Title: Enhancement of Visuospatial Working Memory by Transcranial Direct Current Stimulation (tDCS) on Prefrontal and Parietal Cortices

Authors: Yousef Moghadas Tabrizi¹, Meysam Yavari Kateb²*, Shahnaz Shahrbanian³

1. Assistant Professor, Department of Health & Sport Medicine, University of Tehran, Tehran, Iran.
2. PhD Student in Sports Psychology, Department Sport Psychology, University of Tehran, Tehran, Iran.
3. Assistant Professor, Department of sport science, Tarbiat Modares University, Tehran, Iran.

*Corresponding author: Meysam Yavari Kateb, Department of Sport Psychology, Faculty of Physical Education and Sport Science, University of Tehran, Tehran, Iran. E-mail: Meysam.Yavari@ut.ac.ir

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Abstract:

**Objective:** Previous studies have reported dorsolateral prefrontal cortex (DLPFC) and posterior parietal (PPC) activation during the performance of spatial working memory (SWM), so we decided to investigate the comparison of Transcranial Direct current stimulation (tDCS) effect between these two areas.

**Methods:** Fifty-four healthy right-handed students (27 female, 27 male; age = 24.3±2 years) were randomly assigned to anodal (N=27) and sham group (N=27), each of these groups was further divided into F4 (representing right DLPFC) or P4 (representing right PPC) subgroups, respectively. A Computerized Corsi Block Tapping task has then used to measure spatial working memory. The t-DCS intervention consisted of five daily sessions with a direct current of 1.5 mA for 15 minutes over the F4 or P4 area of the brain at 24-hour intervals.

**Results:** Significant enhancement of the SWM span as well as a faster response were seen after anodal tDCS in both the forward and backward direction. Moreover, the right DLPFC stimulation induced a faster reaction time compared to the right PPC.

**Conclusions:** Both DLPFC and PP cortices stimulation, as an element of the frontoparietal network, showed SWM enhancement, with the DLPFC being more effected. Our finding provides new evidence for the comparison of the effect of stimulation on the two main activated cortical areas during visuospatial WM.

**Keywords:** Spatial Working Memory, Transcranial Direct Current Stimulation, Computerized Corsi Block Tapping Task
Introduction:

Working memory (WM) refers to the mental ability that allows a person to temporally store and manipulate a limited amount of information. WM is necessary for complex cognitive tasks like reasoning, problem solving, comprehension, and learning. Neuroimaging studies have demonstrated WM-related cortical activity in the sensory and prefrontal areas, and the dorsolateral prefrontal cortex (DLPFC) plays a particularly crucial role (Curtis & D'Esposito, 2003; Linden, 2007). In the classical model, WM includes phonological and visuospatial stores (two temporary buffers) as well as being the central executive system (Baddeley & Hitch, 1974). Spatial WM (SWM), a specific type of WM, includes information within the spatial domain. Cortical high-relevant activity in the SWM network includes in the DLPFC, posterior parietal cortex (PPC) and frontal eye field (Curtis & D'Esposito, 2003; Vogel & Machizawa, 2004). Among SWM related cortical areas, the DLPFC seems to be mostly involved in selection operations (Bledowski et al.2010).

The left DLPFC mostly controls verbal WM, while the visuospatial WM is mainly handled by the right DLPFC (D'Esposito et al., 2000; Smith & Jonides, 1999). Frontoparietal network activity has been identified as part of the WM function (Mottaghy et al., 2002) referring to the parietal cortex role in processing the spatial information of sensory cues and prefrontal role in maintenance of this presentation. This neural processing in the dorsal stream includes spatial location. Frontoparietal network dysfunction, leading to WM impairment, has been seen in fibromyalgia patients (Seo et al., 2012), and schizophrenia (Kyriakopoulos et al., 2012).

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that modulates cortical activity via the application of a weak electrical current. In this technique, cortical excitability is increased by an anodal (positive charged) electrode and decreased by a cathodal (negative charged) electrode. The duration of cortical excitation is prolonged and can persist for an extended time, ranging from 5 to 90 minutes, depending on the length of stimulation (Nitsche & Paulus, 2000). Several studies have recently confirmed that tDCS produces long-lasting neuroplastic changes, representing its potential...
therapeutic effects (Nitsche & Paulus, 2001; Olma et al., 2013). tDCS effect on working memory, motor learning, and verbal frequency has also been investigated in previous studies (Fregni et al., 2005). Therefore, tDCS is considered a tool to enhance cognition ability in both normal persons and patients and has been used in the rehabilitation of cognitive function in neurologic disorders.

Most of the time, improvement in WM performance is reported for applying tDCS on the DLPFC of healthy subjects (Fregni et al., 2005) and patient groups (Nitsche et al., 2008). A meta-analytic review reported improvement in only speed but not the accuracy of WM performance using tDCS (Mancuso et al., 2016). In SWM, a specific subtype of WM, it has recently been found that anodal tDCS over the right DLPFC enhances performance in “visuospatial function training” (Jeon & Han, 2012). Furthermore, the effect of right DLPFC stimulation was shown by using a computerized Corsi Block Tapping task, a widely used paradigm that measures visuospatial short-term and working memory (Wu et al., 2014). Giglia and co-author showed the right DLPFC was more effective in enhancing SWM functioning as comparing to the left DLPFC (Giglia et al., 2014). There are a few studies that investigated the effect of right parietal tDCS on SWM performance (Heimrath et al., 2012). Their findings show that DLPFC and PPC are important in SWM, but to our knowledge, no study has compared the effects of tDCS on these two main cortical areas in SMW performance. So, the aim of this randomized sham-controlled study was to investigate the effects of tDCS on DLPFC and PPC in order to enhance SWM ability (span and response time) and then compare the effect of stimulation on these two areas.

**Material and methods:**

Fifty-four healthy undergraduate students with similar educational backgrounds from the University of Tehran participated in the present study (27 females, 27 males, age: 24.30±0.20 years). All of the participants were right-handed based on the Edinburgh Handedness Inventory (Oldfield, 1971) and had normal or corrected-to-normal vision. The participants were then randomly assigned into anodal (A=27) and sham groups (S= 27), and each of these groups was further divided into F4 (corresponding to the right DLPFC) or P4 (corresponding to the right PPC) subgroups (A-F4=14, S-F4=13; A-P4=13, S-P4=14).
Individuals with psychiatric or neurological disease and a history of alcohol or drug abuse were excluded. Written consent was obtained from all participants prior to the start of the study, and the study was approved by the Ethics Committee of the University of Tehran.

**Computerized Corsi Block Tapping task (CBT):** In a CBT task that was used to measure the spatial working memory (De Renzi & Nichelli, 1975), the visual targets are presented in different sequences, and the participants are requested to memorize the location and sequence of the presented targets. Then, they remember the location and sequence of the presentation both in forward and backward order (as a reversed sequenced). In the present study, a computerized form of the CBT task was used (Wu et al., 2014) in which 9 blue squares are presented as placeholders for the target demonstration in random locations of the screen. Then yellow targets were randomly shown for 500ms in the blue squares. The participants were requested to memorize the location and sequences of the appearance of the yellow squares. Five seconds after disappearing (retention interval), the participants were asked to point out the order and location of the appearance of the yellow squares using a computer mouse. The stimuli were presented on a 19-inch PC-monitor screen from a 57 cm distance. The subjects were asked to respond as quickly and correctly as possible. Every individual SWM span was defined as the highest correct presented yellow targets level response. The lowest/easiest level of the task started with only 2 appearances of the yellow targets and increased with each correct response by the participant. The task was terminated if the subject could not correctly respond to two successive trials at the same level, and this level was defined as their SWM span.

Electrical stimulation was delivered by a tDCS device (Active Dose, manufactured by ActivaTeK) with sponge pads of 5×7 cm². The positive electrode was placed over the F4 or the P4 according to the international 10-20 EEG system, and the negative electrode in both conditions was placed over the left supraorbital in either the anodal or sham group. The intervention consisted of five daily sessions with a 24-hour interval between them, and in each session, a direct current of 1.5 mA was applied for 15 minutes in the anodal group. For the sham group, the tDCS current was applied and then disconnected after 30 seconds.
without informing the participant. The pre-test measurement (CBT task) was performed before the first session and the post-test measurement after the fifth session.

**Statistical analysis:** Paired t-test was used for reaction time and span of SWM comparison in each group. Mixed design ANOVA was used to determine the effect of group and site of stimulation on study participants as data fulfilled prerequisites for conducting (normality & homogeneity). For all statistical calculations, SPSS version 24 was used and P values equal or less than 0.05 were considered as statistically significant.

**Results:**

**Descriptive characteristics of the participants:** All participants (N=54) completed the study. Results of the performance of the Anodal and Sham group did not significantly differ in terms of their reaction time (forward: p =0.895, Backward: p =0.768) and span of response (Forward: p =1, Backward: p = 0.859) at baseline.

**Memory span (Fig.1):**

**Forward memory span:** Means and standard deviations of the CBT span scores are shown in Table 1.

| CBT task direction | Site of stimulation | Pre-Anodal tDCS | Post-Anodal tDCS | Difference P | Pre-Sham tDCS | Post-Sham tDCS | Difference P |
|--------------------|---------------------|----------------|----------------|--------------|---------------|---------------|--------------|
| forward            | F4                  | 5.93±61        | 6.50±94        | .040         | 5.46±77       | 5.54±77       | .721         |
|                    | P4                  | 5±57           | 6.77±72        | .001         | 5.50±76       | 5.71±82       | .272         |
| backward           | F4                  | 5.14±66        | 5.43±64        | .040         | 5.08±95       | 5±70          | .829         |
|                    | P4                  | 5.08±76        | 5.69±75        | .005         | 5.21±69       | 5.07±61       | .435         |

A mixed design ANOVA between-group analysis on the memory span of the CBT task (Design: Group post anodal/post sham + Site F4/P4 + Group*Site) detected a significant main effect for the group (F= 20.216, df=1, P=.001, ηp2=.288) that indicate participant in anodal groups was better than sham groups,
but no significant effects for the site (F=.985, df=1, P=.326, ηp²=.019) or interaction between group and site (F=.043, df=1, P=.836, ηp²=.001) was observed.

**Backward memory span:** A mixed design ANOVA between-group analysis on the memory span of the CBT task by two-way ANOVA (Design: Group post anodal/post sham + Site F4/P4 + Group*Site) detected a significant main effect for the group (F=8.025, df=1, P=.007, ηp²=.138) that indicate in this, anodal group was better than sham group, but no significant effect for the site (F=.819, df=1, P=.370, ηp²=.016) or interaction between group and site (F=.269, df=1, P=.606, ηp²=.005) was observed.

A paired t-test revealed that both Forward (t=-5.428, df=26, P=.001) and Backward (t=-4, df=26, P=.001) memory span improved significantly in the anodal group, but there were no significant differences between the performance of pre- and post tDCS in the sham group (Forward: t=-1.072, df=26, P=.294; Backward: t=.593, df=26, P=.558).

**Fig 1.** Forward and Backward Memory span in of post tDCS between Anodal and Sham groups in two sites (F4 and P4).

**Reaction time (Fig.2):**

**Forward reaction time:** Means and standard deviations of the CBT reaction times are shown in Table 2.
A mixed design ANOVA between-group analysis on the reaction time of the CBT task (Design: Group post anodal/post sham + Site F4/P4 + Group*Site) detected a significant main effect for the group (F=43.963, df=1, P=.001, ηp2=.468), site (F=36.406, df=1, P=.001, ηp2=.421), and interaction between group and site (F=14.023, df=1, P=.001, ηp2=.219). These findings indicate that participants in anodal group performed faster than sham group CBT task and their performances were faster in F4 than P4.

3-3-2: **Backward reaction time:** A mixed design ANOVA between-group analysis on the reaction time of the CBT task by two-way ANOVA (Design: Group post anodal/post sham + Site F4/P4 + Group*Site) detected a significant main effect for the group (F=7.563, df=1, P=.008, ηp2=.131), which indicate anodal group was better than sham group but no significant effect for the site (F=1.115, df=1, P=.736, ηp2=.002) or interaction between group and site (F=1.047, df=1, P=.311, ηp2=.021) was observed.

A paired t-test revealed that both forward (t=7.755, df=26, P=.001) and backward (t=5.034, df=26, P=.001) reaction time improved significantly in the anodal group. But there were no significant differences between the performances pre- and post tDCS in the sham group (Forward: t=1.356, df=26, P=.187; Backward: t=1.230, df=26, P=.230).

ANCOVAs, conducted separately on post anodal RT and post anodal WM span with controlled pre-anodal effects (pre anodal RT and pre anodal WM span as covariates), showed a nonsignificant difference between the males and females’ performances (RT: F=0.006, P=.940, Span: F=.116, P=.706).

### Table 2.
Mean Scores (SD) and Results from Paired t tests of the CBT Task Forward and Backward Reaction Times

| CBT task direction | Site of stimulation | Pre-Anodal TDCS | Post-Anodal TDCS | Diff | Pre-Sham TDCS | Post-Sham TDCS | Diff-P |
|--------------------|---------------------|-----------------|-----------------|------|--------------|--------------|--------|
| forward            | F4                  | 2471.28±231.84  | 2034.72±131.89  | .001 | 2505.81±155.33 | 2450.92±110.21 | .829   |
|                    | P4                  | 2599.98±201.79  | 2426.98±188.99  | .001 | 2571.76±126.77 | 2542.74±147.85 | .511   |
| backward           | F4                  | 2704.55±159.20  | 2470.51±175.51  | .003 | 2684.66±175.85 | 2631.82±167.59 | .442   |
|                    | P4                  | 2660.48±167.61  | 2528.74±146.41  | .001 | 2657.81±126.90 | 2602.55±134.50 | .378   |
Fig 2. Forward and Backward Reaction time of post tDCS between Anodal and Sham groups in two sites (F4 and P4).

Discussion:

In the present study, we investigated SWM recall performance (indexed by a computerized CBT task) in 54 healthy subjects before and after five-sessions of sham-controlled tDCS over the right DLPFC or right PPC. The participants tolerated the intervention well, and none found the tDCS stimulation unpleasant. Results demonstrated an enhancement of the SWM span in both forward and backward directions after five-sessions of anodal tDCS. However, no significant difference was found in the sham tDCS groups. Moreover, the anodal group responded faster after five days of tDCS stimulation than the sham group, and the right DLPFC stimulation induced a faster reaction time than the right PPC.

Neuroimaging investigations have previously reported SWM related cortical hyperactivity, particularly in the prefrontal and PPC areas, during the maintenance phase (Ikkai & Curtis, 2011). The frontoparietal network, which consists of the DLPFC and PPC, plays an essential role in WM performance (Darki & Klingberg, 2014). FMRI findings have revealed that the PPC cortex is also involved in SWM maintenance (Olesen et al., 2003; Vestergaard et al., 2011). In a cross-sectional study using fMRI, WM capacity was correlated with BOLD activity in both frontal and parietal regions (Darki & Klingberg, 2014).
tDCS is a non-invasive stimulant method that can modulate neural activity during cognitive function. An enhancement effect of increases in memory span and response after tDCS over the DLPFC has been reported (Wu et al., 2014).

Fregni et al. showed WM had a better performance when applying anodal tDCS over the left DLPFC as compared to the opposite effect of applying rTMS on the same area (2005). They explained that the weak electrical current in tDCS causes a slight change in the resting potential of the stimulated neurons and lowers their depolarization threshold, while rTMS’s potent stimulation effect induces action potential and disruption of information processing. In line with Brighina et al., our study demonstrated that the right DLPFC is involved in visuospatial WM performance (Adamova et al., 2018). Moreover, when comparing the right versus the left DLPFC, right-side anodal activation showed performance improvement in a visuospatial WM task (Adamova et al., 2018).

Our findings provide new evidence in the comparison of the effects of stimulation on the two main activated cortical areas during visuospatial WM. tDCS stimulation of the DLPFC induced a faster response than the PP in recall WM task performance. Some investigations have suggested that the DLPFC plays a role in the programming and execution of appropriate motor responses during WM task performance (Hamidi et al., 2009; Pochon et al., 2001). DLPFC processing involves updating goal representations based on context information or task-related demands. Thus, DLPFC stimulation by tDCS could enhance its functioning and resulted in shortening recall response time. DLPFC, as an element of the Fronto-parietal network, is activated in the stimulus neural processing during the retention stage (Funahashi et al., 1993). However, the storage of perceptual attributes (Callicott et al., 1999) and maintenance of information, particularly spatial location, are processed in the parietal cortices (Olson & Berryhill, 2009).

Our findings showed no difference in the memory span between the two sites (DLPFC and PPC) after anodal stimulation. Other investigations also reported a tDCS effect on the memory span of both the DLPFC (Wu et al., 2014) and PPC (Tseng et al., 2012). Both prefrontal and parietal hyperactivity after training of the working memory (included a visuo-spatial working memory task, a backward digit span task, and a
letter span task) illustrated these regions’ participation in working memory span (Olesen et al., 2004). Additionally, a correlation of brain areas activity involved in the Fronto–intraparietal network with WM spatial span tasks was reported (Klingberg, 2006). In the present study, the right DLPFC was chosen after considering the spatial processing in this region.

Furthermore, our results showed no significant difference between the performances of males and females. Although it is generally accepted that males show an advantage in spatial processing and females excel at verbal tasks (Driscoll et al., 2005), Kaufman (2007) reported discrepancies according to test strategy and age of participants. In line with the present study, Shah et al. demonstrated no sex differences on the computerized-Corsi test, but male participants performed better than female participants on the standard Corsi test. They explained the sex difference performance on the standard Corsi test was due to the better spatial span of males, and sex differences in computerized-Corsi test were absent which require spatial organizational skills (Shah et al., 2013).

Some of the limitations in this study include a lack of stimulation in the paired area in the PP and DLPFC when comparing the left versus the right hemisphere. In addition, considering the low spatial resolution of tDCS, we cannot rule out the stimulation’s effect on neighboring regions. In this study we don't have any control over subject’s base cognitive abilities in order to choose subjects in a defined range of cognitive abilities so it is better used this item for next studies.

In conclusion, our study demonstrates a visuospatial WM performance improvement (both RT and span) was induced with tDCS over the prefrontal and post parietal cortex, with a faster response in prefrontal stimulation.

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