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The Role of the Posterior Parietal Cortex on Cognition: An Exploratory Study

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Abstract

Theta burst stimulation (TBS) is a form of repetitive transcranial magnetic stimulation (rTMS) that can be used to increase (intermittent TBS) or reduce (continuous TBS) cortical excitability. The current study provides a preliminary report of the effects of iTBS and cTBS in healthy young adults, to investigate the causal role of the posterior parietal cortex (PPC) during the performance of four cognitive functions: attention, inhibition, sequence learning and working memory. A 2 x 2 repeated measures design was incorporated using hemisphere (left/right) and TBS type (iTBS/cTBS) as the independent variables. 20 participants performed the cognitive tasks both before and after TBS stimulation in 4 counterbalanced experimental sessions (left cTBS, right cTBS, left iTBS and right iTBS) spaced 1 week apart. No change in performance was identified for the attentional cueing task after TBS stimulation, however TBS applied to the right PPC did disrupt performance when inhibiting a reflexive response. The sequence learning task revealed differential effects for encoding of the sequence versus the learnt items. cTBS on the right hemisphere resulted in faster responses to learnt sequences, and iTBS on the right hemisphere reduced reaction times during the initial encoding of the sequence. The reaction times in the 2-back working memory task were increased when TBS stimulation was applied to the right hemisphere. Results reveal clear differential effects for tasks explored, and more specifically where

TBS stimulation on right PPC could provide a potential for further investigation into improving oculomotor learning by inducing plasticity-like mechanisms in the brain.

Introduction

Traditionally, the posterior parietal cortex (PPC) was thought to be an 'association area' for sensory input and motor movements (Andersen & Buneo, 2002). However, more recently it has been suggested that the PPC assists in higher-level cognitive functions via the generation of intentions and planning of movements, orienting of attention, use of working memory and representation of the space around us (Culham & Kanwisher, 2001; Andersen & Buneo, 2002). The current study aimed to contribute to the growing understanding of the PPC, by investigating the involvement of the PPC in four cognitive functions using theta burst stimulation in healthy individuals.

It is a well-established finding that the posterior parietal cortex (PPC) plays an important role in ***visual attention*** (Behrmann, Geng & Shomstein, 2004). According to Milner and Goodale (1995) the PPC is part of the dorsal visual stream, which can be described as 'vision-for-action', as it allocates attention to incoming visual information so that an appropriate motor response can be selected. Unsurprisingly, visual attention is thought to be closely linked to oculomotor responses, suggesting that eye movements are the most appropriate indicator of allocation of attention by the PPC (Rushworth, Paus & Sipila, 2001). The dorsal pathway is suggested to be part of a fronto-parietal network of visuo-spatial attention (Corbetta & Shulman, 2002), in which the PPC projects to the dorsolateral prefrontal cortex (dlPFC) after receiving input from visual areas (Milner & Goodale, 1995). Corbetta and Shulman (2002) suggest more simultaneous activation of frontal and parietal regions in controlling allocation of visual attention. More recently, it has been suggested that frontal activation during cue presentation is increased when a cue creates response conflict, for example if distractors are presented alongside the directional cue (Broussard,

2012), as is done in the Flanker Task (Eriksen & Eriksen, 1974). The current study therefore employed a simple attentional task which is likely to activate the fronto-parietal attention network (Green and McDonal, 2008; Markett et al, 2014). The PPC has been suggested to demonstrate lateralization of functions, where the left hemisphere is mainly associated with visuo-temporal attention, and the right hemisphere mainly with visuo-spatial attention (Coull & Nobre, 1998). Xu et al. (2016) studied lateralization effects within the PPC using repetitive Transcranial Magnetic Stimulation (rTMS) and found the right PPC plays a key role in alerting and spatial orienting.

As part of the fronto-parietal network involved in executive functions the posterior parietal cortex has also been implicated in the inhibitory control (Osada et al, 2019). The anti-saccade task (Hallett, 1978) is considered a good measure of ***response inhibition***, as it requires the participant to inhibit a pre-potent eye movement towards the target, and instead move their eyes to the opposite location. The anti-saccade task has been used to study response inhibition in a range of different populations and has been deemed a reliable tool for studying inhibitory control (Hutton & Ettinger, 2006). The PPC has been implicated in anti-saccade performance (Sweeney et al. 1996; Luna et al. 2001) and patients with parietal lesions show more variability in their reaction time and accuracy (Braun, Weber, Mergner & Schulte-Mönting, 1992). Although the contribution of the PPC to voluntary control of eye movements is recognised (Bender et al. 2013), its specific role in response inhibition remains unclear (Zhou, Qi & Constantinidis, 2016). Most data implicating the PPC comes from activation patterns in fMRI, and the PPC has been found to show general activation in association with many executive tasks (Culham & Kanwisher, 2001). A number of studies have shown the PPC forms part of a network involved in response inhibition that includes the inferior frontal cortex and presupplementary premotor area (Robbins, 1996). However, the causal role of the PPC in response inhibition is still very much

under debate. The current study aimed to address this role by utilizing the anti-saccade (i.e. nogo) task (Hallett, 1978) to study the involvement of the PPC in response inhibition. The task also included prosaccade (i.e. go) trials whereby the participant looked toward the target, which does not require response inhibition. The PPC has been implicated in both pro- and anti-saccade trials (DeSouza, Menon & Everling, 2003), which suggests perhaps its role is limited to orienting the eye movements, and that the dorsolateral prefrontal cortex is responsible for the decisional and inhibitory processes necessary for an anti-saccade (Pierrot-Deseilligny et al. 2003; 2005). If the PPC's role is limited to initiating and executing eye movements then TMS stimulation should show equivalent effects in both anti and prosaccade trials. However, if the PPC does play a role in response inhibition, the affect of stimulation should only be observed, or been seen to a larger degree, on the anti-saccade trials. The cortical network involved in the process of inhibitory control shows right hemispheric dominance (Garavan, Ross & Stein, 1999; Aron et al. 2003; Aron, Robbins & Poldrack, 2004) suggesting the effects should be evident after right PPC stimulation.

The process of ***sequence learning*** involves a series of motor movements in a specific sequence. Repeated presentations of a sequence have been shown to result in a reduction in reaction time, because participants are learning the structure of the sequence (Nissen & Bullemer, 1987). Previous research has shown that individuals can anticipate the target locations of a learned sequence and will make anticipatory eye movements towards the next target location (Burke & Barnes, 2007). It has been suggested that visuo-spatial attention is a key process in sequence learning in the visual domain, as the learning mechanism is only engaged for locations that are attended to (Remillard, 2009). Furthermore, short-term memory and working memory have been suggested to influence sequence learning (Frensch & Miner, 1994; Bo, Jennett & Seidler, 2012). Given the PPC's well-established role in visuo-spatial attention, and its role in visual short-term memory (Todd & Marois, 2004; 2005) and

spatial working memory (Jonides et al. 1993; Walter et al. 2003), it is unsurprising to see PPC activation during sequence learning (Petit et al., 1996; Petit, Clark, Ingeholm, Haxby, 1997; Alvarez et al. 2010; Gonzalez, Billington & Burke, 2016). Burke et al. (2013) studied sequence learning using single pulse TMS to a specific area of the right PPC (right supramarginal gyrus) and found that TMS disrupted performance on predicted (learned) sequences, and not random. We predict that inducing plasticity-like effects within the right PPC, using cTBS, will also reduce prediction in the current study, and likewise iTBS over the right hemisphere could theoretically improve performance of learned sequences.

The fronto-parietal network discussed in the previous sections, is also suggested to be involved in ***working memory*** (Cohen et al. 1997; Courtney et al. 1997; Walter et al., 2003). As a part of this network, the PPC shows increased activation during a range of different working memory tasks (Wager & Smith, 2003; Owen, McMillan, Laird & Bullmore, 2005). Furthermore, damage to the PPC has been found to result in working memory impairments (Baldo & Dronkers, 2006; Berryhill & Olson, 2008). However, the exact role of the PPC remains unclear (Berryhill, 2012). The internal attention account suggests that the PPC contains attentional mechanisms that can re-launch representations stored in the PPC into the focus of attention, a process called 'attentional refreshing' (Corbetta, Kincade & Shulman, 2002; Berryhill, Wencil, Coslett & Olson, 2010). The PPC has been found to be mainly associated with recognition rather than recall, which gives weight to the internal attention account, as it is thought that recognition relies more on attentional refreshing of stored information (Berryhill & Olson, 2008; Berryhill et al. 2010). The role of attentional refreshing in working memory shows parallels to sequence learning in that both require a timely release of information as suggested by Gonzalez and colleagues (2016). Thus, refreshing of the memory store in the PPC, which brings the item into attentional focus, is a possible overlapping mechanism in both working memory and sequence learning tasks (Bo et

al. 2012). The current study has implemented a visual N-Back task as a measure of working memory performance due to its reliable activation of the frontoparietal network, and more specifically in PPC with increasing WM load (for meta-analysis see: Owen, Mc Millan, Laird and Bullmore, 2005). Owen et al (2005) found, when contrasting activation from verbal versus non-verbal (visual) identity monitoring in N-Back studies, a greater activation in the left PPC for verbal and right PPC for non-verbal. These findings suggest the effects of TBS on the right hemisphere could influence reaction time in the visual N-Back task implemented here.

One way of assessing causal relationships between brain area and function is via TMS. TMS induces action potentials in neurons by using a magnetic field to generate an electrical current in the brain. When this current is applied repetitively (rTMS) it can induce changes in cortical activity long enough to study brain functions (Pascual-Leone, Valls-Solé, Wassermann & Hallett, 1994). In addition, rTMS effects can induce long term depression (LTD) when applied at a frequency of <1 Hz or long term potentiation (LTP) when applied at >5Hz in the targeted neuronal network (Zafar, Paulus & Sommer, 2008). These two sources of neuroplasticity can reduce or enhance synaptic transmission respectively, and hence decrease or increase activity in the targeted brain area.

A newer form of rTMS called theta burst stimulation (TBS) has been suggested to be particularly appropriate for inducing plasticity due to the frequency band it employs (Orr et al. 2001; Tsanov & Manahan-Vaughan, 2009). The delivery timing of TBS is much shorter than rTMS, yet no difference in the duration of effects has been found with comparisons to 10Hz rTMS (Blumberger et al., 2018) when applied for treatment in drug-resistant major depressive disorder patients. TBS applies triplets of pulses (bursts), that can be delivered continuously (cTBS) or intermittently (iTBS), in order to decrease and increase cortical excitability through LTD-like and LTP-like processes

respectively (Huang, Edwards, Rounis, Bhatia and Rothwell, 2005). Huang et al (2005) were the first to demonstrate these cTBS and iTBS effects in the motor cortex. Since then, the excitability effects have been replicated both in the motor cortex and in non-motor regions (Wischnewski & Schutter, 2015). Although these findings are well replicated, the effects of TBS remain variable, and the exact mechanism of effects remain unclear (Freitas, Farzan & Pascual-Leone, 2013). Furthermore, the effects on more functionally complex brain areas are shown to have more variability compared to the well-studied motor cortex (Zafar et al. 2008). Further study of the effects of TBS on other brain areas can add to understanding of the function of those areas, as well inform the use of TBS to induce neuroplasticity as a potential way of enhancing cognitive functions.

The current study aimed to investigate the “modes of action” in the posterior parietal cortex during the performance of four cognitive task in healthy young adults. No study has investigated iTBS and cTBS using this variety of tasks within a single study previously, and hence modes of action in the brain for these tasks are relatively unknown. The current study used iTBS and cTBS to establish whether LTP- or LTD-like plasticity induced by rTMS would influence performance in visual spatial attention, response inhibition, sequence learning and working memory tasks. This would be exhibited as altered performance such as decreased reaction time and increased accuracy during the tasks, post TBS. We principally aimed to establish the causal role of the PPC in a range of cognitive tasks by temporarily increasing or decreasing activity within PPC. We hypothesized that temporarily increasing or decreasing activity within PPC would result in faster and slower releases of stored information respectively, as utilized by the visuomotor sequence learning and the 2-back working memory task. We also hypothesized that the right hemisphere would be more influential in altering responses given its role in spatial allocation of attention in visuomotor processing.

Results

The aims of the current study assess the effects LTP-like and LTD-like activity in the PPC has on four cognitive functions. Participants were tested on four tasks before the stimulation (iTBS or cTBS) was applied to the PPC (left or right), and were tested again on these four tasks after stimulation. Cognitive testing post-TBS all took place within a 15 minute window after stimulation.

This MANOVA revealed a significant main effect of TBS condition (Left iTBS, Left cTBS, Right iTBS and Right cTBS) on the dependant variables (attention, inhibition, sequence learning and N-back) ($F_{(9,62)} = 2.667$, $p = 0.011$) across all tasks. To ensure effects found were not due to the psychological effects of receiving TBS stimulation, the baseline score obtained from the first session, where the participants had not yet received real or control site TBS, was compared to the baseline scores obtained from the second session, where the participant had received a control TBS to the vertex prior to the baseline tasks. A repeated measures t-test showed no significant differences ($F_{(1,19)} = 0.14$, $p = 0.908$) between the baseline samples (control site and no-stimulation) for each testing session indicating little psychological effects of the TBS in our participants. One potential limitation of our study design is that we could have included an additional control condition whereby we would additionally stimulate the vertex using iTBS (in addition to cTBS). This approach would additionally control for any physiological effects of iTBS on the vertex. However, a recent study by Jung and colleagues (2016) found that during simultaneous TMS and fMRI acquisition, no significant increases in BOLD activations were found between vertex 1Hz rTMS (equivalent to iTBS stimulation) and baseline (no stimulation) measures. This study supports the current study by suggesting limited physiological effects of vertex stimulation, regardless of whether the stimulation is excitatory or inhibitory.

Attention Task

Mean reaction times for each condition in the attention task for all participants is shown in Table 1. A 2 x 2 x 2 x 2 repeated-measures MANOVA with time (pre / post) hemisphere (left/right), TBS (iTBS/cTBS) and task (cue/no cue) used as within subject variables in this GLM model. A significant effect of task was observed with a cued response revealing faster reaction times than the un-cued task ($F(1,16) = 6.618$, $p = 0.022$, $np2 = 0.321$).

[Table 1 here]

Inhibition: Anti-saccade Task

Mean reaction times with standard deviations (in ms) for each task across all participants is shown in Table 2. We performed a 2 x 2 x 2 x 2 repeated-measures ANOVA with time (before / after), Hemisphere (left / right), TBS protocol (continuous/intermittent), and task (pro-saccade/anti-saccade) on the mean reaction time change scores (post-TBS minus pre-TBS) from each participant. We found a significant main effect of task, whereby the go task revealed a significantly shorter RT than the no-go task ($F_{(1,18)} = 96.56$, $p < 0.001$, $np2 = 0.858$, see figure 1).

[Table 2 here]

[Figure 1 here]

Sequence Learning Task

Firstly, to verify oculomotor learning had occurred, we collapsed across stimulation type and hemisphere and conducted a 2 (task: random (RND)/predictable (PRD)) x 2 (time: before TBS/after TBS) repeated measures ANOVA on the mean RTs for each participant (see Table 3). We found significantly faster RTs for predictive sequences when compared to random sequences ($F_{(1,71)} = 382.5$, $p < 0.001$, $\eta_p{}^2 = 0.957$)). We

also found an interaction between PRD and RND conditions in the mean RT scores from before and after TBS ($F_{(1,71)} = 79.7$, $p < 0.001$). A Bonferroni post-hoc test found a significant difference between mean RT data in PRD and RND conditions before TBS ($p < 0.001$), but no significant difference after TBS ($p = 0.39$). This suggests that PRD RT was increased after TBS stimulation bringing it in-line with RND conditions (see figure 2).

[Table 3 here]

[Figure 2 here]

Working Memory: N-back task

The N-back task data consisted of mean accuracy (proportion of correct responses); score between 0 and 1, and mean reaction time performance scores (see Table 4). A 2 x 2 x 3 Greenhouse-Geisser corrected ANOVA (due to sphericity violation) with TBS (continuous/intermittent), hemisphere (left/right) and N-back (0-back/1-back/2-back) was performed for the $\log_{10}$ transformed accuracy change scores due to these not being normally distributed. A significant main effect of Task (between the 0, 1 and 2 back) was found ($F_{(2, 14)} = 5.664$, $p = 0.016$, $\eta_p^2 = 0.447$, $1\text{-}\beta = 0.774$), and a main effect of hemisphere was also approaching significance ($F_{(2,16)} = 3.542$, $p = 0.079$, $\eta_p^2 = 0.191$, $1\text{-}\beta = 0.421$) (see Figure 3). Due to the significant main effect of task ($p=0.016$), a post-hoc analysis was performed on the task data and revealed TBS (both iTBS and cTBS) produced a significantly larger increases in RT when applied to the right hemisphere ($F_{(1, 16)} = 5.627$, $p = 0.031$, $\eta_p^2 = 0.260$, $1\text{-}\beta = 0.606$) compared to the left in the 2-back task only. No significant effects were observed for the 1-back ($p = 0.078$) or 0-back ($p = 0.119$) tasks (see Figure 3). Although, it can be noted right hemisphere TBS stimulation resulted in an increasing effect on RT, with increasing task demand (from 0 to 2 back).

[Table 4 here]

[Figure 3 here]

Responder Data

The effectiveness of Transcranial Magnetic Stimulation (TMS) can be subject dependent and so analyses were performed to assess the proportion of individuals who responded as assessed by a change in performance (Before – After) by greater than ± 1 SEM (see figure 4). We have segregated the data into those showing improvements in task performance (positive responders) as measured by a reduction in RT, versus those who shown a decline in performance (negative responders, increased RT), and indeed those who did not deviate more than ± 1 SEM (non-responders) for each of the tasks. Furthermore, we used a multiple linear regression model to assess if individual participants revealed similar changes in RT across the different tasks and stimulation types/locations i.e. if positive responders were always positive and negative always negative. The result of the regression revealed there was no relationship between tasks and TBS within participants ($F_{(1,17)} = 0.429$, $p = 0.845$ and $R^2 = 0.190$.

Discussion

This study had two main aims: firstly, to explore the causal role of the posterior parietal cortex (PPC) in four cognitive functions and secondly to study the differential effects of continuous theta burst stimulation (cTBS) and intermittent theta burst stimulation (iTBS) on the PPC. The literature suggests cTBS will reduce firing within PPC and lead to LTD-like effects, conversely, iTBS will provide an enhancement of the firing (similar to LTP) and theoretically lead to decreases in reaction times post stimulation (Huang et al., 2005).

A number of limitations using TMS should be noted prior to acknowledging the findings of this study. It has been suggested that two of the many possible reasons for irregular findings in human TBS studies could be genetic differences or variations within and between participants in the levels of attention during stimulation (Wischnewski & Schutter, 2015). Another inter-individual difference affecting the workings of TBS could be the stimulator threshold, as we used a generic 40% stimulator output for all our participants. Future studies could employ a more individualistic approach by finding parietal phosphene thresholds in P3 and P4.

It should be noted that using the 10–20 EEG cap for placement of the coil is not as optimal as other techniques, such as fMRI-based neuronavigation, that could have provided more accurate localization of the PPC within each individual. However, given the relatively large size of the PPC within the cortex, we feel the approach used was effective in targeting this area within our volunteers. Furthermore, it should be noted that many studies, have also found large inter and intra-subject variability in TBS stimulation within the motor cortex (Jannati et al, 2017; Schilberg et al, 2017). This was a limitation with the current design and is demonstrated in Figure 11, whereby although the majority of participants revealed an effect, the direction of this effect (positive versus negative responders) was not always in the expected direction given the stimulation (iTBS versus cTBS). Caution is needed when interpreting the data as although cTBS is thought to induce a LTD-like effects, it is possible that this down regulation of the PPC could in fact enhance performance in certain tasks, and reduce performance in others. Future studies should include more within subject assessments across sessions to help identify the cause for this direction of effects and variability. In addition, due to this variability a larger number of subjects would also add to the power of this study.

In-line with this, the cTBS protocol is thought to stimulate in such a manner that initial post-synaptic LTP changes into LTD after a certain duration of the stimulation, whereas iTBS remains in LTP (Wischnewski & Schutter, 2015). However, this

threshold for switching to LTD in cTBS is highly variable within and between individuals. Recently, a crucial role of dopamine in the control of the LTD-LTP threshold was suggested (Sheynikhovich, Otani & Arleo, 2013), and neural dopamine levels could easily vary within and between individuals. Although this role of dopamine is primarily suggested in the prefrontal cortex, and still partly relies on animal data, it could be possible that there is a similar function of dopamine in the LTD-LTP thresholds in other areas of the fronto-parietal network, especially as dopamine is thought to play an important role in fronto-parietal connectivity and the dorsal attention network (Dang, O'Neil & Jagust, 2012; Cole et al. 2013). Furthermore, the state of post-synaptic activity prior to stimulation could alter the effect of stimulation, such that stimulation of a synapse already experiencing LTP could result in LTD (Scheynikhovich et al. 2013). These findings demonstrate the likelihood of a variable postsynaptic response to TBS and hence provides some background to the exploratory nature of this study.

Effects of TBS in PPC on Attention

We found that stimulating PPC with TBS had no effect on the simple cue based task we employed in this study. Initially, this appears to be a surprising effect based on literature identifying the right PPC as a locus for hemi-spatial neglect (Mort et al., 2003) and maintained spatial attention (Malhotra et al., 2009). However, it is worth noting these previous findings are mainly attributed to the superior temporal gyrus and inferior parietal lobule. Our P3 and P4 10-20 electrode placement location is located close to the angular gyrus based on previous localization studies (Kabdebon et al., 2014) this area of the PPC often demands more complex tasks such as spatial memory (Husain & Nachev 2007), navigation (Spiers & Maguire, 2006; van Assche et al. 2014), sequence learning (Burke et al., 2013) and binding (object and space, Seghier, 2012; van Assche et al. 2014) in order to give robust effects. In addition, we aimed to induce plasticity-like effects in the brain resulting in longer term adaptation of the PPC

neuronal firing pattern. One interpretation of the data is that, due to the lack of a significant difference on the attention task using TBS, it is possible that plasticity-like mechanisms may not play an important role when allocating spatial attention in a simple cued task. This result is in direct contrast to the findings of Xu and colleagues (2013) who found right hemisphere PPC stimulation with cTBS resulted in increased reaction times in a mouse button press during the Attention Network Test (ANT). One reason for this conflicting evidence might be due to differences between the saccadic measures taken in the current experiment, versus a hand response in the Xu paper, given the role of the PPC in sensorimotor transformations. Indeed, a paper by Christopoulos et al (2015) showed that deactivation of the PRR (Parietal Reach Region) in the PPC in monkeys resulted in increased RT in the hand, but not in saccades. Finally, another possible reason for the lack of effect of TBS on this attention task, could be due to the dominant role of frontal regions on this endogenous task. If the PPC only serves to support this function, then stimulation of this site alone may not have been enough to elicit a change in performance from our participants. A future study could aim to disrupt both frontal and parietal regions to assess differential contributions of frontal and parietal brain regions in endogenous attentional processing.

Effects of TBS in PPC on Inhibition

In the current study, the cognitive process of response inhibition was selected for further examination due to existing literature suggesting involvement of the PPC in this process (Sweeney et al 1996; Luna et al. 2001). Based on a paper by Osada et al (2019) who performed single-pulse TMS in the right intraparietal sulcus, we hypothesised that the effects of the stimulation to the right PPC would prolong reaction times in the anti-saccade (nogo) trials, which required response inhibition. However, the current study is the first study to investigate the effects of TBS on the PPC during an inhibition task and thus effects of inducing plasticity are currently unknown.

In accordance with Osada et al (2019) we found a significantly greater difference from before versus after TBS on the right hemisphere, and this was particularly potent for the nogo condition. Right hemisphere dominance for executive functions and inhibition in prefrontal and parietal cortex are supported by a number of previous studies (e.g. Garavan et al., 1999), and our data further support the literature in this regard. Furthermore, the No-Go tasks specifically employs inhibitory control, indicating TBS in right PPC disrupted normal anti-saccade programming.

Effects of TBS on Sequence Learning

This study also aimed to look into the involvement of the PPC in sequence learning, using an oculomotor sequence learning task. It was hypothesised that effects from the stimulation would only be seen on predicted trials, which have been found to show much shorter reaction times than random sequences, due to learning of the structure of the sequence (Nissen & Bullemer, 1987). The results of the current study did follow this expected pattern: predicted sequences resulted in much faster reaction times across conditions, demonstrating oculomotor learning had occurred. Analysis of the change scores in reaction times (before-after) demonstrated a facilitation in the predicted sequences when cTBS was applied, but a slowing with iTBS. Conversely, the random responses revealed the reverse effect with cTBS reducing RT and iTBS increasing it. When looking at the magnitude of the effect using the absolute change scores, stimulation on the left PPC revealed a significant difference between iTBS and cTBS stimulation, whereas either stimulation type produced a similar alteration in response when applied to the right hemisphere. Our results can be summarized as the iTBS protocol appears to be assisting initial encoding of the sequence (as required in the 1st presentation), whereas cTBS is then needed for longer term learning of the sequence. In addition, there is possibly a greater involvement of the left PPC for directing this mechanism of action. This is the first study to demonstrate the possible shift from LTP-like to LTD-like mechanisms within PPC for initial encoding versus more

prolonged oculomotor learning strategies in eye movements. Interestingly, a number of studies support lateralization effects in motor learning in the PPC with left hemispheric dominance for motoric preparation and attention processing, and the right hemisphere for spatial attention (Rushworth et al., 2001). These findings are consistent with the trend observed here where we found evidence for the left hemisphere showing a higher sensitivity to the stimulation protocols when compared to the right hemisphere in our oculomotor learning task. It should be noted that the oculomotor sequence learning is an example of a simple learning task requiring limited feedback, as Wulf and Shea (2002) acknowledge in their review, many aspects of this learning might not be transferable to more complex tasks and therefore this paves the way for investigating more complex motor learning in the future. Furthermore, our task implemented a saccadic eye movement task which may also show differences when compared to limb movements in the PPC given the role of the PPC in sensorimotor transformations (as mentioned above). In summary, more research is needed into this effect, given the variability in response, lack of ecological validity, and the need for more direct neurophysiological measures.

Effects of TBS in PCC on Working Memory

The fourth cognitive function investigated in relation to the involvement of the PPC was working memory. This study is one of the first to assess the effects of TBS on the PPC during a working memory task. Previous studies using rTMS have shown either facilitation (i.e. decreases) in reaction time (e.g. Hamidi et al., 2008, Luber et al., 2007), or indeed interference (i.e. increases) in reaction times (Postle et al, 2006). Hamidi et al (2008) suggests that facilitation in RT is observed when stimulating at the alpha-band frequency of 5-10Hz, and interference at other frequencies in PPC.

In-line with these studies, we found a significant effect on reaction time in the N-Back task with both types of TBS stimulation when applied to the right hemisphere. The 2-back tasks specifically revealed significantly longer RTs when TBS was applied to right

PPC. Also in-line with previous studies (Hamidi et al., 2008) we observed, no changes in accuracy after TBS in PPC, as retention of information during working memory is considered to be associated with prefrontal cortex activity (Postle et al., 2006). Hence, our data suggests that the effects of TBS are specific to timing mechanisms within the right PPC, and interference is only effective during increased memory demand (i.e. the 2-back task). The evidence also provides support that TBS does not simply induce an attentional disruption, as no effects were observed in the 0-back or attention task. The measured effects cannot also be attributed to a learning effect between sessions, given no change was observed with left hemisphere stimulation in the 2-back condition. Our results are consistent with the role of the right PPC in re-launching stored information into working memory for attentional focus, as is proposed by the internal attention account (Corbetta et al. 2002; Berryhill et al. 2010). Following this TBS on the right PPC interferes with this process and slows down response time for target identification. Association of the PPC with reaction time, but not accuracy, further supports this argument, as the attentional focus of information is linked to reaction time, but the PPC is not suggested to be linked to the accuracy of that information. The current study's findings could thus provide evidence for the internal attention account.

Conclusions and Future Directions

To conclude, the most significant effects of theta burst stimulation (TBS) were found with the longer term learning paradigm (sequence learning). The effects of TBS were task dependent, with excitatory changes in cortical activity assisting the initial encoding of the response (RND task), and a decrease in cortical activity resulted in earlier prediction during the repeated presentations when learning was established. We also found that for working memory the TBS revealed a disruption in the reaction time when applied to the right PPC. The more complex working memory task (2-back) revealed this significant effect, suggesting a role of the right PPC in the re-launching of

information into attentional focus. We found that TBS had no influence on the simple allocation of spatial attention, suggesting LTP and LTD processes are not needed for this function. Finally, an additional novel finding was evidence for LTP- and LTD-like processing in the right PPC for inhibitory processing. This suggests a further role of adaptive neural dynamics in the PPC specific to inhibiting reflexive responses as a possible target for inhibitory failures in a number of patient populations. In terms of future directions, there is still further work needed in understanding how individual differences in fronto-parietal attentional networks (FPAN) in the brain, affect TMS propagation patterns. More research is needed on why correlations exist between the default mode networks (DMN) and the dorsal attentional networks (DAN) and TMS propagation measures, and how these affect cognitive performance.

Experimental Procedure

Participants

20 healthy individuals (6 Male / 14 Female, 15 right-handed / 5 left-handed) with normal, or corrected to normal vision, aged 18-22 (M = 19.90; SD = 1.25) participated as volunteers from the University of Leeds. In line with TMS safety guidelines (Rossi et al. 2009), all participants were screened using a medical history questionnaire to ensure they were neurologically healthy, did not have any metal implants in their brain or skull and did not have a history of epilepsy or seizures. Individuals taking any form of anti-depressant or anti-anxiety medication were excluded from the study in order to avoid any possible effects of these drugs on neuroplasticity (Castrén & Hen, 2013) and possible increased risk through potential lowering of seizure threshold (Rossi et al. 2009). All participants had no known neurological or visual defects. The study was approved by the University of Leeds ethics committee on 17/11/2017 (ethics number: PSC-147) and was fully compliant with British Psychological Society ethics guidelines.

Experimental Design and Protocol

This study employed a 2 x 2 repeated measures design, with hemisphere (left/right) and TBS protocol (intermittent/continuous) as the independent variables (see figure 1). The dependant variables were the scores obtained for the cognitive tasks employed (outlined below: attention, inhibition, sequence learning and N-Back). The participants completed the four experimental conditions (right iTBS, left iTBS, right cTBS and left cTBS) in a fully counterbalanced order in four separate testing sessions (an example is shown in Figure 1). Within each testing session, the cognitive task order (and trials within each task) was also fully randomized before and after TBS. Each session lasted an hour and sessions were spaced a minimum of seven days apart to ensure participants were experiencing no delayed detrimental effects of TBS. At the start of their second session, all participants received a control site application of TBS (continuous TBS to the vertex, located at Cz on the 10-20 EEG cap) before starting their baseline tasks. Application of TBS to the vertex has been established an appropriate control site (Jung, Bungert, Bowtell & Jackson, 2016). This control site-performance data was compared to baseline data without control site TBS to ensure no psychological effects of having TBS were influencing task performance.

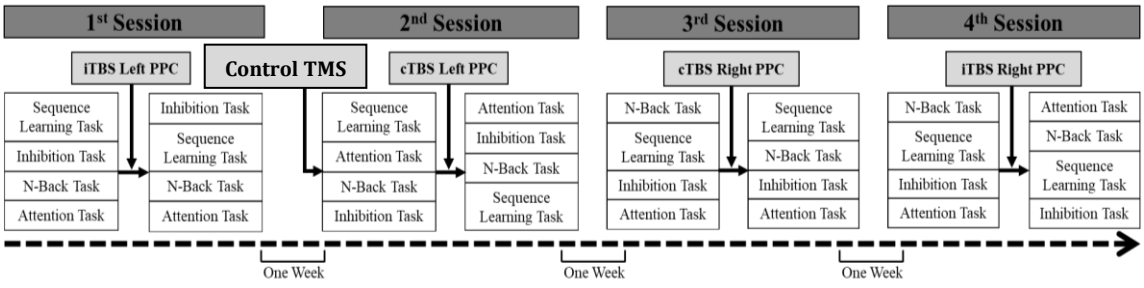

Figure 4: Shows an example of the study design used in the experiment with 4 sessions in total spaced 1 week apart; one for each stimulation type. Please note that session order and task order within a session were randomized across all 20 participants.

Materials

The visual stimuli were developed using Experimental Builder (SR Research Limited) and were shown on an Illyama computer with a 1024 x 768 display. The attention, inhibition, and visual learning tasks utilized eye movements to measure reaction time (RT) and accuracy responses (Eyelink II, SR Research Ltd). The tower mount with forehead and chin rest stabilized the head during testing. Participants completed a calibration and validation prior to each of the 3 tasks implementing eye-tracking. For the N-back task, the participants used a button box (Cedrus Corporation, USA) to log their accuracy and RT responses. Experiments took place in the dark to avoid any visual distractions, but lights were turned on in between each of the tasks to maintain alertness and reduce the effects of dark adaptation.

After completing the induction, consent and all four of the cognitive tasks (taking ~30mins), participants received the TBS on the pre-allocated brain site (see TMS details below) and again completed the 4 cognitive tasks outlined below within 20 – 25 mins post TBS stimulation (see figure 1).

Stimuli: Attention Task

The attention task required participants to direct their attention to a target following a cue that either indicated the target location (cued condition), or that did not indicate the target location (uncued condition). The central cue was an arrow, 15 pixels in length, pointing left (<), or right (>), or was non-informative (< >). The target then appeared after a random interval (of ~750, 1000, or 1250ms) and required a 1000ms fixation from the participant before moving onto the next trial. There was 36 trials in total taking ~1.5 minutes to complete.

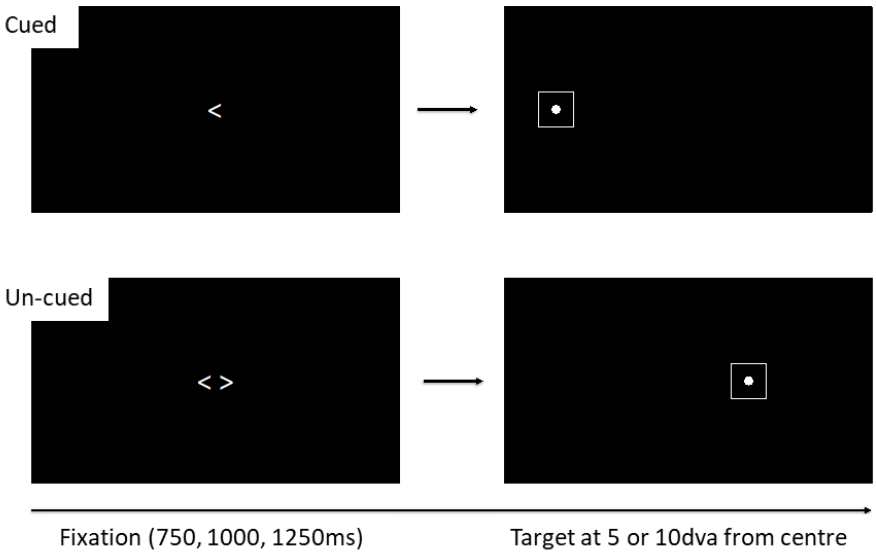

Figure 5. Visual stimuli presented in the attention task on a cued trial (upper figures) and an uncued trial (lower figures). The target appeared at randomized distance of 5 or 10 degrees of visual angle from the centre of the screen, where the cue was presented.

Stimuli: Inhibition (Anti-saccade Task)

The inhibition task aimed to measure response inhibition using the anti-saccade task. Participants were presented with a green or red square in the centre of the screen. Green indicated that participants were required to move their eyes towards the target (pro-saccade), while red required that participants move their eyes away from the target (anti-saccade). The target expired when the eye fixated for 1000ms on a target. An inter-stimulus interval of 1000ms between each of the 32 trials was used resulting in an overall duration for all trials of ~2 minutes. The target location and latency of cue were randomized to prevent prediction during these tasks. Figure 3 outlines the stimuli used for the inhibition task.

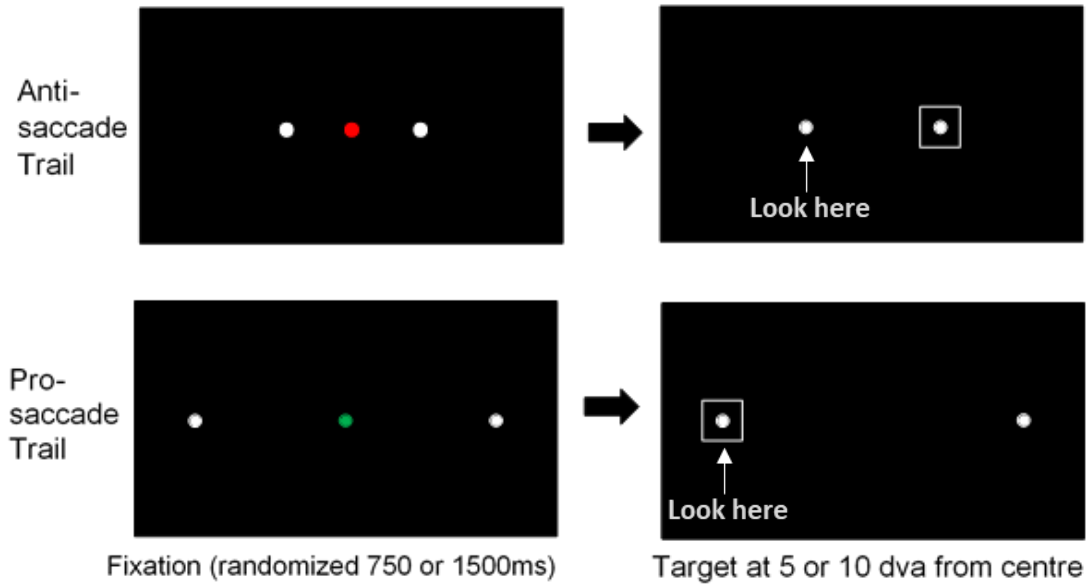

Figure 6. Visual stimuli presented in the inhibition task on a pro-saccade trial (upper figures), where participants look towards the highlighted target, and an anti-saccade trial (lower figures), where participants look in the opposite direction to the highlighted target. In both of these example trials, looking towards the right of the screen is the correct response. The duration of the coloured (red or green) fixation square (15 pixels in length and width) was randomized for either 750ms or 1500ms. The highlighted target randomly appeared on either the left or right of the screen at either 5 or 10 degrees of visual angle from the centre.

Stimuli: Sequence Learning Task

The sequence learning task aimed to measure visuo-spatial learning. The participants were presented with a target presented on the screen that jumped location every 750ms either up, down, left or right. The target jumped 4 times and this comprised a sequence of saccadic eye movements. This sequence of 4 target positions was repeated 4 times in a row with a 1000ms break between each one. 10 unique sequences were performed by the participants resulting in 40 sequences taking ~3 minutes to perform. Burke et al. (2013) demonstrated the first presentation of a

sequence can be used as a measure of a random sequence (i.e. reactive measure of behaviour), and the following presentations as predictable responses to the sequences. Figure 4 shows an example of a sequence presented in the task, and outlines the details of the stimuli used.

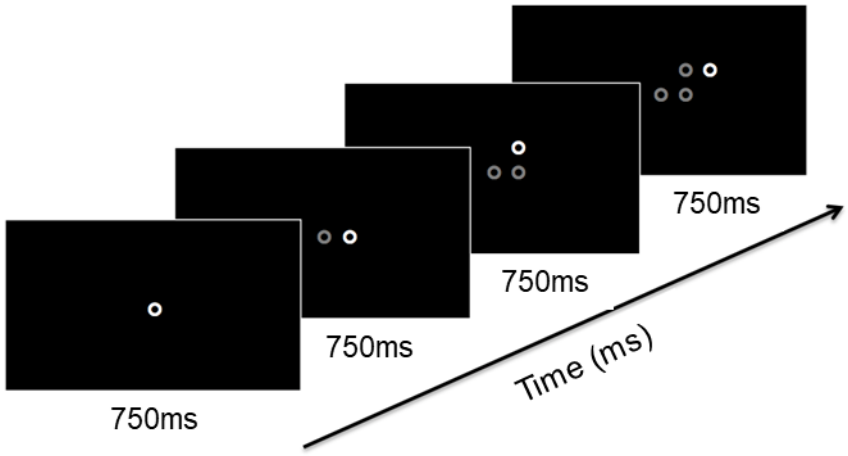

Figure 7. An example of a sequence presented in the sequence learning task. Only the white targets are visible to the participant, the grey targets indicate previous target locations. Every sequence started at the centre of the screen. The target (16 pixel diameter) changed position every 750ms by 5 degrees of visual angle either up, down, left or right. Each sequence consisted of 4 steps. Each sequence lasted 3000ms and was presented 4 times in a row with a 1000ms ISI. 10 unique sequences were performed.

Stimuli: Working Memory (N-back Task)

An N-Back task was used to measure working memory speed and accuracy. The task requires the participant to respond to sequential presentations of letters. For each letter, the participant responds whether it matched a letter presented one letter previously (1-back) or two letters previously (2-back). We also included a control condition (0 back) where participants just had to identify when the letter M was presented (Figure 5). Participants responded using a button box where green signalled

'match' and red 'no match'. This resulted in 3 block of 48 trials (i.e. 48 letters) for each condition taking ~ 6 minutes to perform in total.

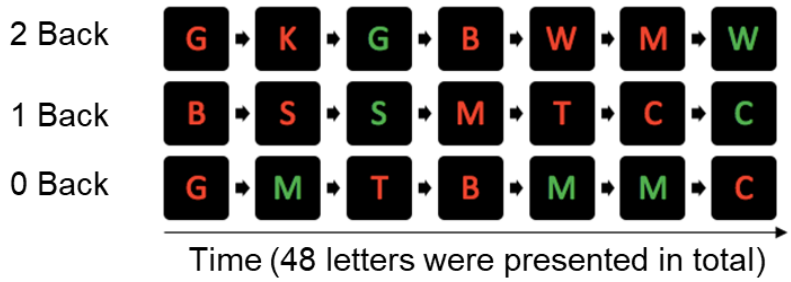

Figure 8. Examples of possible sequences in the N-back task for the 0-back (bottom row), the 1-back (middle row) and 2-back (upper row) tasks. All letters were presented in white during the task, whereas the image displays items that required a "no-match" response in red (i.e. press the red button), and "match" letters in green (i.e. press the green button). Letters were presented for 1000ms, followed by a blank screen for 1000ms. Each block of trials consisted of 48 letters.

Theta Burst Stimulation (TBS)

The brain area was identified by locating the vertex (Cz) using fiducial points on the head, and then implementing the standard international 10-20 EEG positioning system to locate the left or right PPC (P3 and P4 respectively). The appropriate locations were marked (using a highlighter pen) on the participant's skull for subsequent stimulation. TMS was applied (either cTBS or iTBS, for details see below) tangential to the skull (only cTBS used on vertex stimulation) and participants were given 5 minutes of rest post-TMS, prior to repeating the cognitive tasks to ensure optimal effects (Di Lazzaro et al. 2005).

A Magstim-Rapid stimulator (Magstim, Whitland, UK) was used to deliver Theta Burst Stimulation (TBS). The current study used both continuous TBS (cTBS) and intermittent TBS (iTBS) that delivered triplets (3) of pulses at a frequency of 50Hz. These triplets were repeated at a rate of 5 Hz. To induce cTBS, 200 bursts (600 pulses)

were delivered in a continuous train lasting 40s (Huang et al. 2005). For iTBS, a 2s train of bursts followed by an 8s interval of rest, was delivered for 190s, also resulting in 200 bursts/600 pulses in total (Huang et al., 2005). All TBS was delivered at 40% stimulator output via a 70mm figure-of-eight coil (2.6T) held by an experimenter on the P3 or P4 location perpendicular to the scalp during stimulation. These locations relate to MNI coordinates of -40,-66,46 (for P3) and 46 -62 42 (for P4) within Brodman area 39 as part of the inferior parietal lobe, although the authors acknowledge that due to no available neuronavigation this is an estimate of the location of stimulation. This output level was chosen based on previous studies identifying little correlation between motor thresholds obtained in M1 and other cortical regions (Stewart et al., 2001; Boroojerdi et al., 2002). In addition, a number of studies have shown fixing the stimulator output between 40-65% to be effective in stimulation of the PPC, the supramarginal and angular gyrus regions (Burke et al., 2013; Cantteneo et al., 2009). Wischnewski and Schutter 2015's review of sixty-four studies on the time course of TBS found that effects of iTBS and cTBS on the motor cortex, delivering 600 pulses at 50Hz, lasted up to 60 and 50 minutes, respectively.

Data Analysis

Data Viewer (SR Research Limited) was used to pre-process the data, identify onset of saccades (velocity >30º/s and acceleration >800º/s^2), and correct versus incorrect responses. Blinks were removed from the raw data before analysis and Matlab (The MathWorks Inc.) was used to sort the data into the experimental conditions and generate a mean score and standard deviation for each participant. Saccadic RT data was filtered to remove any eye movements made >500ms after target onset as these indicate failures to react to the stimuli, button box responses were also filtered to remove RT > 800ms as these responses did not fall within the response window of the task. Raw RTs were included in a MANCOVA model whereby before iTBS data was

used as covariates in the model. A Hemisphere (left / right) x iTBS (intermittent / continuous) x task (cued / uncued; prosaccade / antisaccade; 0-back / 1-back / 2-back; random / predictive). ANOVAs were also implemented in SPSS Statistics 22 (IBM Inc) to interrogate significant effects. For reasons of brevity only significant findings are reported. Bonferroni tests were employed for post-hoc tests throughout to correct for multiple comparisons and avoid type 1 errors. A Shapiro-Wilk test for normality showed the data did not violate the assumption of normality, with the exception of the N-back accuracy change scores. For this dataset, a non-parametric Man-Whitney U test was applied in the analysis.

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Figures

Figure 1

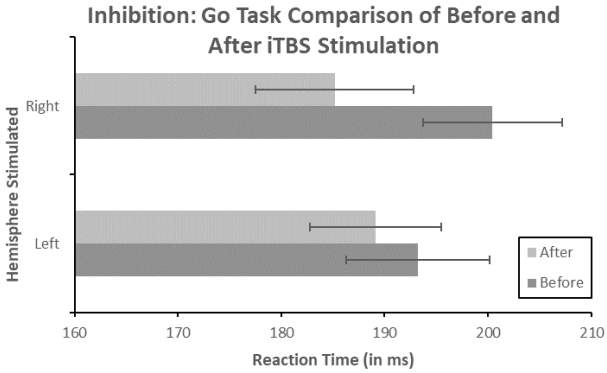

Figure 2

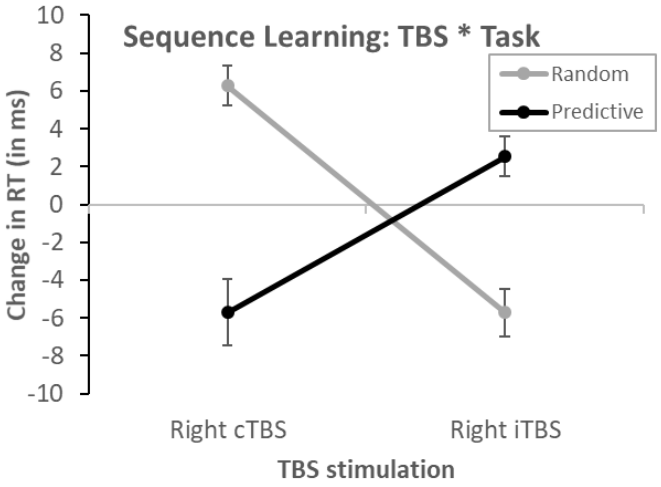

Figure 3

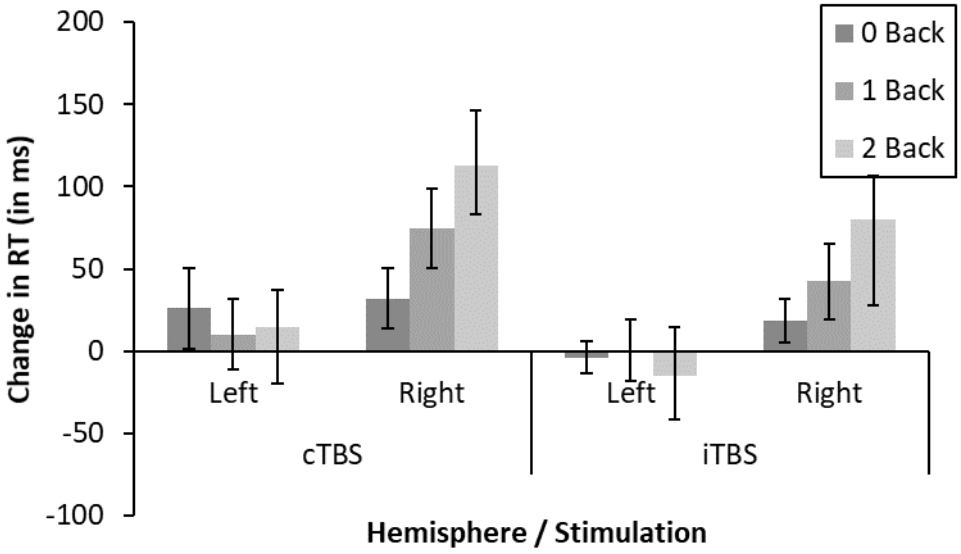

Figure 4:

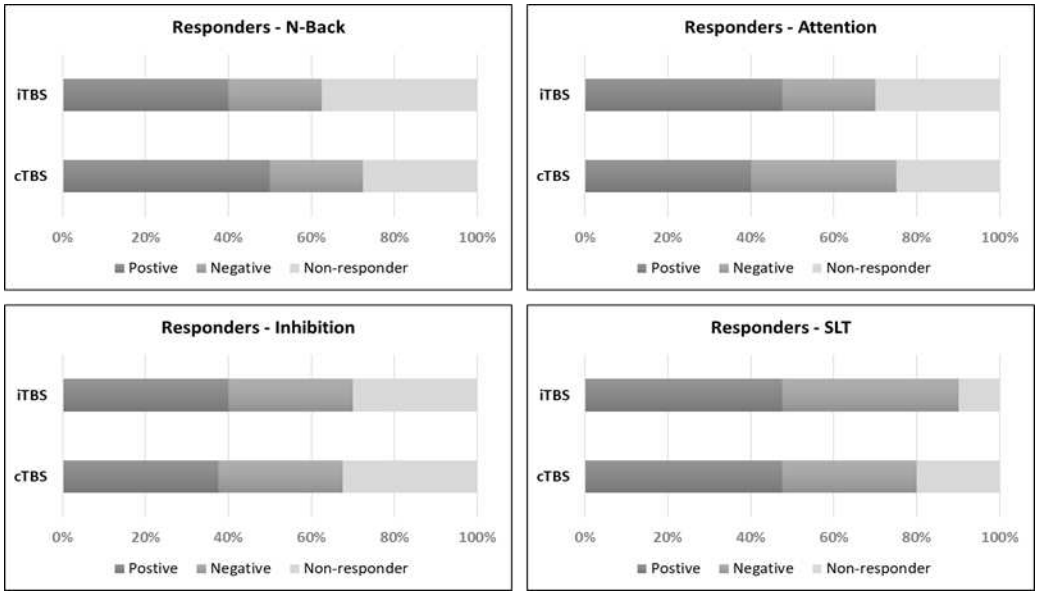

Figure Legends:

Figure 1: The RT data showing Hemisphere * Task interaction for the ***Inhibition (Go-NoGo) task***. The change score data for both stimulation types on the right (grey line) and left (dark grey) hemispheres is shown for the Go task (pro-saccades) versus the NoGo task (anti-saccades). Error bars denote Standard Error from the Mean (SEM).

Figure 2. The change scores from pre to post TBS showing the TBS * Task interaction in the ***sequence learning task***. The random sequence (1st sequence) is shown in grey and the predictive sequence data is shown in black. Error bars represent the Standard Error from the Mean.

Figure 3: Reaction time data from ***N-back task*** showing change in reaction from pre to post TBS for each of the different stimulation protocols on the X-axis. Error bars denote the Standard Error from the Mean.

Figure 4: The graphs show the proportion of positive responders (>+1 SEM), negative responders (<-1 SEM) and non-responders (within ± 1SEM) for each of the TBS stimulation types (iTBS/cTBS) as calculated from the difference in RT (before TBS - after TBS).

Table 1

ATTENTION (in ms)		Left				Right			
		iTBS		cTBS		iTBS		cTBS	
		cue	no cue	cue	no cue	cue	no cue	cue	no cue
Before	**Mean RT**	133.22	144.41	126.20	143.58	125.63	140.87	137.02	148.51
	STD RT	32.31	23.82	36.19	23.83	30.73	25.38	40.86	34.26
After	**Mean RT**	119.57	146.23	128.01	138.09	119.25	140.19	124.24	137.35
	STD RT	34.01	21.92	38.46	23.61	37.74	23.48	27.85	24.64

Table 1: Shows mean reaction times (in ms) and standard deviation (STD) of all participants to each condition, both before TBS and after TBS.

Table 2

INHIBITION (in ms)		Left				Right			
		iTBS		cTBS		iTBS		cTBS	
		Go	NoGo	Go	NoGo	Go	NoGo	Go	NoGo
Before	**Mean RT**	193.22	226.68	195.67	233.22	200.45	234.01	190.09	233.75
	STD RT	28.49	51.20	35.71	46.94	34.23	44.21	27.83	38.98
After	**Mean RT**	189.12	223.00	191.88	232.50	185.16	217.46	189.25	225.65
	STD RT	30.97	39.68	35.60	44.32	29.98	38.48	26.62	40.36

Table 2: Mean reaction times and standard deviations (in ms) across all participants for each condition during the inhibition task. The upper two rows are date from before TBS and the lower from after TBS.

Table 3

SEQUENCE LEARN (in ms)		Left				Right			
		iTBS		cTBS		iTBS		cTBS	
		PRD	RND	PRD	RND	PRD	RND	PRD	RND
Before	Mean RT	145.87	20.68	158.97	25.30	153.07	13.60	150.67	19.44
	STD RT	21.04	28.05	24.75	40.24	24.19	33.65	31.10	35.66
After	Mean RT	141.74	19.78	156.20	20.55	151.74	17.12	150.38	14.98
	STD RT	33.63	32.78	25.68	38.90	24.16	36.84	25.88	36.69

Table 3: Mean and STD (in ms) for all participants from before and after TBS for the sequence learning task. Data is split according to condition i.e. left/right hemispheres of stimulation, intermittent (iTBS) and continuous (cTBS) theta burst stimulation and predictable (PRD) and random (RND) responses.

Table 4

N-BACK RT (in ms)		Left						Right					
		iTBS			cTBS			iTBS			cTBS		
		0	1	2	0	1	2	0	1	2	0	1	2
Before	Mean RT	390.30	418.54	464.19	402.83	442.32	485.25	397.78	453.51	570.49	417.10	469.40	530.30
	STD RT	57.57	77.14	125.44	49.28	72.56	150.34	58.77	91.03	207.02	75.19	92.15	132.14
After	Mean RT	396.03	435.49	492.05	393.47	432.24	474.01	377.06	416.69	472.83	384.81	392.78	417.70
	STD RT	59.43	91.97	157.92	53.29	73.59	96.74	42.17	54.43	117.14	63.60	91.25	104.78
N-BACK Accuracy													
Before	Mean RT	0.99	0.98	0.96	1.00	0.98	0.93	1.00	0.98	0.96	0.99	0.98	0.96
	STD RT	0.02	0.01	0.03	0.00	0.01	0.15	0.00	0.02	0.03	0.02	0.01	0.04
After	Mean RT	1.00	0.98	0.96	1.00	0.98	0.96	1.00	0.99	0.97	1.00	0.95	0.93
	STD RT	0.00	0.01	0.03	0.01	0.01	0.03	0.00	0.01	0.03	0.00	0.17	0.15

Table 4: Mean and standard deviations of reaction times in ms (upper rows) and accuracy percentage (lower rows) in N-Back task. Data is segregated into conditions (left/right hemisphere, iTBS/cTBS, and 0/1/2 back tasks).