ELSEVIER

Clinical Neurophysiology 112 (2001) 1672–1675

www.elsevier.com/locate/clinph

Transcranial magnetic stimulation of left prefrontal cortex impairs working memory

Brendan R. Mull, Masud Seyal*

Department of Neurology, Section of Clinical Neurophysiology, University of California, Davis, 2315 Stockton Boulevard, Room 5308, Sacramento, CA 95817, USA

Accepted 18 May 2001

Abstract

Objectives: Several lines of evidence suggest that the prefrontal cortex is involved in working memory. Our goal was to determine whether transient functional disruption of the dorsolateral prefrontal cortex (DLPFC) would impair performance in a sequential-letter working memory task.

Methods: Subjects were shown sequences of letters and asked to state whether the letter just displayed was the same as the one presented 3-back. Single-pulse transcranial magnetic stimulation (TMS) was applied over the DLPFC between letter presentations.

Results: TMS applied over the left DLPFC resulted in increased errors relative to no TMS controls. TMS over the right DLPFC did not alter working memory performance.

Conclusion: Our results indicate that the left prefrontal cortex has a crucial role in at least one type of working memory.

Keywords: Working memory; Dorsolateral prefrontal cortex; Functional disruption; Transcranial magnetic stimulation

---

1. Introduction

Working memory refers to temporary storage and manipulation of the information necessary for complex tasks such as language comprehension, learning, and reasoning (Baddeley, 1992). Fuster et al. (1982) found that some neurons of the prefrontal cortex increase their firing when a cue is presented and continue to fire during a delay period after the cue disappears. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies indicate that the frontal cortex plays a crucial role during working memory tasks (e.g. Roland, 1984; Paulesu et al., 1993; Jonides et al., 1993; Petrides et al., 1993a,b; Cohen et al., 1994). PET and fMRI studies have shown increased metabolic activity in the frontal lobes during working memory tasks, with other cortical areas also activated depending on the task involved (e.g. Berman et al., 1995; Smith et al., 1996; Salmon et al., 1996; D'Esposito et al., 1995). The activation of frontal cortex appears to be proportional to working memory demands and not 'mental effort' more generally (Barch et al., 1997). Using EEG techniques with high spatial resolution, Gevins et al. (1996) identified several frontally localized waveforms modulated by working memory task manipulations. A left-lateralized slow frontal positivity with a mean peak latency of 450 ms (P450) was larger in both spatial and verbal memory tasks than in the respective controls.

Single-pulse transcranial magnetic stimulation (TMS) can transiently disrupt the function of restricted regions of cortex. For example, TMS over sensory cortex can decrease perception of cutaneous stimuli delivered to the fingers of the contralateral hand (Cohen et al., 1991; Seyal et al., 1992) for up to 500 ms after the TMS pulse (Seyal et al., 1997). Repetitive TMS (rTMS) of the frontal cortex has been shown to increase errors in a visuospatial delayed-recall task when stimulation was applied throughout the entire delay period, but not with a shorter duration of stimulus (Pascual-Leone and Hallett, 1994). TMS of human cortex causes brief disruption of cortical activity and can therefore provide information on dynamic cortical processes with sub-second temporal resolution. Single-pulse TMS can be safely used in normal human subjects without the risks inherent with rTMS (Wassermann, 1998).

We proposed that under certain conditions single-pulse TMS should be effective in disrupting verbal working memory. First, we targeted the pulse to an approximate time and location where Gevins et al. (1996) found EEG

---

* Corresponding author. Tel.: +1-916-734-2636; fax: +1-916-736-2976. *E-mail address:* mseyal@ucdavis.edu (M. Seyal).

1388-2457/01/$ - see front matter © 2001 Elsevier Science Ireland Ltd. All rights reserved.
PII: S1388-2457(01)00606-X

CLINPH 2001036

evidence of dorsolateral prefrontal cortex (DLPFC) activity in a verbal working memory task. Second, we ensured that subjects were engaged in a task with a high working memory load by having them participate in a relatively difficult '3-back' working memory task. This '3-back' sequential letter matching task activates the DLPFC (Cohen et al., 1997) Third, we explored a number of regions on the left frontal scalp of each subject to find the location where TMS appeared to have the greatest effect on task performance.

2. Methods

Nine healthy human subjects were tested. The age range was 23–59 years (mean 34 years). Eight were strongly right-handed; one was strongly left-handed. Subjects gave informed consent, and the local Human Subjects Review Committee approved the study.

Subjects were presented with a pseudo-random set of 33 letters (A–J). Letters were displayed serially on a backlit LCD screen for 30 ms every 2 s. Subjects were required to state if the letter just presented was the same as the letter presented three-back. In this way, 30 responses were obtained from each set. The true frequency of matches was approximately 25%. Subjects were allowed to practice the task until they achieved approximately 75% accuracy or better, which generally required about 30 min.

TMS was generated using a Cadwell MES-10 stimulator with a figure-eight coil. The coil was held tangential to the skull with the handle pointing up. The output was adjusted to 15% above the motor threshold. Motor threshold was defined as the lowest output of the MES-10 required to produce a reproducible twitch of the contralateral first dorsal interosseous muscle when stimulating over motor cortex.

We began with 4 sets of trials intended to determine the optimal site for left DLPFC stimulation. Initially, the midpoint of the distal edge of the coil was placed at F7 (international 10–20 system). The peak electric field of the figure-eight coil is at its center, 2.8 cm from the midpoint of the distal edge (Cohen et al., 1990). Thus, with the distal edge of the coil at F7, the peak electric field is medial to F7 in the vicinity of DLPFC (Brodmann's area 46) (Homan et al., 1987; Steinmetz et al., 1989). In the next 3 trials, the coil was repositioned 2 cm rostro-medially, 2 cm posteriorly, and 2 cm posteriorly and rostro-medially relative to the original site. The site where the subject made the most errors was chosen for further study.

Testing consisted of 8 sets with TMS, each set of 30 responses was immediately preceded by a control set of 30 responses in which no TMS was applied. In 4 of the sets, the selected region of left scalp was stimulated. In the other 4, the corresponding area on the right received stimulation. Set order was determined randomly for each subject. The TMS pulse was delivered 400 ms into the delay period following the presentation of each letter.

Statistical analysis was performed using a commercially available software package (SigmaStat). The data were checked for normality (Kolmogorov–Smirnov). If the data passed the normality test, Student's *t* test was used to compare each TMS set with its preceding control set. Otherwise, the Wilcoxon signed rank test was used. The Mann–Whitney *U* test was used for interhemispheric comparisons.

3. Results

Seven subjects completed the entire experiment; two completed 6 of 8 sets. In all, there were 34 sets of data following TMS (1020 responses) and the same number of no TMS controls for each hemisphere. Fig. 1 shows the errors made by each subject during the TMS condition and the corresponding control condition.

With left frontal scalp stimulation, significantly more errors were made following TMS than in the corresponding controls ($P = 0.008$). There were 183 (17.9%) incorrect responses in the left frontal TMS condition and 128

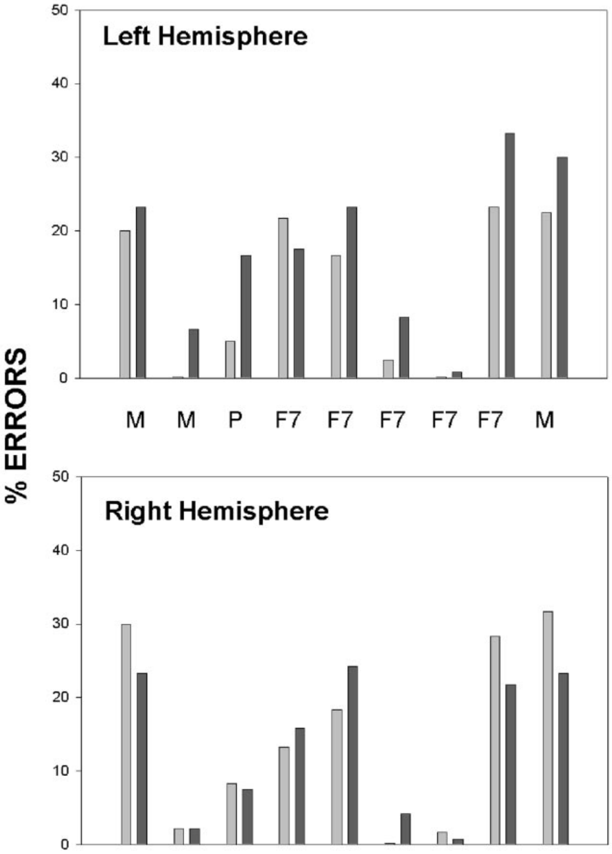

Fig. 1. Percent errors for each of the 9 subjects are shown. Data from the left and right hemispheres appear separately. Lighter bars represent errors in the control condition (no TMS). Dark bars indicate errors in TMS sets. The stimulation site chosen for each subject is indicated: F7, midpoint of the distal edge of the coil at F7; M, 2 cm rostro-medial; P, 2 cm posterior. For right hemisphere stimulation the homologous sites over the right scalp were stimulated in each subject.

(12.5%) incorrect responses in the left frontal control condition, an increase of 5.4%.

With right frontal scalp stimulation, the TMS condition was not significantly different from the controls. There were 140 (13.7%) errors in the right frontal TMS condition and 151 (14.8%) incorrect responses in the right frontal control condition.

The change in errors attributable to TMS (TMS condition errors minus ipsilateral control errors) was significantly greater for the left hemisphere than for the right ($P = 0.03$). The errors made during the control conditions for the left and right hemispheres were not significantly different.

4. Discussion

In this study, there was a significant increase in task errors related to TMS applied over the left DLPFC relative to the control condition. This degradation in task performance is likely related to transient functional inactivation of the left DLPFC by TMS. Right prefrontal cortex stimulation resulted in no significant change in working memory performance relative to the control condition.

The effect of single pulse TMS on working memory in this study is less pronounced than that reported with rTMS in a simple delayed-response task. In the latter study, rTMS applied over the DLPFC at 5 Hz, throughout the delay period, resulted in rTMS related increase in percent errors to approximately 25% from about 5% errors in the control condition (Pascual-Leone and Hallett, 1994). The smaller effect seen in the present study probably reflects constraints of the experimental design.

The duration of any functional disruption induced by single-pulse TMS is brief. In the somatosensory cortex, single-pulse TMS causes disruption of a stimulus localization task that gradually decays over 500 ms (Seyal et al., 1997). If one assumes that the DLPFC is similarly affected by TMS, the functional disruption of the DFPLC lasts less than 25% of the interval between presentation of the successive letters. During this interval, the neuronal circuitry in the DLPFC may be continually refreshed through connections with other cortical regions, minimizing any TMS-induced dysfunction.

Increasing the working memory load, as with a 3-back task, results in increased brain activation observed by fMRI changes (Cohen et al., 1997). It is likely that in an experimental design with a lower memory load, single pulse TMS would be insufficient to cause a detectable degradation in working memory. Indeed, when a relatively easy delayed response task was employed, there was no detectable decrease in performance unless rTMS was applied throughout the delay period (Pascual-Leone and Hallett, 1994).

There is inter-subject variation in the timing of the EEG P450 (Gevins et al., 1996) It is possible that the fixed timing of the TMS pulse in this study (coinciding with the published mean onset of P450) resulted in less than maximal degradation of working memory performance. Nevertheless, a significant degradation in working memory performance was observed. Further studies will be required to determine whether there is a link between TMS-induced interference with working memory and the neuronal circuits underlying generation of the P450.

The relatively focal cortical stimulation by the figure-8 coil may not uniformly affect the entire region of DLPFC engaged in working memory. Within the DLPFC, the extent and localization of cortex involved with working memory may vary between subjects. Our limited mapping may not have completely accounted for this variation. Finally, we did not study the effect of coil orientation. Coil orientation does determine optimal stimulation of focal regions of sensory and motor cortex; this orientation-related sensitivity is more critical when transcranial magnetic stimulators that generate a monophasic pulse are used and less so with the MES-10 system (used in this study) that produces a biphasic sinusoidal field (Brasil-Neto et al., 1992). The effects of the TMS pulse may have extended into cortical regions adjacent to DLPFC. However, the magnetic field degrades rapidly with distance from the center of the coil, making it unlikely that stimulation of nearby Broca's area could account for our findings.

To keep testing time to a reasonable length, we did not map over the right scalp. Right frontal stimulation was undertaken primarily as a control to ensure that subject distraction related to noise associated with the TMS pulse, or TMS-associated muscle contraction, did not account for the effects observed with left scalp TMS. However there is other evidence for involvement of the non-dominant hemisphere in working memory tasks and varying lateralization is observed that appears to be, at least in part, dependent on the type of task required of the subject (Fuster, 1989; Milner, 1985; Manoach et al., 1997). A review of human functional imaging studies indicates that non-spatial tasks selectively activate the left prefrontal cortex while spatial tasks result in greater activation of the right prefrontal cortex (D'Esposito et al., 1998).

5. Conclusion

The results of this study indicate that working memory performance, in a sequential-letter-matching task, is impaired by TMS-induced functional inactivation of left prefrontal cortex. This effect occurs during the period when EEG evidence suggests that this region of cortex is engaged in a working memory task. PET and fMRI provide localizing information but have relatively poor temporal resolution as these techniques are dependent on hemodynamic changes that are delayed and temporally dispersed relative to periods of neural activity. EEG has excellent temporal discrimination and improving spatial resolution, while TMS allows precise targeting of focal and rapidly changing cortical events. These tools should allow further studies of cortical dynamics involved in working memory with temporal resolutions on the order of a fraction of a second.

Acknowledgements

This project was supported by the Predoctoral Research and Enrichment Fellowship, University of California, Davis, School of Medicine (Dr Mull).

References

Baddeley A. Working memory. Science 1992;255:556–559.

Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD. Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia 1997;35:1373–1380.

Berman KF, Ostrem JL, Randolph C, Gold J, Goldeber TE, Coppola R, Carson RE, Herscovitch P, Weinberger DR. Physiological activation of a cortical network during performance of the Wisconsin card sorting test: a positron emission study. Neuropsychologia 1995;33:1027–1046.

Brasil-Neto JP, Cohen LG, Panizza M, Nilsson J, Roth BJ, Hallett M. Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. J Clin Neurophysiol 1992;9:132–136.

Cohen LG, Bandinelli S, Sato S, Kufta C, Hallett M. Attenuation in detection of somatosensory stimuli by transcranial magnetic stimulation. Electroenceph clin Neurophysiol 1991;81:366–376.

Cohen JD, Forman SD, Braver TS, Casey BJ, Servan-Schreiber D, Noll DC. Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. Hum Brain Mapp 1994;1:293–304.

Cohen JD, Perttein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, Smith EE. Temporal dynamics of brain activation during a working memory task. Nature 1997;386:604–618.

D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. Nature 1995;378:279–281.

D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J. Functional MRI studies of spatial and nonspatial working memory. Cogn Brain Res 1998;7:1–13.

Fuster JM. The prefrontal cortex: anatomy, physiology and neuropsychology of the frontal lobe, 2nd ed. New York: Raven Press, 1989.

Fuster JM, Bauer RH, Jervey JP. Cellular discharge in the dorsolateral prefrontal cortex of the monkey in cognitive tasks. Exp Neurol 1982;77:679–694.

Gevins A, Smith ME, Le J, Leong H, Bennett J, Martin N, McEvoy L, Du R, Whitfield S. High resolution evoked potential imaging of the cortical dynamics of human working memory. Electroenceph clin Neurophysiol 1996;98:327–348.

Homan RW, Herman J, Purdy P. Cerebral location of international 10-20 system electrode placement. Electroenceph clin Neurophysiol 1987;66:376–382.

Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, Mintun MA. Spatial working memory in humans as revealed by PET. Nature 1993;363:623–625.

Manoach DS, Schlaug G, Siewert B, Darby DG, Bly BM, Benfield A, Edelman RR, Warach S. Prefrontal cortex fMRI signal changes are correlated with working memory load. NeuroReport 1997;8:545–549.

Milner B. How we know. In: Shafto M, editor. Memory and the human brain, San Francisco: Harper and Row, 1985. pp. 31–59.

Pascual-Leone A, Hallett M. Induction of errors in a delayed response task by repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. NeuroReport 1994;5:2517–2520.

Paulesu E, Frith CD, Frackowiak RS. The neural correlates of the verbal component of working memory. Nature 1993;362:342–345.

Petrides M, Alivisatos B, Evans AC, Meyer E. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc Natl Acad Sci USA 1993a;90:873–877.

Petrides M, Alivisatos B, Meyer E, Evans AC. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proc Natl Acad Sci USA 1993b;90:878–882.

Roland PE. Metabolic measurements of the working frontal cortex in man. Trends Neurosci 1984;7:430–435.

Salmon E, Van der Linden M, Collette F, Delfiore G, Maquet P, Degueldre C, Luxen A, Franck G. Regional brain activity during working memory tasks. Brain 1996;119:1617–1625.

Seyal M, Masuoka LK, Browne JK. Suppression of cutaneous perception by magnetic pulse stimulation of the human brain. Electroenceph clin Neurophysiol 1992;85:397–401.

Seyal M, Siddiqui I, Hundal NS. Suppression of spatial localization of a cutaneous stimulus following transcranial magnetic pulse stimulation of the sensorimotor cortex. Electroenceph clin Neurophysiol 1997;105:24–28.

Smith EE, Jonides J, Koeppe RA. Dissociating verbal and spatial working memory using PET. Cereb Cortex 1996;6:11–20.

Steinmetz H, Furst G, Meyer BU. Craniocerebral topography within the international 10-20 system. Electroenceph clin Neurophysiol 1989;72:499–506.

Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroenceph clin Neurophysiol 1998;108:1–16.