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The Role of the Left Dorsolateral Prefrontal Cortex in Spatial Working Memory: A Transcranial Magnetic Stimulation (TMS) Study

Stergios Makris[1,2]* and Emma Seddon[1]

[1]*Department of Psychology, Edge Hill University, Ormskirk, UK*

[2]*Research Centre for Arts and Wellbeing, Edge Hill University, Ormskirk, UK*

***Corresponding Author:** Stergios Makris, Department of Psychology, Edge Hill University, Ormskirk, Lancashire, L39 4QP, UK.

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Abstract

Previous research on the neural underpinnings of working memory has indicated the role of the prefrontal cortex (PFC) and more specifically that of the dorsolateral prefrontal cortex (DLPFC) (Manoach., *et al*. 1997). However, up to day there is inconclusive evidence with regards to the lateralisation concept; that is the involvement of left and right DLPFC in different aspects of working memory (i.e. spatial vs verbal). The present study aimed to elucidate the role of the left DLPFC in spatial working memory by means of Transcranial Magnetic Stimulation (TMS). An offline continuous theta burst protocol (cTBS) was applied over our subjects' left DLPFC and the Vertex (control) prior to completing the symmetry span test (SymmSpan), measuring spatial working memory capacity. Previous research has indicated that TMS stimulation over the DLPFC can interfere with working memory capacity (Schicktanz., *et al*. 2015). Our results have indicated that cTBS over the left DLPFC, compared to Vertex, has significantly impaired spatial working memory, as indicated by the SymmSpan score. Even though the exact role of the DLPFC in working memory remains unclear, our causative evidence along with further research can help to reach some consensus.

Keywords: *Spatial Working Memory; DLPFC; Symmetry Span Test; TMS*

Introduction

Working memory conceptualises a dedicated system, with limited capacity, which stores and maintains information for the short-term (Baddeley, 2003). Numerous studies have investigated the neural basis of working memory, with fMRI studies presenting persistent neural activity in brain areas during memory delays, such as the frontal eye field (FEF) (Offen, Gardner, Schluppeck & Heeger, 2010). However, lesions of the FEF in both human (Rivaud, Muri, Gaymard, Vermersch & Pierrot-Deseilligny, 1994) and non-human primates (Lynch, 1987) have been found to result in impaired voluntary eye movements of a topographic fashion (Muggleton, Juan, Cowey & Walsh, 2003), thus providing inconclusive evidence on how much FEF is involved in executive eye movements as compared to working memory per se.

Moreover, there has been a vast amount of neurophysiological evidence that has linked working memory to the prefrontal cortex (PFC) (Manoach., *et al*. 1997; Siddiqui, Chatterjee, Kumar, Siddiquin & Goyal, 2008; Smith & Jonides, 1999). Domain-general models propose that the lateral PFC is functionally organised according to the type of working memory engaged (Barbey, Koenigs & Grafman, 2013). Specifically, the dorsolateral prefrontal cortex (DLPFC), has been suggested to be involved in monitoring and manipulating items in working memory (Miller & Cohen, 2001) and thus, allowing active retentions of information (Petrides, 2000). Lesion studies exhibiting damage to the DLPFC have consistently resulted in subjects forgetting relevant information (Goldman-Rakic, 1999), which can be used to support the domain-general model. More recently, transcranial magnetic stimulation (TMS) studies have indicated that virtual lesions over the DLPFC can detrimentally affect working memory (Mottaghy., *et al*. 2000; Osaka., *et al*. 2007; Tanaka, Dessing, Malik, Prime & Crawford, 2014), such as increasing errors in a spatial delayed working memory task (Mottaghy, Gangitabo, Sparing, Krause & Pascual-Leone, 2002). Contrastingly, advocates of the domain-specific model suggest that the lateral PFC is functionally organised to the domain of processed information (Van Asselen., *et al*. 2006) and the DLPFC has been proposed to be functionally specialised to process visuospatial information (Courtney, Petit, Maisog, Ungerleider & Haxby, 1998). Furthermore, neuroimaging studies (Jonides., *et al*. 1993), have shown a greater activation in the right prefrontal cortex during a spatial working memory task, whilst other studies have found a greater activation in the left prefrontal cortex for object or non-spatial working memory tasks, such as verbal working memory (Reuter-Lorenz., *et al*. 2000). This may suggest that the domain specificity for spatial and object working memory is primarily a hemispheric laterality than a dorsal-ventral distinction (Courtney., *et al*. 1998).

Nevertheless, the anatomical segregation of the PFC with regards to working memory remains indeterminate (Petrides, 2000). The DLPFC has been suggested to be specialised for spatial working memory, whilst the ventrolateral PFC has been linked to object working memory (Curtis, 2006). However, studies have failed to reach unanimity (Curtis & D'Esposito, 2003) and the DLPFC has been linked to the maintenance, encoding, response and executive functioning of working memory (Levy & Goldman-Rakic, 2000; Zarahn, Aguirre & D'Esposito, 2000). Hence, its exact role in working memory remains heavily debated and neurophysiological studies have failed so far to provide clear evidence in support of either domain hypothesis (Koch., *et al*. 2005).

In the current study, we applied a continuous theta burst stimulation (cTBS) protocol over the left dorsolateral prefrontal cortex (LDLPFC) area of our subjects prior to performing the dual-task Symmetry span test (SymmSpan). Previous TMS studies have indicated the role of the left DLPFC in working memory (Osaka., *et al*. 2007), while others (i.e. Mull and Seyal, 2001), found no significant involvement of the right DLPFC in working memory tasks. This is also in agreement with neuropsychological studies suggesting that the left DLPFC is necessary for processing spatial information in working memory (Barbey., *et al*. 2013). Furthermore, in order to measure working memory in our subjects we applied the dual-task Symmetry span test, which has been shown to be a reliable and valid measurement of spatial working memory, correlating well with other complex span tasks (Foster., *et al*. 2014; Redick., *et al*. 2012). As far as the researchers can establish, this is the first TMS study to determine whether the left DLPFC plays a critical role in working memory under the dual task of the SymmSpan.

Overall, the aim of this study was to add further support for the role of the left DLPFC in working memory, specifically its involvement in executive functioning, by applying TMS stimulation prior to performing a spatial working memory task. Similar studies have investigated the effects of TMS on the DLPFC executive function in the form of a 2-back (Mottaghy., *et al*. 2003) and Reading Span test (Osaka., *et al*. 2007), both of which found a significant deterioration in performance after TMS stimulation. Therefore, this study hypothesised that the results would show an impaired SymmSpan score immediately after a course of offline continuous theta burst stimulation (cTBS) applied over the left DLPFC of our subjects, as compared to the same stimulation protocol over a control area (vertex).

Methods

Participants

A volunteer sample of 18 students (10 females) from Edge Hill University, with age range from 19 to 38 years old (M = 21.7, *S.D.* = 4.17), were recruited for this study. Handedness was determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Fifteen participants were right-handed as indicated by the Lateralisation Index (*L.I*) (*L.I* = 86.3, *S.D.* = 15.4), one participant was left-handed (*L.I* = -100) and two were ambidextrous (*L.I* = 39.4, *S.D.* = 8.6). All participants gave written informed consent for both taking part in the study and the use of Transcranial Magnetic Stimulation (TMS). In addition, all participants passed the TMS screening questionnaire recommended by Rossi, Hallet, Rossini and Pascual-Leone (2011). Exclusion criteria included a history of epilepsy, fainting or concussion, the presence of a pacemaker or neurostimulator, metal in the brain, cochlear implants or being pregnant. In addition, participants must have been alcohol, recreational drug and caffeine free for 24 hours prior to testing. Ethical approval was granted by the Edge Hill University Psychology Department Ethics Committee.

Stimuli

The Symmetry Span Test (SymmSpan) was implemented, via the Inquisit Lab experimental software, in order to measure spatial working memory (Conway., *et al*. 2005). It was administered to participants seated at a comfortable distance in front of the computer screen, adjacent to the TMS machine. SymmSpan was used to measure spatial working memory at both the vertex (Cz) and the left dorsolateral prefrontal cortex (LDLPFC). Participants were presented with a visual sequence of two to five highlighted red squares in a four-by-four matrix. Each square in the sequence was preceded by a symmetry judgement in an eight-by-eight matrix. Participants were required to recall the sequence of the red squares, by clicking the squares in the four-by-four matrix in the correct order. A practice session of 22 trials was initially presented. Once the practice was over, participants completed 36 trials. On conclusion of the experiment, the Span score was recorded. Span score was calculated by adding all the perfectly recalled sets, meaning that only the complete recall sets were considered, with partial recall or no recall sets being ignored.

Transcranial Magnetic Stimulation

Continuous theta burst stimulation (cTBS) was delivered by means of a 70mm figure-of-eight stimulation coil (Magstim D70^2 Coil), connected to a Magstim SuperRapid 2 Stimulator (The Magstim Company, Carmarthenshire, Wales), producing a magnetic field up to 0.8T at the coil surface. The resting motor threshold (rMT) for the first dorsal interosseous muscle (FDI) of the dominant hand, as determined by the Edinburgh Handedness test (Oldfield, 1971), was visually determined for each participant in order to appropriately select the stimulation intensity in the TMS experiment. During this session, the coil was positioned over either the right or left motor cortex, determined by handedness, and in correspondence with the optimal scalp position (OSP), defined as the position from which motor-evoked potentials (MEPs) with maximal amplitude were observed. The OSP was detected by moving the intersection of the coil in 1-cm steps around the motor hand area of the appropriate motor cortex and by delivering TMS pulses at constant intensity. The rMT was defined as the lowest stimulus intensity able to evoke (visually inspected) 5 of 10 MEPs. rMT levels were on average 63.4% (SD = 15.92, Range = 40 – 88%). The cTBS was delivered over the left dorsolateral prefrontal cortex. Vertex was chosen as a control site to account for non-specific effects of TMS.

The approximate locations of the stimulating areas were identified on each participant's scalp by means of the 10-20 EEG System Positioning. In keeping with past research, for left DLPFC stimulation the coil was positioned on the F3 location and for vertex stimulation on the Cz location, as identified by means of a 10-20 system EEG cap (Jasper, 1958). Three-pulse bursts at 50Hz repeated every 200ms for 40s (equivalent to "continuous theta burst stimulation" cTBS) were delivered at 80% of the subject's rMT (600 pulses). The inhibitory effect of cTBS with these characteristics is supposed to last about 60 minutes. The coil was positioned tangentially to the scalp, with the handle pointing superiorly. This orientation is able to modulate contralateral M1 excitability and to interfere with cognitive functions. The stimulating coil was held by a stand and coil position and was continuously monitored throughout the experiment. At the end of each session, no adverse effects of the cTBS were reported.

Design and Procedure

Before testing could begin, participants were screened using the TMS screening questionnaire recommended by Rossi, Hallett, Rossini and Pascual-Leone, (2011), to ensure that participants were eligible to take part in the study. Once the researchers were happy and the participant was safe to continue with the study, informed consent was established. In addition, the Edinburgh Handedness Inventory (Oldfield, 1971) was completed to determine handedness.

Once the rMT had been ascertained, it was recorded and used to commence testing. Participants were seated at the computer adjacent to the TMS machine to reduce their disruption between stimulation and testing. Continuous theta-burst stimulation (cTBS) was then administered at either the vertex (Cz), used as a control condition, or the left DLPFC (the order of stimulation site was counterbalanced between subjects) to investigate whether there had been any significant change in their SymmSpan score. Participants were reminded of their right to both withdraw and to terminate the study, should they be uncomfortable at any point during the session. Once the stimulation had finished, participants were asked to complete the SymmSpan test.

The study took participants around 60 minutes to complete, with times varying for participants based on the time taken to determine rMT. At the end of each testing session all subjects were debriefed to the purpose of the study and asked to report any adverse effects from the use of TMS.

Results

All data were processed offline using SPSS software version 25. The SymmSpan score was submitted to a repeated measures analyses of variance (ANOVA) with stimulation site (Vertex or left DLPFC) as the within-subject factor.

The descriptive statistics associated with the SymmSpan score across the stimulation sites are reported in Table 1. The span score was largest at the vertex site (M = 93.2, SD = 5.53) and smallest at LDLPFC (M = 86.6, SD = 8.49). The repeated measures ANOVA revealed a significant effect, $F(1, 17) = 1.40$, $MSE = 11.538$, $p < .05$, $np^2 = .667$.

	Vertex	**LDLPFC**
Symmetry Span Score	93.2 (5.54)	86.6 (8.49)

Table 1: *Mean (SD) of Symmetry Span scores at each Stimulation Site*

Hence, the results support the hypothesis for this study, in that SymmSpan score was significantly impaired in the left DLPFC condition after TMS stimulation, as compared to the vertex (control) condition.

Discussion

This study aimed to investigate the role of the left dorsolateral prefrontal cortex (LDLPFC) in working memory by means of Transcranial Magnetic Stimulation (TMS). The results have indicated that continuous theta burst stimulation (cTBS) applied to the left DLPFC significantly impaired the subjects' span score in a spatial working memory test, as compared to stimulation over the vertex (control) site. The findings from this study corroborate with those found by other researchers (Mottaghy., *et al*. 2000; Mull & Seyal., *et al*. 2001; Osaka., *et al*. 2007). For example, Mull and Seyal (2001) observed increased errors in a verbal 3-back test after TMS stimulation over the left DLPFC and Hoy., *et al*. (2016) used theta burst stimulation (cTBS), akin to this study, to investigate the relationship between the left DLPFC and working memory using an n-back test. Overall, the present study provides some critical evidence on the role of the left DLPFC in working memory, as it has shown that impaired excitability of the DLPFC can alter working memory ability as measured by the symmetry span test.

Previous research has suggested the concept of spatial-object lateralisation; the idea that the left prefrontal cortex is not specialised for spatial working memory, but rather for object or verbal working memory, and thus contradicting the findings of this study. Smith., *et al.* (1995), found activation of the left hemisphere by means of positron emission tomography (PET) only when participants completed an object-related working memory task and not during a spatial working memory task. In addition, Nelson *et al*. (2000) and Nagel., *et al*. (2013) revealed a spatial-right and object-left lateralisation by means of fMRI, in both children and adolescents. Therefore, they concluded that the right prefrontal cortex (PFC) may be specialised for spatial working memory and the left DLPFC for object or verbal working memory.

However, the findings of the present study have indicated a causative relationship between the left DLPFC and spatial working memory, thus contradicting this lateralisation concept. Some initial evidence for this was also provided by earlier studies. For example, Sandrini., *et al*. (2008) applied TMS to both the left and right DLPFC, during a spatial and verbal n-back test and they found a significant effect in the right DLPFC for the verbal test and in the left DLPFC for the spatial test. Overall, the lateralisation concept of PFC remains highly debated and no solid consensus exists. Therefore, future research is deemed as necessary to investigate and compare the roles of the left DLPFC on spatial and non-spatial working memory.

Spatial working memory capacity has been previously linked to the measurement of executive function (McCabe., *et al*. 2010) and the DLPFC has been seen as the anatomical area responsible for executive function. For example, D'Espositio et al. (1995) found activation in the DLPFC to only increase during a dual-task and not a single task. Additional complex span tests, such as the reading span test, have shown increased activation in the DLPFC (Bunge et al., 2000), thus supporting its role in executive function. Furthermore, Dubreuli-Val., *et al*. (2019) used transcranial Direct Current Stimulation (tDCS) to stimulate the left DLPFC and reported improved reaction times during the Erikson Flanker Task. However, other research has contradicted this evidence. Levy and Goldman-Rakic (1999), for example, found that the DLPFC was equally important for low working memory demands, as compared to more complex sequential processing with high working memory demands, and thus suggesting that the DLPFC may have a different role, other than executive function, in working memory. However, a meta-analysis of neuroimaging data has reported that there is a significant increase in right-lateralised peaks during executive demand tasks, therefore the DLPFC may still be critical for executive functioning, but it may just follow the same lateralisation effects of spatial and non-spatial working memory (Wager & Smith, 2003).

A limitation of the present study can be considered the use of a single working memory test. It has been previously suggested that in order to obtain a valid measurement of working memory capacity, only a single indicator cannot be considered, due to the fact that a working memory task may contain variance from both working memory capacity and the test itself (Foster., *et al*. 2014). In that sense, it would be beneficial if future studies could include at least two or more complex span tasks in order to investigate visuo-spatial working memory. Nevertheless, the SymmSpan test has been linked to a greater spatial complexity than other spatial working memory tasks (i.e. the rotation span; Healey., *et al*. 2011) and its validity as a measure of visuo-spatial working memory has not been debated. Moreover, this greater spatial complexity of the SymmSpan task may explain why previous studies using other tasks have failed to find significant results of the role of the left DLPFC in spatial working memory.

Another issue for consideration is the fact that the SymmSpan has been related to and correlated with high levels of intelligence, in particular fluid intelligence, which is involved in the storage and transformation of information in order to solve abstract problems (Engle, Tuholski, Laughlin & Conway, 1999). Working memory capacity has been positively correlated with performance in educational settings (Colom, Escorial, Shih & Privado, 2007). The current study was performed on a group of university students, who by default are at a higher educational level than non-students in the general population (Van Lange & Sedikides, 1998). Therefore, it is possible that the participants used in this study will have generated higher SymmSpan scores as compared to the general population. In addition, Reuter-Lorenz et al. (2000) reported that during a PET scan, younger adults have a greater left lateralisation for verbal working memory, in comparison to older adults, with older adults showing a more bilateral activation for both verbal and spatial working memory. The current study consisted primarily of young participants that could have skewed the task scores to a specific direction.

Finally, in the present study cTBS was applied over the F3 electrode of the electroencephalography (EEG) cap as suggested by the international 10-20 system used in EEG electrode placement (Jasper, 1958). Previous TMS studies have stimulated the DLPFC at either the F3 or F4 electrodes for either left or right hemispheres, respectively (Rossi., *et al*. 2001). However, Rusjan., *et al*. (2010) have previously suggested some issues with the 10-20 system as a method of TMS coil placement, such as its inability to take into account head shape that may result in the F3 placement not being the appropriate electrode to stimulate the left DLPFC. However, Herwig., *et al*. (2001) found that the 10-20 system is more reliable in coil positioning for the DLPFC than the standard procedure proposed by Pascual-Leone., et al. (1996), which suggests that the optimum positioning is 5cm rostral to the motor cortex, established by the evoking of a response in the contralateral hand muscles. In addition, the 10-20 system has been praised for taking into consideration head size due to its placement of electrodes at fixed distances from anatomical landmarks in steps of 10 or 20% (Herwig *et al*, 2003). In addition, the majority of studies using TMS to stimulate the DLPFC have been successful in using the 10-20 system, finding significant results in their application of TMS (Graffman., *et al*. 1994; Mottaghy., *et al*. 2000), and thus suggesting that the 10-20 system is an appropriate coil placement technique for certain TMS protocols and cortical areas.

In conclusion, the present study aimed to provide causative evidence on the role of the left DLPFC in spatial working memory by means of a non-invasive brain stimulation technique. Previous research has demonstrated that the left DLPFC plays a critical role in working memory, however, there has been conflicting evidence on its precise role, which could be due to methodological differences. Further research is deemed as necessary in order to reach a consensus with regards to the spatial-verbal lateralisation concept of working memory and elucidate the roles of the DLPFC.

Compliance with Ethical Standards

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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