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Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex

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Background
Transcranial direct current stimulation (tDCS), applied to the left dorsolateral prefrontal cortex (DLPFC) has been found to improve working memory (WM) performance in both healthy and clinical participants. However, whether this effect can be enhanced by cognitive activity undertaken during tDCS has not yet been explored.

Objective
This study aimed to explore whether tDCS applied to the left DLPFC during the persistent performance of one WM task would improve performance on a subsequent WM task, to a greater extent than either tDCS or cognitive activity alone.

Methods
Ten healthy participants took part in three counterbalanced conditions. The conditions involved 10 minutes of either anodal tDCS while completing an n-back task, anodal tDCS while at rest, or sham tDCS while completing an n-back task. The n-back that was used in this study was a computer-based letter WM task that involved 5 minutes of two-back, followed by 5 minutes of three-back. Digit span forward and backward was administered immediately before and after each treatment, and performance change (pre- to posttreatment) calculated and compared across conditions. The digit span tasks involved a series of numbers being read to the participant, and the participant was required to repeat them back, either in the same order (Digits forward) or in the reverse order (Digits backward).

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Results
tDCS applied during completion of the n-back task was found to result in greater improvement in performance on digit span forward, compared with tDCS applied while at rest and sham tDCS during the n-back task. This finding was not evident with digit span backward.

Conclusions
These results indicate that there may be potential for the use of adjunctive cognitive remediation techniques to enhance the effects of tDCS. However, further research needs to be undertaken in this area to replicate and extend this finding.

Keywords cognitive remediation; dorsolateral prefrontal cortex; transcranial direct current stimulation; working memory

Working memory (WM) refers to the temporary storage and manipulation of information in the brain, facilitating an individual's capacity for complex thought and action. WM has been shown to be crucial for a number of key processes, including language comprehension, learning, and long-term memory consolidation.[1] The dorsolateral prefrontal cortex (DLPFC), which includes Brodmann Areas 46 and 9, has been shown to be highly involved in WM processing.[2]

WM impairment is a major feature of a number of neurologic and psychiatric disorders, including schizophrenia, Alzheimer's disease, Parkinson's disease, and major depression.[3-6] Despite this, no effective treatment has yet been established. Some studies have indicated that antipsychotics, particularly the newer atypical antipsychotics, may improve cognitive functioning in schizophrenia.[7,8] However, results in this area have been inconsistent.[9] Cognitive remediation is a behavioral intervention designed to improve cognition through a combination of drill and practice exercises, and teaching of compensatory strategies.[10] A number of studies have found small but significant improvements in WM in patients with schizophrenia from the use of these techniques,[10-12] while a meta-analysis of 26 studies of cognitive remediation in schizophrenia has indicated that the technique may be more effective when used as an adjunct to other treatment methods.[10]

Transcranial direct current stimulation (tDCS), a noninvasive form of brain stimulation, has been explored as a way to increase cortical excitability in the DLPFC and enhance WM. tDCS involves the application of mild electrical currents to the scalp via large electrodes. In contrast to other brain stimulation methods, which generally involve the active initiation of action potentials, tDCS involves much milder stimulation that is believed to modulate cortical excitability by shifting the resting membrane potential in either a hyperpolarizing or depolarizing direction.[13] In this way, anodal tDCS has been shown to increase excitability in the cortex, whereas cathodal tDCS has been shown to decrease excitability.[13] tDCS has been shown to be safe, very tolerable, and an effective sham condition can be created by having the machine fade out the stimulation after a few minutes.[14-16]

In a study with healthy participants, Fregni et al.[17] found that 10 minutes of 1 mA anodal tDCS, applied to the left DLPFC, improved performance of a verbal WM task completed during the last 5 minutes of stimulation, compared with sham stimulation. Anodal tDCS has also been found to improve WM performance, also during stimulation, in patients with Parkinson's disease; however, 2 mA, rather than 1 mA, was needed to induce significant improvements.[18,19] More recently, Ohn et al.[20] showed that the effects of tDCS on WM in healthy participants can be sustained poststimulation. Compared with sham, performance on a computer-based three-back Korean letter WM task was significantly improved at 20 and 30 minutes of anodal tDCS, and this effect was sustained 30 minutes poststimulation. Performance after 10 minutes of stimulation showed a trend toward improvement in accuracy compared with sham, but this was not significant. The authors concluded that the effects of anodal stimulation are time-dependent.[20] However, another consideration is that completing the n-back task, while undertaking tDCS may have enhanced the effects of stimulation. As cognitive remediation itself has been shown to improve WM performance, it is possible that the combination of completing a WM task while having tDCS could increase the excitability of the DLPFC cortex to a greater extent than simply tDCS alone.

The possibility that tDCS combined with a form of cognitive remediation could enhance the effects of stimulation has not yet been systematically investigated. Traditionally, effective cognitive remediation has involved hours of training each week, for a number of weeks.[10,11] However, in their meta-analysis of cognitive remediation, McGurk et al.[10] discuss the possibility of improved cognitive functioning after only 5-15 hours of remediation. If cognitive remediation paired with brain stimulation could result in an improvement in WM, albeit temporary, after only a matter of minutes, then this would therefore be of clinical significance. However, to date cognitive remediation as an adjunctive technique to brain stimulation has not been studied.

The current study aimed to investigate whether anodal left DLPFC tDCS applied during the persistent performance of an n-back WM task resulted in a greater subsequent improvement on a digit span WM task compared with either tDCS applied at rest, or sham tDCS applied during the completion of the n-back. Left DLPFC stimulation was chosen as it is consistent with the past research,[17,18,20] and as verbal WM tasks have generally been shown to activate the left DLPFC.[21] It was hypothesised that participants' performance on the digit span tasks would show a greater improvement after the anodal tDCS applied, while performing the n-back task, compared with either sham stimulation while undertaking the n-back, or anodal tDCS applied while at rest.

Methods and materials

Participants

Eleven participants were recruited for the study; however, one participant withdrew after the first testing session because of other commitments. Ten healthy adults, four men and six women, aged between 20 and 51 years (mean = 28.10, standard deviation [SD] = 8.72), therefore completed all arms of the study. Participants who had a history of seizure or had metal implanted in the cranium were excluded from the study, as were pregnant women. Ethical approval was granted from human ethics committees at both the Alfred Hospital and Monash University, and written consent provided before the commencement of the study.

Design

All participants took part in the following three counterbalanced experimental conditions: active tDCS applied during an n-back task, sham tDCS applied during an n-back task, and active tDCS applied while at rest. To limit the total number of sessions, and because previous research has consistently found anodal tDCS to enhance WM performance compared with sham tDCS,[17,18] a decision was made not to include a sham tDCS without n-back condition in the current study. A digit span WM task was administered before and after treatment, to measure any change in performance. The conditions were separated by 1 week to prevent any carry-over effects from the tDCS. The design is shown in Figure 1.

Procedure

In each condition, the experimenter first verbally administered the digit span tasks to the participant. Digit span forward was administered first, followed by digit span backward. Consistent with the administration procedures of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III), the digit span tasks were discontinued only if both trials of an item were failed. Next, active tDCS and n-back, sham tDCS and n-back, or active tDCS alone were administered for a total of 10 minutes. After this phase, digit span forward, then digit span backward, were readministered.

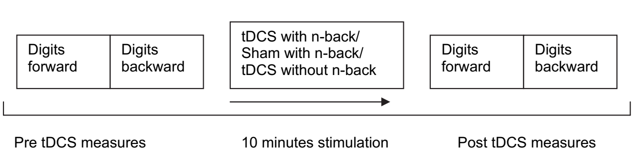

Figure 1 The experimental protocol design.

tDCS

Ten minutes of 1 mA direct current was applied to the scalp using a saline-soaked pair of 35 cm^2 surface sponge electrodes, and delivered via a battery-driven, constant current DC-stimulator, manufactured by neuroConn GmbH, with a maximum output of 10 mA. To stimulate the DLPFC, the anodal electrode was placed over F3 according to the 10-20 international system for EEG electrode placement. Using previously applied methods,[17,18,20] the cathode electrode was placed over the contralateral supraorbital area. During the active condition, the current faded in over 120 seconds, was constant at 1 mA for 10 minutes, and then faded out over 15 seconds. During the sham stimulation condition, the current faded in over 120 seconds to 1 mA, was constant at 1 mA for 30 seconds, and then faded out over 15 seconds.

Intra-tDCS WM task

An n-back task was continuously performed by participants during stimulation in two of the three conditions. This task involved asking participants to remember the identity of a series of random letters presented consecutively and to respond via a response box whenever a letter is presented that has been presented n letters previously. The stimuli were generated using E-Studio and E-Prime 1.1.[22] This n-back task used the letters A to J, pseudorandomly presented for 300 milliseconds every 2 seconds. Targets were presented 25% of the time. For this study, 5 minutes of two-back was presented, followed by 5 minutes of three-back.

Outcome WM measures

The digits forward and digits backward digit span tasks from the WAIS-III[23] were used to measure WM performance pre- and post-tDCS. The digits forward task involved the participant being read out a series of digits, which they then had to repeat back in the same order. The digits backward task involved the participant being read out a series of digits, which they then had to repeat back in the reverse order. These tasks were administered according to the instructions provided in the WAIS-III administration manual, and the same digits were read each time.

Data and statistical analyses

The primary outcome measures were scores on the digits forward and backward tasks. As the n-back task was used as a stimulus material, and was only used in two of the three conditions, participant scores from this task were not studied. Results were analyzed using the statistical software

Table 1 Mean scores (SD) and results from paired *t* tests, of digits forward and backward scores, by time and condition

	Active tDCS with n-back (n = 11)			Sham tDCS with n-back (n = 10)			Active tDCS without n-back (n = 10)		
	Pre	Post	Difference pre-post	Pre	Post	Difference pre-post	Pre	Post	Difference pre-post
Digits forward	13.36 (1.36)	14.09 (1.30)	P = .04	13.90 (1.66)	14.00 (1.49)	P = .87	14.00 (1.49)	13.40 (2.17)	P = .17
Digits backward	9.64 (2.80)	10.55 (2.46)	P = .11	10.40 (2.50)	10.50 (3.14)	P = .84	11.50 (2.17)	11.80 (2.15)	P = .28

package SPSS 16.0. To assess any effect of condition or time, or any interaction effects, 2 × 3 repeated measures analyses of variance (ANOVAs) were carried out for each of the outcome measures. Because of the exploratory nature of the study and the small sample size, post hoc paired *t* tests were used to explore any trend level findings ($P < .10$), as well as any significant results. All tests were two-tailed and used an alpha level of .05 to determine significance, unless otherwise specified.

Results

Digit span: digits forward scores

Means and standard deviations of the digits forward scores are shown in Table 1, and means and standard errors are shown in Figure 2. There was no significant main effect of Condition, $F(2, 8) = 0.08, P > .05$. There also was no significant main effect of Time, $F(1, 9) = 0.12, P > .05$. Further, there was no significant interaction effect, but a trend level interaction effect was found, $F(2, 8) = 3.31, P = .09$.

Paired *t* tests revealed that in the active tDCS with n-back task condition, participants' accuracy improved significantly after stimulation, $t(10) = -2.39, P < .05$. There were no significant differences between performances pre- and post-tDCS in the sham with n-back task condition, $t(9) = -0.17, P > .05$, or in the active tDCS without n-back task condition, $t(9) = 1.5, P > .05$.

Digit span: digits backward score

Means and standard deviations of the digits backward scores are shown in Table 1, and means and standard errors are shown in Figure 3. There was a significant main effect of Condition, $F(2, 8) = 8.66, P < .05$. Contrasts revealed that scores in the tDCS without n-back task condition were significantly higher than those in either the tDCS with n-back task condition, or the sham with n-back condition. The main effect of Time was not significant, $F(1, 9) = 1.35, P > .05$. There was also no significant interaction between Time and Condition, $F(2, 8) = 0.42, P > .05$. Further, paired *t* tests showed no significant differences between performances pre and post active tDCS with n-back task condition, $t(10) = -1.77, P > .05$. There were also no significant differences between performances pre- and post-tDCS in the sham with n-back task condition, $t(9) = -0.20, P > .05$, or in the active tDCS without n-back task condition, $t(9) = -1.152, P > .05$.

Discussion

This study provides some evidence that administering tDCS during the performance of a WM task may result in improved performance on a subsequent task of WM. This was demonstrated via a trend toward an overall interaction on the ANOVA for the digits forward condition and statistically significant effects seen on the post hoc tests. Specifically, the significantly larger improvement in performance on the digits forward in the tDCS with n-back, compared with the tDCS alone condition, indicates that the effects of tDCS may be enhanced by using the n-back as an adjunctive technique. These findings could possibly be due to the mechanism of long-term potentiation (LTP), whereby a brief episode of strong synaptic activation leads to a persistent strengthening of synaptic transmission. LTP is a widely accepted model of neural plasticity that is hypothesized to underlie learning and memory. In their review of the literature, Floel and Cohen[24] suggested that noninvasive cortical stimulation, in combination with memory training, may enhance the effects of training via LTP. Indeed, cognitive remediation has been recommended as an adjunctive technique to enhance the effects of other interventions, such as pharmacologic treatments.[11]

Unlike the improvement observed in the forward digit span measure during the tDCS with n-back condition, there was no significant improvement on the backward digit span measure in the same condition. This is an unexpected finding, given the strong association between DLPFC and the

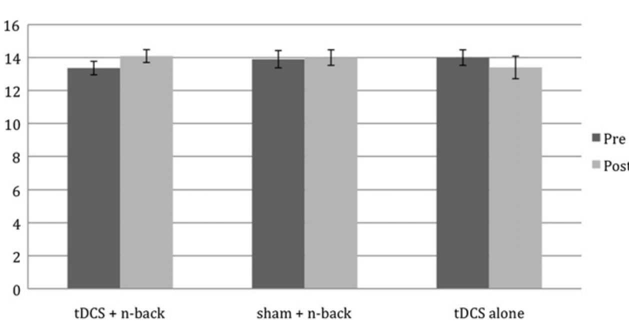

Figure 2 Mean digits forward scores with standard errors, by time and condition.

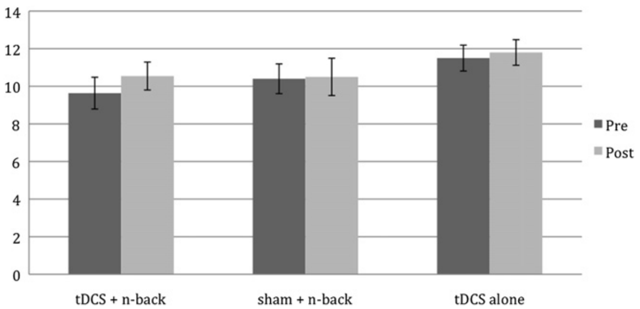

Figure 3 Mean digits backward scores with standard errors, by time and condition.

complex WM processes present in the backward digit span task.[21,25,26] One possible explanation is that any effect from the tDCS is likely to have been stronger immediately after stimulation (when the forward digit span was measured), rather than a few minutes later (when the backward digit span was measured). This study differs from previous studies in that WM performance was measured after 10 minutes of stimulation to the DLPFC, rather than either during tDCS, or after 30 minutes of stimulation. Research into the effects of only 10 minutes of tDCS on the motor cortex has shown that changes are sustained poststimulation.[27] However, it is possible that this is not the case with the prefrontal cortex, or that stronger stimulation, or a longer period, is needed to induce longer-lasting changes. It is feasible that 10 minutes of 1 mA of tDCS applied to the DLPFC did not induce a strong enough change in cortical excitability to result in a reliable WM improvement poststimulation, and this could account for the inconsistency in results observed across digits forward and backward. In addition, the current study may have lacked the power to reliably detect the subtle improvements in WM using these relatively insensitive digit span measures.

A number of limitations to this study exist. The small sample size meant that the ANOVA analysis was underpowered to detect a difference between groups, which limits the generalizability of the study. As the digits forward measure was consistently administered before the digits backward measure, it is difficult to know if the pattern of results seen was due to the task, or the time-dependent nature of the effects of tDCS. Future research could counterbalance the order of task presentation to further explore this question. The current study also lacked a pure control condition. Had a sham tDCS without n-back condition been included, it would have been possible to more closely examine the unique contributions of cognitive activity, and stimulation, toward improved WM performance. Future research would benefit from including this condition in the research protocol. Another possible limitation is that using the digit span tasks as outcome measures with healthy participants may potentially have resulted in a ceiling effect. Future studies could use more sensitive measures of WM.

Despite these limitations, this finding tentatively supports the possibility that cognitive remediation could be used as an adjunctive technique with tDCS. If replicated, such a finding could have important implications for the use of cognitive remediation and brain stimulation as adjunctive techniques to enhance WM across a number of neurologic and psychiatric conditions.

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References

1. Baddeley A. Working memory, thought, and action. In: D'Esposito M, Schacter D, Driver J, et al., editors. Oxford: Oxford University Press; 2007.
2. Courtney S. Attention and cognitive control as emergent properties of information representation in working memory. Cogn Affect Behav Neurosci 2004;4(4):501-516.
3. Goldman-Rakic PS. Working memory dysfunction in schizophrenia. J Neuropsychiatry Clin Neurosci 1994;6(4):348-357.
4. Morris RG. Working memory in Alzheimer-type dementia. Neuropsychol 1994;8(4):544-554.
5. Winograd-Gurvich C, Fitzgerald PB, Georgiou-Karistianis N, Bradshaw JL, White OB. Negative symptoms: a review of schizophrenia, melancholic depression and Parkinson's disease. Brain Res Bull 2006;70:312-321.
6. Marini P, Ramat S, Ginestroni A, Paganini M. Deficit of short-term memory in newly diagnosed untreated parkinsonian patients: reversal after L-dopa therapy. Neurol Sci 2003;24(3):184-185.
7. Lindenmayer J-P, Khan A, Iskander A, Abad MT, Parker B. A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. J Clin Psychiatry 2007;68(3):368-379.
8. Riedel M, Spellman I, Strassnig M, et al. Effects of risperidone and quetiapine on cognition in patients with schizophrenia and predominantly negative symptoms. Eur Arch Psychiatry Clin Neurosci 2007;257:360-370.
9. Harvey PD, Keefe RSE. Studies of cognitive change in patients with schizophrenia following a novel antipsychotic treatment. Am J Psychiatry 2001;158(2):176-184.
10. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry 2007;164(12):1791-1802.
11. Wykes T, Reeder C, Corner J, Williams C, Everitt B. The effects of neurocognitive remediation on executive processing in patients with schizophrenia. Schizophr Bull 1999;25(2):291-307.
12. Wykes T, Reeder C, Landau S, et al. Cognitive remediation therapy in schizophrenia. Br J Psychiatry 2007;190:421-427.
13. Wagner T, Fregni F, Fecteau S, Grodzinsky A, Zahn M, Pascual-Leone A. Transcranial direct current stimulation: a computer-based human model study. NeuroImage 2007;35:1113-1124.
14. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 2006;117(4):845-850.
15. Nitsche M, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W, editors. Modulation of cortical excitability by weak direct current stimulation—technical, safety and functional aspects. 2nd International Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) Symposium 2003. Gottingen, Germany; Elsevier Science B.V.

16. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull 2007;72:208-214.
17. Fregni F, Boggio PS, Nitsche M, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 2005;166:23-30.
18. Boggio PS, Ferrucci R, Rigonatti SP, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci 2006;249:31-38.
19. Zgaljardic DJ, Borod JC, Foldi NS, et al. An examination of executive dysfunction associated with frontostriatal circuitry in Parkinson's disease. J Clin Exp Neuropsychol 2006;28(7):1127-1144.
20. Ohn SH, Park C, Yoo W, et al. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Neuroreport 2008;19(1):43-47.
21. Smith EE, Jonides J. Storage and executive processes in the frontal lobes. Science 1999;283:1657-1661.
22. Wechsler D. Wechsler Adult Intelligence Scale. 3rd edition. The Psychological Corporation;1997.
23. E Prime. 1.1. Software Psychology Tools, Inc; 2002.
24. Floel A, Cohen LG. Contribution of noninvasive cortical stimulation to the study of memory functions. Brain Res Rev 2007;53: 250-259.
25. Postle BR. Working memory as an emergent property of the mind and brain. Neuroscience 2006;139(1):23-38.
26. Wilde NJ, Strauss E, Tulsky DS. Memory span on the Wechsler Scales. J Clin Exp Neuropsychol 2004;26(4):539-549.
27. Nitsche M, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001;57:1899-1901.