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# The contribution of imbalance between interhemispheric parietal – motor facilitation and visual neglect in healthy adults.

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## Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

## Abstract

Spatial neglect is a common disorder following stroke, characterised by a failure to acknowledge stimuli in contralesional space. One neurophysiological model to explain neglect is based on an imbalance of interhemispheric inhibition (IHI); however, evidence is emerging that the IHI imbalance model may not explain neglect in all cases. The aim of this study was to investigate the IHI imbalance model of neglect in healthy adults, using paired-pulse transcranial magnetic stimulation (TMS) to probe excitability of projections from the posterior parietal cortex (PPC) to the contralateral primary motor cortex (M1) bilaterally.

Motor-evoked potentials (MEPs) were recorded from the first dorsal interossei muscle of each hand. The excitability of the PPC to M1 projections was determined by MEP facilitation, determined as a ratio of conditioned to non-conditioned MEP amplitude. A laterality index (LI) reflecting the balance of excitability between the two hemispheres was then calculated. A temporal order judgement task and a landmark task assessed visual attention. To evoke a visual neglect-like response in healthy adults, continuous theta-burst stimulation was used to transiently suppress right parietal cortex activity. The effect on laterality and visual tasks was assessed, along with associations between baseline and post-stimulation measures.

Stimulation had conflicting results on the LI, with most participants demonstrating a non-significant effect in the negative direction, with no decrement in the temporal order judgement or landmark task. The negative shift in LI reflected a small rightward shift in hemispheric balance. Correlation analysis suggested a strong association between laterality direction and degree of facilitation of left PPC to right M1 following stimulation ($r = 0.902$).

The findings indicate that there was relative balance between the cortices at baseline, but that right PPC suppression did not evoke left PPC facilitation in most participants, contrary to

predictions of the IHI imbalance model. The degree of left M1 facilitation prior to stimulation may predict an individual's response to continuous theta-burst stimulation of right PPC. (Killington, Barr, Loetscher, & Bradnam, 2016)

# Introduction

## Brain anatomy for visual attention

The traditional view is that visual attention is controlled by two anatomically and functionally distinct neural networks: the dorsal attentional network and the ventral attentional network (Vossel, Geng, & Fink, 2014). The dorsal attentional network is a bilateral fronto-parietal network, centred on the posterior parietal cortex (PPC) and frontal eye field (Figure 1). The PPC is located posterior to the pre-central sulcus and anterior to the parieto-occipital sulcus, and is divided into the superior and inferior parietal lobe by the intraparietal sulcus (Sack, 2009). The dorsal attentional network has been described as a top-down driven system, responsible for directing attention towards extrapersonal space and identifying visual stimuli in contralateral space (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; He et al., 2007; Lunven & Bartolomeo, 2016). In basic functional terms, the dorsal attentional network is referred to as the "where" visual processing stream, as it spatially codes the location of a stimulus (Sack, 2009). In contrast, the ventral attentional network is lateralised to the right hemisphere and comprises the ventral frontal cortex and tempo-parietal junction (Figure 1). It is described as a bottom-up network, responsible for detecting salient unexpected visual stimuli in either hemifield (He et al., 2007; Lunven & Bartolomeo, 2016). Functionally, the ventral processing stream is referred to as the "what" visual processing stream, as it is responsible for object identification (Sack, 2009).

**Figure 1. Schematic representation of the components of the dorsal and ventral attention networks has been removed due to copyright restrictions.**

Whilst both the ventral and dorsal attentional networks function separately, they also interact by exerting suppressive influences over each other in order to direct visual attention. During a top-down driven visual search, lesion studies have demonstrated that activity in ventral areas such as the tempo-parietal junction are suppressed by inputs from the frontal eye field and activity in the intraparietal sulcus of the dorsal attentional network. Conversely, in response to detection of unexpected stimuli, the tempo-parietal junction of the ventral attentional network acts as a circuit breaker, inhibiting activity of the dorsal attentional network to direct attention towards the salient stimuli (Sack, 2009).

Alternative theories regarding the function of the two networks have also been described. One popular theory developed by Goodale and Milner suggests that the difference between the dorsal and ventral networks is not related to the input they receive, but how the information is used. This theory distinguishes the two networks into a ventral “vision for perception” stream and a dorsal “vision for action” stream (Goodale & Milner, 1992; Sack, 2009). It proposes that the dorsal attentional network acts as a sensorimotor interface for

visually guided movements, such as guided reach and grasp of an object, whilst the ventral attentional network is involved primarily in perception of space (Goodale & Milner, 1992; Jackson & Husain, 2006). Brain lesion studies have partially supported this theory, with patients suffering lesions in the superior parietal lobe of the PPC experiencing impairments in visuomotor control. However, studies investigating the role of the inferior parietal lobe of the PPC do not support this theory. Patients with lesions here demonstrate difficulty detecting salient stimuli and control of sustained visual attention. This difference in function between the superior and inferior parietal lobes suggests the superior parietal lobe is a dorsal-to-dorsal stream, involved in the control of actions. In contrast, the inferior parietal lobe is a ventral-to-dorsal stream, involved with higher-level perception of space and understanding of actions (Sack, 2009).

In basic functional terms, the PPC is activated by heterogeneous stimuli and tasks; however, it is considered to have a number of other functional roles in various higher-level cognitive and perceptual processes. Brain lesion studies suggest the PPC is made up of multiple spatial representations, each linked with a different action or region of space. The PPC plays a crucial role in spatial cognition, which refers to the ability to process, analyse and integrate multisensory information (Colby & Goldberg, 1999). It is a crucial element of numerous higher-level cognitive abilities, such as spatial orientation, object recognition, abstract reasoning and memory, and is essential for interaction with the environment (Sack, 2009).

The dorsal and ventral attentional networks are connected by white matter tracks called the superior longitudinal fasciculi (SLF). There are three branches of the SLF: SLF1, 2 and 3 (Figure 2). SLF1 is the most dorsal branch, projecting from the percuneus to the anterior cingulate gyri, and connects brain regions within the dorsal attentional network. The

intermediate branch, SLF2, projects from the anterior intraparietal sulcus to the superior and middle frontal gyrus, and connects frontal regions of the dorsal attentional network with parietal regions of the ventral attention network. The ventral branch, SLF 3, projects from the tempo-parietal junction to the inferior frontal gyrus, and connects brain regions in the ventral attention network (Lunven & Bartolomeo, 2016).

**Figure 2. Diagram representing the superior longitudinal fasciculi 1, 2 and 3 has been removed due to copyright restrictions.**

## Transcranial magnetic stimulation

Transcranial magnetic stimuli (TMS) is a form of non-invasive brain stimulation (NBS) used to deliver magnetic stimuli to the brain through the scalp. It can be used to investigate normal brain anatomy and function of different systems, such as the visual attention networks, and can investigate the pathophysiology and functional impact of a brain lesion or disease. TMS was developed in 1985, following initial experiments that used transcranial electrical stimulation (TES) to stimulate neurons in the primary motor cortex (M1) by placing two electrodes on the scalp connected to a high capacity condenser (Merton & Morton, 1980). A visible twitch in the corresponding muscle was observed upon M1 stimulation, and electromyogram (EMG) electrodes were used to record the amplitude of muscle contraction

(Merton & Morton, 1980). While TES was able to stimulate neurons in the motor cortex, it was very uncomfortable as it caused simultaneous contraction of scalp muscles. In contrast, TMS was considered a safe and relatively comfortable form of NBS, and it therefore superseded the use of TES by human neurophysiologists (Klomjai, Katz, & Lackmy-Vallée, 2015).

There are a number of different coil orientations and sizes used to deliver TMS, including figure-of-eight coils, circular coils and double-cone coils. The figure-of-eight coil provides the most focal stimulation at the point where the two coils meet. The circular coil provides a more widespread superficial stimulation, whilst the double-cone coil is used for stimulating deeper cortical structures such as lower limb corticomotor neurons (Klomjai et al., 2015). During stimulation, a high-current pulse is evoked by the coil, producing a magnetic field that travels perpendicularly to the coil and penetrates the scalp and skull to reach brain tissue. As the magnetic current changes rapidly, circular electrical currents (eddy currents) travelling perpendicularly to the magnetic current are induced in the brain. The electrical currents depolarise nerve axons, transynaptically activating corticomotor neurons of local cortical networks (Hallett, 2000; Klomjai et al., 2015; Kobayashi & Pascual-Leone, 2003). TMS can deliver either a monophasic pulse, used commonly for single-pulse TMS, or a biphasic pulse, used primarily for repetitive TMS (rTMS) (Klomjai et al., 2015). Depending on the direction of current evoked in the brain, TMS can activate pyramidal cells directly at the axon hillock to evoke a direct wave (D-wave) of descending neural activity, or indirectly through activating cortical interneurons to cause indirect waves (I-waves) (Day et al., 1989; Kernell & Chien-Ping, 1967; Klomjai et al., 2015; Kobayashi & Pascual-Leone, 2003). There are three different types of I-waves (1,2,3) characterised by whether they occur early, intermediate or later following stimulation, and they are thought to represent activation of interneurons with increasing distance from the pyramidal cell (Klomjai et al., 2015). With increasing intensity

of TMS, the I3 wave appears to be recruited first, followed by I2 and then I1 (Klomjai et al., 2015). In general, fast-conducting axons (> 75 m/s) have a lower threshold for D-waves, and slow-conducting axons (< 55 m/s) have a lower threshold for I-waves (Kobayashi & Pascual-Leone, 2003). However, TMS appears to preferentially activate I-waves rather than D-waves (Kobayashi & Pascual-Leone, 2003). Due to grey matter impedance of the magnetic current, TMS is only strong enough to stimulate superficial structures in the cortex. Hence, even at high intensity, TMS is unable to stimulate subcortical neurons (Klomjai et al., 2015; Kobayashi & Pascual-Leone, 2003).

## Clinical/ research applications of TMS

### Single-pulse TMS

Single-pulse TMS can be used to activate corticospinal neurons by stimulating pyramidal cells and tracks in the motor cortex that project onto spinal motoneurons (Figure 3) (Klomjai et al., 2015). The activity in the corticospinal tract can be measured by placing EMG surface electrodes over the muscle belly of corresponding muscles and measuring peak-to-peak amplitude responses, referred to as a motor-evoked potential (MEP) (Klomjai et al., 2015; Kobayashi & Pascual-Leone, 2003). MEP is a measure of corticomotor and spinal excitability and corticospinal tract integrity (Klomjai et al., 2015; Kobayashi & Pascual-Leone, 2003). MEP amplitude can be increased or decreased through the application of excitatory or inhibitory neuronal modulators. Suppression is caused by sodium channel deactivation, which reduces excitability of I-waves, whilst MEP excitation occurs through the application of dopamine agonists (Klomjai et al., 2015). These mechanisms influence membrane excitability of the corticomotor cell, rendering it more or less excitable (or moving it closer or further away from firing threshold). The alteration in cell excitability will be reflected in the amplitude of the MEP.

The presence or absence of a MEP after a neurological event, such as a stroke, provides valuable information about corticospinal integrity and can help therapists predict the likelihood of recovery of motor function (Stinear, Barber, Petoe, Anwar, & Byblow, 2012). The ability to evoke a MEP in an affected upper limb 72 hours after stroke corresponded with a notable return in upper limb function. In contrast, the absence of a MEP corresponded with limited or no functional recovery of the affected upper limb (Stinear et al., 2012). TMS can be used to measure central motor conduction time, which is useful in the assessment of demyelinating diseases, such as multiple sclerosis, or diseases affecting the neuromuscular junction, such as motor neurone disease. In these conditions, central motor conduction time can assist in diagnosis and also track progress of the disease (Kobayashi & Pascual-Leone, 2003).

**Figure 3. Diagrammatic representation of TMS being applied over the motor cortex to stimulate corticospinal neurons and activate the target muscle has been removed due to copyright restrictions.**

## Motor threshold

MEPs can be used to determine resting and active thresholds of motor neurons, providing a measure of membrane excitability of corticospinal neurons and interneurons projecting onto these neurons, and also spinal motoneuron excitability (Kobayashi & Pascual-Leone, 2003). Resting motor threshold (RMT) refers to the minimum stimulus intensity that elicits a 0.05mV MEP in four out of eight trials when the subject keeps their hand muscles relaxed. Active motor threshold (AMT) refers to the minimum stimulus intensity that elicits a 0.10mV MEP in four out of eight trials during contraction of the selected test muscle (Rossini et al.,

1994). AMT is less variable and usually lower than RMT, as spinal motoneurons are depolarised by the muscle contraction.

TMS can also be used for functional mapping of cortical regions and measuring long-term potentiation of the motor cortex. Focal TMS can be used to perform detailed mapping of muscle representations in motor cortical areas, and can also demonstrate cortical plasticity resulting from injury or changes in behaviour. Variation to a cortical map, such as the expansion of a cortical representation, reduction in motor threshold or increased MEP size at a given stimulation intensity can all represent neuroplastic changes in the motor cortex (Hallett, 2000).

## Paired-pulse TMS

Paired-pulse TMS provides information about inhibitory and excitatory intracortical circuits in the brain. The technique involves combining a subthreshold or suprathreshold conditioning stimulus with a suprathreshold test stimulus, which will either excite or inhibit the test stimulus depending on the intensity of the conditioning stimulus and the interstimulus interval (ISI) chosen (Klomjai et al., 2015; Kobayashi & Pascual-Leone, 2003). Paired-pulse TMS can be delivered to the same cortical hotspot using one coil, or to two separate cortical regions using a twin-coil approach, to study interactions between motor and non-motor areas. It can be used to develop a paired-pulse stimulus-response curve, which has been used to study psychiatric and neurological disorders such as schizophrenia, Parkinson's disease and dystonia (Klomjai et al., 2015).

In the study of visual attention, paired-pulse TMS has demonstrated strong cortical-cortical connections between the PPC and the M1. These regions are connected through SLF white matter fibres, and are thought to be crucial for planning of movements in space and

integration of visuomotor control (Koch et al., 2007). Facilitatory projections between the right PPC and ipsilateral M1 have been observed at ISIs of 4 and 15 m/s at a conditioning intensity of 90% RMT. Facilitatory projections between the left PPC and ipsilateral M1 have been observed at ISIs of 4 and 6 m/s at a conditioning intensity of 90% RMT (Koch et al., 2007). When stimulating this pathway using TMS, the conditioning stimulus is first delivered to the PPC and the test stimulus subsequently delivered to the contralateral M1 4–6 ms later (Koch et al., 2007).

Paired-pulse TMS can also be used to probe interhemispheric connectivity and transcallosal inhibition between the two hemispheres (Kobayashi & Pascual-Leone, 2003; Koch et al., 2011; Koch et al., 2009). Interhemispheric connectivity of facilitatory and inhibitory projections between the PPC and contralateral M1 have been examined using paired-pulse TMS, with different effects demonstrated depending on the location of the PPC test stimulus (Koch et al., 2009). Stimulation at the anterior intraparietal sulcus (aIPS) activates an inhibitory projection, whilst stimulating the caudal intraparietal sulcus (cIPS) activates an excitatory projection. The facilitatory projection between the right PPC and left M1 was demonstrated at ISIs of 6, 8 and 12 ms and at a conditioning intensity of 90% RMT. In contrast, facilitation between the left PPC and right M1 was demonstrated at ISIs of 6 and 12 ms with a conditioning intensity of 110% RMT (Koch et al., 2009). The lower threshold demonstrated in the right hemisphere may be related to right hemisphere dominance in visuospatial attention (Koch et al., 2009). A novel three-coil technique has also been trialled to measure transcallosal interactions between the PPCs, demonstrating that the right but not the left PPC exerts strong transcallosal inhibition over the contralateral PPC (Koch et al., 2011). Paired-pulse techniques provide valuable information about the connectivity of

intrahemispheric and interhemispheric circuits of the PPC, which has increased the understanding of visual attention in both the healthy and stroke-affected brain.

## Repetitive TMS (Neuromodulation)

A train of TMS pulses applied to a brain area at a specific frequency and intensity is referred to as repetitive TMS (rTMS) (Kobayashi & Pascual-Leone, 2003). The train can be applied to both motor and non-motor areas, and can temporarily modulate cortical activity depending on the frequency and intensity used; this is referred to as neuromodulation. Although responses between individuals vary, it is generally accepted that frequencies of 1Hz suppress cortical excitability whilst higher frequencies (greater than 5 Hz) increase cortical excitability (Chen et al., 1997; Pascual-Leone et al., 1998). Changes in cortical excitability have been demonstrated for up to 90 min. The duration of after-effects is related to the length of the rTMS train, with longer trains inducing longer-lasting modulation of cortical excitability (Klomjai et al., 2015; Kobayashi & Pascual-Leone, 2003). Although the exact mechanisms underlying the cortical modulation are unknown, it is believed to occur as a result of long-term potentiation and long-term depression-like mechanisms (Klomjai et al., 2015; Pascual-Leone et al., 1998). On a molecular level, rTMS appears to modulate neurotransmitters such as N-methyl-D-aspartate, resulting in long-term potentiation through reduced threshold of post-synaptic neurons (Cooke & Bliss, 2006; Klomjai et al., 2015; Kobayashi & Pascual-Leone, 2003). Inhibitory rTMS may result in long-term depression via increasing the activity of inhibitory interneurons at the site of stimulation, or through reducing the synaptic efficiency of stimulated neurons (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Lee et al., 2003).

Specific rTMS protocols, such as theta-burst stimulation (TBS), have been developed to reduce induction time and increase response duration. TBS is a patterned form of repetitive TMS based on the brain's theta rhythm occurring in the hippocampus. It consists of bursts of

high-frequency stimulation, with intensity usually set between 80 and 90% of RMT (Huang et al., 2005). There are different paradigms of stimulation which produce different effects, with intermittent TBS (iTBS) increasing cortical excitability and continuous TBS (cTBS) supressing cortical excitability (Huang et al., 2005; Klomjai et al., 2015). Both paradigms use a TBS pattern in which three pulses of stimulation are delivered at 50Hz with bursts repeated every 200m/s. In the iTBS paradigm, 600 pulses are delivered using 2-sec trains of TBS, repeated every 10 sec for a total of 190 sec. In the cTBS paradigm, 600 pulses are delivered via a 40-sec uninterrupted train of TBS (Huang et al., 2005; Klomjai et al., 2015). While a single train of TBS consisting of 600 pulses can alter cortical excitability for up to 60 min, two spaced trains has been demonstrated to lengthen effects for up to 2 hours post-stimulation, which has significant implications for clinical applications (Goldsworthy, Pitcher, Ridding, 2012; Huang et al., 2005). For research purposes, sham rTMS or TBS has also been developed, and utilises the same protocol as real rTMS or TBS; however, a sham coil is used where no current is applied to the brain (Cazzoli et al., 2012).

Both rTMS and TBS have been used extensively in stroke research to model and study the functional and neurophysiological effects of a virtual lesion on different brain regions. In the study of visual attention, they have been used frequently in the healthy brain to transiently modulate activity in the right or left PPC to induce a visual neglect-like behavioural response (Bagattini, Mele, Brignani, & Savazzi, 2015; Cazzoli, Wurtz, Muri, Hess, & Nyffeler, 2009; Nyffeler et al., 2008; Pascual-Leone et al., 1994). This use of rTMS and TBS has increased understanding of the brain pathophysiology contributing to neglect and assisted with development of novel interventions aimed at addressing the neurophysiological mechanisms involved.

## Pathophysiology of stoke

Stroke is a clinically defined syndrome of vascular origin, characterised by a rapid loss of focal cerebral function, with symptoms lasting longer than 24 hours or leading to death (Khaw, 1996; Warlow, 1998). Stroke is classified as being of either ischaemic or haemorrhagic origin, with the pathophysiology determined through a combination of clinical assessment and neuroimaging, using either computed tomography or magnetic resonance imaging (MRI). Ischaemic stroke accounts for approximately 80% of total stroke presentations, and is either due to a cardio-embolism occluding blood flow in an artery, or small vessel disease occluding smaller subcortical arteries, known as a lacunar infarct (Khaw, 1996; Warlow, 1998). Common risk factors for ischaemic stroke include atrial fibrillation, hypercholesterolemia and carotid artery stenosis. Haemorrhagic stroke, also referred to as intracerebral haemorrhage, accounts for around 20% of stroke presentations (Donnan, Fisher, Macleod, & Davis, 2008). The most common cause is hypertension, resulting in the development and rupture of an aneurysm, with the second-most common cause being haemorrhage into a previous infarct. Other reasons for haemorrhage include intracranial vascular malformations or cerebral amyloid angiopathies (Donnan et al., 2008).

## Stroke epidemiology

Stroke accounts for approximately 9% of deaths worldwide, the second-highest behind ischaemic heart disease, with mortality rates of 50–100 per 1,000,000 people per year in developed countries (Donnan et al., 2008). There has been a consistent downward trend in mortality rates each year, which has been attributed to improved identification and management of risk factors, such as hypertension, diabetes and a reduction in smoking rates (Donnan et al., 2008). The overall incidence of stroke varies between populations, ranging from 240 per 100,000 in France to up to 600 per 100,000 in Russia, with the incidence in western society trending significantly downward (Donnan et al., 2008; Warlow, 1998).

## Physical limitations after stroke

The physical limitations and subsequent recovery of function after stroke are varied, ranging from complete recovery within 24 hours of the onset of symptoms, to partial recovery of function, to limited recovery of function resulting in significant disability (Waklow, 1998). It is estimated that one-third of stroke survivors rely on regular assistance to perform activities of daily living in the community, with significant variation between individuals in the type and level of assistance required (Warlow, 1998). Health-related costs combined with equipment and services essential for stroke survivors to live in the community come at a considerable cost to society. In Australia alone, an estimated $1.3 billion is spent on the management of stroke annually. Due to the ageing population, and as mortality rates are declining faster than incidence rates, these costs are set to continue to rise (Donnan et al., 2008).

## Impairments after stroke

Different impairments observed after stroke can affect function. Common deficits affecting the motor system include weakness, altered tone, impaired co-ordination and dexterity, impaired balance and gait dysfunction. Common deficits affecting the sensory system include numbness, impaired light touch or proprioception, impairment to the vestibular system and perceptual impairments, including visual field loss, neglect and visual inattention (Buxbaum et al., 2004). Common cognitive impairments include memory impairment, delayed or slowed cognitive processing and impaired executive cognitive function (Duncan, 1994). The level of disability experienced after stroke is associated with the type, number and severity of impairments (Duncan, 1994). Perceptual disorders affecting the visual system, such as spatial neglect, have a particularly negative impact on recovery of function and are associated with longer-term dependence and increased level of disability (Di Monaco et al., 2011; Duncan, 1994).

## Spatial neglect overview

Spatial neglect is a severe neurological disorder, characterised by a failure to attend and respond to stimuli in the contralesional side of space. The spatial bias co-exists with deficits in attentional capacity and impaired vigilance (Corbetta et al., 2005; Milner & McIntosh, 2005). Neglect occurs in 25–30% of people following stroke, with more than 90% of sufferers sustaining damage to the right hemisphere (Appelros, Karlsson, Seiger, & Nydevik, 2002; Pedersen, Jørgensen, Nakayama, Raaschou, & Olsen, 1997). It has been shown to negatively correlate with functional measures and patient outcomes, with severe neglect being a poor prognostic indicator for functional recovery (Di Monaco et al., 2011).

## Subtypes of spatial neglect

Neglect can be classified as perceptual, affecting attention and perception, or motor, affecting actions and movement. Perceptual neglect may affect the perception and response to visual stimuli in the contralesional hemifield, whilst motor neglect may result in directional hypokinesia, where a person has difficulty moving towards or within contralesional space (Buxbaum et al., 2004). Studies suggest that motor neglect is associated with damage to the frontal lobe, whilst perceptual neglect arises following lesion in the parietal lobe (Bisiach, Ricci, Lualdi, & Colombo, 1998; Buxbaum et al., 2004; Ghacibeh, Shenker, Winter, Triggs, & Heilman, 2007). Neglect is further classified into either personal (affecting a person's body awareness), peripersonal (affecting close space within arm's reach) or extrapersonal (affecting space further than arm's reach away) (Buxbaum et al., 2004). People may present with one or more subtypes of neglect, with greater disability more common after right than left hemisphere lesions. Not all deficits from neglect, however, are lateralised, and neglect can often affect visual attention in both hemifields (Buxbaum et al., 2004). Anosognosia, a lack of awareness of a visual deficit, is also more common following right hemisphere stroke. It has been reported in up to 70% of patients with neglect, but generally resolves

spontaneously after a short time (Gialanella, Monguzzi, Santoro, & Rocchi, 2005). The presence of anogsognosia in patients with neglect has been shown to be a negative prognostic indicator, resulting in prolonged hospital admission, less functional recovery and a reduced chance of returning to independent community living (Buxbaum et al., 2004; Gialanella et al., 2005). Visual extinction is another impairment of visual attention, commonly occurring following damage to the PPC. It refers to a failure to respond to a visual stimulus in the contralesional hemifield, when a simultaneous stimulus is presented in the ipsilesional hemifield. Although visual extinction is a distinct phenomenon, it is caused by an ipsilesional shift in visual bias and reduced visual representation in contralesional space, which is similar to the behavioural change observed in visual neglect (Oliveri et al., 1999).

## Anatomy and pathophysiology of spatial neglect

Neglect is most common following lesion to the tempo-parietal junction, ventral frontal cortex, inferior parietal lobule, superior temporal cortex or subcortical nuclei (Corbetta et al., 2005). Brain lesion anatomy shows that neglect often results from structural damage to the ventral attentional network, whilst the dorsal attentional network is commonly spared. Although structurally undamaged, the dorsal attentional network demonstrates a breakdown in functional connectivity following damage to the ventral attentional network. This results in widespread dysfunction to fronto-parietal networks of both dorsal and ventral attentional networks in patients with neglect (Corbetta et al., 2005). Imaging studies have demonstrated this altered activation pattern in the dorsal attentional network in acute neglect patients (Corbetta et al., 2005). During a cued visual task, patients showed weak or no task-related activity in the superior parietal lobe and intraparietal sulcus of the PPC of the affected right hemisphere, despite these regions being structurally intact. In contrast, there was increased activation of the posterior parietal and sensory cortex in the left hemisphere (Corbetta et al., 2005). In chronic stroke, imaging revealed reactivation of activity of the right PPC and

reduction in activity of the left PPC. This subsequent recovery of normal activation in the PPC and restoration of function to fronto-parietal networks results in a resolution of the attentional deficits observed in patients with neglect (Corbetta et al., 2005).

## Hemispheric rivalry model of neglect

The hemispheric rivalry model (also known as the IHI imbalance model) is one theory of neglect that proposes that visual perception and internal representation are controlled by reciprocally interactive, inhibitory, opponent processors between the two hemispheres (Kinsbourne, 1976). Both the right and left hemispheres direct attention to the contralateral visual field, with the interaction between the two opposing processors determining the direction of visual attention along a lateral left-right axis (Kinsbourne, 1976, 1993, 1994). Attention is shifted along the lateral plane in a graduated fashion, with the gradient of attention moving leftward under right brain influence and rightward under left brain influence (Kinsbourne, 1976, 1994). Lateral shifts in attention can occur across all sensory modalities, such as somatosensory, imagery, memory, and visuomotor control (Kinsbourne, 1994). Kinsbourne proposed that the opponent processors between the two hemispheres were likely transmitted through brainstem centres; however, a more recent study has suggested that the interhemispheric connectivity is transmitted through the posterior portion of the corpus callosum (Koch et al., 2011). A lesion to one hemisphere causes an imbalance in opponent processors, resulting in dis-inhibition and over-excitability in the undamaged hemisphere. This causes bias of visual attention towards the hemifield controlled by the unlesioned hemisphere, referred to as hemispatial visual neglect (Kinsbourne, 1976, 1993).

Kinsbourne's theory also explained the increased incidence of left compared to right neglect, by proposing that humans had a greater rightward orienting tendency. However, the theory of

rightward orienting bias has since been disproved. More recent studies demonstrated that humans actually have a leftward visual bias, or pseudo-neglect, due to the lateralisation of visuospatial function in the right hemisphere (De Schotten et al., 2011). Brain activation patterns shown by imaging studies strongly support lateralisation of visuospatial function, and correlations have been demonstrated between the lateralisation of integrity of SLF2 fibres in the right hemisphere with leftward visual bias in healthy individuals (Corbetta et al., 2005; De Schotten et al., 2011; He et al., 2007). A current explanation for the greater incidence of left neglect after stroke is that the right hemisphere has a global role, directing visual attention towards both hemifields, while the left hemisphere only directs attention to the contralateral hemifield. The right PPC can compensate for a left hemisphere lesion; however, the left PPC is unable to compensate for a lesion in the right hemisphere (Muri et al., 2002).

Imaging studies in stroke patients with neglect have investigated the IHI imbalance model. One study supporting the model used functional MRI (fMRI) to analyse activation patterns of neglect patients during a visuospatial task, comparing differences between the acute and chronic phases after stroke (Corbetta et al., 2005). The authors found that in the acute phase, participants demonstrated increased excitability of the left PPC, which correlated with deficits in visuospatial attention. In the chronic phase, they found the imbalance had resolved, correlating with improvement in visuospatial attention. These findings appear to support an IHI imbalance model for hemispatial neglect; however, the study was undertaken in patients approximately 4 weeks after their stroke. The changes observed in cortical activation may therefore not directly relate to a release of hemispheric inhibition and could be due to cortical re-organisation occurring over time. A more recent trial also used fMRI to determine if acute stroke patients with neglect (average 53 hours post stroke) demonstrated hyper-activation of the left PPC, as observed previously in subacute and chronic neglect patients (Umarova et al.,

2011). The authors compared imaging data between patients following right hemisphere stroke who had neglect or visual extinction with patients without neglect and with healthy controls. Interestingly, they found a hyper-activation of the left parietal lobe in all patients, regardless of whether they experienced neglect (Umarova et al., 2011). Instead, dysfunction in the right parietal and lateral occipital cortex was better associated with neglect than left parietal activity, which would oppose the IHI imbalance model. The authors suggested that left parietal hyper-excitability was a consequence of severe structural damage to the right hemisphere, but did not cause the attentional deficits (Umarova et al., 2011).

## TMS investigatations of the IHI imbalance model

A number of interventional studies in subacute and chronic stroke patients have supported the IHI imbalance model. Trials have used either rTMS or cTBS to suppress the "over-excitability" of the left PPC after right hemisphere lesion and demonstrated significant improvements in behavioural measures of visual neglect (Brighina et al., 2003; Cazzoli et al., 2012; Koch et al., 2008; Koch, Veniero, & Caltagirone, 2013). One of these trials aimed to directly measure the hyper-excitability of the left PPC in subacute stroke patients with neglect following a right hemisphere lesion (Koch et al., 2008). They used paired-pulse TMS to measure cortical excitability of parieto-motor circuits in the left hemisphere following stoke, and demonstrated increased excitability of left PPC to M1 projections in subjects experiencing neglect associated with a right parietal lesion (Koch et al., 2008). This study also demonstrated correlation between the degree of pathological over-excitability and the number of left-sided omissions on the line cancellation and letter cancellation tests, where more severe neglect was associated with greater excitability of left PPC to M1 projections. Participants experiencing neglect also subsequently underwent 1 Hz rTMS applied to the left PPC at an intensity of 90% RMT, which normalised PPC to M1 hyper-excitability in 7 out of

10 participants, and improved visual neglect as assessed by a visual chimeric test (Koch et al., 2008).

While TMS has been used to study neglect in subacute and chronic stoke, there are a number of barriers preventing safe and effective use of TMS in acute stroke. When considering rTMS or TBS neuromodulation to redress left hemisphere over-excitability in acute stoke, there are contraindications related to risk of seizure. There are also barriers to using paired-pulse protocols of PPC–M1 circuits in patients with neglect. First, there are logistical barriers because these techniques can take 1–2 hours to conduct. Investigation of networks in the right hemisphere is also difficult, as many patients would not have a MEP present in their right M1. In order to study IHI imbalance in acute stroke using TMS, a stroke model has been used in healthy subjects, where activity of the right PPC is suppressed using low frequency rTMS or cTBS. This induces transient visual neglect-like behaviour which is subsequently resolved following suppression of the left PPC (Bagattini et al., 2015; Cazzoli et al., 2009; Nyffeler et al., 2008; Pascual-Leone et al., 1994; Petitet, Noonan, Bridge, O'Reilly, & O'Shea, 2015). Despite variability reported in the response to rapid stimulation protocols to modulate excitability of M1, the majority of trials using low frequency rTMS or cTBS to induce a virtual lesion to the PPC in healthy people have consistently demonstrated behavioural change in visual bias as expected (Bagattini et al., 2015; Cazzoli et al., 2009; Fitzgerald, Fountain, & Daskalakis, 2006; Nyffeler et al., 2008; Petitet et al., 2015). These earlier trials provided support for the IHI imbalance model; however, two recent studies conducted in healthy adults have suggested this model may not explain visual neglect in all cases of stroke (Bagattini et al., 2015; Ricci et al., 2012). Both trials demonstrated reduced excitability bilaterally in the brain following suppression of the right PPC (Bagattini et al., 2015; Ricci et al., 2012). One of these trials used an online design, whereby single-pulse TMS was applied to either the vertex or right PPC at 115% RMT whilst participants performed a line bisection

task. Changes in BOLD signal were measured using fMRI, with results demonstrating bilateral suppression of the inferior parietal lobule (IPL) that was associated with neglect-like bias, induced by the single-pulse TMS to the right PPC (Ricci et al., 2012). The other trial used an offline design, whereby they applied 1hz rTMS for 30 min (1800 pulses) to suppress the right PPC at stimulation intensity of 90% RMT. They measured cortical excitability with electroencephalogram (EEG) electrodes placed on the scalp and demonstrated bilateral reduction in PPC excitability following suppression of the right PPC (Bagattini et al., 2015). Bilateral PPC suppression opposes the IHI imbalance model, which would dictate a release of inhibition over the left PPC, producing hyper-excitability (Bagattini et al., 2015; Petitet et al., 2015; Ricci et al., 2012)**.** A trial conducted by Petitet and colleagues challenged these results, as they found a leftward shift in the balance of parietal activity, measured by fMRI, which correlated with neglect-like changes in behavioural measures following rTMS to the right IPL (Petitet et al., 2015). The variation in these results and lack of evidence supporting the IHI imbalance model reveal that in healthy populations, changes in neglect-like behaviour following TMS suppression of right PPC are not necessarily due to IHI imbalance. The mechanism for the behavioural neglect response in healthy populations is therefore unknown, and requires further investigation.

Another method to study the IHI imbalance model following suppression of right PPC in healthy adults is two-coil, paired-pulse TMS, to test excitability of projections from a PPC to the contralateral M1 (Koch et al., 2009). Because TMS cannot probe interhemispheric PPC pathways directly, projections from each PPC to its contralateral M1 may provide surrogate information regarding PPC interhemispheric output. Using TMS, the effect of transient interhemispheric imbalance induced by cTBS of the right PPC can be explored in healthy adults. Furthermore, the impact of PPC to contralateral M1 excitability prior to stimulation on

responses to right PPC suppression can be examined to further understand neural contributions to IHI imbalance and visual neglect.

## Assessment of neglect

There are various standardised and non-standardised assessment tools to examine visuospatial neglect. However, there is no consensus as to which are the most appropriate and sensitive for identifying different subtypes of neglect and measuring change over time. A review paper found only two tests that measured personal neglect, the comb and razor test, and the semi-structured scale for functional evaluation of hemi-inattention in personal space (Menon & Korner-Bitensky, 2004). Both tests had weak psychometric properties. The review also identified a number of pen-and-paper tests that measure peripersonal or extrapersonal neglect, with the line bisection and letter cancellation tests having the strongest psychometric properties (Menon & Korner-Bitensky, 2004). The star cancellation and bell cancellation tests had good construct validity for testing visual discrimination; however, both had limited published information regarding reliability or sensitivity to change (Milner, Harvey, Roberts, & Forster, 1993). A potential limitation of pen-and-paper testing is the influence of directional hypokinesia on the response bias, which can result in poor differentiation between perceptual and motor neglect as the cause of response errors. Pen-and-paper testing may also not be sensitive enough to detect all subtypes and presentations of neglect, with some patients who perform normally on pen-and-paper testing demonstrating clinically significant neglect in everyday life (Azouvi et al., 2002). In order to increase the sensitivity of neglect measures, functional tests such as the Catherine Bergego Scale and comprehensive neglect batteries have been developed. The Catherine Bergego Scale involves observation of 10 activities of daily function, such as grooming or eating, and scoring each activity separately depending on how neglect impacts on the activity. It has strong psychometric properties and is more sensitive than pen-and-paper testing at identifying neglect and monitoring change over time

(Azouvi et al., 2003). The Catherine Bergego Scale can also be used to determine the presence of anosognosia, as patients can score each activity according to the perceived impact that neglect had on each task, which can then be compared to therapist scores. The behavioural inattention test is a neglect battery, including six conventional and three behavioural subtests of neglect. It has good psychometric properties, and the overall battery correlates well with all of the subtests. Due to the comprehensive nature of the battery, it has better sensitivity and can provide far greater insight into the overall impact of neglect on vision and function than each subtest on its own (Halligan, Cockburn, & Wilson, 1991).

## Assessment of neglect in healthy subjects

Conventional tests of visual attention are not sensitive enough to detect the subtle changes observed in visual bias when assessing behavioural effects of a transient virtual lesion induced by rTMS or TBS in healthy subjects. Higher-level computer-based assessments of visual attention have subsequently been developed to increase sensitivity when investigating visual attention and neglect in healthy adults.

### Landmark task

One test is the landmark task, which is a modified line bisection test. Participants are shown a number of pre-bisected lines on a computer screen and have to indicate which end of the line they think is longer by pressing a corresponding key on the keyboard (Milner et al.,1993). Reviews of the landmark task have shown it to be valid and sensitive at detecting visual neglect in stroke patients (Harvey, Milner, & Roberts, 1995; Harvey & Olk, 2004). The landmark task is also sensitive enough to detect rightward changes in visual bias induced by rTMS and TBS in healthy populations (Bjoertomt, Cowey, & Walsh, 2002; Fierro et al., 2000; Harvey et al., 1995; Harvey & Olk, 2004).

**Temporal order judgement task**

The temporal order judgement (TOJ) task is another computer-based assessment of visual attention used to assess visual bias in healthy people. It is different to other conventional assessments of visual attention, in that it measures the speed of processing of the visual system (Stelmach & Herdman, 1991; Ulrich, 1987). Participants are positioned in front of a computer screen and then two stimuli are presented, one in either hemifield, with an onset asynchrony of 0, 16.7, 33.3, 50, or 66.7 msec. As attention affects the speed at which information is transmitted in the visual system, a visual bias towards one side will cause the participant to perceive the stimulus earlier in that hemifield, resulting in a response bias towards that side (Stelmach & Herdman, 1991).

## Aims of the Research and hypotheses

Spatial neglect is modelled on an imbalance of IHI; however, evidence is emerging that it may not explain neglect in all cases.

The aim of this study was to investigate the IHI imbalance model of visual neglect in healthy adults, using paired-pulse TMS to probe excitability of projections from the PPC to the contralateral M1 bilaterally and cTBS of the right PPC to experimentally induce neglect.

The objectives of this study are:

1) to use paired-pulse TMS to measure interhemispheric connectivity between PPC and the contralateral M1 bilaterally and create a laterality index (LI) reflecting the balance of excitability between the two hemispheres
2) to determine visual bias in healthy subjects at baseline using the TOJ and landmark tasks
3) to suppress activity of the right PPC using continuous TBS to experimentally induce neglect
4) to investigate the effects of right PPC suppression on the TMS-evoked LI and visuospatial tasks.

It was hypothesised that:

- the excitability of the right PPC would be reduced relative to the left following cTBS of the right PPC, producing a more positive LI
- there would be a rightward shift in visual bias (visual neglect) measured by the landmark and TOJ tasks following cTBS to the right PPC
- changes in the LI would correlate with changes in visual bias on the landmark and TOJ tasks.

# Methodology

## Participant selection

**Inclusion criteria**: Potential participants who were aged 18 years or older and right-hand dominant were recruited for the study.

**Exclusion criteria**: Participants were excluded from the study if they had a pre-existing neurological condition, were left-hand dominant, had a history of seizures, were pregnant, were taking psychoactive drugs, had cochlear implants, had a metal implant in the head or neck, had an implanted neuro-stimulator, a cardiac pacemaker or intracardiac lines, had severe cardiac conditions, or had previous problems using TMS.

In addition to the inclusion/exclusion criteria, participants completed a TMS screening questionnaire used to check for contraindications to TMS, such as seizures, head injury or pregnancy. The form was reviewed and signed by a medical doctor to ensure participants were safe to be included in the trial. Post hoc correlational sample size calculation was performed, assuming an alpha of 0.05 and beta of 80% with 10 participants sufficient to find a strong ($r > 0.8$) correlation. Fourteen subjects were recruited according to the inclusion/exclusion criteria, and consented to participate in the study. Ethical approval was gained from the Southern Adelaide Clinical Human Research Ethics Committee and site-specific assessment granted by the Repatriation General Hospital.

## Procedure

Participants attended one session lasting approximately 2.5 hours, at a TMS laboratory in the Repatriation General Hospital. Baseline assessments included the TOJ and landmark tasks to assess visuospatial attention and TMS to probe excitability of PPC to contralateral M1 projections bilaterally. Participants then received the intervention: suppressive cTBS to the right PPC. Following a 5-min rest period, participants repeated the baseline assessments.

## Apparatus

### Electromyography

Electromyograpy was recorded using self-adhesive electrodes applied to the right and left first dorsal interossei (FDI) muscle (Ambu® BlueSensor ECG Electrodes). EMG was amplified and filtered (20–2000Hz) using a CED 1902 and Signal software (V6, Cambridge Electronic Design, UK).

### Transcranial magnetic stimulation

The equipment used for delivering the TMS included two Magstim 200 units (Magstim Co., WHitland Dyfed, Wales), a figure-of-eight coil with a 70-mm wing diameter (Magstim Co., WHitland Dyfed, Wales) and a figure-of-eight coil with a 50-mm wing diameter (Magstim Co., Whitland, Dyfed, Wales).

### Theta-burst stimulation

The equipment used for delivering the theta-burst stimulation included a Magstim Rapid unit delivering a biphasic pulse and a figure-of-eight coil with a 70mm wing diameter (Magstim Co., WHitland Dyfed, Wales).

### Behavioural tasks

The equipment used for the behavioural tasks included a Dell laptop with 14-inch screen (E7440) running E-prime 2.0 software (Psychology Software Tools, Inc.).

## Screening assessment

Prior to enrolment in the study, participants completed a TMS screening questionnaire to ensure medical suitability to undergo TMS (Appendix 1). If it was deemed unsafe for participants to have TMS they were excluded from the trial. Participants also completed the Edinburgh handedness inventory screening questionnaire (Oldfield, 1971) to confirm right-hand dominance (Appendix 2). The inventory includes twelve items and participants are required to indicate which hand they would use to perform each item by placing a cross in either the left-hand or right-hand column. A laterality index was calculated for each participant using the equation: LI = ((Right) – (Left)) / ((Right) + (Left)). A positive LI reflected right-hand dominance, whilst a negative LI reflected left-hand dominance (Oldfield, 1971).

## Neurophysiological assessment

### Electromyography

The skin surface overlying the FDI muscle was prepared to ensure signals were uncontaminated by electrical noise. This involved shaving, lightly abrading and cleaning with alcohol the area of skin where the recording electrodes were to be placed. EMG traces were recorded from the FDI muscle bilaterally using surface electrodes. The active electrode was placed over the muscle belly and the reference electrode was placed over the distal forearm. EMG signals were sampled at 2000 Hz. Resting EMG recordings were analysed to check electrode conductivity and to ensure there was no external interference. If the resting EMG root mean square (rmsEMG) was greater than 0.009 mV then the recordings were

contaminated by electrical noise, and the electrodes were removed, skin preparation repeated and new electrodes applied.

**Transcranial magnetic stimulation**

A paired-pulse twin-coil TMS technique was used to examine interhemispheric projections between the PPC (cIPS) and the contralateral M1 from both hemispheres (Figure 4). The twin-coil technique required two people to hold the coils in position, with one person holding the test coil over the M1 and the other person holding the conditioning coil over the PPC.

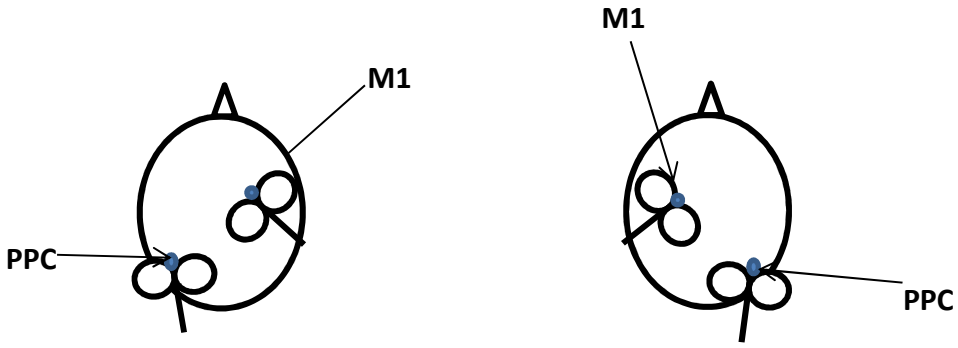


**Figure 4. Coil placement for the paired-pulse twin-coil technique.**

The test stimulus was delivered with a figure-of-eight coil (Magstim Co., WHitland Dyfed, Wales) positioned over the M1 to induce a posterior-to-anterior directed current in the underlying brain. The scalp location (M1 hotspot) for the FDI muscle for both hemispheres was defined as the point that induced the largest MEP in the contralateral muscle. Once the M1 hotspot was located, RMT was determined for M1 in the right hemisphere, followed by the left hemisphere. RMT was defined as the minimum stimulus intensity that elicited 0.05 mV MEP in four out of eight trials when the subject kept their hand muscles relaxed (Rossini et al., 1994). A stimulus intensity that elicited a reasonably sized MEP was tested first, and the intensity then reduced in 20% maximum stimulator output increments until RMT was

determined. Test stimulus intensity was determined for each hemisphere, with the stimulus intensity adjusted to evoke a MEP of approximately 1 mV peak-to-peak in the relaxed FDI (Rossini et al., 1994). The RMT was used to estimate the trial test stimulus intensity; 10 MEPs were recorded and averaged. The stimulus intensity was then adjusted higher or lower until an average MEP of ≈ 1 mV was achieved. AMT was then determined for right M1, defined as the minimum stimulus intensity that elicited a 0.10 mV MEP in four out of eight trials during contraction of the left FDI (Rossini et al., 1994). A figure-of-eight coil (Magstim Co., Whitland, Dyfed, Wales) was attached to the Magstim Rapid to determine AMT. The coil was held over the right M1 while the participant was instructed to hold their left index finger in an abducted position. The same protocol to establish RMT was used to determine AMT.

The conditioning figure-of-eight coil was centred over the left and right PPC using the 10–20 EEG standard locations of P3 and P4, respectively (Figure 5) (Herwig, Satrapi, & Schönfeldt-Lecuona, 2003). These locations have been previously identified as being close to the posterior part of the adjoining intraparietal sulcus (Herwig et al., 2003; Koch et al., 2007; Rushworth & Taylor, 2006). The 10–20 EEG system is based on the identification of anatomical landmarks (nasion, inion, and pre-auricular points) and placing electrodes at fixed distances from these points in 10% and 20% increments (Herwig et al., 2003). The 10–20 EEG system is a more accessible and cost-effective approach to TMS coil positioning than expensive neuroimaging and neuro-navigation equipment. In order to locate P3 and P4, the EEG point at the vertex, known as CZ, was determined. A tape measure was used to locate the midpoint of the centre line of the scalp from the nasion to the inion and the midpoint between the two pre-auricular points, with the intersection between the two points marked on the head as Cz. The point known as Pz was determined by measuring back 20% from Cz

towards the inion. The distance between the pre-auricular points passing through Pz was measured, and P3 and P4 located 20% to the left and right of Pz.

**Figure 5. Diagram representing the 10–20 EEG electrode placement has been removed due to copyright restrictions.**

The conditioning coil was held by a trained assistant to ensure robust and reproducible measures. It was positioned tangentially to the skull, with the handle pointing downward and slightly medially rotated in order to induce a posterior-to-anterior current in the underlying brain tissue (Koch et al., 2009). A previous protocol demonstrated that a test MEP evoked from the M1 is facilitated when conditioned by a stimulus over the contralateral cIPS at specific intensities and ISIs (Koch et al., 2009). The same protocol was used in the current study. The intensity of the conditioning stimulus was set at 90% and 110% RMT of the ipsilateral M1 (Koch et al., 2009). The ISI between the cIPS and contralateral M1 was 8 ms. Extensive piloting prior to the study was undertaken to determine the most effective ISI to produce PPC to contralateral M1 MEP facilitation. This process revealed that an ISI of 8 ms

produced the largest and most consistent MEP facilitation for both hemispheres. The left PPC–right M1 projection was measured first, followed by the right PPC–left M1 projection. One block of TMS was recorded for each hemisphere, consisting of one single-pulse TMS to M1 (test stimulus) to evoke a non-conditioned (NC) MEP, and two paired-pulse TMS trials to evoke conditioned (C) MEPs. In total, 16 NC-MEPs and 16 C-MEPs at each stimulus intensity were delivered in random order, for a total of 48 MEPs per hemisphere. Neurophysiology measures were first recorded from the right M1, followed by the left M1, both pre- and post-intervention. Baseline TMS measures were reviewed immediately after collection, to ensure that facilitation of the test MEP was achieved at one of the two intensities for both hemispheres. MEP facilitation was defined as a 5% or greater increase in C/NC MEP amplitude. The presence of MEP facilitation confirmed accurate coil placement over the cIPS (Koch et al., 2009). To ensure correct positioning of the conditioning coil, if the test MEP was not facilitated by either conditioning intensity, the conditioning coil was repositioned by 0.5 cm in a grid-like configuration until facilitation occurred. If the test MEP could not be facilitated at baseline, despite multiple attempts to reposition the conditioning coil, then the participant did not continue with the trial and their data were discarded.

## Behavioural measures

Two computer-based behavioural tasks assessing visuospatial attention and visual bias were completed by participants at baseline and following the intervention. Subjects first completed the landmark task, followed by a short rest, before completing the TOJ task.

### Landmark task

Stimulus presentation was controlled with a Dell laptop (E7440) running E-prime 2.0 software (Psychology Software Tools, Inc.). The centre of the 14-inch screen was at eye level and in line with the participants' midsagittal plane at a distance of 500 mm. Responses were

made using the laptop's keyboard. The stimulus parameters consisted of pre-transected horizontal lines of 180 mm (Szpak, Nicholls, Thomas, Laham, & Loetscher, 2015). The lines were composed of two black and two white bars, arranged in diagonally opposite pairs against a grey background. Each line was transected 0.5, 1 or 2 mm either to the left or right of true centre. To prevent assistance through the use of extrinsic markers, the lines were presented 9 mm to either the left or right of the screen (Szpak et al., 2015). Participants completed a practice test consisting of eight trials before undertaking the baseline assessment. The baseline and intervention assessment comprised 108 trials each, consisting of three repetitions of the factorial combination bisection deviation (0.5, 1, 2), side longer (left, right), jitter (left, right) and polarity of line (upper left part black, upper left part white). The order of presentation was randomised and each trial began with a blank screen presented for 1000 msec. The line stimulus was then shown for 500 msec followed by a blank screen, during which time participants indicated by key presses whether the left or right segment of the line was longer. If participants responded before the presentation of the blank screen or not within 2000 msec, the trial was rejected and repeated. The response bias was calculated as (number of right responses – number of left responses) / the sum of all trials. Negative and positive response biases thus indicate leftward and rightward biases, respectively (McCourt, 1999).

**Temporal order judgement task**

The centre of the 14-inch screen was at eye level and in line with the participants' midsagittal plane at a distance of 500 mm. Responses were made with the laptop's keyboard. The stimuli were two squares with a size of 15 mm, located 60 mm to the left and right of the screen's centre, respectively. Each trial began with the presentation of white squares outlined against a black background for 300 msec. The colour of the squares then changed from white to black, at the same time or immediately after each other. The onset asynchrony between the squares was either 0, 16.7, 33.3, 50, or 66.7 msec. Participants first completed a practice test

consisting of 18 trials before undertaking the baseline assessment. Each baseline and intervention assessment consisted of 180 trials. The participants indicated by key presses whether the left or right square changed colours first. There were no time restrictions for responding. The response bias was calculated as (number of right responses – number of left responses) / the sum of all trials. Negative and positive response biases thus indicate leftward and rightward biases, respectively (Stelmach & Herdman, 1991).

## Continuous theta-burst stimulation

Following completion of the baseline neurophysiological and behavioural assessments, participants underwent inhibitory cTBS of the right PPC. The cTBS was delivered with a figure-of-eight coil (Magstim Co., WHitland Dyfed, Wales). The intervention consisted of two trains of inhibitory cTBS (600 pulses delivered in three bursts every 200 ms at 50Hz), applied to the right PPC (Figure 6). Each train took 40 sec to complete. Participants were given a 5-min rest between trains and another 5-min rest at the completion of the second train prior to post-intervention testing (Goldsworthy et al., 2012; Huang et al., 2005). The intensity of stimulation was set at 90% of AMT established in the right M1 representation of the FDI muscle (Huang et al., 2005).

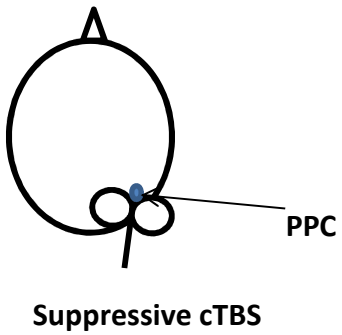


**Figure 6. Coil position over the right posterior parietal cortex for suppressive cTBS intervention.**

## Data analysis

Normality was confirmed by checking for skewness and kurtosis. Group analysis was undertaken using the conditioned MEP intensity (either 90% or 110%) that produced the largest MEP facilitation for each hemisphere at baseline. RMS data were reviewed, and any MEPs recorded when the muscle was not at rest were removed from the analysis. Excitability of each PPC was established by calculating a ratio of conditioned to non-conditioned MEP amplitude (C/NC) (Koch et al., 2008; Koch et al., 2009; Koch et al., 2013). The ratios were used to calculate LI, reflecting the balance of excitability between the two hemispheres, using the formula: LI = ((Left C/Left NC) – (Right C/Right NC)) / ((Left C/Left NC) + (Right C/Right NC)). A value of zero indicated that the excitability of both PPCs was identical. A positive value signified a relatively greater excitability of the left PPC and a negative value signified a relatively greater excitability of the right PPC. The LI calculation was individualised for each participant. The effect of stimulation on M1 NC MEP, LI, TOJ task, landmark task and PPC to contralateral M1 MEP facilitation for each hemisphere were statistically analysed using paired t-tests. Pre-stimulus rmsEMG was analysed using repeated measures ANOVA with CONDITION (C/NC MEP) and TIME (pre/post) as factors. To assess whether baseline excitability predicted response to cTBS, the difference in LI and MEP facilitation pre- to post-stimulation was calculated (Post–Pre; ΔLI, ΔPPC–M1 MEP facilitation). Then correlation analysis was used to examine associations between baseline LI and ΔLI, and baseline PPC–M1 MEP facilitation and ΔPPC–M1 MEP facilitation for each hemisphere. Furthermore, ΔLI, ΔPPC–M1 MEP facilitation for each hemisphere and ΔLI were tested with correlation analyses. Finally, potential associations between ΔLI and ΔTOJ, ΔLI and Δlandmark, ΔM1 NC MEP and ΔTOJ, and ΔM1 NC MEP and Δlandmark were assessed. Significance was set at $p < 0.05$.

## Results

All participants recruited to the trial had a positive LI on the Edinburgh handedness inventory, indicating right-hand dominance. Four participants (two female and two male) were excluded from data analysis as PPC to contralateral M1 MEP facilitation was not observed at baseline; therefore, analysis was performed on 10 participants (seven female and three male, ages 23–49).

### Group analysis

Group analysis was performed using the conditioning intensity that evoked the largest baseline PPC to contralateral M1 MEP facilitation per hemisphere for each participant. For right PPC–left M1 MEP facilitation, seven participants (1, 3, 4, 6, 7, 8 and 10) had the highest facilitation at baseline with conditioning intensity of 90% RMT and three participants (2, 5 and 9) at 110% RMT. For left PPC–right M1, seven participants (1, 2, 4, 6, 7, 9 and 10) had the highest facilitation at baseline with conditioning intensity of 90% RMT and three participants (3, 5 and 8) at 110% RMT.

There was no effect of CONDITION ($p = 0.230$) or TIME ($p = 0.227$) on rmsEMG (all > 0.01 mV). Group analyses performed to assess changes in cortical excitability of M1, using the NC MEP post-cTBS, revealed no changes in left ($p = 0.062$) or right ($p = 0.423$) NC MEP size following stimulation (Table 1).

**Table 1**

**Non-conditioned MEP amplitude for right and left M1 before and after cTBS of right PPC and ΔMEP amplitude for each participant. A +Δ indicates an increase in MEP amplitude whilst a -Δ indicates a reduction in MEP amplitude.**

| | Right M1 NC MEP amplitude | | | Left M1 NC MEP amplitude | | |
|---|---|---|---|---|---|---|
| **Participant** | **Pre-cTBS** | **Post-cTBS** | Δ | **Pre-cTBS** | **Post-cTBS** | Δ |
| 1 | 1.01 | 0.67 | -0.34 | 1.56 | 2.56 | 1.00 |
| 2 | 1.05 | 0.72 | -0.33 | 0.85 | 0.87 | 0.02 |
| 3 | 0.77 | 1.67 | 0.90 | 0.37 | 0.56 | 0.19 |
| 4 | 1.28 | 1.40 | 0.12 | 0.85 | 1.51 | 0.66 |
| 5 | 0.94 | 0.59 | -0.35 | 0.85 | 0.55 | -0.30 |
| 6 | 1.95 | 0.42 | -1.53 | 0.25 | 0.37 | 0.12 |
| 7 | 0.57 | 0.67 | 0.10 | 0.37 | 1.24 | 0.88 |
| 8 | 0.16 | 0.27 | 0.12 | 0.78 | 0.84 | 0.05 |
| 9 | 0.48 | 0.10 | -0.38 | 0.73 | 0.76 | 0.03 |
| 10 | 1.08 | 1.13 | 0.05 | 0.62 | 0.80 | 0.18 |
| Mean | 0.93 | 0.76 | -0.16 | 0.72 | 1.01 | 0.28 |

LI measures for each participant at baseline, after stimulation and ΔLI are shown in Table 2. Group-level analysis revealed cTBS of right PPC had no significant effect on LI ($p = 0.664$). The LI data revealed variable responses to stimulation, with six participants demonstrating –ΔLI (indicating increase in excitability of left PPC relative to right PPC) and four participants demonstrating +ΔLI (indicating increase in excitability of right PPC relative to left PPC) (Table 2).

**Table 2**

**The laterality index before and after cTBS of right PPC and ΔLI for each participant. A value in the direction of +1 indicates relative greater excitability of left PPC and a value towards -1 indicates relative greater excitability of right PPC. A positive ΔLI indicates an increase in excitability of the left PPC relative to the right. A negative ΔLI indicates an increase in excitability of the right PPC relative to the left.**

| Participant | LI pre-cTBS | LI post-cTBS | ΔLI |
|---|---|---|---|
| 1 | -0.08 | 0.22 | 0.30 |
| 2 | 0.03 | 0.04 | 0.01 |
| 3 | -0.21 | -0.30 | -0.09 |
| 4 | 0.06 | 0.00 | -0.06 |
| 5 | -0.08 | -0.24 | -0.16 |
| 6 | -0.16 | 0.08 | 0.24 |
| 7 | -0.12 | -0.09 | 0.03 |
| 8 | 0.38 | 0.04 | -0.34 |
| 9 | 0.15 | 0.00 | -0.14 |
| 10 | -0.06 | -0.12 | -0.05 |
| Mean(SD) | -0.01(0.17) | -0.03(0.15) | -0.03(0.19) |

The hemispheres were then analysed individually to probe this ΔLI variation (Table 3). There was a reduction in right PPC–left M1 MEP facilitation following cTBS to right PPC ($p = 0.019$), producing –Δ values (decrease). For left PPC–right M1 MEP facilitation, only two participants (1 and 6) demonstrated the expected post-stimulation increase (+Δ), resulting in a strong trend for overall –Δ for left PPC–right M1 MEP facilitation ($p = 0.070$) (Table 3).

**Table 3**

**The PPC to contralateral M1 MEP facilitation for each hemisphere before and after cTBS of right PPC and ΔMEP facilitation. A negative Δ indicates a reduction in PPC excitability, and a positive Δ indicates an increase in PPC excitability.**

| | Facilitation right PPC to left M1 | | | Facilitation left PPC to right M1 | | |
|---|---|---|---|---|---|---|
| **Participant** | **Pre-cTBS** | **Post-cTBS** | Δ | **Pre-cTBS** | **Post-cTBS** | Δ |
| 1 | 1.35 | 1.01 | -0.34 | 1.15 | 1.57 | 0.42 |
| 2 | 1.08 | 1.03 | -0.05 | 1.16 | 1.12 | -0.04 |
| 3 | 2.71 | 1.47 | -1.24 | 1.77 | 0.80 | -0.97 |
| 4 | 1.21 | 0.86 | -0.36 | 1.36 | 0.86 | -0.51 |
| 5 | 1.44 | 1.33 | -0.11 | 1.23 | 0.81 | -0.42 |
| 6 | 1.49 | 1.09 | -0.39 | 1.08 | 1.29 | 0.21 |
| 7 | 1.37 | 1.26 | -0.11 | 1.07 | 1.06 | -0.02 |
| 8 | 1.17 | 1.03 | -0.14 | 2.60 | 1.11 | -1.49 |
| 9 | 1.16 | 1.02 | -0.14 | 1.55 | 1.02 | -0.52 |
| 10 | 1.36 | 1.11 | -0.25 | 1.20 | 0.88 | -0.33 |
| mean (SD) | 1.43(0.47) | 1.12(0.18) | -0.31(0.35) | 1.42(0.47) | 1.05(0.24) | -0.37(0.56) |

## Correlational analyses

There was no association between baseline LI and LI post-cTBS ($r = 0.340$, $p = 0.336$). There was a strong correlation between ΔLI and Δleft PPC–right M1 (Figure 7a, $r = 0.902$, $p < 0.001$) but not between ΔLI and Δright PPC–left M1 (Figure7b, $r = –0.094$, $p = 0.797$). This indicates the direction of ΔLI (positive or negative) was driven by Δleft PPC–right M1. The correlation analyses revealed a more –ΔLI was associated with more –Δleft PPC–right M1 MEP facilitation and a more +ΔLI was associated with more +Δleft PPC–right M1 MEP facilitation.

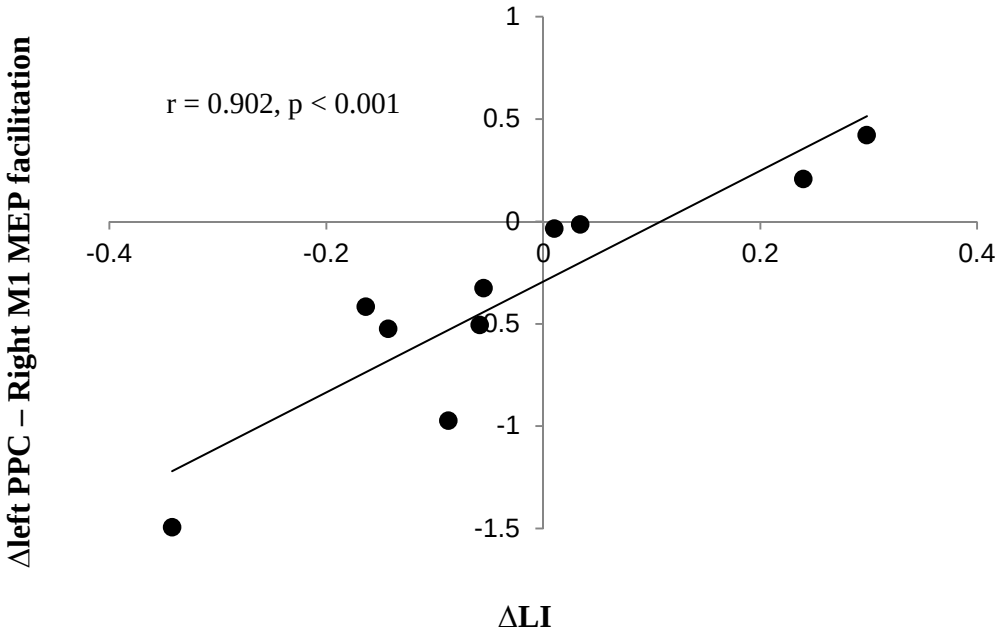


**Figure 7a. Correlation between ΔLI and Δleft PPC–right M1 MEP facilitation.**

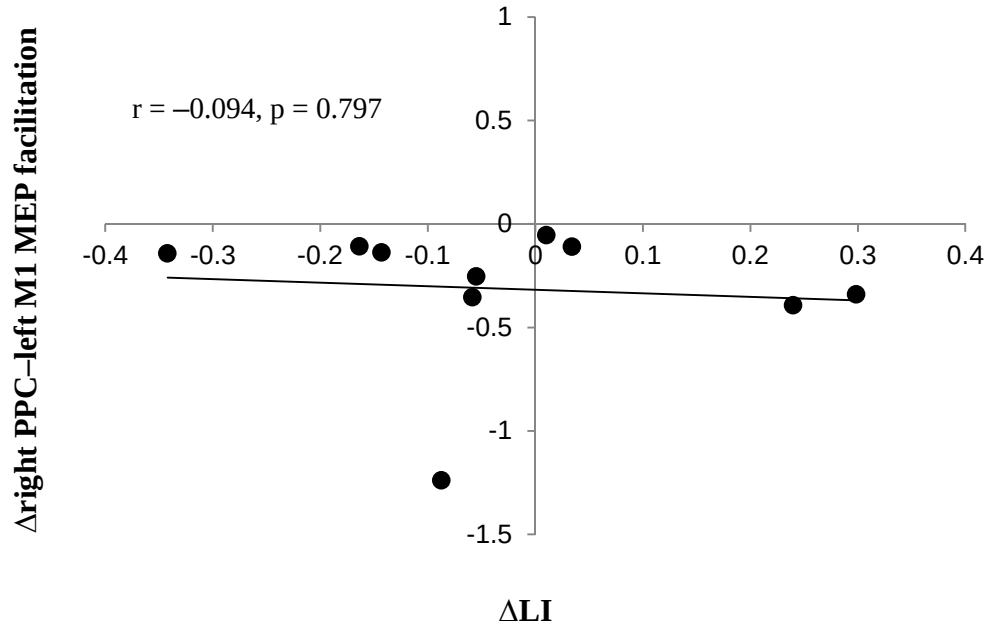


**Figure 7b. Correlation between ΔLI and Δright PPC–left M1 MEP facilitation.**

The correlation to determine if baseline excitability could predict ΔLI revealed a moderate negative association between LI and ΔLI (Figure 8a, $r = –0.640$, $p = 0.046$); however, with one outlier removed, the association was not significant ($r = –0.353$, $p = 0.352$). There was a strong association between baseline PPC–M1 MEP facilitation and ΔPPC–M1 MEP facilitation for both hemispheres (Figure 8b and 8c). Participants with larger MEP facilitation at baseline demonstrated greater reduction (–Δ) following stimulation (left PPC–right M1 MEP facilitation, $r = –0.908$, $p < 0.001$; right PPC–left M1 MEP facilitation, $r = –0.944$, $p < 0.001$). However, the association between right PPC–left M1 MEP facilitation and Δright PPC–left M1 MEP facilitation, may have been influenced by an outlier, which when removed was no longer significant ($r = –0.446$, $p = 0.229$). Left PPC–right M1 MEP facilitation prior to stimulation may determine the individual response to cTBS of right PPC, as the two participants (1 and 6) with +Δleft PPC–right M1 MEP facilitation displayed little MEP facilitation at baseline (Figure 8b). There was also a moderate negative association between left PPC–right M1 MEP facilitation at baseline and the ΔLI following cTBS to the right PPC ($r = –0.732$, $p = 0.016$).

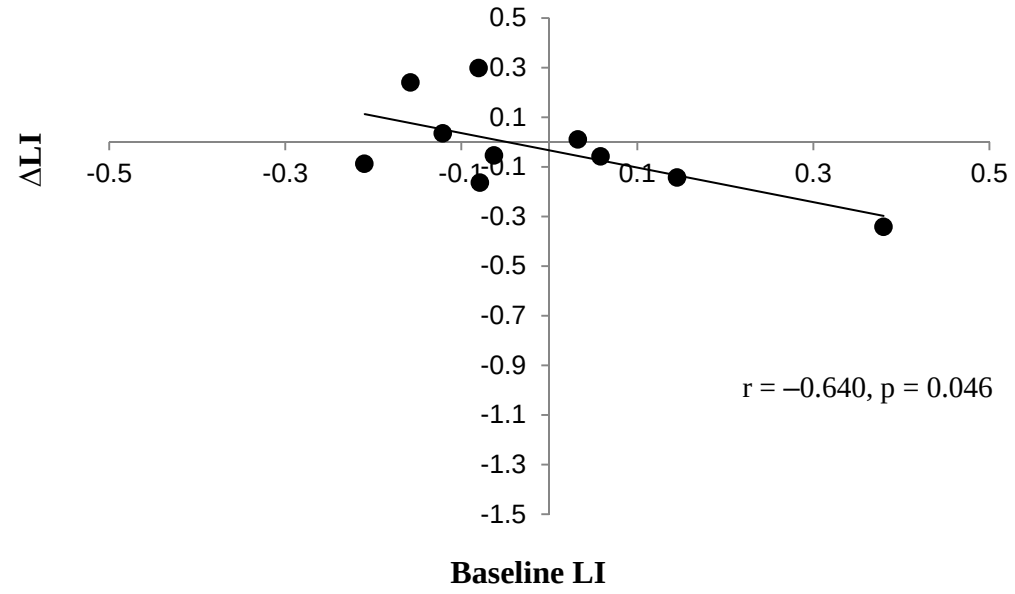


**Figure 8a. Correlation between baseline LI and ΔLI.**

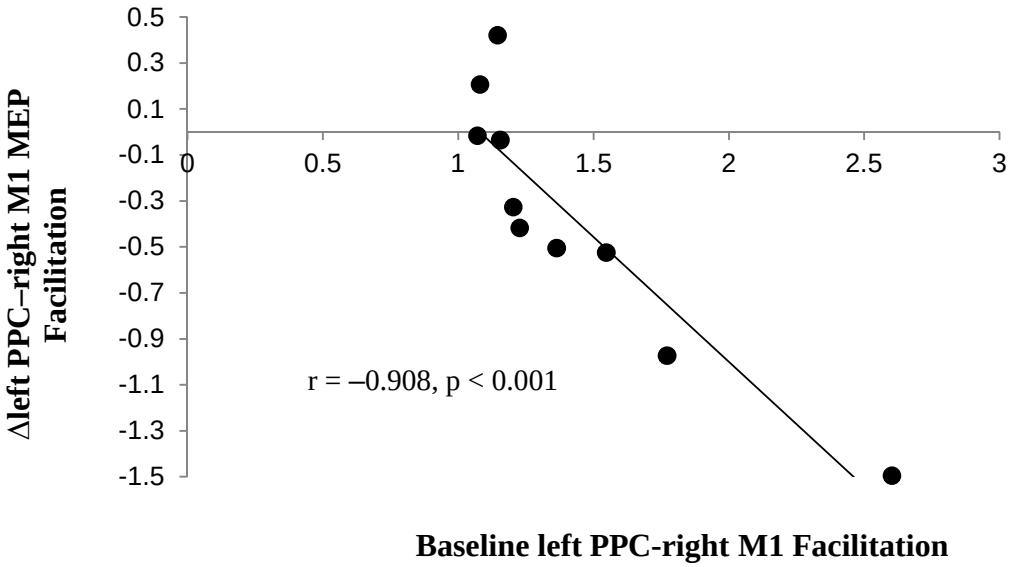


**Figure 8b. Correlation between baseline left PPC–right M1 MEP facilitation and Δleft PPC–right M1 MEP facilitation.**

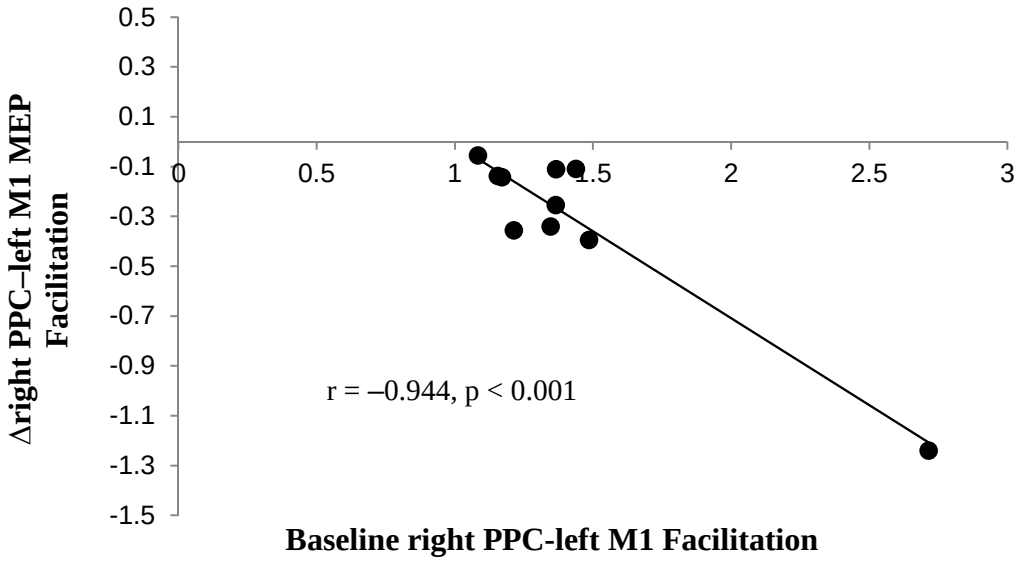


**Figure 8c. Correlation between baseline right PPC–left M1 MEP facilitation and ∆right PPC–left M1 MEP facilitation.**

## Behavioural measures

### Landmark task

LI measures for each participant at baseline, after stimulation and ΔLI are shown in Table 4. At a group level, there was no visual bias present at baseline, with two participants having a positive LI, indicating a rightward visual bias, and eight participants having a negative LI, indicating a leftward visual bias ($p = 0.250$). There was no effect of cTBS on the landmark task ($p = 0.429$). Individual analyses revealed variable responses to cTBS, with five participants demonstrating the expected rightward shift in visual bias, four exhibiting a leftward shift and one demonstrating no change.

**Table 4: Landmark Task LI before and after cTBS of right PPC and ΔLI for each participant. A positive value indicates a rightward visual bias and a negative value indicates a leftward visual bias. A positive ΔLI indicates a rightward shift in visual bias and a negative ΔLI indicates a leftward shift in visual bias.**

| Participant | LI pre-cTBS | LI post-cTBS | ΔLI |
|---|---|---|---|
| 1 | -1.85 | -1.85 | 0.00 |
| 2 | -20.37 | -12.96 | 7.41 |
| 3 | -5.56 | 16.67 | 22.23 |
| 4 | -20.37 | -5.56 | 14.81 |
| 5 | -3.70 | -16.67 | -12.97 |
| 6 | -50.00 | -68.52 | -18.52 |
| 7 | -42.59 | -9.26 | 33.33 |
| 8 | 27.78 | 14.81 | -12.97 |
| 9 | 25.93 | 22.22 | -3.71 |
| 10 | -7.41 | 7.41 | 14.82 |
| Mean(SD) | -9.81(25.23) | -5.37(25.86) | 4.44(16.98) |

**Temporal order judgement**

LI measures for each participant at baseline, after stimulation and ΔLI are shown in Table 5. At a group level, there was no visual bias at baseline, with six participants having a positive LI, indicating a rightward visual bias, and four participants having a negative LI, indicating a leftward visual bias ($p = 0.827$). There was no effect of cTBS on the response bias in the TOJ task ($p = 0.088$). Individual analyses revealed variable response to cTBS, with only three participants demonstrating the expected rightward shift in visual bias, six exhibiting a leftward shift and one demonstrating no change.

**Table 5: Temporal order judgement LI before and after cTBS of right PPC and ΔLI for each participant. A positive value indicates a rightward visual bias and a negative value indicates a leftward visual bias. A positive ΔLI indicates a rightward shift in visual bias and a negative ΔLI indicates a leftward shift in visual bias.**

| Participant | LI pre-cTBS | LI post-cTBS | ΔLI |
|---|---|---|---|
| 1 | 31.11 | 20 | -11.11 |
| 2 | 12.22 | -4.44 | -16.67 |
| 3 | -7.78 | -3.33 | 4.44 |
| 4 | 13.33 | 16.67 | 3.33 |
| 5 | -7.78 | -17.78 | -10 |
| 6 | 6.67 | -3.33 | -10 |
| 7 | -33.33 | -60 | -26.67 |
| 8 | -8.89 | 0 | 8.89 |
| 9 | 1.11 | -6.67 | -7.78 |
| 10 | 5.56 | 5.56 | 0 |
| Mean(SD) | 1.22(17.22) | -5.33(22.18) | -6.56(10.82) |

There were no associations between the TOJ and landmark tasks when comparing baseline LI scores, ($r = 0.113$, $p = 0.757$), post-cTBS LI scores ($r = 0.108$, $p = 0.766$) or ΔLI scores ($r = –0.209$, $p = 0.563$). Of the ten participants only two, (2 and 3) displayed +Δ (indicating rightward shift in visual bias) for both behavioural tasks. Three participants (5, 6 and 9) displayed -Δ **(**indicating a leftward shift) on both behavioural tasks. The other five participants demonstrated a difference in Δ for each behavioural test, indicating there were conflicting results between the two tests regarding direction of visual bias after stimulation.

## Correlational analyses between neurophysiological and behavioural tasks

There was no association between ΔLI and ΔTOJ task ($p = 0.129$). There was a strong association between the reduction in left PPC–right M1 MEP facilitation and the ΔTOJ task ($r = –0.742$, $p = 0.014$), whereby more –Δleft PPC–right M1 facilitation was associated with a rightward shift in visual attention (Figure 9). There was no correlation between the Δ right PPC–left M1 MEP facilitation and ΔTOJ ($r = –0.439$, $p = 0.205$).

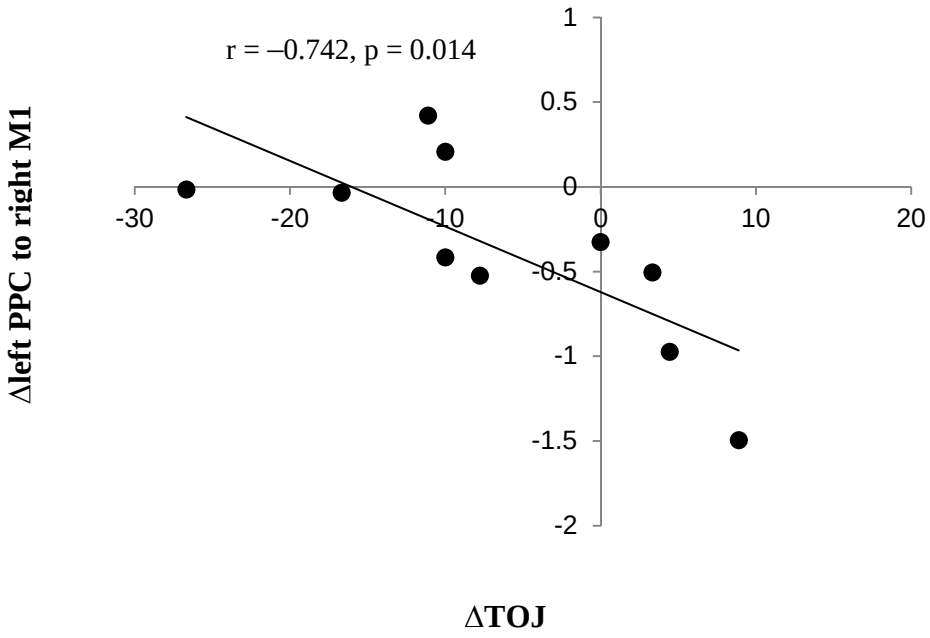


**Figure 9. Correlational between Δleft PPC–right M1 facilitation and the change in TOJ task.**

Correlational analyses (removing one significant outlier) revealed a strong association between Δleft M1 excitability and the TOJ score post-cTBS, ($r = 0.954$, $P < 0.001$. A larger +Δleft M1 was associated with a rightward visual bias (Figure 10). There was no association between Δright M1 and TOJ score post-cTBS ($p = 0.190$).

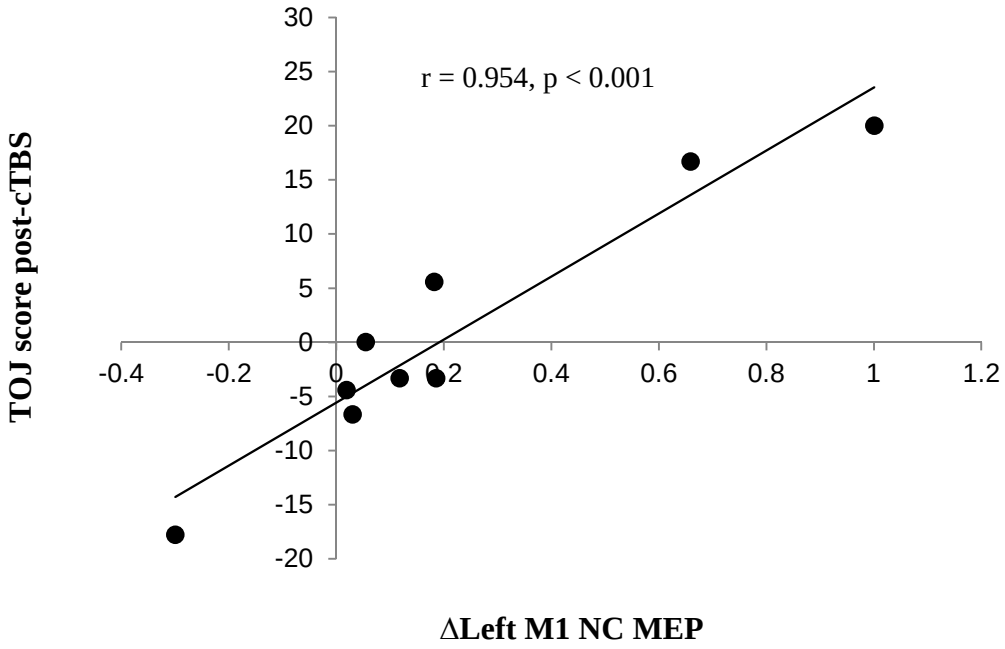


**Figure10. Correlational analysis (outlier removed) between ∆left M1 non-conditioned MEP and TOJ score post-cTBS.**

# Discussion

## Overview

The current study tested the IHI imbalance model by investigating the effect of right PPC suppression, using cTBS, on the excitability of interhemispheric projections from PPC to contralateral M1 bilaterally. Two conditioning intensities were used (90% and 110% RMT), with the stimulus intensity that evoked the highest PPC to contralateral M1 facilitation at baseline for each participant used in the analyses. Results revealed variation between individuals, with seven participants exhibiting the highest facilitation at conditioning 90% RMT and three at 110% RMT for both hemispheres. Relative excitability of the PPCs was determined using a TMS-evoked LI, and the effect of cTBS on visuospatial attention assessed using TOJ and landmark tasks. The main findings were that the LI, TOJ and Landmark task were unaffected by stimulation and there was no relationship between ΔLI and ΔTOJ, ΔLI and ΔLandmark, or ΔLandmark and ΔTOJ at the group level. The lack of change on both behavioural tasks may be due to variability between participants in baseline visual bias and response to cTBS. Although previous studies have demonstrated consistency in visual response to rTMS on a group level, large individual variation related to structural variability in fronto-parietal networks has also been shown previously in healthy people (Cazzoli et al., 2012; Chechlacz, Humphreys, Sotiropoulos, Kennard, & Cazzoli, 2015).

To probe the underlying reason for the lack of response to ΔLI, each hemisphere was analysed individually. As expected, right PPC–left M1 MEP facilitation was reduced following right PPC cTBS. However, there was a strong tendency for a reduction in left PPC–right M1 MEP facilitation, with 8 of 10 participants demonstrating this response. The resulting LI was relatively more negative in these individuals. These findings are inconsistent with the hypothesis, which expected an increase in left PPC–right M1 MEP facilitation, causing a positive directional shift in the LI. There was a moderate association between

baseline LI and ΔLI; however, the stronger associations were between baseline MEP facilitation and ΔMEP facilitation following stimulation for both hemispheres. The direction (positive or negative) for Δleft PPC–right M1 MEP facilitation, which showed variation between individuals and determined the direction of ΔLI, was clearly influenced by baseline MEP facilitation. These results also revealed a surprising association between ΔTOJ and Δleft PPC–right M1. Contrary to the IHI model, analyses demonstrated a strong negative association between ΔTOJ and Δleft PPC–right M1, whereby participants who had greater dis-facilitation demonstrated a rightward shift in visual bias. The reason for this result is difficult to determine. A possible explanation might be that greater dis-facilitation in the left PPC–right M1 projections resulted from a disconnection in fronto-parietal networks in the right hemisphere. Alternatively, it may reflect a breakdown in interhemispheric communication following right PPC suppression. These hypotheses could be explored in future studies by using a paired-pulse TMS protocol to measure intrahemispheric PPC to M1 projections or twin-coil protocols to measure interconnectivity.

The current findings, using paired-pulse TMS, supported two previous studies where bilateral reduction in PPC excitability following cTBS to suppress right PPC was reported using fMRI and EEG (Bagattini et al., 2015; Ricci et al., 2012). The novelty of this current study was that paired-pulse TMS was used to probe activity between PPC and contralateral M1, rather than PPC to ipsilateral M1 projections as per previous studies (Koch et al., 2007; Koch et al., 2009). This approach was considered to provide an indirect measure of PPC interhemispheric output, since interhemispheric connections between PPCs cannot be assessed with TMS. By assessing activity bilaterally, the relative excitability of PPC interhemispheric outputs could be determined using an LI. There was relative balance between the two PPCs at baseline; however, the LI was not altered by right PPC cTBS in most participants. This was due to a

similar reduction in PPC–M1 interhemispheric facilitation on both sides of the brain. LI was shifted in the positive direction in two participants where left PPC–right M1 facilitation increased after stimulation, in accordance with the IHI imbalance model. Surprisingly, this increase in left PPC excitability was not associated with a rightward shift of visuospatial attention. The implications of this finding in healthy adults for visual neglect after right hemispheric stroke are uncertain. Interestingly, a recent fMRI study in acute stroke patients who had experienced right parietal stroke revealed hyper-activation of the left parietal lobe in all patients, regardless of whether they had neglect (Umarova et al., 2011). Instead, dysfunction in the right parietal and lateral occipital cortex was better associated with neglect than left parietal activity. The authors suggested that left parietal hyper-excitability was a consequence of severe structural damage to the right hemisphere, but was not the cause of the attentional deficits (Umarova et al., 2011). Our findings in healthy adults support these opinions, but more research is required. The results add to the growing understanding that the IHI imbalance model might not hold in all cases and more investigation is needed, particularly in how it relates to visual neglect in acute stroke.

To date there have been no imaging studies in acute stroke which conclusively support the IHI imbalance model. A well-referenced trial used fMRI to analyse activation patterns of neglect patients during a visuospatial task, comparing differences between the acute and chronic phases after stroke (Corbetta et al., 2005). The authors found that in the acute phase, participants demonstrated increased excitability of the left PPC which correlated with deficits in visuospatial attention, whilst in the chronic phase the imbalance had resolved, correlating with improvement in visuospatial attention. These results appeared to support the IHI imbalance model of spatial neglect; however, a potential limitation was their classification of acute phase of stroke, which was up to 4 weeks post stroke. In the current study, the mean

time for imaging to occur in the acute phase was 32 days post stroke, which is sufficient time for cortical re-organisation to occur. Therefore, it is difficult to conclude that the changes in activation patterns are due to the release of hemispheric inhibition or, rather, result from maladaptive plasticity. A more recent trial also used fMRI to determine if acute stroke patients (average 53 hours post stroke) with neglect demonstrated hyper-activation of the left PPC as observed in subacute and chronic neglect patients (Umarova et al., 2011). The authors compared imaging data between patients following right hemisphere stroke who had neglect or visual extinction with patients without neglect and with healthy controls. Interestingly, the findings were in contrast to other results that did not support the IHI model (Corbetta et al., 2005). Instead, these authors reported that patients experiencing visual neglect following right hemisphere stroke exhibited reduced activation in the right hemisphere, but no increase in contralesional activation was observed.

There are a number of interventional trials in stroke patients, claiming to support the IHI imbalance theory, using NBS to suppress activity in the left PPC (Brighina et al., 2003; Cazzoli et al., 2012; Koch et al., 2012; Koch et al., 2008). These trials have experimented with different stimulation protocols, ranging from a single intervention session to multiple sessions over consecutive days. The neurophysiological effects of stimulation have been measured using a number of modalities such as TMS and EEG, and behavioural changes measured via a number of different behavioural and functional tasks (Cazzoli et al., 2012; Koch et al., 2012; Koch et al., 2008). Despite these trials demonstrating improvements in behavioural measures, the changes are variable and often very modest, with patients still generally exhibiting ongoing symptoms of visuospatial neglect following the intervention period. To date, only one intervention study in stroke patients with neglect has measured both neurophysiological and behavioural changes following suppressive cTBS to the left PPC.

These results only partially support the IHI imbalance model of visuospatial neglect (Koch et al., 2008). That trial used a paired-pulse TMS protocol in subacute stroke patients to demonstrate increased excitability in left PPC to M1 projections in stroke patients with neglect, compared to stroke patients without neglect and with healthy controls. They also found an association between the degree of excitability of left PPC to M1 projections and the performance on behavioural tasks, with greater excitability associated with a worse performance on visuospatial testing (Koch et al., 2008). That trial used a NBS intervention to suppress activity in the left PPC, demonstrating normalisation of excitability of left PPC to M1 circuits following the intervention. However, there was only modest clinical improvement in the behavioural task, despite group analysis reaching statistical significance. Contrary to the IHI imbalance model, Koch and co-workers found no correlation between the neurophysiological measures and the behavioural task following the intervention. Participants experienced ongoing symptoms of neglect, despite normalisation of their left hemispheric excitability (Koch et al., 2008). These results suggest that while IHI imbalance may contribute in some way to behavioural changes in visuospatial neglect, it is likely not the underlying cause, and instead may be a secondary outcome resulting from maladaptive plasticity.

Studies in healthy populations using NBS have also varied in their support of the IHI imbalance model. A number of trials have used NBS to suppress the right PPC and demonstrated neglect-like changes in behavioural tasks, which could be resolved with NBS to the left PPC (Cazzoli et al., 2009; Nyffeler et al., 2008). Whilst these behavioural results again appear to support the IHI imbalance model, the trials used no imaging or neurophysiological measures to determine changes in cortical excitability; therefore, they could only speculate about underling neurophysiology. There have been three recent trials in

healthy participants that have used NBS to suppress the right PPC (Bagattini et al., 2015; Petitet et al., 2015; Ricci et al., 2012). Two of the trials used an offline protocol, whereby rTMS was applied to the right PPC and cortical excitability was measured using either EEG or fMRI (Bagattini et al., 2015; Petitet et al., 2015). The third trial used an online protocol, applying single-pulse TMS at an intensity of 115% RMT during a line bisection task, and measuring cortical activity using fMRI (Ricci et al., 2012). All three trials were able to induce neglect-like behavioural effects and all three demonstrated reduced activity in the right PPC. Only one of the three studies, however, supported the IHI imbalance model of neglect (Petitet et al., 2015). Two demonstrated bilateral reductions in PPC activity following suppressive NBS to the right PPC (Bagattini et al., 2015; Ricci et al., 2012) and one (Petitet et al., 2015) demonstrated an increase in BOLD signal in the left PPC following the intervention.

Our current results add to the growing body of evidence, using different modalities, that the response of left PPC to right PPC suppression using NBS is variable in healthy adults. However, the predominant direction is coupled to that of the right PPC (Bagattini et al., 2015; Ricci et al., 2012). The inhibitory response of the left PPC following suppression of the right PPC is unclear, but may be due to diaschisis secondary to transcallosal downreglation of neuronal activity in the interconnected contralateral hemisphere (Bagattini et al., 2015). This current study has extended this understanding by demonstrating that pre-stimulus activity of the left PPC was highly correlated to the after-effects of cTBS of right PPC. A less excitable baseline left PPC produced greater facilitation after right PPC suppression, while a more excitable baseline left PPC was coupled to right PPC suppression. Previously, neuroimaging studies using structural and fMRI in stroke patients predicted how individuals respond to NBS (Nicolo, Ptak, & Guggisberg, 2015; Sale, Mattingley, Zalesky, & Cocchi, 2015). The current results indicate that TMS may be a useful alternative to neuroimaging, to provide

information about cortical activity and neural networks and to predict individual patients that might benefit from NBS interventions. Interestingly, it did not appear from this study that relative excitability between the PPCs at baseline was as strongly predictive of the effect of stimulation as was the degree of left PPC–right M1 MEP facilitation. However, these findings in healthy adults must be confirmed in patients with stroke and visual neglect before TMS assessments can be considered useful predictors in clinical practice.

## Behavioural measures

I hypothesised that suppressive cTBS to the right PPC would result in a rightward shift of visual bias on both the landmark and TOJ tasks. However, there was no effect of stimulation on the attentional shift in either task. At baseline, 8 of 10 participants demonstrated a leftward visual bias on the landmark task. A leftward visual bias termed pseudo-neglect is a relatively common phenomenon reported in the literature in healthy populations, arising from the lateralisation of visuospatial function in the right hemisphere (Jewell & McCourt, 2000). Baseline visual bias on the TOJ task was more evenly split in the current study, with four participants demonstrating a leftward visual bias and six a rightward bias. Individual analyses showed significant variance in response to cTBS between participants on both behavioural tasks. For the landmark task, only 5 of 10 participants demonstrated the expected rightward shift in visuospatial attention, while on the TOJ only 3 of 10 participants demonstrated the expected rightward shift. Variation both within and between individuals in response to TBS is not uncommon, with a number of contributing factors, including gender, age, genetics, synaptic history, attention, time of day, pharmacology and aerobic exercise (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2012; Ridding & Ziemann, 2010). Inter-individual variation can also occur due to differences in the population of neurons activated by the TMS pulse (Hamada et al., 2012). In particular, the efficiency of an individual to recruit late I-

waves was able to predict their response to cTBS and iTBS. Individuals who easily recruit late I-waves tend to respond as predicted to cTBS and iTBS protocols, whereas individuals who easily recruit early I-waves demonstrate the opposite effect (Hamada et al., 2012). There were no associations between the TOJ and landmark tasks when comparing baseline LI scores, post-cTBS LI scores or ΔLI scores, and no association between direction of change in LI and rightward shift in response bias. These results were unexpected and did not support the study hypothesis. Both tasks measure visual bias, and therefore correlations between the tasks were expected on baseline and change scores, with a rightward shift in response bias expected on both tasks following the intervention.

Due to the small number of participants, known variability in performance on behavioural tasks and variability in response to cTBS, there was no significant change in visual bias on a group level after stimulation. Two different behavioural measures were used to increase the likelihood of observing a change in visual bias in one or both of the tasks. The Milner landmark task is a modified line bisection test that has long been used to assess for the presence of visual neglect (Milner et al., 1993). Whilst the initial version of the test had difficulty differentiating perceptual from motor/intentional neglect, it has since been revised to remove response errors associated with motor neglect (Bisiach et al., 1998). Previous trials have shown the landmark task to be sensitive to detect rightward changes in visual bias in healthy populations; however, these studies have used rTMS, not cTBS, and have used online protocols rather than the offline protocol used here (Bjoertomt et al., 2002; Fierro et al., 2000). As the landmark task has been shown to detect perceptual neglect in near space (50 cm) but not far space (150 cm), the computer was located at a distance of 50 cm from participants' eye level, in order to increase the likelihood of a group-level change in response bias (Bjoertomt et al., 2002). However, there was only a rightward change in visual bias in

half of the participants. There are a number of potential explanations for these findings. It has been shown that different factors affect performance on the line bisection task, such as age and sex, and external factors such as line length and spatial location, and that there is significant variability in response bias between participants (Jewell & McCourt, 2000). The small sample size of 10 participants in the current study may not have been large enough to account for this variability in task performance. A protocol was used whereby two trains of cTBS were delivered in succession in an attempt to evoke a more robust suppression of right PPC in healthy adults and evoke neglect-like behaviour (Mitchell et al., 2012). Modulation was observed at the neurophysiological level, as evidenced by TMS, so the finding of no effect on the behavioural tasks was more likely due to a lack of sensitivity in the landmark task to detect subtle changes in visual bias. Alternatively, the explanation could be due to homeostatic mechanisms in the healthy participants counteracting any potential effect on visual bias as a result of the cTBS. Choosing to stimulate the PPC may be another reason for the lack of behavioural change. Despite imaging studies generally revealing that the PPC is structurally undamaged in patients with neglect, the majority of studies in healthy subjects choose to stimulate this site to induce a virtual lesion. Stimulating a different region more closely associated with lesion anatomy in stroke patients may increase the behavioural response and also increase the applicability of our results to stroke patients with neglect.

The other task used in the current study was the TOJ task, which is a behavioural test measuring the speed of processing of the visual system (Sternberg & Knoll, 1973; Ulrich, 1987). In the visual system there is evidence that attention affects the perception of temporal order, with increased speed of processing to stimulus when attention is directed towards it (Stelmach & Herdman, 1991). This study used a basic test of temporal order judgement, where participants were asked to fixate their attention on a central cross, then presented with

stimulus in the left and right hemifield and asked to make a decision as to which stimulus arrived first. It was hypothesised that following the suppressive cTBS intervention, each participant's visual bias would be directed towards the right, and hence they would perceive the stimulus onset to be earlier in the right hemifield. For this group of participants, however, there was no change in the TOJ task. Once again it appears that the task was too easy to detect any subtle changes in visual bias following suppressive cTBS to the right PPC. An alternative task, such as the Posner paradigm, which incorporates a component of directed visual attention towards a specific hemifield, may have been more sensitive at detecting subtle changes in visual bias in our group of participants, and a future study could investigate this.

Other studies investigating visuospatial neglect in healthy participants have employed similar PPC suppression stimulation paradigms (non-invasive magnetic) to our trial and they were able to demonstrate a rightward shift in visuospatial attention. One trial investigating different stimulation paradigms suggests that increasing the number of cTBS trains to four, and extending the inter-train interval to 15 min, may be more effective than single- or double-stimulation trains with inter-train intervals of 5 or 10 min. Using this protocol may have improved the degree and duration of behavioural change in our subjects and could be the subject of a future investigation (Nyffeler et al., 2006). Previous studies have also used different behavioural tasks, which may be more sensitive to changes in the healthy population. The most common is a visual exploration task, where the participant looks at an image and the time they spend with their vision fixed in the right or left hemifield is recorded (Cazzoli et al., 2009; Nyffeler et al., 2008). Another recent study using rTMS to suppress right PPC activity was able to show a rightward shift on a line bisection task following stimulation (Bagattini et al., 2015). The trial also used a reaction time task, testing response

time to visual stimuli in the left or right hemifield before and after stimulation. They found no change in pre/post-reaction times in the intervention group; however, there was a reduction in the reaction time in the sham stimulation group, indicating a perceptual learning effect of the task. Interestingly, they also found that reaction times were not modulated by the particular hemifield to which the stimulus was presented, contrary to their expectation of slower reaction times to stimuli in the left hemifield due to a rightward shift in visual bias. They concluded their result might be because the task was too simple to detect changes between sides in healthy populations (Bagattini et al., 2015). The effect of perceptual learning of the behavioural task may also have influenced results in the current study. Similar to the trial by Bagattini and colleagues, the current study demonstrated an unexpected leftward shift in visual bias in a number of participants on both behavioural tasks, which may be due to perceptual learning of the task. As the participants became more familiar with the task, their predisposition to a leftward visual bias (pseudo-neglect) may have resulted in a leftward change on the behavioural task. If a learning effect was indeed present, then an unchanged visual bias or a small leftward shift in visual bias on the task may actually reflect a rightward shift in visual bias. There is no way of proving this without undertaking further studies; however, it could be a potential explanation for why only a small number of participants demonstrated a behavioural effect despite nearly all participants having changes in cortical excitability on their neurophysiological measures. A subsequent study could include more practice attempts of the behavioural task prior to recording baseline measures, to try to remove the influence of perceptual learning on the results.

## Alternative models for spatial neglect

Due to the emergence of new evidence suggesting that the IHI model may not hold in all subjects, it is important to consider other models of spatial neglect. One alternative describes neglect as a disconnection syndrome between fronto-parietal networks in the right hemisphere. The model is based on the anatomy-functional model of visuospatial neglect, which describes the dorsal and ventral attention networks (Corbetta et al., 2005; Lunven & Bartolomeo, 2016). These two fronto-parietal networks communicate through the SLF white matter tracks. The dorsal attentional network is supported by SLF1, while the ventral attentional network is supported by SLF3. The two networks interact through SLF2, which connects parietal regions of the ventral network with frontal regions of the dorsal network. The model proposes that rather than pure cortical damage resulting in neglect, it is damage to the white matter tracts that causes a disconnection in these fronto-parietal networks and contribute to the development of neglect (Lunven & Bartolomeo, 2016). This theory has been supported in a small study reporting tumour resection surgery that demonstrated that intracranial electrical stimulation to temporarily deactivate SLF2 fibres resulted in temporary neglect on a line bisection task (Lunven & Bartolomeo, 2016). Further support of fronto-parietal disconnection in neglect has been obtained through imaging of subacute stroke patients with neglect, demonstrating hypo-activation of anatomically intact spatial brain regions (inferior parietal sulcus, superior parietal lobule, dorsolateral prefrontal sulcus) during a visuospatial task (Corbetta et al., 2005). Reactivation in these regions in the chronic phase of recovery also correlated with a resolution of visuospatial neglect symptoms (Corbetta et al., 2005). Another trial comparing the difference in integrity of white matter tracts between participants with and without neglect in the subacute and chronic phase of stroke also supported the disconnection theory (Lunven & Bartolomeo, 2016). These authors found that damage to fronto-parietal networks in the right hemisphere was predictive of neglect in both the subacute and chronic phases of stroke, and also found that people

experiencing chronic neglect had reduced white matter integrity in the posterior portion of the SLF. Another trial had similar findings, suggesting that ongoing fronto-parietal disconnection due to damage to SLF fibres appears to be an indication of more severe and long-lasting neglect (Doricchi & Tomaiuolo, 2003).

Whilst the IHI imbalance model is based on an imbalance of transcallosal inhibition between the two hemispheres, an alternative model based on transcallosal excitation has also been proposed (Chechlacz et al., 2015). This model argues that rather than transcallosal projections inhibiting the contralateral hemisphere, the corpus callosum reinforces information transfer between hemispheres, with stronger connectivity corresponding with a rebalancing of hemispheric activity (Chechlacz et al., 2015). A right hemisphere lesion causes a disconnection between the hemispheres and contributes to the development of spatial neglect. This model proposes that the left PPC has a compensatory role following right hemisphere lesion, rather than further inhibiting the damaged right PPC. Support for this model has come from studies showing that behavioural laterality is negatively correlated with corpus callosum size, where a smaller corpus callosum correlates with greater laterality of function due to reduced interhemispheric connectivity (Bloom & Hynd, 2005). A larger corpus callosum has also been associated with individuals able to perform more demanding tasks, suggesting the importance of interhemispheric connectivity. Support for the interhemispheric excitation model in visual attention has been provided by an imaging study that demonstrated reduced white matter integrity in the splenium of the corpus callosum in people experiencing persistent chronic neglect. In this example, the model suggests that the left hemisphere is unable to compensate for visual deficits due to the absence of effective interhemispheric communication (Lunven & Bartolomeo, 2016). The study also proposes that improving interhemispheric communication of parietal and occipital regions should be the focus of

rehabilitation methods and interventions, as this will result in a resolution of the behavioural symptoms of neglect (Lunven & Bartolomeo, 2016).

Due to conflicting evidence supporting both an excitatory and inhibitory model of the corpus callosum in spatial neglect, another model was proposed suggesting that the corpus callosum has both an excitatory and inhibitory role in interhemispheric communication (Bloom & Hynd, 2005; Chechlacz et al., 2015). In this model, the corpus callosum is described as an active body, facilitating communication between the hemispheres through both inhibition and excitation, depending on the task being undertaken. A recent cTBS study in healthy subjects has added support to the dual purpose inhibition and excitation model of the corpus callosum in spatial neglect (Chechlacz et al., 2015). They determined that participants with a high fractional anisotrophy (FA) of the corpus callosum exerted greater interhemispheric inhibition (IHI) over the left PPC, and had a greater right hemisphere lateralisation of visuospatial function. Participants with low FA had less IHI, suggesting greater interhemispheric communication between the two hemispheres. The authors also found that cTBS to the right PPC had different behavioural effects depending on the size of the corpus callosum. Participants with a larger corpus callosum had a small rightward shift in attention, suggesting that higher interhemispheric connectivity resulted in a rebalancing of activity across the hemispheres. Participants with a small corpus callosum had a greater rightward shift, suggesting there was ineffective interhemispheric connectivity affecting the rebalancing of activity across hemispheres (Chechlacz et al., 2015). Although these findings need to be confirmed in stroke patients, they add support to the theory that the left hemisphere may have a compensatory role in visual neglect, and that improving interhemispheric connectivity may improve signs of neglect after stroke.

## Summary

Our findings, combined with those of others, may have relevance for stroke patients. Growing evidence that the IHI imbalance model may not hold in healthy adults suggests that the increased excitability of the left PPC of subacute stroke patients with neglect may result from maladaptive plasticity as opposed to a release of inhibition from the right PPC. Before novel interventions to treat visual neglect in stroke patients can be implemented in clinical practice, such as left PPC suppression with NBS, greater understanding of the relationship between PPC IHI in acute stroke is required. These findings suggest that TMS may be useful in predicting how patients will response to NBS, which may help clinicians and researchers determine who may benefit most from NBS interventions.

## Limitations

There were limitations to this study. First, the PPC–M1 interhemispheric pathway, an indirect measure of PPC excitability, might not reflect PPC–PPC activity, explaining our lack of correlation between neurophysiological and behavioural data. Second, the small number of participants means the results of our correlation analysis should be interpreted with caution, until confirmed in a larger study. Third, the location of the conditioning coil over the PPC was determined using the 10–20 EEG system, and therefore accurate coil placement over the cIPS cannot be confirmed. However, we only included participants who demonstrated PPC to contralateral M1 facilitation on paired-pulse TMS at baseline, as this was the effect reported in previous studies using MRI-guided coil positioning over the PPC (Koch et al., 2009). Fourth, intra-session reliability of dual-coil PPC to contralateral M1 facilitation has not been investigated, which may have affected our results. However, we were careful to use the same landmarks as in the pre-stimulation trials, and so do not consider this to be an issue. Finally, we were only able to induce a rightward shift in visual bias in five participants on the landmark task and three participants on the TOJ; therefore, despite postulating a possible

mechanism underlying spatial neglect from the current study, the results must be interpreted accordingly.

This was a preliminary study investigating a novel TMS technique to measure PPC interhemispheric excitability; a larger follow-up study is required to corroborate our findings. Further studies in stroke patients are also required before clinical interpretations about the mechanisms of spatial neglect in acute stroke can be drawn.

## Implications for future research

Recent research, including the findings of the present study, indicate that rather than neglect being a result of an IHI imbalance, it may be better described as a disconnection between fronto-parieto networks of the dorsal and ventral attention streams. Future research should focus on improved understanding of changes occurring to these fronto-parietal networks in the right and left hemisphere of people with neglect. Currently, paired-pulse TMS investigations of parieto-motor connectivity in stroke patients with neglect have focused on the left hemisphere, whilst changes occurring in the right hemisphere remain largely unknown. Paired-pulse TMS protocols have already been used to investigate parieto-motor connectivity in the right hemisphere in healthy people, and exploring these pathways following right PPC lesion by NBS or in stroke-affected people may increase understanding of pathophysiological mechanisms of neglect and assist in the development of new interventions and rehabilitation strategies (Koch et al., 2007). Breakdown in interhemispheric communication has also been implicated in the development of and ability to compensate for neglect, and this should be investigated in the future. Studies using paired-pulse or three-coil TMS protocols could be undertaken to determine how a disconnection between hemispheres contributes to the development of and recovery from visual neglect symptoms. A three-coil

technique, where the conditioning stimulus is applied to the left and right PPC and then a test stimulus applied to either the right or left M1, has already been used in healthy people to demonstrate IHI between PPCs (Koch et al., 2011). A similar technique could be used in conjunction with suppressive cTBS to the right PPC, to explore pathophysiological changes in hemispheric communication associated with visuospatial neglect. Alternative methods of measuring interhemispheric communication, such as EEG, could also provide additional information regarding how hemispheric disconnection may contribute to hemispatial neglect. Another possible direction for future research could be to investigate whether stroke severity contributes to the underlying mechanism of neglect, and the contribution of the IHI imbalance model. Hemispheric imbalance and brain re-organisation related to recovery of upper limb function following stroke appear to be related to stroke severity (Bradnam, Stinear, & Byblow, 2013). It has been suggested that in more severe strokes, a rebalancing of hemispheres via NBS may affect recovery of function through inhibiting ipsilateral descending pathways that could assist with control of the paretic upper limb (Bradnam et al., 2013). Similar considerations may need to be taken when looking at interventions to rebalance PPC excitability in stroke patients with neglect, as suppression of the left PPC may inhibit the ability to compensate for the damaged right hemisphere.

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