2/ Serial (hard) feature; 3/ parallel (easy) conjunction and 4/ serial (hard) conjunction (see figure 1.8). Parallel searches are the simplest form of visual search as they don't require attention and are therefore known as 'pre-attentive'. Search tasks where the target is not unique and is made up of a conjunction of features also present elsewhere in the array require binding of features in order to be processed. These are known as serial search tasks and denote an attentional spotlight which is required for feature integration of conjunction search (Wolfe, 1994). Right hemisphere patients with left hemifield neglect often demonstrate abnormal visual search, re-examining stimuli to the right while ignoring those stimuli to the left (Mannan *et al.* 2005). Patients show hyperattention or a stronger bias to allocate attention to the most ipsilesional items (D'Erme *et al.* 1992). Eye movement studies have shown that neglect patients make fewer ipsilesional than contralesional saccades, are slower to initiate leftward saccades, make multiple saccades to locate the contralateral target, have prolonged search times for ipsilesional targets and adopt a rightward position for starting their visual exploration (Chedru, 1976; Duhamel *et al.* 1992; Ishiai *et al.* 1987,1992; Walker and Findlay, 1996). Kristjansson *et al.* (2005) examined priming of visual search by repeated target location or colour in patients with left visual neglect following strokes to the inferior parietal lobe. Patients showed intact priming even when a return of fixation back to display-centre was required between successive trials. This study demonstrates intact priming of visual search by colour and location in patients with right parietal damage meaning that a spared area is responsible for priming.



a b

Figure 1.8a shows a hard feature task **b** shows a hard conjunction task

While there is a large body of work in normal brain studies supporting the roles of intraparietal sulcus (IPS)-superior parietal lobule (SPL) and frontal eye field (FEF) in visual attention (Corbetta, 1998; Corbetta *et al.* 1998; Luna *et al.* 1998; Nobre *et al.* 2000), there is much less support that these are the particular areas involved in patients with unilateral spatial neglect. As previously stated, the parietal region most commonly damaged in neglect patients is the inferior parietal lobule (Vallar and Perani, 1986). In fact, patients with lesions to the IPS more commonly show optic ataxia and rarely show neglect. There is therefore a discrepancy between the location of parietal areas active during visuospatial tasks, and the location of lesions that cause neglect. However, the possibility that damage to IPL can modulate activity in SPL cannot be discounted.

1.3.4 Other substrates

Small lesions confined to parietal cortex rarely cause conspicuous neglect. Even neglect in the context of parietal damage usually indicates an extended subcortical lesion. Clinical reports have shown that almost identical behavioural deficits can arise after cortico-subcortical lesions to the frontal lobes (Damasio *et al.* 1980), temporal lobes (Samuelsson *et al.* 1997) and subcortical lesions of the cingulate gyrus (Watson *et al.* 1973), basal ganglia (Ferro *et al.* 1987) and thalamus (Watson and Heilman, 1979; Rafal and Posner, 1987) as well as damage to the parietal lobe (Vallar and Perani, 1986). Until recently, studies indicating temporal involvements in neglect were restricted to studies that reported visuospatial neglect highly associated with large lesions, converging on the middle temporal lobe and/or the temporo-parietal paraventricular white matter. Ptak and Valenza (2005) have shown that patients with inferior temporal damage show impaired visual search. Involvement of the parietal lobe did not predict the degree of distractibility in visual search. Neglect patients with high distractibility showed damage to the inferior temporal lobe suggesting a role for this region in competitive attentional processes involved in visual search. Absence of neglect symptoms was, however, a common finding following lesions to these brain areas, indicating a rather weak association between neglect in these structures (Samuelsson *et al.* 1997).

Recently, a controversial paper by Karnath *et al.* (2001) suggested that the crucial locus of brain damage that causes neglect symptoms was not in the posterior parietal lobe at all but in the middle of the superior temporal gyrus (STG). This study has caused a re-evaluation of the neural substrate for spatial neglect. Karnath *et al.* (2001) used a different approach than was used in previous neglect studies in that they only included 'pure neglect' cases, that is, only patients without visual field defects. They found that the centre of lesion overlap in neglect patients was the superior temporal gyrus (STG). They also found no evidence for a predominant involvement of the inferior parietal lobe (IPL), the temporal-parietal-occipital (TPO) junction, cingulate gyrus or the middle temporal gyrus. Previous reports on lesion location have included cases of patients who not only suffered from neglect but of hemianopia also (Vallar and Perani, 1986). This original study by Karnath *et al.* (2001) has 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). The study by Mort *et al.* (2003) reconfirmed the traditional findings by including hemianopic neglect patients.

It would seem then that these results would exclude each other, however, instead of supporting the idea that there is one cortical area associated with neglect, they suggest the possibility that there are at least two areas depending on the presence or absence of hemianopia as well as on the functional definition of neglect by the screening tasks used. It would seem that different tasks tap into different mechanisms of spatial attention. In the study by Karnath *et al.* (2001), screening was strongly biased towards tasks involving visual search such as cancellation and scene copying. In contrast, the patients studied in Mort *et al.* (2003) were assessed in a more traditional way using both line bisection and cancellation tasks.

Since Karnath and colleagues' study, a number of studies have been performed to pinpoint the exact underlying mechanism and substrate of both the cancellation and line bisection tasks. It has been suggested that the cancellation task is sensitive to motor-intentional neglect, whereas the line bisection task is sensitive to sensory attentional neglect (Coslett *et al.*, 1990; Bisiach *et al.*, 1990). Although these studies could dissociate attentional from intentional neglect, they couldn't be used to compare line bisection performance with cancellation performance. Na *et al.* (1998) developed a method to dissociate attentional and intentional neglect in both the line bisection and cancellation task. There were three distinct groups of patients; those with attentional neglect in both the line bisection and the cancellation task showed lesions in the parietal lobe, those with intentional neglect in both the line bisection and cancellation task showed lesions in anterior and subcortical regions and patients with intentional neglect in the line bisection task but attentional neglect in the cancellation task showed anterior lesions.

Reports of double dissociations between line bisection and cancellation task in neglect patients suggest fundamental differences in the tasks' respective demands on selective and sustained attention. Studies of anatomy underlying line bisection errors have consistently included patients who exhibited cancellation deficits perhaps resulting in the believed area involved as being more anterior than it actually is. Likewise, spatial neglect may have been mislocalized posteriorly by including a separate group of patients who exhibit line bisection deficits. Rorden *et al.* (in press) used a subtraction technique that codes the relative incidence of damage specific to line bisection errors. They found the centre of overlap to be at the junction between middle occipital gyrus and middle temporal gyrus. They therefore speculated that the dorsal intraparietal lobe (IPL) was the best predictor of line bisection deficits, rather than the TPJ. All these areas implicated comprise a large-scale network involved in spatial attention. It is therefore possible that neglect is a syndrome of this network as a whole and its complexity reflects the clinical heterogeneity of neglect.

In the following studies, I will be using tasks involved in the diagnosis of neglect as an indicator of functions in the normal brain using Transcranial Magnetic stimulation (TMS). This may aid dissociation between task and area of involvement in the brain, delineating some of the issues prevalent in the neglect literature.

CHAPTER 2

THE ROLE OF SUPERIOR TEMPORAL GYRUS LESIONS IN NEGLECT-LIKE SYMPTOMS: AN INVESTIGATION USING TRANSCRANIAL MAGNETIC STIMULATION.

2.1 Introduction

The aim of this study was to investigate the claim by Karnath *et al.* (2001) that the main locus of neurological damage in neglect patients is right superior temporal gyrus (STG) and not right posterior parietal cortex (PPC). As previously mentioned in chapter 1, it is necessary to consider that there are two areas involved, depending on the presence or absence of hemianopia as well as on the functional definition of neglect by the screening tasks used. In the study by Karnath *et al.* (2001), neglect screening involved tasks associated with visual search (cancellation and scene copying), and excluded line bisection. This study tests the functional role of right STG using line bisection as well as a visual search paradigm. We use the perceptual version of the line bisection task: the landmark task.

As previously mentioned in chapter 1, modified versions of the landmark task in healthy subjects has shown that such visuospatial judgements activate inferior parts of the right posterior parietal cortex as well as more superiorly along the intraparietal sulcus (IPS) (Fink *et al.* 2000). Thus, the inferior right PPC is involved with spatial processing, as tapped by the landmark task. It is however possible that the IPS activation was caused by the scanning eye movements needed in the landmark task. It has already been shown that it is possible to induce similar contralateral effects on the landmark task in healthy subjects using repetitive pulse TMS (rTMS) over right PPC (Fierro *et al.* 2001), and that this is restricted to near space (Bjoertomt *et al.* 2002). If, then, rTMS to the right STG results in similar neglect-like symptoms in the landmark task, clear support would be provided for the theory put forward by Karnath and colleagues (Karnath *et al.* 2001).

It is well documented that neglect patients show difficulty with exploratory search (Mannan *et al.* 2005; D'Erme *et al.* 1992). One way to investigate this deficit is to use visual search tasks. Based on visual search studies in normal subjects, assumptions can be made as to how the neglect syndrome may affect the processing of visual search tasks. If neglect is merely a deficit of attention then neglect patients should perform at a similar rate as normal subjects in a feature search (pre-attentive) task. In comparison, neglect patients should perform worse than controls for conjunction search tasks when the target appears on the contralateral side. To investigate this, we carried out a second experiment in which we sought to test the involvement of the right STG in visual search tasks. The involvement of right PPC in such tasks is widely known, with TMS evidence arguing strongly for its critical involvement being in the processing of conjunction items in space (Ellison *et al.* 2003). Other evidence, however, including functional MRI data has suggested that the critical determinant of brain processing in visual search tasks was defined by the difficulty of the search, and thus the attention required for its processing. It has therefore been suggested that it is this difficulty aspect that involves right PPC (e.g. Nobre *et al.* 2003).

The problem with previous discussions of visual search is that that there is a conflation between 'difficult/easy', 'serial/parallel', and 'conjunction/feature' search tasks. The search stimulus used, however, is not 100 % correlated with the search pattern required to find it. Four distinct search tasks can be constructed: 1/ parallel (easy) feature; 2/ Serial (hard) feature; 3/ parallel (easy) conjunction; and 4/ serial (hard) conjunction. It is therefore possible to have feature search arrays that require a serial search and conjunction search arrays that require only parallel search (Ellison *et al.* 2003). With regard to the literature concerning neglect and visual search, it is agreed that 'the binary distinction between preattentive/featural and attentive/conjunction processing does not obviously hold in neglect' (Behrmann *et al.* 2004). Ellison *et al.* (2003) showed that right PPC is involved in the processing of any search for conjunction items even if the search was extremely easy and parallel, showing that the critical involvement of right PPC is in conjunction search in space, irrespective of difficulty. In comparison, rTMS of this region does not have any effect on a very difficult serial feature search so it is predicted that the difficulty found in neglect patients should be related to the anatomy of their damage (Ellison *et al.* 2003).

The present study attempts a complementary approach to lesion studies, using TMS to investigate the functional involvement of the right STG in tasks related to the two traditional diagnostic paradigms for neglect (landmark and visual search). As an experimental comparison and in order to replicate earlier studies, we have also examined the effects of TMS on the right PPC in each case.

2.2 Methods

Subjects

Five healthy subjects, aged 21-36, with normal or corrected to normal vision (all right handed; 2 female), participated. All subjects complied with current guidelines and gave their signed informed consent in accordance with Durham University Ethics Advisory Committee, and could withdraw from the experiment at any time. Subject selection complied with current guidelines for rTMS research (Wasserman, 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 their head position was controlled by a chinrest. Apart from the light from the PC screen , the room was darkened, and the stimuli were equiluminant at 120 cd/m^2 .

Landmark task

The landmark paradigm used in this experiment was a modified version of that used by Bjoertomt et al. (2002) in their original study. 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 the trials, the line was asymmetrically bisected to make either the left or right 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 500 ms followed by the appearance of the stimulus for 300 ms which was immediately followed by a mask (30° x 30°), 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 2.1) Each instruction was used 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. The inter-trial interval was 4000 ms.

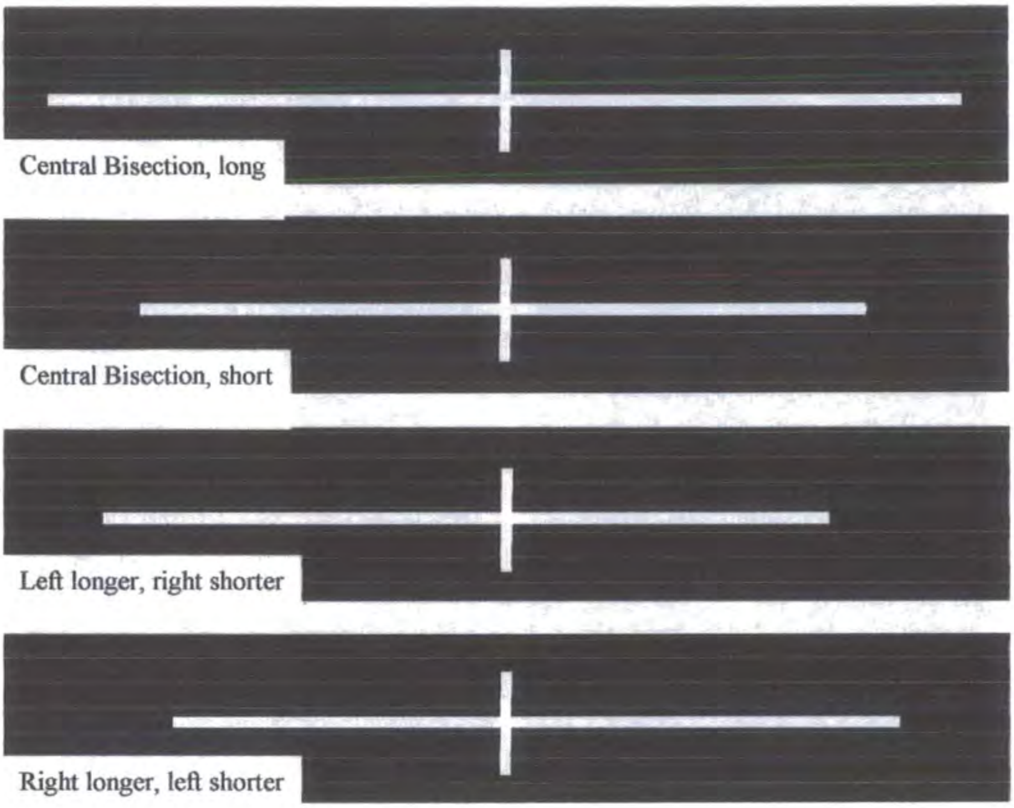


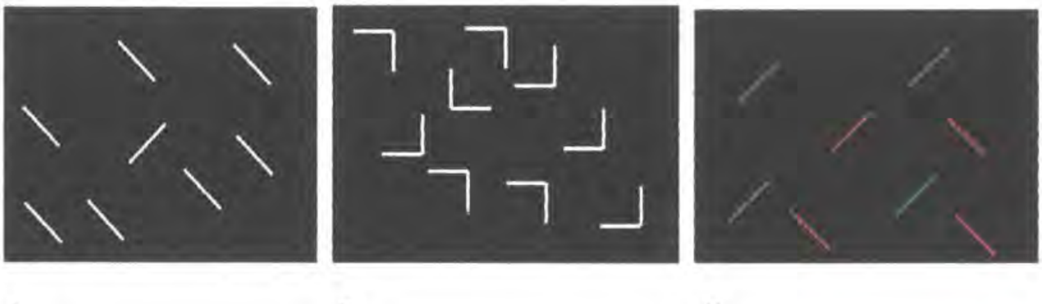
Figure 2.1: Landmark task arrays. Subjects were asked to decide which side of a bisected line was longer or which was shorter. In a third of trials, lines were bisected centrally.

Visual search tasks

Three visual search tasks were used (see figure 2.2) Two of the tasks (feature and conjunction) required serial search (>10ms/item) and constitute "hard" search in terms of difficulty. The third task (feature) was a simple "pop-out" search with a parallel search function (<5ms/item) and is termed "easy" search. The target could appear anywhere in the 8 x 6 array of virtual boxes on the screen.

In the feature tasks, the target was unique amongst the distractors whereas in the conjunction task, both the orientation and colour of the target were shared among the distractors. All items subtended 2° x 2° visual angle and were presented against a black background. Subjects were asked to respond as quickly and as accurately as possible as to the presence or absence of the target on a button box (left button for target-present, right button for target-absent). Each trial was preceded by a central fixation cross (0.5° x 0.5°) for 500ms followed immediately by the stimulus array. There were eight items in each array. In trials in which the target was absent, and extra distracter 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 1500 ms, whichever was shorter, and the inter-trial interval was 4000 ms.

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 2.2).



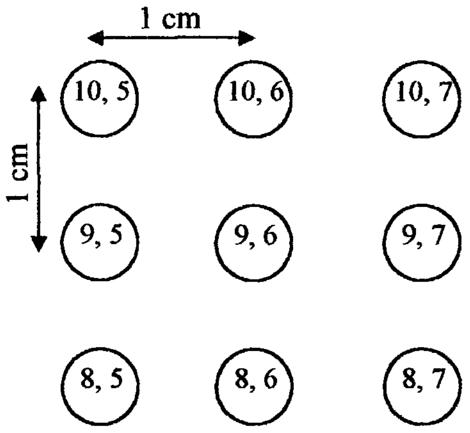
A **B** **C**

Figure 2.2: Visual search tasks. A is the easy feature task. The target being a white slash (/), amongst white backslashes (\). B is the hard feature task. The target was an upright L shape amongst rotated L shapes. C is the hard conjunction task. The target being a red slash amongst red backslashes and green slashes.

TMS

A Magstim (Whitland, UK) Model 200 was used and stimulation was applied at 65% of the stimulator's maximum power (2 Tessler). This level of stimulation is greater than the thresholds required to induce movement (over primary motor cortex) or the perception of phosphenes (over primary visual cortex).

Two sites of stimulation were used- right superior temporal gyrus and right posterior parietal cortex. The STG site (the main area of lesion overlap in Karnath *et al.*'s analysis) was located using frameless stereotaxy with each subjects' individual structural MRI scan (Brainsight, Rogue Research, Montreal, Canada) at the beginning of the session. This area is located approximately 1cm posterior to vertex and 14cm lateral on the scalp (see figure 2.3). 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 posterior within the typical area to which 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 2.3) around a central point 9cm dorsal to the mastoid inion and 6cm lateral. This functionally localised position was then verified using Brainsight (see figure 2.4) before the experimental procedure.



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

Figure 2.3: The 3 x 3 grid used to functionally localize right PPC using the hard conjunction search task and the resultant position in each subject.

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 here was 4 Hz for 500ms. This resulted in 2 pulses per trial.

Right PPC TMS was applied with a 70mm figure of 8 coil at 10Hz for 500ms, resulting in 5 pulses per trial.

In the no-TMS condition, the TMS coil discharged the pulses near to but directed away from, the subjects' head. Therefore, the audible effect of TMS was always present but without the accompanying pulse delivery at 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 of 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 x12 trials at each stimulation site. The order of all tasks was randomised across subjects. Three testing sessions (one per week), lasting approximately 1.5 hrs, were required per subject and each of them completed all tasks.

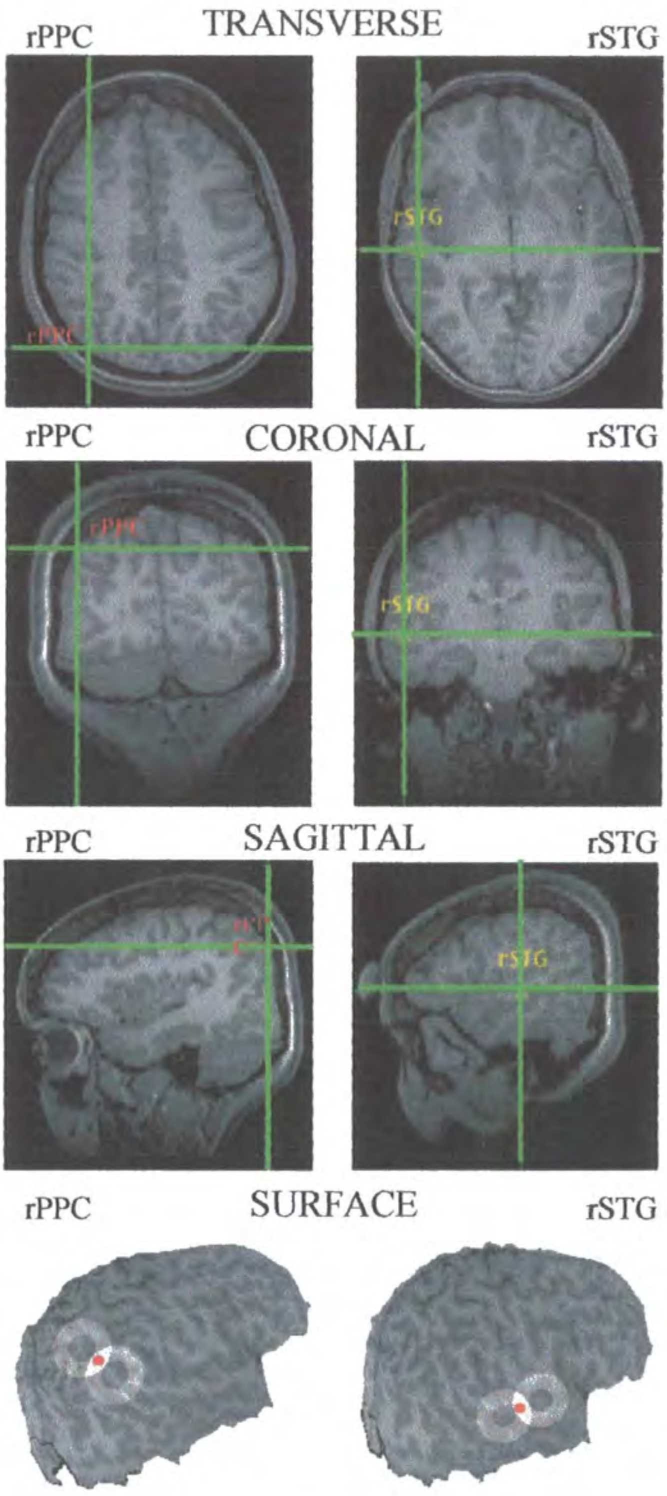


Figure 2.4: Stimulated areas were localized using each subjects' MRI scan co-registered to their skull co-ordinates using Brainsight software.

2.3 Results

Landmark task

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

The most noticeable results in this task resulted from the pattern of subjects' responses when lines were centrally bisected. When TMS was applied to rPPC, subjects responded that the left side of the line was shorter in 20% more trials than without TMS (t (4) = 4.080, 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 (4) = 6.326, 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 2.5).

In contrast, there was no significant difference in response patterns when TMS was applied over rSTG (t = 0.214, df = 4, p = 0,841, longer condition; t = 0.412, df = 4, p = 0.701, shorter condition).

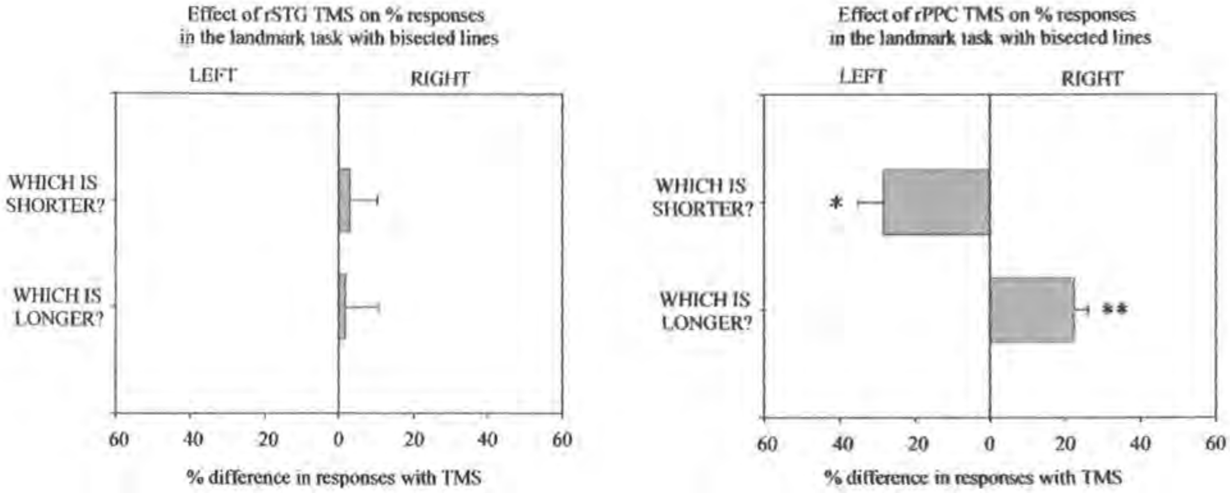


Figure 2.5: Response patterns when the line was bisected in the landmark task. Only TMS over right PPC induces contralateral neglect-like effects.

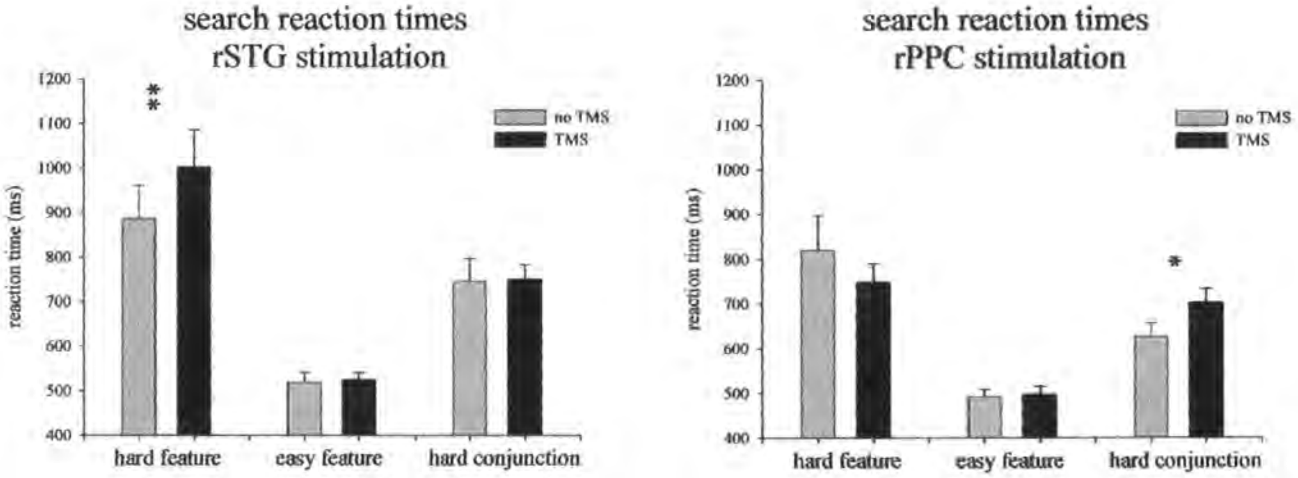
Visual search

The visual search tasks displayed a clear difference between the effect of TMS over rSTG and rPPC on target-present reaction times. A 3 factor [site of stimulation x task x TMS] repeated measures ANOVA was performed on the data. There was a significant main effect for task [F (2,8) = 32.772, P < 0.001] and a significant interaction between the three factors [F (2,8) = 15.991, 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 (4) = 8.039, P = 0.001] but not in the easy feature task, [t (4) = 0.516 P = 0.633] or in the hard conjunction task [t (4) = 0.228, P = 0.831].

Conversely, TMS over rPPC had a significant effect on reaction time in the serial conjunction task [t (4) = 3.790 P = 0.019], but not in the hard feature task [t (4) = 1.186, P = 0.301], or the easy feature task [t (4) = 0.666, P = 0.542] (see figure 2.6).

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 target 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 <2% and again, there was no significant difference between error rates for TMS and no-TMS trials.


search reaction times
rSTG stimulation

search reaction times
rPPC stimulation

Figure 2.6: 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.

2.4 Discussion

This study replicated previous findings of contralesional neglect-like symptoms on the landmark task following TMS over right PPC (Fierro et al. 2000; Bjoertomt et al. 2002) which is also supported by recent fMRI data, which showed activation in inferior as well as superior parts of the parietal lobe, particularly in the right hemisphere (Fink *et al.* 2000, 2001). In contrast, TMS over right STG failed to produce such an effect on the landmark task. This may seem inconsistent with argument made by Karnath *et al.* (2001) that the crucial locus of neurological damage in neglect patients is Brodmanns area 42, in the superior temporal gyrus.

However, as discussed in chapter 1, neglect has been assessed by a variety of clinical tests used to detect the disorder. Although these tests are helpful diagnostic tools they were not designed to pin point the specific mechanisms that underlie the defective performance of a particular patient, and it is known that different neglect patients can be differentially impaired in a variety of tasks. Mort *et al.* (2003) used both line bisection and cancellation tasks for the screening of their patients. A number of these patients showed a double dissociation between line bisection and cancellation.

The existence of double dissociations between tasks in neglect patients made Halligan and Marshall (1992) and later Ferber and Karnath (2001) question neglect as a 'meaningful theoretical entity'. These indications of the multifarious nature of the neglect syndrome are borne out by the results of the present study, in which a particular exploratory search task revealed an involvement of the right STG, but not the PPC. 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 depend 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.

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, it is clear that these visual search findings are not simply caused by a generalized TMS effect on search. Neither can the effects be explained by the difference in stimulation parameters between areas either. To minimise muscle twitch and eye blinks, which would affect the subject's ability to do the task it was necessary to use a lower frequency of stimulation over right STG due to its position on the scalp. If it had not have been possible to find effects in any of the tasks using these lower stimulation parameters then it would not have been clear that our stimulation of this site was sufficient to cause a disruptive effect on processing. However, 4 Hz did allow us to induce clear task-specific disruption to processing in right STG. It is possible that stimulating at 10 Hz would have produced stronger effects, as brain activity at the critical time would be disrupted to a more selective degree. However, the parameters used were sufficient to detect clear deferential effects, thus showing an important double dissociation in our results. No deficits in processing were observed in the landmark task with 4 Hz stimulation which is all that is necessary to find the effects in all other visual tasks, so it is unlikely that a higher frequency of stimulation over right STG would uncover effects in the landmark task. Although the effects were not large enough to reach significance, separate (unpublished) data have shown that 4 Hz stimulation over right PPC replicated our results in the 10 Hz condition. Using 4 Hz in the landmark condition, subjects underestimated the length of the left line 18 % more than without TMS. In the search conditions, 4 Hz TMS over PPC induced a 36.25 ms increase in reaction time in the hard conjunction condition.

One of the concerns regarding TMS experiments is that inferences made about the involvement of a particular area in a particular task may be inaccurate due to the spread of current following a TMS pulse. It is already known that current does spread to adjacent cortex and along neurological pathways (Ilmoniemi *et al.* 1997) but this is unlikely to be of enough strength to cause cognitive disruption in these areas.

In order to avoid practice effects, the order of the testing sessions was randomised across weeks. Each testing session used a different site of stimulation and the order of the tasks was randomised within each testing session. No-TMS reaction times were taken on each testing day, so even if subjects were faster on day 2 for example, their TMS reaction times on that day were directly comparable to their no-TMS reaction times collected in the same session.

As neither PPC nor STG has been found in TMS studies to be involved in the processing of simple pop-out search, it can be suggested that highly parallel feature search is processed earlier in the visual system than either of the sites studied here. Although it is known that the temporal cortex is involved in feature search processing (Chelazzi et al, 1998) this is the first study to demonstrate critical involvement of the superior temporal gyrus in this kind of processing.

It is notable, however, that asymmetrical (i.e contralesional hemisphere) 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 failure of neglect patients to orient to contralesional stimuli occurs not only with respect to egocentric-reference frames but also with respect to object-based reference frames. Our finding of no disproportionally increased reaction times contralaterally may suggest that we produced an object-based deficit.

A second reason may be the immense plasticity of the brain. Following a lesion to the right PPC, the left PPC may take over processing by default, even though only the contralateral hemispace can be processed. This would result in left hemispatial neglect following a right hemisphere lesion in patients tested after their damage had occurred. Contralateral neglect can occur minutes after stroke and it is possible that these minutes are crucial for the switch to left hemisphere control. In contrast, the very brief TMS stimulation period may not be long enough for this switch over to occur.

A third reason may be the decision demands of the task. In this study, subjects' response were 'target present' or 'target absent', perhaps requiring a left/right response would more closely resemble the directional nature of responses in clinical cancellation tasks.

Chapter 3 investigates these questions further.

CHAPTER 3

UNCOVERING HEMISPATIAL ASYMMETRIES IN VISUAL SEARCH USING TMS AND WHAT IT CAN TELL US ABOUT NEGLECT

3.1 Introduction

In the previous study (chapter 2) a double dissociation was found between PPC and STG on exploratory search tasks and was unique in providing the first report of a search deficit when applying TMS to the STG. It has therefore become apparent that different areas of the brain are primarily involved in the processing of different tasks used to diagnose neglect. Therefore, from this evidence in normal brain, it seems that neglect as a syndrome and its associated damage are clearly related to the task used to diagnose it.

The effects that TMS has in an experimental setting would indeed be more like those seen following neglect without hemianopia by virtue of the fact that subjects have no contalateral visual deficiency, nor can TMS of areas of interest in this question (either PPC or STG) induce one. TMS serves to introduce a brief cortical desynchronisation. Therefore if an area is critically involved in the processing of the concurrent task, some detriment to performance, such as an increase in reaction time, will be seen. TMS can therefore be used to delineate the exact functional nature of the involvement of normal brain areas in tasks in which impairment is usually seen after neurological insult, such as stroke.

However, one difference between the effects of TMS on the brain and the performance seen in these tasks following damage is the lack of a disproportionate hemispatial effect in visual search tasks (see chapter 2) although this was uncovered in the landmark task. Therefore simulated neglect could not be claimed during TMS at either PPC or STG. Chapter 2 touched on four proposed reasons as to why an overall TMS effect was uncovered (as opposed to a disproportionate effect on reaction time to items appearing in the left hemifield).

Two un-testable reasons stem from the obvious difference between lesion size resulting from neurological insult and the relatively restricted area of neuronal disruption. Also, the widespread reorganisation which happens as a consequence of damage, cannot be discounted, which may lead to left hemisphere processing of predominantly right hemifield as previously mentioned in chapter 2.

The third reason no asymmetrical effects of TMS were shown may be due to the special characteristics of neglect itself. The failure of neglect patients to orient to contralesional stimuli occurs not only with respect to egocentric-reference frames (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). It is possible that in the previous study (chapter 2), an object-based deficit my have been produced. That is, if each fixated objects' processing were impaired, there would be the same degree of reaction-time deficit for targets appearing in both left and right hemifields. This effect may be peculiar to TMS-induced effects, in mimicking a rather atypical form of neglect that is only sometimes present in patients (Driver *et al*, 1999). The present study sought to investigate this by constraining the array to be searched to the left or right hemifields and also a central presentation.

Finally, the fourth reason may be due to a lack of a clear spatial requirement in the performance indicator of the original experiments. The effects seen in chapter 2 in the landmark task were contralateral and, in this case the subjects' response was explicitly based on spatial catergories relevant in neglect, i.e, 'left' or 'right'. However, in the visual search tasks, the response was 'target present' or 'target absent'. It may be that the processing of a present/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 versus localisation). Indeed, Behrmann *et al.* (1997) showed that patients with neglect have a deficient search pattern biased to the right hemispace. Such a deficient search pattern may be sufficient to complete a target present or absent search without disproportionate effects. However, if an added spatial component were added to the performance indicator such as asking the subject to indicate whether the target appeared on the left or on the right hemispace (as in the landmark task), TMS may affect the processing of contralateral stimuli more in this case.

The present study has aimed to address some of these issues. As the previous study showed clear double dissociations between task and site, this study selected the suitable search task known to be impaired by TMS at each stimulation site (STG or PPC). When testing the effects of right STG stimulation, a difficult feature item search was used, and a difficult conjunction task was used when testing the effects of right PPC stimulation. The present study consisted of three experiments. For continuity, the same subject cohort was used to maximise comparability between not only present experiments but also with the previous experiment.

In experiment 1, the tasks replicated those used in the previous study (chapter 2) except that subjects were required to report the spatial location of the search target (left or right) on each trial instead of indicating a simple present/absent response. This would test whether spatial coding of the target was required in order to demonstrate 'neglect'.

In experiment 2, a smaller, structural stimulus array was used and presented briefly (in central space) in order to eliminate eye movements (as in the landmark task) to ensure that the target item was projected to either the left or right hemisphere directly. The small array used here could be seen in a single fixation and was structured as a 'good gestalt' (a diamond pattern) which is suggested to successfully recruit ventral stream areas (Fink et al., 2000). If contralesional TMS effects could be demonstrated here it would offer support for an object-centred neglect effect.

In experiment 3, a similar, small stimulus array was used but on different trials was either placed in left, right or central visual space to test whether the left of the array is disadvantaged even when it appears on the right of the viewer.

3.2 Methods

Subjects

Subjects included were the same as in chapter 2.

Experimental set-up

The present study used the same experimental set-up as chapter 2.

Transcranial magnetic stimulation

This followed the same procedure as chapter 2. Due to the double dissociation uncovered by the previous study between task and site of stimulation, the same parameters were adopted for the present study (see chapter 2).

The order of all tasks were randomised across subjects. Three testing sessions (one per week), lasting approximately 1.5 hrs, were required per subject, each of whom completed all tasks.

Stimuli

Stimuli were the same as in chapter 2.

As previously mentioned, only the stimuli for which significant deficits in performance were seen with TMS over each area in the previous study (chapter 2) were used. These two tasks, a feature and conjunction array, required serial search (>10ms/item) and constitute 'hard' search tasks in terms of difficulty.

In the feature task, the target was entirely unique amongst the distractors, whereas in the conjunction task, both the orientation and colour of the target were present among the distractors.

Tasks

3.2.1 Experiment 1. Random array visual search

Two visual search tasks were used (see figure 3.1). Both of the tasks (feature and conjunctive) required serial search (>10 ms/item) among 8 items and thus constitute 'hard' search tasks in terms of difficulty. The target, which was present on every trial, could appear anywhere in a 6 x 6 array of virtual boxes (overall size 18° x 18° of visual angle) on the screen, equally often on the left or right. On all trials there were 4 stimulus items in the left half and 4 in the right half of the array.

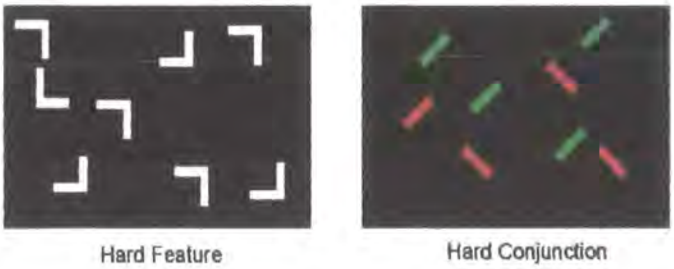


Figure 3.1: Random array visual search tasks used in Experiment 1. The 'hard feature' search was for a white L shape amongst rotated white L shapes. The 'hard conjunction' (orientation and colour) search target was a red slash amongst red backslashes and green slashes.

In the feature task, the target was entirely unique among the distractors, whereas in the conjunction task, both the orientation and colour of the target were present among the distractors (see figure 3.1). All items subtended 2° x 2° 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-left, right button for target-right) to indicate the position of the target. Each trial was preceded by a central fixation cross (0.5° x 0.5°) for 500 ms followed immediately by the stimulus array. The visual array remained present until response or for 1500 ms, whichever was shorter, and the inter-trial interval was 4000 ms.

3.2.2 Experiment 2. Structured array visual search without eye movements

The search arrays were centrally presented in a diamond configuration (9° high by 9° wide) consisting of 8 stimulus items of the same type as in Experiment 1. The stimulus items were smaller, however, the angle subtending only 1° (see figure 3.2A). The target was presented in pseudo-random order at one of the six lateral positions of the array. Each trial was preceded by a central fixation cross (0.5° x 0.5°) for 500 ms which remained present for the duration of the trial, followed by the appearance of the stimulus array for 300 ms, which was followed by a mask. The mask remained present until the subject responded, or for 1500 ms. The mask consisted of an array of hatched black and white squares (1° x 1°) which covered all of the previously displayed stimuli. The inter-trial interval was 4000 ms. Subjects were asked to make a target present/absent response or a left/right response. Each response mode was tested in separate blocks of trials. In the present/absent trials the target was present on 50% of the trials, while in the left/right trials it was present on all trials. Responses were made on a button box with the left button denoting present or left and the right button denoting absent or right. Subjects were asked to respond as quickly as possible but without sacrificing accuracy for speed. Each task was administered in 4 x 12 trials for each stimulation condition (Baseline and TMS). Prior to this experiment subjects were given sufficient practice training to maintain reliable fixation.

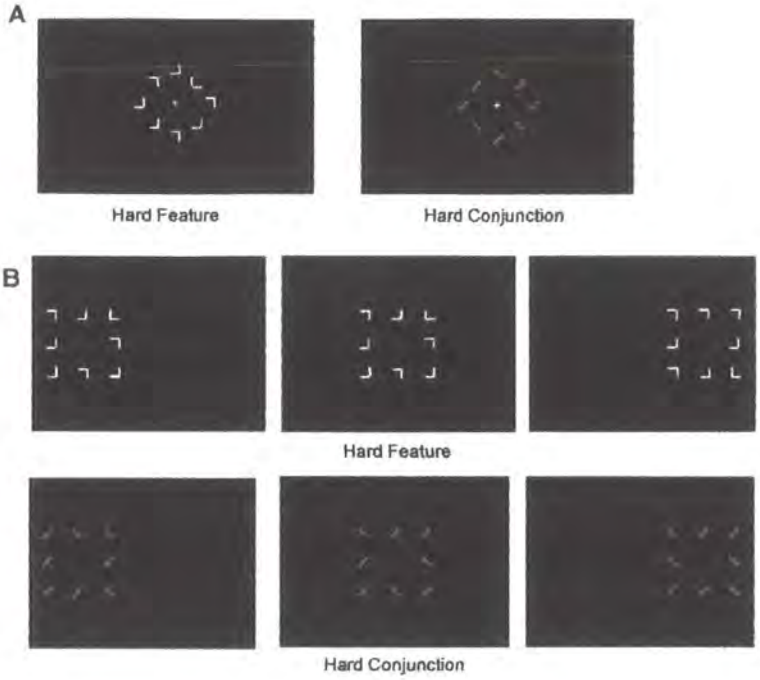


Figure 3.2: Structured-array visual search tasks for Experiments 2 and 3. The stimulus elements used were the same as in the random array tasks used in Experiment 1. (A) Stimulus arrays for 'objectbased' visual search without eye movements (Experiment 2). The array was always shown in the centre of the screen. (B) Stimulus arrays presented on the left, centre and right of the screen (Experiment 3).

3.2.3 Experiment 3. Structured array visual search in free vision

The search arrays for feature and conjunction search were square shaped and of the same dimensions (9° x 9°) as the stimulus configuration used in Experiment 2. Each array consisted of 8 feature or conjunction items identical to those in Experiment 2. The search arrays were presented either centrally, to the left, or to the right (see figure 3.2B). The outer border of the lateral arrays was 18° from the centre of the screen. The targets were presented in pseudo-random order at one of the six lateral positions of the square. Each trial was preceded by a central fixation cross (0.5° x 0.5°) for 500 ms, followed immediately by the stimulus array. The visual array remained present until response or for 1500 ms, whichever was shorter, and the inter-trial interval was 4000 ms. The modes of response, and the other experimental procedures, were the same as in Experiment 2. Each task was administered in 4 x 18 trial blocks for each stimulation condition (baseline and TMS).

3.3 Results

The data from each of the experiments were analysed in two steps. In the first step the raw data were subjected to an analysis of variance and post-hoc comparisons. Post-hoc comparisons were made using Bonferroni adjusted t-tests. All comparisons of TMS effects were one-tailed since we had clear directional hypotheses not only of increased TMS response times but also that these effects would be greater for the left (contralateral) side of the stimulus array. (The only exception to this rule was for certain comparisons made in experiment 3 between central and lateral array locations, where a two-tailed test was deemed more appropriate). Where TMS stimulation had a significant effect, additional analyses were performed on the relative TMS effects. This was done using normalized data, that is by calculating [(TMS – sham TMS)/ (TMS)*100 for each cell in the analysis.

3.3.1 Experiment 1. Random array visual search

Figure 3.3 shows both the raw and normalized response time (RT) data for Experiment 1, presented separately for PPC (conjunction search) and STG (feature search). In each case separate repeated measures ANOVAS were performed on the raw mean RT data, with within subject factors of 'stimulation' (No-TMS, TMS) and 'hemispace' (left, right). For PPC the results revealed a significant interaction between stimulation x hemispace [$F(1,4) = 37.21$, $p<0.005$] but no main effects for stimulation or hemispace [$F(1,4) \leq 3.943$, $p > 0.1$]. Subsequent paired t-tests showed that TMS resulted in a significant increase in response times for targets in left hemispace compared to the baseline [$t(4) = 3.02$, $p <0.05$, one-tailed] but not for targets in right hemispace [$t(4) = 0.6$, $p > 0.5$, one-tailed]. For the STG raw data, ANOVA yielded a significant main effect of TMS [$F(1,4) = 9.81$, $p < 0.05$]

but no main effect for hemispace and no stimulation x hemispace interaction [$F(1,4) \leq 1.01, p > 0.2$].

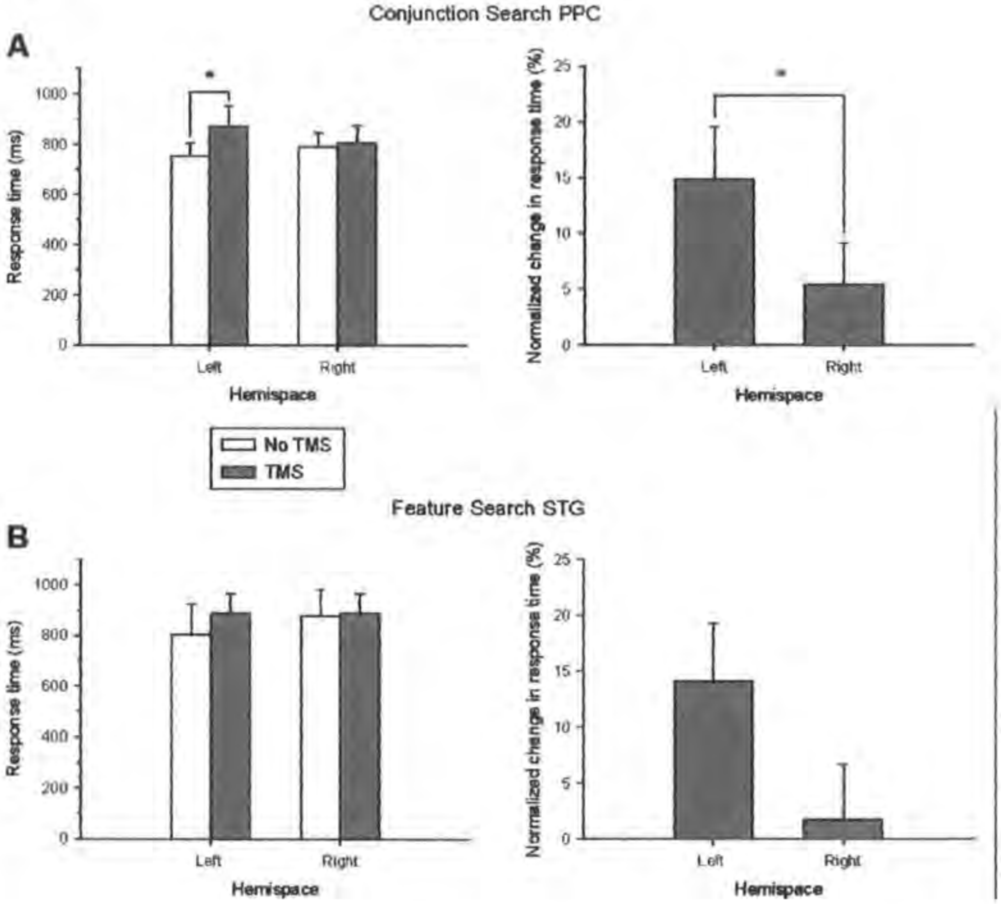


Figure 3.3: Experiment 1. Effect of TMS on response times in the random array visual search tasks across target position. (A) Hard conjunction visual search, TMS over right PPC. (B) Hard feature visual search, TMS over right STG. TMS over PPC causes a significant increase in response time for targets on the left side of the array. There is no significant TMS effect for STG stimulation.

Analysis of the normalized RT data (see figure 3.3) confirmed that only for PPC stimulation was the increase in response times significantly larger for target locations in the left hemispace as compared to the right hemispace [$t(4) = 2.85, p > 0.05$], despite a trend for STG in the same direction: [$t(4) = 1.434, p > 0.2$, one-tailed]. Error rates in all of the search tasks were less than 2.8% and there was no significant difference between error rates for TMS and no-TMS trials.

Table 3.1: Mean response times (SE_M) in Experiment 2 for the two modes of response and the two stimulation sites.

Stimulation area	Response	No TMS		TMS	
		Left[†]	Right	Left	Right
PPC	PA	609.49 (47.47)	622.53 (32.24)	633.70 (55.75)	688.29 (47.86)
	LR	616.22 (26.29)	637.75 (29.27)	656.72 (27.07)	674.39 (36.60)
STG	PA	585.77 (27.16)	580.85 (41.25)	635.32 (53.90)	612.30 (49.43)
	LR	635.48 (14.40)	678.73 (49.23)	669.55 (51.40)	654.52 (55.64)

PPC: posterior parietal cortex, STG: superior temporal gyrus. PA: present/absent, LR: left/right.
[†] Target position.
PPC stimulation was applied during performance of a conjunction search, while STG stimulation was given during performance of a hard feature search.

3.3.2 Experiment 2: Structured array visual search without eye movements

The raw response-time data are shown in table 3.1. Four repeated measures ANOVAS (stimulation x side) were performed on the data for STG and PPC and for the two different modes of response (target present/absent and target left/right). There were neither significant main effects nor interactions in any of the analyses [$F(1,4) \leq 1.96$, $p > 0.2$]. Given the relatively high error rate in this experiment (see Table 3.2) we performed an identical set of analyses on the error rates. The results showed no significant effect on errors for target present/absent responses for STG nor for PPC [$F(1,4) \leq 5.73$, $p > 0.05$]. This finding was repeated for STG and target left/right responses [$F(1,4) \leq 7.03$, $p > 0.05$]. In contrast, for the left/right responses during PPC stimulation there was a highly significant main effect for side [$F(1,4) = 34.41$, $p > 0.005$] but no significant main effect for stimulation nor a significant interaction between stimulation and side [$F(1,4) \leq 6.54$, $p > 0.05$].

Table 3.2: Mean percentage of errors (SE_M) in Experiment 2.

Stimulation area	Response	No TMS		TMS	
		Left†	Right	Left	Right
PPC	PA	2.76 (1.69)	8.83 (4.23)	1.43 (1.43)	13.39 (4.64)
	LR	1.57 (0.96)	34.33 (2.22)	0.00 (0.00)	29.36 (2.51)
STG	PA	25.16 (9.93)	30.61 (12.73)	29.33 (7.05)	30.18 (14.23)
	LR	9.51 (6.77)	5.44 (3.63)	13.13 (4.82)	3.91 (2.40)

Please see Table 3.1 legend for details of abbreviations.

There were considerably more errors on the right side compared to the left side in the baseline condition [$t(4) = 14.28$, $p < 0.005$]. However, the basic pattern did not change during TMS application over right PPC (see table 3.2) Thus, a comparison of the change in errors with TMS yielded no significant differences between the two sides [TMS Left side: -1.57%, Right side: -3.38%; $t(4) = 0.69$, $p > 0.1$, one-tailed].

3.3.3 Experiment 3. Structured array visual search in free vision

Four separate 2 x 3 x 2 repeated measures ANOVAS with the within-subjects factors stimulation (No-TMS, TMS), array position (left, centre, right), and within-array side (left, right) were performed on the raw response time data. These four ANOVAS examined the four combinations of stimulation sites (STG/feature search and PPC/conjunction search) and response modes (target present/absent and target left/right) respectively (see table 3.3). As we were chiefly interested in main effects and interactions reflecting the effects of TMS, we report only those results in detail.

Table 3.3: Mean search times (SE_M) in Experiment 3.

				No TMS			
Stimulation Area	Response	Left Array		Central Array		Right Array	
		Left†	Right	Left	Right	Left	Right
PPC	PA	767.23 (42.64)	752.37 (40.37)	720.19 (71.01)	660.62 (33.00)	724.09 (63.21)	829.15 (50.92)
	LR	773.09 (23.38)	722.83 (31.76)	702.25 (36.70)	682.49 (18.65)	750.72 (31.16)	803.29 (14.51)
STG	PA	763.77 (26.03)	700.59 (68.24)	619.87 (21.59)	679.46 (49.23)	673.59 (59.04)	817.93 (50.94)
	LR	781.99 (45.96)	717.85 (71.44)	657.74 (30.18)	674.04 (78.99)	661.68 (56.32)	781.59 (81.40)
				TMS			
PPC	PA	823.04 (51.01)	819.06 (57.25)	697.39 (52.16)	706.70 (47.39)	760.28 (50.68)	897.15 (36.67)
	LR	850.24 (50.99)	744.62 (37.99)	716.29 (43.76)	715.77 (51.80)	785.51 (51.89)	828.86 (39.04)
STG	PA	852.69 (37.27)	722.01 (57.81)	662.16 (46.88)	712.75 (37.53)	681.02 (42.97)	877.28 (42.47)
	LR	958.39 (81.60)	684.42 (52.37)	706.70 (41.65)	740.37 (71.54)	796.04 (80.17)	784.87 (71.86)

Please see Table 3.1 legend for details of abbreviations.

Present/absent responses

The data summarized in Figure 3.4A. For target present/absent responses the ANOVAS revealed a similar pattern for both PPC (conjunction search) and STG (feature search): there was a significant main effect of array position [$F(1,4) \geq 17.60$, $p < 0.05$] and a significant interaction between array position and side [$F(2,8) \geq 7.56$, $p < 0.05$]. No other main effects or interactions reached significance [$F(1,4) \leq 5.56$, $p > 0.05$]. Overall (data collapsed over side and stimulation condition), subjects responded faster to targets in the central array compared to the left and right array [$t(4) \geq 8.72$, $p < 0.005$]. The comparison of response times with respect to left and right side of each array (data collapsed over stimulation condition) revealed for both STG and PPC overall increased response times on the right side of the array compared to the left side [t(4) = 4.30, p > 0.02] but no side differences for the left and central array [t(4)< 2.99, p > 0.05, Bonferroni corrected].

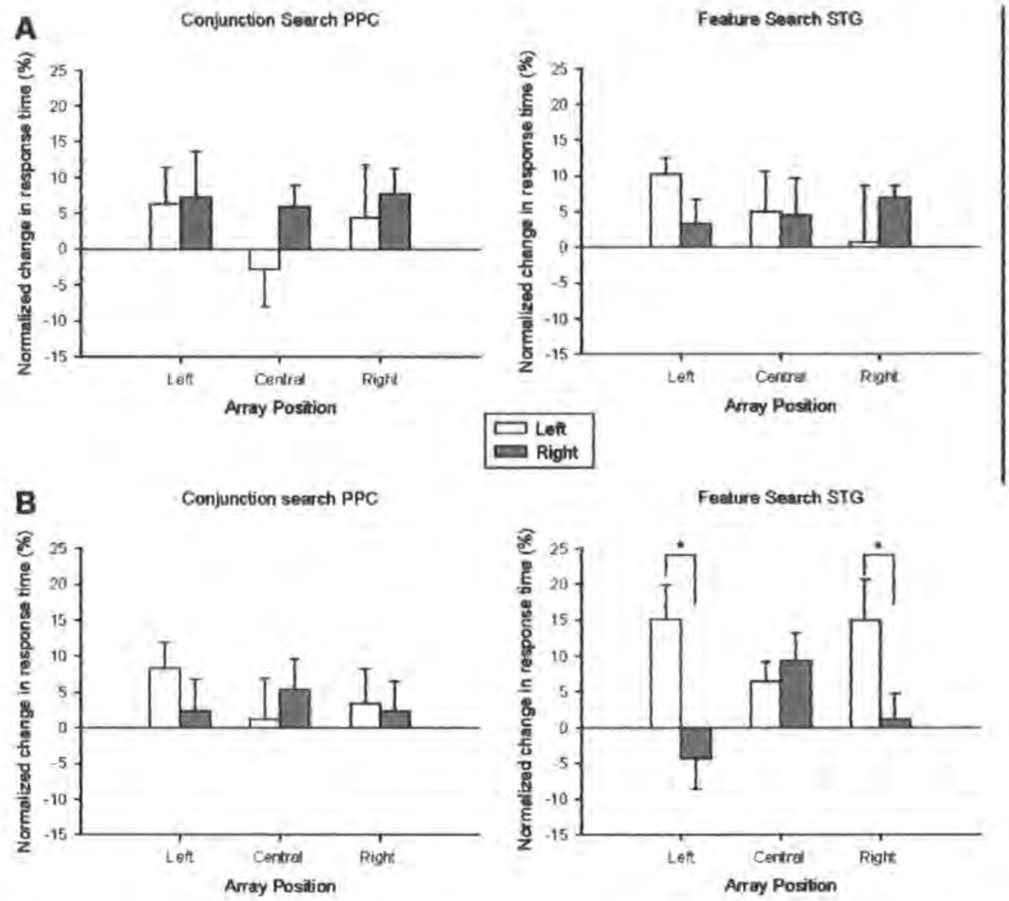


Figure 3.4: Experiment 3: Effect of TMS on response times in the structured-array visual search tasks. The graphs show group means and SE_M.

(A) Target present/absent responses: There were no significant effects of TMS on response times.
(B) Target left/right responses: TMS over STG (but not PPC) causes a significant increase in response time for targets on the left sides of both left and right laterally-presented array.

All error rates were under 2%, and there was no significant difference between error rates when TMS and baseline at either site for either task. Thus, there were no effects of TMS on present/absent search behaviour.

Left/right responses

The data are shown in Figure 3.4B (left). For PPC (conjunction search) with target left/right responses, the ANOVA showed a similar pattern as for target present/absent responses. Thus apart from a significant main effect for array position and a significant array position by side interaction [$F(2,8) \geq 8.58$, $p < 0.05$], there were no other significant effects [$F(1,4) \leq 1.30$, $p > 0.2$]. Overall responses were significantly faster for targets in the central array compared to left and right array [$t(4) \geq 5.39$, $p < 0.05$, two-tailed], while the latter two did not differ [$t(4) = 1.25$, $p < 0.5$, one-tailed]. Bonferroni-adjusted comparisons between the left and right side of each array revealed no significant differences [$t(4) \leq 2.99$, $p > 0.05$, one-tailed].

In contrast, for STG (Figure 3.4B, right), the results yielded significant main effects of array and of TMS [$F(1,4) \geq 8.73$, $p < 0.05$], and significant interactions between array x side, stimulation x side, and stimulation x array x side [$F(1,4) \geq 12.82$, $p < 0.05$]. In addition, there was an overall increase in response times with TMS compared to the baseline [$t(4) = 3.00$, $p < 0.05$, one-tailed]. Specific comparisons between TMS and baseline for each side of the arrays revealed a significant increase in response times for only the left side of the left and right arrays [$t(4) \geq 3.98$, $p < 0.05$, one-tailed] but not for the central array [$t(4) = 2.34$, $p > 0.2$, one-tailed].

In agreement with this, the analysis of the normalized response time data yielded significantly greater TMS effects on the left side for the left and right arrays [$t(4) \geq 7.22$, $p > 0.005$] but not for the central array [$t(4) = 1.72$, $p > 0.1$, one-tailed].

Error rates for the left/right responses were below 5.5% in each of the tasks and there was no difference in TMS and baseline error rates at either site.

3.4 Discussion

In this study, an impairment in a difficult search for a conjunction item when TMS was applied to right PPC (but not STG) and an impairment in a difficult search for a single feature item when TMS was applied to right STG (but not PPC) was confirmed and additionally, it has been shown that under different conditions TMS can produce contralateral search deficits akin to those associated with unilateral visual neglect patients.

In the first experiment, subjects were asked to report the spatial location of the search target (left/right response) instead of simply detecting the target (present/absent response). A significant contralateral effect of response times in a conjunction search task when TMS was applied to right PPC was found. The same trend was found when TMS was applied to right STG in a difficult feature search task although this did not reach significance. On present evidence, however, only the significant PPC result can be discussed. This we interpret as indicating that the introduction of a spatial element into the response (even though this spatial element was not goal directed) was sufficient to induce an asymmetrical TMS effect. This would make sense if a critical problem that neglect patients have with search or cancellation tasks was in terms of *locating* the target rather than merely *detecting* it. In support of this, it is relevant that a well-known symptom seen in neglect patients is a mislocalization of items present on the contralateral side, such that they are treated as being present instead on the ipsilateral side of space. This type of mislocalisation, known as allochiria, has recently been argued to be due to a failure of spatial binding (Marcel *et al.* 2004). Our contralateral deficit arose in the context of conjunction search, which presumably intrinsically requires attentional binding, in our case between orientation and colour (Treisman and Gelade, 1980) It therefore seems that by introducing a spatial component into the response requirement puts additional strain on the subjects' attentional resources, rendering them vulnerable to contralateral search deficits when exposed to PPC TMS.

In experiment 2 and 3, the aim was to investigate whether the previous failure to find a TMS effect on contralateral *spatial* search might have masked the presence of a neglect-like effect on the perception of the individual items within the search array themselves. The aim was to address the possibility that TMS might be able to elicit an object-based neglect effect (Driver, 1999; Walker, 1996). In experiment 2, where a small array was presented centrally with a brief exposure time, no evidence was found of any TMS effect of this kind, using either of the two sites of stimulation. However in Experiment 3, where a long enough stimulus duration to permit eye movements was used, and also lateral as well as central presentations of the stimulus arrays, clear and significant evidence of neglect-like effects were found. These were limited to stimulation applied to the right STG while subjects were performing a difficult feature search. The effects were also limited to lateral presentations of the search arrays, but were present in both left and right hemispace. Just as with PPC stimulation during conjunction search (chapter 2) these lateralized effects were only present in a testing regime where left/right responses were required. No lateralized effects were apparent in any of our experiments for present/absent responses.

Although experiments 2 and 3 were designed with the aim of maximizing the possibility of object-based effects emerging, it cannot of course be categorically stated that such effects have been demonstrated. This is because although there were greater response times for targets located in the leftmost parts of the arrays, the arrays were of course themselves displayed within visual space, and thus the asymmetries observed could be a simulated form of *spatial* neglect. Indeed, given that the stimulus arrays, although intended to be perceptually grouped and thereby be treated by the brain as 'object-like' in nature, it is not absolutely certain that subjects did indeed treat the arrays in this way. Despite these reservations, however, given that a clear contralateral effect emerged from Experiment 3 regardless of whether the array was presented in right or left hemispace, and given also that no between-array asymmetries were found, it is at least plausible to suppose that the effect may in part be attributable to a form of object-based neglect. If this is correct, then the interesting possibility presents itself that although TMS applied to the PPC can elicit *spatial* neglect-like effects, TMS over right STG instead can simulate *object*-based effects.

There were no disproportionate hemispatial performance in the hard conjunction search task with right PPC stimulation. As already mentioned, contralateral effects with right PPC disruption were uncovered using a conventional search array with a spatially loaded response indicator, therefore right PPC seems to have a more critical role in the processing of distributed space. Such a scenario would have a certain plausibility, given the probable role of the inferior parietal region in visuospatial working memory (Ellis *et al.*, 1996; Malhotra *et al.*, 2005; Pisella *et al.*, 2004; Wojciulik *et al*, 2004) and the relative proximity of the superior temporal gyrus to the ventral stream of visual processing. The latter is believed to embody the processing system in which the perceptual representations of objects are constructed from the featural elements that define them (James *et al.*, 2003; Kanwisher *et al.*, 1997; Malach *et al.*, 1995). These findings may be taken as further evidence of the difference in crucial processing of right PPC and right STG and how disruption to either can induce different patterns of performance impairment either in the laboratory using TMS or in neglect studies using patients (Karnath *et al.*, 2001; Mort *et al.*, 2003).

Finally, a surprising lateral asymmetry occurred in Experiment 2, whereby irrespective of TMS being applied, many more errors were made for conjunction targets on the right side of the fixated array than on the left. This was highly significant when subjects had to report the side of occurrence of the target rather than simply its presence or absence (see Table 2, line 2). Presumably this task required subjects to covertly scan the visual image for the target, and in this they could have used a left-to-right strategy. Yet there is no evidence that such a strategy was used in the single feature search task, since if anything the pattern of errors there goes in the opposite direction, with more being made on the left side (Table 2, line 4). It is possible that the findings reflect a left visual hemifield/right hemisphere advantage for visual conjunction processing within a single visual snapshot. But if so, since TMS applied to PPC had no effect on this asymmetry, we must assume that it is mediated by circuitry different from that which underlies conjunction search using free eye movements.

The present study shows for the first time that TMS applied to the right hemisphere can cause impairments of contralateral visual search in healthy human adults. Although not as yet fully compelling, the data further suggest that while TMS over the posterior parietal region can under suitable task conditions impair search within contralateral visual *space*, TMS over the superior temporal gyrus may have its contralateral effects primarily on within-*object* search.

CHAPTER 4

GENERAL CONCLUSIONS

Our results support other studies showing that the right PPC has a key role in processing of both the landmark task (Fink *et al.* 2002; Fierro *et al.* 2000; Brighina *et al.* 2003) and hard conjunction tasks (Ellison *et al.* 2003). We also demonstrated a critical involvement of right STG in a hard feature visual search task, supporting the seminal claim by Karnath *et al.* 2001 for the importance of right STG damage in the causation of neglect. Given the double dissociations we have found between task used and brain area stimulated, it is clear that conclusions about the area of brain damage resulting in neglect-like symptoms are highly dependent on the task used to diagnose them. This is consistent with Rorden *et al.* (2005) who found that line bisection and exploratory tasks seem to have neglect different lesion foci. In this study, neither PPC or STG stimulation impaired performance on a parallel feature task, suggesting that this task is processed earlier in the visual system than either of the two sites used here.

It is already known that the temporal lobe is involved in feature search processing (Chelazzi, 1998; Hayakawa *et al.* 2003) and that inferior temporal damage in particular results in impaired visual search (Ptak and Valenza, 2005). However, this study is the first to implicate specifically STG in the processing of these tasks. Our 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 tasks. In contrast, the maximal lesion overlap in patients who were only impaired in cancellation was found in pre-rolandic regions including the pre-frontal 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.* (1992) 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), as well as in parietal patients (Pisella *et al.*, 2004; Malhotra *et al.*, 2005).

Chapter 2, however, showed a lack of disproportionate hemispatial effects in visual search tasks, although the landmark task, with its directional response, uncovered a contralateral effect. A present/absent response may be sufficient to indicate detection of an item but may not be spatially weighted enough to engage parietal lobe to the extent that subjects would be more impaired contralateral to stimulation. Therefore, in chapter 3, the response parameter was changed to a "does the target appear on the left or right?" question. The visual appearance of the array was also manipulated to investigate if TMS was having an effect on egocentric space or in a more object-framed manner.

Chapter 3 successfully showed that under different conditions TMS can produce contralateral search deficits akin to those associated with unilateral visual neglect patients. In experiment 1, a spatial component was introduced into the response. This was sufficient to induce an asymmetrical TMS effect in a conventional serial conjunction search task with right PPC stimulation. As previously mentioned, a left/right response may be more likely to force observers to bind both featural and spatial aspects of the stimuli rather than merely a present/absent response and relies on the subject locating the target instead of merely detecting it. It seems then that introduction of a spatial element in the response indicator puts a strain on the subjects attentional resources which renders them vulnerable to contralateral search deficits when exposed to right PPC TMS. Although there was a similar trend found with STG stimulation in a difficult feature task, this did not reach significance.

In experiment 3, with STG stimulation, a clear contralateral effect emerged regardless of whether the array was presented in right or left hemisphere, and no between-array location asymmetries were found suggesting that the effect may in part be attributable to a form of object-based neglect. This effect was only found when the response indicator was left/right and not present/absent, suggesting that introducing a spatial component into the task response is necessary for contralateral effects with STG stimulation as well as PPC stimulation. PPC stimulation failed to produce such an effect in this experiment.

The results of experiments 1 and 3 combined suggest that not only do right PPC and right STG process different tasks but they process these tasks differently depending on the task response requirement and the spatial reference frame. There is evidence to suggest that a fronto-parietal network is involved in the computation of an egocentric reference frame (Fink *et al.* 2003; Galati *et al.* 2000), whereas object-centred reference frame computation is thought to be managed by a subset of areas of the same network (Galati *et al.* 2000). This is the first study to show any evidence that STG is involved in the computation of an object-centred reference frame. The data suggest that right PPC can disproportionately affect search within contralateral visual space, while TMS to right STG may have within-object contralateral effects.

One question that arises from these experiments with regard to neglect is what would be found in patients with different posterior lesions using the specific tasks here. One would predict that patients with right PPC lesions would be more likely to have deficits on the landmark task and in conjunction visual search, whereas those with right STG-centred lesions should be more likely to have deficits in difficult exploratory single-feature search. It would be interesting to see whether changing the task requirements affects how the patients perform in these different tasks, or whether this is purely a function of TMS stimulation.

These experiments shed light on what is happening in the damaged brain exhibiting symptoms of neglect but it is also interesting to ask what these results tell us about the processing of these brain areas in the normal brain and how this contributes to the attentional literature. The control mechanism of spatial attention remains unclear. In order to gain insight into this, it is necessary to pin-point what structures in the brain underlie the attentional spotlight and what structures are involved in the binding mechanism-two essential components of Feature Integration Theory (FIT) (Treisman and Gelade, 1980) (see page 21). This was investigated using TMS by Ellison et al. 2003 to see if any task requiring binding, irrespective of spatial search would require PPC. They found that PPC was only involved in conjunction search, irrespective of attentional demands but only for search in space.

The experiments carried out in this thesis uncovered a task that requires attention that wasn't mediated by right PPC, but right STG, suggesting that there are at least two areas involved in selective attention. Recent studies have also shown involvement of other areas; for example, if attention to motion is required for processing, it is V5 that is critically involved and not PPC (Walsh *et al.* 1998; Ellison *et al.* in press). Other studies suggest a role for FEF in spatial attention; Ellison *et al.* 2003 showed that PPC becomes disengaged if the target location is repeated, suggesting that there is an area which keeps track of target location. It is possible that this involves slowly decaying saliency maps, thought to reside in FEF (Muggleton *et al.* 2003; Thompson *et al.* 2004).

Attentional demands aside, it is also clear from the experiments presented in this thesis that right PPC involvement is more influenced by visuospatial requirements than STG and this is highlighted by the differences when changing the response requirements and presentation appearance of the task used.

These experiments not only add to the argument surrounding different patterns of deficit and locus of damage in the neuropsychological neglect literature but also have direct ramifications on behavioural neuroscience. They provide further support not only for the growing body of evidence delineating the dissociations between processing of different tasks in different brain areas but also the subtle differences in how these areas are critical in this processing.

References

Aglioti, S., Smania, N., and Peru, A. (1998) Frames of reference for mapping tactile stimuli in brain-damaged patients. *Journal of Cognitive Neuroscience* 11, 67-79

Aguirre, G.K. (2003) Functional Imaging. In: T.E. Feinberg., M.J. Farah (Eds.) Behavioural Neurology and Neuropsychology, 2nd edition, New york. McGraw Hill

Albert, M. (1973). A simple test of visual neglect. *Neurology*, 23, 658-664

Amassian, V.E., Cracco, R.Q., Maccabee, P.J., Cracco, J.B., Rudell, A., and Eberle, L. (1989). Suppression of visual perception by magnetic coil stimulation of human occipital cortex. *Electroenceph. Clin. Neurophysiol.* 74, 458-462

Anton, G. (1899). Uber die selbstwahrnehmung der Herderkrankungen des Gehirns durch den Kranken der Rindenblindheit und Reindentaubheit. *Archiv fur Psychiatrie* 32 86-127

Ashbridge, E., Walsh, V., Cowey, A. (1997). Temporal aspects of visual search studies by transcranial magnetic stimulation. *Neuropsychologia*, 35, 1121-1131

Battersby. (1956). Unilateral spatial agnosia (inattention) in patients with cerebral lesions. *Brain*, 79 (1), 68-93

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

Behrmann, M., Meegan, D.V. (1998). Visuomotor processing in unilateral neglect. *Consciousness and cognition*, 7 (3), 381-409

Behrmann M., Ebert P., Black S.E. (2004). Hemispatial neglect and visual search: A large scale analysis. *Cortex*, 40, 247-263

Behrmann M., Watt, S., Black S.E., Barton J.J.S. (1997). Impaired visual search in patients with unilateral neglect: an oculargraphical analysis. *Neuropsychologia*, 35, 1445-1458

Beschin, N., Cubelli, R., Dela Salas, S., Spinazzola, L. (1997). Left of what? The role of egocentric coordinates in neglect. *Neurol Neurosurg Psychiatry.*, 63 (4), 483-489

Binder, J., Marshall R., Lazar R., Benjamin, J., Mohr, J.P. (1992). Distinct syndromes of hemineglect. *Arch Neurol*, 49, 1187-1194

Bisiach, E., Luzzati, C.(1978). Unilateral neglect of representational space. *Cortex,* 14, 129-133

Bisiach, E., Geminiani, G., Berti, A., Rusconi, M.L. (1990). Perceptual and pre-motor factors in unilateral neglect. *Neurology*, 40, 1278-1281

Bisiach, E., Ricci, R., Lualdi, M., Colombo, M.R. (1998). Perceptual and response bias in unilateral neglect: two modified versions of the Milner landmark task. *Brain Cognition*, 37, 369-386

Bjoertomt, O., Cowey, A., Walsh, V. (2002). Spatial neglect in near and far space investigated by transcranial magnetic stimulation. *Brain*, 125, 2012-2022

Bowen, A., McKenna, K., Tallis, R.C. (1999). Reasons for variability in the reported rate of occurrence of unilateral spatial neglect after stroke. *Stroke*, 30, 1196-1202

Brain, W.R (1941) Visual disorientation with special reference to lesions of the right hemisphere. *Brain.* 64 113-130

Brighina, F., Bisiach, E., Oliveri, M., Piazza, A., La Bua, V., Daniele, O., Fierro, B. (2003) 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. *Neurosci Lett* 16; 336 (2): 133

Chatterjee, A., Mennemeier, M., Heilman, K.M. (1992). Search patterns and neglect: a case study. *Neuropsychologia,* 30, 657-672

Chatterjee, A., Thompson, K.A., Ricci, R. (1999). Quantitative analysis of cancellation tasks in neglect. *Cortex,* 35 (2), 253-262

Chedru, F. (1976). Space representation in unilateral spatial neglect. *Journal of Neurology, Neurosurgery and psychiatry,* 39, 1057-1061

Chelazzi, L., Duncan, J., Miller, E.K., and Desimone, R. (1998). Responses of neurons in inferior temporal cortex during memory-guided visual search. *Journal of Neurophysiology,* 80, 2918-2940

Chiba, Y., Yamaguchi, A., Eto, F. (2005). A simple method to dissociate sensory-attentional and motor-intentional biases in unilateral visual neglect. *Brain Cognition,* 58 (3), 269-273

Chokron, S., Imbert, M. (1993). Egocentric reference and asymmetric perception of space. *Neuropsychologia,* 31(3), 267-275

Colombo, A., De Renzi, E., Gentilini, M. (1982). The time course of visual hemiinattention. *Arch Psychiatr Nervenkr*, 231, 539-546

Corbetta, M. (1998). Frontoparietal cortical networks for directing attention and the eye to visual locations :identical, independent, or overlapping neural systems? *Proceedings of the National Academy of Sciences of the United States of America,* 95, 831-838

Corbetta, M., Akbudak, E., Conturo, T.E., Synder, A.Z., Ollinger, J.M., Drury, H.A. (1998). A common network of functional areas for attention and eye movements. *Neuron*, 21, 761-773

Coslett, H.B., Bowers, D., Fitzpatrick, E., Haws, B., Heilman, K.M. (1990). Directional hypokinesia and hemispatial inattention in neglect. *Brain,* 113, 475-486

D'Erme, M., Robertson, I., Bartolomeo, P., Daniele, A., Gainlotti, G. (1992). Early rightwards orientating of attention on simple reaction time performance in patients with left-sided neglect. *Neuropsychologia,* 30 (11), 989-1000

Daini, R., Angelelli, P., Antonucci, G., Cappa, S.F., Vallar, G. (2002). Exploring the syndrome of spatial unilateral neglect through an illusion of length. *Experimental Brain Research,* 144, 224-237

Damasio, A.R., Damasio, H., Chui, H.C. (1980). Neglect following damage to frontal lobe or basal ganglia. *Neuropsychologia,* 18, 123-132

De Renzi, E., Faglioni, P., Scotti, G. (1970). Hemispheric contribution to the exploration of space through the visual and tactile modality. *Cortex,* 6, 191-203

Denes, G., Semenza, C., Stoppa, E., Lis, A. (1982). Unilateral spatial neglect and recovery from hemiplegia: a follow-up study. *Brain*, 105 (pt 3), 543-552

Denny-Brown, D., Banker, B.Q. (1954). Amorphosynthesis from left parietal lesion. *AMA Arch Neurol Psychiatry*. 71 (3), 302-313

Driver, J., Halligan, P.W. (1991). Can visual neglect operate in object-centred coordinates?: An affirmative single-case study. *Cognitive Neuropsychology*, 8, 475-496

Driver, J., Mattingly, J.B. (1998). Parietal Neglect and Visual Awareness. *Nature Neuroscience*, 1, 17-22

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

Dronkers, N.F., Knight, R. (1988). Right-sided neglect in a left-hander: evidence for reversed hemispheric specialization of attention capacity. *Neuropsychologia*, 27, 729-735

Duhamel, J., Colby, C.L., Goldberg, M.E. (1992). The updating of the representation of visual space in the parietal cortex by intended eye movements. *Science*, 255, 90-92

Eidelberg, E., Schwartz, A.J. (1971). Experimental analysis of the extinction phenomenon in monkeys. *Brain*, 94, 91-108

Ellison, A., Rice, N.J., Walsh, V. (2003). Posterior parietal cortical involvement in visual search with fixed target location. *Journal of Cognitive Neuroscience*, 15, 76

Ellison, A., Walsh, V. (2000). Visual field asymmetries in attention and learning. *Spatial Vision*, 14, 3-9

Ellison, A., Rushworth, M.F.S., Walsh, V. Visual search and posterior parietal cortex: a visuomotor hypothesis. In: Paulus W., Tergau, F., Nitsche, M.A., Rothwell, J.C. Ziemann, U., Hallett, M, editors. Transcranial magnetic stimulation and transcranial direct current stimulation. Clinical Neurophysiology Supplement 56. Amsterdam:Elsevier; 2003. p 321-30

Ferber, S., Karnath, H. (2001). Size perception in hemianopia and neglect. *Brain*, 124, 527-536

Ferro, J.M., Kertesz, A., Black, S.E. (1987). Subcortical neglect: quantitation, anatomy and recovery. *Neurology*, 37 (9), 1487-1492

Fierro, B., Brighina, F., Oliveri, M., Piazza, A., La Bua, V., Buffa, D. (2000). Contralesional neglect induced by right posterior parietal rTMS in healthy subjects. *Neuroreport*, 7, 1519-1521

Fink, G.R., Marshall, J.C., Weiss, P.H., Stephan, T., Grefkes, C., Shah, N.J., Zilles, K., Dieterich, M. (2003). Performing allocentric visuospatial judgements with induced distortion of the egocentric reference frame: an fMRI study with clinical implications. *Neuroimage*, 20 (3), 1505-1517

Fink, G.R., Marshall, J.C., Shah, N.J., Weiss, P.H., Halligan, P.W., Grosse-Ruyken, M. (2000). Line bisection judgements implicate right parietal cortex and cerebellum as assessed by fMRI. *Neurology*, 54, 1324-1331

Fink, G.R., Marshall, J.C., Weiss, P.H., Toni, I., Zilles, K. (2002). Task instructions influence the cognitive strategies involved in line bisection judgements:evidence from modulated neural mechanisms revealed by fMRI. *Neuropsychologia*, 40, 119-130

Fitzgerald, P.B., Brown, T.L., Daskalakis, J.Z. (2002). The application of transcranial magnetic stimulation in psychiatry and neuroscience research. *Acta Psychiatr Scand,* 105, 324-340

Fox, P.T., Mintun, M.A., Raichle, M.E., Miezin, F.M., Allman, J.M., Van Essen, D.C. (1986). Mapping human visual cortex with positron emission tomography. *Nature*, 323, 806-809

Foxe, J.J., McCourt, M.E. (2003) Right hemisphere control of visuospatial attention: line-bisection judgements evaluated with high-density electrical mapping and source analysis. *Neuroimage,* 19 (3), 710-726

Galati, G., Lobel., E., Vallar, G., Berthoz, A., Pizzamiglio, L., Le Bihan, D. (2000). The neural basis of egocentric and allocentric coding of space in humans: a functional magnetic resonance study. *Exp Brain Res.*, 133, 156-164

Galuske, R.A., Schmidt, K.E., Goebel, R., Lomber, S.G., Payne, B.R. (2002). The role of feedback in shaping neural representations in cat visual cortex. *Proc. Natl Acad Sci USA*, 99 (26), 17083-17088

Gauthier, L., Dehaut, F., Joanette, Y. (1989). The bells test: a quantitative and qualitative test for visual neglect. *Int J Clin Neurosci.*, 11, 49-54

Halligan, P.W., Marshall, J.C. (1992). Left visuo-spatial neglect: a meaningless entity? *Cortex*, 28, 525-535

Halligan, P.W., Fink, G.R., Marshall, J.C., Vallar, G. (2003). Spatial cognition: evidence from visual neglect. *Trends in Cognitive Neuroscience*, 7 (3), 125-133

Halsband, U., Gruhn, S., Ettlinger, G. (1985). Unilateral spatial neglect and defective performance in one half of space. *Int. J Neurosci.*, 28 (3-4), 173-195

Harvey, M., Milner, A.D., Roberts, R.C. (1995). An investigation of hemispatial neglect using the landmark task. *Brain and cognition*, 27, 59-78

Harvey, M., Gilchrist, I.D., Olk, B., Muird, K. (2003). Eye-movement patterns do not mediate size distortion effects in hemispatial neglect: looking without seeing. *Neuropsychologia*, 41 (8), 1114-1121

Harvey, M., Olk, B., Gilchrist, I.D., Muir, K. (2002), Are size distortion effects in hemispatial neglect mediated by hemianopia and/or eye-movement patterns? *Cortex*, 38, 864-868

Harvey, M., Milner, A.D., Roberts, R.C. (1995) An investigation of hemispatial neglect using the landmark task. *Brain and Cognition*, 27, 59-78

Hayakawa, T., Miyauchi, S., Fujimaki, N., Kato, M., Yagi, A. (2003). Information flow related to visual search assessed using magnetoencephalography. *Cogn. Brain Res.* 15 (3), 285-295

Heilman, K.M., Bowers, D., Coslett, H.B., Whelan, H., Watson, R.T. (1985). Directional hypokinesia: prolonged reaction time for leftward movements in patients with right hemisphere lesions and neglect. *Neurology*, 35, 855-859

Heilman, K.M., Valenstein, E. (1979). Mechanisms underlying hemispatial neglect. *Neurology*, 95, 166-170

Heilman, K.M., Watson R.T., Valenstein, E., Damasio, A.R. (1983). Localisation of lesions of neglect. In localisation in neuropsychology (ed. A. Kertesz), pp. 455-70. Academic Press, New York.

Hornak, J. (1992). Ocular exploration in the dark by patients with visual neglect. *Neuropsychologia*, 30, 547-552

Ilmoniemi, R.J., Vintannen, ., Ruohonen, J., Karho, J., Aronen, H.J., Naatanen, R. (1997). Neural responses to magnetic stimulation reveal cortical reactivity and connectivity. *Neuroreport*, 8, 8537-8540

Ishiai, S., Furukawa, T., Tsukagoshi, H. (1989). Visuospatial processes, line bisection and the mechanisms underlying unilateral spatial neglect. *Brain*, 112, 1485-1502

Ishiai, S., Sugishita, M., Mitani, K., Ishizawa, M. (1992). Leftward search in left unilateral spatial neglect. *Journal of Neurology, Neurosurgery and Psychiatry*, 55, 40-44

Ishiai, S., Furakawa, T., Tsukagoshi, H. (1987). Eye-fixation patterns in homonymous hemianopia and unilateral spatial neglect. *Neuropsychologia*, 25, 675-679

Jalas, M.J., Lindell, A.B., Brunila, T., Tenovuo, O., Hamalainen, H. (2002). Initial rightward orienting bias in clinical tasks: normal subjects and right hemispheric stroke patients with and without neglect. *J. Clin. Exp. Neuropsychol.*, 24 (4), 479-490

James, T.W., Culham, J., Humphrey, G.K., Milner, A.D., Goodale, M.A. (2003). Ventral occipital lesions impair object recognition but not object-directed grasping: an fMRI study. *Brain*, 126, 2463-2475

Kanwisher, N., Woods, R.P., Lacoboni, M., Mazziotta, J.C. (1997). A locus in human extrastriate cortex for visual shape analysis. *Journal of Cognitive Neuroscience*, 9, 133-142

Karnath, H., Ferber, S., Himmelbach, M. (2001). Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature*, 411, 950-953

Karnath, H., Himmelbach, M., Rorden, C. (2002). The subcortical anatomy of human spatial neglect: putamen, caudate nucleus and pulvinar. *Brain,* 125 (2), 350-360

Karnath, H., Schenkel, P., Fischer, B. (1991). Trunk orientation as the determining factor of the 'contralateral' deficit in the neglect syndrome and as the physical anchor of the internal representation of body orientation in space. *Brain,* 114, 1907-1914

Karnath, H., Christ, K., Hartie, W. (1993). Decrease of contralateral neglect by neck muscle vibration and spatial orientation of trunk midline. *Brain,* 116 (pt 2), 383-396

Karnath, H., Fetter, M., Dichans, J. (1996). Ocular exploration of space as a function of neck proprioceptive and vestibular input-observation in normal subjects and patients with spatial neglect after parietal lesions. *Exp Brain Res.*, 109 (2), 333-342

Kertesz, A., Nicholson, I., Cancelliere, A. Kassa, K., Black, S.E. (1985). Motor impersistence: a right-hemisphere syndrome. *Neurology,* 35, 662-666

Kinsbourne, M. (1970). The cerebral basis of lateral asymmetries in attention. *Acta Psychologica*, 33, 193-201

Kolb, B., Whishaw, I.Q. (1996). Fundamentals of Human Neuropsychology. 4th edition. W.H Freeman, San Francisco.

Kristjansson, A., Vuillemier, P., Malhotra, P., Husain, M., Driver, J. (2005). Priming of colour and position during visual search in unilateral spatial neglect. *J Cogn Neurosci.*, 17 (6), 859-873

Ladavas, E., Pavani, F. (1998). Neuropsychological evidence of the functional integration of visual, auditory and proprioceptive spatial maps. *Neuroreport*, 9 (6), 1195-1200

Leibovitch, F.S., Black, S.E., Caldwell, C.B., Ebert, P.L., Ehrlich, L.E., Szalai, J.P. (1998). Brain behaviour correlations in hemispatial neglect using CT and SPECT: the Sunnybrook Stroke Study. *Neurology*, 36, 362-366

Levine, D.N., Benowitz, L., Calvinio, R.N. (1986). Left spatial neglect: effects of lesion size and premorbid brain atrophy on severity and recovery following right cerebral infarction. *Neurology*, 36, 362-366

Lomber, S.G., Payne, B.R. (2000). Contributions of cat posterior parietal cortex to visuospatial discrimination. *Vis. Neurosci.*, 17 (5), 701-709

Luna, B., Thurlborn, K.R., Strojwas, M.H., McCurtain, B.J., Berman, R.A., Genovese, C.R., Sweeney, J.A. (1998). Dorsal cortical regions subserving visually guided saccades in humans: an fMRI study. *Cerebral Cortex*, 8, 40-47

Malach, R., Reppas, J.B., Benson, R.B., Kwong, K.K., Jiang, H., Kennedy, W.A., Ledden, P.J., Brady, T.J., Rosen, B.R., Tootell, R.B.H. (1995). Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. *Proceedings of the National Academy of Science, USA*, 92, 8135-8138

Malhotra, P., Jager, H.R., Parton, A., Greenwood, R., Playford, E.D., Brown, M.M., Driver, J., Husain, M. (2005). Spatial working memory capacity in unilateral neglect. *Brain*, 128 (pt 2), 424-435

Malhotra, P., Mannan, S., driver, J., Husain, M. (2004). Impaired spatial working memory: one component of the visual neglect syndrome? *Cortex*, 40 (4-5), 667-676

Mannan, S.K., Mort, D.J., Hodgeson, T.L., Driver, J., Kennard, C., Husain, M. (2005). Revisiting previously searched locations in visual neglect: role of right parietal and frontal lesions in misjudging old locations as new. *J Cogn Neurosci*, 17 (2), 340-354

Marcel, A., Postma, P., Gillmeister, H., Cox, S., Rorden, C., Nimmo-Smith, I., Mackintosh, B. (2004). Migration and fusion of tactile sensation-premorbid susceptibility to allochiria, neglect and extinction? *Neuropsychologia*, 42, 1749-1767

Marotta, J.J., McKeeff, T.J., Behrmann, M. (2003). Hemispatial neglect: its effects on visual perception and visually guided grasping. *Neuropsychologia*, 41 (9), 1262-1271

Marshall, J.C., Fink, G.R., Halligan, P.W., Vallar, G. (2002). Spatial awareness: A function of the posterior parietal lobe? *Cortex*, 38, 253-257

Mesulam, M.M. (1981). A cortical network for directed attention and unilateral neglect. *Annals of Neurology*, 10, 309-325

Meyer, E., Ferguson, S.S., Zatorre, R.J., Alivi absatos, B., Marrett, S., Evans, A.C., Hakim, A.M. (1991). Attention modulates somatosensory cerebral blood flow response to vibrotactile stimulation as measured by positron emission tomography. *Annals of Neurology*, 29, 440-443

Michel, C., Pisella, L., Halligan, P.W., Luaute, J., Rode, G., Boisson, D. (2003). Simulating unilateral neglect in normals using prism adaptation: implications for theory. *Neuropsychologia*, 41(1), 25-39

Milner, A.D., Brechmann, M. (1992). To halve and to halve not: an analysis of line bisection judgements in normal subjects. *Neuropsychologia*, 30, 515-26

Milner, A.D., Roberts, H.M., Forster, S.V. (1993). Line bisection errors in visual neglect: misguided action or size distortion? *Neuropsychologia*, 31, 39-49

Milner, A.D., Jeannerod, M. (1987). Animal models for the syndrome of spatial neglect. In Neurophysiological and Neuropsychological Aspects of spatial Neglect. Pp. 259-288

Mort, D.J., Malhotra, p., Pambakian, A., Kennard, C. (2003). The anatomy of visual neglect. *Brain*, 126, 1986-1997

Muggleton, N.G., Juan, C., Cowey, A., Walsh, V. (2003). Human frontal eye fields and visual search. *J. Neurophysiol*, 89, 3340-3343

Na, D.L., Adair, J.C., Williamson, D.J.G., Schwartz, R.L., Haws, B., Heilman, K.M. (1998). Dissociation of sensory-attentional from motor-intentional neglect. *J. Neurol Neurosurg Psychiatry.*, 64, 331-338

Na, D.L., Adair, J.C., Kang, Y., Chung, C.S., Lee, K.H., Heilman, K.M. (1999). Motor perseverative behaviour on a line cancellation task. *Neurology*, 52, 1569-1576

Nobre, A.C., Gitelman, D.R., Dias, E.C., Mesulam, M.M. (2000). Covert visual spatial orienting and saccades, overlapping neural systems. *Neuroimage*, 11, 210-216

Nobre, A.C., Coull, J.T., Walsh, V., Frith, C.D. (2003). Brain activations during visual search: contributions of search efficiency versus feature binding. *Neuroimage*, 18, 91-103

Pascal-Leone, A., Gomez-Tortosa, E., Grafman, J., Always, D., Nichelli, P., Hallett, M. (1994). Induction of visual extinction by rapid-rate transcranial magnetic stimulation of parietal lobe. *Neurology*, 44, 494-498

Pisella, L., Berberovich, N., Mattingley, J.B. (2004). Impaired working memory for location but not for colour or shape in visual neglect: a comparison of parietal and non-parietal lesions. *Cortex*, 40, 379-390

Popplereuter, W.L. (1917). Die psychischen schadigungen durch kopfschuss kreig im 1914-1916: die storungen der nierderen and hoheren leistkungen durch verletzungen des oksipitalhirns vol 1 Leopold Voss, Leipzeig. (cited by Critchley, M. (1949). *Brain* 72, 540)

Posner, M.I., Walker, J.A., Friedrich, F.A., Rafal, R.D. (1987). How do the parietal lobes direct covert attention? *Neuropsychologia*, 25, 135-145

Posner, M.I., Walker, J., Friedrich, F.J., Rafal, R.D. (1984). Effects of parietal injury on covert orienting of attention. *J. Neuroscience*, 4, 1863-1874

Pouget, A., Driver, J. (2000). Relating unilateral neglect to the neural coding of space. *Current Opinion in Neurobiology*, 10, 242-249

Pourtois, G., Vandermeeren, Y., Olivier, E., De Gelder, B. (2001). Event-related TMS over the right posterior parietal cortex induces ipsilateral visuo-spatial interference. *Neuroreport*, 12 (11), 2369-2374

Ptak, R., Valenza, N. (2005). The inferior parietal lobe mediates distractor-resistant visual search of patients with spatial neglect. *J. Cogn Neurosci*, 17 (5), 788-799

Rafal, R.D., Posner, M.I. (1987). Deficits in human visual spatial attention following thalamic lesions. *Proc Natl Acad Sci USA*, 84, 7349-7353

Ricci, R., Pia, L., Gindri, P. (2004). Effects of illusory spatial anisometry in unilateral neglect. *Experimental Brain Research*, 154, 226-237

Robertson, I.H., Halligan, P.W., Bergego, C., Homberg, V., Pizzamiglio, L., Weber, E., Wilson, B.A. (1994). Right neglect following right hemisphere damage? *Cortex*, 30, 199-213

Robertson, I.H., Nico, D., Hood, B.M. (1995). The intention to act improves unilateral left neglect: two demonstrations. *Neuroreport*, 7 (1), 246-248

Rorden, C., Fruhman Berger, M., Karnath, H. Epub 19 February 2005. Disturbed line bisection is associated with posterior brain lesions. *Cognitive Brain Research*

Rushworth, M.F.S., Ellison, A., Walsh, V. (2001). Complementary localization and lateralization of orienting and motor attention. *Nature Neuroscience*, 4 (6), 656-661

Samuellson, H., Jenson, C., Ekholm, S., Naver, H., Blomstrand C. (1997). Anatomical and neurological correlates of acute and chronic visuospatial neglect following right hemisphere stroke. *Cortex*, 33, 271-285

Stewart, L., Ellison, A., Walsh, V., Cowey, A. (2001). The role of transcranial magnetic stimulation in studies of vision, attention and cognition. *Acta Psychologica*, 107, 275-291

Stone, S.P., Halligan, P.W., Greenwood, R.J. (1993). The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. *Age Ageing*, 22 (1), 44-52

Taylor, J.G. (2001). The central role of the parietal lobes in conciousness. *Consciousness and Cognition*, 10, 379-417

Thompson, K.G., Bichot, N.P., Sato, T.R. (2004)|. Frontal eye field activity before visual search errors reveals the integration of bottom-up and top-down salience. *J. Neurophysiol*, 93, 337-351

Tipper, S.P., Behrmann, M. (1996). Object-centred not scene-based visual neglect. *J. Exp. Psychol. Hum. Percept. Perform*, 22, 1261-1278

Treisman, A.M., Gelade, G. (1980). A Feature-integration theory of attention. *Cognitive Psychology*, 12, 97-136

Vallar, G. (2001). Extrapersonal visual unilateral neglect and its neuroanatomy. *Neuroimage*, 14, s52-58

Vallar, G., Dainia, R., Antonuccib, G. (2000). Processing of illusion of length in spatial hemineglect: a study of line bisection. *Neuropsychologia*, 38 (7), 1087-1097

Vallar, G., Perani, D. (1986). The anatomy of unilateral neglect after right-hemisphere stroke lesions: a clinical/CT-scan correlation study in man. *Neuropsychologia*, 24, 609-622

Vandenberghe, R., Gitelman, D.R., Parrish, T., Mesulam, M.M. (2001). Functional specialisation in parietal cortex. *Neuroimage*, 13, 368

Walker, R. (1996). Spatial and object-based neglect. *Neurocase*, 1, 371-383

Walker, R., Findlay, J.M. (1996). Saccadic eye movement programming in unilateral neglect. *Neuropsychologia*, 34, 493-508

Walsh, V., Ashbridge, E., Cowey, A. (1998). Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation. *Neuropsychologia*, 36, 45-49

Walsh, V., Ellison, A., Ashbridge, E., Cowey, A. (1999). The role of the parietal cortex in visual attention-hemispheric asymmetries and the effects of learning: a magnetic stimulation study. *Neuropsychologia*, 37, 245-251

Walsh, V., Ellison, A., Batelli, L., Cowey, A. (1998). Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5. *Proc. R. Soc. Lond.* 265, 537-543

Wasserman, E.M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation. *Electroencephalography and Clinical Neurophysiology*, 108, 1-16

Watson, R.T., Heilman, K.M., Cauthen, J.C., and King, F.A. (1973). Neglect after cingulectomy. *Neurology*, 23, 1003-1007

Watson, R.T., Heilman, K.M. (1979). Thalamic neglect. *Neurology*, 29, 690-694

Weintraub, S., Mesulam, M.M. (1988). Visual hemispatial inattention: stimulus parameters and exploratory strategies. *J. Neurol Neurosurg Psychiatry.*, 51 (12), 1481-1488

Wojciulik, E., Husain, M., Clarke, K., Driver, J. (2004). Spatial working memory deficit in unilateral neglect. *Neuropsychologia,* 39, 390-396

Wolfe, J.M. (1994). Guided search 2.0. A revised model of visual search. *Psycholog. Bull. Rev.*, 1, 202-228