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Unilateral Prefrontal Direct Current Stimulation Effects are Modulated by Working Memory Load and Gender

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A B S T R A C T

Background: Recent studies revealed that anodal transcranial direct current stimulation (tDCS) to the left dorsolateral prefrontal cortex (DLPFC) may improve verbal working memory (WM) performance in humans. In the present study, we evaluated executive attention, which is the core of WM capacity, considered to be significantly involved in tasks that require active maintenance of memory representations in interference-rich conditions, and is highly dependent on DLPFC function.

Objectives: We investigated verbal WM accuracy using a WM task that is highly sensitive to executive attention function. We were interested in how verbal WM accuracy may be affected by WM load, unilateral DLPFC stimulation, and gender, as previous studies showed gender-dependent brain activation during verbal WM tasks.

Methods: We utilized a modified verbal *n*-Back task hypothesized to increase demands on executive attention. We examined "online" WM performance while participants received transcranial direct current stimulation (tDCS), and implicit learning performance in a post-stimulation WM task.

Results: Significant lateralized "online" stimulation effects were found only in the highest WM load condition revealing that males benefit from left DLPFC stimulation, while females benefit from right DLPFC stimulation. High WM load performance in the left DLPFC stimulation was significantly related to post-stimulation recall performance.

Conclusions: Our findings support the idea that lateralized stimulation effects in high verbal WM load may be gender-dependent. Further, our post-stimulation results support the idea that increased left hemisphere activity may be important for encoding verbal information into episodic memory as well as for facilitating retrieval of context-specific targets from semantic memory.

Introduction

Recent studies have demonstrated that weak transcranial direct current stimulation (tDCS) can induce significant effects on working memory function in humans [1–4]. Some of these studies revealed that anodal tDCS to the left prefrontal cortex, presumably the dorsolateral prefrontal cortex of healthy participants, improves working memory, specifically its verbal domains [2,5]. These stimulation effects are considered to be a result of transient cortical excitability changes in the resting membrane potential of neurons underlying the electrode, or a result of modulating their spontaneous firing rate [6]. This facilitation is usually accomplished by delivering a constant weak current of either 1, or 2 mA for 10 up to 30 min over the left dorsolateral prefrontal cortex (left – DLPFC). The facilitation is polarity-dependent as anodal tDCS usually has an excitatory effect on underlying cortical networks, while cathodal tDCS decreases cortical excitability in the region below the electrode [1,5]. More so, tDCS effects could impact electrophysiological activity of remote interconnected cortical networks, and are not solely limited to the particular area below the electrodes [5].

Working memory (WM), the ability to temporarily hold and manipulate task-relevant information, includes an attentional-control function (i.e., central executive), a subordinate system that temporarily holds visual spatial information (i.e. visual spatial sketchpad), and a subordinate verbal-auditory system called the phonological loop [7]. In the present tDCS study, we investigated a prefrontal cognitive sub-function of WM central executive system, called executive attention [7]. *Executive attention* is conceptualized as the core of WM capacity, a prefrontal mechanism responsible for maintaining memory representations in a highly active state in the

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presence of interference. Therefore, the term *active maintenance* is reflective of executive attention's attempt to allow immediate access to task-relevant information in interference-rich conditions (i.e., high level of response competition, which is directly related to increasing WM load). WM load is considered to be the amount of temporarily stored WM items prior to WM retrieval and is hypothesized to impose higher demands on executive attention as its value increases. Thus, WM tasks that require active maintenance of temporarily stored high-load items are considered to be highly dependent on DLPFC function and executive attention [7].

The most obvious challenge in translating the results of tDCS studies that examined working memory [1–3] is the lack of a particular predefined WM sub-mechanism such as executive attention [7], which is the "conductor" of subordinate short-term memory systems and highly related to DLPFC function. In conjunction, these studies used a bilateral stimulation montage, limiting our ability to decipher how this particular left hemisphere mechanism is affected by "online" anodal stimulation. Thus, other WM-related contralateral DLPFC activation cannot be excluded (e.g. visual spatial maintenance, 8). Even more, it has been consistently shown that maintenance of verbal information during working memory tasks is significantly affected by DLPFC inter-hemispheric interactions and that both left and right DLPFC are significantly involved in verbal WM operations [8].

Neuroimaging studies show significant DLPFC involvement during WM encoding [9]. However, Potkin et al.'s study [9] revealed that a significant increase in prefrontal activation was associated with the highest WM load during WM retrieval. As expected, retrieval was significantly reduced in high-load conditions. Additionally, only in medium-load levels, the left hemisphere was significantly more active than the right hemisphere during retrieval.

It has been suggested that WM neural substrates that participate in verbal WM tasks in humans include the DLPFC, inferior prefrontal cortex, cingulated gyrus, parietal cortex, insula, and thalamus [10]. Although it has been reported that men have larger cerebrums than women as well as differing from women in neuronal densities located in structures associated with WM, no consistent sex differences were found in WM function [7,11]. However, sex differences in cognition were found in domains such as verbal fluency and visual spatial skills [10,11]. Interestingly, fMRI studies that investigated WM neural activity have shown that in contrast to females, males exhibit right hemispheric or bilateral activation, while women display a more pronounced left hemispheric activation [10]. Hence, it seems that particular verbal WM functions may be lateralized differently as a result of gender, in phonological, spatial, and verbal WM processing. Furthermore, there is considerable fMRI data that indicates sex differences in the functional organization of frontal cortical areas in tasks related to verbal memory [10].

Critical to our theoretical model related to gender-specific functional organization of cerebral lateralization, Speck et al's findings [12] show that on a verbal 2-Back task men showed significantly stronger activation in the right hemisphere than women, and the women showed a significantly stronger activation in the left (see also Ref. [11]). Thus, we hypothesize that using words as primary target-stimuli in a 2-Back task procedure, will elicit significant bilateral DLPFC involvement across all participants. However, as implied in the literature [12], this prefrontal activity may be lateralized to the right hemisphere in males, and lateralized to the left hemisphere in females.

In the present study, we intended to investigate the involvement of a specific verbal WM mechanism – executive attention [7,10], and how its behavioral output may vary as a result of specific lateralized anodal stimulation of the DLPFC, working memory load [9], and gender [10]. As in Andrews et al.'s study [1], we utilized a verbal *n*-Back task, however, the task we employ is explicitly intended to increase demands on working memory capacity by recruiting its core neurocognitive sub-function defined as executive attention [7]. Specifically, the present *n*-Back task procedure increases demands on executive attention by increasing the level of semantic interference in the presentation of each potential verbal target. Executive attention, mediated by normal DLPFC activity, is recruited in conditions that require active maintenance of relevant target items in memory [7]. Thus, we examined the *active maintenance* component of WM function mediated by executive attention and the DLPFC [7].

In WM tasks such as the *n*-Back task, participants are required to continuously load and unload potential targets in working memory, since the unexpected presentation of the probe demands that they match the current item to an item that appeared *n* items ago. More so, on the *n*-Back task, involved neural substrates (e.g., DLPFC) are constantly attempting to inhibit the activation of non-relevant items that appeared in previously encountered non-target displays. Therefore, this type of cognitive effort is likely to recruit executive attention mechanisms (e.g., DLPFC), which are conceptualized to endorse the capability to regulate goals in attempt to enable coherent and contextually appropriate behaviors in interference-rich conditions [7,13,14]. In relevance, this regulatory prefrontal capability is compromised in an array of clinical population suffering from prefrontal abnormal activity (e.g., stroke patients, schizophrenia patients) [3,9]. In schizophrenia patients, the ability to inhibit the activation of non-relevant items is disrupted, resulting in context inappropriate behaviors and poor functional capacity. Thus, as our investigation aimed to enhance the ability to actively maintain context-specific memory items by prefrontal tDCS, we may be able to apply this stimulation protocol to improve prefrontal function and behavioral-regulation in schizophrenia patients.

Although the main purpose of the present study was to investigate online effects of tDCS on WM function, we also assessed tDCS post-stimulation effects on behavior. Therefore, we employed a post-stimulation task that examined implicit learning by asking subjects to perform a similar task but requiring them to explicitly recall the targets instead of recognizing them.

Thus, in response to the above literature and findings, we hypothesized that in the online tDCS WM task, the four incremental WM load conditions will result in significantly different levels of WM performance, where the highest WM load trials produce the lowest retrieval accuracy scores, and the lowest WM load will result in higher retrieval accuracy scores. Additionally, since anodal tDCS is hypothesized to moderately increase neural excitability [5], we predicted enhancement of WM accuracy only in high WM load conditions (associated with increased DLPFC activation), because this type of interference-rich WM maintenance seems to require a sustained increase in DLPFC excitability to regulate high-load response competition [7,9]. Hence, in healthy humans, excitatory tDCS over the DLPFC may only have a significant enhancing effect on high-load WM accuracy. More so, since we used a unilateral montage, we predicted that 1) right DLPFC stimulation will enhance verbal WM function in both males and females in the highest WM load conditions versus the sham condition, 2) left DLPFC stimulation will increase accuracy only in the male group in the highest WM load condition versus sham condition. Additionally, as a result of the crucial role of left DLPFC involvement in verbal WM tasks [10] we predicted, across all participants, that – 3) high-load accuracy on the online WM task will be significantly related to post-stimulation recall accuracy only in the active left DLPFC condition.

Method

Participants

A total of 41 (22 females), healthy young participants completed the study (mean age 24.59 years, range 18–36, SD = 4.17). All