Anodal transcranial direct current stimulation of the right dorsolateral prefrontal cortex enhances memory-guided responses in a visuospatial working memory task

Giuseppe Giglia, MD, PhD[a,d]
Filippo Brighina, MD[a]
Silvia Rizzo, PsyD, PhD[b]
Angela Puma, MD[c]
Serena Indovino, MD[a]
Simona Maccora, MD[a]
Roberta Baschi, MD[a]
Giuseppe Cosentino, MD[a]
Brigida Fierro, MD[a]

[a] Department of Experimental Biomedicine and Clinical Neurosciences (BioNec), University of Palermo, Palermo, Italy
[b] Fondazione Istituto San Raffaele G. Giglio, Cefalù, Italy
[c] Santa Maria del Prato Hospital, Feltre, Italy
[d] Department of Cognitive Neuroscience - University of Maastricht, Maastricht, The Netherlands

Correspondence to: Filippo Brighina
E-mail: filippo.brighina@unipa.it

Summary

Several studies have shown that transcranial direct current stimulation (tDCS) is able to enhance performances on verbal and visual working memory (WM) tasks. Available evidence points to the right dorsolateral prefrontal cortex (DLPFC) as a critical area in visual WM, but to date direct comparisons of the effects obtained by stimulating the left versus the right DLPFC in the same subject are lacking.
Our aim was to determine whether tDCS over the right DLPFC can differently affect performance as compared with left DLPFC stimulation. Ten healthy subjects performed a memory-guided visuospatial task in three conditions: baseline, during anodal stimulation applied over the right and during anodal stimulation applied over the left DLPFC. All the subjects also underwent a sham stimulation as control. Our results show that only active stimulation over the right DLPFC is able to increase performance when compared to the other conditions. Our findings confirm the crucial role played by the right DLPFC in spatial WM tasks.

KEY WORDS: dorsolateral prefrontal cortex, transcranial direct current stimulation, working memory

Introduction

Working memory (WM) is the ability to temporarily retain and manipulate information needed for complex cognitive abilities, such as language comprehension, learning and reasoning (Baddeley, 1992; Mull and Seyal, 2001). The classical model by Baddeley and Hitch (1974) theorizes that WM is comprised of two specialized temporary memory buffers (a phonological and a visuospatial store) and a supervisory system (the central executive). This complex cognitive function can be subdivided into basic operations like "mnemonic selection of one item amongst others", "updating the focus of attention with the selected item", "updating the content of visual WM with new items", "rehearsal of visuospatial information", and "coping with interference" (Bledowski et al., 2010). Functional neuroimaging studies have found activations of the superior frontal sulcus, posterior cingulate cortex, precuneus, posterior parietal cortex, and dorsolateral prefrontal cortex (DLPFC) and it is likely that distinct brain regions are involved in the different types of operation. The DLPFC seems to be prevalently involved in selection operations (Bledowski et al., 2010). WM can be explored using delayed recognition or recall tasks. In recognition tasks, the observer is asked to judge whether the probe stimulus is the same as or different from the one that was previously presented. In recall trials, the subject's response depends on his/her ability to reproduce exactly what was previously presented and requires a complete reproduction of what was held in the memory. Healthy subjects perform recognition trials better than recall trials (Rock and Engelstein, 1959). The DLPFC, corresponding to Brodmann's areas 9 and 46, plays a critical role in WM tasks: verbal WM is mainly handled by the left DLPFC whilst spatial WM is reported to depend on the right hemisphere (D'Esposito et al., 2000; Mottaghy et al., 2000; Smith and Jonides, 1999). Furthermore, the left DLPFC is likely to be more active in tasks requiring recall activity, while right prefrontal cortex activity increases in recognition tasks (Cabeza et al., 2003).
Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that can modulate cortical excitability through the delivery of weak con-

stant electric currents (Priori, 2003) that act on neuronal membrane polarity. An anodal current causes depolarization, increasing spontaneous firing and excitability, whilst an opposite, inhibitory effect is produced by cathodal stimulation, which causes hyperpolarization. The effects of tDCS are also prolonged: after-effects can persist for a time ranging from five minutes to as long as 90 minutes, depending on the duration of the stimulation itself (Nitsche and Paulus, 2000). These long-lasting effects may be the result of improved NMDA receptor function and may also depend on intracellular calcium concentration levels (Nitsche et al., 2003). On this basis, anodal tDCS has been used to enhance the cortical excitability of the motor, visual and prefrontal cortices and to improve motor skills and verbal fluency in healthy subjects (Fregni et al., 2005; Marshall et al., 2005; Ohn et al., 2008). Anodal tDCS over the left DLPFC is reported to enhance cognitive functions in humans (Fregni et al., 2005). More recently (Jeon and Han, 2012), anodal tDCS over the right DLPFC has been found to enhance performances on "visuospatial function training", which is a subtask of a computerized battery, the CogPack® (Marker Software, Ladenburg, Germany).

Since cognitive performances are characterized by wide inter-subject variability, we designed an intra-subject study in order to evaluate the differential effect, on visuospatial WM, of tDCS applied over the right versus the left DLPFC. We postulated that if visuospatial WM is mediated by the right DLPFC then performances would be enhanced only after right DLPFC stimulation, whereas left stimulation would have no effect.

Materials and methods

Subjects

Ten young adults (6 males, mean age 27±2.3 years, SD) were recruited from the University of Palermo. They all had a high level of education (mean 17.7±0.9 years, SD) and they were all right-handed. Handedness was established on the basis of a 10-item self-report questionnaire adapted from the Edinburgh Handedness Inventory (Oldfield, 1971). The participants had a mean laterality quotient of 86.7±16.7 (SD).

The subjects had no history of psychiatric or neurological disorders. Written consent was obtained from the participants prior to the beginning of the study. The experiments were approved by the local ethics committee and were conducted in accordance with the Declaration of Helsinki.

Direct current stimulation

Direct current stimulation was applied via a pair of saline-soaked surface sponge electrodes (7 x 5 cm, 35 cm^2) and delivered by a CE-certified Eldith DC stimulator (Neuroconn, Ilmenau, Germany). To stimulate the right or left DLPFC, an anode electrode was placed over the F4 or the F3 site, respectively, according to the International 10-20 system of EEG electrode placement. This system has already been used in transcranial magnetic stimulation (TMS) studies (Gerloff et al., 1997; Rossi et al., 2001). The cathode was placed over the contralateral supraorbital area. This reference electrode location has been shown to be functionally ineffective in experimental designs (Nitsche et al., 2003). The current was ramped up during the first eight seconds to a maximum of 1 mA, and then remained at this level for the rest of the 10-minute stimulation period. This resulted in a total current density of 0.03 mA/cm^2 over the stimulated area. The choice of stimulation duration was determined by the fact that the study was designed to explore the after-effects of tDCS rather than the on-line effects.

Literature data claim that a nine-minute stimulation period induces after-effects lasting 30 minutes (Nitsche and Paulus, 2001). Throughout the stimulation period the subjects were asked to rest in a silent room with their eyes closed. At the beginning of the stimulation, the current could be perceived as an itching sensation at both electrode sites, but after a few seconds this sensation faded away completely. In the sham condition, the stimulator was turned off after 30 seconds; thus the sham stimulation caused the same itching sensation as experienced with the real stimulation but without having any biological effects (Giglia et al., 2011). Each subject was examined in two experimental conditions (right DLPFC, left DLPFC) and one control condition (right sham) in separate sessions separated by intervals of least one week. In each subject, the order of the conditions was randomly assigned.

Working memory assessment

The paradigm used in this study was a modified version of the one used by Hamidi et al. (2009) in delayed recognition tasks. On a black screen a central fixation cross was presented for 500 ms, followed by a succession of four white disks that appeared in random locations. Each target was presented for 1 s in one of the two possible positions within one of the screen's nine quadrants (Fig. 1). Afterwards a luminance mask was flashed on the screen for 100 ms, followed by a 3 s delay period. During the subsequent response phase, four identical stimuli (probes) in similar or different positions from the initial targets were presented in succession (1 s each). The subjects were asked to indicate as rapidly as possible whether their location corresponded to that of the previously shown stimulus, pressing a yes/no button (index finger/middle finger) on the computer keyboard. The subjects performed a total of 270 trials, i.e. 90 trials (divided into three blocks of 30 trials) per condition. The sessions, each lasting less than 12 minutes in total, were performed immediately after the end of the stimulation. In a separate session, one week before the start of the sessions (sham, left DLPFC, right DLPFC), all the participants underwent a brief familiarization procedure (five trials), after which they performed the same experimental para-

digm as after each stimulation condition. The data from these sessions were recorded as the participants' baseline performances. Accuracy, expressed as percentage of right answers, and reaction times (RTs) were the outcome measures in each session.

Statistical analysis

Mean accuracy and RT values were compared across sessions by means of two separate one-way ANOVAs with Condition (4 levels: baseline, left DLPFC, right DLPFC, sham) as a within-subject factor. Statistical significance was set at $p<0.05$. Newman-Keuls post-hoc comparisons were run.
In order to control for a time-dependent effect of tDCS, two one-way ANOVAs (accuracy and RTs) were used to compare performance between the three blocks of trials comprising each session.

Results

All the subjects completed the entire experiment. They tolerated the tDCS well and none of them complained of pain or any uncomfortable symptoms during the stimulation. All the participants reported that they could not tell the difference between the active and sham conditions.
ANOVA for accuracy showed a significant main effect of Condition ($F(3,27)=4.80$, $p=.008$). Newman-Keuls post-hoc comparisons showed that subjects gave significantly more correct answers after the right DLPFC stimulation than after the left DLPFC stimulation ($p<.01$), sham ($p<.01$) and baseline ($p<.01$) conditions (Fig. 2).
The RTs for correct answers were analyzed (Fig. 3). RTs were cleaned by deleting values outside mean RT ± 2SD. There was no significant main effect for Condition (comparison of RTs between active, sham and baseline conditions [$F(3,27)=1.39$, $p>.05$.]). One-

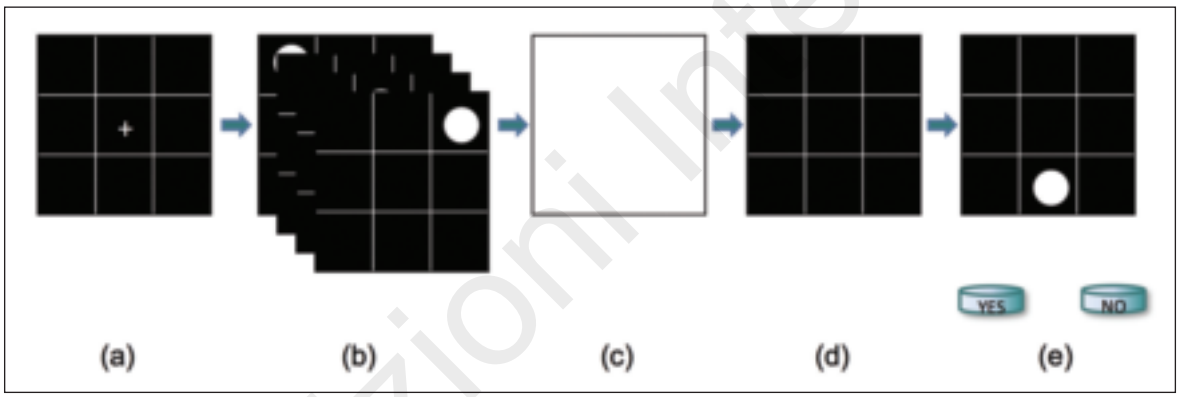

Figure 1 - Delayed recognition trial.
a) central fixation cross (500 ms); b) target set (4 s): the targets were presented one at a time for a duration of 1 s; c) luminance mask (100 ms); d) delay period (3 s); e) response phase: four identical stimuli were presented in the same or different positions compared with those of the initial targets. The subjects were asked to indicate as rapidly as possible whether their location corresponded to the one of the previously shown stimulus, pressing a yes/no button (index finger/middle finger) on the computer keyboard. The target display did not show the division of the screen into nine quadrants.

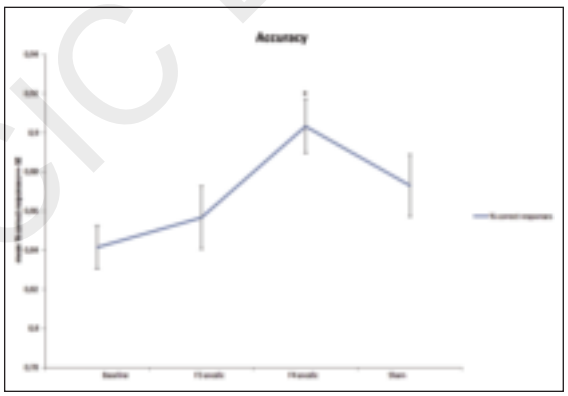

Figure 2 - Analysis of accuracy.
Subjects gave significantly more correct answers during F4 (right dorsolateral prefontral cortex, DLPFC) stimulation than the during F3 (left DLPFC) stimulation ($p<.01$), sham ($p<.01$) and baseline ($p<.01$) conditions.

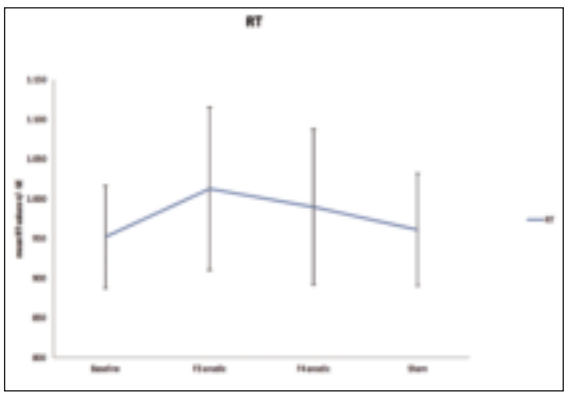

Figure 3 - Analysis of reaction times for correct answers.
There was no significant main effect for Condition (as shown by the comparison of reaction times between the active, sham and baseline conditions [$F(3,27)=1.39$ ns]).

way ANOVA with *Number of repetitions* per experimental session (30 trials x 3 repetitions = 3 levels) as a within-subject factor did not show significant differences either in accuracy [$F(2,18)=0.37$, $p>.05$] or in RTs [$F(2,18)=0.81$, $p>.05$] between the blocks of trials.

Discussion

In this study we explored the effects of DLPFC stimulation on visual WM. Memory-guided responses were evaluated using a visuospatial delayed recognition task, in which anodal tDCS over the right DLPFC was found to improve performance accuracy. Our results provide new evidence about the role of this area in visual WM.

In a previous study Hamidi et al. (2009) reported different effects of high-frequency repetitive TMS (rTMS) over the left or right DLPFC on visual memory-guided responses: left rTMS determined a decrease in accuracy in delayed recognition tasks whilst rTMS over the right DLPFC led to greater accuracy in recognition trials. In agreement with the above-mentioned authors, we found that anodal tDCS over the right DLPFC improved WM during a visuospatial delayed recognition task, and the effect was side-specific. In line with Hamidi et al. (2009), in our study, the accuracy enhancement during active stimulation cannot be explained by slower responses, as the RTs did not change in the different stimulation conditions. Furthermore, non-specific effects, such as learning, seem to be improbable, as the sham stimulation did not produce any performance improvement.

It is generally accepted that the right DLPFC is more active in spatial WM tasks [as, for example, shown by other authors using an oculomotor delayed matching-to-sample task, Curtis et al., 2004)], whereas the left DLPFC is more involved in non-spatial memory-guided responses (Schumacher and Jiang, 2003). Actually, right hemisphere dominance of spatial attention (Mesulam, 1999) has also been recognized in several previous studies of human frontal lobe lesions, in which the damage specifically involved the right frontal cortex (Bor et al., 2006; Miotto et al., 1996; van Asselen et al., 2006).

Several authors have suggested that the DLPFC plays a role in the programming and execution of appropriate motor responses during WM-based tasks (Curtis et al., 2004; Pochon et al., 2001). Nowadays, neuroimaging (MRI-based) studies in this field tend to be used to search for the neuroanatomical basis of WM. Owen (2000) reported activation of bilateral prefrontal areas during execution of verbal and non-verbal WM tasks. Furthermore, Habeck et al. (2012), using a delayed-item recognition task, showed activation of frontoparietal regions on functional MRI in healthy subjects. As a matter of fact, WM is mediated by low-level perceptual processes involving primary sensory cortices and higher-order associative areas such as the posterior parietal, occipital and prefrontal cortices (Ricciardi et al., 2006). Unlike neuroimaging techniques, non-invasive brain stimulation techniques such as TMS and tDCS, given their higher temporal resolution together with their ability to modulate brain activity in specific cortical areas, have the advantage of being better able to determine the causal role of such areas in specific cognitive functions.

Jeon and Han (2012) recently used anodal tDCS over the right DLPFC in healthy adults to evaluate its effects on visuospatial WM as assessed by a delayed recall task. Contrary to the findings of Hamidi et al. (2009), they found that anodal tDCS over the right DLPFC led to enhanced accuracy also in recall trials. These apparently conflicting results on the role of the right DLPFC in WM probably depend on the use of different methodological techniques and tasks exploring different aspects of WM.

Our investigation was restricted to the role of the DLPFC in a delayed recognition task and we therefore have no data relating to its possible role in delayed recall. However, in view of the conflicting data and the absence of conclusive results in the literature, the role of this brain area in WM needs to be further investigated.

Even though our study has several limitations, in particular the small sample size, the crossover design adopted has some methodological advantages that are worth mentioning: i) the decreased influence of confounding factors, as each patient served as his or her own control; ii) the fact that this kind of study, as compared to non-crossover longitudinal studies, requires fewer subjects to reach statistical significance.

Several studies have recently reported the beneficial effects of anodal tDCS on WM in patients with brain injuries (Boggio et al., 2006, Jo et al., 2009). In particular, Oliveira et al. (2013) have shown that tDCS over the right DLPFC could be used to improve visual WM in patients suffering from major depression. Although TMS provides better spatial resolution, tDCS offers several advantages: the technique is portable, inexpensive and can potentially be combined with other treatments in the rehabilitation setting (Peruzzotti-Jametti et al., 2013). Moreover, tDCS allows more reliable sham stimulation, as it is possible to recreate the initial itching sensation after a few seconds of current flow.

Our data, if confirmed in other, larger series of subjects, could open interesting perspectives for the use of tDCS as an effective, easy and low-cost therapeutic tool in patients with frontal lobe lesions and WM deficits.

References

Baddeley AD, Hitch GJ (1974). Working memory. In: Bower GA (Ed.) Recent Advances in Learning and Motivation. Vol. 8. New York, Academic Press, pp. 47-90.

Baddeley A (1992). Working memory. Science 255:556-559.

Bledowski C, Kaiser J, Rahm B (2010). Basic operations in working memory: contributions from functional imaging studies. Behav Brain Res 214:172-179.

Boggio PS, Ferrucci R, Rigonatti SP et al (2006). Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci 249:31-38.

Bor D, Duncan J, Lee AC, et al. (2006). Frontal lobe involvement in spatial span: converging studies of normal and impaired function. Neuropsychologia 44:229-237.

Cabeza R, Locantore JK, Anderson ND (2003). Lateralization of prefrontal activity during episodic memory retrieval: evi-

dence for the production-monitoring hypothesis. J Cogn Neurosci 15:249-259.
Curtis CE, Rao VY, D'Esposito M (2004). Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci 24:3944-3952.
D'Esposito M, Postle BR, Rypma B (2000). Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. Exp Brain Res 133:3-11.
Fregni F, Boggio PS, Nitsche M, et al (2005). Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 166:23-30.
Gerloff C, Corwell B, Chen R, et al (1997). Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. Brain 120: 1587-1602.
Giglia G, Mattaliano P, Puma A, et al (2011). Neglect-like effects induced by tDCS modulation of posterior parietal cortices in healthy subjects. Brain Stimul 4: 294-299.
Habeck C, Rakitin B, Steffener J, et al (2012). Contrasting visual working memory for verbal and non-verbal material with multivariate analysis of fMRI. Brain Res 1467:27-41.
Hamidi M, Tononi G, Postle BR (2009). Evaluating the role of prefrontal and parietal cortices in memory-guided response with repetitive transcranial magnetic stimulation. Neuropsychologia 47:295-302.
Jeon SY, Han SJ (2012). Improvement of the working memory and naming by transcranial direct current stimulation. Ann Rehabil Med 36:585-595.
Jo JM, Kim YH, Ko MH, et al (2009). Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehabil 88:404-409.
Marshall L, Mölle M, Siebner HR, et al (2005). Bifrontal transcranial direct current stimulation slows reaction time in a working memory task. BMC Neurosci. 6: 23
Mesulam MM (1999). Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. Philos Trans R Soc Lond B Biol Sci 354:1325-1346.
Miotto EC, Bullock P, Polkey CE, et al (1996). Spatial working memory and strategy formation in patients with frontal lobe excisions. Cortex 32:613-630.
Mottaghy FM, Krause BJ, Kemna LJ, et al (2000). Modulation of the neuronal circuitry subserving working memory in healthy human subjects by repetitive transcranial magnetic stimulation. Neurosci Lett 280:167-170.
Mull BR, Seyal M (2001). Transcranial magnetic stimulation of left prefrontal cortex impairs working memory. Clin Neurophysiol 112:1672-1675.
Nitsche MA, Paulus W (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 527: 633-639.
Nitsche MA, Paulus W (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57: 1899-1901.
Nitsche MA, Fricke K, Henschke U, et al (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 553: 293-301
Ohn SH, Park CI, Yoo WK, et al (2008). Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Neuroreport 19: 43-47.
Oldfield RC (1971). The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9: 97-113.
Oliveira JF, Zanão TA, Valiengo L, et al (2013). Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder. Neurosci Lett 537: 60-64.
Owen AM (2000). The role of the lateral frontal cortex in mnemonic processing: the contribution of functional neuroimaging. Exp Brain Res 133: 33-43.
Peruzzotti-Jametti L, Bacigaluppi M, Sandrone S, et al (2013). Emerging subspecialties in neurology: transcranial stimulation. Neurology 80:e33-35.
Pochon JB, Levy R, Poline JB, et al (2001). The role of dorsolateral prefrontal cortex in the preparation of forthcoming actions: an fMRI study. Cereb Cortex 11: 260-266.
Priori A (2003). Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin Neurophysiol 114: 589-595.
Ricciardi E, Bonino D, Gentili C, et al (2006). Neural correlates of spatial working memory in humans: a functional magnetic resonance imaging study comparing visual and tactile processes. Neuroscience 139:339–349.
Rock I, Engelstein P (1959). A study of memory for visual form. Am J Psychol 72: 221-229.
Rossi S, Cappa SF, Babiloni C, et al (2001). Prefrontal cortex in long-term memory: an "interference" approach using magnetic stimulation. Nat Neurosci 4: 948-952
Schumacher E H, Jiang Y (2003). Neural mechanisms for response selection: representation specific or modality independent? J Cogn Neurosci 15:1077-1079.
Smith EE, Jonides J (1999). Storage and executive processes in the frontal lobes. Science 283: 1657-1661.
van Asselen M, Kessels RP, Neggers SF, et al (2006). Brain areas involved in spatial working memory. Neuropsychologia 44:1185-1194.