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tDCS *selectively* improves working memory in older adults with more education

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HIGHLIGHTS

- We tested the effect of tDCS to the prefrontal cortex on working memory performance in older adults.
- Stimulation improved working memory in more educated adults.
- Stimulation was not beneficial to the less educated group.

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ABSTRACT

Cognitive performance, including performance on working memory (WM) tasks declines with age. Changes in brain activations are one presumed contributor to WM decline in the healthy aging population. In particular, neuroimaging studies show that when older adults perform WM tasks there tends to be greater bilateral frontal activity than in younger adults. We hypothesized that stimulating the prefrontal cortex in healthy older adults would improve WM performance. To test this hypothesis we employed transcranial direct current stimulation (tDCS), a neurostimulation technique in which small amounts of electrical current are applied to the scalp with the intent of modulating the activity in underlying neurons. Across three testing sessions we applied sham stimulation or anodal tDCS to the left (F3) or right (F4) prefrontal cortex to healthy older adults as they performed trials of verbal and visual 2-back WM tasks. Surprisingly, tDCS was uniformly beneficial across site and WM task, but only in older adults with more education. In the less educated group, tDCS provided no benefit to verbal or visual WM performance. We interpret these findings as evidence for differential frontal recruitment as a function of strategy when older adults perform WM tasks.

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1. Introduction

If you have ever stared blankly into your refrigerator or lost your train of thought mid-sentence, you have experienced a failure of working memory (WM). WM is the mental workspace for maintaining and manipulating information for immediate use. Unfortunately, WM decline begins in the mid-20s and generalizes across verbal and visuospatial tasks [35]. In addition to age, the factor of education level predicts WM performance such that increased education is linked with superior WM performance [13]. Although the mechanism(s) underlying age-related WM decline remain unclear, neural atrophy begins in prefrontal and parietal regions activated during WM task performance [17,40]. There are also changes in functional brain activity that accompany structural changes [3,7,9,24,28,39] revealing a shift from posterior to anterior activations. This shift is thought to reflect the recruitment of additional resources to maintain cognitive task performance [7]. In young adults frontoparietal activations during WM tasks tend to be asymmetrical such that there is greater left lateralized activity for verbal WM tasks and greater right lateralized activity for visuospatial WM tasks (e.g. [42,45,46]). This hemispheric asymmetry for verbal WM-right prefrontal cortex (PFC) has been confirmed using transcranial magnetic stimulation (TMS: [31], see [30] for review). A domain-general executive control mechanism in left dorsolateral PFC has also been identified in young adults [30]. Indeed, older participants who more strongly activate this left dorsolateral frontoparietal region implicated in domain-general executive control functions perform better at memory tasks [22]. However older adults also have notably increased bilateral activations during WM tasks with verbal or visuospatial stimuli [3]. Thus, the older adults may rely more heavily on bilateral frontal structures to perform WM tasks regardless of the type of stimulus (verbal or visuospatial) [9].

WM capacity is difficult to expand in young adults; it is also challenging to maintain WM over the aging process. Two recent meta-analyses of cognitive interventions designed to improve WM

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reached pessimistic conclusions of no improvement [34] or moderate benefit [48]. WM training studies show WM improvement and even performance transfer to unpracticed tasks, although paradigms and results are variable [16,20,27,29,34,43,44,48,50]. However, other techniques, particularly transcranial direct current stimulation (tDCS), offer hope for a growing aging population. TDCS is thought to produce cognitive effects by modulating membrane potentials and the synaptic strength between stimulated neurons [47]. Two further advantages of tDCS are that it is affordable and safe and might eventually be feasible for broad use in the general population. There is some promising evidence that tDCS administered prior to performing a verbal WM task temporarily improves WM performance in young adults [14,33,52], and in patients with right hemisphere stroke [21] or Parkinson's disease [2]. More recent findings suggest that some tDCS paradigms can produce long-term benefits in healthy [8,10] or special patient populations [6,12,18,26]). These findings raise the question of whether tDCS could also be used to improve WM performance in the healthy aging population. One way that tDCS might improve WM in the healthy aging population is to increase PFC activity and thereby enhance top-down maintenance of the items in WM preventing them from decay. Here we tested this hypothesis and examined whether tDCS to the right or left PFC provided WM benefits in a material-dependent or material-general manner. If there was a material-dependent effect of tDCS, we expected to see superior performance in verbal WM after left PFC tDCS and superior visual WM after right PFC tDCS. If there was a material-general effect of tDCS, we expected to see uniform effects of left or right tDCS on both WM tasks. Finally, we anticipated that there would be a relationship between education level and WM performance [13], but we remained agnostic as to whether tDCS would benefit those with low or high education. One possibility was that participants with high education might not benefit from tDCS to the PFC because they were already working at maximum capacity and an effect might only be observed in the low education group. A second possibility was that the low education group might not rely as heavily on the PFC for WM performance and that if the high education group relies more heavily on the PFC for WM performance then an effect would only be observed in the high education group.

2. Materials and methods

Twenty-five neurologically normal adults (mean age of 63.7, range: 56–80) signed consent documents and participated for \$15 h^{-1}. One left-handed participant was excluded. The University of Nevada IRB approved all protocols.

There were three experimental sessions: anodal tDCS to the right (F4) and left (F3) dorsolateral PFC and sham (F3 or F4, counterbalanced across participants). No separate baseline condition was included as comparisons of sham and baseline demonstrate identical performance profiles [11], see also [15]. A wash out period of at least 24 h separated experimental sessions. The cathode served as the reference electrode and it was placed on the contralateral cheek. A continuous current stimulator delivered current (NeuroCon DC Stimulator, GmbH, Germany) to two 5 cm × 7 cm electrodes housed in saline-soaked sponges. During tDCS, 1.5 mA current was applied for 10 min. During sham, participants received 20 s of current at the start and end of the 10 min to mimic tingling associated with current change. Participants performed practice trials during the 10 min wait to make sure that they were accustomed to the task directions and the task response buttons. Electrodes were then removed and the task began. WM tasks were programmed in ePrime (PST, Pittsburgh, USA). Participants completed the minimental status examination (MMSE), and forward and backward digit span tests [51].

There were four pseudorandomized blocks each of the visual and verbal 2-back WM tasks. Prior to each block an instruction screen gave information about what types of trials would follow. Per block, 30 stimuli were sequentially, centrally presented (500 ms). The verbal stimuli were the 20 consonants presented in Palatino font size 30. The visual stimuli were 20 novel $8^\circ \times 8^\circ$ symmetrical shapes [1]. After each stimulus a blank response screen (3000 ms) appeared. Participants made speeded button press responses indicating whether or not the stimulus replicated the stimulus preceding it by two positions (e.g. C–D–C, the second C is a target). This task requires the continual updating of WM because the sequence continues. Continuing our example, if a 'D' were to come next, it would also be a target. The experiment lasted ∼15 min to be within the temporal window of tDCS effects.

Overall analyses were conducted with no between-groups factor. Participants were then divided into two groups by performing a median split on their years of education (mean: high = 16.9, low = 13.5, t_{22} = 6.79, p < .001). The resulting groups did not differ on measures of digit span (forward: p = 0.31; backward: p = 0.90), MMSE (p = 0.46), or age (p = 0.89). To minimize between-subject variability we calculated normalized difference indices (tDCS − sham/tDCS + sham). Each participant had a difference index for each site (left, right PFC) × task (verbal, visual) combination. These values were subjected to repeated measures ANOVA with the within-subjects factors of stimulation condition (left, right PFC) and WM task (verbal, visual) and the between-subjects factor of education (high, low). The raw accuracy data are included as a Supplementary Figure.

3. Results

The first analysis was a repeated measures ANOVA with the within-subjects factors of task (verbal, visual WM) × stimulation site (left PFC, right PFC). There were no significant main effects (task: $F_{1,23}$ = 3.46, p = .08, $\eta_p^2 = .13$; site: $F_{1,23}$ = 1.32, p = .26, $\eta_p^2 = .05$) or interaction (F < 1, p = n.s.). However, this analysis did not fully capture the pattern observed in the data. Consequently, we conducted a second analysis including the between-subjects factor of education (high, low). Here, the main effect of task approached significance ($F_{1,22}$ = 3.80, p = 0.06, $\eta_p^2 = 15$). There was no significant main effect of stimulation condition ($F_{1,22}$ = 1.58, p = 0.22, $\eta_p^2 = .07$) or interaction of stimulation condition × task ($F_{1,22}$ = 1.00, p = 0.33, $\eta_p^2 = .04$). There was a significant main effect of group ($F_{1,22}$ = 4.58, p = .04, $\eta_p^2 = .17$) and a significant interaction of group × stimulation condition ($F_{1,22}$ = 5.61, p = 0.03, $\eta_p^2 = .20$). The group × WM task interaction ($F_{1,22}$ = 3.27, p = 0.08, $\eta_p^2 = 13$) approached significance. Importantly, the interaction of stimulation condition × WM task × group was significant (difference indices: mean Low Education Right PFC visual: −.01, verbal: .002, Left PFC visual: −.06, verbal: −.01; High Education Right PFC visual: .02, verbal: .03, Left PFC visual: .03, verbal: .03; $F_{1,22}$ = 5.86, p = 0.02, $\eta_p^2 = .21$). This complex interaction can be understood in the following way: the high education group universally benefited from tDCS regardless of the hemisphere stimulated or WM task. In the low education group, tDCS, especially to the right PFC, impaired visual WM performance but had no effect on verbal WM (Fig. 1).

4. Discussion

We investigated whether tDCS could improve WM performance in the healthy older adult population. Participants performed verbal and visual WM tasks after receiving sham or anodal tDCS to the right or left PFC. The participants were divided into two groups based on their level of education. Intriguingly, we observed a general improvement in WM performance selectively in participants

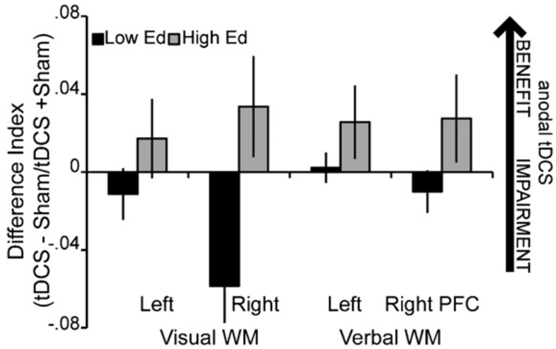

Fig. 1. TDCS to the left or right prefrontal cortex on verbal and visual WM performance improves WM performance in the high education group (gray bars) but not in the low education group (black bars). Left and right refer to the stimulation site, left or right prefrontal cortex (F4). Performance on the visual WM task is plotted on the left and performance on the verbal WM task is plotted on the right. Values greater than 0 reveal a tDCS-related improvement in WM performance; values lower than 0 reveal a tDCS-related impairment in WM performance. Error bars reflect the standard error of the mean.

with *higher* education. In the low education group WM performance was unchanged or impaired by tDCS.

The fact that there was a uniform benefit to the high education group regardless of stimulation site and WM task reveals a material-general improvement. This is consistent with the aging literature that reveals increased bilateral activity during WM tasks [3]. However, the low education group was generally hurt by tDCS. A recent meta-analysis of motor and cognitive tDCS studies shows that it can be difficult to predict the consequence of tDCS on behavior [19]. Indeed, these data raise the question of why there was a selective tDCS benefit to the high education group. One testable possibility is that they employ a different WM strategy than the low education group. This strategy may enable the high education group to better recruit PFC structures during WM tasks. Support for this interpretation comes from a recent neuroimaging study reporting greater PFC activations in expert, but not novice, pilots performing a track-following task [38].

An important step going forward will be to develop tDCS paradigms that provide long-term benefits. The assumption in most tDCS research has been that the effects of a single tDCS session last no longer than an hour (reviewed in [32]). However, there are now studies reporting long-term improvement (lasting up to 12-months) after one anodal and one cathodal tDCS sessions [8] or after repeated sessions [6,12,18,26]. In the first case, performance on the Tower of London task was found to benefit from tDCS, both anodal and cathodal, and this benefit remained significant when tested six or twelve months after the last tDCS [8]. In several patient populations, notably those with stroke [25], major depressive disorder (for a recent meta-analysis see [23]) and those with aphasia (reviewed in [18]), multiple tDCS sessions have found clinically relevant effects. However, there is little consensus regarding the appropriate stimulation paradigms for the condition being treated and considerable work will be needed to identify the optimal stimulation settings. Finally, as we learn more about tDCS it is likely that there will be a growing conversation regarding the use of tDCS in healthy neurotypical participants who want to receive tDCS to promote enhanced cognitive performance [5].

These findings add to the growing number of studies reflecting the importance of individual differences in neurostimulation studies. There is ongoing research attempting to identify the underlying mechanism of these observations including genetic factors (e.g. [4]), personality measures [37], and our own work looking at the importance of cognitive strategy. Further research is needed to see how various paradigms can be applied to extend the benefits of tDCS to therapeutically relevant tasks and durations [36,41,49]. In conclusion, tDCS may be able to provide long-term cognitive benefits to certain individuals. Further research is essential to determine what factors predict who will benefit, which tasks can be improved and what types and durations of tDCS are required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2012.05.074.

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