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Brief Report

Multiple bout rTMS on spatial working memory: A comparison study of two cortical areas

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ABSTRACT

It has been established that acute (within-session) repetitive transcranial magnetic stimulation (rTMS) improves spatial working memory (SWM). However, questions remain regarding the safety and effectiveness of multiple bouts of rTMS and the optimal cortical area to stimulate. This preliminary study investigated, in healthy participants, multiple bouts of rTMS over the dorsolateral pre-frontal cortex (DLPFC), or posterior parietal cortex (PPC) on SWM. Twenty participants (10m, 10f), all naïve to rTMS, where randomized into a DLPFC or PPC group, receiving six sessions of rTMS (5 Hz at 80% of motor threshold) every second day over two weeks. Prior to and post rTMS bouts, all participants completed testing for SWM measuring individuals' accuracy, strategy, and speed. Following repeated bouts of rTMS, significant improvements were observed with no contraindications in stimulating PPC but not DLPFC. This preliminary study has demonstrated that repeated rTMS bouts improve SWM safety providing potential for clinical application.

1. Introduction

Working memory (WM) supports the short-term storage and manipulation or processing of verbal or visual information (Baddeley, 2003; D'Esposito, Postle, & Rypma, 2000). WM has been shown to play important role in a range of everyday tasks including language processing, planning, educational and vocational attainment (Yuan, Steedle, Shavelson, Alonzo, & Oppezzo, 2006). Subsequently, there is a need to better improve WM in cases where this memory system is impaired which can occur following stroke or dementia. One technique suggested to improve WM functioning is via repetitive transcranial magnetic stimulation (rTMS). In this report, we focus on the safety of, and the extent to which multiple bouts of rTMS manipulates spatial working memory (SWM); the short-term storage and processing/manipulation of visual/visuo-spatial information.

There have been a several previous studies that have used rTMS demonstrating improved SWM performance (Luber et al., 2007; Yamanaka, Yamagata, Tomioka, Kawasaki, & Mimura, 2010). In particular these studies have demonstrated that 5 Hz at 100% of an individual's resting motor threshold (rMT) showed improvement in SWM. However, two questions worth exploring persist. First, it is still not certain which cortical area responds better following a multiple bout stimulation protocol on general SWM ability. Previous studies have demonstrated changes in SWM processing with stimulation of the right dorso-lateral pre-frontal cortex (DLPFC) (Müri et al., 2002), whilst others (Hamidi, Tononi, & Postle, 2008) have observed improvements in the right posterior-parietal cortex (PPC). Second, the majority of these studies have examined SWM following a single bout of rTMS. There is a continuing need to investigate multiple rTMS bouts on these two cortical areas. Valero-Cabré, Pascual-Leone, and Rushmore (2008) have posited that multiple bouts of rTMS are used for therapeutic application, yet studies to assess multiple sessions over both these areas are limited. This study, extending on the initial work by Luber et al. (2007), is one of the first to address the question of the efficacy of a multiple bout paradigm on working memory performance.

Therefore, the aim of this preliminary study was to investigate the safety and efficacy of multiple rTMS bouts over either the DLPFC (active control) or PPC on SWM, using a double blind, comparative study design. It was hypothesized that six repeated treatments, over two-weeks, of 5 Hz at 80% rMT over either cortical area would be safe on individuals receiving the treatment and improve SWM (O'Reardon, Peshek, Romero, & Cristancho, 2006). Further, we hypothesized that rTMS over DLPFC would improve

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processing accuracy, whilst rTMS over the PPC would improve SWM speed and strategy, similar to previous single bout study designs.

2. Methods

Twenty right-hand dominant healthy individuals (10m, 10f; M = 27.43, SD = 7.35 years), all naïve to TMS, were recruited for this study. All individuals completed the TMS adult safety questionnaire (Rossi, Hallett, Rossini, & Pascual-Leone, 2011), provided informed consent and were fully familiarized with all methods prior to main studies. All methods were approved by the University Human Research Ethics Committee in accordance with the Declaration of Helsinki.

Participants were randomly allocated to either a group that received stimulation to the PPC ($n = 10$) or a group that received stimulation to the DLPFC ($n = 10$). All participants completed the Cambridge Neuropsychological Test Automated Battery (CANTAB) SWM test (Cambridge Cognition, UK) which participants are instructed to find a blue "token" which is hidden inside a coloured box on the screen. A number of boxes were presented on the screen and touching each box in turn to locate where the token was concealed. Once a token had been found, that box would not hide another one in that search set. Participants completed four test trials with each of two, three, four, six and eight boxes. An error was recorded if the participant returned to this box on the next search trial (total errors), and adopting a search sequence on difficult levels of six and eight box trials was also calculated (strategy). Test duration was also recorded.

Following pre-testing, participants in the PPC and DLPFC groups completed six sessions of rTMS every alternate day (except weekends), over two weeks. rTMS was delivered by an independent operator who did not reveal to the investigators the area (either DLPFC or PPC) the participant received rTMS. A Rapid^2 (Magstim, UK), delivered pulses using a 70 mm figure-of-eight air-film coil (Magstim, UK) at 80% of resting motor threshold (rMT, see Wassermann, Wedegaertner, Ziemann, George, & Chen, 1998) at a frequency of 5 Hz in 10 trains of 30 pulses per train (total pulses per session 300). During each treatment session participants wore a snugly fitted electroencephalography cap (Easycap, Germany) with pre-marked sites based upon the international 10–20 system. Right DLPRC stimulation was delivered over the area F4, whilst PPC stimulation was delivered over area P4.

Following the six stimulation sessions participants completed the CANTAB tests with a gap of 45 min to avoid acute carry over effects which have been shown to influence testing up to 30 min following stimulation protocols (Sandrini, Umiltà, & Rusconi, 2011; Thut & Pascual-Leone, 2010).

Data were analysed using paired samples *t*-tests. Specifically, for each dependent variable we tested whether there was a significant change in pre- and post-test scores within each group. This approach overcame problems with low statistical power associated with using factorial ANOVA design to test for a Pre–Post Test X Group Interaction and independent samples *t*-test investigating a difference in change scores. Both analyses only had 80% power to detect Cohen's *d* of 1.32.

3. Results

All participants completed the testing with no serious adverse reported effects. One participant reported a mild headache after the first session, however, this was in context of poor sleep the previous night. There were no further reports from this participant during the rTMS intervention, completing all sessions without incident. Participants self-reported that, other than the coil being placed "at the front" or "over the top", they had no formal understanding of what area of their brain was being stimulated.

Data and results from paired samples *t*-test are presented in Table 1. Distribution of individual pre- and post-TMS scores are presented in Fig. 1(a–e). Table 1 shows significant decreases between pre- and post-test scores on strategy and test duration measures for the PPC group. There were no significant differences in pre- and post-test scores for the DLPFC group.

4. Discussion

This novel finding from this preliminary study demonstrates that prescribing a similar volume of rTMS to acute studies, but in multiple bouts (six sessions across two weeks) is safe, and improves offline SWM in stimulation of PPC but not DLPFC in healthy individuals. These findings have implications for clinical application, however, we acknowledge the limitations in this short report and caution the reader that further studies are required. In particular, we note that the group's baseline performance levels in the task differ, which may make comparing enhancements following multiple bout rTMS difficult. Secondly, this preliminary study employed a small sample potentially contributing to our observations. Thirdly, our stimulation level of 5 Hz frequency at 80% of rMT could be interpreted as low, however, given the novel aspect of the study, multiple bouts of stimulation with the potential of kindling (Rossi, Hallett, Rossini, & Pascual-Leone, 2009), we aimed to be conservative with the intervention. Finally, this preliminary study had no formal sham condition, utilized a two-group design with the DLPFC as our active control, and random allocation led to group differences on the pre-test measures. However, the strength of this design is that groups may have been similar on non-measured variables (which is likely to occur via the process of random allocation). Our justification for not incorporating a control group was with previous studies (for example Müri et al., 2002; Hamidi et al., 2008) demonstrating, separately, changes in either cortical area following stimulation; and our question focused on comparing differences when stimulating both areas within the same study.

Our findings concur with previous acute bouts of rTMS over PPC but not DLPFC (Hamidi et al., 2008; Luber et al., 2007). Moreover, the finding of improved offline SWM in PPC after a 45 min washout period, to reduce potential carry over effects from the final session following rTMS (Sandrini et al., 2011; Thut & Pascual-Leone, 2010) is notable, particularly with cognitive task performance. Further studies should aim to confirm these findings, as well as extending the protocol to clinical populations where WM has been compromised.

For the present study, we demonstrated the greatest improvement in search strategy, as well as a significant change in speed of performing the SWM test following rTMS. Strategy in the CANTAB SWM test refers to the sequence of "opening" the boxes

Table 1
Summary statistics for pre- and post-test scores reported by group and outcome variable.

Group/outcome variable	Pre-test scores				Post-test scores				Comparison of means	Pre–post test effect size[b]
	M	SD	Min.	Max.	M	SD	Min.	Max.	*p* value[a]	Cohen's *d*
PPC										
Strategy[+]	35.9	5.0	27	45	32.2	6.7	24	45	0.004[*]	1.39
Total errors	28.5	22.9	4	76	25.4	22.3	1	67	0.122	0.68
Test duration (s)	501.6	141.2	375.4	783.8	453.9	170.4	344.1	805.1	0.030[*]	0.95
DLPFC										
Strategy[+]	27.9	6.2	18.0	35.0	25.5	5.6	19	32	0.192	0.59
Total errors	16.2	12.5	3.0	33.0	8.4	10.6	0	28	0.092	0.73
Test duration (s)	407.9	41.8	332.6	479.6	370.6	58.5	295.8	516.3	0.178	0.60

[a] Bonferroni adjusted.
[b] Computed using formula provided by Morris and DeShon (2002) that takes pre–post-test correlation into account.
[+] Strategy score, which indexes the number of times the participant started a search with a different box, the latter being an inefficient strategy (i.e., high strategy scores denote poorer performance).
[*] $p < 0.05$.