



Augmenting cognitive training with bifrontal tDCS decreases subclinical depressive symptoms in older adults: Preliminary findings



Dear Editor,

Transcranial direct current stimulation (tDCS) applied to the frontal lobe, either in isolation or as augmentation to another treatment, has antidepressant properties in depressed adults [1]. Pairing tDCS with cognitive training (CT) results in additional benefit [2,3]. This combination is thought to enhance cortical activity of the underlying frontal neural networks to produce antidepressant effects [4]. However, these studies have primarily targeted depressed adults under age 65 years and less is known about this combination of interventions in older adults, particularly as the combination may affect milder subthreshold depressive symptoms that are both prevalent and associated with negative outcomes [5].

To our knowledge, only one study has investigated tDCS with CT in older adults with subthreshold mood symptoms, finding no benefit [6]. However, several study parameters may have affected findings, including electrode placement (anode: ~F3, cathode: contralateral supraorbital area), duration of tDCS (25-min), nature of CT (working memory training), and choice of mood scales (Total Mood Disturbance on POMS-2, daily mood question). Thus, we were interested in whether combining bifrontal tDCS with CT would improve depressive symptoms in older adults without a clinical diagnosis of major depressive disorder. As apathy also increases with age, we explored whether this treatment combination had effects on apathy, as no other studies have investigated these symptoms outside of dementia [7]. We are reporting secondary analyses from Ref. [8].

Briefly, 30 adults aged 65–89 years in the parent study were randomized to receive active or sham tDCS in combination with CT for 2 weeks (or 10 intervention days). This trial was preregistered in clinicaltrials.gov (NCT02137122), reviewed and approved by the University of Florida, and participants provided their written informed consent prior to the initiation of study procedures. Active tDCS was delivered bifrontally over F3 (cathode) and F4 (anode) for 20-min at 2 mA intensity through two 5 × 7 cm² saline saturated sponge electrodes (10 ml/sponge) using the Soterix Medical 1 × 1 tDCS clinical trials device (which allowed for triple-blinding: participant, interventionist, and investigators). Sham tDCS received identical set-up procedures with 2 mA stimulation for 30-sec with 30-sec ramp up and down. An 8-component multidomain commercially available computerized CT intervention focusing on attention/processing speed and working memory from Posit Science's Brain HQ suite (www.brainhq.com) was administered for 40-min daily, with the first 20-min being paired with active or sham tDCS. Following completion of the 2-week intervention, a blinding questionnaire was given to participants asking: Q1: Which brain

stimulation treatment condition do you believe you received? (Active, Sham/Placebo, Don't know/Unsure), Q2: If you answered "Don't know/Unsure" above, can you please provide your best (or random) guess of the treatment you received anyway? and Q3: On a scale of 0–10, how confident are you that you received (your selection)? Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II) at baseline and after completion of the 2-week intervention.

To allow room for symptom improvement, for these preliminary analyses we only included participants with a BDI-II cut-off score of 5 or greater, which is considered in the "minimal" range of depression severity. Fifteen non-demented healthy older adults (70.93 ± 5.41 years old, 10 females, 16.40 ± 2.32 years education, MoCA = 27.27 ± 2.34) met this cutoff (8 sham, 7 active). The tDCS conditions did not significantly differ in age, sex, years of education, MoCA scores, or number of completed intervention days (sham: 9.63 ± 0.74, active: 9.71 ± 0.49, $t(13) = -0.27$, $p = 0.40$). They also did not significantly differ in baseline BDI-II scores (sham: 11.38 ± 6.44, active: 7.71 ± 2.93, $t(13) = 1.38$, $p = 0.10$). There were no differences in sensation ratings/side effects noted before, during, or after stimulation between the active vs. sham groups (p 's > 0.05) from the parent sample (as reported in Ref. [8]). Likewise, there were no group differences in the parent sample for frequency of endorsement for Active, Sham or Unsure categories, nor were there differences in confidence ratings for whether participants received Active vs. Sham conditions (all p 's > 0.05), suggesting that participant blinding was successful.

Results indicated the combination of active (and not sham) tDCS with CT was associated with reduced depressive symptoms. Fig. 1 shows the active tDCS group had BDI-II reduction of 2.7 points following the intervention, while the sham tDCS group decreased 1.4 points ($\eta_p^2 = 0.18$; large effect size). Including covariates (age, sex, education, MoCA scores, and number of completed intervention days) in the model further strengthened this discrepancy (active: decrease of 3.7 points; sham: decrease of 0.51 points; $\eta_p^2 = 0.37$; larger effect size).

We conducted similar analyses in the initial sample using the Apathy Scale (AS; cut-off ≥ 9; 8 sham, 10 active), which was also administered at baseline and post-intervention. The tDCS conditions did not differ in baseline AS scores (sham: 11.75 ± 2.38, active: 11.80 ± 1.99, $t(16) = -0.05$, $p = 0.48$). We did not find differences in apathy symptoms over time for either condition, without or with covariate adjustment (see Fig. 1).

While preliminary, these results suggest that the combination of bifrontal active tDCS with CT may be a potential method for improving subthreshold depressive (but not apathy) symptoms in

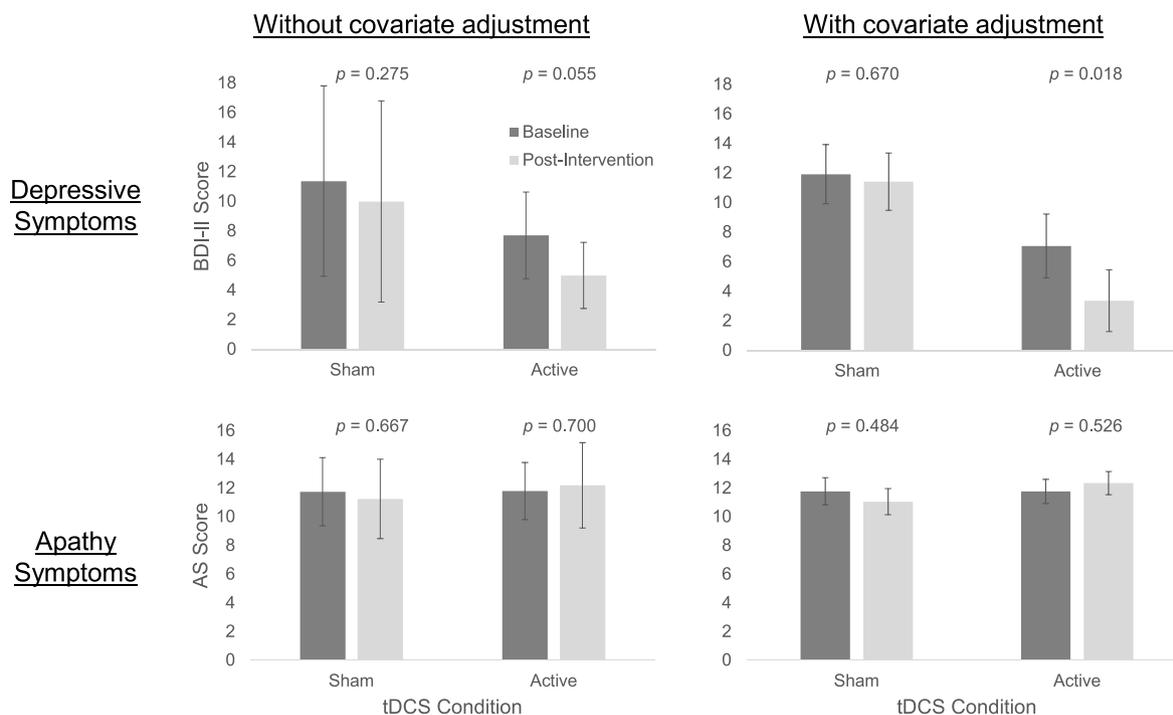


Fig. 1. Differences in depressive and apathy symptoms pre- and post-intervention (active vs. sham tDCS paired with computerized cognitive training) in older adults with subclinical depressive symptoms. Sample size = 15 for depressive symptoms (8 sham, 7 active) and 18 for apathy symptoms (8 sham, 10 active). Covariate adjustment included age, sex, years education, Montreal Cognitive Assessment (MoCA) total score, and number of completed intervention days.

older adults via targeting prefrontal neural circuitry and promoting neuroplasticity of the underlying neural network. While baseline BDI-II scores did not significantly differ, the active tDCS group had a lower score than sham, but saw greater improvement in BDI-II scores post-intervention despite having less room for change. It is more difficult to find effects in those with milder compared to more severe depressive symptoms in depression clinical trials; thus, these results are promising. Adequate treatment of subthreshold depressive symptoms may prevent or reduce negative outcomes associated with depressive symptoms in at-risk older adults, including cognitive dysfunction and reduced brain volumes [9], as well as specific health conditions [10]. Larger randomized clinical trials are needed to better understand tDCS plus CT antidepressant effects in older adults.

Since apathy increases with age, subclinical apathy symptoms may be “normal” and less prone to changes with intervention (and it is when these symptoms crossover threshold to clinically elevated that we see negative relationships with clinical outcomes). In the current study, the range in apathy scores both pre- and post-intervention was restricted (pre: 9 to 15, post: 7 to 17), making it difficult to find an effect. Moreover, in absence of dementia, symptoms of apathy may reflect amotivation rather than a mood disorder and involve dopaminergic pathways and deeper, more subcortical neural circuitry that is not being appropriately targeted with current intervention combination [11]. Pairing tDCS (likely with different electrode placement) with an intervention targeting reward circuitry and/or with dopaminergic modulation may be more beneficial for apathy and is an interesting focus for future research.

Declaration of competing interest

None.

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References

- [1] Wang J, Luo H, Schülke R, et al. Is transcranial direct current stimulation, alone or in combination with antidepressant medications or psychotherapies, effective in treating major depressive disorder? A systematic review and meta-analysis. *BMC Med* 2021;19:319. <https://doi.org/10.1186/s12916-021-02181-4>.
- [2] Brunoni AR, Boggio PS, Raedt R De, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. *J Affect Disord* 2014;162:43–9. <https://doi.org/10.1016/j.jad.2014.03.026>.
- [3] Segrave RA, Arnold S, Hoy K, et al. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. *Brain Stimul* 2014;7: 325–31. <https://doi.org/10.1016/j.brs.2013.12.008>.
- [4] Jog MV, Wang DJJ, Narr KL. A review of transcranial direct current stimulation (tDCS) for the individualized treatment of depressive symptoms. *Personalized Medicine in Psychiatry* 2019;17–18:17–22. <https://doi.org/10.1016/j.pmj.2019.03.001>.
- [5] Meeks TW, Vahia IV, Lavretsky H, et al. A tune in “a minor” can “b major”: a review of epidemiology, illness course, and public health implications of sub-threshold depression in older adults. *J Affect Disord* 2011;129:126–42. <https://doi.org/10.1016/j.jad.2010.09.015>.
- [6] Freidle M, Nilsson J, Lebedev AV, et al. No evidence for any effect of multiple sessions of frontal transcranial direct stimulation on mood in healthy older adults. *Neuropsychologia* 2020;137:107325. <https://doi.org/10.1016/j.neuropsychologia.2019.107325>.

- [7] Nguyen J, Boutoleau-Bretonniere C, Lefaucheur J, et al. Efficacy of transcranial direct current stimulation combined with cognitive training in the treatment of apathy in patients with Alzheimer's disease: study protocol for a randomized trial. *Rev Recent Clin Trials* 2018;13:319–27. <https://doi.org/10.2174/1574887113666180416153316>.
- [8] Nissim NR, O'Shea A, Indahlastari A, et al. Effects of transcranial direct current stimulation paired with cognitive training on functional connectivity of the working memory network in older adults. *Front Aging Neurosci* 2019;11: 1–11. <https://doi.org/10.3389/fnagi.2019.00340>.
- [9] Szymkowicz SM, Woods AJ, Dotson VM, et al. Associations between subclinical depressive symptoms and reduced brain volume in middle-aged to older adults. *Aging Ment Health* 2019;23:819–30. <https://doi.org/10.1080/13607863.2018.1432030>.
- [10] Agustini B, Lotfaliany M, Mohebbi M, et al. Trajectories of depressive symptoms in older adults and associated health outcomes. *Nature Aging* 2022;2: 295–302. <https://doi.org/10.1038/s43587-022-00203-1>.
- [11] Husain M, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. *Nat Rev Neurosci* 2018;19:470–84. <https://doi.org/10.1038/s41583-018-0029-9>.

Sarah M. Szymkowicz*

Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN, USA

Warren D. Taylor

Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN, USA

Geriatric Research, Education, and Clinical Center, Veterans Affairs Tennessee Valley Health System, Nashville, TN, USA

Adam J. Woods

Center for Cognitive Aging and Memory, McKnight Brain Institute, University of Florida, Gainesville, FL, USA

Department of Clinical and Health Psychology, University of Florida, Gainesville, FL, USA

Department of Neuroscience, University of Florida, Gainesville, FL, USA

* Corresponding author. Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, 1601 23rd Avenue South, Nashville, TN, 37212, USA. Tel.: +1 615-875-0032; fax: +1 615 875 0686.

E-mail address: sarah.szymkowicz@vumc.org (S.M. Szymkowicz).

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