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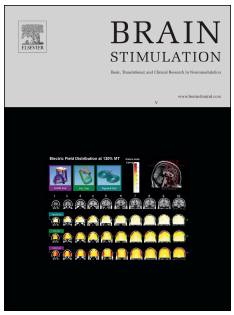

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Cognitive Effects of Spaced Transcranial Direct Current Stimulation in Major Depression

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Dear Editor,

Cognitive deficits are a critical concern in major depressive disorder (MDD), affecting learning, memory (short- and long-term), attention, concentration, executive function, and processing speed [1]. These impairments significantly impact daily functioning and quality of life [2]. Treatment options remain limited, as most interventions primarily target mood symptoms rather than cognitive dysfunction. Transcranial direct current stimulation (tDCS) has emerged as a promising treatment for MDD, with evidence suggesting it can enhance working memory and processing speed in both healthy individuals and clinical populations [3,4]. While growing evidence supports its therapeutic effects, findings remain mixed [5]. Preclinical data suggest that 'spaced' protocols enhance the neuroplastic effects of tDCS [6]. Our team recently conducted the first open-label study of a spaced tDCS protocol for MDD, demonstrating strong feasibility, safety, and preliminary therapeutic effects [7].

In this report, we present the results of the cognitive tests carried out during this study. Twenty-nine participants with MDD underwent a 10-day spaced tDCS regimen, consisting of five daily sessions at 2 mA intensity, targeting the dorsolateral prefrontal cortex (DLPFC) (anode F3, cathode F4) [7]. Cognitive functions were assessed at baseline and 1-week post-treatment using a standardized battery targeting key domains typically impaired in major depressive disorder. The full set of cognitive assessment tests used in the present study were the Rey Auditory Verbal Learning Test (RAVLT), the Rey–Osterrieth Complex Figure Test (ROCFT), the Trail Making Test (TMT), and the Controlled Oral Word Association Test (COWAT). The RAVLT total recall score from Trials 1 to 5 was used to evaluate verbal learning and memory encoding; the ROCFT immediate free recall score assessed visuospatial memory; the TMT Part B completion time measured cognitive flexibility and set-shifting, core components of executive function; and the COWAT

total score (sum of words generated across three phonemic categories) was used to assess phonemic verbal fluency, reflecting lexical access and executive control over language production. Alternate versions of the RAVLT, ROCFT, and COWAT were used for the pre- and post-assessments, to minimize practice effects. These tests were also selected because they offer validated alternate forms and are known to limit practice effects in repeated cognitive assessments [8] . This study aimed to investigate the impact of spaced tDCS on cognitive performance in MDD.

Our results demonstrated significant cognitive improvements across multiple domains (**Table 1**). A paired-sample t-test comparing baseline and 1-week post-treatment scores revealed significant increases for RAVLT ($t(26) = -4.99$, $p < .001$), ROCF ($t(24) = -7.9$, $p < .001$) and TMT ($t(24) = 3.1$, $p = .005$). The percentage improvements were 14.1% (SD = 15.0) for RAVLT, 36.6% (SD = 32.9) for ROCF, and 11.5% (SD = 26.5) for TMT. These findings align with existing literature indicating that tDCS can enhance cognitive performance [3,4] .

However, the cognitive benefits of the intervention were not uniform across all domains. The COWAT total score did not show a statistically significant change between baseline and 1-week post-treatment, although there was a modest increase of 3.6% (SD = 21.2). Notably, some participants (37%, 10 of 27) exhibited a slight decline in their COWAT performance following treatment. On average, these participants had a total reduction of 6.2 words (-2 words per letter), with the largest decline occurring in the second letter category. Importantly, these declines did not impact daily functioning, nor were they noticeable during spontaneous conversation with the examiner. Furthermore, participants reported no perceived changes in their verbal abilities during follow-up meetings. With COWAT's high test-retest reliability in healthy adults ($r \approx 0.80$), this decline is unlikely to be random variability alone [9].

The observed decline in verbal fluency among a subset of participants raises questions about the differential impact of spaced tDCS on cognition. Verbal fluency, particularly phonemic fluency, is a complex cognitive process involving multiple brain regions, most notably the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex, which are central to executive control and strategic retrieval. One possible explanation is that the repeated stimulation sessions within the protocol may have contributed to cognitive fatigue, particularly in participants with pre-existing verbal processing vulnerabilities. Phonemic verbal fluency is a cognitively demanding task that requires sustained executive control, lexical access, and verbal working memory, functions that are particularly vulnerable to transient fluctuations in attentional or mental resources. In contrast, the other cognitive tasks employed (RAVLT, ROCFT, TMT) are more externally structured and may be less susceptible to such fluctuations. However, recent findings in MDD suggest that performance on this task may also be influenced by altered functional connectivity observed in MDD between regions beyond the classical language network, such as the posterior cingulate cortex and the right inferior frontal gyrus [10]. Increased connectivity between these areas has been associated with poorer verbal fluency, possibly reflecting maladaptive network dynamics that interfere with efficient lexical access. These distinct perspectives are not mutually exclusive and may reflect different levels of dysfunction, regional activation versus network-level connectivity, potentially both modulated by tDCS. Similarly, a recent study reported a decline in executive function following tDCS [11].

As a feasibility study, the small sample size and absence of a control group limit the generalizability of the findings and make it difficult to differentiate true treatment effects from practice effects or other non-specific influences. Without a control condition, we cannot rule out the possibility that cognitive improvements resulted from repeated testing rather than spaced tDCS itself. Future randomized, sham-controlled trials are necessary to confirm these findings. Additionally, while improvements in episodic memory, visuospatial memory, and executive function were statistically significant, their real-world

functional impact remains unclear. Future studies should determine whether these cognitive gains translate into meaningful improvements in daily life, such as work performance, social interactions, or independent living. Conversely, the decline in verbal fluency observed in a subset of participants was modest, non-significant, and did not affect daily communication, suggesting that this change may not be clinically relevant. The mechanisms underlying this trend warrant further investigation, particularly in cognitively vulnerable populations. Lastly, the long-term cognitive effects of spaced tDCS remain unknown, underscoring the need for follow-up assessments to evaluate the durability and clinical significance of these changes.

In conclusion, our study examined the cognitive effects associated with spaced tDCS for MDD, demonstrating improvements in most cognitive domains, particularly visuospatial and verbal memory, along with executive function. These findings align with current literature, reinforcing the potential of tDCS to improve cognitive deficits in MDD. However, the observed changes in verbal fluency in a subset of participants underscore the need for further research into the specific effects of spaced tDCS on different cognitive functions. Understanding these differential impacts is crucial for optimizing its use in clinical practice. Future studies should focus on elucidating the mechanisms underlying these varied outcomes and assessing the long-term effects. By advancing our understanding of how spaced tDCS modulates cognitive networks, particularly through controlled trials, we can refine its therapeutic application in MDD and other neuropsychiatric disorders.

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All participants provided informed consent, and the Centre Hospitalier de l'Université de Montréal Research Ethics Board approved the study (#2021-9546).

Table 1 – Cognitive measures scores at baseline and 1-week post-spaced tDCS

Outcome measure	n	Baseline	1-week post-treatment	% change	P-value
RAVLT	27	50.3 ± 7.4	57.4 ± 6.9	14.1%	**< .001**
ROCF	25	20.4 ± 6.8	27.5 ± 4.7	36.6%	**< .001**
TMT	25	93.02 ± 60.1	61.8 ± 16.8	11.5%	**.005**
COWAT	26	35.4 ± 10.0	37.2 ± 9.9	3.7%	.72

Mean ± standard deviation. Rey Auditory Verbal learning Test (RAVLT); Rey-Osterrieth Complex Figure (ROCF); Trail Making Test (TMT); Controlled Oral Word Association Test (COWAT). Percentage change between baseline to 1-week post-treatment. P-value of paired-samples t test. Higher scores indicate better performance for the RAVLT, ROCF,

and COWAT, whereas lower scores indicate better performance for the TMT (measured in seconds).

REFERENCES

[1] Chakrabarty T, Hadjipavlou G, Lam RW. Cognitive Dysfunction in Major Depressive Disorder: Assessment, Impact, and Management. FOCUS 2016;14:194–206. https://doi.org/10.1176/appi.focus.20150043.

[2] Lam RW, Kennedy SH, McIntyre RS, Khullar A. Cognitive Dysfunction in Major Depressive Disorder: Effects on Psychosocial Functioning and Implications for Treatment. Can J Psychiatry 2014;59:649–54. https://doi.org/10.1177/070674371405901206.

[3] Brunoni AR, Vanderhasselt M-A. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. Brain Cogn 2014;86:1–9. https://doi.org/10.1016/j.bandc.2014.01.008.

[4] Narmashiri A, Akbari F. The Effects of Transcranial Direct Current Stimulation (tDCS) on the Cognitive Functions: A Systematic Review and Meta-analysis. Neuropsychol Rev 2023:1–27. https://doi.org/10.1007/s11065-023-09627-x.

[5] Burkhardt G, Kumpf U, Crispin A, Goerigk S, Andre E, Plewnia C, et al. Transcranial direct current stimulation as an additional treatment to selective serotonin reuptake inhibitors in adults with major depressive disorder in Germany (DepressionDC): a triple-blind, randomised, sham-controlled, multicentre trial. Lancet 2023. https://doi.org/10.1016/s0140-6736(23)00640-2.

[6] Agboada D, Mosayebi-Samani M, Kuo M-F, Nitsche MA. Induction of long-term potentiation-like plasticity in the primary motor cortex with repeated anodal transcranial direct current stimulation – Better effects with intensified protocols? Brain Stimul 2020;13:987–97. https://doi.org/10.1016/j.brs.2020.04.009.

[7] Couture M, Jodoin VD, Bousseau E, Sarshoghi A, Nitsche MA, Blumberger DM, et al. Spaced Transcranial Direct Current Stimulation for Major Depression. Am J Psychiatry 2025;182:276–84. https://doi.org/10.1176/appi.ajp.20240083.

[8] Lemay S, Bédard M-A, Rouleau I, Tremblay P-L. Practice Effect and Test-Retest Reliability of Attentional and Executive Tests in Middle-Aged to Elderly Subjects. Clin Neuropsychol 2004;18:284–302. https://doi.org/10.1080/13854040490501718.

[9] Ross TP, Calhoun E, Cox T, Wenner C, Kono W, Pleasant M. The reliability and validity of qualitative scores for the Controlled Oral Word Association Test. Arch Clin Neuropsychol 2007;22:475–88. https://doi.org/10.1016/j.acn.2007.01.026.

[10] Li D, Zhang H, Liu Y, Liang X, Chen Y, Zheng Y, et al. Abnormal Functional Connectivity of Posterior Cingulate Cortex Correlates With Phonemic Verbal Fluency Deficits in Major

Depressive Disorder. Front Neurol 2021;12:724874. https://doi.org/10.3389/fneur.2021.724874.

[11] Zanão T, Mattar RAMPFD, Pinto BS, Oliveira J, Vaughan RR, Benseñor IM, et al. Cognitive changes in post-stroke depression patients undergoing treatment with transcranial direct current stimulation (tDCS): an exploratory, ancillary analysis of a randomized, sham-controlled clinical trial. Braz J Psychiatry 2025. https://doi.org/10.47626/1516-4446-2024-3847.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Reports a relationship with that includes:. Has patent pending to. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.