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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 modeled on an imbalance of interhemispheric inhibition (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 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 judgment task (TOJ) assessed visual attention. Continuous theta-burst stimulation was used to transiently suppress right parietal cortex activity and the effect on laterality and judgment 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 decrement in the TOJ task. Correlation analysis suggests 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 ($r = -.908$). Findings indicate 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.

Key words: interhemispheric inhibition, posterior parietal cortex, primary motor cortex, theta-burst stimulation.

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 behavior (Pascual-Leone et al., 1994; Nyffeler et al., 2008; Cazzoli et al., 2009; Bagattini et al., 2015; Petitet et al., 2015). These findings have led to interventional studies where rTMS or TBS have been 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., 2015). However, two studies conducted in healthy adults have suggested the IHI imbalance model may not explain visual neglect in all cases (Ricci et al., 2012; Bagattini et al., 2015). In both, continuous TBS (cTBS) to suppress activity of right PPC reduced excitability bilaterally, assessed by functional

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Abbreviations: cTBS, continuous TBS; EEG, electroencephalography; EMG, electromyography; FDI, first dorsal interosseous; fMRI, functional magnetic resonance imaging; IHI, interhemispheric inhibition; M1, primary motor cortex; MEPs, motor-evoked potentials; NBS, non-invasive brain stimulation; PPC, posterior parietal cortex; rTMS, repetitive TMS; TBS, theta burst stimulation; TMS, transcranial magnetic stimulation; TOJ, temporal order judgment.

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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; Petitet 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 probe IHI following suppression of the PPC in healthy adults is that of two coil, paired-pulse TMS, to test excitability of projections from a PPC to 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 PPC-contralateral M1 excitability prior to stimulation on responses to right PPC suppression can be examined to further understand IHI imbalance and 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 the right PPC. A temporal order judgment task (TOJ) assessed stimulation-induced effects on visual attention (Stelmach and Herdman, 1991). Based on the IHI imbalance model we hypothesized 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 hypothesized that baseline LI and/or baseline PPC-M1 interhemispheric facilitation would predict the response to right PPC suppression by cTBS.

EXPERIMENTAL PROCEDURES

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 h. 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 center 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 center, respectively. Each trial began with the presentation of white squares outlined against a black display background for 300 ms. The color 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 ms. Participants completed 180 trials per assessment. The participants indicated by key presses whether the left or right square changed colors 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 the PPC (caudal intraparietal sulcus, cIPS) and 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 0.5 cm in a grid-like configuration until facilitation occurred. Motor-evoked potentials (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 8 ms (Koch et al., 2009). The intensity of the test stimulus was established to evoke a MEP of approximately 1 mV 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 three pulses at 50 Hz with bursts repeated every 200 ms), 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