To Catherine

The Modulation of Visuospatial Awareness in the Human Brain using Transcranial Magnetic Stimulation

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'I, Rupert Max Oliver, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

Signature:

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Abstract

This thesis describes a series of studies, involving healthy subjects and a carefully selected stroke patient, in which the techniques of Transcranial Magnetic Stimulation (TMS) and Signal Detection Theory (SDT) were combined to explore processing in the posterior parietal cortex (PPC) and the phenomenon of unilateral spatial neglect:

1) A new SDT-based TMS 'hunting' technique was developed and then employed successfully over the right PPC. This revealed a cortical node which could be modulated with 'online' 10Hz-TMS to exert control over subjects' visuospatial perception.
2) By targeting this 'hotspot' and an equivalent area in the left PPC with disruptive 'cTBS' (continuous 'Theta Burst' simulation), neglect-like effects in the healthy brain could be induced and alleviated. These effects were quantified using a newly developed, fully balanced, bihemifield detection paradigm
3) By using TMS to map visuospatial function over healthy right PPC, the 'hotspot' could be enlarged after exposure to excitatory, intermittent TBS (iTBS).
4) cTBS was applied to the left PPC of a patient with a right sided stroke and visuospatial neglect. In doing this, neglect and its alleviation were described for the first time in fully balanced SDT terms.
5) The cerebellum was targeted in healthy subjects with 1Hz inhibitory TMS which induced a shift in their subjective midline for 'imaginary' but not 'real' space, as measured with number or physical line bisection respectively.

These TBS studies lend support to Kinsbourne's hemispheric rivalry hypothesis and suggest that the extent of 'spatially eloquent' cortex in the right PPC can be increased. Both strategies could be useful in larger therapeutic studies of patients suffering from USN after right sided brain injury. The final study opens up an additional therapeutic target for patients with imaginal neglect and, for the first time, implicates the cerebellum in number line bisection.

Contents

Abbreviations

ACA	Anterior Cerebral Artery
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMT	Active Motor Threshold
ANOVA	Analysis of Variance
A-P	Antero-posterior
APB	Abductor Pollicis Brevis
BIT	Behavioural Inattention Test
c	criterion
CBS	Catherine Bergego Scale
CS	Central Sulcus,
CT	Computed Tomography
cTBS	Continuous Theta Burst Stimulation
d’	d-prime
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalogram
EMG	Electromyography
F	False alarm rate
FDI	First Dorsal Interosseous
fMRI(B)	Functional Magnetic Resonance Imaging (of the Brain)
GABA	γ-aminobutyric acid
H	Hit rate
HSD	Honestly Significant Difference
IPS	Intraparietal Sulcus
iTBS	Intermittent Theta Burst Stimulation

LED	Light Emitting Diode
LGN	Lateral Geniculate Nucleus
LTD	Long Term Depression
LTP	Long Term Potentiation
LVF	Left Visual Field
M1	Primary Motor Cortex
MCA	Middle Cerebral Artery
MEP	Motor Evoked Potential
Mg	Magnesium
MRI	Magnetic Resonance Imaging
N	Noise Distribution
NMDA	N-Methyl D-Aspartate
ns	not significant
PaHS	Parietal ‘Hot Spot’
PC	Personal Computer
PD	Presentation Duration
PPC	Posterior Parietal Cortex
RMT	Resting Motor Threshold
ROC	Receiver Operating Characteristic
rTMS	Repetitive Transcranial Magnetic Stimulation
RVF	Right Visual Field
S	Signal Distribution
S1	Primary Somatosensory Cortex
SDT	Signal Detection Theory
TBS	Theta Burst Stimulation
TMS	Transcranial Magnetic Stimulation

VIP Ventrolateral intraparietal (area)

Units

° Degrees

mA Milliamperes

mm Millimetres

ms Milliseconds

mg Milligrams

ml Millilitres

µs Microseconds

cm Centimetres

mV Millivolts

µV Microvolts

T Tesla

Hz Herz

SEM Standard Error of the Mean

SD Standard Deviations

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Overall Summary

Transcranial Magnetic Stimulation (TMS) is a powerful technique which enables the experimenter to excite or inhibit cortex in focal manner and thus scrutinise or alter the cortical systems that lie within. Signal detection theory (SDT) is an elegant probabilistic tool for quantifying perception and behaviour. Both techniques have been used separately to some extent in the study of one particular disorder of perception, that of unilateral spatial neglect. The central questions posed in this study are:

1) How well have TMS and SDT been combined thus far in the study of parietal cortical function and spatial neglect?
2) Could they be used together, to provide a new model of neglect in normal subjects and to explore neglect further in the clinical setting?

These questions are tackled in a series of experiments detailed in Chapters 3-6 and in the preceding introduction which reviews the literature on attention, neglect & TMS. In Chapter 2, a primer of SDT is offered and its use in the data analysis is explained; in Chapter 1 the methodology common to all experiments is described (more specific details are left to the relevant chapters).

Chapter 3 outlines a novel method for modulating visuospatial awareness in normal subjects by using TMS over the right PPC; it is the first such 'hunting' procedure to employ a signal detection approach.

Chapter 4 demonstrates the use of high frequency low intensity inhibitory 'Theta Burst' (TBS) TMS to create a temporary neglect-like virtual lesion in normal subjects. This is the first such

lesion to be described in complete SDT terms using a newly developed, fully balanced, bi-hemifield detection paradigm.

In the second half of Chapter 4, and in Chapters 5 and 6, two potential therapeutic avenues for the combined TMS/SDT approach are explored. The first stems from Kinsbourne's theory of hemispheric balance and uses TBS to disrupt the left PPC, whereas the second uses TBS to expand available visuospatial processing resources in the right PPC, by making a small part of it more 'visuospatially eloquent'.

The final Chapter explores one further question: can spatial judgment be modulated by applying TMS to brain areas which are not traditionally implicated in visuospatial awareness? Here the cerebellum is targeted with low frequency high intensity (1Hz) TMS whilst measuring another aspect of spatial awareness, the generation of the subjective midline, in both 'real' and 'imaginary' space.

These experimental chapters each lead on to a discussion of their methodological validity, their relevance to previous work and the new insights into spatial neglect which they provide. In the final chapter, the overall conclusions drawn from this work are discussed along with some ideas for future projects.

Introduction

This work is at heart a study of attention as directed selectively to different regions of visual space. In particular, it explores how cortical systems which distribute spatial attention can be manipulated by the experimenter both in the normal brain and therapeutically after stroke. The vast wealth of background knowledge which underpins this study can be focused into three broad introductory questions:

1) How does the normal brain distribute attention across visual space?
2) If the cortical systems which achieve this are disrupted e.g. in conditions such as unilateral spatial neglect, what clinical consequences follow?
3) Once damaged, what treatments exist to repair these systems, or at least to rebalance them?

We therefore begin with a description starting from the 'bottom-up', outlining the function of cortical areas involved in early visual processing, and the two major streams of information (the 'what' and 'where' pathways) which issue from them. A discussion of selective attention follows, including the various axes (spatial-temporal, object based-location based, bottom- up-top-down) along which selection occurs. This leads onto an account of one major clinical manifestation of disordered selective attention i.e. 'spatial neglect', and current treatment approaches. These include a powerful, relatively novel technique: Transcranial Magnetic Stimulation (TMS). The technical aspects of TMS are described along with an account of its modulatory effects on cortical functioning and how these relate to the concept of neuroplasticity.

i) Visual Processing and Attention in the Normal Brain

i.1 Anatomical and Functional Pathways

i.1.1 Early Visual Areas

Visual information from the retina flows to posterior areas of cerebral cortex via the lateral geniculate nucleus of the thalamus, and the optic radiations. The recipient of the vast majority of this information is the primary visual cortex or 'V1' which lies in the medial occipital lobe, almost entirely buried within the calcarine sulcus. Its other name, 'the striate cortex', results from its striped cytoarchitectural appearance when viewed under microscopy. Individual constituents of the visual information stream such as motion and colour are not fully processed in V1 but in a widely distributed network of areas, extending from the occipital poles to the posterior border of the parietal cortex (Zeki, 1995). This network (previously known as visual association cortex) surrounds V1, from which it receives the vast majority of its input. The retinotopic organization of V1 and its role as the primary gateway for retinal information travelling to higher cortical areas, earned it the former alias: 'the cortical retina' (Henschen, 1893). However, information also reaches the association areas directly, through pathways from the lateral geniculate nucleus, pulvinar or superior colliculus that do not pass through V1 (Fries, 1981; Yukie & Iwai, 1981; Standage & Benevento, 1983). These pathways may aid the rapid detection of moving objects (Sincich et al., 2004) and are thought to underlie the phenomenon of 'Blind sight', whereby patients with severe damage to either or both V1 areas, can still extract information from their blind hemifield(s) at a subconscious level (Cowey & Stoerig, 1991).

The cortical network that subserves visual processing (as mapped in the Macaque), contains over 30 distinct areas (Felleman & Van Essen, 1991), though for clarity the focus is best narrowed to 5 main areas: V1, V2, V3, V4 and V5. Evidence of function within these areas comes mainly from cell recordings in primates. Within V5, neurons fire selectively in response to moving stimuli and are sensitive to the direction of motion, whereas the colour of the stimulus has little influence on activity (Zeki, 1974). In humans, imaging studies locate V5 in the occipital lobe, posterior to the junction of the inferior temporal lobe and lateral occipital sulci (Dumoulin et al., 2000). Activation occurs in this area (on imaging with Positron Emission Tomography, or fMRI) when human subjects view moving checkerboards (Zeki et al., 1991; Watson et al., 1993; Dumoulin et al., 2000) or moving dot arrays (Tootell et al., 1995). Neurological lesions involving V5 cause a range of deficits, from near- total imperception of motion (Zihl et al., 1983) to more subtle deficits such as the inability to perceive movement of texture defined contours ('second-order' motion) (Plant & Nakayama, 1993).

In area V4, neurons are not sensitive to motion, but respond to specific wavelengths of light, and also the orientation of a stimulus' constituent lines (Desimone & Schein, 1987; Schein & Desimone, 1990). Area V3 has intermediate properties, responding to the shape and orientation (and to a lesser extent colour) of objects that are moving (Baizer, 1982; Felleman & Van Essen, 1987; Gegenfurtner et al., 1997). The overall functions of these areas have thus been summarized as V5: motion; V4: colour and 'form with colour'; and V3: 'dynamic form' (Zeki, 1992). The combined role of V1 and V2 has been likened to the 'post office' of the visual system in which different visual signals are assembled before being relayed to more specialized visual areas. Defined on the basis of cytoarchitectural and metabolic characteristics, regions of V1 termed 'blobs' contain high concentrations of wavelength selective cells, whereas cells in the intervening 'interblob' regions are form- and orientation-selective (Zeki, 1995). Both 'blob' and 'interblob' regions connect with corresponding regions of V2 defined on the basis of staining characteristics, ('thin stripe' and 'interstripe' regions respectively) and pass onward to area V4

thus providing information on 'form with colour'. Layer 4B of V1 contains cells which respond only fleetingly to stimuli and which are indifferent to colour (Zeki, 1992). This layer thus forms the principle output to areas V5 (Motion) and V3 ('dynamic form'). Both areas also receive input from the 'thick stripes' of V2 which contain cells sensitive to directional motion (see figure i.1). There is a high degree of connectivity between these and other visual areas of the primate cortex (Felleman & Van Essen, 1991). These connections, which tend to be reciprocal (Tigges et al., 1973), form a processing hierarchy within the visual system of some 14 or so layers. Within this complex intertwined hierarchy, 2 distinct processing complexes in the temporal and parietal lobes emerge, encoding crucial 'what' and 'where' information about objects in the visual field.

i.1.2 Higher Level Visual Processing: the 'What' and 'Where' Pathways

Neurons in early visual areas have narrow receptive fields e.g. < 1 degree^2 in Macaque V1 (Hubel & Wiesel, 1974), and are tuned to specific components of visual stimuli such as their luminance, contrast, orientation, direction of motion etc. (Schiller et al., 1976). Neurons in higher visual areas and have much wider receptive fields, e.g. 409 degrees^2 in the Macaque inferior temporal cortex (TE) (Gross et al., 1972). They are tuned to more complex stimuli such as faces, and facial expressions (Desimone & Ungerleider, 1989; Sugase et al., 1999), and to more complex stimulus properties, such as location in space (Yin & Mountcastle, 1977) and direction of motion (Steinmetz et al., 1987). In humans this pattern is replicated, with smaller receptive fields in V1 and larger fields in V4, as estimated from fMRI data (Smith et al., 2001). There is an overall gradient, marking a transition from abstract, fragmented aspects of visual perception, to more holistic aggregates which resemble our everyday visual experience (see Lamme, 2000). This flow of increasingly complex information is split into 2 parallel processing streams, the

'what' and 'where' pathways (Mishkin et al., 1983). To understand these fully, it is useful to revisit the neural processing for colour and motion described above.

In the Macaque, the segregation of visual information into 'colour' and 'motion' occurs very early in the visual system, at the level of the retinal ganglion cells producing a dichotomy of function which continues through higher levels of cortical processing. 'P-type' ganglion cells terminate in the parvocellular layers of the LGN, which in turn project to layers 4A and 4B of V1. Output from

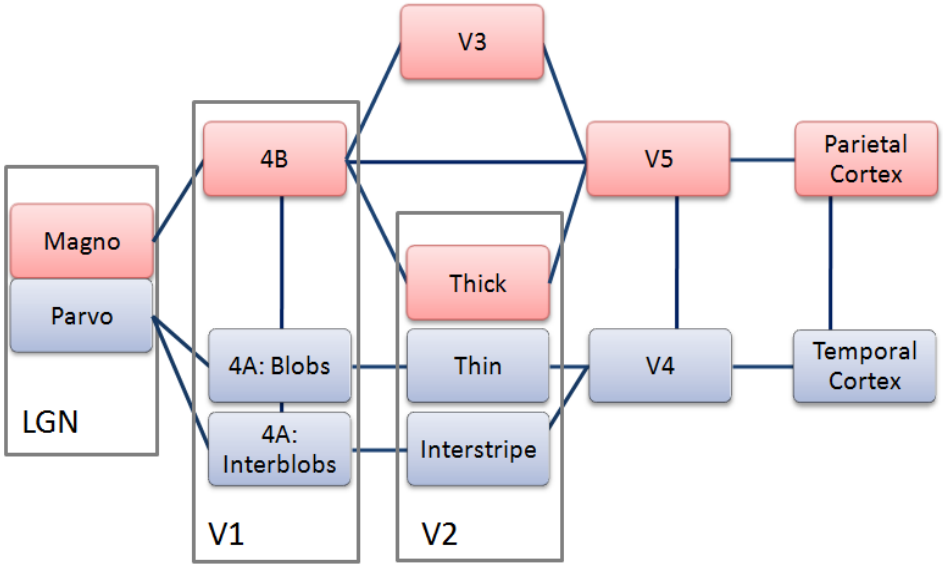

Figure i.1. A schematic representation of the main human visual cortical areas, and their subdivision into 'what' (blue) and 'where' (red) pathways. The 'what' pathway terminates in inferior temporal cortex and is concerned principally with object recognition and perception. The 'where' pathway projects to inferior parietal areas and processes information relating to space, movement and action. Interconnection between the 2 pathways occurs at numerous levels (vertical blue lines). Adapted from Lamme 2000.

these layers is to V4 (principally via V2) which in turn projects to the inferior temporal cortex, area 'TE'. This neural system is thought to process the 'what' characteristics of objects such as size colour texture and shape. The synthesis then emerges, of a unique configuration of characteristics that can be sorted and compared with subsequent stimuli (and which ultimately allows object recognition) (Tanaka, 1996). 'M-type' ganglion cells terminate in the magnocellular

layers of the LGN, which project to layer 4B of V1, which in turn has outputs to area V5 (directly and via V2), and area V3. This 'where' pathway ends in the inferior parietal cortex and processes information about an object's location in space, leading ultimately to the selection of certain objects for spaced-based-motor-action (Schneider, 1995). The streams of information are not mutually exclusive; the ventral system for instance does contain information about the retinal location of complex object features (Desimone & Duncan, 1995). There also exists considerable cross communication between the two streams e.g. at the level of V4 and V5 (Van Essen & Maunsell, 1983), and via common projections to pre-frontal cortex (Wilson et al., 1993). The existence of these 2 separate processing streams in the human brain is supported by fMRI studies in which object-identity and spatial-localization tasks activate ventral occipitotemporal cortex and dorsal occipitoparietal cortex respectively (Haxby et al., 1994; Ungerleider & Haxby, 1994). Objects in our visual world compete within and across these and other pathways to enter conscious perception and thus ultimately to influence our actions. These competitive processes, encompassed by the umbrella term, 'selective attention' are vast topics in themselves, but are described in outline below.

i.2 Selective Attention

i.2.1 Attention as a Filter

The finite nature of perception as a cognitive resource renders us unable to monitor all events (at least those which occur within range of our sensory receptors) simultaneously. The potentially overwhelming stream of everyday sensory input is instead narrowed by the selective focus of our attention, so that only the most relevant information reaches consciousness and guides behavior. This is vividly demonstrated by the phenomenon of sustained 'attentional blindness' where observers miss a hugely salient but unexpected event (a person wearing a

gorilla suit walking through a team of basketball players) whilst engaged in a cognitively demanding task (counting passes between players) (Simons & Chabris, 1999). The concept of attention as a filter is an old one; a century ago William James described attention as:

> *"the taking possession by the mind in clear and vivid form of one out of what seem several simultaneous objects or trains of thought."*

This idea was developed further by Donald Broadbent in 1958 using evidence from dichotic listening tasks. Subjects were played 2 different spoken messages (via headphones) but attended only to one of them. After hearing the messages, they were able to recall very little about the unattended message apart from gross changes in 'physical' attributes such as a change in pitch (e.g. a male voice changing to female). Based on this, Broadbent proposed two distinct stages for perceptual processing in which only a selection of stimuli from the first stage reach the second. In the first stage perceptual processing for simple 'physical' properties (such as pitch or location of sounds) are extracted in parallel for all incoming stimuli, whereas in the later stage more complex properties (e.g. the meaning of spoken words) are processed serially. To protect the limited capacity of the later stage, all stimuli without a particular physical property are filtered out and remain unattended. The degree to which stimuli are processed before the attentive 'filtering' stage is still not fully resolved. Some (like Broadbent above) argued that items are selected 'early' for further sensory processing, on the basis of rudimentary (pre-categorical) properties. Perception viewed in this manner is a *limited* process that requires selective attention to proceed. On the other hand, 'late selectionists' (e.g. Duncan, 1980) proposed that unattended stimuli were processed fully, and that attended stimuli were selected for action rather than identification. Put this way, perception is an *unlimited* process with selection occurring 'late' after full perception, its purpose being to provide the relevant motor response. In the 'late selectionist' model, the apparent paradox between full sensory processing and yet minimal awareness of unattended stimuli can be resolved if these stimuli fail to enter explicit

memory (Deutsch & Deutsch, 1963). Experimental evidence appears to support either viewpoint depending on the way in which it is interpreted, one example discussed below is the 'flanker effect' (Eriksen & Eriksen, 1974). A subject is asked to fixate on the centre of a screen and required to make a specific responses depending on the stimuli presented, e.g. respond left if shown a letter 'K' and right if shown an 'H'. Performance deteriorates (reaction times rise) if the target letter is flanked by 'noise' letters (distractors), with the largest effect produced by flankers encoding the opposite response direction to the target (i.e. 'K' flanked by 'H's as opposed to other random unspecified letters). Late selectionists would argue that full processing of both target and flankers has occurred, despite the subject only attending to the target. This must happen to allow the extraction of letter-encoded response information (the conflicting nature of which prolongs reaction times), as the letters cannot be identified on the basis of simple physical characteristics (such as orientation, size, or colour) alone. Early selectionists would retort that the subject must have unwittingly attended (serially) to both target and flankers, despite maintaining fixation on the target. This view is in turn supported by the fact that the flanker interference effect diminishes as the distance between target and flanker increases (see Driver, 2001). Attempts to bridge the 'early versus late' divide include the compromise that unattended stimuli are not completely filtered out but instead 'attenuated' (Triesman, 1969). This weak information could reach the second stage of processing but would not normally support the extraction of abstract concepts such as words, unless primed by the context and demands of the task. According to this view late selection can occur but only in exceptional circumstances, thus re-iterating a limited perception system. Another potential solution to the 'early vs. late' conflict is the 'perceptual load theory' (Lavie, 1995, 2004), where both early and late selection occurs depending on the task difficulty. High perceptual loads leave no perceptual capacity left for distractor processing and so early selection occurs, whereas low perceptual loads leave spare capacity for distractor processing and thus selection occurs later. This was

based on the observation that most of the evidence supporting late selection was collected under low perceptual load conditions (e.g. one target and one distractor) and vice versa.

i.2.2 Feature Integration and Visual Search

One influential example of early selection, the 'feature integration theory', was formulated in the 1980s specifically for the modality of vision (Triesman & Gelade, 1980). In this model, simple physical features are coded in parallel in the first stage of processing (i.e. no selective appraisal of individual locations is required) and then integrated serially in the second stage to form objects which are then attended and enter consciousness.

The model was based principally on evidence from studies of visual search tasks. In these the subject must identify the presence or absence of a target stimulus such as a vertical line, from a field of 'distractor' stimuli e.g. horizontal lines, as quickly as possible. In this example the discriminating physical property (orientation) is processed pre-attentively and the target 'pops out' from the distractor background almost immediately (see figure i.2). For this situation increasing the number of distractors in the search array makes no difference to performance (the function of the two is 'flat'), re-enforcing the view that for this single physical characteristic the whole array can be searched simultaneously. However when the target is no longer distinguishable on the basis of a single physical characteristic (e.g. a red vertical line in a field of green *vertical* and *red* horizontal lines), performance is much less efficient and deteriorates in a linear fashion as the number of distractors is increased (an increase of 50ms in target detection for each additional distractor is typical, Treisman & Gelade, 1980). In this case the features of each stimulus in the array must be integrated, requiring a serial search of the array with integration of each stimulus in turn until the target is reached.

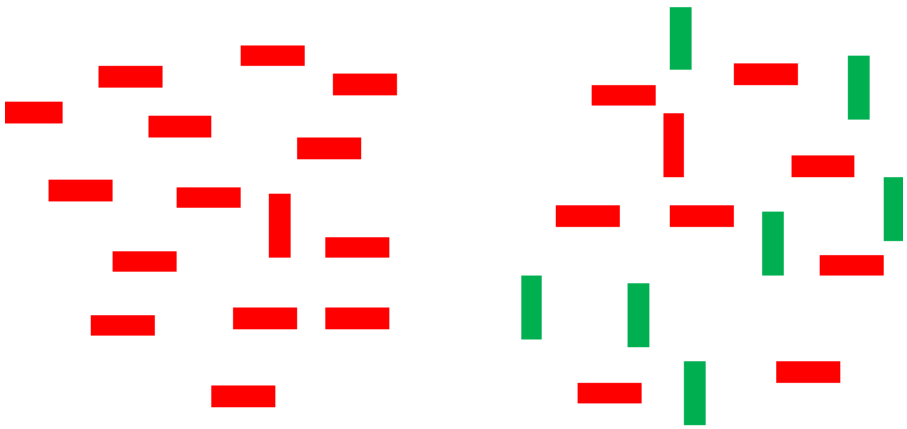

Figure i. 2. Examples of a simple ‘pop out’ array (left) and a more complex array (right) which requires serial attentive search to find the target (red vertical rectangle).

The feature integration theory does not provide a full explanation of selective attention because exceptions still exist to the rule of serial search for feature integration. Humphreys et al. (1989) found parallel search processes for complex targets that required an integration of features for recognition (inverted letter ‘T’s with upright ‘T’ distracters). Crucially this occurred when the array components formed a shape themselves (i.e. the stimuli were presented as if inscribed on the circumference of an imaginary circle), allowing group effects (see ‘Spaced-based and object based attention’ below) to segment distractors from targets, rather than a combination of individual stimulus features. Sophisticated targets such as Kanizsa figures (Davis & Driver, 1994) can also be detected in parallel without focal attention, suggesting that under the right circumstances even complex features such as shape can be extracted at an early pre-attentive stage (see figure i.3).

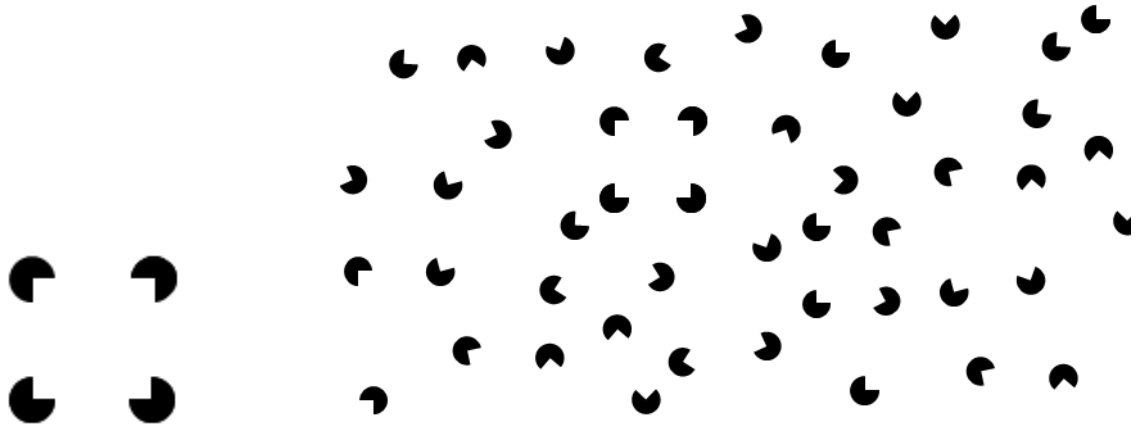

Figure i.3. Example of a Kanizsa figure (an illusionary square) is shown on the left, and again on the right amongst distracters. Note how the square shape 'pops-out' from the array without requiring a serial attentive search. Adapted from Davis & Driver, 1994

i.2.3 Attention as a 'Spotlight'

Visual search invokes the concept of a 'mental spotlight', which travels at high speed (usually but not always with an accompanying eye movement) to scan each item in the visual field until the target is found (Posner, 1984; Schneider & Shiffrin, 1977; Olhausen et al., 1993; Treisman & Gelade, 1980). The target may 'pop out' on the basis of a single simple property, in which case the 'spotlight' need not actively search but is instead drawn to the target (see 'bottom-up versus top-down influences' below). The idea of a moving spotlight is attractive as it fits well with the everyday experience of moving our eyes when attention is re-directed, and is intuitively re-enforced by common optically-derived phrases such as 'focus' of attention. It is also supported by studies showing a distance effect, where performance is disrupted only when target and distractors are close together (Eriksen & Eriksen, 1974). Thus near distractors interfere because they lie within the attentional spotlight focused on the target, whereas distant distractors fall outside the spotlight and are ineffective (Broadbent, 1982). The spotlight metaphor for attention

is however contradicted by other evidence which demonstrates that attention can be spatially dispersed (see 'Spaced-based vs. object-based attention below'). Other metaphors for attention include a 'zoom-lens', or a 'gradient' or contour map with (a) peak(s) at the most salient location(s) (Cheal et al., 1994). A gradient in attention between the left and right sides of space is a concept with particular importance in certain neurological disorders such as spatial neglect and is discussed in more detail later on pages 32-33.

i.2.4 'Covert' and 'Overt' Attention.

Attention may travel with or without an accompanying eye movement and subsequent foveation of the location of interest (i.e. an 'overt' shift in the former case and a 'covert' shift in the latter). However the reverse is not true, subjects cannot move their eyes to one location and attend to another (Hoffman & Subramaniam, 1995); saccades can thus be characterized as the overt manifestation of an internal shift of attention. Though a full account of eye movement control is beyond the scope of this work, there is little doubt that attention and saccadic eye-movements are intimately bound together. Covert shifts of attention are believed to help guide the eyes to appropriate locations in the visual field (Posner, 1990). In fact evidence suggests that a saccade from one location to another cannot be initiated until attention has been 'disengaged' from the first location. This process is thought to account for the gap in saccadic latency (typically 200ms) between the afferent signal (about 30ms) and efferent occulomotor delay (about 25ms) (Groner & Groner, 1989). Disengagement can be sped up if the start and end locations appear sequentially with no temporal overlap, evidence that these locations are in competition for attentional selection (Saslow, 1967).

i.2.5 Spaced-based and Object based Selection.

The feature integration theory, and mental 'spotlight' metaphor support a 'space-based' account of visual attention. The features to be integrated are specified by their common spatial location and the attentional spotlight selects these spatial locations in sequence for further processing. However competing evidence for 'object-based' selection also exists, where selection occurs on the basis of physical properties which group objects together such as colour or movement. For example, distractors which are spatially distant but contextually grouped with the target (e.g. both are moving) interfere more with performance than those which are closer to the target but static (Driver & Baylis, 1989). This result therefore conflicts with the 'spotlight' metaphor in which attention is allocated only to contiguous regions of the visual field, suggesting instead that attention is directed to perceptual groups whose components may be spatially dispersed. When subjects are cued to targets at one end of an object, they perform better than for targets placed at the un-cued end (Egly et al., 1994). This result is not particularly surprising in that pre-cues align covert attention to the location of target appearance (see p31). However this study also found that performance for targets at the uncued end of the same object was better than for other targets the same distance away but in a different object. This again supports the notion of selective attentional effects based on group attributes (being part of an object) rather than spatial location. Selective attention based on object selection has clear advantages over spatial selection in certain situations. For instance when faced with two objects that require different motor actions but occur intermingled in the same spatial location (e.g. a predator partially hidden by a tree) (Humphreys & Riddoch, 1993), spatial selection may weaken the 'flight response' generated by the partially occluded predator (whereas selection by object would group the visible parts into a 'whole' predator). Regardless of whether selection is made on the basis of object features or spatial location, a sought-after item (such as the target in a visual search task) must be held working memory, so that subsequent competition between the

elements of a visual scene can be resolved. This function of memory is referred to as the 'attentional template' (Duncan & Humphreys, 1989) and has been ascribed, on the basis of single cell recordings, to neurons of the inferotemporal cortex (Chelazzi et al., 1993).

i.2.6 Spatial and Temporal Competition for Selection

Behavioural evidence suggests that competition for attentional selection occurs in both temporal and spatial domains. Firstly, when healthy subjects are asked to monitor 2 streams of information simultaneously (on the left and right of the midline), performance suffers when targets appear in both streams at the same time, the 'two-target cost' (Duncan, 1980). Secondly, if attention is divided between two objects presented simultaneously at different spatial locations, performance is almost always poorer than if attention is focused on a single object. This decrement occurs largely independent of the objects' complexity or their degree of spatial separation (Desimone & Duncan, 1995). Thirdly, when subjects monitor a single spatial location, target-detection performance drops when two targets are presented in rapid succession. The second target is often missed if presented within a certain time interval (180-450ms) after the first, a phenomenon termed 'attentional blink' (Raymond et al., 1992).

Evidence from single cell recordings reflects this competition for selection in both spatial and temporal domains. When 2 stimuli are shown together within the receptive field of a single neuron (Moran & Desimone, 1985; Reynolds et al., 1999), the overall response does not depend on the sum of the stimuli but rather on the weighted average e.g. if response to stimulus 1 is x and to (stronger) stimulus 2 is $2x$, the overall response when both are presented simultaneously is not $3x$, but $1.5x$. This suggests a mutually suppressive spatial interaction between stimuli, resulting in a form of competition for neural representation (Kastner & Ungerleider, 2000). Stimuli that stand out from their background are processed preferentially at

nearly all levels of visual system. The response of a cell in V1 to its optimal stimulus can be almost completely suppressed by the encirclement of the original stimulus with multiple similar stimuli, and the suppression effect increases with the density of the surrounding stimuli (Knierim & Van Essen, 1992). Away from the spatial domain, studies of the infero-temporal cortex in the Rhesus Monkey reveal a suppressive temporal surround effect. In this area the number of neurons activated by a novel visual stimulus falls as the stimulus is presented repeatedly and becomes more familiar (Li et al., 1993). One important consequence of this reducing visual signal (in the context of visual search), is that the orienting system is not fixed to one location or object; after a certain period of time it will be free to re-engage in favour of a more novel competitor.

Under Positron Emission Tomography, brain areas (in healthy subjects) involved in early visual processing (such as the striate and extra striate cortex) are activated less by a contralateral stimulus when it is presented with a competing stimulus on the ispilateral side, than when presented alone. Thus when bilateral stimuli are shown, activity drops in visual areas on both sides even though the overall amount of stimulation has increased (Fink et al., 2000). This was interpreted as a form of inter-hemispheric competition between early levels of visual processing and may also be a neural correlate of the 'two-target cost'.

i.2.7 'Bottom-up' Versus 'Top-down' Influences on Attention

Selective attention relies on automatic stimulus-dependent processes that is not influenced by cognition or task demands, and which are said to occur in a 'bottom'-up direction. These operate on unprocessed sensory input to shift attention rapidly and involuntarily to salient visual features of potential importance (e.g. a red spot in a field of grass that could be a piece of fruit or the unexpected movement of a snake in the same field) (Connor et al., 2004). However an

attention system also needs to take long term goals into account (the need to eat, versus the need to avoid a snake bite) and thus exert control from the 'top-down'. In this way attention can be biased appropriately towards colour or motion detection, depending on how hungry or fearful of snakes we are at that moment. The visual search studies described above demonstrate both processes in the experimental setting. Attention can be captured by salient stimuli which 'pop out' from the background of distracters (i.e. bottom-up influences), whereas the volitional shifts of attention that occur as the visual array is searched are driven by knowledge of the current task (top-down influences).

A simple yet seminal example of how covert attention can be directed in a top-down manner is the 'pre-cued' task. When the spatial location of targets are indicated by a pre-cue, performance in terms of targets detected improves, but when the location indicated is false (invalid pre-cue) performance declines (Posner, 1978). Prior knowledge of the task allows observers to monitor only the relevant location(s) instead of all possible ones, and to allocate their attentional resources appropriately (when the cue is valid). More recent studies have characterised the benefit of spatial covert attention (as directed by precues) in terms of increased contrast sensitivity (Carrasco et al., 2000), and spatial resolution (Yeshurun & Carrasco, 1999). Performance is thus optimal when the central attention system is in alignment with the pathways to be activated by the visual input (Posner, 1980), a view supported by several converging lines of evidence as described below.

Single cell recordings from primate visual cortex (area V4) show an increased response when the animal (which has been trained to maintain central fixation) covertly attends to a location within the cells receptive field, as opposed to outside it (Spitzer et al., 1988). Similar results have been found for cells in V1, V2 and in dorsal stream areas such as V5 and the lateral intraparietal area (Kastner & Ungerleider, 2000). In human studies involving fMRI and event related potentials, further evidence of top-down influence emerges (Heinze et al., 1994;

Vandenberghe et al., 1997). Subjects were asked to direct attention covertly to either the right or left whilst presented with identical visual stimuli, appearing simultaneously at corresponding locations to the right and left of fixation. Despite the physical similarity of the stimuli, responses were enhanced only in the extrastriate cortex containing the representations of the attended hemifield (i.e. activity in the right extrastriate cortex increased when subjects covertly attended to the left and vice versa), a finding inexplicable solely through top-down mechanisms.

The top-down bias of covert attention need not be purely spatial, as demonstrated in the example of sustained attentional blindness given on pages 21-22. The attended (basketball players) and unattended ('gorilla') stimuli occupied the same spatial (and retinal) location at numerous point during the task, though the latter was often missed. In this case attention was directed by the complex demands of the task (follow and record the number of movements of one object between certain other objects), rather than a simple spatial cue.

i.2.8 Attention as a Gradient

In addition to the 'spotlight' metaphor for selective attention, other metaphors exist such as the 'zoom –lens' (Eriksen & St. James, 1986) or 'gate' (Reeves & Sperling, 1986). One metaphor with particular clinical relevance is that of the gradient. In theoretical terms attention can be viewed as a two-dimensional contour map in which the peaks are formed by prior biasing events, such as the appearance of pre-cues (Cheal et al., 1994). On a simpler level attention can be viewed along a single dimension such as left to right, a notion supported by well established anatomical models. In the normal brain the left-right gradient appears (almost) flat, but this can change radically (usually in favour of the right) after damage to the parietal lobe. Recordings from the ventrolateral intraparietal (VIP) areas in monkeys show that cells with receptive fields to a stimulus (e.g. dot of light) at a particular visual location fall in number as the stimulus moves across the visual field from contralateral to ipsilateral. Thus in the left VIP area

more neurons have more receptive fields for right sided visual locations than left, with the reverse situation in the right VIP (Andersen et al., 1990; Driver & Vuilleumier, 2001). Note that unlike earlier visual areas, there is no sharp change in the response of parietal neurons to a stimulus as it crosses the visual midline, but rather a gradual drop if the stimulus moves ipsilaterally or a gradual rise if the movement is contralateral. This gradient (as opposed to step) is reflected in the lateralised attentional deficit seen after parietal lobe damage. Other parietal neuron recordings demonstrate alternative representations of space within the parietal cortex. For instance a head-centered representation exists in VIP in addition to the retinocentric representation described above (Colby & Goldberg, 1999).

In humans the contribution of right and left parietal lobes to the distribution of attention is not symmetrical, PET evidence demonstrates activation of the right parietal lobe during shifts of attention in either direction, whereas activation of the left parietal lobe occurs only with shifts to the right (Corbetta et al., 1993). Overall it appears that the left hemisphere distributes attention almost exclusively over the right hemispace and co-ordinates rightward rather than leftward shifts of attention. In contrast, the right hemisphere distributes attention more evenly over both hemispaces and co-ordinates shifts in both directions (Mesulam, 1999).This underlying asymmetry is reflected in the clinical observation that patients with damage to the right parietal lobe often show deficits of attention to the left side of space, but those with damage to the left often display no deficit to the right side of space. This complex syndrome known as unilateral spatial neglect forms the focus of discussion in the following section.

ii) Disordered Attention: Unilateral Spatial Neglect

ii.1 Definitions

Neglect has been defined in clinical terms as: "the failure to report, respond, or orient to novel or meaningful stimuli presented to the side opposite a brain lesion, when this failure cannot be attributed to either sensory or motor defects" (Heilman 1993). It can also be viewed as a disruption to the normal allocation of attention between the left and right hemispaces, with attention biased towards the ipsilesional side (Mesulam 1999). For the afflicted patient, spatial neglect in its most severe form abruptly erases the meaningful existence of one half of their perceptual universe. This complex syndrome is described below in terms of its history, epidemiology, clinical presentation, underlying mechanisms and potential treatments.

ii.2 Historical Context

The leading role of the right hemisphere in visuospatial processes (in tandem with the language specialisation of the left hemisphere) was recognized in 1874 by Hughlings Jackson, who described 'imperception' for the left hand side in a patient with a large right sided cerebral tumour (Jackson, 1874, 1876). The First World War accelerated the study of spatial neglect (and clinical neuroscience as a whole) by providing (at a high price), many young patients with discrete cerebral lesions (Horrax, 1921). Towards the War's end, in 1917, Walter Popplereuter described 'inattention' in injured soldiers, whereby an object (e.g. the examiner's finger) was

detected when presented in isolation but went unreported when a competing object was presented at the same time (usually to the right) (see Halligan & Marshall, 1993). Modern terminology in fact designates this phenomenon as 'extinction' (see p33). George Riddoch (also in 1917) used clinical data to bring forward the concept of a localized, neural representation of space. He reported a series of patients with damage to the occipital cortex (area V1) including one with the inability to localise objects (in terms of describing their position, or when reaching out to touch them) despite perfect perception of light and shade, and intact binocular vision. They were also unable to determine which of 2 objects was nearest to them. Taken together, these deficits implied a problem that went beyond simple object representation, to encompass the space in which the objects were embedded. In 1918 Gordon Holmes also used the term 'inattention' to describe an important dissociation between 'visual disorientation' and 'object agnosia', showing that inattention could be linked to a particular region of space as well as to individual 'unrecognised' objects. Adding to these observations, Athanasio-Benisty concluded in her 1918 thesis that visual orientation depended on the integrity of the parietal lobe (Athanasio-Benisty, 1918).

The term 'neglect' is attributed to Pineas who used the German equivalent *'vernachlässigung'* in 1931 when describing a 60 year old patient with inattention to the left side in the absence of a field defect or sensorimotor deficit (Pineas, 1931; Halligan & Marshall, 1993). However it was not until a decade later that the seminal paper on neglect was published by Russell Brain (Brain, 1941). This case series built on previous observations, synthesizing together many key features of the neglect syndrome for the first time, the most important of which were: a) the localisation of the critical lesion to the posterior right hemisphere, b) the inadequacy of an explanation built solely on sensory deficits such as visual field defects (indeed in 1953 Critchley pointed out that in a certain patients, neglect could manifest clinically before the onset of visual defects and that in others, it could persist after the field defects had disappeared), and c) the manifestation of

inattention for both the left half of the body (as a form of amnesia) and the left half of external space.

Despite these advances in understanding, the field of neglect fell into a period of relative obscurity in the following decades. This may have been a consequence of the difficulty in conceptualising a deficit in spatial awareness which occurs counter intuitively, in the presence of normal vision, verbal, and cognitive function. It is also presents in a very variable fashion and cannot be elicited with the same consistency as can motor or 'pure' sensory deficits (Halligan & Robertson, 1992). In 1970's and 1980's renewed interest in neglect came from the development of new theories of normal spatial processing and selective attention (theories such as 'feature integration', p24). This has led to the modern formulation of neglect as a syndrome in which the spatial deficit can dissociate in a number of different ways. Firstly, depending on the reference frame used, neglect can be expressed in terms of retinal, egocentric, allocentric, or gravitational co-ordinates (Bisiach & Vallar, 1988; Vallar, 1998). Secondly, the deficit can be expressed in numerous distinct spatial domains such as personal, peripersonal, or far space (Halligan & Marshall, 1991) and even in imaginary space (Bisiach & Luzzatti, 1978). Finally, the deficit can occur in and across the sensory modalities of vision, audition, and tactile sensation, as well as in certain aspects of motor behaviour.

ii.3 Clinical aspects of Spatial Neglect

ii.3.1 Epidemiology, Natural History

Spatial Neglect affects approximately 25-30% of all stroke affected individuals (3-5 million/year worldwide) (Pedersen et al., 1997; Appelros et al., 2002). It manifests more frequently with right sided lesions (43 -82% of right brain damaged patients vs. 21-65% of left brain damaged

patients) (Bowen et al., 1999; Buxbaum et al., 2004; Parton et al., 2004; Milner & McIntosh 2005; Stone et al., 1993), reflecting a pre-existing lateralised distribution of attention. The normal variations that occur in the side of cerebral dominance may contribute to the variation in the side of neglect and location of the stroke. In general neglect of the right side following left hemisphere damage is harder to measure, and has less clinical consistency than left sided neglect following damage to the right hemisphere (Beis et al., 2004). The rate of recovery from neglect is greatest in the first month post stroke (Cassidy et al., 1998), and in one study of twenty patients, recovery (at 10.5 months) varied widely between none (20%), partial (65%), and full (15%) (Colombo et al.,1982).

Spatial neglect takes longer to resolve when it results from right hemisphere damage (Stone et al.,1991), and predicts poor overall outcome after right hemisphere stroke (Cassidy et al. 1998; Buxbaum et al. 2004). In particular functional recovery from associated hemiplegia after right hemisphere damage is slowed by the presence of unilateral left sided neglect (compared to right hemisphere damaged patients without neglect) (Denes et al., 1982).

ii.3.2 Clinical Features - Outline

Neglect may occur as part of a constellation of prominent motor and cognitive deficits following stroke and in the acute phase, severe spatial neglect can be detected by looking at the patient from the end of the bed. The patients head, eyes, and trunk may be drawn towards the ipsilesional side, and they may fail to attend or orient to people or events on their contralesional side (most commonly the left). This may produce bizarre, 'lop-sided' interactions with their environment such as failing to fill out one half of a form, or only eating from one side of a plate of food (Halligan & Robertson, 1992). Stimuli from the left may be perceived as coming from the right so that patients may turn rightward to address people standing on their left and may report a tactile stimulus to the left hand as being applied to the right (allesthesia). Despite intact

extraocular movement, scanning saccades are often reduced to the left (after right hemisphere damage) (Ishiai, 2006), a phenomenon that can be observed even during sleep (Doricci et al., 1993). This contralesional attentional void may encompass the patient's own body and, in the absence of a debilitating hemipariesis, they may fail to wash, dress or shave the contralesional side. In some cases the patient may appear unconcerned, and attempt to 'down-play' the severity of their problem inappropriately (anosdiaphoria). In extreme cases they may deny that a problem exists at all (anosognosia), or by denying ownership of their paretic limbs, try to rationalize it away as someone else's concern. Not surprisingly, these aspects of neglect are major obstacles to motor rehabilitation.

ii.3.3 Neglect as distinguished from hemianopia

Neglect is very different from the retinotopic blindness that follows occipital cortical damage. Light will remain invisible in the hemianopic visual field no matter which direction the patient's eye head or body faces. In the neglect patient however, a light which seems invisible when presented to the patient's left can be brought back into awareness if the patient's trunk is rotated leftward (whilst keeping the eyes and head straight ahead, see figure ii.1) (Karnath et al., 1991).

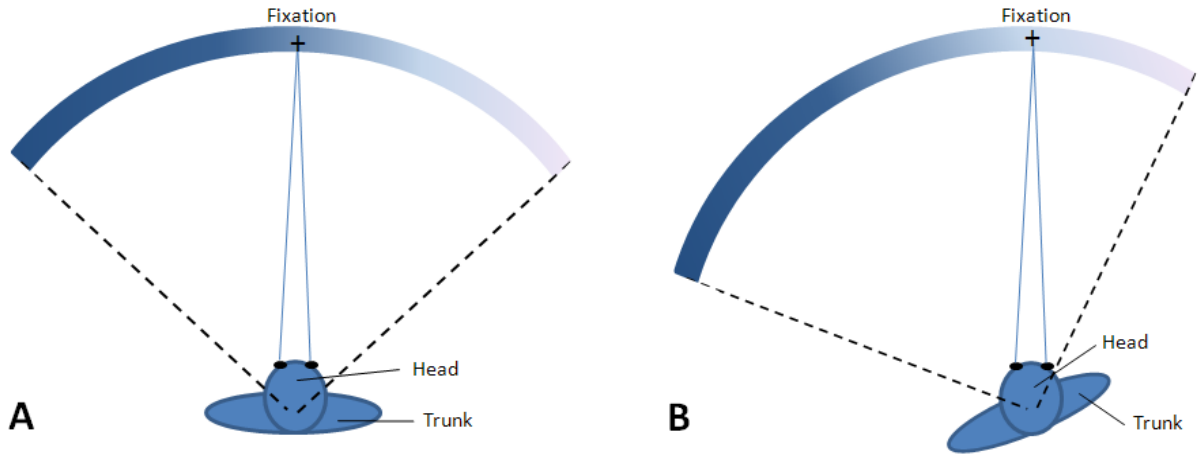

Figure ii.1. A Diagram of a patient (viewed from above) with *trunk-centered* (as opposed to retinotopic) neglect, with their gradient of attention represented by the shaded arc. The darker leftward end corresponds to areas of space to

which little attention is directed whereas the brighter shades towards the right indicate that attention is allocated normally. In A. the patient's head and trunk are aligned, with gaze also directed straight ahead (for simplicity the patient is shown facing forwards, though in reality many patients orient their eyes, head and even trunk towards the right) . Stimuli to the left of fixation therefore lie in an area to which relatively little attention is distributed. In B. the trunk is rotated anticlockwise (as viewed from above), whilst the head remains pointed straight ahead. Note how the region of space to the left of fixation now receives a greater allocation of attention, allowing previously unreported stimuli to reach awareness.

This supports the theory that neglect can be defined in number of different co-ordinate systems, not just retinotopic. In addition, hemianopic patients do not typically display neglect in everyday life or on cancellation tasks because they actively shift their gaze and bring objects into their unaffected hemifield. Indeed these patients exhibit a line bisection error in the opposite direction to those with neglect; probably as a consequence of a strategic adaptation to hemianopia i.e. attention and eye movements are biased towards the *contralateral* hemispace (Barton & Black, 1998). Testing with semantic priming and Kanizsa-figure tasks shows that neglect patients are still able to process and use complex information from the neglected hemifield, in contrast to hemianopic patients (Driver & Mattingley, 1998).

Extinction is an important phenomenon which also distinguishes neglect from visual cortical damage (Driver & Vuilleumier, 2001), and exists when a patient "fails to respond to one of two simultaneously presented stimuli; despite the fact that each stimulus is correctly detected and localized in isolation" (Rapsak et al., 1987). The spatial deficit in such patients is only apparent in competitive situations, for instance ipsilateral visual stimuli can 'extinguish' contralesional stimuli when both are presented simultaneously. Afflicted patients can detect a single left-sided event in isolation, missing this only when presented in combination with another event further to the right (Desimone & Duncan, 1995; Driver et al., 1997; Driver & Vuilleumier, 2001; Marzi et al., 2001). Extinction may also be seen in the normal brain. When healthy subjects are asked to monitor 2 streams of information simultaneously (on the left and right of the midline),

performance suffers when targets appear in both streams at the same time (Duncan, 1980, Shiffrin et al., 1972). This physiological limitation for multiple targets (the 'two-target cost') is not strictly lateralised however, distinguishing it from clinical extinction where targets are missed in a predictable (left-sided) fashion. Extinction can thus be viewed as an exaggerated, spatially-lateralised version of the 'two-target' cost. In healthy subjects, inter hemispheric competition occurs between early visual areas when stimuli are shown simultaneously in both visual fields. The resulting bilateral drop in visual cortical activity seen under PET has been interpreted as the physiological basis for visual extinction (Fink et al., 2000).

ii.3.4 Clinical Features – Classification

Neglect is not a single 'all-or-nothing' phenomenon, but a constellation of deficits which may overlap or dissociate to differing extents in different patients. One broad classification system divides neglect by modality into sensory, motor and representational; and also by distribution into personal, peripersonal or extrapersonal neglect.

Sensory Neglect involves the failure to attend to sensory input in one or more sensory modalities (e.g. visual, auditory, touch) from the contralateral side of space (Plummer et al., 2003).

Motor Neglect describes the failure to initiate movement to a contralesional stimulus even though the limb involved is not weak. When such movements do occur they are often hypometric and bradykinetic, but if the patient's attention is deliberately focused on the contralesional hemispace, they become more normal (Heilman et al., 1979). These phenomena occur on a background of general under utilization of the affected limb. In addition, interactions akin to visual extinction have been observed in the motor system of neglect patients. For example left sided visual neglect reduces if the 'neglected' object is touched or manipulated by

the left hand, but this advantage completely disappears if the right hand is co-activated (Robertson & North, 1994).

Representational Neglect occurs when a patient ignores the contralesional half of internally generated images. This was first demonstrated in 2 Milanese patients who were asked to imagine that standing in the 'Piazza del Duomo' (in Milan) and describe the familiar landmarks to their right and left (Bisiach & Luzzatti, 1978). The patients consistently under–reported the left sided landmarks even when asked to rotate 180º in their imaginary space. Another form of representational space is the 'mental number line' where numbers are aligned left to right with smaller numbers to the left and larger numbers to the right. Number line judgment is disrupted in spatial neglect after right hemisphere damage, with patients showing positive deviation (rightward along the number line) when asked to define the midpoint between two numbers (Zorzi et al., 2002).

The terms *Personal*, *Peripersonal* and *Extrapersonal Neglect* refer to a dissociation seen in some patients, where neglect occurs only for areas of space on the person or within or beyond a certain distance, demarcated by the patient's reach. Thus severe rightward deviation on line bisection as performed with a pen may disappear completely when the line is moved backwards, and a hand held torch is used instead to indicate the midpoint (Halligan & Marshall, 1991). Interestingly, the peripersonal region of space affected by neglect can be artificially extended by tool use. For example in a similar patient to that described above, the rightward line bisection error disappeared when marking the distant line with laser pointer and then returned when marking the same line with a pointer stick (Berti & Frassinetti, 2000).Clinical studies in neglect patients (Halligan & Marshall, 1991), and TMS 'virtual lesion' studies in normal subjects (Bjoertomt et al., 2002) both place the anatomical lesion for near space in the posterior parietal cortex and for 'far' space in the inferior temporal cortex. This difference of anatomical location is thought to reflect the greater reliance on the dorsal 'where' stream for directing grasping

movement to objects within reach, and on the ventral 'what' pathway for the recognition of more distant objects (e.g. as a prelude to moving within reach if the object is desirable).

Patients with neglect may also display non-lateralised deficits such as: impairments in sustained attention; a bias to local features in a visual scene; a deficit in spatial working memory; and a prolonged time course of visual processing, depending on the cortical areas affected (Parton & Husain, 2004).

ii.3.5 The Anatomical Lesions Associated with Spatial Neglect

There has been much debate surrounding the anatomical location of the 'neglect lesion' and its constituent components. Most of the current evidence comes from imaging studies which look for the common lesion overlap in a group of patients with a particular spatial deficit. Early studies of this type collated evidence from Computed Tomography scans and found an area of lesion overlap located over the supramarginal gyrus of the inferior parietal lobule and temporoparietal junction (Heilman et al., 1983; Vallar & Perani, 1986). However these studies did not properly distinguish the clinical components of neglect such as inattention and extinction, and patients both with and without visual field deficits were included. Karnath et al. addressed these issues by comparing lesion overlap on MRI scans for patients with either 'pure neglect' without extinction or 'pure extinction' without neglect; only patients without visual field defects were studied. The different spatial deficits dissociated in terms of anatomical lesion location i.e. the temporoparietal junction in patients with 'pure extinction' and the superior temporal gyrus in patients with 'pure neglect' (Karnath et al., 2003). Husain & Rorden questioned this rather anterior locus for 'pure neglect', suggesting that an anterior bias could have arisen from the exclusive selection of patients without visual field deficits (Husain & Rorden, 2003). In fact a subsequent study using higher resolution lesion mapping methods which included patients *with* visual field deficits, found areas of lesion overlap in more posterior locations: the angular gyrus

of the parietal lobe and medial temporal lobe (Mort et al., 2003). This was countered the following year by Karnath et al. (2004) with a large study (involving 140 patients – unselected in terms of visual field loss) that re-confirmed the area most consistently associated with neglect as the right superior temporal cortex. Attempts to resolve these different viewpoints have been made in subsequent years. Such studies suggest a role for *both areas* depending on the reference frame studied (i.e. involvement of the right angular and supramarginal gyri in egocentric neglect, and the right superior temporal gyrus in allocentric or 'object centred' neglect) (Hillis et al., 2005), or clinical tests used (line bisection vs. cancellation tasks) (Golay et al., 2008). Overall the areas implicated in spatial neglect encompass an 'attentional network' stretching from occipital visual association areas (Hillis et. al., 2006) to the middle and inferior frontal gyri (Mort et al., 2003), and which include sub cortical structures such as the basal ganglia and thalamus (Hillis et al. 2002).

Patients with spatial neglect after damage limited to the frontal lobe have been reported but are rarer than those with parietal (or parietofrontal) damage, and tend to recover earlier (Parton & Husain, 2004). In such patients the area most commonly involved is the dorsal aspect of the inferior frontal gyrus, believed to be a right sided homologue of Broca's area (Husain & Kennard, 1996). This area (close to the Frontal Eye Field in monkeys) is thought to aid in the generation of exploratory eye movements to the opposite side of space. Hence patients with localised frontal right sided damage tend to exhibit deficits for cancellation tasks (which require visual search), rather than line bisection tasks, in which performance is relatively preserved. In contrast parietal neglect patients suffer reduced performance in both tasks (Husain & Kennard 1996, 1997). Motor neglect is usually seen in the setting of frontal lobe damage (Husain et al. 2000), though the link is by no means absolute. In one study, neglect patients with either frontal or right inferior parietal lesions were tested, but only the latter displayed motor neglect (Driver & Mattingley, 1998).

ii.4 Clinical Tests Used to Measure Spatial Neglect

Most clinical tests involve observing the patient's behaviour whilst they perform a simple paper and pencil based task. One of the simplest and most commonly used of these bedside tests is line bisection. Here patients are asked to mark the centre of pre-drawn horizontal lines, presented on an A4 sheet of paper. The paper is usually centred on the patient's midline, and the preferred or unaffected hand is used. Neglect patients tend to ignore the leftward portion of the lines and mark to the right of the midline. This behaviour contrasts with that found in hemianopic patients (without neglect) who show an adaptive increase of attention directed eye movements towards the affected hemifield, and tend to mark the line to the left of midline (Barton & Black, 1998). As neglect is often associated with hemianopia, careful assessment of the visual fields is important (Gianutsos & Matheson, 1987). Line bisection has a good inter test-reliability but relatively poor sensitivity (60%) when compared with other paper based tests such as cancellation tasks (Ferber & Karnath, 2001), in fact some studies put its sensitivity as low as 23% (Marsh & Kersel, 1993).

Cancellation tasks involve the patient searching for and crossing out target symbols presented on a page (e.g. letters, stars, bells etc.). The most effective version of the cancellation task is the 'star cancellation' test, which has a diagnostic sensitivity of 80-100% and specificity of 91% (Marsh & Kersel, 1993; Jehkonen et al., 1998). The test consists of a page printed with 56 small stars, 52 large stars, 13 letters, and 10 short words, with the goal to have the patient locate and cross out all of the small stars. The maximum score that can be achieved on the test is 54 points (56 small stars in total minus the 2 used for demonstration) with a score of less than 44 indicating the presence of unilateral spatial neglect. The number of stars cancelled on the left/total number cancelled = the 'Laterality Index' or 'Star Ratio' (0 to 0.46 indicates neglect of

the left hemispace, 0.54 to 1 indicates neglect of the right hemispace). In the research setting, it can be particularly revealing to record patient's eye movements during these tasks. Patients with neglect miss the left sided targets and tend to repeatedly scan the same rightward areas with their eyes, as if unable to disengage attention from the right (Mannan et al., 2005).

A simple fore-runner of the star cancellation test is the 'Albert cancellation task' where forty 2.5cm lines are presented on a sheet of paper (Albert, 1973). Though this test correlates well with line bisection (r=0.83) (Agrell et al., 1997), it has rather poor sensitivity (57%) and low specificity (43%) (according to one study of 205 patients, Fullerton et al., 1986). Other more recent versions of the cancellation task include the Mesulam shape cancellation test and the Bell cancellation test. In the Bells Test for example, the patient is asked to circle all 35 targets (bells) embedded within 280 distractors (houses, horses, etc.). The distribution of the objects on the sheet of paper appears random but actually consists of 7 columns containing 5 targets and 40 distractors each (for lateralised coding of patient errors).

The copying of figures (e.g. a clock face) is widely used to test for spatial inattention; neglect patients will often miss out the left hand part of the figure or displace the left sided elements to the right. The diagnostic sensitivity of these tests is generally low (57.5%) (Bailey et al., 2000) but remains consistent over long periods, even for patients at 1.3 years post stroke (Johannsen & Karnath, 2004). The most sensitive figures are generally thought to be the clock face, a human form, or a butterfly (Halligan et al., 1991). The specificity of such tests suffers however, in that cognitive impairment and constructional apraxia may also result in poor copying and drawing performance (see Plummer et al., 2003).

Of course, the assessment of spatial neglect is not complete without some simple observation of behavior, in particular watching the patient walking, dressing, grooming, and reading (e.g. by using the indented paragraph test). Indeed the behavioural assessment of neglect in daily life is

(according to one large study) the most sensitive (77%) single measure of neglect (Azouvi et al., 2002). Such observations can be formalised in the form of a checklist known as the Catherine Bergego Scale (CBS) (Azouvi et al., 1996). This consists of 10 items, covering aspects of behavior in (left) neglect patients such as failing to shave the (left) side of the face, not wearing the (left) sleeve of clothing or the (left) slipper, collisions with objects on the (left) etc. Neglect-like behaviour is rated for each item on a scale of 0-3 (absent: 0, mild: 1, moderate: 2, severe: 3), yielding a total score out of 30. This method of assessment has considerable validity in that the scores obtained correlate well with other tests of neglect such as cancellation tests and figure copying (Azouvi et al., 1996).

Many of the tests described above are combined in various different batteries, the most prominent of which is the Behavioural Inattention Test' (BIT) (Wilson et al., 1987). This comprises of six 'conventional' subtests: line crossing, letter cancellation, star cancellation, figure copying, line bisection, free drawing, and nine 'behavioural subtests' (including picture scanning telephone dialing, coin sorting etc.). The test is simple to administer, taking 45 minutes to complete and is thought to have good ecological validity (Plummer et al., 2003).

All the tests described above are limited in the degree to which personal and peripersonal neglect can be distinguished, as all are completed within grasping distance. This problem is addressed by the Semi-structured Scale for Functional Evaluation of Hemi-inattention which divides tasks into personal (e.g. hair combing) and extrapersonal (e.g. picture description). Although the extra personal test scores correlate well with standard diagnostic tests such as line cancellation, the personal tests do not (Zoccolatti et al., 1992), and the administration of the test itself requires intensive training.

Another major limitation which applies to all of the tests is the inability to separate sensory and motor neglect. This is because all tests require some form of motor response so, for instance, a rightward line bisection error could be due visual inattention of the left hand edge of the line or a general reluctance to make leftward movements i.e. motor neglect.

ii.5 Treatment of Spatial Neglect

ii.5.1 Behavioural Approaches

One of the simplest methods is verbal encouragement, e.g. asking patients to attend more to the left side of space during reading so that after a period of training, they habitually find the left hand edge of the page before reading each line of text. This can be facilitated with a sensory 'anchor', such as a red bookmark on the left hand edge of the page. Though reliable, therapeutic results are very narrow and specific, failing to generalise to other everyday tasks and or even beyond a particular book (Lawson, 1962). More generalisable effects are obtained with intensive systematic training, e.g. for 40 hours a week using a variety of different tasks (such as reading, naming objects in arrays, tracking objects as they move into the left visual field) (Pizzamiglio, 1992).

Knowledge that neglect can operate in different reference frames lead to the successful employment of a very simple therapeutic techniques such as asking patients to rotate their trunk to the left as they looked straight ahead. This manoeuvre leads to more of the visual scene falling to the right of their egocentric midline, and thus markedly reduced left sided inattention (as delineated in craniotopic coordinates) (Karnath et al., 1991). The drawback to this technique is that neglect patients are unlikely to make this trunk rotation to the left without prompting, preferring instead to orient their trunk head and eyes to the right.

In general, therapeutic training that closely resembles actual day-to–day tasks encountered by patients (e.g. guided navigation in the patient's own wheelchair, avoiding objects on the left) is more successful than more abstract techniques (Manly, 2002).

ii.5.2 Eye Patching and Hemifield Occlusion

This technique involves the patient wearing either a patch over one eye (usually the right), or glasses which occlude vision to one hemifield (usually the right). The former approach may seem odd given that the left eye receives input from both sides of space (so covering the right eye causes only a minimally lateralised reduction of visual input). The reduction in visual input from the right eye was thought to reduce activity in the left superior colliculus (which receives input from the right eye rather than from the right hemifield). In neglect patients this structure is thought to be overactive and inhibiting of the right colliculus. The technique was therefore envisaged as a benign form of the 'Sprague' effect, where left sided hemianopia (experimentally induced in cats) can be alleviated by lesioning the left superior colliculus (Sprague, 1966). Results on the whole have been disappointingly variable, with some studies reporting improvement (Butter & Kirsch, 1992) and others finding a worsening of neglect for some patients, or improvements with left eye rather than right eye patching (Walker et al., 1996). More reliable results were obtained by blocking vision from the right hemifield. In one study patients wore glasses with lenses that where opaque on the right side. After 1000 hours of use, spontaneous eye movements to the left increased in parallel with a general improvement in the patients' daily function (Beis et al., 1999).

ii.5.3 Prism Adaptation

Prisms produce an optical shift of the visual field. For instance wedge-shaped prisms with the thick end or base on the left produce an optical shift (e.g. 10 degrees) of the visual field towards the right. In normal subjects this shift is largely unnoticed until the subjects wearing the prisms (set into goggles to exclude any 'unshifted' part of the visual field) attempts to point at a target. They find themselves unable to hit the target, instead deviating to the right of the true target location, (towards the perceived target location). With practice (50 or 60 trials), this terminal

error reduces, but once the prisms are removed the subjects make errors in the opposite direction (leftward) (Redding et al., 2005). During practice, vision of the starting hand position is usually occluded to ensure optimal development of this leftward visuo-manual adaptation. Two different mechanisms are thought to underlie the adaptive process: 1) An immediate 'strategic' component mediated in the posterior parietal cortex, and 2) a longer term true 'adaptive' component which relies on the cerebellum (Pisella et al., 2006). The former process involves rapid 'conscious' recalibration of the pointing movement, largely under feed-forward control. The latter process requires an incremental re-alignment of the visual and proprioceptive spatial maps that have been misaligned by the prismatic optical shift, under feedback control (Redding & Wallace, 2006). This leftward adaptive shift can be harnessed to ameliorate left sided neglect in stroke patients by exposing them to rightward deviating prisms (as demonstrated by Rossetti et al., 1998). Before exposure the patients' pointing movements deviated to the right by 9°, an error exaggerated by the rightward shifting prisms. However, after a short period of adaptation (lasting 2-5 minutes), the error reduced back to baseline levels and then remarkably, when the prisms were removed, the patients rightward error shrank to only 2°. This improvement in midline judgement was reflected in other clinically based tests such as line bisection, target cancellation and figure copying, and lasted for up to 2 hours. More recent studies in using 20 prism exposures over a 2 week treatment period reported therapeutic effects lasting up to 17 weeks (Frassinetti et al., 2002). The adaptive leftward shift in patients (Rossetti, 1998) represents a large compensation (70%) for the 10° rightward shift caused by prism exposure, considerably greater than the compensation seen in normal subjects (30%). This is thought to reflect the reliance of neglect patients (who have parietal damage), on the cerebellar-mediated 'true' adaptive component-, rather than the parietal-based strategic component of prism adaptation.

ii.5.4 Neck Muscle Vibration

Vibrating the left posterior neck muscles simulates muscle lengthening and gives an illusory sense of the head turning to the right (and thus the trunk to the left). This causes a leftward shift in the subjective sense of straight ahead (relative to the trunk), and thus should improve spatial judgment in some patients with spatial neglect. This technique was used in one illustrative study to treat 6 neglect patients (20 minutes for 10 days). The treatment resulted in a significant improvement of the patients' left sided inattention (as measured with a target detection task) with effects lasting for up to 2 weeks (Johannsen et al., 2003).

ii.5.5 Pharmacological intervention

One promising intervention is the administration of oral Guanfacine, a noradrenergic agonist. This agent is thought to act on post synaptic α2A receptors in the dorsolateral prefrontal cortex (DLPFC), improving sustained attention via central noradrenergic pathways. The hypothesis that this action would improve the non-spatial aspects of neglect has been tested in patients with right parietal, or both right frontal and right parietal damage (Malhotra et al., 2006). Performance in a computerised cancellation task improved after administration of Guanfacine (as compared to placebo) but only in those patients with intact frontal cortices. This finding suggested that modulation of sustained attention with Guanfacine (specifically via its action on the DLPFC) improved visual exploration of space and maintained attention on task goals (reflected in extended visual search times). The beneficial effects were seen up to seven days after administration, highlighting Guanfacine as a potentially useful adjunct in the rehabilitation of patients with visual neglect.

ii.5.6 Transcranial Magnetic Stimulation (TMS)

This technique is explained in more detail in the following section. Put simply, TMS involves the induction of small electrical currents in the cortex by powerful, rapidly changing magnetic fields, generated in coils of copper wire that are positioned over the scalp. With the right timing and frequency, these induced currents can activate or inhibit the area of cortex in which they flow.

Previous work using this technique in patients with neglect has focussed on inhibiting the intact left hemisphere, an idea which may seem counterintuitive, but which (like eye patching and the superior colliculi) is aimed at restoring the balance in activity between the two sides of the brain. The idea that damaged areas of brain are suppressed by corresponding areas on the opposite side is attributed to Kinsbourne, and is expounded in his 'Interhemispheric rivalry theory' (Kinsbourne, 1977). According to this view, mutually inhibitory interhemispheric connections exist (which travel across the Corpus Callosum), so that damage to one hemisphere increases the inhibitory input from its undamaged fellow, exacerbating the disruptive effects of the original insult. In accordance with this theory, left frontal disruption with TMS reduces contralesional extinction in patients with unilateral right brain damage (Oliveri et al., 1999), and TMS over the unaffected parietal area ameliorates contralateral visuospatial neglect (a beneficial effect which can persist for 2-6 weeks) (Oliveri et al., 2001; Brighina et al., 2003; Shindo et al., 2006, Nyffeler et al., 2009). Though TMS remains a promising therapeutic tool for spatial neglect, the findings described above have not yet been replicated in large-scale studies, and other therapeutic avenues (such as direct up-regulation of the damaged areas with excitatory TMS) remain relatively unexplored.

iii) Transcranial Magnetic Stimulation

iii.1 Historical Context

The technique of Transcranial Magnetic Stimulation continues a long tradition of applying magnetic and electric fields to the head in an effort to excite brain tissue. The ancient Egyptians were amongst the first in recorded history to do so, exploiting the natural ability of certain fish (the Nile catfish) to produce bursts of electrical current. They applied catfish directly to the scalp in an attempt to treat headache and other ailments (Kane & Taub, 1975).

In more modern times, an intense alternating magnetic field was used to stimulate the visual cortex and produce 'phosphenes' (the perception of light, as a blob or shape, without light actually entering the eye) (D'Arsonval, 1896). This was followed up some half-century later, when much smaller magnetic fields were used near the retina and over the occipital cortex. Bright phosphenes were perceived only during stimulation over the former site, confirming the notion that different parts of the nervous system have different thresholds of excitability (Walsh, 1946; Barlow et al., 1947). The origins of modern TMS can be traced to the early 1980s when a high voltage electric simulator, built to stimulate muscle rather than cortex, was tested over the scalp. This stimulated not just the scalp musculature, but also fast conducting corticospinal neurons in the motor cortex (followed by spinal motor neurons), the end result being a visible muscle twitch (Merton & Morton, 1980). However the use of *magnetic induction* to achieve the same result (with less uncomfortable scalp stimulation) was not demonstrated until five years later (Barker et al., 1985). From this founding moment the discipline of TMS grew rapidly (in terms of TMS related papers published, Rossini & Rossi, 2007), heralding the emergence of a wide array of different TMS paradigms. Today, these involve a multitude of different shaped coils and utilise a variety of different pulse frequencies, making TMS a flexible tool in the

treatment of conditions as diverse as tinnitus (Kleinjung et al., 2008) and depression (Loo & Mitchell, 2005).

iii.2 Magnetic Induction as a Means of Stimulating the Brain

Magnetic induction is the production of an electric current in a conducting medium that is exposed to a time-varying magnetic field. This phenomenon was discovered by Faraday in 1831 who found that by moving a magnet through a loop of wire, an electric current flowed through the wire. In TMS the 'magnet' is a tightly wound coil of copper wire (through which a capacitance is discharged) and the 'wire' is the targeted region of the brain. Electrical energy held in a capacitor is discharged though a coil held over the scalp, resulting in a brief surge of current through the coil and a transient magnetic field. The time varying change of this field as it rises and then collapses causes a small electrical current to flow in the excitable neural elements of the cortex below. The magnetic field generated and strength of the current induced depend on factors such as the amount of charge in the storage capacitor, the shape of the coil, and the wave-form of the magnetic field as a function of time (e.g. monophasic or biphasic), and the number of turns in the coil winding. For example, a single circular coil (typically 5-20 turns of wire), with a monophasic pulse and peak coil current of about 8000 Amperes produces a magnetic field in the order of 2.5 Tesla, and an induced tissue current of approximately 15 mA/cm^2 (Mills, 1999; Wassermann et al, 2008). The most common pulse waveforms used are monophasic or biphasic which require different stimulators to generate. Monophasic stimulators are generally slower to recharge but are easily paralleled to allow paired stimulus delivery at very short intervals (e.g. a few milliseconds). On the other hand, biphasic machines are faster and can generate high frequency repetitive trains of pulses (Pascual-Leone et al., 1999).

The coil can take a variety of forms but the one used consistently through this work is the 'figure-of-eight' coil (diameter 70mm), in which double windings carry two currents in opposite

directions. These currents summate at the midpoint of the coil where the two loops meet; producing a focal magnetic field (Ueno et al., 1988). When used in conjunction with a biphasic stimulator (such as the Magstim 'Rapid', the Magstim Company Ltd., Whitland UK), a field output of 1.2 Tesla is produced at surface of the coil, with a biphasic, single (cosine cycle) pulse of period 400µs. For both types of coil the magnetic field strength drops rapidly away from its peak over an area of approximately $1cm^2$ (Mills, 1999) but the area of induced cortical current extends for several centimeters. Nonetheless the focality of effect remains impressive, for instance with figure-of-eight coil positions 5-10mm apart over the visual cortex, and the region of visual field affected (by a transient scotoma) can be varied in steps of just 1 º of visual angle (O'Shea & Walsh, 2007). Over the motor cortex similar coil spacing can be used to selectively activate muscles of the hand, arm, face, trunk, and leg (Brasil Neto et al., 1992a, 1992b). It should be borne in mind that distant brain areas which are directly connected to the site of stimulation are also affected. For example, the excitability of the motor cortex can be influenced by TMS pulses delivered over the ipsilateral parietal cortex (Koch et al., 2008), or by stimulation of the contralateral M1 (via connections across the corpus callosum) (Ferbert et al., 1992).In general figure of eight coils offer a more focal stimulus of defined orientation than circular coils (Mills et al., 1992).

The orientation of the coil relative to the underlying cortex is also important as the efficacy of a TMS pulse is dependent on the orientation of the underlying cell bodies and fibres relative to the direction of the induced current (Walsh & Cowey, 2000). Over the motor cortex, the optimal orientation for the activation of the First Dorsal Interosseous (FDI) muscle is with the current flowing (anterior-posterior in the coil and posterior-anterior in the cortex) at 45º to the sagittal plane, i.e. the handle of the coil lies perpendicular to the central sulcus (Mills et al., 1992). In studies of TMS effects on perception, effects over the parietal lobe can be found with the coil

current flowing backward, parallel to the sagittal plane (e.g. Oliveri et al., 2000a; Oliveri et al., 2000b; Koch et al., 2005).

iii.3 TMS as a Probe of Motor Cortical Excitability

The induced magnetic field depolarizes nerve cell bodies, axons and dendrites at points where current leaves them and are hyperpolarized where current enters. The degree of depolarisation depends on the current intensity and its duration, as well as the threshold of the particular neural element (axons have lower thresholds than cell bodies, Ranck, 1975). With the coil positioned over the motor cortex, the net result is a depolarization of large pyramidal (Betz) cells in layer V, a descending volley of impulses through the corticospinal tract and down the spinal cord, transynaptic excitation of the relevant anterior horn cells and contraction of the targeted muscle (usually the First Doral Interosseous or Abductor Digiti Minimi of the contralateral hand). Descending corticospinal axons are stimulated directly by the magnetic field (producing a 'direct' volley of impulses, or 'D' wave) and also indirectly via transynaptic connections with cortical interneurons which have themselves been excited by the magnetic field. The latter type of activation produces indirect 'I' waves which occur at intervals of 1.5ms; the underlying mechanisms are not clear but are thought to involve either increasingly long polysynaptic networks or recurrent synaptic networks (Hallett, 2007).

The Compound Muscle Action Potential (CMAP) evoked by magnetic stimulation of the motor cortex varies considerably in both amplitude and latency from trial to trial, unlike the CMAP obtained from peripheral nerve stimulation, which stays more-or-less constant. The peripherally evoked CMAP is also larger, principally because the *cortically* evoked descending volley becomes dispersed on its journey through the corticospinal tract, cortico-motoneuronal synapse and peripheral nerve. When it reaches at the neuromuscular junction it arrives desynchronized

and of lower amplitude. This 'magnetic evoked potential' (MEP) is measured as the potential difference across 2 silver plated (or nickel) electrodes, one placed over the belly of the target muscle and the other over its tendon (the reference electrode). A third (ground) electrode is placed over the wrist. The tiny signal (millivolts) generated by muscle activation is passed through a preamplifer and manipulated with specialized software (e.g. the '1401' preamplifier and 'Signal' software package, Cambridge Electronic Design), producing measurable MEPs which are used in turn to quantify motor cortical excitability. This is usually derived in relation to the intensity of single TMS pulses delivered with a coil connected to a large capacitance stimulator. The maximum output of the stimulator is defined as an intensity of 100% with intensity adjustable up to or down from this level in 1% gradations. This allows the quantitative definition of motor excitability in terms of the 'threshold' needed to produce of MEPs of a certain amplitude on a certain proportion of trials (as standardised by Rossini et al., 1994). Motor threshold is most commonly measured with the muscle relaxed (Resting Motor Threshold, or RMT) or at a constant proportion of maximal contraction (Active Motor Threshold, or AMT). AMT tends to be lower than RMT because (during sustained muscle contraction) the motor neuron pool is at a higher level of activity than at rest, and is easier to excite. In fact, pre-activation also reduces the threshold for trans synaptic activation of pyramidal tract neurons so that the descending corticospinal volley is larger. For the same reason MEPs produced during muscle contraction are larger than those elicited at rest (Hallett, 2007).

iii.4 Frequency-dependent Excitatory and Inhibitory Effects of TMS

Depending on the timing of stimulation used, the net effect of a series of TMS pulses on underlying cortex can be inhibitory or excitatory. For example, a pulse given at sub-threshold intensity 1-6ms before a second, suprathreshold pulse reduces the size of the MEP produced

by the second pulse (inhibition). If the interstimulus interval is increased to 10-15ms, facilitation occurs and the MEP associated with the second pulse increases in size (Claus et al., 1992, Kujirai et al., 1993, Ziemann et al., 1996). The mechanisms behind this phenomenon are not fully understood, though inhibition is thought to depend on intracortical circuits in which GABA – ergic neurons (γ-aminobutyric acid) predominate (Hallett, 2007). Trains of TMS pulses (repetitive TMS or 'rTMS') also have differing effects on cortical excitability depending on the frequency and timing used. For instance, low frequency stimulation of the motor cortex (1 Hz) reduces the size of MEPs evoked by subsequent single-pulse TMS (Wassermann et al., 1996; Fitzgerald et al., 2002). This inhibitory effect of 1 Hz TMS extends to the visual cortex, manifesting as a post-rTMS increase in subjects' phosphene threshold (Boroojerdi et al., 2000). Conversely, rTMS at frequencies of 5-10Hz leads to a transient increase in corticospinal excitability (Berardelli et al., 1998; Pascual-Leone et al., 1998), and 20Hz stimulation can increase MEP size for up to 2 days (Maeda et al., 2000).

One recently developed form of rTMS: 'Theta Burst' Stimulation (TBS), combines short stimulation times with low stimulation intensities and a relatively long duration of effect. During TBS, pulses are delivered repetitively at high frequency, for example over the Motor Cortex in which the effects last up to one hour. To date the effects of TBS have only been fully characterised for the primary motor cortex (M1), over which continuous TBS (cTBS) produces an inhibitory effect whilst intermittent TBS (iTBS) produces an excitatory effect (Huang et al., 2005). With cTBS, pulses are given in 50Hz triplets, with the triplets themselves occurring at a rate of 5 Hz, for 40 seconds (600 pulses in total). A similar pattern is used for iTBS, though gaps of 8 seconds occur after each 2 second stimulation burst; this requires a longer stimulation period of 200 seconds to deliver the 600 pulses. The low intensity (80% of AMT) and short stimulation time (40seconds) needed make TBS an appealing candidate for possible therapeutic intervention in stroke patients.

TMS is now used commonly to interfere with function in the stimulated area of brain, a phenomenon that has been termed the “virtual lesion” (see Walsh & Cowey 2000). At a given brain location, normal neural processing depends on highly intricate timings in the interaction of individual circuits. The local effect of TMS is therefore more likely to be disruptive (if only temporarily) though an individual ‘virtual lesion’ may in fact up-regulate more distant (but connected) brain areas. A single pulse of TMS may disrupt activity (in the motor cortex) for 100ms or so (Uncini et al. 1993) whilst repeated stimuli (e.g. cTBS) lead to after effects on function that can last 30min or more (Huang et al. 2005)

iii.5 Neuroplasticity and TMS

iii.5.1 Cortical Maps

Until relatively recently, the prevailing wisdom dictated that the adult nervous system was ‘fixed and immutable’, a system in which ‘nothing could be regenerated’ (Ramon y Cajal, 1928). A wealth of recent evidence undermines this rather nihilistic view and in contrast reveals a plastic system which changes throughout life in response to normal and abnormal experience. Much of this new evidence comes from studies which utilise TMS to construct functional motor cortical maps before and after a therapeutic intervention. One such study looked at the hand muscle cortical motor map in two different groups of blind individuals, one group that could read Braille and a control group that could not. The cortical representation of two key muscles (FDI and APB) was mapped out using single pulses of TMS. In the Braille readers the representation of FDI in the reading hand was significantly larger than in the other hand or in either hand of the control group (Pascual-Leone et al., 1993). TMS has also been used to map out the cortical representation of APB in stroke patients after 2 weeks of constraint-induced therapy (in which

the unaffected arm is immobilised, forcing the patient to use their paretic limb) (Liepert et al., 2001). Improvement in hand function was associated with expansion or contraction of areas projecting respectively to the exercised and constrained limb. Away from the hand muscles, pharyngeal sensory stimulation (at 5 Hz for 10 minutes using an oesophageal electrode) enhances the recovery of swallowing in stroke patients. This functional change is accompanied by reorganization of the pharyngeal motor maps in the damaged hemisphere as demonstrated by TMS mapping and pharyngeal EMG recording (Hamdy et al., 1998; Fraser et al., 2001). The changes in cellular connectivity which underlie these functional changes are thought to occur within a dense network of horizontal (lateral) fibres which form both short and long range intracortical connections (Rioult-Pedotti & Donoghue, 2003). Cortical maps can also change over a timescale of minutes rather than days or hours. For example, the direction of a TMS induced thumb movement (generated by stimulation of a specific primary motor cortex location) can be reversed after a subject performs repetitive voluntary thumb movements in the opposite direction to that elicited by TMS. This result was interpreted as a rapid re-structuring of **the** cortical neural networks that store kinematic information in the motor cortex; in some subjects this re-organisation took place after only 5-10 minutes of training (Classen et al., 1998).

iii.5.2 Synaptogenesis

At a cellular level, rapid increases in intracortical connectivity can be achieved by the activation of previously silent synapses. This occurs with the insertion of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors into the post-synaptic membrane (Liao et al., 1999), but longer lasting plasticity probably requires the formation of entire new synapses. Synaptogenesis does in fact happen in rat motor cortex, reflected in an increase in the number of synapses per neuron after motor skill learning (Kleim et al., 1996).The same process increases synaptic turnover in the somatosensory cortex (measured by the rate of dendritic

spine appearance and disappearance) in response to novel sensory experience (Trachtenberg et al., 2002).

iii.5.3 Long-term Potentiation and 'Theta Burst' Stimulation

Plasticity also occurs at a molecular level, dependent for example on dendritic postsynaptic N-Methyl D-Aspartate (NMDA), glutaminergic receptors which act as coincidence detectors. These receptors only activate during simultaneous glutamate binding and post-synaptic depolarization (the latter of which removes a Mg^{2+} ion blockade) (see Bliss & Collingridge, 1993). As a result of this selective activation, they contribute little to basal postsynaptic activation during low frequency synaptic transmission (Malenka, & Nicoll, 1999). Other post-synaptic glutaminergic receptors, i.e. AMPA receptors, activate via glutamate binding alone but open only briefly (10-20ms) and cause a small degree of post synaptic depolarization. As such they provide the majority of inward current for basal synaptic transmission when the cell is close to it s resting membrane potential. If enough of these open and a large depolarisation occurs (e.g. because more than one pre-synaptic terminal is active), then NMDA receptors also open. These stay open for longer (hundreds of milliseconds) allowing a large influx of Na^{+} and Ca^{2+} ions which in turn (via activation of several kinases) up-regulate the post-synaptic AMPA receptors (see Huerta & Volpe, 2009). The end result is that subsequent pre-synaptic glutamate release is more likely to result in post synaptic depolarisation. In addition the probability of pre-synaptic glutamate release is in turn influenced by retrograde messengers released from the post-synaptic cell (candidate molecules include nitrous oxide, carbon monoxide, arachidonic acid and platelet activating factor, but their true identity remains elusive) (Malenka & Nicoll, 1999; Malenka & Bear, 2004). This process, termed Long Term Potentiation (LTP) (Bliss & Lømo, 1973) is thought to modify synaptic efficiency during learning and skill acquisition. It was first discovered in the hippocampus where it can be enhanced by high frequency electrical stimulation and APMA receptor activation, and was demonstrated subsequently in neocortical

areas (Artola & Singer 1987). One example of this, termed 'theta burst stimulation', involves 4-pulse bursts at 200ms intervals from electrodes sited in layer CA1 of the hippocampus (Larson et al., 1986). This critical 5Hz frequency is designated 'Theta', based on a 5Hz network oscillation (the 'theta rhythm') that occurs in animals during periods of heightened attention. A LTP-like process may therefore underpin a subsequent discovery, that repetitive 5Hz electrical stimulation of inputs to rat visual cortex results in a potentiation of intracortical synapses and enhanced cortical response to visual stimuli (Heynen & Bear, 2001). In humans a 'Theta Burst' stimulation paradigm is used non-invasively (as mentioned above) during rTMS to induce lasting plastic changes in the underlying cortical target. This may also involve NMDA-dependent LTP like processes (Teo et al., 2007), whereas inhibitory forms of TMS (such as 1Hz rTMS) may invoke the opposite process, Long Term Depression (LTD). Both forms of rTMS have been used in the past for therapeutic purposes, whether to inhibit the undamaged hemisphere after stroke (1Hz) (Oliveri et al., 2001; Brighina et al., 2003; Mansur et al., 2005; Takeuchi et al., 2005; Shindo et al., 2006; Nyffeler et al., 2009), or directly to stimulate damaged motor cortex (TBS) (Uy et al., 2003; Khedr et al., 2005; Kim et al., 2006; Talleli et al., 2007; Mally & Dinya, 2008; plus see Talelli & Rothwell, 2006 for review).

iii.6 'Theta Burst' Stimulation and Spatial Neglect- A New Therapy?

The actions of rTMS (and in particular TBS) on the parietal cortex, whether in health or after stroke, remain relatively unexplored in comparison with those on the motor cortex. TMS studies of neglect patients have thus far found only on-line effects (Oliveri et al., 2001), have not compared the off-line effects found with true (sham) control conditions (Brighina et al., 2003; Shindo et al., 2006), or have not used true signal detection measures (Nyffeler et al. 2009). This line of investigation is therefore continued in the following experimental studies (as

described in Chapters 3-6), beginning with a novel rTMS parietal localising technique, progressing through TBS neglect-like virtual lesion studies, and ending with the successful therapeutic application of cTBS in a patient with neglect. In a further refinement to previous TMS studies of neglect, the effects of TMS on behavior are measured here using signal detection parameters (d-prime and criterion) in a fully balanced bihemifield detection paradigm. As described in Chapter 2 these allow a detailed, individualised assessment of performance for targets in the left and right visual field, which is free from internal response bias. Unlike tests for neglect based on line bisection, cancellation tasks, or bedside testing with finger movements, signal detection also provides a robust means of quantifying extinction.

Chapter One: General Methods

A series of novel paradigms were developed with the dual aims of:

a) localising a suitable cortical target in the right PPC, over which neglect-like TMS effects could be elicited and then
b) quantifying these effects using fully balanced signal detection measures.

The first of these paradigms is described in detail in Chapter 3 (section 3.4.1, pages 88-91) and the second, used in Chapters 4-6, is described in section 1.3 below. In the last study of the experimental series a novel 'Landmark' variant task was employed alongside an established number line bisection paradigm to study the effects of 1Hz cerebellar TMS on spatial judgment and these are described in full in Chapter 7 (section 7.3.1, pages 163-167).

1.1 Participants

All studies were approved by the local ethics committee and all participants gave their written informed consent. With the exception of the patient studied in Chapter 6 (details given in section 6.3, pages 149-150), all were healthy volunteers with normal or corrected vision by self-report. The exclusion criteria employed in all participants' selection conformed to current guidelines for rTMS research (Wassermann et al.,1998, Rossi et al., 2008). The sizes and demographics of the groups used in each experiment are given in Table 1.1 below:

Chapter	Experiment	Participants	Gender	Handedness (±SE)	Age (Range)
3	1	9	8 Male 1Female	84±10	25-36
3	2	6	6 Male	92±4	25-33
3	3	6	6 Male	92±4	25-33
3	4	8	7 Male 1 Female	82 ± 10	25-36
4	1	10	9 Male 1 Female	82±11	25-36
4	2	8	7 Male 1 Female	83±12	26-36
5	1	9	7 Male 2 Female	96±2	22-35
6	1	1	1 Female	Left	66
7	1	8	6 Male 2 Female	93±5	24-33

Table 1.1. Demographic data for the participant groups in the series of experiments. Handedness scores were recorded using the Edinburgh Handedness Inventory (Oldfield, 1971).

1.2 Materials

In all experiments, participants sat in a darkened room with head and chin stabilised in a frame at 50cm from a PC laptop screen (refresh rate 50Hz). A view of the overall experimental set-up is shown in figure 1.1.

Figure 1.1. Overall experimental set up. The head and chin rest is visible in the foreground; beyond that are the eyetracking LEDs for left and right eyes, and at the rear, a laptop PC. A keyboard is positioned just beyond the head and chin rest to record subjects' manual responses. The eyetracker is displayed in the configuration used in the patient study (Chapter 6). To improve comfort and make the paradigm as tolerable as possible, the eyetracker LEDs were removed from their plastic helmet-fame and mounted on the head and chin rest. The patient's head was then supported at the back with a Velcro-fastened strap. In the other studies the LEDs were kept mounted on the helmet-frame (Photograph: A. Nuruki).

1.2.1 Visual Stimuli

Four different visual stimuli were used (see fig. 1.1 A-D), comprising either a continuous horizontal line with no gaps (fig 1.1A); or such a line but with a target-gap at the far left (fig 1.1B); or a line with a target-gap at the far right (fig 1.1C); or a line with target-gaps at both the left and right ends (fig 1.1D). Each horizontal line extended across 29 degrees of visual angle, with a small vertical mark at its centre to indicate the central fixation point. The gaps when present appeared at an eccentricity of 14 degrees.

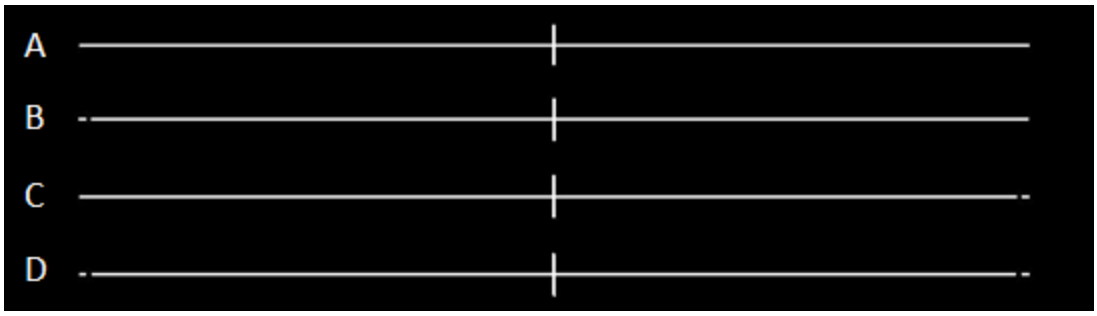

Figure 1.2.The stimuli used: A. ‘No Gaps’, B. ‘Left Sided Gap’, C. ‘Right Sided Gap’, D. ‘Gaps on Both Sides’. Stimuli were presented using the ‘E-prime’ software package (Psychology Software Tools Inc., Pittsburgh). In all experiments the stimuli comprised white lines on a black background, bisected with a vertical marker that corresponded to the middle of the preceding fixation cross. The lines occupied 29.36 degrees of visual angle (26.2cm long at a distance of 50cm) with any gap if present being 1.5 mm (0.17 degrees) wide, situated 2mm from the left or right end of the line (eccentricity of 14.31 to 14.47 degrees from the midline).

For the experiments described in Chapter 3 only the stimuli shown in figure 1.2 A-C were used (i.e. ’no gaps’, ‘left-sided gap’ or ‘right sided gap’), as this study aimed to test participants’ target detection performance in each hemifield separately. The rationale behind this choice of stimuli is described in more detail in Chapters 3 (p87). In the later experiments (Chapters 4, 5 and 6) the stimulus shown in figure 1.2 D was added so as to form a simultaneous bi-hemifield detection paradigm (capable of quantifying any TMS-induced ‘virtual lesion’ extinction-like effects). For the final experimental study (Chapter 7), separate ‘landmark’ variant and number line bisection tasks were used which are described in detail, along with their stimulus parameters, in Chapter 7 (pages 163-167).

1.2.2 Transcranial Magnetic Stimulation

In all studies, TMS was delivered using a Magstim Super Rapid stimulator (Magstim, Whitland UK) and a single cased figure-of-eight coil with diameter 70mm. The areas targeted with the main TMS intervention, as well as the intensity and frequencies used varied between experiments; they are summarised in Table 1.2 below:

Chapter	Experiment	TMS Target Area	TMS Frequency	TMS Intensity
3	1-3	Right PPC	10 Hz	100% RMT
3	4	Right PPC	10 Hz	10-100% RMT
4	1	Right PPC	cTBS (600)	80% AMT
4	2	Right PPC Left PPC	cTBS (300) cTBS (300)	80% AMT 80% AMT
5	1	Right PPC	iTBS (600) and 10 Hz	80% AMT 100% RMT
6	1	Left PPC	cTBS (600)	80% AMT
7	1	Right & Left Cerebellum/Neck	1 Hz (600)	90% RMT

Table 1.2. An overview of the principle forms of TMS intervention used in the series of experiments, along with the areas targeted. The total number of cTBS or 1Hz pulses given is shown in brackets.

In Chapters 3-6 (and as in other studies in which visual or tactile perception has been affected with TMS over parietal cortex) the coil was held with the handle pointing backwards so as to induce a current with initial phase flowing in the posterior-anterior direction in the underlying brain (see Oliveri, Caltagirone, Filippi et al., 2000a; Oliveri, Rossini, Filippi et al., 2000b; Koch, Oliveri, Torriero, & Caltagirone, 2005). The PPC target was localised and defined functionally using the novel detection-based 'hunting procedure' described fully in Chapter 3. The

cerebellum was stimulated as in previous work, at a point 3cm lateral and 1cm inferior to the inion, on a line joining the inion to the external auditory meatus (a point previously demonstrated with neuronavigation to lie over the cerebellar hemisphere, Del Olmo et al., 2007), with the handle pointing superiorly (Théoret et al., 2001; Oliveri et al., 2005).

10 Hz TMS was given in 3-pulse (Chapter 5) or 5-pulse bursts (Chapters 3 and 4) to provide direct 'on-line' disruption to task performance; the specific details regarding the timing of these bursts in relation to the stimulus displays are given in the corresponding chapters. cTBS (Chapters 4 and 6) and 1Hz TMS (Chapter 7) were used to induce off-line disruption, i.e. 'virtual-lesion' effects which outlasted the period of stimulation. cTBS was given as described by Huang et al. in 2005, and consisted of 300 or 600 pulses given in 50Hz triplets, with the triplets themselves delivered at a rate of 5 Hz (and thus a total stimulation time of 20 or 40 seconds). In Chapter 5, excitatory iTBS (described on page 58) was given over the right PPC in an effort to alter cortical processing and induce a form of neuroplasticity rather than simply to cause a disruptive 'virtual-lesion'. Both forms of TBS were given at an intensity corresponding to 80% of each subject's individually determined AMT. When used, sham stimulation was given at the same intensity and for exactly the same number and rate of pulses, but with the coil first rotated 90º around its (figure-of-eight) long axis before placement on the scalp. With this coil orientation no MEP is produced when held over motor cortex (even at 100% of maximum stimulator output), and substantially less intracerebral TMS-induced voltage is recorded when held over monkey parietal cortex (Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001); yet comparable acoustic noise, and non-zero scalp stimulation, still occur. As an alternative to sham stimulation, neck muscle control sites were targeted with TMS in the final study to control for any muscle activation effects that might result from Cerebellar TMS stimulation (see Chapter 7, pages 167-168).

In each subject Resting Motor Threshold (RMT) and Active Motor Threshold (AMT) were determined using the FDI muscle. RMT was determined to the nearest percent of maximum stimulator output, and was defined as the minimal stimulus intensity required to produce an MEP of more than 100 μV, in at least five of 10 consecutive trials. AMT was determined during approximately 5% to 10% of the maximal voluntary FDI contraction, and was defined as the minimum intensity that produced either a MEP of more than 100 μV, or a silent period, in at least five of 10 consecutive trials (cf. Sohn, Kaelin-Lang, Jung, & Hallett, 2001; Rossini et al., 1994).

1.2.3 Eyetracking

An IRIS Skalar infra red eye tracker was used in all experimental series to determine eye position in relation to pre- and post-TMS calibrations, and to exclude eye movement as a confounding cause of any hemifield-specific visual sensitivity changes. In the final study eye position and the variance in eye position were measured to exclude any confounding effects on visual fixation caused by the cerebellar rTMS. The eyetracker consisted of a lightweight head-mounted frame and 2 LED arrays, each positioned to reflect infra red light off the irido-scleral junction of the right or left eye. In the patient study described in Chapter 6, the configuration of the LED-head rest was changed to make the paradigm as tolerable and as comfortable as possible (see figure 1.1 legend for details). Eye position data were recorded in intervals spanning 1000 ms, starting 500 ms before onset of the visual stimulus display. Data were captured in the form of a voltage deflection to the right or left and analysed using the 'Signal' software package version 4.04 (Cambridge Electronic Design, UK). The modal eye position during each 1000ms recording period was averaged over each block of trials (60-120 depending on the particular experiment) and compared to eye position deflections recorded during calibration sessions (where participants was viewed a set of 2 crosshairs, a constant distance apart i.e. 29 degrees of visual angle.

1.3 Main Experimental Paradigm

Participants were asked to discriminate via key press between the 4 different visual stimuli shown in fig. 1.2 A-D). They responded to indicate whether they saw no-gap, or a gap on the left, or a gap on the right, or a gap at both ends. The task was thus analogous to the none, left, right or both responses used in traditional clinical measures for visual extinction, but now using stimuli comprising a line-with-possible-gap(s). On each trial, the brief line stimulus was preceded for 1000ms by a centrally positioned fixation cross (white on a black background). The subject was instructed to keep their eyes fixed at this point during each trial (confirmed with eye-tracking as described above).

Before the main experimental blocks, the stimulus display duration was determined individually for each participant using a 'staircase' procedure. This used blocks of 60 trials, comprising 15 of each of the four stimulus types shown in fig 1.2, in randomly intermingled order. At the end of each block, the % hit rate for left-sided stimuli (averaged across those presented with and those presented without a competing stimulus in the right visual field) was calculated automatically (as described in Chapter 2, section 2.2) and displayed to the experimenter. Starting at 200ms, the stimulus presentation duration was varied from block to block (reduced in 40ms steps) until a 'Hit' rate for left sided targets of approximately 75% was achieved (half-way between a 'chance' 'Hit rate' of 50% and a 'perfect' 'Hit rate' of 100%). Once determined, this display duration was used for every trial in that experimental session, i.e. the same duration for pre- and post-TMS blocks. The number of blocks performed varied between experiments (as did the type of TMS intervention used) and thus specific details are given later in the relevant chapter. The data obtained was analysed using a signal detection based approach which is described in the following chapter.

Chapter Two: Data Analysis Using Signal Detection Theory.

Signal detection theory tests an observer's ability to discriminate between signal and noise. It is used throughout the experimental studies detailed in Chapters 3-6, and underpins the interpretation of the results both in terms of a subject's ability to detect visual targets, and their innate 'response-bias' (which determines their likelihood of answering 'yes' or 'no' at a given moment) . Signal detection theory provides a measurement of subjects' ability to distinguish signal from noise (d-prime, or d', also known as 'discriminability' or 'sensitivity') which is independent from and uninfluenced by response bias (criterion, c). The separation of these two variables makes signal detection theory a powerful tool in any study of behaviour, and hence its utilsation here in a novel bihemifield detection paradigm. As described in this chapter, the analysis of the output from this paradigm employed both d' and c, incorporated all subjects' responses and balanced these fully, taking into account the visual field tested and whether or not a contralateral competing stimulus was present.

The majority of the work presented in this Chapter was originally published as part of a larger review article:

Oliver, R. M., Bjoertomt, O., Greenwood, R.J., & Rothwell, J.C. (2008). 'Noisy patients', can signal detection theory help? *Nature Reviews Neurology*, 4(6), 306-16. doi:10.1038/ncpneuro0794

2.1 An Overview of Signal Detection Theory

SDT originated during the Second World War as a means to improve the performance of radar operators in detecting enemy bombers. SDT entered psychological science through work by Green and Swets in 1966, and it remains an important approach to the study of decision processes.

A fundamental principle of SDT is that decisions must often be made on the basis of incomplete information, and always with a degree of uncertainty. In the clinical setting, for example when radiologists are being audited on their performance, a suitable approach might be to measure the percentage of tumors that they correctly identify. It does not take much thought to realize that an easy way to score 100% on this measure is to answer"yes, a tumor is present" on viewing every scan. Clearly this perfect 'hit rate' is only half the story—the equally high 'false-alarm' rate reflects the true cost of adopting this unhelpful strategy.

The neural response elicited by scans that contain a signal (signifying a tumor) is not a single, predictable value, and the same is true for scans that contain noise only (no tumor). Instead, the responses (are assumed to) produce two normal distribution curves along an arbitrary axis of 'response'. If the observer has any ability at all to discriminate between noise and signal, the curves will be separated to some degree. Given the nature of normal distribution (which tails off to infinity), however, there will always be some overlap between the two curves, and the overlap is where errors occur (Figure 2.1).

2.2.1 D-prime and Criterion

In its simplest form, SDT assumes that the signal is constant, so, when signal is superimposed on noise, the resulting 'signal-plus-noise' (S+N) curve is identical in shape to the curve depicting

noise alone. The S+N curve has the same variance as the noise curve, but its mean is shifted by a distance that increases with the strength of the signal (figure 2.1). This distance (the observer's sensitivity) can be expressed mathematically as'd-prime'. As the separation between the curves increases, the subject becomes more accurate and their d-prime grows larger.

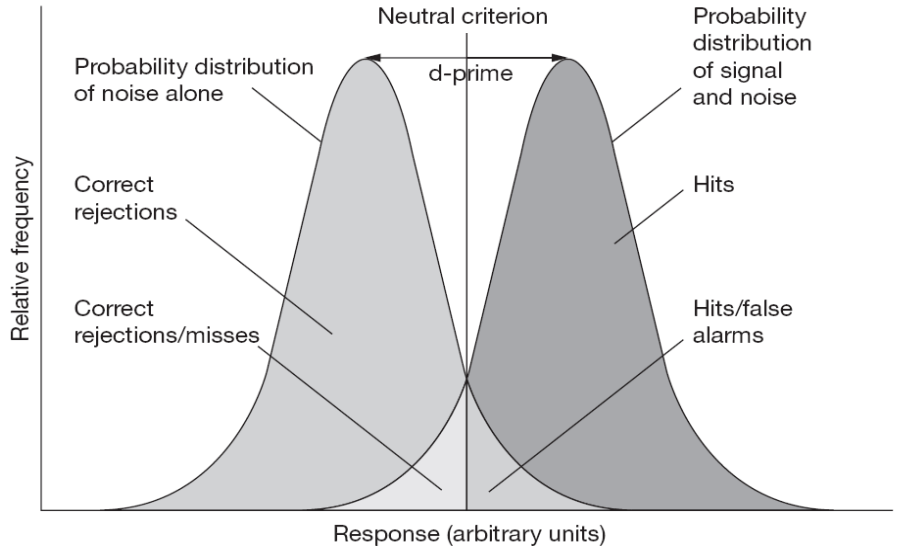

Figure 2.1. Calculation of d-prime. D-prime (sensitivity) increases with the distance between the two distribution peaks. In SDT terminology 'sensitivity' refers to an observer's ability to *discriminate* between 2 different stimuli (signal or noise) and incorporates both 'false alarm' and 'hit rates'. Medical parlance differs in that 'sensitivity' refers just to the 'hit rate'. The term 'specificity' is not commonly used in SDT, but in medical parlance refers to the 'correct rejection' rate (which is the inverse of the 'false alarm' rate).

To determine the separation of the noise and S+N curves in an observer, one could record their responses to a set number of signal and noise stimuli (e.g. 100 signal stimuli and 100 noise stimuli shown intermingled in a random order). If they correctly identify 90 out of the 100 signal stimuli (by verbalizing"yes" or with a relevant key press), they achieve a 'hit rate' of 0.90. The responses to these signal stimuli within the observer's brain can be said to form a population of which 90% of stimuli will be strong enough to produce the external response "yes", whereas 10% will not. If this population is normally distributed (an assumption of SDT), the point of transition between "yes" and "no" can be said to lie a certain number of SDs from the mean.

Deviation from the mean of one particular member of the population—in terms of height in humans, for example—can also be expressed in units of SD to produce a z-score (in this case z = [person's height -average height for the population] ÷SD for the population). If a value lies 1.98 SDs above the mean, its z-score is also 1.98 (or –1.98 if the value lies below the mean). These particular z-scores (plus or minus 1.98) correspond to deviations from the mean that encompass 95% of a population (and form the 95% confidence interval for that population).

With the hit rate of 0.90, one must work in the reverse direction and derive the z-score from the probability instead. In practical terms, this is usually done with statistical tables or a spreadsheet, and the mathematics involved (usually a form of iterative search) are beyond the scope of this work. In our example, a probability of 0.90 corresponds to a z-score of 1.28, providing half the information needed to calculate d-prime (figure 2.2 A).

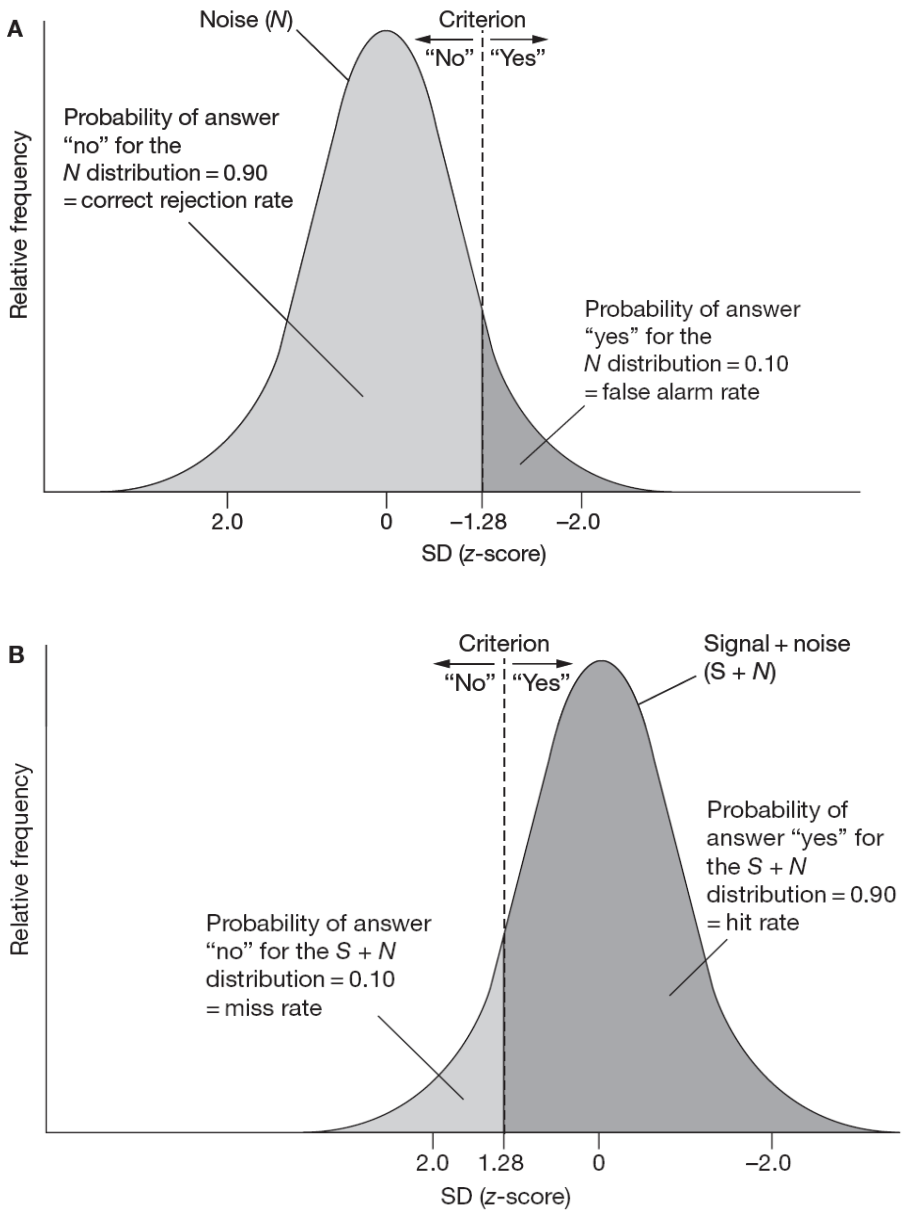

Figure 2.2. The 'Criterion'. (A) The observer's criterion separates the noise distribution into two areas. In the noise distribution, 90% of the area lies within the observer external response "no, signal not present"; that is, the correct-rejection rate is 0.90, whereas 10% lies within the external response "yes", which gives a false-alarm rate of 0.10. (B) The same criterion applies to the signal-plus-noise distribution, in which 90% of the area lies within "yes" (a hit rate of 0.90), and 10% lies within"no" (a miss rate of 0.10).

The other half of d-prime is derived from the observer's responses to the noise stimuli. If they correctly reject 90 out of 100 noise stimuli (by saying"no"), they achieve a false-alarm rate of

0.10. Their external responses therefore deviate from the mean by the same amount as before, but in the opposite direction; that is, the z-score for 0.10 is –1.28 (figure 2.2 B). It is now possible to calculate d-prime as the difference between these two z-scores: d-prime (d') = z(Hit Rate) – z(False Alarm Rate) = 1.28 minus –1.28 = 2.56.

In this example, the observer was equally likely to say"yes" or"no" ("yes" to 90 signals and 10 noises, and"no" to 90 noises and 10 signals). The cut-off point between saying "yes" or "no" is termed the 'criterion', which, in the example above, is neutral, or 'unbiased'. A change in criterion does not change d-prime; indeed, a key advantage of signal detection measures is that d-prime and the criterion are independent of each other. Observers who are more liberal (more likely to say"yes") but do not increase their sensitivity will increase the hit rate but will also proportionally increase the false-alarm rate. For example, if the observer above felt more relaxed, they might say "yes" more often and correctly identify 99 out of 100 signal stimuli. They would also, however, only correctly reject 59 out of 100 (rather than 90 out of 100) noise stimuli, saying "yes" to 41 of the noise stimuli. D-prime remains constant (z[hit rate] – z [false alarm rate] = z[0.99] – z[0.59] = 2.33 minus –0.23 = 2.56), despite the shift in bias.

Returning to the example of the radiologist, a cautious individual might answer"yes, tumor present" to a high proportion of scans to avoid the high cost of a 'miss'. Such a response does not make this radiologist any better than a neutral one at distinguishing between positive and negative scans (the false-alarm rate will rise as the miss rate falls), but if the cost of a miss is much greater than a false alarm, this 'liberal criterion' might be the best strategy (see figure 2.3).

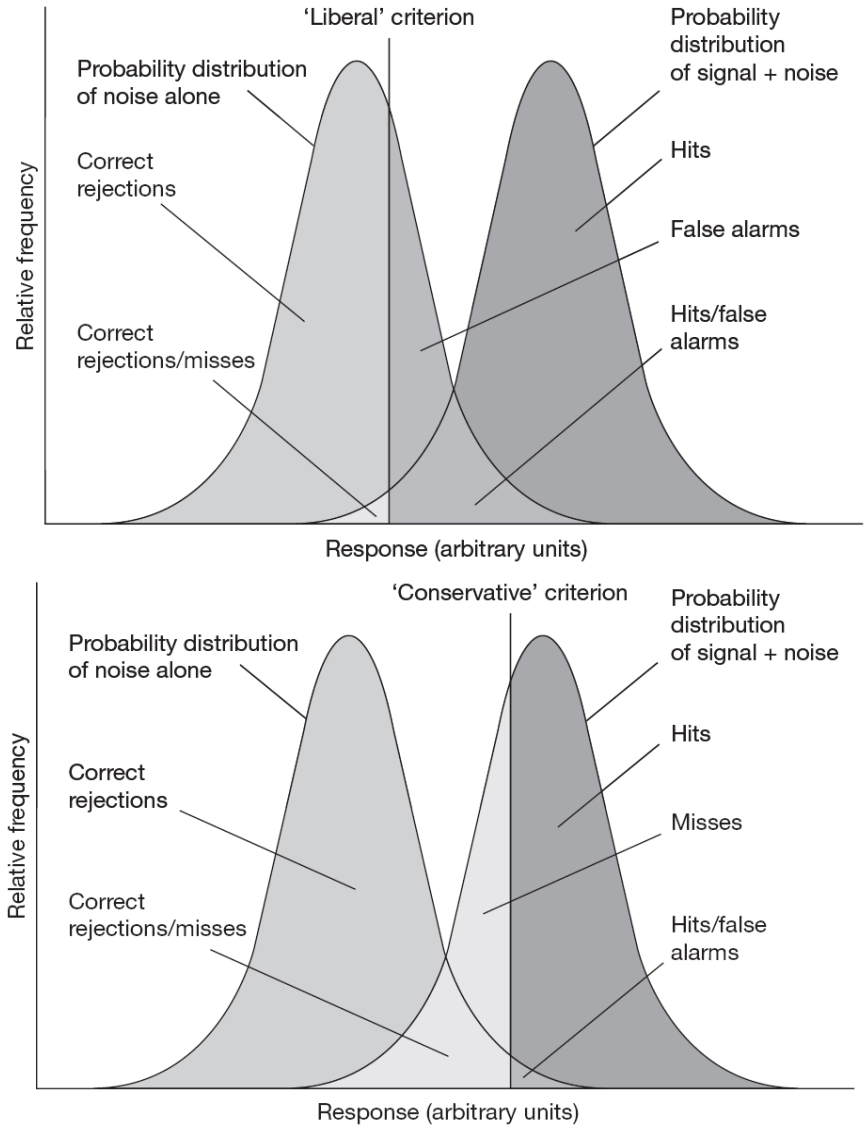

Figure 2.3. The effect of shifts in the criterion. Note how shifts in the criterion change the 'area of error' in the figures, which corresponds to a change in raw 'percent correct' value, but d-prime remains constant once hit and false-alarm rates are z-transformed.

2.2.2 The receiver operating characteristic curve

If the false-alarm rate is plotted against the hit rate for all possible values of the criterion, a curve is traced out in which each point represents a location where d-prime is constant but the

criterion changes. Known as the receiver operating characteristic, or ROC, curve, this is in fact a diagonal line when d-prime is zero (and the hit rate equals the false-alarm rate). The line 'bows' towards the upper left-hand corner as d-prime increases and accuracy improves (figure 2.4). As one travels leftward along a particular d-prime curve, the criterion becomes more conservative; that is, there are fewer hits but also fewer false alarms. The greater the area under the curve, the more accurate the observer: an area of 1.0 represents perfection (a d-prime of infinity), and an area of 0.5 represents chance (a d-prime of 0).

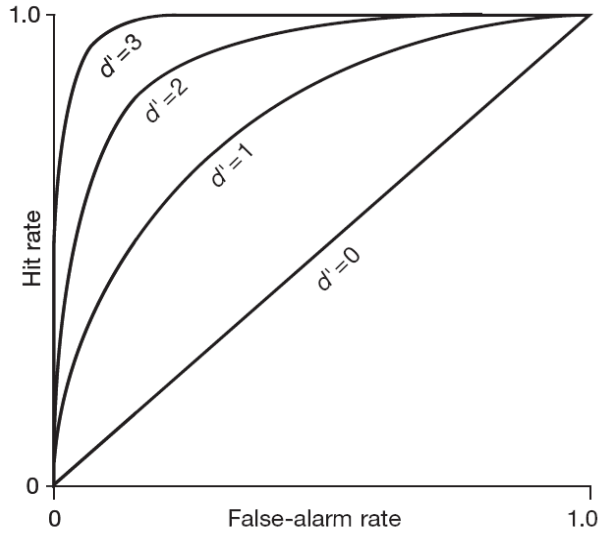

Figure 2.4. The receiver operating characteristic curve for different values of d- prime. (d'= d-prime).

2.2.3 Criterion in the presence of multiple signals

Decision-making also changes when two signals are presented simultaneously. When subjects had to simultaneously judge stimuli (vertical bars) of two different contrasts, which appeared with different frequencies, they tend to under-report the weaker ones and over-report the stronger ones compared with a situation in which the stimuli were each presented in isolation (Gorea & Sagi, 2000). The subjects seemed to be unable to generate a separate criterion for each stimulus, instead adopting a single criterion on the basis of a 'composite' distribution of the

two stimuli. This averaged criterion was therefore a suboptimal compromise, being too conservative for weaker signals (more misses) but too liberal for stronger signals (more false alarms; figure 2.5). This in turn translated into three times as many ”not seen” responses for less-visible targets and 1.3 times more ”seen” responses for more-visible targets when the signal stimuli were shown together compared with when they were shown in isolation, a phenomenon termed ‘natural extinction’ (Gorea & Sagi, 2002).

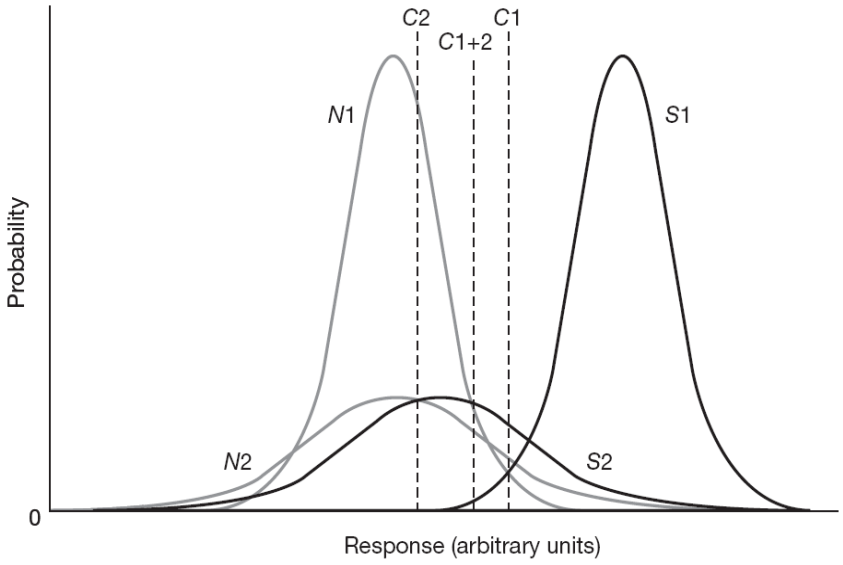

Figure 2.5. The merging of criteria in a multi-stimulus environment. The S1 and S2 curves show distributions of two stimuli when presented separately. The N1 and N2 curves show the corresponding noise distributions. C1 is the optimal criterion for S1 alone, C2 is the optimal criterion for S2 alone and C1+2 is the suboptimal, ‘unique’ criterion set by the observer. In this case, S1 represents a strong, high-frequency signal, and S2 represents a weak, low-frequency signal. C1 and C2 represent the behavior of an ideal observer, able to set a criterion separately for each signal. ‘C1+C2’ represents the experimental finding in the human observer, in whom the two criteria merge, causing the stronger signal to be over-reported and the weaker signal to be under-reported. Adapted from Gorea et al., 2005.

2.2 Data Analysis

In all experiments where the line/gap stimuli (Chapter 1, figure 1.2) were displayed, d-prime (d') was used to measure participants' ability to distinguish the presence of a (gap) target from its absence. As discussed in above, this parameter was derived from the z-transformed 'Hit' (H) and 'False Alarm' (FA) rates (d'= z[H]-z[FA]) as the distance between the means of the underlying noise and signal distributions (both presumed to be Gaussian) expressed in units of their common standard deviation (Green & Swets, 1966). The subjects' intrinsic bias towards giving 'yes' or 'no' responses for gap-presence was derived as the 'criterion' measure (c), where c = -1/2[z(H) + z(F)]. Criterion is independent of sensitivity in signal-detection terms, and is also expressed in standard deviation units.

Each participant's responses to each stimulus type were analysed to yield separate hit rate and false alarm data for the left and right visual fields. For example if the stimulus shown was an unbroken line (fig.1.2A) but the subject reported seeing a gap on the left (as in fig.1.2B), this would be recorded as a 'false alarm' on the left, and a 'correct rejection' on the right. Or if the stimulus shown had gaps at both ends (fig.1.2D) but the subject reported 'right gap' (as in fig.1.2C), a 'hit' was recorded for the right and a 'miss' for the left. In this way a 4X4 matrix (table 2.1) can be constructed relating the four possible stimulus types shown to the four possible responses to each stimulus type, thereby leading to separate signal-detection scores for each visual field. Thus the stimulus shown in fig.1.2A can yield 'false alarm' or 'correct rejection' rates for both left and right visual fields; whereas that shown in fig. 1.2C can yield 'false alarm' or 'correct rejection' rates for the left hemifield, but 'hit' or 'miss' rates for the right hemifield.

		Stimulus Displayed							
		No Gaps		Left Sided Gap		Right sided Gap		Gaps Both Sides	
Response	No Gaps	**CR**	**CR**	**M**	**CR**	**CR**	**M**	**M**	**M**
	Left Sided Gap	**FA**	**CR**	**H**	**CR**	**FA**	**M**	**H**	**M**
	Right Sided Gap	**CR**	**FA**	**M**	**FA**	**CR**	**H**	**M**	**H**
	Gaps Both Sides	**FA**	**FA**	**H**	**FA**	**FA**	**H**	**H**	**H**
Overall Information Derived		False Alarm Rate	False Alarm Rate	Hit Rate	False Alarm Rate	False Alarm Rate	Hit Rate	Hit Rate	Hit Rate

Table 2.1. This shows the analysis of participants' responses to each stimulus type to yield data for left (unshaded columns) and right (shaded columns) visual fields. CR = Correct rejection, M = Miss, FA = False Alarm, H = Hit.

Sensitivity (d') and criterion (c) can then be calculated not only separately for the 2 visual hemifields, but also separately under 2 different visual conditions (here, with or without a gap-target appearing in the other hemifield). Pairings of the scores submitted for each signal-detection calculations were chosen so as to keep the stimulus in the other visual field constant for any one signal-detection score considered. For example, when calculating signal-detection scores for the left visual hemifield, a left hit-rate for the stimulus shown in fig. 1.2D would be paired with the left false-alarm rate for the stimulus shown in fig 1.2C, to hold the presence of a gap on the right constant; and so on. As described by Macmillan and Creelman (2005), corrected values were used for any subjects yielding scores for hit rates of 1.0 or for false-alarm rates of 0.0 (i.e. 1-1/(2N) and 1/(2N) respectively, where N is the number of trials on which the proportion is based) as these could otherwise yield d-prime values of infinity. Statistical testing including ANOVA was carried out with the aid of a statistics software package (SPSS 18, SPSS Inc., Chicago, Illinois). Where justifiable a priori hypotheses existed, signed predictions in the form of one-tailed t-tests were made, and where no such hypotheses existed two-tailed t-tests were used instead.

Chapter Three: Hunting in the Parietal Cortex.

TMS is used commonly over the motor cortex to localise the area of maximum response or 'motor hotspot' (as measured by MEP size, recording from the small muscles of the hand). This first group of experiments describes a novel functional localisation technique, which instead employs TMS to search over the parietal cortex for a 'parietal hotspot'. The effects of TMS are measured in behavioural terms (rather than with MEPs) and are quantified using the signal detection measures d-prime and criterion.

The work presented in this Chapter was originally published in the form of a research article:

Oliver, R., Bjoertomt, O., Driver, J., Greenwood, R., & Rothwell, J. (2009). Novel 'hunting' method using transcranial magnetic stimulation over parietal cortex disrupts visuospatial sensitivity in relation to motor thresholds. *Neuropsychologia* , 47, 3152-3161. doi:10.1016/j.neuropsychologia.2009.07.017

3.1 Summary

There is considerable inter-study and inter-individual variation in the scalp location of parietal sites where transcranial magnetic stimulation (TMS) may modulate visuospatial behaviours (e.g. see Ryan, Bonilha, & Jackson, 2006); and no clear consensus on methods for identifying such sites. Here a novel TMS "hunting paradigm" is introduced that allows rapid, reliable identification of a site over the right anterior intraparietal sulcus (IPS), where short trains (at 10 Hz for 0.5s) of TMS disrupt performance of a visuospatial task. The task involves detection of a small peripheral gap (at 14 degrees eccentricity), on one or other (known) side of an extended (29 degrees) horizontal line centred on fixation. Signal detection analysis confirmed that TMS at the right IPS site reduced sensitivity (d') for gap targets in the left visual hemifield. A further experiment showed that the same right-parietal TMS increased sensitivity instead for gaps in the right hemifield. Comparing TMS across a grid of scalp locations around the identified 'hotspot' confirmed the spatial specificity of the effective site. Assessment of the TMS intensity required to produce the phenomena found that this was linearly related to individuals' resting motor TMS threshold over hand M1. This approach provides a systematic new way to identify in each subject an effective site and intensity, at which TMS over right parietal cortex reliably changes visuospatial sensitivity.

3.2 Introduction

Previous work has shown that transcranial magnetic stimulation (TMS) can alter performance in some visuospatial tasks when delivered over posterior parietal (PPC) sites; for instance, producing a rightward bias in line bisection or landmark-based tasks (e.g. Fecteau et al., 2006; Fierro et al., 2000, 2006; Muggleton et al., 2008; Pourtois et al., 2001; Valero-Cabré et al., 2006). The effects may be lateralised (with right parietal TMS typically more effective) and may also interact with the visual field tested. For example, numerous studies using right parietal TMS in healthy participants reveal disruption of visual performance in the contralateral left visual hemifield (e.g. Dambeck et al., 2006; Jin, & Hilgetag, 2008; Koch et al., 2005; Meister et al., 2006; Muggleton et al., 2006; Pascual-Leone et al., 1994) and/or enhancement for the right hemifield (see Fecteau et al., 2006 for a detailed review). Right parietal TMS can also produce enhanced ipsilateral somatosensory sensitivity (Blankenburg et al., 2008; Seyal et al., 1995). In one prominent visual example, Hilgetag et al. (2001) reported that extended 1Hz repetitive TMS over right parietal PPC led not only to subsequent contralateral impairment, but also to ipsilateral enhancement of visual target detection. Chambers et al. (2006) reported that short (0.5s) bursts of right PPC TMS at 10Hz may selectively enhance the localisation of ipsilateral targets in bilateral visual arrays.

Clinically, TMS has been used to explore possible therapeutic effects of TMS or repetitive TMS in patients with spatial neglect after unilateral brain injury, when applied over the undamaged hemisphere. As discussed in the Introductory chapter (page 51), the notion of 'interhemispheric rivalry' (Kinsbourne, 1977) suggests that the undamaged hemisphere may become hyperexcitable in neglect, and hence that applying TMS to that hemisphere might potentially rebalance or normalise this. Single or short trains (up to 5 TMS pulses at 20Hz) of left parietal or

frontal TMS have been reported to reduce contralateral extinction for tactile stimuli in unilateral right-hemisphere stroke patients (Oliveri et al., 1999a). Moreover, forms of rTMS such as 1 Hz stimulation or TBS applied over the unaffected hemisphere may ameliorate a rightward spatial bias for up to 15 days (Brighina et al., 2003; Shindo et al., 2006; Nyffeler et al., 2009), and cause some improvement in the perception of chimeric figures (Koch et al., 2008) in neglect patients.

In all of the PPC studies above, TMS was applied over a parietal target defined either with MRI-based frameless stereotaxy (which is not always practical, as in some clinical patient studies); or by simply targeting a point (P3, P4, P5, or P6) defined by the 10/20 EEG electrode placement system. However, neuroimaging studies indicate that the anatomical network underlying visuospatial attention in normals may be rather widely distributed (e.g. see Corbetta & Shulman, 2002; Mort et al., 2003). Moreover, at the level of each individual participant or patient, it can be unclear exactly which site of potential parietal TMS stimulation should produce the greatest impact on visuospatial function (see Ryan et al., 2006). Recent TMS work in normals has shown that merely using the scalp coordinates of conventional EEG electrode-sites can be rather ineffective (Sack et al., 2008). Moreover, for electrode sites such as P3 and P4, the anatomical structures underlying them have been shown to vary rather substantially between individuals. For instance, the two structures most likely to underlie P4 are not only the right angular gyrus (~63% of the time), but also the right superior occipital gyrus (~22% of the time), according to Okamoto, et al. (2003).

Using a target site that is defined *functionally* within each participant, rather than anatomically, might enhance systematic impacts on visuospatial processing, thereby speeding progress both in understanding these effects and in seeking to exploit them clinically. One solution is a ‘hunting procedure’, whereby the effect of TMS on a visuospatial task is assessed briefly over a number of different sites, and the optimal site defined functionally (in terms of behavioural

impact) is then selected as the TMS target for more detailed testing, with the same and/or other visuospatial tasks. For example, according to one influential proposal (Ashbridge et al., 1997), a 3 x 3 grid can be drawn around P3 or P4 and the best TMS site to disrupt visuospatial search may then be found by comparing the effects for 16 trials at each site. The 'hotspot' in this particular protocol has been defined as the point where TMS increases participants' reaction time by 100ms or more (Ashbridge et al., 1997). Subsequent TMS over such a pre-defined point was shown to cause a contralateral deficit in line-judgement tasks but no lateralised deficit in visual search tasks, hinting at some possible mismatch between the hunting procedure and subsequent experimental findings (Ashbridge et al., 1997; see also Ellison et al., 2004).

Although influential, the particular hunting procedure of Ashbridge et al. (1997) is time-consuming, and moreover it relies on reaction-time effects that might not necessarily reflect genuine changes in visuospatial sensitivity or 'd-prime' (d'). The aim of the present study was to develop a modified hunting procedure for right parietal TMS effects upon visuospatial performance, in a task which is well suited for application of signal detection theory to allow sensitivity measures such as d'. This chapter describes a rapid and simple method of localising an effective TMS site over right parietal cortex, which provides an alternative or supplement to the established techniques mentioned above. This new protocol is then validated in a subsequent series of experiments, which show that it is both reliable and specific.

In the first set of studies below the new procedure is described, its reproducibility tested, and the most effective right parietal site identified. In the second and third sets of studies, signal detection analysis is used to examine these findings in detail, to confirm a genuine effect on perceptual sensitivity, and to verify that the induced visuospatial effects differ between contralateral and ipsilateral visual hemifields. Finally, the relationship between TMS intensity needed to disrupt visuospatial sensitivity and individual participants' RMT is explored. A strong correlation would then allow the TMS intensity for visuospatial experiments to be readily

adjusted to match each individual participant, along with an individual parietal TMS-site location as identified via the new hunting procedure.

3.3 Methods

The participants (see table 1.1, page 64) performed a target detection task in which they were asked to judge the presence (as in fig. 1.2B or C) or absence (as in fig. 1.2A) of a small gap, which could appear near the far left (fig. 1.2B) or far right (fig. 1.2C) of each line when present, at 14◦ of eccentricity. Unlike the well-known line-bisection task, this gap-detection task is unambiguous regarding which visual hemifield is most relevant for a particular detection judgement. This is because the gap (when present) was either at the far-left (Experiments 1, 2 and 4) or far-right (Experiment 3), but was never present on both sides concurrently. This contrasts with the horizontal extents that are compared between sides during the line-bisection task, or standard variants upon that task such as judgements of prebisected lines. Moreover, in all experiments the participants were instructed regarding which side (far-left or far-right) the gap could appear on with this remaining constant throughout each experiment. They nevertheless had to maintain central fixation, as was confirmed with eye-tracking. The foreknown nature of the task-relevant location where the gap might appear contrasts with other paradigms involving potential search of either or both sides, and should minimize any strategies that trade-off different locations, since here a single location was task-relevant and this was always known in advance.

Visual stimulus duration was tailored for each participant to achieve a % correct rate of ~95%, using a 'staircase' procedure as described in detail below. TMS was delivered over right parietal (5 biphasic pulses at 10Hz), starting 100ms before visual display onset and ending with the final pulse being delivered 400 ms after initial visual display onset. These TMS bursts were chosen

on the basis of previous studies where 5 pulses at 10Hz led to reported 'neglect-like' (visuospatial) deficits in line bisection tasks, when given over the right PPC (Bjoertomt et al., 2002; Ellison et al., 2004). The train of pulses starting 100ms before visual stimulus aimed to disrupt participants' covert monitoring of the gap target's future location as well as during the visual stimulus, thereby maximising any effect of the TMS pulses. The initial TMS intensity used was 100% of the participant's Resting Motor Threshold (RMT), apart from in Experiment 4 for which TMS intensity was varied.

3.4 Experiment 1

3.4.1 Experiment 1: Procedure

Following a fixation cross, 9 participants were shown on each trial either an unbroken horizontal line (fig. 1.2.A) or a line with a 'gap' at the far left (fig.1.2.B), equiprobably. They were instructed to keep their eyes fixed on the centre of the screen (as confirmed later with eye-tracking) and to indicate their perception ('gap' or 'no gap') with a key press. Note that the gap, when present, could only appear on the far left in this particular experiment, as was known to the participants. For each participant, a suitable presentation duration (PD) was determined (in the absence of TMS) with a staircase procedure, aiming for 95% of the stimuli being correctly identified as containing a gap or no-gap. Using single blocks of 20 trials, the PD was adjusted in 20 ms steps starting at 80 ms. If performance for one block was lower or higher than the desired 1/20 error rate, the PD was adjusted one step up or down, respectively. The staircase ended if the desired error rate was attained, with the last PD then being deemed suitable. Alternatively, if a reversal in performance occurred around the desired error rate, a retest was administered using the shorter PD of the preceding two blocks. The shorter or longer PD of these two blocks was

deemed suitable if the retest error rate was below or above (respectively) the desired rate. For all participants, the selected PD was typically 20-40 ms (mode of 20 ms, mean of 29 ms). During the TMS hunting procedure itself, the left 'gap' was in fact presented more often (now 90% of trials, unknown to the naïve participants), but as explained below was often missed nevertheless due to the TMS. The aim was to keep the hunting procedure for identifying a hotspot as simple as possible initially, basing it only on 'misses' and 'hits' (though full signal detection measures that incorporate 'false alarm' and 'correct rejection' rates were used in subsequent cross-validation experiments). For this reason the proportion of 'no gap' trials (which yield neither 'misses' nor 'hits' and thus did not contribute to initial localisation of the 'hotspot') was kept low at 10% during the hunting procedure. Once the participant was able to correctly identify 4 consecutive 'gap' stimuli (as a final confirmation of good performance), TMS was delivered during stimulus presentation as described above (i.e. 5 TMS pulses at 10Hz and 100% RMT, beginning 100 ms prior to display onset).

The coil position at the start of the experiment was EEG 10-20 position P4 in all participants. This location was selected on the basis of previous TMS studies (Pascual-Leone et al., 1994; Hilgetag et al., 2001; Oliveri et al., 2000a; Oliveri et al., 2000b; Pourtois et al., 2001; Koch et al., 2005, Dambeck et al., 2006, Jin et al., 2008) in which reliable effects on spatial judgments were found using P4 as the target TMS site. Those past studies suggest that a procedure hunting for a particularly effective parietal-TMS site (as here) should meet with success relatively fast if sites near P4 are sampled initially. Starting at P4, the coil was moved along a spiral-shaped path using a 'miss- stay', 'hit- shift' protocol, until a site was reached where the participant missed four consecutive gaps. Hence a TMS site was judged as effective when participants demonstrated a rise in the 'miss-rate' for left gaps as compared to the 4/4 hits scored just before the start of the TMS.

With this new hunting procedure, the aim was to sample a relatively large number of points in a short space of time, rejecting those points unlikely to provide a true 'hotspot' as quickly as

possible (hence the low proportion of 'no-gap' trials), while at the same time maintaining a low risk of declaring a false hotspot. A spiral-shaped path gives a particularly effective spatial coverage of a sampling surface in a time-efficient manner, a property exploited in techniques as diverse as MRI (see Sykora, 2005, their fig. 6) or the production of machine tools (see Wieczorowski, 2001). The coil was moved from P4 in 0.5cm steps along a path which approximated a clockwise spiral drawn through the intersections of a grid (e.g. lateral, posterior, medial, medial, anterior, anterior, lateral, lateral, lateral, posterior and so on). Accuracy was improved by first marking out a grid for the experimenter's visual reference, centred on the point formed by the coil's anterior concavity, given that the coil's initial centre lay over P4 (a grid centred over P4 would hence have been obscured by the coil for most of the hunting procedure). To prevent a sampling bias towards those points postero-lateral (or antero-medial) to P4, the first movement of the coil alternated across participants between medial or lateral (with the overall spiral shifts still clockwise). Even this counterbalancing of first shift leaves some potential for sampling 'bias', in the sense of anterior-lateral and posterior-medial points being sampled somewhat later , but as shown later in the Discussion (Section 3.8), any such residual sampling bias was in practice very small) The spatial resolution of typical TMS coils has been quoted as approximately $1cm^2$ (e.g. Walsh, 1998), though sites established as empirically distinguishable on the basis of TMS effects range from 0.5 cm apart (as over motor cortex, Brasil-Neto et al., 1992) through to 0.5-1.5cm apart (as over occipital cortex, O'Shea & Walsh, 2007, or over visual association areas, Beckers & Hömberg ,1992; Pascual-Leone, et al., 1999) . By moving the coil in steps of 0.5cm here, one could therefore be confident that a functionally distinct location such as the 'hotspot' should not be missed.

In each individual participant the scalp location of the coil at the end of the hunting procedure, hereafter termed the (parietal) 'hotspot', was recorded relative to the EEG '10/20' position P4. In addition, this point was recorded using an infrared positioning system (Northern Digital,

Waterloo, Canada), and the Brainsight Frameless software package (Rogue Research, Montreal, Canada). The separate motor TMS hotspot was defined as the optimal site for eliciting MEPs in the left FDI muscle, and was likewise marked on the participant's structural MRI scan. In a follow-up study the right parietal hotspot was again determined initially by the hunting procedure as before. This time, however, participants continued with the 'left gap'/ 'no gap' discrimination task for 20 more trials (still with 90% of trials actually containing 'left gaps' during TMS), now while wearing an IRIS Skalar Infra-red Eye Tracker (as described in Chapter 1, section 1.2.3) This was to confirm that any reduction in perception of gaps at the far-left of the horizontal line during right parietal TMS over the hotspot could not be due to substantial TMS-induced deviations of the eyes towards the right.

3.4.2 Experiment 1: Results: Reproducibility of the hunting procedure

In all 9 participants the hunting procedure yielded a point over right parietal cortex where TMS led to increased misses for left gaps, on average taking 62 ±7 trials to find. The average site across all 9 participants was 2.2 ± 0.3cm (mean ± SE) anterior and 1.3 ±0.3 cm medial to the P4 '10/20' EEG site. In all participants the site was mapped onto each individual's structural MRI scan using neuronavigation (figure 3.1.). This corresponded to a point along the anterior intraparietal sulcus, just posterior to its junction with primary somatosensory cortex (mean Montreal Neurological Institute coordinates of X = 42.3 , Y = -50.3, Z = 64.4) During stimulus presentation (and thus after 2 of the 5 TMS pulses), mean eye position deviated only a very small amount, and to the left rather than right (by 0.46 degrees of visual angle, compared to a total line length of 29 degrees of visual angle, and an eccentricity for the left gap when present of 14 degrees). During TMS, eye blinks occurred during stimulus presentation on less than 2% of trials. Thus, neither changes in eye-position, nor blinks due to TMS, can plausibly explain the substantial impairment of detection for left gaps also observed in the subsequent experiments (Experiments 2 and 4) . Please note also that Experiment 3 found that the same right-parietal

TMS actually enhanced rather than suppressed detection of gaps when present in the *right* visual field instead. This opposite outcome for the other hemifield is inconsistent with any account in terms merely of TMS-induced blinks obliterating some of the visual displays.

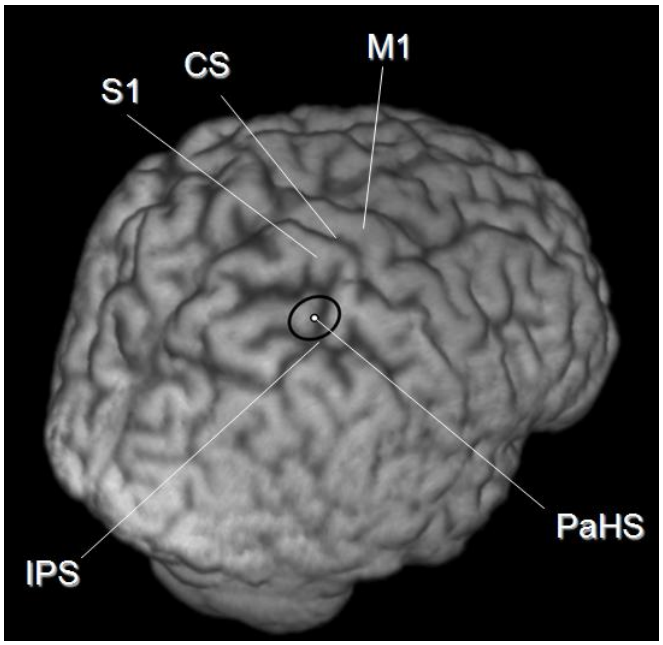

Figure 3.1. The position of the 'Parietal Hotspot' (PaHS) averaged over 9 participants' structural MR scans. CS = Central Sulcus, M1 = Primary Motor Cortex, S1= Primary Somatosensory Cortex, IPS = Intra Parietal Sulcus, PaHS = 'Parietal Hot Spot'. The coordinates of the coil location at the end of the hunting procedure (see main text) as reported in MNI space (ICBM152 template) and using the Talairach stereotaxic convention (Talairach & Tournoux, 1988), were averaged. The coordinates were transformed using the FLIRT program (FSL 3.2 package, fMRIB, University of Oxford, UK; http://www.fmrib.ox.ac.uk/fsl/) from native space to normalized structural image space. The black ellipse represents the 95% confidence limits. Note that the long-axis of the ellipse lies in the same direction as the TMS coil handle and short axis of the coil, along which the induced magnetic field is more variable. The narrower axis of the ellipse lies along the long axis of the figure of 8 coil where the magnetic field induced is less variable. This may explain the elliptical shape of the 95% confidence limits on site location shown.

3.5 Experiment 2

3.5.1 Experiment 2: Procedure

For practical reasons only 6 of the original 9 participants (as described in Table 1.1, page 64) were studied in this time-consuming and demanding follow-up experiment. The parietal hotspot was marked using the scalp coordinates for each participant from the previous experiment. However, in order to confirm that the hotspot does indeed identify the most effective site in its scalp neighbourhood, it was now reassigned as providing the centre of a new 9-point grid (4 x 4 cm, i.e. 2cm between all nearest points in a square grid) which was marked on the scalp. The effect of TMS applied to all of these nine sites was then assessed, to examine how the impact on performance might vary as TMS was shifted away from the putative hotspot. Participants again had to discriminate between left-gap and no-gap stimuli, as for Experiment 1, but now in blocks of 60 trials (30 no-gap and 30 left-gap stimuli, in randomly intermingled order, with no-gap trials now more common in order to enable formal signal-detection-theory analyses), first performed without TMS (one block, baseline), and then with TMS disruption (using exactly the same parameters as Experiment 1 and given with each trial, for 10 blocks). TMS was initially delivered over the putative parietal hotspot, and then in randomised order over the 8 other points in the new square grid centred on the hotspot. A final block was then performed with TMS again over the putative hotspot, to provide an average value for this site before and after extended experience, and to assess any impacts of practice (figure 3.3). Thus the dual aims of Experiment 2 were to obtain confirmation of the spatial specificity of the identified TMS hotspot, via follow-up testing of a grid of positions on the scalp centred around that site; and to do so while collecting enough psychophysical data to allow full application of signal detection measures (including d').

3.5.2 Experiment 2 Results: Perceptual effects of parietal stimulation on sensitivity for left sided targets, with spatial specificity of the TMS effect confirmed via the scalp-grid comparisons

Sensitivity (d') for left-gaps was indeed found to be impaired during TMS over the right-parietal putative 'hotspot' (as identified by the preceding hunting procedure), and the spatial-specificity of the hotspot TMS site was then confirmed by comparing 9 TMS positions in a grid centered on the putative hotspot.

Signal detection analysis was used to yield the parameters 'd-prime' (d') and criterion from the 6 participants' responses. The effect of TMS at the right parietal putative 'hotspot' was compared with the averaged effect of TMS applied over the 8 equally spaced surrounding sites, to determine whether or not the hunting procedure had in fact located the optimal site in its neighborhood. Although typically expressed in standard deviation units, d' is reported here in terms of a proportional (%) change from the (no TMS) baseline: [d-prime during TMS/d-prime at baseline] x 100. In this way TMS effects at different locations are all normalized relative to participants' pre-existing level of performance. The data showed a significant difference ($t(5) = -2.59$, $p = 0.048$, two-tailed; see fig. 3.2 and Table 3.1) between: a) participants' performance with TMS given over the right parietal hotspot (where d' fell to 89 ± 14% of its baseline value), and b) performance with TMS given over the eight surrounding sites in the grid (where d' rose to 112 ± 9% of its baseline value).

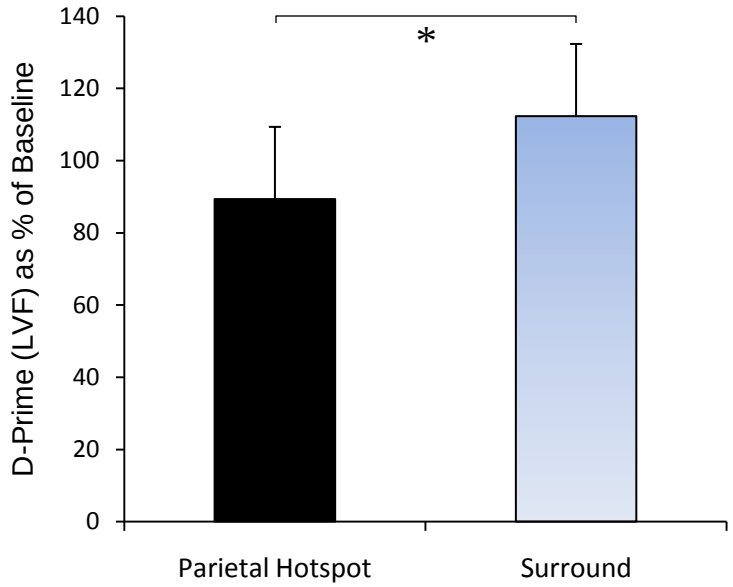

Figure 3.2. Visual sensitivity (d-prime, as % of the no-TMS baseline: [d-prime during TMS/d-prime at baseline] x 100) in the left visual field (LVF) for Experiment 2, which found it to be significantly lower with TMS over the right-parietal hotspot as compared to the 8 surrounding sites in the 9-point grid. The asterisk represents a significant difference between the 2 conditions; see main text.

Finally, there were no significant TMS impacts on criterion (c) for left gaps; see Table 3.2. (all $p>0.10$). The data were also plotted in block sequence order (i.e. now shown in the order of time, rather than just spatially organised) as in figure 3.3. Performance over those blocks which did not involve TMS over the hotspot was examined for evidence of any ongoing learning effect. There was a modest overall increase in performance; as a linear function, d' increased by 0.030 per block (dashed line), but across all blocks d' values were not correlated significantly with block order ($r_s(6) = 0.488$, $p = 0.22$). As a precaution against potential order confounds, TMS was delivered over the right-parietal hotspot for both the first and last TMS blocks, and their values averaged before comparison with the surround sites. As demonstrated in figure 3.3, the performance for both of the hotspot blocks (black symbols) was comparable despite their very different sequential position.

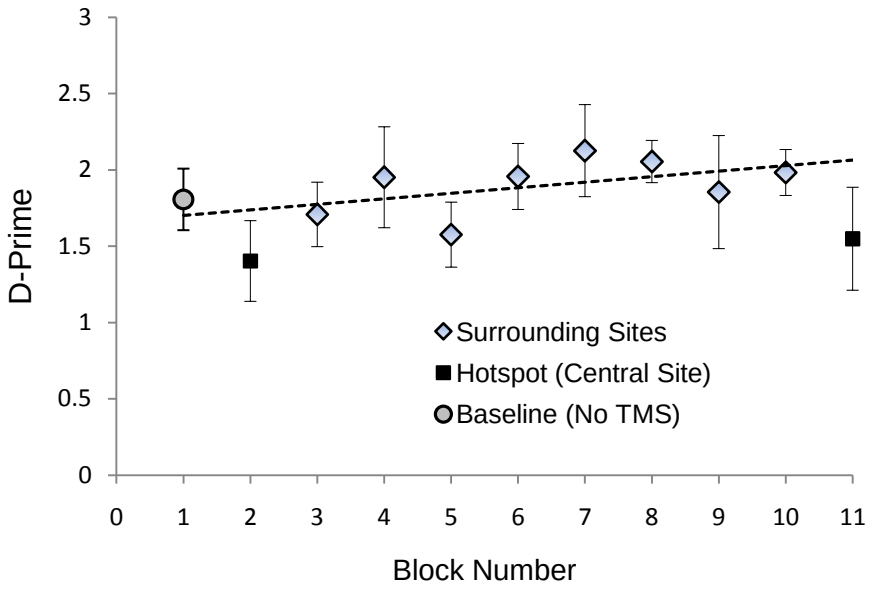

Figure 3.3. D-prime values from Experiment 2 are shown for the baseline condition (no TMS, grey symbol at far left); for 10 Hz TMS over the right parietal hotspot (black symbols, second from left and rightmost) and for 10Hz TMS over the eight surrounding sites in the scalp grid (open symbols), plotted against sequential block order along the x-axis. Error bars show SEM. Performance over blocks 3-10 (those which did not involve TMS over the hotspot), was examined for evidence of any ongoing learning effect. There was a modest overall increase in performance; as a linear function, d' increases by 0.030 per block (dashed line), but across all blocks, d' values were not correlated significantly with block order ($r_s(6) = 0.488$, $p = 0.22$). In any case, as a precaution against any increase in d' over successive blocks, TMS was delivered over the right-parietal hotspot for both the first and last TMS blocks (black symbols), and their values averaged before comparison with the surround sites. Note that comparable performance for both of the hotspot blocks (black symbols) despite their very different sequential position.

Position Relative to Parietal Hotspot	2cm Medial	Level	2cm Lateral
2cm Anterior	112 (12)	120 (13)	106 (11)
Level	109 (17)	89 (13)	114 (11)
2cm Posterior	119 (17)	114 (17)	103 (19)

Table 3.1. Participants' d-prime values, expressed as a % of baseline (no TMS) performance ([d-prime during TMS/d-prime at baseline] x 100) for each of the 9 points. The SEM is shown in brackets.

Position Relative to Parietal Hotspot	2cm Medial	Level	2cm Lateral
2cm Anterior	-0.05 (0.23)	0.10 (0.27)	-0.06(0.16)
Level	-0.16 (0.16)	0.14(0.11)	0.24 (0.21)
2cm Posterior	-0.16 (0.19)	0.10(0.14)	0.16 (0.16)

Table 3.2. Participants' criterion values shown as the numerical deviation from baseline (no TMS), for each of the 9 points, during TMS. The SEM is shown in brackets.

3.6 Experiment 3

3.6.1 Experiment 3: Procedure

In this experiment, the 6 participants were tested (including five who had participated in both Experiments 1 and 2, and one who had participated in just Experiment 1). They were now tested in their ability to detect right sided gaps instead (fig. 1.2C), when these were intermingled with no-gap stimuli (fig. 1.2A) in a random order. They now knew in advance that any gap could appear only on the far right. Their ability to detect such gaps was first measured without TMS (one baseline block, 60 trials as in Experiment 2, with gap presence or absence equiprobable)

and then with both real or sham TMS disruption (same TMS parameters with the coil still held over the same hotspot, but now at 90 degrees to the scalp), during two further blocks of 60 trials. TMS was given over the same right parietal hotspot determined by the preceding hunting procedure, with the order of real and sham TMS blocks counterbalanced across the 6 participants. Based on Hilgetag et al. (2001) and the hemispheric-competition notion of Kinsbourne (1997), one might expect that TMS over the right parietal hotspot site, selected to *impair* detection of left gaps, might conversely *enhance* detection of right gaps. But if the TMS disruption for left gaps was somehow nonspecific (e.g. merely reflecting, say, induced blinks), then the same TMS should presumably impair sensitivity to right gaps in the same or similar manner to the impact on performance for left gaps, rather than having an opposite effect.

3.6.2 Experiment 3 Results: Perceptual effects of parietal stimulation on sensitivity for right sided targets

As in Experiment 2, the data were first normalised as a % of baseline (no TMS) performance, for both real and sham TMS conditions i.e. [d-prime during TMS/d-prime at baseline] x 100. Compared to baseline values, sensitivity (d') for gaps in the right visual field (RVF) was found to increase during real TMS over the right parietal hotspot (i.e. on average d' increased to 130 ± 16% of baseline values). This change was less marked during sham TMS (d' rose only to 114±15 % of baseline values), leading to a significant difference between real and sham TMS conditions ($t(4) = -4.25$ $p = 0.010$, two-tailed; see fig 3.4). Note that the *enhancement* by right-parietal TMS over the hotspot is the *opposite* outcome to the reduced sensitivity found (in Experiment 2) for gaps in the left visual hemifield. As in Experiment 2, there were no significant TMS effects on the criterion (c) measure in Experiment 3 ($p = 0.53$).

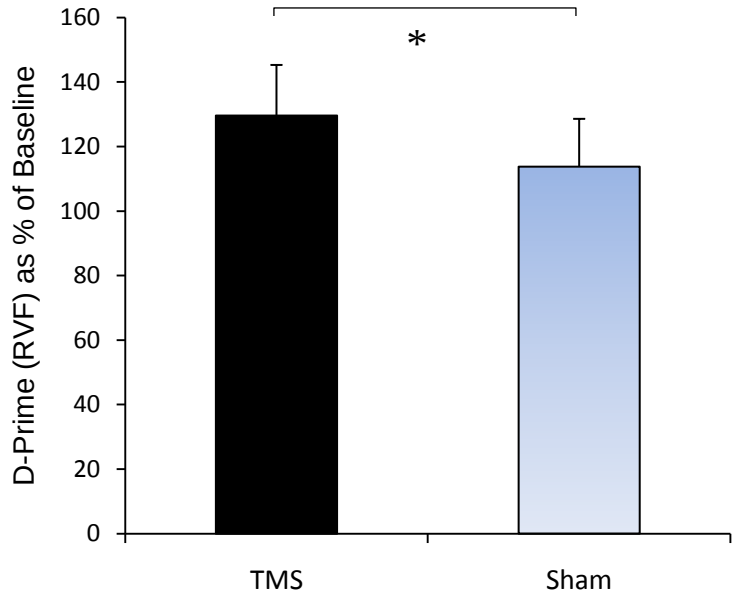

Figure 3.4. The effect of TMS over the right-parietal hotspot on d-prime (as % of no-TMS baseline: [d-prime during TMS/d-prime at baseline] x 100) for targets in the right visual field (RVF), showing a significant rise compared to the Sham condition see main text.

3.7 Experiment 4

3.7.1 Experiment 4: Procedure

The aim of this final study was to examine how TMS intensity over the right parietal hotspot, effective in disrupting sensitivity to left gaps, might relate to individual motor thresholds when stimulating over M1 instead. 8 participants (from the original 9 in Experiment 1), were asked to discriminate between 'left gap' or 'no gap' stimuli in blocks of 60 trials, just as in Experiment 2. However, blocks were now performed in successive pairs: one with TMS delivered over the right parietal hotspot and one using sham TMS, with the order of these TMS types within each successive block-pair counterbalanced. Each block-pair was randomly assigned 1 of 10 different TMS intensities (10% RMT, or 20% RMT, or 30% RMT, and so on up to 100% RMT) and thus each of the 10 TMS intensity levels was performed in a different, pseudorandomized

order for each participant. For block-pairs, the sequence (TMS first or Sham first) alternated with each 10% increase in TMS intensity. For half the participants (chosen at random) the sequence was: TMS first for 10% RMT, Sham first for 20% RMT, TMS first for 30% RMT and so on. For the other half, the sequence also alternated in similar fashion but starting with Sham first for 10% RMT. This was done to avoid weighting the higher TMS intensity blocks with more TMS-first block pairs (and thus to circumvent any possibility that poorer performance at higher TMS intensities might somehow reflect intra-block-pair practice effects). In this way the impact of TMS at different intensities over the right parietal hotspot (on visuospatial sensitivity to left gaps) could be related to the intensity of TMS required to reach resting motor threshold in individual participants.

3.7.2 Experiment 4: Results: Relationship between perceptual effect at the parietal hotspot for different intensities, and motor threshold for each participant.

For the 8 participants tested, the RMT range was 40-69% of maximum stimulator output, with a mean of 53±9.7%. For each of them, sensitivity for gaps in the left visual hemifield fell as right-parietal TMS intensity over the hotspot was increased. The rate at which this occurred was studied by comparing the change in d' after real TMS (expressed as a % of sham TMS performance: [d-prime during real TMS/d-prime during sham TMS] x 100), against TMS intensity (% of maximum stimulator output) in each participant, and then fitting a linear trend line to each resulting function (the individual participant data for this is shown in figure 3.5).

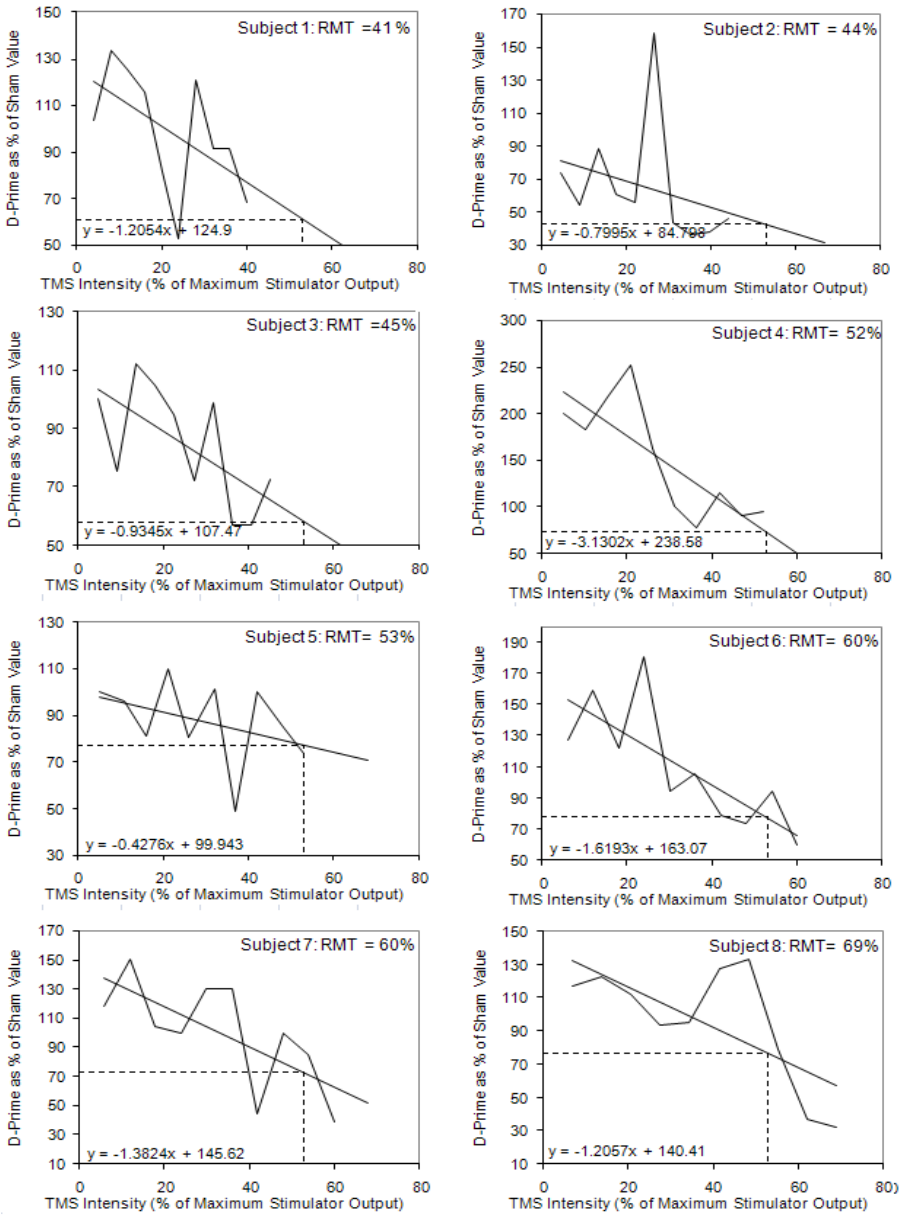

Figure 3.5. The individual participant plots for data from Experiment 4, displayed in order of increasing RMT (as shown in the top right corner of each plot) showing the fall in d' for left gaps with increased intensity of TMS over the right-parietal hotspot. D-prime is shown (along the y-axes) as a % of the corresponding Sham value and TMS intensity as % of maximum stimulator output along the x-axes. A linear trend line is fitted to each plot, with the function equation displayed in the bottom left hand corner of each plot. The d' value at a constant reference TMS intensity (i.e. at a stimulator output of 53% corresponding to the grand mean of all participants' RMT- see main text) is calculated for each participant (represented by the dashed lines). These values were then used in the correlation with individual participant RMT's (cf. fig. 3.6).

Further analysis tested whether the disruptive effect of right-parietal TMS (over the hotspot) at different intensities, upon visuospatial sensitivity to left gaps, was linked to participants' RMT. If so, one would expect a given level of TMS intensity to produce more disruption in individuals with a lower RMT (and less in those with a higher RMT). Accordingly, the best spread of d' values (for comparison with individual participant RMT values) should be found at a TMS intensity corresponding to the *average* RMT across participants. Thus for each of them, the % drop in d' at the average RMT (53% of maximum stimulator output) was read off along their linear trend-line. A significant correlation (Spearman's rho, $r_s(6) = 0.794$, $p = 0.019$, two- tailed) was found between the d' drop due to TMS (at 53% of maximum stimulator output) for each participant and their RMT; see fig. 3.6. Hence a key finding from Experiment 4 is that for TMS over the right parietal hotspot, the amount by which left-gap-sensitivity declines (relative to sham) at a given level of TMS intensity relates systematically to each individuals' resting motor threshold. Since the latter can be readily assessed for any healthy person or patient, it can now provide a natural way to scale TMS intensity when targeting a right parietal site with the aim of changing visuospatial sensitivity for peripheral targets, as for the gaps used here. Note that this may not always apply for other TMS effects, for which scaling by motor threshold may be inappropriate (see Stokes et al., 2005, 2007, plus Antal et al., 2004; Boroojerdi et al., 2002; Stewart et al., 2001). Here it can be shown that this approach is at least viable for right-parietal TMS effects upon visuospatial sensitivity for left gaps.

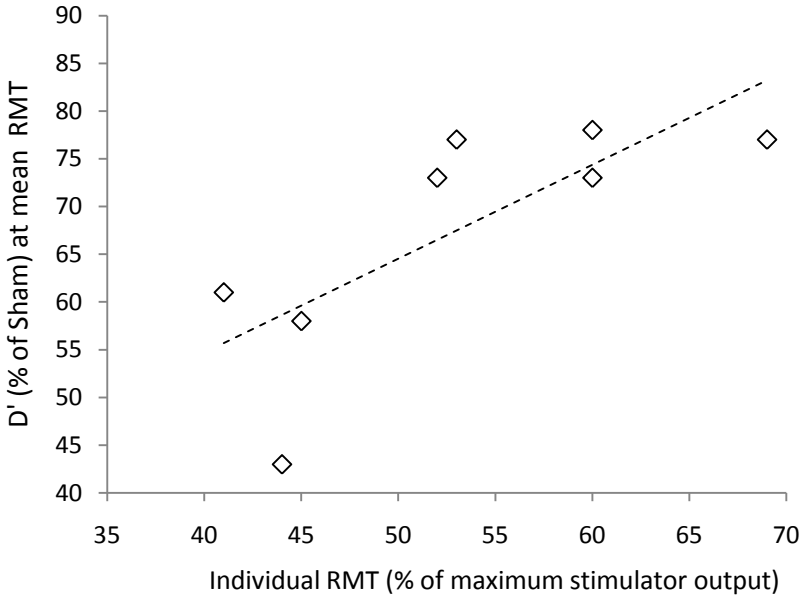

Figure 3.6. Scatterplot illustrating the positive correlation (dotted line: $r_s(6) = 0.79$, $p = 0.019$) between the d' drop (as a % of d' scores during Sham rather than real TMS, along the y-axis) for each participant (at the average RMT *across* participants i.e. 53% of maximum stimulator output), with each participant's individual RMT shown along the x-axis, for the 8 participants of Experiment 4

Next the 8 structural MRI scans of those participating in Experiment 4 were examined, to investigate possible underlying causes of the correlation described above (as illustrated in figure 3. 6.). This analysis found that the reconstructed scalp-to-cortex depths at each individual parietal or motor hotspot (for parietal, the mean depth was 16.2mm, SD 2.5mm; for motor this was 14.0 mm, SD 2.5mm) correlated tightly with the other depth in a participant-by-participant manner ($r_s(6) = 0.94$, $p<0.05$, two-tailed). To assess the influence of scalp-cortex distance on the relationship found between individuals' RMT and their susceptibility to parietal-hotspot TMS (fig. 3.6), partial correlations were next performed, now entering the individual scalp-cortex depths at parietal or motor hotspots as further controlling factors. Either of these each rendered the original correlation less significant. Specifically, entering RMT as factor W, % real-versus-sham d' at mean RMT as factor X, scalp-to-cortex distance for the parietal hotspot as factor Y,

and this distance for the motor hotspot as factor Z, yielded: $r_s(5)_{WX.Y} = 0.72$, $t = 2.10$, $p = 0.10$, and $r_s(5)_{WX.Z} = 0.70$ $t = 1.92$, $p = 0.13$. This implies that individual differences in scalp-to-cortex depth contribute to the observed relationship between individual RMTs and the impact of parietal-hotspot TMS on left-gap sensitivity (fig. 3. 6). This does not, however, undermine the usefulness of scaling TMS intensity relative to RMT, when seeking an individually-effective TMS intensity for the parietal hotspot.

3.8 Discussion: The Parietal Hotspot

3.8.1 Overall assessment

Chapter 3 introduces, explores and validates a novel hunting procedure for identifying a distinct point over right posterior parietal cortex at which TMS disrupts visuospatial sensitivity in the contralateral visual hemifield; while leading to enhanced visuospatial sensitivity instead for the ipsilateral hemifield. The right-parietal site identified lies along the antero-superior edge of parietal regions commonly implicated in 'neglect-related' lesions (such as the temporo-parietal junction, angular and supramarginal gyri , see Parton & Husain, 2004; Golay et al., 2008), though it should be noted that extensive lesions after stroke versus TMS disruption in normals, as here, may be very different in their physiological consequences. The location of the identified effective TMS site along the anterior intraparietal sulcus (IPS) appears consistent with several other TMS studies in normals that disrupted visuospatial processing (e.g. Fierro et al., 2000; Hilgetag et al., 2001; Oliveri et al., 1999b; Sack et al., 2007; Schenkluhn et al., 2008). This study introduces a systematic and cross-validated way to identify the optimal site functionally, and at an effective TMS intensity, for individual participants.

3.8.2 The validity of the hotspot as a distinct node in the cortical network sub-serving visuospatial awareness.

The cross-validation of the hotspot's properties included: a) confirmation of genuine effects upon visuospatial sensitivity (d'), with signal-detection measures (Experiments 2-4); b) confirmation that the site yielded by the hunting procedure was indeed significantly the most effective within a 9-point grid subsequently tested around it, via collection of further data independent of the original hunting procedure (Experiment 2); c) demonstration that sensitivity to targets in the right visual hemifield actually showed the opposite pattern to left hemifield targets, for the same right-parietal TMS site, with enhanced sensitivity for right targets but impaired for left targets (Experiment 3); and finally (d) demonstration in Experiment 4 that the effect of right-parietal TMS as a function of intensity related systematically to each individual's motor threshold for TMS over M1 (in a manner that may in turn relate to scalp-to-cortex depths, as implied by partial correlations with those for both parietal and M1 sites).

The opposite pattern of effects for left versus right hemifield visuospatial sensitivity (i.e., impaired sensitivity for the left hemifield, but enhanced sensitivity for the right during right-parietal TMS) rules out a nonspecific disruption of all visual processing (as might have arisen if, say, the TMS had induced actual blinks, or some internal 'attentional blink' regardless of target location). The opposing pattern for the two hemifields accord with classic notions of hemispheric rivalry (Kinsbourne, 1977) and with other TMS work (Hilgetag et al., 2001), though now confirming this opposing pattern for actual perceptual sensitivity, d', in signal-detection terms for the first time.

3.8. 3 The hunting procedure and the role of covert attention

It has been suggested that when judging non-foveal targets (such as an eccentric 'gap' in the extended horizontal line here) several processes occur that draw on specific circuits involving

the parietal cortex. Such processes include decoupling attention from fixation and shifting the attentional focus covertly to a target location (Giesbrecht & Mangun, 2005; Posner et al., 1984). In the present experiments, the possible location of the gap target on one or other side was always known in advance, and the burst of TMS pulses began shortly before display onset. Therefore the first pulse in this burst may have contributed to the overall effect on visual sensitivity by disrupting the intended covert attentional focus. A recent brain imaging study compared activation during holding or shifting of covert attention for both central and peripheral locations (Kelley et al., 2008). Their analysis revealed activity during maintenance of covert attention at *peripheral* locations (during central eye fixation, as here) in anterior PPC, with a peak approximately 1 cm medial to the location found in the present study. This activation for *maintained* peripheral attention fell closer to the stimulation site used here than those for *shifting* attention from central fixation to periphery. This may accord with the present use of a paradigm in which the peripheral target location was foreknown and constant, and which required covert attention to be held at the target location rather than frequently shifted.

3.8.4 The risk of finding a 'false hotspot' during the hunting procedure

The 'hunting procedure' introduced in Experiment 1 is intended to provide a quick and practical heuristic for locating a right parietal area that influences visuospatial sensitivity. Despite this brevity, the risk of falsely identifying the wrong area as the 'hot spot' appears relatively low. If one supposes that participants responded entirely at random, the probability of scoring 4 initial consecutive hits followed by 4 consecutive misses (as the 'hotspot' was defined) would be 0.0039 for a given test location (i.e. $p(correct)^4 \times p(incorrect)^4 = 0.5^4 \times 0.5^4 = 3.9 \times 10^{-3}$). However if they maintain the 95 % correct performance level achieved during the 'staircase' thresholding trials, the risk of a false positive during the hunting procedure arguably is lower still, at just 5.1×10^{-6} per stimulation site ($p(correct)^4 \times p(incorrect)^4 = 0.95^4 \times 0.05^4 = 5.1 \times 10^{-6}$). Data from Experiment 4 reveal how well participants actually maintained their % correct

performance under conditions that mimic the hunting procedure (recall that in this experiment, one of the blocks was performed with sham TMS given over the hotspot at 100% RMT). The average % correct score from this block for all participants was 85±7% (understandably less than the 95% scored without any distraction from the coil, but far greater than chance levels of accuracy). When this value is inserted into the previous hypothetical calculation, the probability of finding a false hotspot remains very low: $0.85^4 \times 0.15^4 = 2.6 \times 10^{-4}$ per TMS site tested. Thus it seems that despite its simplicity and speed, the hunting procedure introduced in Experiment 1 should not be particularly susceptible to false-positive 'hotspots'.

As touched on in the Procedure section for Experiment 1, a slight spatial 'sampling-bias' might still arise during the hunting procedure, despite the alternating start direction of the spiral path. Because the spiral search pattern ran clockwise for all participants during the hunting procedure, anterior-lateral and posterior-medial points would be sampled somewhat later. However by analysing the actual sampling paths of all participants it was determined that the anterior-lateral or posterior-medial locations (when grouped into quadrants) were tested only 0.8 (on average) sites later than the other two quadrants. As implemented, this new hunting procedure thus seems sufficiently robust in practice not to be substantially affected by spatial sampling bias, though for future work any such bias could be reduced still further by adding anterior and posterior starting directions (to the existing medial and lateral ones).

3.8.5 Can a measure of motor cortical excitability be used reliably to find the parietal hotspot?

The significant correlation between the effectiveness of parietal TMS (on visuospatial sensitivity) at different intensities, with motor threshold in individual participants here, builds on a previous observation (Oliveri et al., 2000a) that the average level of TMS intensity (given over P4 in that study) required to disrupt tactile perception can relate to RMT. It contrasts however with other

work reporting little or no correlation of RMT with phosphene thresholds over occipital cortex (Antal et al., 2004; Boroojerdi et al., 2002; Stewart et al., 2001). The latter outcome might reflect idiosyncrasies in the depth of early visual cortical structures (from the scalp) in individuals (cf. Stokes et al., 2005). By contrast the MR-reconstructed depth from the scalp, to parietal or motor cortex under either hotspot site, did show parietal-motor correlations within the participants in this study. Subsequent partial correlations implicated this underlying scalp-to-cortex anatomical relationship as one contributor to the initial correlation demonstrated in Experiment 4 (and fig. 3. 6), between individual RMT, and the impact of real versus sham parietal-hotspot TMS on left-visuospatial sensitivity. Nevertheless, the data still show that by using TMS (over the individually-hunted, functional defined parietal hotspot) at an intensity equal to the individually-determined RMT over M1, one can expect to obtain a reliable effect on visuospatial sensitivity.

Given the greater scalp-to-cortex distance for the parietal than the motor site, over-stimulation of underlying parietal cortex seems unlikely. Thus right-parietal TMS at the spot identified via the new “hunting” procedure, at an intensity equal to RMT, should have the dual virtues of inducing a robust effect on visuospatial sensitivity (as shown in Experiments 2 and 4, see figs. 3.2. and 3.6.) yet with a low risk of any adverse effect. Experiment 4 also illustrates the potential importance of tailoring the intensity of stimulation used in each participant (e.g. in relation to RMT) rather than using a single constant intensity across participants (which may result in over- or under stimulation of the underlying cortex for some participants). Contrary to studies on earlier visual areas (Antal et al., 2004; Boroojerdi et al., 2002; Stewart et al. 2001) - which may be distinct for the reasons noted earlier, such as highly variable distance from the scalp- RMT may thus still provide a useful and easily measured physiological surrogate for other TMS sites, in this case for the intensity of stimulation over right-parietal cortex needed to disrupt visuospatial sensitivity.

Chapter Four: Theta Burst TMS Effects over the Parietal Cortex.

Having demonstrated an on-line TMS effect on visuospatial attention, the next group of experiments sought to extend that effect beyond the period of stimulation and thus increase its potential usefulness for clinical situations. In these experiments the effect of 'off-line' continuous Theta Burst stimulation was explored, as given over the right parietal hotspot in healthy participants. In accordance with Kinsbourne's theory of hemispheric balance, cTBS was also used simultaneously over the left PPC to see if this would neutralise any neglect-like effects caused by cTBS over the right. This work presented in this Chapter will be submitted to *Experimental Brain Research:*

Oliver, R., Bjoertomt, O., Driver, J., Greenwood, R., and Rothwell, J. Theta Burst TMS over Posterior Parietal Cortex: Inducing and ameliorating imbalances in visuospatial attention for neurologically intact participants

4.1 Summary

Neurologically intact subjects were asked to perform a 4-choice visual detection task in which targets were presented bilaterally or in isolation, in both or either visual hemifields respectively, in the form of small 'gaps' at the far left and/or far right of an otherwise continuous horizontal line. In Experiment 1, 600 pulses of continuous 'theta burst' (cTBS) transcranial magnetic stimulation, or sham stimulation, were given over right posterior parietal cortex (PPC). Real cTBS reduced visual sensitivity (d-prime) for gap-targets appearing in the contralateral left visual field, particularly when a competing gap-target appeared concurrently in the opposite hemifield. In Experiment 2, a similar gap-detection task was performed, but 300 pulses of cTBS over right PPC could now be followed immediately by 300 pulses of cTBS (or sham) over left PPC. Changes in d-prime seen after right PPC cTBS were ameliorated by subsequent left PPC cTBS. Experiment 1 demonstrates that visuospatial awareness can be manipulated by right PPC cTBS in a way that mimics some symptoms of visual extinction/neglect after right parietal damage. Experiment 2 lends new support to proposals that the hemispheres compete to direct attention. Though right PPC cTBS can disrupt this competitive balance, it can be restored by following right PPC cTBS with left PPC cTBS. These results indicate that cTBS can serve as an effective "virtual lesion" model in studies of spatial inattention. This approach may also offer a practical intervention for the undamaged hemisphere after focal brain injury, in cases requiring restoration of hemispheric balance.

4.2 Introduction

A number of previous studies on healthy participants have applied a range of TMS methods to create “virtual lesion” models of neglect/extinction in neurologically intact individuals, as well as to explore potential therapeutic interventions. In one of the earliest studies, on-line 25Hz TMS bursts (5 pulses at 25 Hz) were applied over right parietal cortex during a visual detection task. This caused contralateral misses when visual targets were presented bilaterally, but no significant misses when a left target was presented alone (Pascual-Leone et al., 1994). Some more recent studies that also used TMS approaches to interfere with right-parietal function (e.g. Meister et al., 2006; Dambeck et al., 2006; Chambers, Stokes, Janko, & Mattingley, 2006; Koch, Oliveri, Torriero, & Catagirone, 2005) similarly reported a significant contralateral worsening (relative to baseline and/or to sham TMS) for bilaterally presented visual stimuli, but not for isolated left sided stimuli. Such results seem reminiscent of the extinction phenomenon in patients (see also Hilgetag et al., 2001) but none of these experiments to date have used formal signal detection methods (that can separate sensitivity, d’, from response criterion, c) to characterise the effect of TMS in detail (though see Oliver et al., 2009/Chapter 3). One aim of the present study was to apply formal signal detection theory analysis in the development of a visual detection paradigm (described in section 1.3, page 70), capable of measuring any visual extinction/neglect-like phenomena in healthy subjects after right PPC TMS. A further key aim was to do so while using the recently introduced cTBS protocol for TMS, since this shows considerable promise not only for studies in healthy participants, but also for potential therapeutic studies in patients (e.g. Shindo et al., 2006; Nyffeler, Cazzoli, Hess, & Müri, 2009)

A final aim was to test whether any effects of right PPC cTBS on visual detection sensitivity (d’) might reflect an induced hemispheric imbalance, consistent with the Kinsbourne (1977) account

in terms of hemispheric rivalry (see also Koch et al, 2008). If so, then presumably applying left PPC cTBS immediately following the right PPC cTBS here might reintroduce a balance between hemispheres, and thereby reinstate more normal performance. This suggestion has a similar logic to some recent patient studies that have applied TMS over the intact hemisphere in stroke patients exhibiting extinction and/or neglect (e.g. see Oliveri et al., 1999, 2001; Brighina et al, 2003; Shindo et al., 2006; Koch et al., 2008; Nyffeler et al., 2009; see also Dambeck et al., 2006). Here this logic was applied in neurologically intact subjects while, for the first time, using cTBS in the context of formal signal detection measures of visual-detection performance.

4.3 Experiment 1

4.3.1 Experiment 1: Procedure

The right PPC target area was localised with 10Hz TMS, given at 100% RMT, in 10 participants (as described in table 1.1) using the 'hunting procedure' described in Chapter 3. In brief, the TMS coil was moved over and around the scalp near P4 until the subjects' ability to detect the presence of left sided visual target-gaps in an otherwise continuous horizontal line (figure 1.2B, page 66) was impaired by on-line bursts of 10 Hz TMS during the brief visual stimulus. Once found, this 'parietal hot spot' was then marked and used as the site for subsequent cTBS stimulation in the new experiments. The averaged hotspot scalp co-ordinates as measured from the subjects in the current Experiment 1 were 2.2±0.2cm anterior, and 1.5±0.2cm medial to P4, which did not diverge significantly in any direction from the hotspot coordinates found previously in the Oliver et al. (2009) study (unpaired t-test comparisons, all p values >0.40, ns).

Participants performed the four-choice bihemifield detection task described in Chapter 1, before and after cTBS disruption to the right PPC target area (cTBS parameters as given on page 68). For each trial the stimulus display duration had been determined using the staircase procedure described in Chapter 1, section 1.3. Following 1 training block in the four-choice task, subjects

performed 1 pre-cTBS baseline block and then 2 post-cTBS blocks, with each block comprising 240 trials and lasting approximately 12 minutes (4 stimulus types as in fig.1.2 A-D, presented 60 times each in pseudo-randomised order). cTBS or Sham stimulation (the latter with a rotated coil, see section 1.2.2, page 68) was given over the right PPC immediately after the baseline block, with the alternative given in an otherwise identical subsequent session between 3 and 5 days later (i.e. order of real or sham PPC cTBS was counterbalanced across the 10 participants between sessions in Experiment 1).

After cTBS delivery, 3 minutes was allowed for repositioning and recalibration of the eyetracker, thus the first block covered the period 3-15 minutes post cTBS; while the second block covered the period 15-27 minutes post cTBS. In this way data was gathered during the period where, based on previous cTBS work (e.g. on the motor cortex by Huang et al., 2005), one might expect cTBS to reach its maximum effect, particularly for the first block after cTBS here.

4.3.2 Experiment 1: Results

To yield measures of any right PPC cTBS-induced effects, the data were first normalized to the pre-intervention baseline in each subject (by subtracting the pre intervention block values from each post intervention block), and then normalized to Sham stimulation (by subtracting the baseline-normalised sham values from the equivalent TBS values). Thus the resultant overall change in d' due to right PPC cTBS was computed as: $[d'_{POST}-d'_{PRE}]_{TBS}$ minus $[d'_{POST}-d'_{PRE}]_{SHAM}$, for each of the two successive blocks after cTBS. The mean results (with SEs) are plotted in figure 4.1.

A 2-way ANOVA was then performed for each visual hemifield on the d' change-scores, with factors of: stimulus type, with or without a competitor target present in the other hemifield; and

time point at 2 successive levels, for the first and second blocks following cTBS, at 3-15 minutes post cTBS, and separately at 15-27 minutes. The a priori expectation was that as in Chapter 3, TMS over right PPC should cause a drop in sensitivity to the gap targets primarily for the left hemifield and that any such effect would be larger on trials with bilateral targets than with unilateral targets.

For the left visual hemifield a significant interaction was found between stimulus type and block ($F1, 9) = 6.2$, $p = 0.03$); fig 4.1A. This was due to a larger change in d' (reduction after right PPC cTBS compared to Sham) on trials with a competitor target present in the opposite hemifield, that occurred only during the first block post cTBS. Paired t-tests confirmed a significant drop in d-prime for left visual field targets in the presence of a right hemifield competitor after right PPC cTBS versus sham, specifically for the first post-TBS block (mean reduction for d' of 0.43± 0.14 standard errors; $t(9) = 3.01$, $p = 0.01$, one tailed). There was no significant reduction due to PPC-TBS in the same block when a left gap was presented alone (mean change of 0.05±0.15 relative to Sham; $p = 0.36$, ns). This led to a reliable difference between the right PPC-TBS-induced decrement for left gaps in bilateral versus unilateral target situations ($t(9) = 4.81$, $p<0.01$,) in the first block (the leftmost pair of data points in fig 4.1A).

There was no such difference in the subsequent second block ($t(9) =0.24$, ns) which showed no impact of right PPC cTBS versus sham, neither with nor without a concurrent target gap in the other hemifield ($p> 0.50$ in both cases for this second block; the rightmost pair of data points in fig 4.1A).

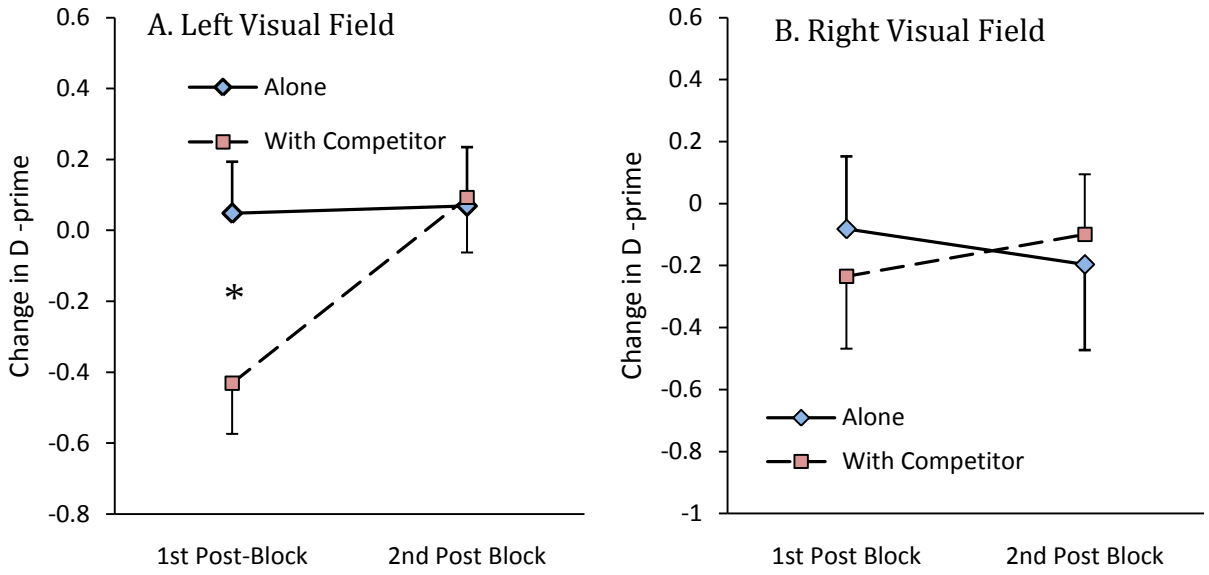

Fig. 4.1. The effect of TBS on visual sensitivity (d-prime), normalized to Sham stimulation in 10 subjects. Targets appearing in isolation are compared to those with a contralateral competitor. The first post block incorporates the time period 3-15 minutes after cTBS delivery whereas the second post block covers minutes 15-27. Asterisk denotes a significant drop in d-prime seen for left sided stimuli: 'With Competitor 'condition' compared to the 'Alone' condition (post-hoc t-test, Tukey's HSD, $p<0.05$, see main text).

The corresponding ANOVA on d' for right hemifield gap targets (see figure 4.1B) showed neither significant main effects nor an interaction (all $p > 0.3$, ns). Likewise there were no significant effects on the signal detection measure of criterion (which is independent of d') for either left or right side targets.

In sum, Experiment 1 showed that 600 pulses of right PPC cTBS impaired d' for left hemifield gap targets in the first block but not the second block after cTBS, particularly when the left gap target co-occurred with a right gap target that could potentially compete for attention.

Eye Tracker data

These data did not reveal any significant deviation from zero after right PPC cTBS (as compared to sham stimulation) for either of the 2 successive blocks after stimulation. A 2-way ANOVA with factors of TBS (real or sham) and block (first or second), as for the d' analyses above, showed no effect of TBS type ($F(1,9) = 0.57$, $p = 0.82$, ns) nor block ($F(1,9) = 0.51$, $p = 0.49$) nor any interaction($F(1,9) = 0.08$, $p = 0.79$, ns) The mean horizontal eye-position (relative to that during sham stimulation) in the first and second blocks was respectively-0.26±0.91º and -0.06±0.66º (in mean degrees of visual angle ± SEM, with negative values indicating leftward deflection), which did not differ from zero nor from each other (see ANOVA above). Since average horizontal eye position was within less than 0.5 degrees from central fixation in both blocks after cTBS, and both were if anything very slightly leftward, eye position does not appear to offer any plausible explanation for the reduction in left hemifield detection sensitivity observed in Experiment 1 (i.e. for left targets on bilateral trials in the first block after right PPC cTBS).

4.4 Experiment 2

4.4.1 Experiment 2: Procedure

This second experiment was designed to test whether the effects of right PPC cTBS could be ameliorated by a prompt second application of cTBS over the left PPC. Given Kinsbourne's hemispheric-rivalry hypothesis, less impairment of (left hemifield) detection sensitivity, d', was expected when right PPC cTBS was immediately followed by potentially 'rebalancing' left PPC cTBS.

This follow-up study was conducted in a similar way to Experiment 1. The right PPC 'hotspot' was first found in 8 new participants (described in table 1.1, page 64), using exactly the same

hunting procedure described in Chapter 3. Once that hotspot was found and marked over the subject's right hemisphere relative to P4 (first along an antero-posterior axis running from EEG '10/20' position F_{P2} to O_2, and then parallel to a medio-lateral axis running from A_1 to A_2), the analogous site over the left hemisphere was also marked, relative to P3. The averaged scalp co-ordinates were 2.4±0.2cm anterior, and 1.4±0.2cm medial to P4 (and P3) which are similar to values in Experiment 1 and to reported in Chapter 3 (unpaired t-tests, all p values >0.40, ns).

As in Experiment 1, cTBS was applied to the right PPC site before subjects were re-tested on the 4 choice detection task though with less pulses necessarily being used now (see below). A key difference was that in Experiment 2 cTBS could now also be applied to the corresponding site over the left hemisphere immediately after the right hemisphere stimulation, in a critical potentially 'rebalancing' condition that sought to test whether cTBS over left PPC could ameliorate the impact of preceding cTBS over right PPC. In total, three cTBS conditions were tested; cTBS over the right PPC and then over the left PPC ('right-PPC-then-left-PPC'); cTBS over the right PPC then sham stimulation over the left ('right-PPC-then-left-sham');or successive sham stimulation over both hemispheres ('right-sham-then-left-sham'). The order of these three different cTBS protocols was counterbalanced across participants, with four permutations, which depended on whether the double-sham was performed first or last, which was equiprobable, and then within that constraint, allowing the two possible relative orderings of right-PPC-then-left-PPC and right-PPC-then-left-sham to be equiprobable. For each participant, one condition was tested per experimental session with a gap of 3-5 days between each session.

In order to make the total TMS "dose" the same as in Experiment 1, despite potentially two successive applications of real cTBS within a session now, only 300 pulses was used for each of the two successive cTBS applications. This was done (in line with the latest available safety guidance, Rossi et al., 2009) so that the total number of TMS pulses given to the participants did not exceed 600 in any given experimental session. Thus right-PPC-then-left-PPC comprised

300 pulses over right PPC followed by 300 over left PPC, and so on. This meant that the actual effects of right PPC cTBS itself might differ from Experiment 1, since only 300 right PPC cTBS pulses were used, compared with 600 in Experiment 2.

Only one experimental block of the visual task (now comprising 120 trials) was acquired following each TMS protocol, given that all 3 protocols now had to be applied to each participant. This block covered the time period of 4 to 10 minutes after the end of the first 300 pulses over the right hemisphere, thereby allowing one minute for pulses over the left hemisphere to be applied when required, plus three minutes for repositioning and recalibration of the eyetracker prior to acquisition of the visual task data. This 4-10 minute period corresponded to the onset of maximum effect seen in earlier studies for 300-pulse cTBS over the motor cortex (Huang et al., 2005), while also overlapping with much of the period of the first block in Experiment 1.

4.4.1 Experiment 2: Results

As in Experiment 1, d' scores were derived and these data were initially normalised to pre-TMS 'baseline' performance. Data were considered separately for the left and right hemifields, with or without a target in the other hemifield, for the two different 'active' TMS protocols in Experiment 2 (i.e. right-PPC-then-left-PPC, or right-PPC-then-left-sham). These were both normalized to the right-sham-then-left-sham protocol. Figure 4.2 plots the resulting inter-subject mean changes in d' for the two different 'active' protocols, separately for gap targets presented alone (fig 4.2A) or with a competing gap target in the opposite hemifield (fig 4.2B). An ANOVA on these scores had three factors: the two different active TMS protocols; the visual hemifield of the gap target; and stimulus type (i.e. presence of a competing target in the opposite hemifield in fig 4.2B or its

absence, in fig 4.2A). This ANOVA revealed a significant 3-way interaction ($F(1,7) = 8.76$ $p = 0.021$). Inspection of fig 4.2A indicates that for unilateral targets, the potentially 'balancing' left PPC-TBS given in the right-PPC-then-left-PPC condition (white bars in fig 4.2A) appears to have neutralized changes in d' that were evident in the right-PPC-then-sham condition (blue bars in fig 4.2A). Any differences between the two active TMS protocols appeared less evident for the bilateral-targets trials (see fig 4.2B).

To confirm the source of the high-level interaction, the initial 3-way ANOVA was split down into two separate 2-way ANOVAs (active TMS protocol x target hemifield), one for each stimulus type. For unilateral targets, a significant 2-way interaction was found ($F(1,7) = 6.90$ $p=0.034$). The observed changes in d' after right-PPC-then-left-sham, for left hemifield targets (mean reduction in d' of -0.44±0.19), were more pronounced than for the potentially balancing protocol of right-PPC-then-left PPC (+0.09±0.26). This lead to a significant difference between these two protocols for left unilateral targets ($t(7)= 2.90$, $p<0.05$, one-tailed in accord with the signed prediction of a potentially 'balancing' effect due to left-PPC TBS after right-PPC TBS); see leftmost pair of bars in fig 4.2A.

Intriguingly, for unilateral right hemifield targets (see rightmost pair of bars in fig 4.2A) some facilitation of detection sensitivity (cf. Hilgetag, 2001; Dambeck et al. 2006; Oliver et al, 2009) was seen following 300 pulses of right PPC-then-left sham (mean d' enhancement of 0.38±0.20); but no such right hemifield enhancement was seen after right-PPC-then-left PPC (mean d' change of - 0.10±0.28). This again led to a significant differences between the right-PPC-then-sham protocol versus the potentially balancing right-PPC-then-left-PPC protocol, now for right hemifield unilateral targets ($t(7) = 2.70$, $p<0.05$). Thus in the neurologically intact subjects of Experiment 2, subsequent cTBS over left PPC appeared to cancel out the effects produced by cTBS over just the right PPC, with the latter effects now being apparent even for

unilateral targets (please see the later Discussion in section 4.5, and note that the present cTBS protocol for right PPC comprised 300 rather than 600 pulses, unlike Experiment 1).

For bilateral targets in Experiment 2 (fig 4.2B), no significant effects were found (although there was a minor trend for reduced d' in both hemifields in the right-PPC-then-sham protocol). Unlike the unilateral targets, a two-way ANOVA (again with factors of active TMS protocol x target hemifield) found no significant interaction ($F(1,7) = 0.22$ $p = 0.65$), nor main effects (both p values >0.30). Thus the significant high-level three-way interaction in the initial omnibus ANOVA (active TMS protocol x target hemifield x target type) had arisen because with the 300 pulse protocols of Experiment 2 the impact of right-PPC TBS on visual performance, and its 'balancing' in the right-PPC-then-left-PPC protocol, was now most apparent for unilateral targets (fig 4.2A) rather than bilateral targets (fig 4.2B). Moreover the unilateral targets revealed not only a left hemifield decrement after right-PPC TBS, but also a right hemifield enhancement in this same situation. Most importantly, both of these effects of right-PPC TBS were eliminated when right-PPC TBS was immediately followed by potentially balancing left-PPC TBS.

The effects of right PPC cTBS itself (when followed by left sham) did not appear to be exactly the same in Experiment 2 as had been observed in Experiment 1. As discussed below, this presumably reflects the different TMS doses in the two experiments (only 300 pulses were given over right PPC in Experiment 2, but 600 had been given there in Experiment 1). Nevertheless, the most important point is that the observed effects of right-PPC TBS within Experiment 2 were effectively neutralized by giving left-PPC TBS immediately after right-PPC TBS, as found in the unilateral target data.

Eye-Tracker

There was no effect of TMS protocol on eye-position ($F(1,7) = 0.57$, $p = 0.58$, ns). Eye tracker data from Experiment 2 showed that mean eye-position was -0.27± 0.34 degrees of visual angle

from the intended central fixation point (negative value indicates very slight leftward average deviation) in the right-PPC-then-left-sham protocol; -0.57±0.60º in the right-PPC then-left PPC protocol; and -0.95±28º in the sham-sham protocol.

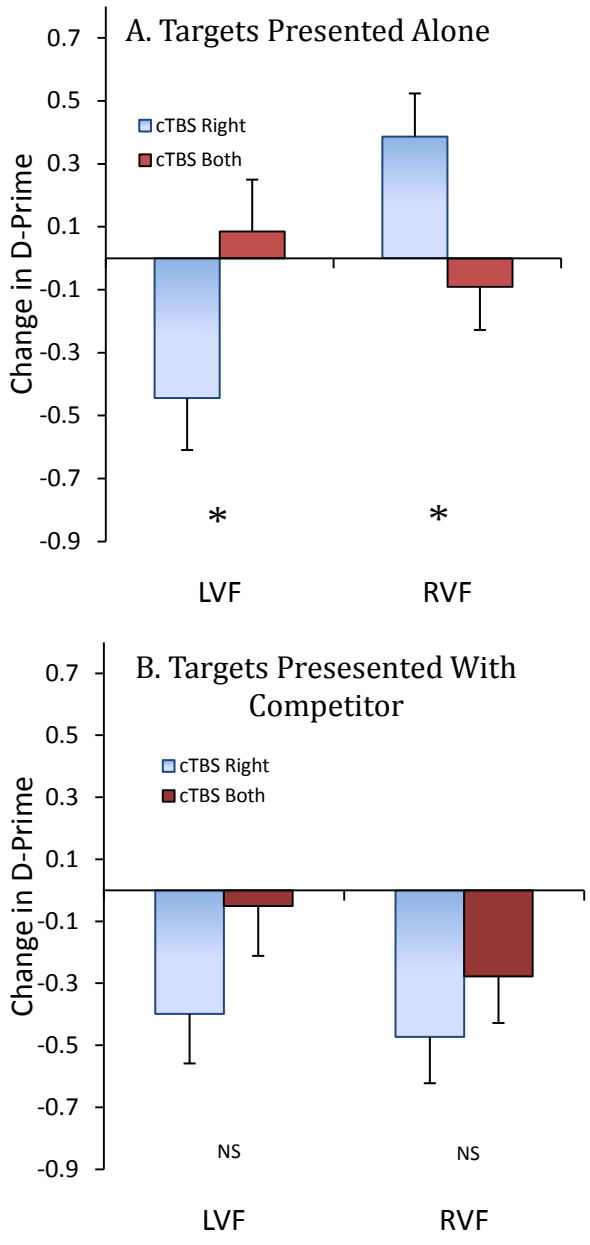

Fig.4.2. The effects of bi-parietal cTBS on left (LVF) and right (RVF) visual hemifield sensitivity. The 2 TBS stimulation conditions: 300 pulses of cTBS over right PPC and sham cTBS over left PPC ('cTBS Right', blue bars), and cTBS-300 pulses over both PPC's ('cTBS Both', red bars), are shown normalised to the sham condition (sham cTBS over both PPC's). Visual stimuli were presented in isolation in the 'alone' condition (A) and simultaneously with a contralateral competitor in the 'with competitor condition' (B). The asterisks indicate significant post hoc differences between 'cTBS Right and 'cTBS Both' conditions (Tukey's HSD, $p<0.05$, see main text). For clarity error bars show the Standard Error of the interaction across cTBS protocols (cTBS R vs. cTBS B) with inter-subject variance removed (as per Loftus and Masson, 1994).

4.5 Discussion: cTBS Effects over the Parietal Hotspot

4.5.1 Overall assessment

In Chapter 4, neurologically intact participants were tested with a 4-choice visual detection task, which built on that introduced in Chapter 3, This visual task was performed under 3 different active cTBS conditions over the course of the two experiments: with 600 pulses of cTBS over right PPC (as compared to sham over right PPC, in Experiment 1); or with 300 cTBS pulses over right PPC followed by 300 pulses of sham or real cTBS over left PPC in Experiment 2 (which also included a right-sham-then-left-sham baseline protocol).

Right PPC cTBS in Experiment 1 (600 pulses) caused an extinction-like effect, such that detection sensitivity (d') for left hemifield targets was disrupted, in the first block of testing post cTBS, when there was a competing target stimulus on the right. When left cTBS (300 pulses) was applied after right-side cTBS (300 pulses) in Experiment 2, the effects observed for the 300 pulses of right PPC stimulation alone (which applied more for unilateral targets, see below) were abolished, indicating a 'rebalancing' effect due to the left PPC cTBS. Eye tracker data showed that cTBS did not induce any systematic deflection of the eyes towards one or other side that could have contaminated visual performance. The present effects seem unlikely to reflect a

transient ‘scotoma’ like remote effect of cTBS upon visual cortex either, since they depended on whether the gap targets were presented unilaterally or bilaterally. The impacts on visual performance were thus unlike a transient scotomatous or hemianopic effect, which should have applied to a particular hemifield regardless of whether the display comprised unilateral or bilateral targets.

4.5.2 A TBS/SDT model of extinction

In Experiment 1 (Chapter 4) 600 pulses of cTBS were used over the right PPC. This impaired subsequent detection of left hemifield targets in the first block post cTBS, but only when the left targets gap was accompanied by a simultaneously presented target gap on the right side. This ‘extinction-like’ effect seems analogous to the phenomena classically described in some patients with extinction after unilateral right brain damage, who can respond accurately to unilateral stimulation from either side, yet consistently miss left sided stimuli under conditions of bilateral simultaneous stimulation, when the two targets presumably compete for attention (see Heilman, Watson,& Valenstein, 2003; Mesulam, 1999; Bisiach & Vallar,1988; Mattingley, 2002; Marzi, Girelli, Natale, & Miniussi, 2001; Driver & Vuilleumier, 2001; Driver, Mattingley, Rorden,& Davis, 1997; Karnath, 1988). Several previous TMS studies have come close to demonstrating an extinction-like disruption to visual performance in neurologically intact participants, but typically fell short of demonstrating an impact on sensitivity (d’) as assessed with signal-detection theory. In one of the earliest studies, ‘on line’ 25Hz TMS caused left misses when visual targets (asterisks) were presented bilaterally, but apparently no misses when a left target was presented alone (Pascual-Leone et al., 1994). Though highly suggestive of extinction, given that the misses in the bilateral condition tended to occur for the left side, contralateral to the TMS, no direct statistical comparison between unilateral and bilateral conditions was reported, and signal detection theory was not utilized. In more recent studies (e.g. Cazzoli, Müri, Hess, &

Nyffeler, 2009; Meister et al., 2006; Dambeck et al., 2006; Chambers et al., 2006; Koch et al. 2005), a significant worsening after active TMS (versus baseline or sham) was reported for bilateral stimulation but not for isolated left sided stimuli, thus suggestive of extinction, but without a direct comparison between them. While in general accord with such previous TMS work, Experiment 1 is the first to confirm an extinction-like effect on signal-detection sensitivity (d'), when comparing unilateral to bilateral targets, following right PPC cTBS. The pattern of d-prime change observed in Experiment 1, a significant drop for the left visual field in the presence of a contralateral competitor target, after right parietal disruption, appears in agreement with clinical studies of visual extinction (Ricci, Genero, Colombatti, Zampieri, & Chatterjee, 2005; Ricci & Chatterjee, 2004), tactile extinction (e.g. Vaishnavi, Calhoun, Southwood, & Chatterjee, 2000) and even cross-modal extinction (Sarri, Blankenburg, & Driver, 2006) in right-hemisphere patients. This suggests that PPC cTBS might serve as a useful 'virtual lesion' model for such deficits. It would be interesting in future work to extend the current right PPC cTBS protocol to examine tactile and visual-tactile situations, as well as the visual paradigm studied here; and to examine whether different TMS sites have differential impacts on visual, tactile, or cross-modal extinction-like phenomena.

4.5.3 Bilateral cTBS restores inter-hemispheric balance

In Experiment 2 (Chapter4), only 300 pulses of cTBS (rather than 600) were now applied to right PPC; this was done to limit the total TMS dose to 600 pulses in the 'right-PPC-then-left-PPC' protocol sessions (see Methods section). There was a qualitative difference in the impact on perception for the 300 pulses of right PPC cTBS in Experiment 2, as compared with the 600 pulses of right PPC cTBS in Experiment 1.The very clear extinction-like pattern from Experiment 1 was no longer apparent. Instead within Experiment 2 the impact of the 300 pulses of right PPC cTBS was to impair detection sensitivity (d') for left unilateral targets, while enhancing this for right unilateral targets (see fig 4.2A, blue bars). In some respects this pattern seems

reminiscent of reports of some patients with neglect who show left sided inattention (where contralesional space is underexplored or ignored even in the absence of competing ipsilesional stimuli), but not extinction (Karnath, Himmelbach, & Küker, 2003; Azouvi et al., 2002). Inattention versus extinction may involve different lesions sites in patients (e.g. see Karnath et al., 2003; Hillis et al., 2006; Golay, Schnider, & Ptak, 2008), but here the same right PPC region was targeted with cTBS in both Experiment 1 and 2, with only the TMS 'dose' (600 pulses or 300 pulses in Experiment 1 and 2 respectively) differing. It seems conceivable that the higher dose might lead to a greater 'spread' of the impact upon cortical excitability, but this would require direct corroboration in future work with physiological measures of such excitability following cTBS (c.f. Esser et al., 2006; Mochizuki et al., 2007; Di Lazzaro et al., 2008; Stagg et al., 2009).

Whatever the ultimate resolution of such issues, for present purposes the main importance of Experiment 2 does not concern the different outcome from Experiment 1, but rather the way in which 300 pulses of cTBS over left PPC, immediately subsequent to the right PPC cTBS, was able to neutralize and eliminate the effects of the preceding 300 pulses of right PPC cTBS (see fig 4.2A, red bars, compared to blue bars without left PPC cTBS). In other words, the "virtual lesion" effect of (300 pulses of) right PPC stimulation could evidently be alleviated by a subsequent "virtual lesion" of the left PPC. These new results in healthy participants are reminiscent of other recent data from neglect patients, in which TMS over the left hemisphere has been used transiently to ameliorate neglect after a right side lesion (Nyffeler et al., 2009; Koch et al., 2008; Shindo et al., 2006; Brighina et al., 2003; Oliveri et al., 2001; Oliveri et al., 1999). The results appear similar to those reported by Dambeck et al. (2006) in healthy participants, though in this study the effects outlive the period of stimulation, lasting up to ~15 minutes subsequent to cTBS, and could be demonstrated with formal signal detection sensitivity (d') rather than just changes in percent correct, which can sometimes be misleading according

to Macmillan & Creelman (2005).The present study is the first which employs signal detection measures to confirm an interhemispheric 'virtual lesion' model of neglect, complementing earlier pioneering work which used cTBS to model neglect and hemispheric rivalry during a visual exploration task (Cazzoli, Wurtz, Müri, Hess, & Nyffeler, 2009), but without signal detection measures.

In the clinical situation, substantial bilateral PPC lesions may cause 'simultanagnosia' as one aspect of Balint's syndrome, such that the patient is unable to perceive multiple visual objects simultaneously (e.g. Coslett & Saffran, 1991; Smith, Mindelzun, & Miller, 2003). However no bilateral worsening in detection d' was found here, and in particular no problem with bilateral gap targets was observed during the right-PPC-then-left-PPC 'rebalancing' cTBS protocol. The impact of cTBS is most likely a local reduction in excitability (see Huang et al, 2005), rather than being equivalent to a substantial complete 'lesion'. This might explain why right-PPC-then-left-PPC cTBS could return performance essentially to normal in this study (see red bars in fig 4.2A), rather than producing a more severe simultanagnosic-like transient deficit.

Chapter Five: Neuroplasticity induced in the Parietal Cortex by Theta Burst TMS.

The studies detailed in chapters 2 and 3 had shown that the parietal hotspot lay in effect, at the centre of a cortical map of function, and that TBS at that location induced neglect-like perceptual effects. The question then arose: could this map be altered by, and then re-mapped with TMS in a way analogous to that shown previously with other interventions (such as motor learning paradigms) in the motor cortex (see Introduction section iii.5.1, pages 58-59)? This study sought to change the shape of the parietal hotspot with iTBS and therefore demonstrate for the first time that parietal cortical function could be both mapped and manipulated with TMS. One hope was that such an effect might one day prove useful in the clinical setting, for example after parietal cortical damage. The work presented in this chapter will be submitted to *Cerebral Cortex*:

Oliver, R., Nuruki, A., Greenwood, R., and Rothwell, J. rTMS used over the posterior parietal cortex to delineate and manipulate maps of visuospatial attention.

5.1 Summary

In this study, a previously 'silent' area of the right posterior parietal cortex was encouraged to participate in the network sub-serving visuospatial attention, by the application an excitatory form of rTMS: 'Intermittent Theta Burst Stimulation' (iTBS).

Nine subjects performed the 4-choice bihemifield target detection task described in Chapter 1, with accuracy in each visual field recorded as the signal detection measure 'd-prime'(d'). Using the hunting procedure described in Chapter 3, a parietal 'hotspot' was located in each subject (near P4), where a short burst of TMS pulses (at 10Hz) could disrupt attention in the left visual field. The effect of this disruptive TMS was measured in both visual fields over a grid of 9 locations centred on the hotspot. The effect was considered large if d' fell more in the left visual field (LVF) compared to the right visual field (RVF), and also if d' fell only in the presence of a competing stimulus in the opposite visual field.

Before this 10Hz mapping paradigm was carried out, either excitatory iTBS 'conditioning' or Sham stimulation was applied to the point on the grid directly medial to the hotspot (grid point no.4, see figure 5.1). After Sham stimulation, the 10 Hz TMS effect at all locations was substantially less than at the hotspot. However after iTBS, the disruptive effect at point 4 was enhanced in all subjects (exceeding even that seen over the hotspot). This result can be interpreted as an enlargement or movement of the parietal hotspot, and a change in the distribution of parietal visuospatial processing. It may be possible in future experiments to make use of this effect to reduce visual neglect in stroke patients with localised sub-total damage to the parietal cortex.

5.2 Introduction

Cortical maps of function are perhaps best characterised in the motor cortex (see Sanes & Donoghue, 2000 for a detailed review) and have been therapeutically manipulated in stroke patients (Liepert et al., 1995, 2000; Wittenberg et al., 2003). Equivalent maps in the parietal cortex also exist, for example topographic maps of visual spatial attention have been demonstrated with fMRI within the intraparietal sulcus (Silver et al., 2005), and superior parietal cortex (Sereno et al., 2001). In cats, a visuotopically specific neglect syndrome can be induced by rTMS over the visuo-parietal region (Valero-Cabré et al., 2006), and in humans somatotopic maps within S1 that are distorted in patients with phantom limb pain (Kew et al., 1994), can be beneficially manipulated with TMS (Töpper et al., 2003). Despite these previous efforts, a map of *visuospatial* function over the *posterior* parietal cortex that can be delineated and manipulated with TMS has not yet been described. Such a map could prove very useful as a guide for future studies in which focal interventions such as TBS are targeted at or around the damaged parietal cortex in patients with neglect, in an effort to induce useful neuroplasticity. To help rectify this omission, this study aimed to change the functional characteristics of the right PPC in normal participants using rTMS over and around that part of the right PPC designated previously as the parietal 'hotspot' in Chapter 3. 10Hz TMS was used to probe a 9x9 point grid centred on this hotspot (whilst subjects were engaged in a 4-choice visual detection task), and thus construct a map of disruptive-TMS effect on spatial processing. The level to which 10Hz TMS disrupted performance was used as a proxy measure of the underlying area's involvement in the spatial processing demanded by the task; the more disruption caused, the greater the inferred involvement. Before the parietal map-of-effect was constructed, iTBS or Sham stimulation was given over one of the 8 peripheral points (the same point in all subjects – see methods, section 5.3.1 below for rationale). The hypothesis tested was that excitatory stimulation to an area of

cortex with little prior task-involvement (as measured by 10Hz TMS disruption), would increase its participation, and thus susceptibility to subsequent 10Hz disruption. The area of highest effect on the map would thus move or enlarge to encompass the area 'pre-treated' with iTBS. If successful in normal subjects, parietal cortical plasticity induced in this way could be a useful therapeutic tool in stroke patients with spatial neglect. For example, in those with sub-total damage to the parietal cortex, it may be possible to ameliorate spatial deficits by using peri-lesional iTBS to enlarge the parietal cortical network involved in spatial processing.

5.3 Methods

5.3.1 Procedure

In each of the 9 healthy participants, the RMT and AMT were determined, and the PPC target area was localised (with 10Hz TMS given at 100% RMT) as described in Chapters 1 and 3. In the preceding studies, 5 pulses were given (at 10Hz) with each trial, however in the current work, this was reduced to 3 pulses (the first given at 100ms before stimulus presentation, the second with stimulus presentation, and the last at 100ms after stimulus presentation). This was done to reduce the total pulse load delivered to each subject over the course of a session, and to prevent the coil overheating before a session (lasting approximately one hour) was complete. Participants were then introduced to the 4 choice detection task described in Chapter 1, and the optimum stimulus duration was determined individually for each as described on page 70.

Next participants received either iTBS (at 80 % AMT) or Sham iTBS (same stimulator parameters but with the coil held at 90 degrees to the scalp) with the order counterbalanced across participants as described below. This iTBS/Sham 'pre-treatment' was given over the point in the 9-point grid lying directly medial to the 'hotspot' (which in turn defined the centre of

the grid, see figure 5.1). This point lies medial to the hotspot which in turn is situated medially within the PPC (as in Chapter 3, figure 3.1) and was chosen with future stroke patient-based studies in mind. In those patients with parietal neglect, this point should lie more often outside the damaged area (in cortex supplied by the anterior as opposed to middle cerebral artery); than the 6 more lateral points (see Driver and Vuilleumier, 2001, their figure 2). Of the 3 medial points, the middle one was chosen (i.e. directly medial to the hotspot) simply to maximize the number of directly adjacent non-iTBS-stimulated points available for comparison. This same point was used in all participants.

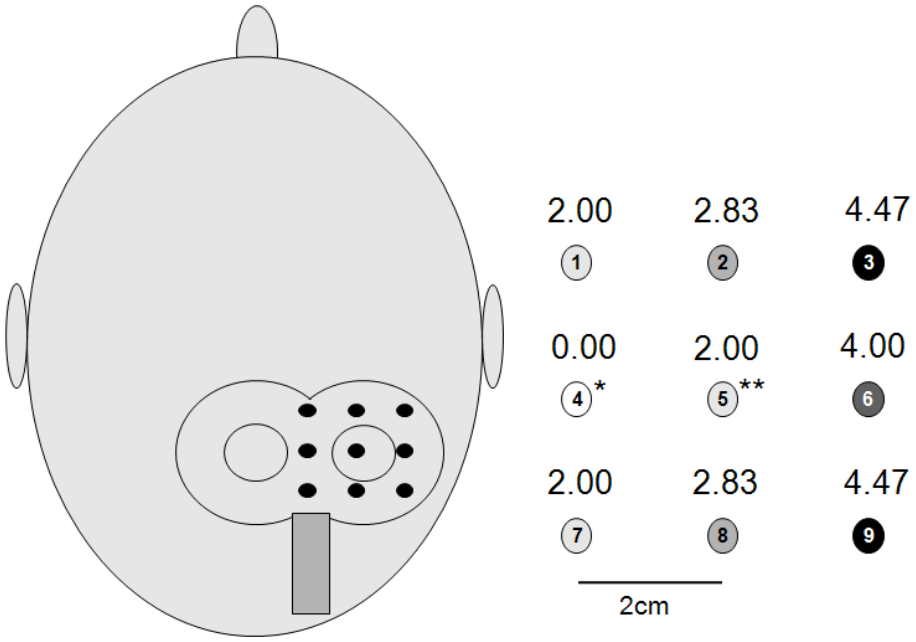

Figure.5.1. A simple sketch is shown on the left of the TMS coil in position over the 9-point grid, marked out on the subject's head. In all subjects the coil was placed over grid point no.4 for pre-treatment iTBS or Sham stimulation, with the handle pointing posteriorly and parallel to the A-P axis of the skull. Following this all 9 points were probed with disruptive 10hz TMS. The 9-point grid is shown labeled on the right, with point numbers (encircled) and distances from the centre of the coil at the time of iTBS delivery (above each circle, given in centimeters). Grid point 9 approximately corresponds to position P4 of the EEG 10/20 system. Distances were calculated (assuming minimal skull curvature), using the hypotenuse of a triangle of sides x and y, where

x=distance (cm) lateral to point 4, and y=distance (cm) anterior or posterior to point 4. Circles of the same shade are grid points equidistant from point 4.

* = Grid point 4, stimulated with iTBS or Sham 'pre-treatment' in all subjects

** = Grid point 5, the 'parietal hotspot' localised in each subject (see methods)

Following iTBS/Sham pre-treatment, participants performed the 4 choice task in 10 blocks each consisting of 60 trials (each stimulus type shown 15 times in pseudorandomised order). The first block (used as a baseline measurement) was performed with no TMS interference. The following 9 blocks were all performed with 10Hz TMS disruption (3 pulses given at 100% RMT, at zero, 100, and 200 ms after stimulus presentation) over corresponding points on the 9-point grid. Participants' responses were analysed to yield visual sensitivity data (in the form 'd-prime') for left and right visual fields as in Chapter 2, section 2.2.

5.3.2 Randomisation

Each grid point was allocated a number as shown in figure 5.1 (the same system for all participants), no.1 for the most anteromedial point, no.3 for the most anterolateral point, no. 4 for the iTBS/Sham pre-treated point, no.5 for the centre (hotspot) no. 9 for the most posterolateral point etc. The order in which the grid positions were tested was randomized across the 9 participants with a 9x9 Latin Square design. Within this sequence, the testing of point no.4 in relation to that of point no. 5 was balanced across the 9 participants (point no. 4 coming before no. 5 in an equal number of experimental sessions- see below). This was done to control for any 'hangover effect' on point 4 resulting from preceding 10Hz stimulation of the 'parietal hotspot' at point 5 The 'pre-treatment' given was also randomized and counter-balanced, with each participant receiving iTBS or Sham on alternate experimental sessions, a

minimum of 3 days apart, using identical grid-point testing sequences. As there were 9 participants, counterbalancing iTBS and Sham sessions was achieved by having the first participant perform the experiment twice (4 sessions, iTBS then Sham, followed by Sham then iTBS) and then averaging the results. To complete counterbalancing, the sequence order of point 4 and 5 10Hz stimulation for this participant was reversed in the latter 2 sessions.

5.3.3 Eyetracking

During the baseline block and nine 10Hz TMS blocks participants wore a Skalar 'IRIS' infra-red eye-tracker. The period of time 500ms before and after stimulus presentation was recorded and compared to calibrations done at the start and end of each block.

5.4 Results

5.4.1 The parietal 'hotspot'

The hypothesis that the parietal hotspot existed as a distinct functional unit before its manipulation with iTBS, was tested using data from the Sham 'pre-treatment' session. Data from the 8 points that surrounded the hotspot were averaged and compared to the hotspot (i.e. centre vs. surround). Performance for left sided targets presented in isolation was worse with 10Hz TMs over the centre (d' = 1.44±0.28) compared to surround (1.64±0.19), though this difference was not significant ($t(8) = -0.75$, $p = 0.47$, paired t-test, two-tailed). The effect direction is consistent with that found in Chapter 3 (shown in figure 3.2, page 95), though the lack of significance here may reflect a lesser disruptive effect of 3 pulses at 10Hz as opposed to

the 5 pulses used previously. In the current study, the visual task is more demanding, requiring target detection in competitive situations. When this aspect of the task was analysed, a statistically distinct 'hotspot' did emerge i.e. with a competing contralateral target present, and with performance measured across hemifields, responses were significantly more right-biased (d'LVF-d'RVF became more negative), over the hotspot (-0.21±0.54) compared to the surround (0.38±0.14), ($t(8) = 2.59$, $p=0.03$, paired t-test, two-tailed).

The distances of the parietal 'hotspot' in centimeters anterior and lateral to EEG 10/20 position P4 was compared to those found in Chapter 3. In the current study the hotspot was 2.4±0.1 cm anterior, and 1.6±0.2 cm medial to P4, these were not significantly different from previous values (2.2±0.3 anterior and 1.3±0.3 cm medial, p-values 0.55 and 0.39 respectively, paired t-tests, two-tailed).

5.4.2 Comparing the effects of iTBS vs. Sham pre-treatment

A number of assumptions were incorporated into the data before the main analysis:

1) 10Hz TMS should cause greater disruption to performance than no-TMS, thus the 9-point grid data was first normalized to the no-TMS baseline in each subject (by subtracting baseline values from each of the 9 TMS blocks).
2) If the effect of the disruptive 10hz TMS over right PPC is truly 'neglect-like', performance should drop more in the left visual field relative to the right. All data was therefore expressed across hemifields in the form: d-prime for left visual field – d-prime for right visual field (d'LVF-d'RVF).

Therefore negative values represent a right sided performance bias and increased neglect-like disruption of spatial processing as a result of the 10Hz TMS. Having normalized the data in this

way (d' $[LVF\text{-}d'RVF]_{10hzTMS}$-$[d'LVF\text{-}d'RVF]_{BASELINE}$) the effect in the presence of iTBS 'pre-treatment' was compared to that in the presence of Sham 'pre-treatment', for each of the 9 grid-points (see table 5.1 below). The entire analysis was performed for each of 2 target detection conditions: 'with competitor' and 'without competitor'. The main predictions tested were: a) the most negative values would occur over point no.4 (directly under the coil at TBS delivery) after 'real' iTBS as opposed to sham 'pre-treatment', and b) the effect would generally be stronger in the 'with competitor' condition, where extinction-like effects would add to those resulting from right-sided attentional bias.

These hypotheses were tested with an omnibus 3-way Analysis of Variance (ANOVA), the factors were: iTBS type (real, sham); Visual Stimulus type (with competitor, without competitor); and grid position (9 values). This resulted in a significant 3-way interaction ($F(8,64) = 2.36$, $p = 0.027$); Mauchly's test of sphericity was not violated. Post hoc testing was carried out first for the 'with competitor condition'. In all subjects, the disruptive effect was most enhanced at position 4 after iTBS, with smaller changes at neighbouring points 1 (directly anterior) and 7 (directly posterior), as shown in table 5.1. A significant difference between the changes seen with iTBS (-0.58±0.32) and sham (0.72±0.55) was however, only found at grid point no.4 ($t(64) = 5.53$, $p<0.05$, two-tailed t-test, Tukey's HSD). Post-hoc testing for the 'without competitor' condition did not reveal any significant differences between iTBS and Sham stimulation (all p-values >0.10).

	iTBS			Sham		
Without Competitor	0.12 (0.35)	-0.13 (0.41)	-0.37 (0.51)	-0.16 (0.32)	0.17 (0.51)	0.08 (0.52)
	0.24 (0.41)	-0.15 (0.49)	0.05 (0.55)	-0.15 (0.42)	-0.12 (0.40)	-0.28 (0.71)
	0.38 (0.26)	0.29 (0.27)	0.55 (0.42)	-0.40 (0.43)	-0.12 (0.43)	-0.24 (0.46)
With Competitor	-0.37 (0.39)	-0.25 (0.27)	-0.26 (0.33)	0.68 (0.44)	0.10 (0.42)	0.05 (0.64)
	-0.58* (0.32)	-0.26 (0.16)	-0.25 (0.24)	0.72* (0.55)	-0.21 (0.54)	0.10 (0.55)
	-0.42 (0.31)	-0.49 (0.28)	0.40 (0.30)	0.62 (0.44)	0.20 (0.55)	0.56 (0.48)

Table 5.1. The experimental data is shown for each of the nine grid points, for both 'pre- treatment' TMS conditions (iTBS or Sham) and both task conditions (with competitor, without competitor). In each nine-cell quadrant the layout is identical to that shown in figure 5. 1 (top left = point1, top right = point 3, middle left = point 4/pretreatment site, centre = hotspot/point 5 etc.). The figures shown represent the mean effect of 10Hz TMS expressed as: [d' LVF-d'RVF]$_{10hzTMS}$-[d'LVF-d'RVF]$_{BASELINE}$ followed by the SEM in brackets. Asterisks represent a significant difference ($p<0.05$) in the effect of 10Hz TMS, between the iTBS and Sham conditions. This occurs only at point 4 (the site of iTBS or Sham delivery), and only when targets are presented with an identical competing target in the opposite hemifield.

5.4.3 Comparing the effect of stimulus type

To compare the 'with competitor' and 'without competitor' conditions directly, the data collected after iTBS pre-treatment was normalized to that collected after sham pre-treatment. The overall effect of 10Hz TMS, visual field, and pre-treatment on d-prime (d') could now be expressed with the following formula:

$$d'_{EFFECT} = ([d' \text{ LVF-d'RVF}]_{10hzTMS}\text{-}[d'\text{LVF-d'RVF}]_{BASELINE})_{iTBS} - ([d' \text{ LVF-d'RVF}]_{10hzTMS}\text{-}[d'\text{LVF-d'RVF}]_{BASELINE})_{SHAM}$$

This effect was calculated for each of the 9 grid points and for both competitor conditions, once again the more negative the value, the more neglect-like the effect. A 2-way ANOVA with factors: Visual Stimulus Type (with competitor, without competitor); and Grid Position (9 values), yielded a significant interaction between stimulus type and grid location ($F(8,64) = 2.364$, $p=0.027$). Over grid position 4, the neglect-like effect was significantly stronger with a competitor present (-1.30±0.50) than without (0.39±0.67) ($t(64)=5.12$, $p<0.05$, Tukey's HSD, two-tailed). This was also true over neighbouring position 7 (directly posterior), i.e. stronger with competitor (-1.05±0.48) than without (0.78±0.40) ($t(64)=5.54$,$p<0.05$, Tukey's HSD, two-tailed). Over position 1 (directly anterior) the difference was of comparable magnitude (-1.07±0.40) vs.(0.30±0.44) and approached, but did not quite reach significance ($t(64) = 4.15$, $p<0.10$).

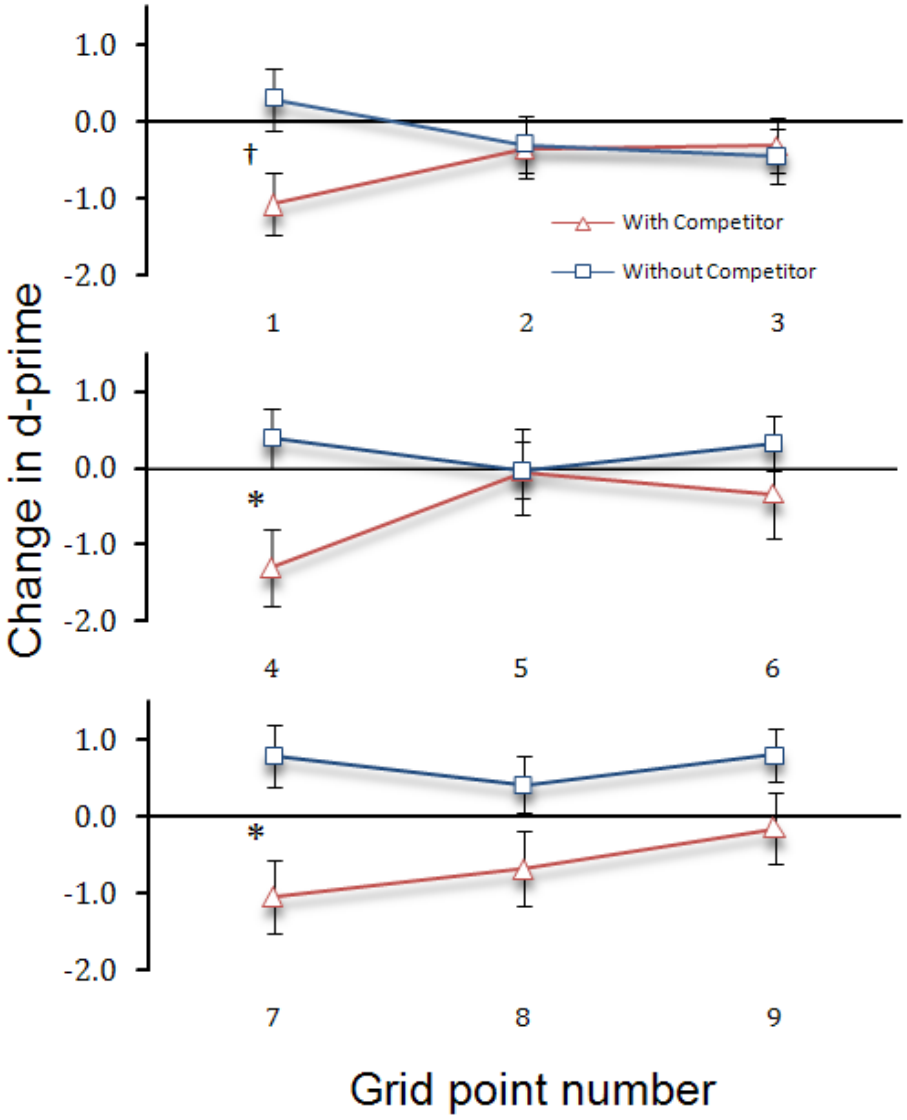

Figure.5.2. Interplay between the types of visual stimulus used, pre-treatment given to grid point 4, and the disruptive effect of 10Hz TMS over each of the 9 grid points. The change in d-prime (d'_{EFFECT}) is plotted for each grid point no. (1-9), showing data from the 'with competitor' condition (open squares), and 'without competitor' (closed triangles), error bars=SEM. The effect (x-axis) is that of 10Hz TMS disruption in the presence of iTBS pre-treatment over grid point no.4 (see results section for further details). Therefore the more negative the value, the greater the drop in d-prime in the left visual field (relative to right) caused by 10 Hz TMS and the greater the effect of iTBS conditioning (relative to Sham). Markers at grid positions 1, 4 and 7 indicate significant, (or near significant) post-hoc differences between 'with competitor' and 'without competitor' conditions (Tukey's t-test, two-tailed, *$p<0.05$, †$p<0.10$).

5.4.4 Effect of distance

The distance in centimetres from the centre of the coil at iTBS delivery, to each of the 9 points was calculated as in figure 5.1 (the distance to grid point 4 equals zero). The values for effect size as above were averaged across grid points when those points were at the same distance, e.g. points 1,5, and 7 (all 2 cm away); points 3 and 9 (4.47 cm away). Linear regression analysis revealed a significant positive relationship between distance and effect size (becoming less negative with increasing distance) for the 'with competitor condition' (b=0.45±0.18, t=2.43, p=0.02) (see figure 5.3). This did not occur for the 'without competitor' condition (b=-0.011±0.18, t=-0.06, p=0.95).

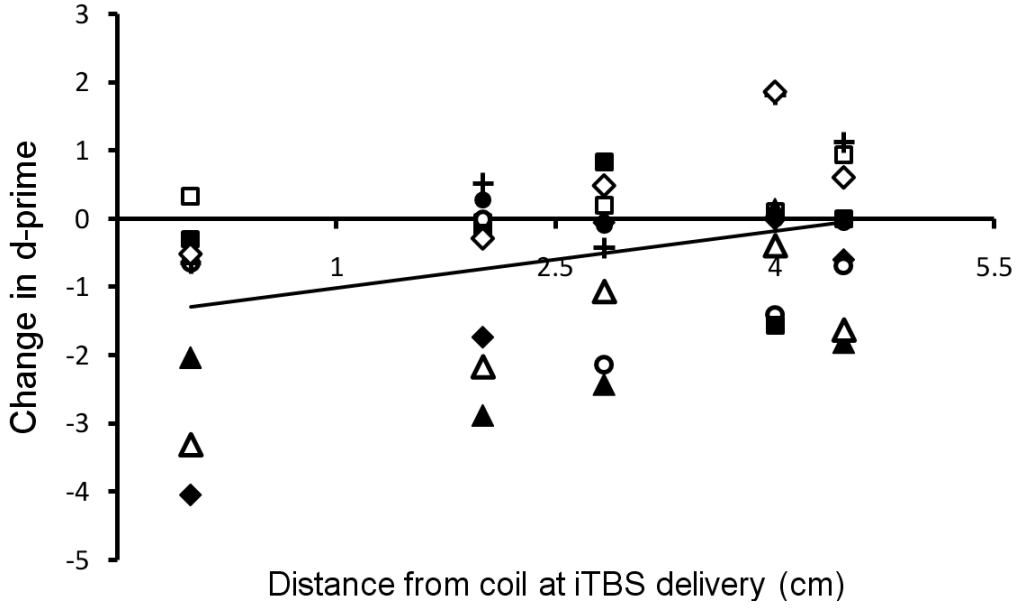

Figure 5.3. Scatterplot showing data from the 'with competitor' condition and the correlation between the change in d-prime (d'_{EFFECT}) and distance from the coil at the time of iTBS/Sham 'pre-treatment'. The 45 data points represent 9 subjects at 5 distances, symbols (e.g. filled circle) remain consistent for a given subject across distances. The leftmost column of data points represents the effect size at grid position 4, i.e. zero cm from the coil. The effect (change in d-prime) is calculated using the equation given on page 145. A significant positive relationship was found between the variables with effect decreasing (becoming less negative) as distance increased (linear regression, solid

line: y=0.28x – 1.28, r^2 = 0.123, p=0.02). No correlation was seen for the 'without competitor' condition (linear regression: y=-0.010x +0.320, r^2 =0.014, p=0.95).

5.4.5 Effect of iTBS in isolation

iTBS was delivered in close proximity to the hotspot (2cm away) so a direct effect on the hotspot, and thus task performance, was a reasonable possibility. This hypothesis was tested and subsequently rejected, by comparing data from the baseline blocks (i.e. before any 10Hz TMS). For stimuli presented without competitor the values (d' $[LVF\text{-}d'RVF]_{10hzTMS}$-$[d'LVF\text{-}d'RVF]_{BASELINE}$) for iTBS (0.32±0.33) and Sham (0.47±0.36) were not significantly different (t(8) = -0.445, p = 0.67, paired t-test, two-tailed). For stimuli presented with a competitor, values for iTBS (0.43±0.31) were slightly more positive (the opposite direction to a neglect-like effect) than for Sham (0.17±0.35), but again, were not significantly different (t(8) = 0.576, p =0.58, paired t-test, two-tailed).

5.4.6 Eye tracking

Eye position was recorded (relative to calibration) for the 500ms before and after the start of 10Hz TMS stimulation (for each trial). These same time periods were also recorded during the no-TMS baseline block for comparison. The data was studied, (using paired t-tests) to control for three possible effects of TMS on eye position:

1) A 'simple' effect of 10Hz TMS on eye position, i.e. in the absence of iTBS pre-treatment (using data from the sham pre-treatment session). On average, 10Hz TMS caused a very small deviation to the left of 0.013±0.063 degrees of visual angle. Even with the coil over the 'parietal hotspot' (grid point no.5), the deviation was effectively zero (0.005±0.16 degrees of visual

angle). Eye deviation during 10Hz TMS did not differ significantly from the (no-TMS baseline) at any of the 9 grid positions (all p-values >0.20)

2) An iTBS induced 'drift' in eye-position, outlasting the actual period of stimulation and independent of effect 1. Eye position in the baseline block (which always directly followed the 'pre-treatment' TMS), did not differ significantly between iTBS (0.66±0.49 degrees to the left) and Sham (0.41±0.63 degrees to the left) conditions (p =0.67). In addition, eye position (for the 500ms preceding 10Hz TMS delivery) did not differ significantly between iTBS and Sham conditions during any of the 9 following blocks (blocks arranged in time order for each subject, all p-values >0.20).

3) A difference in effect 1 caused by iTBS as opposed to Sham 'pre-treatment': The difference in eye position before and after 10Hz stimulation did not differ significantly between these conditions for any of the (nine) TMS-blocks following 'pre-treatment' (all p-values >0.20).

5.5 Discussion: iTBS Effects over right PPC

5.5.1 Overall assessment

In Chapter 5, subjects were tested with the same 4 choice detection task as used in Chapter 3. This task was performed with 10Hz TMS disruption given over a grid centred on the subject's 'parietal hotspot'. This point's location was on average, consistent with that found in Chapter 3 where the hotspot lay situated over the anterior intraparietal sulcus (see figure 3.1, page 92). Preceding the 10Hz TMS disruption, either iTBS or Sham stimulation was given over a point 2cm medial to the 'hotspot'. The pre-treatment with iTBS changed the response (relative to Sham stimulation) of the underlying parietal cortex to subsequent 10Hz TMS disruption. This change was characterised by a drop in d-prime in the left visual field relative to right, and only

occurred in the presence of a contralateral competing target. The effect was greatest at the point directly under the coil at iTBS delivery but was also present at adjacent points, and appeared to fall in a predictable fashion with increasing distance. The post iTBS/Sham data was recorded as one time point, so an accurate determination of the duration of the effect is not possible. However the significant findings suggest that the effect was at least present through the majority of each 60 minute long recording session.

The fact that the 10Hz TMS disruptive effect was seen only in the presence of a competitor may reflect the clinical situation where extinction can be viewed as a mild form of spatial neglect (Heilman & Watson, 1977). The milder 'deficit' in the subjects tested here may in turn reflect the lesser disruptive effect of 3 pulses at 10Hz as opposed to the 5 pulses used previously (which caused subjects to miss left sided targets presented without a competitor, Oliver et al., 2009). The findings could also be interpreted as a generalised, direct effect of iTBS on the 'hotspot', independent of the 10Hz TMS. However, the spatial coding of the effect and the absence of any immediate difference in task performance between iTBS and Sham stimulation (i.e. in the pre-10Hz TMS baseline blocks) go against this.

5.5.2 Altering cortical networks with iTBS

iTBS was targeted at part of a visuospatial cortical network that stretches from occipital visual association areas (Hillis et. al., 2006) to the middle and inferior frontal gyri (Mort et al., 2003). The findings suggest that areas stimulated by iTBS then contribute more to task-related visuospatial processing, a process which effectively increases the functional extent of this network. One could argue to the contrary that, rather than boosting an area's contribution, iTBS simply enhances the effect of subsequent 10Hz TMS disruption in a generic fashion, analogous to say, increasing the TMS stimulation intensity. However, this alternative interpretation appears less convincing after further scrutiny of the data. Looking at the 4 grid points closest to the iTBS site (point 4, and adjacent points 1, 7 and 5), the effect of iTBS per se, (and this effect relative to

Sham) is far larger at points 4, 1 and 7 than at point 5 (see table 3). At point 5 (the hotspot) almost no change occurs and in fact of all nine grid points it returns the smallest effect size i.e., for both 'with competitor' (iTBS: -0.26±0.16, Sham -0.21±0.54), and 'without competitor' (iTBS: -0.15±0.49, Sham -0.12±0.40). If iTBS did have a generic influence on cortical susceptibility to 10Hz TMS one would expect it to spread equally into adjacent areas, not just into points 1 and 7. Of course the hotspot was from the outset, chosen for its greater susceptibility to 10Hz TMS, so one could argue that the effect (without iTBS) over this point already approaches the maximum attainable (and hence does not change much further after iTBS). However, the post-iTBS data go against this 'floor effect' explanation, because points 1, 4 and 7 all yield effects (-0.37±0.39, -0.58±0.32, and -0.42±0.31 respectively) that reach lower than the putative 'floor' set by the hotspot/point 5 (-0.21±0.54). The data in fact suggests that in the post iTBS period, task performance becomes more reliant on areas 1, 4, and 7 and less reliant on the hotspot area 5. Viewed in this light the original assertion seems more convincing, that iTBS encourages nearby areas of parietal cortex to participate in the network of visuospatial processing needed to perform the (4-choice detection) task. Perhaps 'off-line' excitatory iTBS primes underlying and adjacent areas of cortex, so that during the following TMS-free baseline block their behaviour is patterned by the most active site in the cortical neighbourhood, in this case the parietal hotspot. Acting in this way as a template, the hotspot itself does not change, and is to some extent 'bypassed' post-iTBS, as adjacent areas exert more influence on task performance.

Another finding of interest is the effect of 10Hz TMS disruption over points medial to the hotspot (1,4 and 7) in the absence of iTBS stimulation to point 4 (i.e. after Sham stimulation). The data recorded in the 'with competitor' situation reveal changes in performance which occur in the opposite direction to that seen for the adjacent hotspot: a leftward bias rather than a neglect-like rightward bias. Though firm conclusions are difficult to draw from the current data set, a possible explanation might involve putative inhibitory inputs travelling from these neighbouring areas into

the parietal hotspot, which are themselves disrupted during the 10Hz TMS mapping paradigm. This would allow the cortical area under the right parietal hotspot to activate more strongly and thus drive attentional bias towards the left. If such inhibitory inputs did exist, one might have expected excitatory iTBS given over point 4 to suppress activity in the hotspot and cause a change in the pre-10Hz TMS baseline as compared to Sham. However, as demonstrated in section 5.4.5 above, iTBS had no independent effect on spatial bias, suggesting that its action here was more complex than simple up-regulation. iTBS in fact reversed the leftward biasing response of areas 1, 4, and 7 to 10Hz TMS, such that these areas appeared to develop a closer functional resemblance to the hotspot. Though speculative, these suggestions could be explored further by repeating the experiment with iTBS given over some of the other peripheral grid locations.

One important potential source of error to consider is a systematic lateral displacement of the 9-point grid markings in iTBS 'pre-treatment' sessions compared to sham sessions. In this context, effects can be explained entirely by 10 Hz TMS given over the hotspot in the sham session and then again over the hotspot (erroneously 're-labelled' as 'point. 4') in the iTBS session. In this 'reference frame shift' explanation, the negative effect (of iTBS compared to sham) seen over point 4 should accompany an equal and opposite change over the 'hotspot'. However, as detailed above there is in fact no change over the 'hotspot', making this viewpoint difficult to support. Another potential source of error is systematic eye deviation but the eye-tracker data do not support a direct effect of 10Hz TMS, or iTBS on eye position (or an interaction between the two).

5.5.3 Altering parietal maps of visuospatial function

This study demonstrates for the first time, a parietal map of visual-spatial function that can be recorded and manipulated with TMS. The iTBS stimulation technique demonstrated here, which enlarges the area involved in spatial processing in normals, might also improve visuospatial

awareness in patients with spatial neglect (e.g. from sub-total damage to the parietal cortex). Useful cortical targets would include those areas in the medial parietal lobe (for example across the IPS in the anterior cerebral artery territory) that are more likely to remain intact after middle cerebral artery infarction. iTBS delivered over intact areas of the damaged hemisphere could, as part of future studies, complement those TMS techniques which target the uninhibited intact hemisphere and ultimately, enhance other rehabilitative therapies used for spatial neglect.

Chapter Six: Visuospatial Neglect Explored with 'Theta Burst' Transcranial Magnetic Stimulation and Signal Detection Theory.

In the studies described in chapter 4, neglect-like effects were demonstrated in normal subjects using cTBS disruption over the parietal hotspot, which were then reversed with (near) simultaneous cTBS over the opposite hemisphere. In this chapter these techniques were utilised in the clinical setting, with the aim of alleviating spatial neglect in a patient after right parietal stroke. This study describes visual neglect and extinction for the first time using fully balanced bi-hemifield signal detection measures (d-prime and criterion), and shows how this deficit can be alleviated using cTBS over the left PPC. The work presented in this chapter will be submitted to *Neuroreport*:

Oliver, R., Stolwijk, R., Greenwood, R., & Rothwell, J. Visuospatial Neglect Explored with 'Theta Burst' Transcranial Magnetic Stimulation and Signal Detection Theory.

6.1 Summary

Visual extinction occurs when single targets detected in either hemifield, are missed when those same stimuli are displayed bilaterally and simultaneously. Extinction is tested in the clinical setting with relatively crude measures such as the perception by the patient of an examiner's finger movements (as presented in both hemifields). In this case study a novel, fully balanced, signal detection paradigm was used to quantify extinction accurately for the first time in a patient with spatial neglect. This study also demonstrates an improvement in their deficit after the application of continuous 'Theta Burst' (cTBS) Transcranial Magnetic Stimulation (TMS) over the patient's intact left hemisphere in accordance with the notion of hemispheric rivalry (Kinsbourne, 1977). The findings are discussed throughout in terms of the signal detection parameters: 'd-prime' and 'criterion', along with the novel insights they provide into the patient's disrupted internal decision making processes.

6.2 Introduction

In patients exhibiting extinction after right parietal damage, single objects detected in the neglected left side of space go unreported in the presence of more salient events occurring simultaneously to the right (see Driver & Vuilleumier, 2001; Milner & McIntosh, 2005). Extinction has been well described in terms of targets (e.g. fingers, or dots) missed, but also in more depth for the modalities of touch and vision using signal detection measures such as 'd-prime' (d') and 'criterion' (c) (Ricci et al., 2004, 2005; Vishvani et al. 2000; Olson et al., 2003; see also Malhotra et al., 2009 ,who demonstrated a non-lateralised vigilance decrement in neglect patients). However none of these studies account fully for errors made in the right visual field and, as argued below in section 6.6.3, they cannot provide a complete description of the extinction phenomenon.

In this study the newly-developed paradigm described in Chapter 1 was used, which allowed the recording of d' and c from both visual fields simultaneously, for both unilateral and bilateral target situations. Using this fully-balanced approach the aim was to demonstrate extinction in true signal detection terms, for the first time, in a patient with right parietal damage after stroke. A drop in the patient's performance was predicted for left sided targets presented with a competing target on the right (with no equivalent d' deficit for right sided targets, or for unilateral left sided targets).

Spatial neglect and extinction may be explained as a disruption to the normal balance of attention in favour of the undamaged left hemisphere, i.e. towards the right side of space (Posner et al., 1987; Karnath, 1988; diPellegrino & De Renzi, 1995). This view is supported by 'virtual lesion' studies using TMS, in which extinction reduces during temporary TMS-disruption of the undamaged (left) hemisphere (Oliveri et al., 1999; Nyffeler et al., 2009). This technique

was used here in the hope that (in accordance with Kinsbourne's hemispheric rivalry hypothesis) the application of inhibitory 'theta burst' TMS over the left posterior parietal cortex and would rectify the patient's visuospatial deficits.

6.3 Clinical History

Patient JC (66 years of age and left handed), was admitted to hospital with sudden onset left sided weakness. Magnetic resonance imaging showed an acute infarct in the territory of the right middle cerebral artery which involved the right temporo-parietal cortex (as well as the right frontal operculum, right insular cortex and right corona radiata, figure 6.1), but did not include the occipital cortex. On initial clinical examination, profound left sided hemi-inattention and visual extinction were found (accompanying a dense left sided hemipariesis), the visual fields were however intact (to finger movement in confrontation). Visual acuity was correctable to normal in both eyes. Testing at one week showed continued extinction for visual stimuli such that movement of the examiner's index finger in the patient's left visual field went unreported when accompanied by simultaneous presentation of finger movement on the right, in 5/5 trials. Additional evidence of contralesional spatial neglect was found after more formal testing with line bisection: five 15cm lines printed on an A4 sheet of paper were transected with a mean error of 7mm to the right; and with the star cancellation task: 2 targets were missed on each side. The non-lateralised deficit in this latter task may reflect disrupted sustained attention secondary to frontal damage (see Husain & Rorden, 2003). Motor function at one week had improved considerably compared to admission, to the point that the patient could walk unaided. By 3 weeks post infarct, extinction as defined above was only present on 2/5 trials, the line bisection error had reduced to 2.75mm rightward, and star cancellation errors had fallen to 1 on each side. By 4 weeks extinction remained unchanged, though line bisection erred less to the

right than before (2.50mm), and no cancellation errors were made. It was in this context of continuing clinical recovery that the 2 experimental sessions were carried out, the first at three weeks post stroke and the second at four weeks. The patient was unusual, being selected for study on the basis of a) the presence of contralesional inattention and visual extinction, b) the absence of clinically significant hemianopia, c) the ability to comprehend and co-operate with the relatively complex experimental paradigm, d) sufficient mobility to sit upright unaided, in a head and chin rest, and e) the absence of any contraindications to TMS (as stipulated by Wassermann et al., 1998; Rossi et al., 2009).

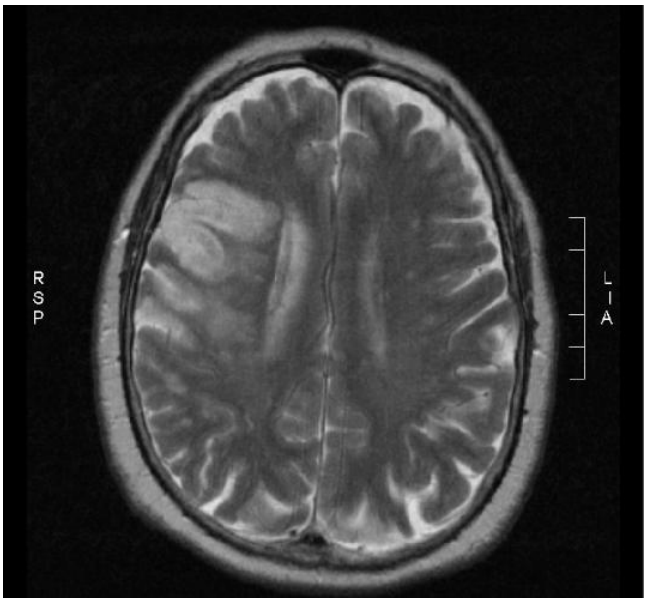

Figure 6.1. An axial slice through the patient's T2-weighted brain MRI. This demonstrates an acute infarct in the territory of the right middle cerebral artery involving the frontal, temporal and parietal lobes.

6.4 Methods

The study was approved by the Local Regional Ethics Committee. The first experimental session took place at three weeks post-stroke, after first obtaining the patient's written, informed consent. They sat in a comfortable chair in a head and chin rest, 50cm from a laptop PC screen

(refresh rate 50Hz) and were asked to discriminate via key-press between 4 different visual stimuli (see Chapter 1, section 1.3 and figure 1.2 A-D). On each trial, the brief line stimulus was preceded for 1000ms by a centrally positioned fixation cross (white on a black background) on which the patient was asked to keep their eyes fixed during each trial. Eye position was recorded (relative to calibrations done at the start, one quarter, midway, three quarters through, and at the end of each bock) with an 'IRIS' Skalar Infra-red Eye Tracker which recorded eye position for 1000 ms on each trial, starting 500 ms before line onset.

Before the main experimental blocks, a staircase procedure was performed using blocks of 60 trials (15 of each of the four stimulus types in randomly intermingled order). At the end of each block the % hit rate for left sided targets appearing with a contralateral competitor (Chapter 2, fig 2.2 D) was calculated automatically and displayed to the experimenter. Starting at 200ms, the stimulus presentation duration was varied from block to block (reduced in 40ms steps) until a 'Hit' rate for left sided targets of approximately 75% was achieved (half-way between a 'chance' 'Hit rate' of 50% and a 'perfect' 'Hit rate' of 100%). Adjustments were made on the basis of 'hit' rate for left sided targets appearing with a contralateral competitor rather than using left sided targets appearing alone to avoid 'floor' effects on target detection in the context of pre-existing clinical extinction.

Once the appropriate stimulus presentation time (500ms) had been found, a block of 120 trials (30 of each stimulus type, taking approximately 8 minutes) was performed before and immediately after cTBS (600 pulses) applied to the left PPC. cTBS was given using a cased figure-of-eight coil (diameter 70mm, handle pointing backwards), at 80% of the patient's AMT ,over the left PPC, at a point 2.2 cm anterior and 1.3 medial to EEG 10/20 position P3. This location was chosen based on the findings in Chapter 4, in which a neglect-like 'virtual lesion' (caused by cTBS over the right PPC) was alleviated by cTBS given immediately afterward, over the left PPC. cTBS was delivered with the coil held tangential to the scalp and with the coil's

handle pointing backwards so as to induce a current with initial phase flowing in the posterior-anterior direction in the underlying brain. The second experimental session (sham condition) took place one week later and was carried out in identical fashion apart from the cTBS, which was delivered with the coil rotated 90 degrees around its long axis and held against the scalp (see Chapter 1, section 1.2.2 for further details). The data from the 4-choice detection task was analysed using the 4 x 4 matrix described in Chapter 2, section 2.2.

6.5 Results

6.5.1 General points

This study employed the methods described by Macmillan & Creelman (their chapter 13, see equation 13.4) and used in previous work (Ricci, 2004,2005), to construct confidence intervals (95% , 99% and 99.9%) around the difference in d-prime (and criterion) values across conditions and thus determine statistical significance.

6.5.2 D-prime

Initial testing revealed a clear discrepancy in performance between left and right visual fields; d-prime was near perfect for right sided targets (4.24, both with and without a contralateral competitor), but relatively poor for left sided targets (figure 6.2A, leftmost data points). On the left, performance suffered most in the presence of a contralateral competing target (d'=1.60, vs. 4.24 on the right, $p<0.001$), than when presented alone (d'= 2.64, vs. 4.24 on the right, $p<0.01$); this difference between left sided stimulus types was also significant (1.60 vs. 2.64, $p<0.05$). After cTBS to the left PPC, performance improved considerably for left sided targets, d' rose to 3.27 for targets presented alone (though this change was not significant compared to pre-cTBS

values) and 2.96 for those with a competitor (1.60 pre- vs. 2.96 post cTBS, $p<0.05$); performance fell slightly for those on the right (figure 6.2A, rightmost data points). In the sham session done one week later, performance for left sided targets was still worse than for right sided targets which remained near perfect at 3.95, though this difference was only significant for left sided targets presented with a contralateral competitor (3.95 on the right vs. 2.74 on the left, $p<0.05$) (figure 6.2B, left most data points) . On the left, there was a small non-significant divergence in performance when targets were presented alone (d'= 2.96) compared to presentation with a contralateral competitor (d'= 2.74). Overall, there was little change at all after sham cTBS apart from a small universal improvement in performance; the difference between right and left sided (with competitor) target performance remained significant (4.24 on the right vs. 2.86 on the left, $p<0.05$) (figure 6.2B, rightmost data points). For left sided targets presented with a competitor, the change in d' pre and post cTBS was also compared to that seen before and after Sham stimulation. A larger post-TBS increase was predicted, as previous studies which had shown a reduction in extinction after left sided cTBS (Oliveri et al., 1999; Nyffeler et al., 2009). Given this a priori assumption, a significant ($p<0.05$) one-tailed difference was found between the change after cTBS (an increase in d' of 1.39) and that seen after Sham (an increase of 0.14).

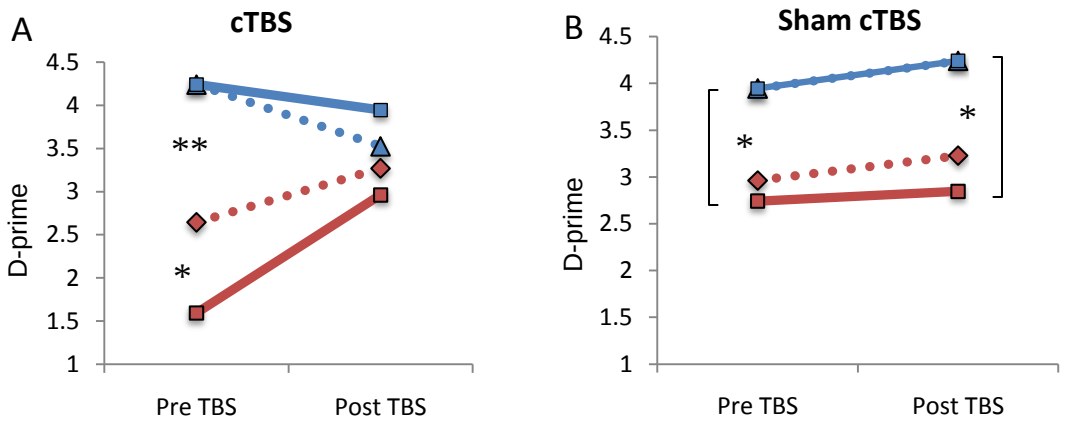

Figure 6.2. Line graph showing the patient's performance (d-prime) in the left (red) and right (blue) visual fields, for targets presented alone (dotted lines) and with a contralateral competitor (solid lines). Performance (d') is shown before and after cTBS (or sham cTBS) delivery over the unaffected left posterior parietal cortex. Asterisks represent significant d' differences between different visual target types (*p<0.05, **p<0.01, see main text). Left sided inattention and extinction improved after cTBS, partly at the expense of a drop on performance for right sided targets. Though extinction was no longer present for the sham session 1 week later, performance was still significantly worse on the left relative to the right, and this did not change after sham cTBS.

6.5.3 Criterion

Changes in criterion (see table 6.1) after cTBS paralleled those in d-prime, though in the reverse direction, becoming smaller (less conservative) for left sided targets. Response bias (criterion) was more conservative in the left visual field for targets presented with a contralateral competitor than in isolation (1.32 vs. 0.80, $p<0.05$) and both these LVF values were significantly more conservative compared to those on the right, which were both neutral i.e. zero (1.32 vs. 0.00, $p<0.001$; 0.80 vs. 0.00, $p<0.05$). After cTBS stimulation this left sided conservative bias shifted towards neutrality (new values: 0.64 for bilateral targets and 0.48 for unilateral targets), though this shift was only significant for targets presented with a contralateral competitor (1.32 pre- vs. 0.64 post cTBS, $p<0.05$); bias for right sided targets remained essentially neutral throughout. There was no significant change in criterion before and after sham cTBS stimulation, though both before and after stimulation, there was a conservative bias

trend on the left in contrast to the prevailing neutrality on the right. The eye-tracker recording showed that in all trials, no saccadic eye-movements (defined as a movement of more than 1° from fixation with a velocity greater than 35°/second, Olincy et al., 2003; Bahill et al., 1981) occurred in the time period between the appearance of the fixation cross and the end of stimulus.

	Pre-stimulation				Post-stimulation			
	LVF	LVF+	RVF	RVF+	LVF	LVF+	RVF	RVF+
cTBS	0.80*	1.32** †	0.00*	0.00**	0.48	0.64†	0.14	0.00
Sham	0.64	0.75	0.15	0.15	0.51	0.70	0.00	0.00

Table 6.1. Changes in response criterion for the four target stimuli, pre and post stimulation, shown for both real and sham cTBS conditions (LVF = left visual field, RVF = right visual field, '+' indicates the presence of a competing contralateral target). Note the conservative (positive values) reporting bias in the left visual field as compared to the right which is near zero (and thus essentially neutral). This left-sided conservative response bias is more pronounced in the presence of a contralateral competitor and moves towards neutrality after cTBS stimulation (see main text for details of statistical comparisons). Paired criterion comparisons are indicated as follows: LVF vs. RVF *p<0.05, **p<0.01; pre vs. post †p<0.05.

6.6 Discussion: Spatial Neglect explored with TBS and SDT

6.6.1 Overall assessment

In Chapter 6, cTBS was applied to the intact left PPC in a patient with unilateral spatial neglect after a right sided stroke. Signal detection measures revealed a large discrepancy in performance for left and right sided targets presented in isolation; d-prime was worse for left-

sided targets and near ceiling for right-sided targets. This deficit for target discrimination in the left visual field (LVF) was exacerbated by the simultaneous presence of a target on the opposite side. Taken together these findings confirm and quantify the presence of visual extinction and left sided spatial neglect (as indicated on initial testing with respectively, detection of finger movement in both visual fields, and line bisection). Building on previous work, cTBS was used to inhibit the undamaged hemisphere and show for the first time, a TMS-induced improvement in extinction as quantified accurately with signal detection measures. cTBS has a beneficial effect on performance for left sided targets which prevents their extinction by targets appearing on the right and which occurs in conjunction with a shift in reporting bias from conservative, towards neutrality. The improvement in performance for left sided targets after cTBS could in theory be a simple practice effect, though if this were the case one would expect a similar increase in performance after Sham stimulation. If the patient's neglect had fully resolved in the intervening week performance might have reached its ceiling, though both before and after Sham stimulation, d-prime on the left is well below that on the right (which in turn, is more representative of true ceiling performance).

Studies in normal subjects show that an extinction like effect can be elicited when a low salience target is presented with a highly salient distractor to the right (but not vice versa) (Pollmann, 1996). It could thus be postulated that in this study, the effect on left sided d-prime scores (both with and without a contralateral competitor) was driven by a subtle pre-existing discrepancy between the patient's visual pathways (e.g. an early cataract or small scotoma on the left), resulting in unequal stimulus visibility rather than a true disruption to visual attention. However it is difficult to reconcile this hypothesis with the finding that the patient's performance for left sided targets improved after TBS to the left parietal cortex, in accordance with established theories of attentional hemispheric rivalry (Kinsbourne, 1977).

6.6.2 Criterion as a marker of pathological decision-making in neglect.

The extinction-like pattern of deficits demonstrated in this study can be interpreted as a diversion of 'Top-Down' attentional resources away from the left, in favour of the right, resources which are thought necessary for successful target discrimination in early visual areas (Heinze, 1994; Vandenberghe, 1997). The conservative response bias for left sided targets may reflect a degree of insight of the patient, into their poorer performance for left sided targets (as compared to the right). In the face of greater 'noise' in the left (visual) sensory 'channel' they appear more reluctant to report these targets. This reluctance may also reflect a pathological over-estimation of the 'noisiness' of left sided visual inputs (and thus their partial abandonment as a source through which targets are perceived). In this patient at least, this interplay between response bias and performance forms a dissociable component of spatial neglect which only emerges through signal detection measurement.

6.6.3 The findings in relation to previous SDT-based studies of neglect

The results agree with and also improve on previous studies that used signal detection measures (Ricci et al. 2004, 2005) to demonstrate visual extinction in stroke patients. These previous studies fell short in one crucial respect: they only took into account errors made in the LVF (errors made on the right were not reported). True enough, they correctly separated left sided errors into those made in the presence of a competing contralateral target and those made without (or made in the presence of a contralateral non-target distractor). They did not, on the other hand, perform the same analysis for the right visual field (RVF). When bilateral targets were displayed, only the LVF 'hit rate' was collected, and when the 'hit rate' was recorded for left sided targets presented alone, no 'false alarm' rate was recorded for the RVF. Why is this data so important? Without it one cannot be sure that the extinction-like process recorded in these studies for left sided targets did not occur in 'mirror image' form for the right side. Rather than extinction, such a deficit would indicate a pathologically exaggerated version of the

physiological ‘two-target’ cost (Duncan, 1980) whereby subjects’ performance drops on both sides when targets appear simultaneously in 2 separately monitored sensory channels. The fully-balanced method of analysis used here is the first to properly disambiguate the constituency of errors made in the right- as well as left visual field, and by doing so demonstrates extinction in the LVF which at the same time, does not occur in the right.

6.6.4 The findings in relation to previous TMS-based studies of neglect

TMS has been used previously over the undamaged hemisphere to improve neglect in patients after stroke (Oliveri et al. 2001, Brighina et al. 2003, Shindo et al. 2006, Nyffeler et al. 2009), though unlike the present study none of these employed a bihemifield detection paradigm of the type capable of demonstrating extinction. This work improves on these earlier studies in 2 other key respects. Firstly, a point (over the left PPC) was targeted which is known to produce a behaviourally-relevant functional effect (as described in Chapters 3 and 4) rather than anatomical landmarks (e.g. P3,P5 or P6 as used in the other studies) which do not always correspond reliably to specific underlying cortical structures (Okamoto et al., 2004) . Secondly, d-prime and criterion measures were used which reveal something about decision-making as well as performance, rather than conventional clinical tests of neglect such as cancellation and line bisection which gauge only accuracy.

Chapter Seven: The Role of the Cerebellum in 'Real' and 'Imaginary' Line Bisection.

This final study sought to explore part of the brain not classically associated with spatial awareness or spatial neglect, the cerebellum. This area was selected for its strong connectivity with cortical areas which have been implicated in spatial judgement such as the parietal and pre-frontal areas. Perception of the midline was tested in both 'real' and 'imaginary' space using physical and number line bisection paradigms. The aim was to find a task-dependent difference in the level of disruption to performance caused by TMS that would indicate differential cerebellar involvement in the generation of the subjective midline in 'real' as opposed to 'imaginary' space.

The work presented in this Chapter was originally published in the form of a research article:

Oliver, R., Opavsky, R., Vyslouzil, M., Greenwood, R., & Rothwell, J.(2011). The Role of the Cerebellum in 'Real' and 'Imaginary' Line Bisection explored with 1Hz rTMS. *European Journal of Neuroscience*, 33, 1724–1732.
doi: 10.1111/j.1460-9568.2011.07664.x

7.1 Summary

The role of the cerebellum is well characterised for many motor processes and for some cognitive tasks, however its contribution to lateralised spatial judgement has never been probed directly. To address this omission, the effects of cerebellar disruption on two different line bisection tasks was investigated in eight healthy subjects. Based on previous evidence of crossed cerebellar-cortical connections one would predict a shift in the perceived midline occuring in opposite directions depending on the cerebellar hemisphere targeted. Repetitive Transcranial Magnetic Stimulation (rTMS), given at 1Hz (600 pulses), was used as a non-invasive way to interfere with processing in the cerebellar cortex. Performance was assessed for both 'physical' line bisection using a newly developed Landmark variant task and for 'mental' line bisection using number pairs. The effects for number line bisection were lateralised: left but not right cerebellar rTMS increased rightward errors, whereas for physical line bisection, rTMS to either hemisphere did not affect performance . Effects due to neck muscle contraction and changes in eye position were ruled out with appropriate control stimulation sites, and eye-tracking. The results confirm the role of the cerebellum in spatial judgement, and, for the first time, demonstrate direct cerebellar involvement in the generation of the midline in 'imaginal' (number) space. The difference between number line and physical line bisection effects is discussed with reference to pre-existing models of cerebellar hemispheric specialisation and functional topography.

7.2 Introduction

The role of the cerebellum is well characterised for aspects of motor performance such as timing (Ivry and Keele, 1989; Del Olmo et al., 2007), motion perception (O'Reilly et al., 2008), and motor planning (Fisher et al., 2006), but less so for cognitive processing (Leiner et al.,1995). Clinical studies suggest a role for the cerebellum in the perception of space, for example right sided spatial neglect has been reported in a patient with damage to the right cerebellar hemisphere, implicating this structure in left-right spatial judgement (Silveri et al., 2001), and cerebellar damage can lead to spatial misperception as part of the 'Cerebellar Cognitive Affective Syndrome' (Schmahmann and Sherman, 1998). The role of the cerebellum in lateralised spatial judgment can also be inferred indirectly from studies of pointing movements, performed as subjects adapt to the effects of optical prism exposure (Pisella et al., 2006).

Anatomical and functional studies suggest a model of crossed connection via thalamus between the cerebellar hemispheres and contralateral prefrontal and parietal cortices (Middleton & Strick, 2001; Clower et al., 2001; Dum & Strick, 2003; Pisella et al., 2006).Other studies show connections running in the opposite direction, from the dorsal parietal areas to the cerebellum via relays in the pontine nuclei (see Glickstein 2000). Despite the well established connection between the cerebellum and cortical areas involved in spatial perception, the role of the healthy cerebellum in lateralised spatial judgement has never been probed directly.

To address this issue, the disruptive effect of 'offline' 1Hz repetitive Transcranial Magnetic Stimulation (Wassermann et al., 1996) was employed which, when given over the cerebellum, interferes with tasks such as procedural learning (Torriero et al., 2004) and time perception (Lee et al., 2007). In this study, cerebellar 1Hz rTMS was given to healthy subjects before they

performed two simple tasks. The first task involved 'physical' line bisection, (a modified Landmark task), whilst the second task involved the bisection of mental 'number lines'.

The cortical networks required to navigate along number lines are appreciably different from those recruited by navigation along physical ones (Doricchi et al., 2005). The Landmark task is known to activate right parietal cortex and left cerebellar hemisphere in normal subjects (Fink et al., 2000), and elicits lateralised performance errors from patients with parietal damage (Driver and Vuilleumier, 2001). Number line bisection is also disrupted after right hemisphere damage, with patients showing positive deviation (rightward along the number line) (Zorzi et al., 2002). However imaging studies in such patients implicate right prefrontal rather than right parietal damage as a source of the pathological rightward bias (Doricchi et al., 2005)

Based on the evidence described above, one prediction was that cerebellar disruption with rTMS would interfere with line bisection performance. In particular, one might anticipate that the interaction between the cerebellar hemispheres and contralateral parietal and prefrontal cortices would manifest post-TMS as a spatial lateralisation of performance error.

7.3 Methods

The subjects' demographics and details of the equipment are given in tables 1.1, and 1.2, and section 2.2.2. The subjects were asked to perform 2 different tasks, a line bisection/Landmark based task, and a mental number line bisection task, before and after 1Hz rTMS.

7.3.1 Tasks

A) Modified Line Bisection ('Landmark') Task.

Subjects were presented with a white vertical line 3 x 0.5 cm (0.17 x 3.43 degrees of visual angle), which remained stationary in the centre of a black screen. A black dot was situated half

way down the line, on which subjects were asked to maintain fixation throughout the task. A white horizontal line (of variable width – see below, but constant thickness: 0.5cm or 0.17º) then appeared along the horizontal meridian of the screen, to the left or right of the vertical marker. The aim of the task was to move the horizontal line towards the middle of the screen so that it came to rest exactly bisected by the vertical line. The starting location of the horizontal line (as measured by its centre point) varied randomly, with an equal chance of appearance, anywhere along the horizontal meridian from the left most edge of the computer screen to the right (i.e. from 15cm, 17 ºleft of the vertical marker, to 15cm, 17ºto the right, or -17 º to +17 º). To prevent ceiling effects in performance resulting from repeatedly bisecting the same line, line width also varied randomly with each trial (one of 4 possibilities: 6.0cm, 9.0cm,12.0cm, or 15.0cm, equivalent to 6.8º, 10.2º, 13.5º, or 16.7º respectively). In all experimental sessions, the subjects moved the horizontal line with their dominant hand (the right hand for all subjects) using keyboard presses, (the '<' key for left and the '>' key for right). Each key press moved the line to a point half way between its current and its last position, except for the first movement where the point lay half way between the line's current position and the edge of the screen. For example, if the horizontal line appeared 10 degrees to the left (-10 degrees), and the subject correctly decided to move the line rightwards, the next position would be 3.5 degrees to the right (+3.5 degrees) from the calculation: (-10+17)/2. If the subject then correctly decided to move the line leftward, the next position would be -3.25 i.e. (-10+3.5)/2. The subject made as many of these decisions as necessary until they were satisfied that the horizontal line lay in the middle of the screen, exactly bisected by the stationary vertical line. At this point they indicated verbally that the line was bisected, and the next trial began. If the subject made an error early on in the sequence of left-right decisions, they would quickly find that the line became 'trapped' on one side of the vertical marker (moving a smaller and smaller distance towards it). In this situation they could re-start the trial by pressing the space bar, and the data would not be recorded. The subjects performed the task in blocks of 50 trials, each line width appearing 10 times. Eye

position was recorded in time frames, from the start of each trial to the subject's final decision. There was no set time limit for each trial, and subjects were asked to maximize their accuracy rather than speed.

The modified version of the Landmark task used here, aimed to extract the maximum possible amount of information from each trial whilst retaining the key inherent advantages of the 'classical' Landmark task. In the 'classical' version the subject is asked to compare the sizes of the leftward and rightward segments of a pre-transected line and point towards the end which appears closer to the transection. One interpretation of the deficit in spatial neglect is that the representation of space on the affected side is 'compressed' (Milner et al., 1993), thus neglect patients performing the Landmark paradigm generate a movement *towards* the 'neglected' part of the line (which they perceive as shorter). This paradigm therefore reduces any lateralised error caused by directional hypokinesia, rather than true visuospatial inattention (Milner et al, 1993).

When performing the modified Landmark task the participants in effect still 'pointed' toward the end of the line closest to the vertical marker (though with a keyboard arrow rather than their hand and arm), thus retaining the classical Landmark task's ability to screen out effects from directional hypokinesia. However by using a key press rather than a pointing movement this modified version had the added advantage of removing as a potential source of error, any subtle motor inaccuracies from rTMS induced cerebellar disruption. A final advantage of the Landmark Task with regard to this study was that the subject could maintain fixation centrally on the vertical marker (as confirmed with eye-tracking here), thus minimizing eye movement as a source of error.

The disadvantage of the classical Landmark task is that the overall midpoint estimate of the subject can only be inferred from an error score derived from many trials, where lines with a variety of pre-transection points are presented (e.g. Milner et al., 1993; Harvey et al., 1995;

Toraldo et al., 2004). In the modified version used here, a similar overall process occurred: each time the line 'moved' the subject was in effect presented with a new transection point; they then had to decide whether the left or right segment was larger and thus which direction to send it next. However, the crucial modification in the modifed version of the Landmark Task was that on each trial this process was repeated until subjects judged the segments to be equal, thus a midpoint estimate was generated after a only few seconds, not after a block of many trials.

B) Number Line Task

Number space can be thought of as a non-verbal representation of numerical quantity analogous to a spatial map where smaller numbers correspond to 'left' and larger number to 'right' (Galton, 1881). The interval between 2 numbers can therefore be thought of as a 'number line' (bounded at its leftmost extent by the lower number and at the opposite end by the higher number) which can be 'transected' (if the subject is asked to indicate which number lies exactly half way between).

In the number line transection task, subjects were presented with 2 numbers, 2cm (1.72º) to the left and right of a central fixation dot (all were coloured black, and presented on a white background). The numbers were 2cm (2.4 º) tall and 1cm (1.15º) wide; the fixation dot was 0.3 cm (0.34º) wide. The number pairs were generated randomly for each trial with the smaller number always appearing on the left, and the larger on the right. The smaller numbers ranged from 10 to 80 and the larger from 24 to 99; computer selection of the pairs was manipulated so that the difference between the numbers ranged from 12 to 88 (intervals not divisible by 2 were discarded). These parameters were chosen on the basis of earlier studies (Longo and Lourenco, 2007), which showed that number bisection bias (in their study due to pseudoneglect) was minimized with the smaller number on the left, and that ceiling effects in performance occur

with interval sizes of 10 or less. The subjects were asked to state verbally, the number which lay between the two presented: thus for the pair '10 • 60' the correct answer was '35'. The numbers were randomly generated for each trial rather than re-cycling pre-selected pairs. This was done to minimize practice effects, as the subjects would otherwise see each pair 12 times over the course of the whole experiment (3 blocks x 4 conditions, see paradigm below). The number pairs were presented (either side of the fixation dot) for 2 seconds, following 1 second of the fixation dot alone. A blank white screen was then displayed for 2 seconds during which time the subjects responded. As with previous studies of number line bisection (Göbel et al., 2006; Longo and Lourenco, 2007), subjects were asked not to try and calculate the midpoint arithmetically (e.g. by adding left to right and dividing by 2). This was done with the aim of testing subjects' internal spatial representation of number rather than their ability to perform exact calculations, and also because previous studies indicate greater cerebellar involvement in approximate calculation (Stanescu-Cosson et al., 2000). Unlike the previous studies a more robust method was employed here to elicit approximate or 'intuitive' judgments by allowing subjects only 2 seconds for each number line trial. If the subject failed to respond within the time limit, the trial was aborted and no data recorded. In practice, this occurred very rarely; 'time-out' errors occurred on average once per 60 trials. The hypothesis that this small error rate would bias the data recorded (towards smaller number intervals for some but not other stimulation conditions) was tested nonetheless (see results). The subjects bisected 50 number pairs (within the 2 second time limit) per block. Eye position was recorded for the time period during which each number pair was visible (2 seconds).

7.3.2 Experimental paradigm

All blocks were performed in pairs (line bisection task and number line bisection task), with the order counterbalanced across subjects and stimulation conditions as described below. TMS

stimulation sites included ‘active’ cerebellar sites and ‘control’ neck stimulation sites (controlling for the effects of neck muscle vibration, as detailed in the next paragraph below). In each experimental session, the subjects performed a training block (20 trials for each task, 4 minutes total duration), and then a pre-rTMS baseline block (50 trials for each task) which took 10 minutes to complete (5 minutes for each task). rTMS stimulation was then given over 1 of 4 stimulation sites: left cerebellum, right cerebellum, left neck, or right neck (see ‘TMS’ section below for stimulation parameters). Following rTMS, four 5-minute blocks of 50 trials were performed which alternated between tasks (a total of 100 line bisection trials and 100 number line bisection trials). To balance any additional inter-subject variability in task performance caused by the rTMS intervention, and thus to enhance statistical power, more trials were collected post rTMS than pre rTMS.

Some degree of neck muscle contraction occurs in most subjects with stimulation over the cerebellum site, due to direct stimulation of cervical motor nerve roots, and previous studies indicate that repeated posterior neck contraction is an important factor to isolate when studying putative effects on spatial judgment. Neck muscle vibration is known to displace the body-centered representation of the midline in the ipsilateral direction, as a result of false information that the ipsilateral posterior neck muscles have lengthened (Taylor and McCloskey 1991). This phenomenon has been exploited in neglect patients, with therapeutic effects that outlast the period of neck muscle stimulation, and may be stable for at least 2 months (Schindler et al., 2002). The neck muscle stimulation sessions were therefore done to control for any direct, lasting effect of repeated neck muscle contraction on spatial bias. Given the longevity of the effect found by Schindler et al., the neck stimulation sessions (where one would expect any effect from muscle vibration to be greatest) were not intermingled with the cerebellar sessions but were instead all performed afterwards, at an interval of 4 weeks for each subject. Though we expected any ‘hang over’ effect from neck muscle vibration to be less after the cerebellar

sessions, this interval was left between the cerebellar and neck stimulation sessions as a precaution. As the left and right sided stimulation sessions were separated by 3-5 days rather than 4 weeks, we looked carefully for any effects persisting between them i.e. left and right baseline pre-TMS values were compared for each task. Pooled baseline data from the cerebellar sessions were also compared to those from the neck sessions to check for any 'hangover' effects persisting beyond the precautionary 4 week interval (see 'results' section).

In the first experimental phase subjects were given left or right cerebellar stimulation (followed by stimulation to the other side 3-5 days later), and performed either the line bisection or number line bisection first in each block-pair. The order (left or right first, physical line bisection or number line bisection first) was counter balanced across subjects using a 4x4 Latin Square design. In the second phase, a month later, the sessions were repeated using the same design, but substituting left and right neck stimulation sites for the previous cerebellar stimulation sites.

7.3.3 TMS

In each subject Resting Motor Threshold (RMT) was found using the FDI muscle. RMT was determined to the nearest 1% of the maximum stimulator output by adjusting the stimulus intensity until reliable MEPs (usually around 100 μV, as defined by Rossini et al., 1994) were produced on at least five of 10 consecutive trials. rTMS was given at 1Hz for 600 pulses (10 minutes) at 90% of the subject's RMT, an intensity thought sufficient in previous work to directly affect cerebellar cortex (Del Olmo et al., 2007). The cerebellum was stimulated as in previous studies at a point 3cm lateral and 1cm inferior to the inion) on a line joining the inion to the external auditory meatus (a point previously demonstrated with neuronavigation to lie over the cerebellar hemisphere, Del Olmo et al., 2007), with the handle pointing superiorly (Théoret et al., 2001; Oliveri et al., 2005). The posterior neck musculature (control site) was stimulated at a

point 3cm lateral to and 8cm inferior to the inion. To minimise discomfort for the subject, a tailored stimulation intensity was used for the 600-pulse stimulation (still at 1Hz) rather than the fixed intensity applied over the cerebellar sites. This was found prior to the main 600 pulse intervention, starting at a stimulation intensity of 90% RMT, and then reducing in 5% steps to the minimum level needed for reliable, visible, unilateral twitches of the posterior neck muscles (in the majority of subjects stimulation intensity remained at 90% RMT).

7.3.4 Data analysis

For both tasks the midpoint estimate made in each trial (whether in degrees of visual angle for the physical line task, or digits in the number line task) was expressed as a percentage of the line transected. Because line bisection biases in patients with spatial neglect and in normal subjects are known to correlate with line length (Halligan et al., 1990), this method of analysis was chosen to avoid attributing undue significance to large errors made along long lines and vice versa . This estimate was also signed according to whether it was made to the left (negative) or right (positive) of the true midline e.g. a leftward transection error of 3 digits for a 20-digit-long number line was coded as -15%. These positive and negative percentages were summed and averaged, giving an overall bias score for each subject and for each block. The overall average length of the number lines generated was 38 (digits) and that of the physical lines was 9cm (or 10 degrees of visual angle at a viewing distance of 50cm).

All data sets were first checked for normality with Anderson Darling tests (all p-values >0.05) and all post hoc t-tests were two-tailed, and were corrected using Tukey's HSD method.

The data was also analysed to rule out any systematic bias that might occur during the computer generation of the number line pairs (in effect to check the veracity of the computer's

'random' seed). All number lines generated immediately 'pre' TMS were compared to those generated 'post' TMS, and all number lines generated during the 'cerebellum' stimulation site condition were compared to those generated (4 weeks later) during the 'neck' stimulation site condition. Finally all 'left' condition number lines were compared to all 'right' condition number lines. The number line 'width' values (right-hand number minus left-hand number), were compared in large pooled blocks:

a) 'pre' (8 subjects x 50 trials x 4 stimulation sites = 1600 number lines) vs. 'post' (8 subjects x 100 x 4 stimulation sites = 3200 number lines);
b) 'cerebellum' (8 subjects x 150 trials x 2 sides = 2400 number lines) vs. 'neck' (also 2400 number lines);
c) 'left' vs. 'right' (both 2400 number lines).

As expected, the data sets for these 3 comparisons were non-normal (the computer was programmed to generate the number lines with equal probability); therefore non-parametric tests were used (Anderson-Darling tests performed on each of the 6 number line pools all returned p values of <0.01). For all 3 comparisons (pre vs. post, cerebellum vs. neck, or left vs. right), no significant differences were found (Mann Whitney U-tests, all p-values > 0.10), indicating that the number lines generated were statistically homogeneous across stimulation conditions. This finding discounted 'time-out' errors (which might bias the number line population toward smaller widths and smaller bisection errors-see methods) as a significant source of the differences in error rates measured across stimulation sites.

Increasing the numerical 'magnitude' of a numberline i.e. its left-right position in number space (as represented by the mean of its number pair), results in an increasing leftward bisection error (Longo and Lourenco, 2007). Therefore a large pre-existing difference in number line magnitude between stimulation conditions could feasibly account for any lateralised left-right bisection error

seen after cerebellar rTMS, rather than the TMS itself. However this hypothesis was discarded after a similar analysis to that above, carried out for number line magnitude, revealed no significant differences (again comparing pre vs. post, cerebellum vs. neck, or left vs. right with unpaired two-tailed t-tests, all p-values >0.20). Finally, the starting positions of each physical line generated were also analysed in the same way to that above (the data sets were again non-normal according to Anderson-Darling tests) and once again no significant differences were found (pre vs. post, cerebellum vs. neck, or left vs. right compared with Mann Whitney U-tests, all p-values >0.10).

7.4 Results

7.4.1 Lateralisation biases pre and post rTMS in physical and number line bisection.

At baseline, small biases in error direction were found in both tasks. For the sessions in which subjects performed the physical line task, there was an overall shift towards the left (-0.13 ± 0.34%), whereas this shift occurred in the opposite direction for the number line sessions (0.20±0.43%). The baseline rightward shift for the number line task ran contrary to what one might have expected, given previous evidence of an overall leftward number line transection bias ('pseudoneglect') in normal subjects (Gobel et al., 2006; Oliveri et al., 2004; Longo and Lourenco, 2007); this discrepancy is explored further in the 'discussion' section.

The main experimental data was analysed separately for the cerebellar stimulation sites and the neck control sites. For the cerebellar stimulation data, a 3-Way ANOVA was performed with factors : 'task' (physical or number line bisection), 'rTMS stimulation side' (left or right) and 'time' (baseline or post cerebellar rTMS). This returned a strongly significant interaction between the

three factors ($F(1,7) = 28.21$, $p = 0.001$) though revealed little in terms of any differential effect on the number line task versus the physical line task (and thus on error shifts in 'imaginal' versus 'real' space). To find the source of this higher order interaction, the data from the two tasks were analysed separately, each with its own 2-Way ANOVA (factors: 'rTMS stimulation side' and 'time'). The a priori expectation was that rTMS over either cerebellar hemisphere would cause a shift in the subjects' perception of the midline and that, given the crossed nature of cerebello-cortical connections, this should occur in opposite directions. For the number line task a significant 2-way interaction between side and time was indeed found($F(1,7) = 21.36$, $p = 0.002$, figure 7.1A). This suggested a differential effect of rTMS on left and right cerebellar hemispheres which is explored further in the post hoc analysis described below. There was no significant interaction ($F(1,7) = 1.66$, $p = 0.238$, figure 7.1B) or main effect for the physical line task which was surprising given that this task and the number line task involve processing in some shared cerebral cortical areas (e.g. parietal areas). This absence of rTMS effect on the physical line task is explored further in the discussion section.

As we predicted, post hoc testing showed a divergence in number line bias after left and right cerebellar stimulation (figure 7.1A). For the number line task, left cerebellar stimulation caused a significant rightward deviation from baseline ($0.33 \pm 0.57\%$ vs. $1.35 \pm 0.49\%$, $t(7) = 6.8$, $p < 0.01$; equivalent to a 0.34 digit shift), whereas right cerebellar stimulation caused a smaller, leftward deviation from baseline which was not significant ($0.23 \pm 0.72\%$ vs. $-0.20 \pm 0.58\%$, $t(7) = 2.87$, $p > 0.05$). After rTMS the divergence between midpoint estimates of the number line was strongly significant for left and right cerebellar stimulation sites (1.35% vs. -0.36%, $t(7) = 11.40$, $p < 0.01$). This finding, coupled with the non-significant effect after right cerebellar rTMS suggested that the ability to induce a shift in the subjects' perceived midline was exclusive to left cerebellar rTMS. This was somewhat unexpected given pre-existing evidence for a bilateral parietal representation of the mental number line (Dehaene et al., 2003), but is still explicable when

viewed in the context of cerebral and cerebellar hemispheric specialisation for spatial tasks (see 'discussion' section).

The equivalent 3-way ANOVA for the neck stimulation sites (see figure 7.2), where rTMS was delivered directly over the posterior neck musculature, showed no significant main effects and no significant interactions (all p values >0.30). This important finding effectively ruled out any confounding effects due to neck muscle vibration that might have otherwise rendered the cerebellar rTMS data invalid.

Analysis of baseline values across conditions

As mentioned previously, baseline values for left and right cerebellar stimulation sessions were compared to check for any 'hangover' effects e.g. from neck muscle vibration . For the physical line bisection task the average error was -0.11 ± 0.36% for sessions in which rTMS was given over the left side, and -0.29 ± 0.37% for those in which the right side was targeted (paired t-test, two tailed, p = 0.46) . For the number line bisection task the corresponding values were 0.33 ± 0.57% (left sided stimulation sessions) and 0.23 ± 0.43% (right sided stimulation sessions) with no resultant significant difference between them (paired t-test, two tailed, p = 0.83). A similar analysis of baseline values for left and right neck stimulation sessions also showed no significant differences (both p values >0.20).

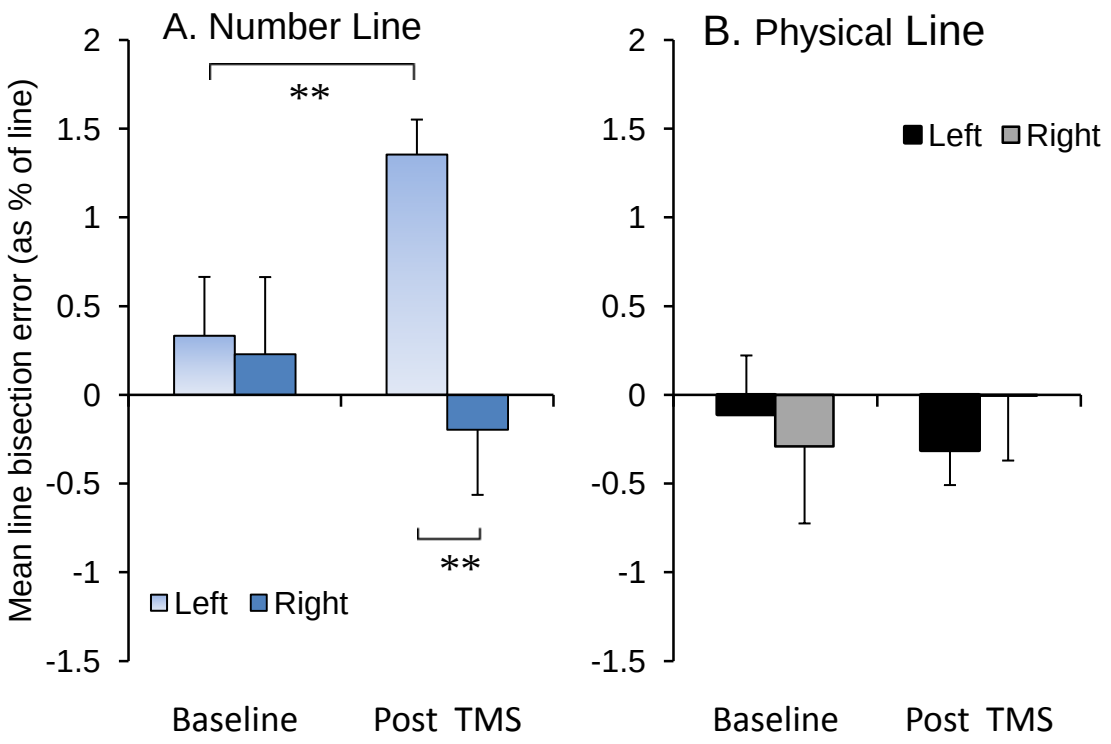

Figure 7.1. Cerebellar rTMS: Number Line (A) and Physical Line (B) Bisection Tasks. Histograms show the change in mean error (expressed as % of line bisected, negative values = leftward error and vice versa) at baseline and after rTMS (light blue/blue = number line task, left and right sided stimulation respectively, grey/black = physical line task left and right sided stimulation respectively). rTMS parameters: 600 pulses at 1Hz, 90% RMT. For the number line task, left cerebellar rTMS resulted in a significant increase (** $p<0.01$) in rightward error; and error direction following left and right cerebellar rTMS differed significantly (**$p<0.01$). For the physical line task there were no significant shifts in right-left bias. All post hoc tests were two-tailed t-tests (Tukey's HSD); error bars show the SEM, adjusted for clarity as per Loftus and Masson 1994 to remove inter-subject variance.

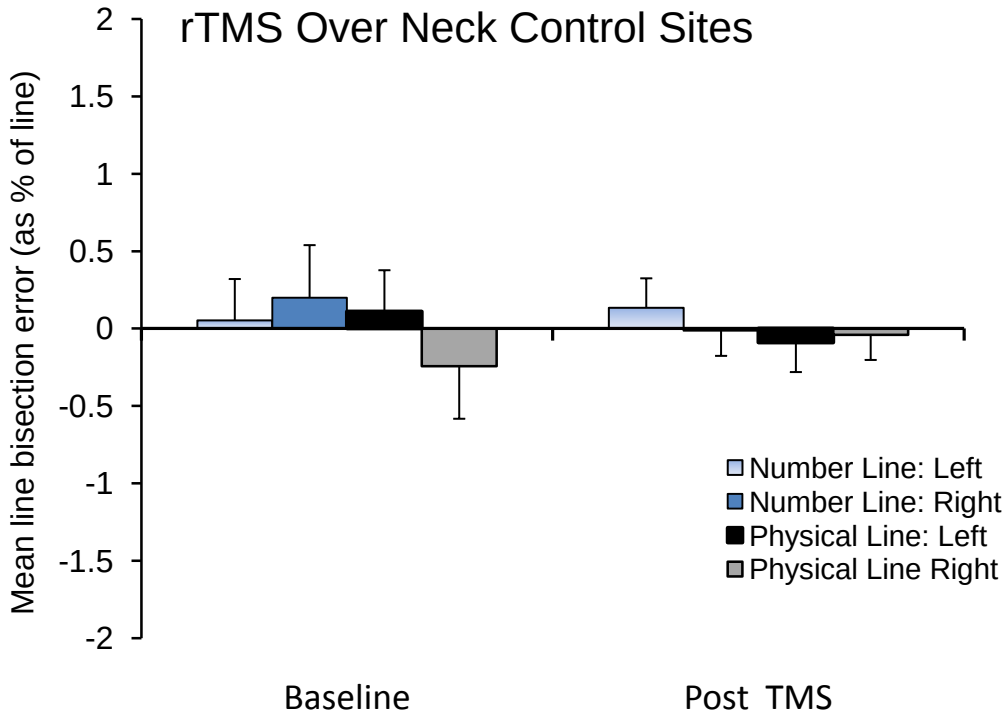

Figure 7.2. Physical Line and Number Line Bisection Tasks: Neck rTMS. Histograms show the change in mean error (expressed as % of line bisected, negative values = leftward error and vice versa) at baseline and after rTMS all as in figure 7.1. rTMS stimulation parameters remain as per figure 7.1. No significant effects were found (all ANOVA interaction and main effects associated with $p>0.30$).

7.4.2 Practice effects

The baseline error scores during the cerebellar and neck stimulation sessions (each averaged across left and right stimulation sites) were compared to test for any overall practice effects that might outlast the four week interval between cerebellar and neck stimulation sessions. There was no significant difference in the baseline scores in either the physical line bisection task (-0.20 ± 0.35% for the cerebellar sessions; -0.07 ± 0.35% for the neck sessions; paired t-test, two tailed, $p =0.81$) or the number line task (0.28 ± 0.60% for the cerebellar stimulation sessions; 0.13 ± 0.43% for the neck sessions; paired t-test, two-tailed, $p = 0.54$).

7.4.3 Eye position

Eye position and variance in eye position were analysed to test the hypothesis that TMS disruption to the cerebellum could destabilize visual fixation (see discussion) and thus increase the absolute error rate independently of any effect on cerebral processing.

Eye-position (relative to calibration) was averaged over the recording period for each trial (for physical line bisection this period encompassed the whole trial, and for number line bisection just the 2 seconds for which the numbers were visible). The eye position values for each individual trial were calculated and then pooled across subjects, yielding blocks of 400 baseline trials and 800 post-TMS trials. For each site (left cerebellum, right cerebellum, left neck, right neck), the baseline and post TMS blocks were compared with unpaired t-tests. All deviations in eye position after TMS were less than 0.25 degrees of visual angle from their respective baselines, and no deviation was significant (all p-values >0.10, see table 7.1). This was true for both physical line bisection and for number line bisection. A similar analysis was carried out for the variance in eye position, again comparing pooled blocks pre (400 trials) and post (800 trials) TMS. Pre and post TMS variances were compared with f-tests, and for both tasks, all pre-post increases were associated with p-values >0.05, see table 7.2.

Site	Number Line Task			Physical Line Task		
	Baseline	**Post-TMS**	**p-value**	**Baseline**	**Post-TMS**	**p-value**
Left Cerebellum	0.75±0.11	0.72±0.07	0.78	0.06±0.07	0.15±0.05	0.29
Right Cerebellum	0.02±0.12	0.19±0.07	0.20	0.39±0.09	0.50±0.05	0.25
Left Neck	0.62±0.11	0.57±0.08	0.71	0.66±0.10	0.72±0.10	0.52
Right Neck	0.52±0.10	0.73±0.09	0.12	0.27±0.08	0.16±0.06	0.27

Table 1. Eyetracker data comparing eye position before and after TMS for each of the four stimulation sites. Eye position is averaged across all subjects and trials (400 baseline trials and 800 post TMS trials) and is given in degrees of visual angle ± SEM (positive values indicate rightward deviation; negative values indicate leftward deviation). The p-values result from individual unpaired t-tests comparing the pooled data from all subjects before (400 trials) and after (800 trials) TMS.

Site	Number Line Task			Physical Line Task		
	Baseline	**Post-TMS**	**p-value**	**Baseline**	**Post-TMS**	**p-value**
Left Cerebellum	5.73	4.26	<0.001	1.84	1.8	0.83
Right Cerebellum	6.93	4.76	<0.001	2.88	2.09	<0.001
Left Neck	5.46	5.62	0.73	3.08	2.94	0.59
Right Neck	5.04	5.89	0.06	2.65	2.46	0.37

Table 2. Eyetracker data comparing the variance in eye position before and after TMS for each of the four stimulation sites. The p-values result from individual f-tests comparing the pooled data from all subjects before (400 trials) and after (800 trials) TMS. After TMS, no significant increases in variance were found.

7.5 Spatial Judgment and the Cerebellum

7.5.1 Overall assessment

The study described in Chapter 7 demonstrated that 1Hz rTMS over the cerebellar hemispheres disrupted healthy subjects' ability to bisect lines in number space but not those in 'real' space. This is the first study to demonstrate a lateralised effect (in terms of hemisphere targeted and error direction) on spatial judgement caused by rTMS disruption of the cerebellum, and the first to demonstrate the involvement of the cerebellum in number line bisection. The lateralisation in error and dependence on cerebellar hemisphere stimulated suggests a true effect on spatial awareness rather than a non-specific disruption to, for example, subjects' concentration or sustained attention. In one recent functional imaging study, approximate calculation could be localised to the left cerebellum (Stanescu-Cosson et al., 2000) thus rTMS here could in theory disrupt number line bisection independently of any cerebral cortical effect. However that study found no evidence that arithmetical processing in the left cerebellum was lateralised in number space (at least for numbers greater than '10', as tested here) thus the rightward biased error seen here cannot be explained by cerebellar effects alone.

Control experiments with direct stimulation of neck muscles showed that these effects were not due to lateralized sensory input from the rTMS. Although neck stimulation sessions always followed the cerebellar sessions, there were no differences in baseline performance prior to neck stimulation to suggest a practice effect.

The cerebellum is also involved in the maintenance of gaze (Guerrasio et al., 2010) and this visual fixation becomes unstable in cerebellar disease (see Hocking et al., 2010). It is therefore conceivable that the cerebellar TMS virtual lesions used here could also destabilise visual fixation and disrupt task performance independently of any effect on cerebral cortical processing. However this hypothesis seems unlikely given that the analysis of variance in eye

position before and after TMS showed no significant increases (at some sites variance decreased significantly, though it is difficult to see how this could adversely affect task performance). Given that both cerebellar hemispheres contribute to the stabilization of visual fixation (Haller et al., 2008), one would expect any putative rTMS effects on visual fixation (and subsequent worsening of task performance) to occur regardless of which hemisphere was stimulated. The data from this study, which show a side-dependent effect of cerebellar stimulation on task performance, do not support this view.

It is possible that cerebellar rTMS could have spread to and disrupted activity in the primary visual cortex so as to produce a contralateral scotoma. This could conceivably result in a misreading of one or both numbers in the number line task and thus increase total error rates after stimulation to either cerebellar hemisphere. However this view does not fit with the finding of a rightward biased error after stimulation to the right, but not left cerebellar hemisphere. In addition the intensity of TMS used (47±8.4% (±SD) and 48.5±5.9 of maximal stimulator output for right and left cerebellum stimulation respectively) was much less than that typically needed over V1 to elicit visual field scotomata (70-90% of maximum stimulator output) (Kamitani and Shimojo, 1999; Kammer, 1999).

7.5.2 Pseudoneglect and Line Bisection

Normal subjects generally deviate slightly to the left when transecting lines in both physical (Jewell and McCourt, 2001) and number line space (Gobel et al., 2006; Oliveri et al., 2004; Longo and Lourenco, 2007). This phenomenon, termed ‘pseudoneglect’ is thought to result from the dominance of the right hemisphere in matters of spatial judgement and is subject to a great variety of different factors e.g. the demographics of the participants, the dimensions of line, and the hand used to transect it. However, according to one large metanalysis (Jewell and McCourt, 2001), one of the most significant factors is the direction in which the participants initiate visual scanning during the task, i.e. a left-to-right scan pattern leads to large leftward errors and vice

versa. In agreement with previous pseudoneglect studies we found a small leftward bias for physical line bisection (0.13 % of the line transected), though for number line bisection the bias was in the opposite direction (0.20 % of the line transected). One key factor which might explain the discrepancy is that in this study, subjects were required to maintain their gaze at a central fixation cross (and their ability to do so was confirmed with eyetracking), whereas in other studies of number line bisection subjects were free to move their eyes. For instance subjects would write down numerical midpoint estimates on sheets of paper (Longo and Lourenco, 2007), or respond verbally to spoken numerical intervals whilst blindfolded (Gobel et al., 2006). Although eye-tracking was not used in either study it seems feasible that left-to-right scanning movements occurred as subjects read the printed numerical intervals in the first study; and rightward eye movements are known to occur under similar conditions to the second (Raine et al., 1988). No scanning eye movements were found in this study and this may have allowed a subtle, hemisphere-mediated divergence between task and error bias to emerge, i.e. the additional verbal and mathematical demands of the number line task activated the left hemisphere relative to the right, and pushed the balance of attention rightward, whilst the purely spatial demands of the physical line task had the opposite effect. Relative left hemisphere activation during the number line task might also explain the discrepancy between the current findings and those of Oliveri et al. (2004), who asked subjects to fixate a central target, compare number line segments and respond with a button press. This lack of verbal report may have contributed to their subjects' (leftward) response bias by tipping the overall balance of activation in favour of the right hemisphere.

Whether or not these postulates are correct, pseudoneglect remains a complex phenomenon over which many factors exert an influence and it is difficult to draw any definite conclusions about its underlying cause from this data. However, when taken in the context of previous work they at least hint at possible confounding factors such as eye movement and the modality of task response for any future studies of pseudoneglect.

7.5.3 Effects on physical and number line bisection

Previous evidence suggests that performance in these two tasks depends on different cortical networks. Physical line bisection is disrupted by posterior brain lesions centred around the temporo parietal junction and superior temporal gyrus (Mort et al., 2003; Karnath et al., 2003) whereas number line bisection is thought to depend more on the ventrolateral prefrontal cortex i.e. rightward deviation along the mental number line is seen in neglect patients with (but not in those without) right prefrontal damage (Doricchi et al., 2005). On the other hand there is also evidence that attentional orientation along the mental number line is supported by a bilateral posterior parietal system, specifically the horizontal segments of the intraparietal sulcus (Dehaene et al., 2003); and rightward deviation along the number line occurs in normal subjects after TMS stimulation to the right PPC (Göbel et al., 2006). Kinsbourne's hemispheric rivalry theory (1977) suggests that the location of attention along both types of line is determined by the balance of competition between right and left hemispheres (right directing attention leftward and vice versa). Based on this evidence and taking into account models of crossed cerebellar-parietal interaction, a lateralised rTMS effect would be expected on number and physical line bisection error. For example, right cerebellar rTMS should disrupt the flow of information between it and left sided cortical areas (including prefrontal cortex and PPC), favouring the equivalent areas on the right, and thus shifting attention leftward and vice versa. In fact an effect was found only for number line bisection suggesting that cerebellar rTMS had a greater effect on cerebellar-frontal rather than cerebellar-parietal connections. The possible causes for this outcome are discussed below.

The effect of left cerebellar rTMS on number line bisection: how does this fit with pre-existing knowledge of cerebellar circuitry?

According to the model of crossed cerebello-cortical interaction described above, left cerebellar rTMS could have caused disruption to both left cerebellar and right cerebral processing, leading to the observed rightward bias. In anatomical terms the deep cerebellar nuclei (which have an overall inhibitory effect; see for example Daskalakis et al. 2004, their figure 8) are unlikely to have been within the effective stimulation range of our figure-of-eight rTMS coil. At a distance of 2.34 cm, the magnetic field generated by the coil would have already dropped to a third of its maximum value (Thielscher and Kammer, 2004) and in other studies of the effect of rTMS on the cerebellum, the surface of the cerebellar cortex was found to lie some 1.8-2.4cm below the scalp (see Brighina et al., 2006, Del Olmo et al., 2007), the cerebellar nuclei being deeper still. Therefore a cerebellar cortical rTMS effect seems more plausible, perhaps involving stellate and basket interneurons in the most superficial layer of the cerebellar cortex, and/or the deeper situated Purkinje cells (which have dendrites extending centripetally towards the cerebellar cortical surface). These elements exert differing effects over the deep cerebellar nuclei (Voogd and Glickstein, 1998, their figure 1) and thus the overall balance of cerebellar output could have been modulated by rTMS towards inhibition or excitation, both of which could in theory disrupt the finely tuned balance of intracerebral processing. Therefore it should be borne in mind that one cannot determine from this data set alone, whether inhibitory or excitatory drive from the cerebellum was responsible the observed effect on number line bisection.

The dissociation between the effects of left and right cerebellar rTMS for the number line task and the dissociation in effect between tasks

No effect was found on number line bisection after right cerebellar TMS (and putative left cerebral disruption) or on physical line bisection after TMS to either cerebellar hemisphere, outcomes which both require further explanation.

The lack of effect on number line bisection bias after right cerebellar TMS can be explained by the specialisation of the right cerebral (see Driver & Vuilleumier, 2001) and left cerebellar hemispheres (Stoodley and Schmahmann, 2008) for visuospatial functions. These could compensate for any right cerebellum-related disruption to spatial processing in the left hemisphere, and thus underlie the side-specific cerebellar rTMS effects found here.

According to a recent meta-analysis of neuroimaging studies (Stoodley and Schmahmann, 2008), non-motor processing within the cerebellum is localisable to distinct anatomical areas. For instance verbal working memory is represented laterally in the right and left hemispheres (at the junctions of lobule VI and Crus 1) whilst spatial judgement causes activations more medially and superiorly, predominantly in left lobule VI.

In this study the TMS coil was targeted at a scalp location which had been shown previously by Del Olmo et al. to lie laterally, over the centre of the cerebellar hemisphere (2007, their figure 1A) . As a consequence of choosing a single target location over each cerebellar hemisphere, the TMS technique may have been limited in its ability to disrupt the different components of this broad cerebellar network simultaneously. In particular, the areas associated with spatial processing (which lie superiorly within the cerebellum, more anteriorly within the skull, and thus further from the TMS coil than other areas) may have been disrupted less, hence the lack of any left-right error bias in the physical line bisection task. In contrast, performance in the number line task which includes judgment between two numerical values and has a working memory component (albeit spatial rather than verbal) (Doricchi et al., 2005), depends on areas of

cerebellar cortex which are not only more superficial but more widespread. These factors may have both contributed to the greater susceptibility of the number line task to cerebellar rTMS disruption. In theory it might be possible to target the deeper situated cerebellar areas that contribute more to spatial judgment, and thus obtain an effect on physical line bisection. However such a study would be difficult as the stimulation intensities required would be much higher, resulting in much less specific stimulation of structures closer to the coil (and perhaps intolerably powerful neck muscle twitches).

In terms of the model of cerebello-cortical interaction described above, the cerebellar TMS used here may have had its greatest effect on the cerebellar-frontal circuits which contribute to working memory (see Hayter et al., 2007), rather than cerebellar-parietal circuits.

7.5.4 Overall Assessment of the findings

This study re-enforces the involvement of the cerebellum in cognitive function; its role goes beyond global spatial processing to include a lateralised influence on spatial judgement. With cerebellar rTMS we achieved changes in number line bisection error (rightward shift of 0.34 digits per trial after left cerebellar stimulation) which are of a similar order to those found in previous studies in which rTMS was targeted directly at the parietal cortices (a rightward shift of 0.39 digits per trial after right posterior parietal stimulation, Göbel et al., 2006).

In attempting to explain the difference in effect between the tasks, one can speculate that the larger cerebellar and/or cerebral networks required for number line judgement renders this task more vulnerable to TMS disruption than the physical line bisection task, though given the single 'node' targeted here it is difficult to draw any definitive conclusions from the current data. Future studies which target specific regions of the cerebellum or which compare the additive effects of suitably timed paired-pulse TMS applied to the cerebellum and prefrontal areas, to that used over cerebellum and parietal areas, might help to clarify these issues.

Chapter Eight: General Discussion and Conclusions

This series of studies demonstrates the power and flexibility of TMS as a tool to interrogate cortical systems in the parietal lobe. TMS was used at different frequencies, first in an 'on-line' paradigm at 10hz to find an reliable locus of control of visuospatial awareness and then 'off-line' in various TBS paradigms which enlarged the duration of the neglect-like effects and the cortical area from which they could be elicited. Finally, 1Hz TMS was used over the cerebellum to demonstrate its role in the generation of the subjective midline in number space. Though of interest in their own right, the findings open up options for further study into the therapeutic potential of TMS in spatial neglect and also into the nature of neglect itself

8.1 Further Studies

8.1.1 Refinements to the hunting procedure

Future studies using variations on the new hunting paradigm introduced in Chapter 3 could study the timing of these TMS effects in more detail, either by using single TMS pulses at different points in time relative to the visual displays, and/or by jittering the 10Hz bursts relative to those stimuli. One further refinement to the paradigm for future work would be to incorporate trials without TMS as a within-session baseline and thus fully integrate the no-TMS condition in terms of block performance-order. The 9 participants tested were naïve to the change in gap-present proportions (from 50 % to 90%) when moving from the initial 'staircase' thresholding stage to the hunting procedure of Experiment 1. This may be an important consideration for future studies utilising a similar procedure, as if participants were cognizant of the change, a problematic liberal shift in their response criteria might occur.

8.1.2 Further clinical TBS studies

In the clinical setting the simplest next step would be to confirm the SDT model of spatial neglect in a larger group of stroke patients with right parietal damage, and then try two strategies to alleviate their deficits. One would follow on from the studies in Chapters 4 and 6, using TBS over the intact hemisphere to restore hemispheric balance. The other, perhaps more interesting strategy would involve targeting adjacent intact cortical areas, with iTBS in the hope that these might take on a larger role in visuospatial processing and thus supplement neighbouring damaged areas. Such a study could, with the help of neuro-navigation and carefully reconstructed cortical surface maps, benefit those patients with infarcts involving the territory of the MCA and who have relative sparing of more medial, ACA-supplied cortex.

8.1.3 The disengagement of d-prime from criterion

For the patient with neglect described in Chapter 6, criterion was highest (most conservative) under conditions where d' was simultaneously at its lowest i.e. in the left hemifield with a contralateral competitor present. This echoes previous studies of neglect in the visual and tactile domains (Ricci et al., 2004, 2005; Vishvani et al. 2000; Olson et al., 2003). However the exact nature of the relationship between d' and c in spatial neglect remains unexplored i.e. how c might change as the detection task gets more difficult. An approximate model of this relationship was constructed by re-analysing the data from Chapter 3 (that used to construct figure 3.5). This data showed how, in each subject, LVF field d' drops with increasing levels of TMS disruption to healthy right PPC. By changing the x-axis from 'TMS intensity' to 'criterion' (and averaging across subjects) it can be shown that for targets presented in the left visual, subjects' response bias becomes more conservative as TMS intensity increases and target detection (d') is increasingly impaired (figure 8.1 below).

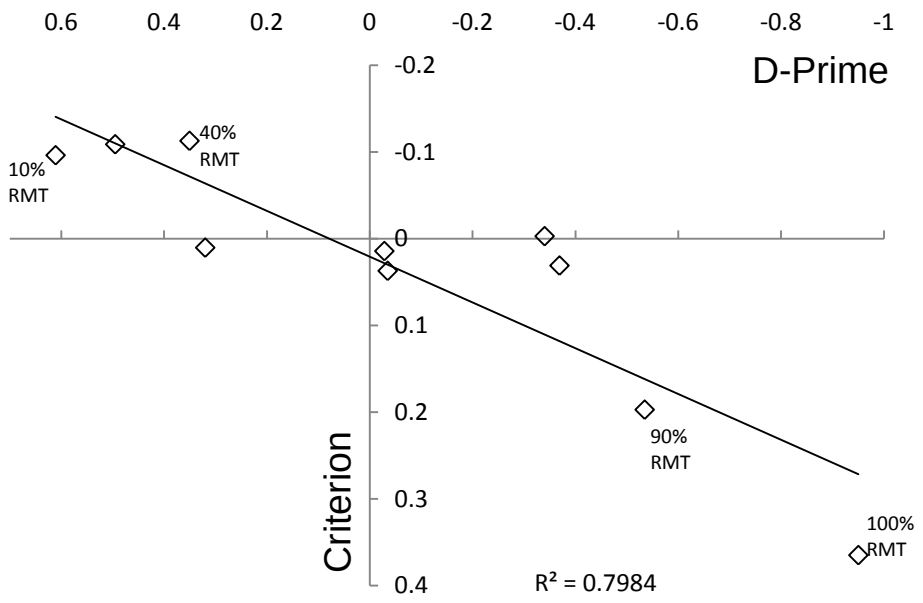

Figure 8.1. A graph showing the relationship between sensitivity (d-prime, x-axis) and response bias (criterion, y-axis) for left visual field targets, at varying levels of on-line-rTMS disruption over right PPC, in healthy subjects. The values shown are normalised to sham TMS stimulation values and are the mean of 8 normal subjects. Each data point represents one of ten TMS intensity levels used (10% of RMT, 20%RMT, 30% RMT and so on up to 100% RMT) and to illustrate this, selected data points are labelled with their corresponding TMS intensity. A significant correlation was found between the two variables, $r(8)=0.89$, $p<0.01$.

As TMS intensity increases, an inverse relationship between d-prime and criterion emerges, i.e. as performance declines subjects are more conservative in reporting the presence or absence of targets. This may be a general strategy of healthy subjects to minimise false-alarm errors in the face of increasing task difficulty (and it so happens that this was caused by right PPC TMS disruption). On the other hand this robust linkage between criterion and d-prime (that should not normally exist according to the tenets of signal detection theory; Green and Swets, 1966) may represent a TMS 'virtual-lesion' effect and thus may echo an as yet unexplored component of the (clinical) neglect syndrome.

The relationship between d' and c should differ between healthy individuals and those with spatial neglect as:

a) Error minimisation strategies would require insight by the subject into their left hemifield detection ability, insight which patients with unilateral neglect and left sided inattention are likely to lack, or alternatively,
b) Left sided inattention may in part result from a pathological *exaggeration* of the d-prime/criterion association described above.

This leads on to some very interesting questions: does part of the clinical phenotype of neglect result from an extreme bias towards under-report for objects on the left side of space? Could this bias be amenable to cognitive or TMS intervention? As an initial step towards answering these questions, the bihemifield detection paradigm could be used in a small number of carefully selected patients (able to sit upright in a head and chin rest, able to press a key pad or to vocalise their responses, and non-hemianopic), with age-matched healthy controls. Rather than using rTMS, the task difficulty could be varied simply by using increasingly brief target presentation durations or decreasing target/background contrast. If a pathological relationship between d' and c was found it could be normalised by using the TBS techniques described in Chapters 4 and 5.

8.2 Conclusions

TMS in its various forms can be combined successfully with SDT to provide new insights into normal parietal cortical processing and its main pathological correlate, spatial neglect. In particular:

1) A systematic new way to identify an effective right-parietal site for inducing specific effects on visuospatial sensitivity now exists, with the effective TMS intensity now also being guided in a principled manner by that 'anchor' for TMS researchers, the RMT.

2) The cTBS protocol is rapid (20-40 seconds), can be given at a comfortably low intensity (80%AMT here), and yet produces reliable impacts on visual detection sensitivity in neurologically intact participants that show some of the hallmarks of specific aspects of clinical neglect and extinction. cTBS may thus provide a good model for studying the neural basis of these disorders, and given the're-balancing' results of Chapters 4 and 6, an approach of potential promise that may contribute to the rehabilitation of neglect and extinction when applied over the intact hemisphere in clinical patients.

3) 'Online', 10Hz Transcranial Magnetic Stimulation is a powerful, flexible tool for exploring previously unmapped areas of cortical function and long-acting, excitatory iTBS alters parietal maps' topography in a way which may one-day prove useful in patients with sub-total parietal damage. This technique may ultimately extend therapeutic cortical plasticity, used extensively after motor stroke, into the domain of attentional disorders such as unilateral spatial neglect.

4) In selected patients, signal detection measures demonstrate extinction in such a way that disentangles the patient's performance from their response bias. This hints at a

component of neglect which arises from the patient's own internal uncertainty with regard to their (left-sided) target-detection ability.

5) Performance in the number line bisection task is susceptible to disruption by cerebellar rTMS. This confirms cerebellar involvement in the processing of left-right spatial information and the generation of a subjective midline in 'number' space, a finding which may have future therapeutic implications for patients with 'imaginal' neglect.

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