Variation in left posterior parietal-motor cortex interhemispheric facilitation following right parietal continuous theta-burst stimulation in healthy adults

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Abstract

Spatial neglect is modelled on an imbalance of interhemispheric inhibition (IHI); however evidence is emerging that IHI imbalance 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 transcranial magnetic stimulation to probe excitability of projections from posterior parietal cortex (PPC) to contralateral primary motor cortex (M1) bilaterally. Motor evoked potentials (MEPs) were recorded from the first dorsal interossei and facilitation was determined as ratio of conditioned to non-conditioned MEP amplitude. A laterality index reflecting the balance of excitability between the two hemispheres was calculated. A temporal order judgement task assessed visual attention. Continuous theta-burst stimulation (cTBS) was used to transiently suppress right parietal cortex activity and the effect on laterality and judgement task measured, along with associations between baseline and post stimulation measures. Stimulation had conflicting results on laterality, with most participants demonstrating an effect in the negative direction, with no impairment of the temporal order judgement task. There was a strong association between laterality direction and degree of facilitation of left PPC-to right M1 following stimulation (r=.902), with larger MEP facilitation at baseline demonstrating greater reduction (r=-.908). There was relative balance between the cortices at baseline but right PPC suppression did not evoke left PPC facilitation in most participants, contrary to the IHI imbalance model. Left M1 facilitation prior to stimulation may predict an individual's response to continuous theta-burst stimulation of right PPC. These findings may have relevance for using cTBS in stroke patients to address visual neglect.

INTRODUCTION

Spatial neglect is a severe neurological disorder common after stroke, characterized by a failure to attend and respond to stimuli in the contralesional side of space (Heilman et al., 1993, Karnath et al., 2002, Vallar et al., 2003, Driver et al., 2004, Stein et al., 2009). A well-researched model to explain spatial neglect after stroke is the imbalance of inhibition between the brain hemispheres, known as interhemispheric inhibition (IHI) (Kinsbourne, 1976). The model proposes that in the healthy adult brain, normal visual attention depends on comparable inhibition passed between the two posterior parietal cortices (PPC's) (Kinsbourne, 1976). Following a right hemisphere stroke, inhibition of the left PPC by the right is reduced, so that excitability of the left PPC is enhanced (Koch et al., 2008). The result is a rightward shift of visuospatial attention (Kinsbourne, 1976, 1993, Oliveri et al., 1999). Interhemispheric imbalance between the PPCs has been reported in neuroimaging and Transcranial Magnetic Stimulation (TMS) studies in subacute and chronic stroke patients who experience right visuospatial neglect. Furthermore, the model is supported by studies in healthy adults using repetitive TMS (rTMS) or theta burst stimulation (TBS), where activity in the left or right PPC is modulated to induce transient visual neglect-like behaviour (Pascual-Leone et al., 1994, Nyffeler et al., 2008, Cazzoli et al., 2009, Bagattini et al., 2015, Petitet et al., 2015). These findings led to interventional studies where rTMS or TBS was used to restore interhemispheric balance and improve visual neglect in subacute and chronic stroke patients (Brighina et al., 2003, Cazzoli et al., 2012, Koch et al., 2012, Sale et al., 2015a). However, two studies conducted in healthy adults suggested the IHI imbalance model may not explain visual neglect in all cases (Ricci et al., 2012, Bagattini et al., 2015). In both studies, continuous TBS (cTBS) to suppress activity of right PPC reduced excitability bilaterally, assessed by functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Bilateral PPC suppression opposes the IHI imbalance model, which would dictate a release of inhibition over the left PPC, producing hyper excitability (Ricci et al., 2012, Bagattini et al., 2015). Interhemispheric imbalance may, therefore, be an adaptive response in subacute and chronic stroke whether it contributes to visual neglect in acute stroke is yet to be determined (Bagattini et al., 2015).

Another method to test interhemispheric inhibition following suppression of the PPC in healthy adults is two coil, paired-pulse TMS, to probe excitability of projections between a PPC and the contralateral primary motor cortex (M1) (Koch et al., 2007, Koch et al., 2008, Koch et al., 2009, Koch et al., 2011). 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 right PPC can be explored in healthy adults. Furthermore, the impact of pre stimulation PPC-contralateral M1 excitability on responses to right PPC suppression can be examined to further develop the understanding of IHI imbalance and contribution to visual neglect.

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 PPC to contralateral M1 bilaterally. A laterality index (LI) was calculated to determine the relative balance of excitability between the two PPC's, before and after cTBS to suppress right PPC. A temporal order judgement task (TOJ) assessed stimulation-induced effects on visual attention (Stelmach and Herdman, 1991). Based on the IHI imbalance model we hypothesised that excitability of the right PPC would be reduced relative to the left following cTBS of right PPC, producing a more positive LI. Moreover, we expected that higher left than right PPC excitability after cTBS would be reflected in a rightward shift in visual attention, as measured

by the TOJ. Finally, we hypothesised that baseline LI and/or baseline PPC-M1 interhemispheric facilitation would predict the response to right PPC suppression by cTBS.

MATERIALS AND METHODS

Participants. Fourteen right handed healthy participants provided informed consent in accordance with the declaration of Helsinki. Ethical approval for the study was granted by the regional ethics committee.

Experimental design. Participants attended one session lasting approximately 2.5 hours. Handedness was confirmed by the Edinburgh Handedness Inventory. Baseline assessments included the TOJ to assess visuospatial attention and TMS to probe excitability of PPC to contralateral M1 projections bilaterally.

Temporal Order Judgment 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 500mm. Responses were made with the laptop's keyboard. The stimuli were two squares with a size of 15mm, 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 display 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 randomly delivered at 0, 16.7, 33.3, 50, or 66.7msec. Participants completed 180 trials per assessment. 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 and Herdman, 1991)

Transcranial Magnetic Stimulation. A paired pulse, twin coil TMS protocol was used to probe facilitation between each PPC (caudal intraparietal sulcus, cIPS) and its contralateral M1 (Koch et al., 2009). The PPC was located by marking the 10-20 EEG system on the head of each individual and confirmed by observing TMS-evoked PPC-contralateral M1 facilitation on the computer screen. If PPC-M1 facilitation was not present, the conditioning coil was repositioned by 0.5cm in a grid-like configuration until facilitation occurred. MEPs were recorded using electromyography (EMG) from the first dorsal interosseous (FDI) muscle bilaterally via surface electrodes (Ambu® BlueSensor ECG Electrodes, Denmark). One block of TMS was recorded for each hemisphere, consisting of one single-pulse TMS of M1 trial (test stimulus) to evoke a non-conditioned (NC-) MEP and two paired-pulse TMS trials to evoke conditioned (C-) MEPs. The conditioning stimulus applied to the PPC was set at 90% and 110% resting motor threshold of the ipsilateral M1 representation of the FDI with an interstimulus interval between the conditioning and test stimulus set at 8ms (Koch et al., 2009). The intensity of the test stimulus was established to evoke a MEP of approximately 1mV in the relaxed contralateral FDI. Sixteen NC-MEPs and sixteen C-MEPs at each stimulus intensity were delivered in random order, for a total of 48 MEPs per hemisphere.

Continuous theta-burst Stimulation. The intervention consisted of two trains of cTBS (each train consisting of 600 pulses delivered in bursts of 3 pulses at 50Hz with bursts repeated every 200ms), applied to the right PPC with a five minute rest between trains (Huang et al., 2005, Goldsworthy et al., 2012). The intensity of stimulation was set at 90% of AMT established in the right M1 representation of the FDI muscle (Huang et al 2005). The post

intervention TOJ task and TMS were collected five minutes after completing the second cTBS train.

Data Analysis. The 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 an LI 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 excitability of both PPCs was equal. A positive value signified a relative greater excitability of left PPC and a negative value signified relative greater excitability of right PPC. For each individual, the conditioned stimulation intensity (either 90 or 110%) that produced the largest MEP facilitation at baseline was identified for each hemisphere and used to calculate LI pre and post cTBS. The effect of stimulation on LI, TOJ task, and PPC-M1 MEP facilitation for each hemisphere was statistically analysed using paired t-tests. Pre-stimulus root mean square EMG (rmsEMG) was analysed using repeated measures ANOVA with CONDITION (C/NC MEP) and TIME (pre, post) as factors. To assess if baseline excitability could predict responses to cTBS, the difference (post – pre stimulation) in LI and MEP facilitation was calculated and expressed as ΔLI and ΔPPC-M1 MEP facilitation. A correlation analysis examined associations between baseline LI and ΔLI, and between baseline PPC-M1 MEP facilitation and ΔPPC-M1 MEP facilitation for each hemisphere. Finally, potential associations were tested between ΔLI and ΔPPC-M1 MEP facilitation for each hemisphere and between ΔLI and ΔTOJ. Significance was set at $p<0.05$.

RESULTS

Four participants were excluded from data analysis as PPC-M1 MEP facilitation was not observed at baseline; therefore analysis was performed on 10 participants (7 female, ages 23-49). Laterality index measures for each participant at baseline, after stimulation and ΔLI are shown in Table 1. Group level analysis revealed cTBS of right PPC had no effect on LI ($p=0.664$). Observation of the LI data revealed variable responses to stimulation, with six participants demonstrating negative ΔLI and four participants positive ΔLI (Table 1). The hemispheres were then analysed individually to probe this ΔLI variation (Table 2). There was a reduction in right PPC-left M1 MEP facilitation following cTBS to right PPC ($p=0.019$), producing -Δ values. 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 negative Δ left PPC-right M1 MEP facilitation ($p=0.07$) (Table 2). There was no effect of CONDITION ($p=0.230$) or TIME ($p=0.227$) on rmsEMG (all > 0.01mV).

There was strong correlation between ΔLI and Δleft PPC - right M1 (figure 1a, $r=0.902$, $p<0.001$) but no association between ΔLI and Δright PPC to left M1 (figure 1b, $r=-0.094$, $p=0.797$). This indicates the direction of ΔLI (positive or negative) was driven by Δleft PPC-right M1. The correlation to determine if baseline excitability could predict ΔLI revealed only a moderate association between LI and ΔLI (figure 2a, $r=-0.640$, $p=0.046$). However, there was strong correlation between baseline PPC-M1 MEP facilitation and ΔPPC-M1 MEP facilitation for both hemispheres (figure 2b and 2c). 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 to left M1 MEP facilitation, $r=-0.944$, $p<0.001$). 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 2b). Continuous TBS had no effect on the response bias in the temporal order judgment task at the

group level (pre cTBS LI mean1.22, SD 17.21; Post cTBS LI mean -5.33, SD 22.18, p=0.09). There was no association between ΔLI and ΔTOJ task (p=0.13).

DISCUSSION

According to the IHI imbalance model, reducing excitability of the right PPC should increase excitability of the left PPC, through a release of interhemispheric inhibition. The current study tested this model by investigating the effect of right PPC suppression using cTBS, on the excitability of inter-hemispheric projections from PPC to contralateral M1 bilaterally. Relative excitability was determined using a TMS-evoked laterality index, and the effect of cTBS on visuospatial attention assessed using a temporal order judgement task. The main findings were that the LI and TOJ were unaffected by stimulation and there was no relationship between ΔLI and ΔTOJ at the group level. To probe the underlying reason for the lack of response of ΔLI, each hemisphere was analysed individually. As expected, right PPC to 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 too, with 8 of 10 participants demonstrating this response. The resulting LI was relatively more negative in these individuals compared to their baseline. These findings are inconsistent with our hypothesis, as we expected an increase in left PPC-right M1 MEP facilitation and a positive directional shift in the LI. For the other findings, there was a moderate association between baseline LI and ΔLI, however the stronger associations were between baseline MEP facilitation and ΔMEP facilitation for both hemispheres. The direction (positive or negative) for Δleft PPC-right M1 MEP facilitation, which was variable between individuals and determined the direction of ΔLI, was clearly influenced by baseline MEP facilitation.

Our current findings using paired pulse TMS supported two previous studies where bilateral reduction in PPC excitability following cTBS to suppress right PPC using fMRI and EEG was reported (Ricci et al., 2012, Bagattini et al., 2015). The results add to the growing understanding that the IHI model might not hold in all cases and more investigation is needed to understand how it relates to visual neglect in acute stroke. The novelty of the 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 in previous reports (Koch et al., 2007, Koch et al., 2008). We considered this approach 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 a 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 because there was 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 hyperactivation of the left parietal lobe in all patients, regardless of whether they had neglect or not (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 hyperexcitabilty was a consequence of the severe structural damage to the right hemisphere, but was not the cause of the attentional deficits (Umarova et al., 2011). Our finding in healthy

adults support these opinions, but more research is required in both healthy models and in stroke patients.

The current results add to the growing body of evidence, using different modalities, that the response of left PPC to right PPC suppression using non-invasive brain stimulation (NBS) is variable in healthy adults. Our findings support that the predominant direction of left PPC response is coupled to the right PPC (Ricci et al., 2012, Bagattini et al., 2015). The reason underlying inhibition of the left PPC following right PPC suppression is unclear but may be due to diaschisis secondary to transcallosal downreglation of neuronal activity in the contralateral hemisphere (Bagattini et al., 2015). Our study has extended this understanding by demonstrating that prestimulus 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. Therefore, the baseline excitability state may impact on responses to cTBS, which could have important implications for using cTBS as an intervention in stroke patients. Previously, neuroimaging studies utilising structural and fMRI in stroke patients have been used to predict how individuals respond to NBS (Nicolo et al., 2015, Sale et al., 2015b). The current results indicate that TMS may also provide information about cortical activity to predict individual patients that might benefit from NBS interventions. Interestingly, it did not appear from the current results that relative excitability between the PPCs at baseline was as strongly predictive of the effect of stimulation as was baseline left PPC-right M1 MEP facilitation. A single hemispheric measure may suffice, negating the requirement to test both hemispheres to generate an LI. 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.

There was no effect of stimulation on the attentional shift in the TOJ task at the group level in the current study and no association between direction of change in LI and rightward shift in response bias. Therefore, the impact of the balance of excitability between the PPCs on visual neglect-like behaviour could not be determined. We followed a protocol where two trains of cTBS were delivered in succession, in an attempt to evoke a more robust suppression of right PPC in healthy adults to evoke neglect-like behaviour (Goldsworthy et al., 2012). Modulation occurred at the neurophysiological level, as evidenced by the TMS findings, but this was not reflected in the behavioural task. It might be that the pathways modulated in this study were not associated with the neurophysiology underlying behavioural change measured by the TOJ, or that the healthy brain was able to compensate for the impact of stimulation via homeostatic mechanisms. A subsequent study could examine different pathways, attempt a different task or alter the parameters of the TOJ to make it even more challenging to help answer this question.

There were several limitations to this study. First the PPC –M1 interhemispheric pathway, an indirect measure of PPC excitability, might not reflect PPC-PPC activity. If this is the case, it would explain the lack of correlation between neurophysiological and behavioural data. Second, the small number of participants means the results of our correlation analyses 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 IPL cannot be confirmed. However, we only included participants who demonstrated PPC-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). Finally, we were only able to induce a rightward shift in

visual bias in 3 participants, so we are unable to postulate a possible mechanism underlying spatial neglect. This was a preliminary study investigating a novel TMS technique to measure PPC interhemispheric excitability and a larger follow up study is required to corroborate our findings.

Summary. Our findings combined with that of others has relevance for stroke patients. Growing evidence that the IHI imbalance model may not hold in healthy adults suggests 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. Our findings suggest that TMS may be useful in predicting how patients will response to NBS, which may assist clinicians and researchers to determine who may benefit most from NBS interventions.

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Table 1
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 toward -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.

Table 2
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, following cTBS of right PPC.

Figure 1 (a) Correlation analysis demonstrated a strong positive association between ΔLI and Δleft PPC – Right M1 MEP facilitation. A more negative ΔLI was associated with more negative Δleft PPC – Right M1 MEP facilitation and a more positive ΔLI was associated with more positive Δleft PPC – Right M1 MEP facilitation (b) There was no association between ΔLI and Δ right PPC to Left M1 MEP facilitation.

Figure 2. (a) Correlation analysis demonstrating a moderate association between baseline LI and ΔLI. A positive LI at baseline was associated with a negative ΔLI and a negative LI at baseline was associated with a positive ΔLI. (b) Correlation analysis demonstrating a strong association between baseline left PPC –right M1 MEP facilitation and Δ left PPC –right M1 MEP facilitation. Larger baseline facilitation was associated with more negative Δ. (c) Correlation analysis demonstrating a strong association between baseline right PPC –left M1 MEP facilitation and Δ right PPC –left M1 MEP facilitation. Larger baseline facilitation was associated with more negative Δ.