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Research Report

Effect of online tDCS to left somatomotor cortex on neuropsychiatric symptoms among older adults at risk for dementia



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ABSTRACT

Background: Neuropsychiatric symptoms (NPS) in mild cognitive impairment (MCI) cause distress to patients and caregivers, and accelerate progression to dementia. Transcranial direct current stimulation (tDCS) is a promising non-invasive treatment for NPS.

Objective/hypothesis: This pilot study assessed behavioral and neural effects of a 4-week anodal tDCS intervention targeting left sensorimotor cortex (LSMC: left precentral/post-central gyri) during visual attention (compared to online sham tDCS), in 40 older adults (24 females, mean age = 71) with MCI.

Methods: A phase 0 double-blinded randomized control trial was conducted. NPS (patient-reported mood symptoms plus a caregiver-reported questionnaire) and fMRI were measured at baseline and immediately post-intervention.

Results: Generalized Estimating Equations found no significant group by time interactions for either NPS measure. However, there was evidence of decreased patient-reported NPS (Wald's $\chi^2 = 3.80$, $p = .051$), decreased LSMC activation during visual attention (Wald's $\chi^2 = 2.93$, $p = .087$), and increased LSMC-amygdala resting-state functional connectivity (rsFC; Wald's $\chi^2 = 3.13$, $p = .077$) in intervention group from pre-to post-intervention. Decrease in LSMC activation (Wald's $\chi^2 = 9.20$, $p = .002$) and increase in LSMC-amygdala rsFC (Wald's $\chi^2 = 4.72$, $p = .030$) related to decreased patient-reported NPS. Increased positive valence across sessions was significantly associated with intervention-related NPS improvement (Wald's $\chi^2 = 22.92$, $p < .001$). There were no findings for caregiver-reported NPS. Effects were stronger for left postcentral compared to left precentral gyrus.

Conclusion: We found tentative evidence that tDCS applied to LSMC during visual attention in older adults with MCI improved NPS via changes in LSMC activation and LSMC-

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amygdala rsFC, suggesting improved emotion regulation. Patient-reported NPS was more sensitive to these changes than caregiver-reports, and effects were strongest for left postcentral gyrus. Follow-up studies should perform precise mechanistic investigation and efficacy testing.

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1. Introduction

Neuropsychiatric symptoms (NPS) are a set of behavioral disturbances prevalent in mild cognitive impairment (MCI) and Alzheimer's disease (AD). Increased NPS can cause significant distress to patients and caregivers, and accelerate cognitive/functional decline (David et al., 2016). Existing studies have primarily focused on neural mechanisms and management of individual NPS in MCI/AD (Veitch et al., 2018; Victoroff et al., 2018). However, multiple NPS often co-exist, necessitating a focus on understanding shared biological mechanisms underlying multiple NPS. The most commonly experienced NPS in MCI/AD include depression, anxiety, irritability, and irritation, implicating emotion dysregulation as a potential shared mechanism (Ismail et al., 2018). Previous research identified a shared neural circuit that can predict the existence of multiple NPS; including several regions related to emotion, including ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex, as well as prefrontal and sensorimotor regions (Wang et al., 2019). Optimal management of multiple, concomitant NPS is a major challenge in MCI/AD care (Geda et al., 2013), but treatments that focus on directly alleviating NPS in MCI/AD are limited (Ismail et al., 2018).

Transcranial direct current stimulation (tDCS) is a non-invasive treatment that involves applying a low electrical current to an area of the scalp. This is hypothesized to modulate cortical neuronal membrane potentials in brain areas closest to the stimulation site, increasing plasticity and facilitating long-term changes in regional activation and functional connectivity (FC) of targeted regions (Stagg & Nitsche, 2011). tDCS in younger adults has been effective at improving symptoms of mood disorders (Labree et al., 2022). tDCS has also shown promise for improving NPS, general cognitive function, and memory in MCI/AD (Elder & Taylor, 2014; Majdi et al., 2022), although results have been mixed, and there is significant heterogeneity in the literature (Teselink et al., 2021). Two critical aspects of methodological heterogeneity involve the regions targeted and the states of participants during tDCS. tDCS is primarily targeted using brain regions close to the surface (which are closest to the electrodes), such as lateral frontal, temporal, and parietal cortices, and tDCS has been shown to elicit region-specific effects (Bradley et al., 2022). Research also suggests that tDCS is state-dependent (Bradley et al., 2022; Silvanto et al., 2008), meaning effects differ depending on the cognitive/affective state of participants (e.g., performing an attention task vs. performing a working memory task) during tDCS.

In this study, we assessed the effects of tDCS to the left sensorimotor cortex (LSMC) in 40 older adults with MCI, while they performed a visual attention task (multiple object

tracking; MOT). We chose LSMC as the tDCS target because: (1) SMC is a primary tDCS target for psychosomatic symptoms (DosSantos et al., 2016; Khedr et al., 2017; Slaby et al., 2015); and (2) SMC and amygdala form a sensory-limbic network (Toschi, Duggento, & Passamonti, 2017) related to emotion regulation (Canbeyli, 2013) that is implicated in NPS. The MOT task was chosen as the state during which tDCS was administered as low level visual attention tasks are known to activate LSMC-associated networks that are relatively spared from neurodegeneration/pathology in MCI (Li et al., 2015), enhancing plasticity (Bradley et al., 2022). SMC is affected by neurodegeneration and AD pathophysiology relatively late in AD progression (Braak et al., 1998; Yu et al., 2021); its capacity for plasticity may be intact in MCI compared to higher order brain regions (including lateral prefrontal and temporal cortices) that are more vulnerable to pathology (Koch et al., 2017; Okamura et al., 2014). Anodal tDCS of LSMC has also been shown to enhance brain synchronization and whole-brain resting-state FC, FC between LSMC and neighboring regions (especially parietal cortex), and between LSMC, frontal regions, and the caudate (DaSilva et al., 2015; Hordacre et al., 2017; Pellegrino et al., 2018; Polania et al., 2012).

The objective of the study was to determine whether anodal tDCS to LSMC during MOT improves multiple NPS in MCI. We hypothesized that our tDCS protocol would result in altered activation of LSMC and a reorganization of FC between LSMC and regions involved in emotional regulation, changes that would be linked to improvements in multiple NPS.

2. Material and methods

2.1. Design

We proposed a Stage 0 double-blinded randomized control trial study for mechanistic understanding: <https://clinicaltrials.gov/ct2/show/NCT04099524>. There were no deviations from the registered protocol. A sample of 40 older adults with MCI and NPS were randomly assigned to an intervention (anodal C3+MOT) or control (sham C3+MOT) group. Participants, informants, and outcome assessors were blinded to group assignment. Assessments were conducted at baseline and within 7 days after completing a 4-week intervention; we also collected intervention progress-related data during the 4-week intervention. The intervention consisted of five consecutive sessions for two weeks, followed by two sessions per week for two weeks. This protocol (one session per weekday for two weeks, followed by booster sessions on selected days for two further weeks) was based on a systematic review of tDCS approaches (Kekic et al., 2016). Each tDCS session lasted 20 minutes. Recruitment began in October 2019,

and data collection finished in January 2022 due to 9 months COVID-related mandatory pause. For participants whose interventions got disrupted by COVID, their interventions were restarted after the study resumed. CONSORT diagram is displayed in Fig. 1. Human subjects research procedure was approved by the Research Subject Board at University of Rochester. Written informed consent was obtained from both participants and their informants. The clinical trial was pre-registered as NCT04099524 at *clinicaltrials.gov*. Data were also collected for the assessment of sustained changes at 4-week follow-up post intervention, but analyses in this mechanism-focused paper have been restricted to baseline and immediate post-intervention sessions (i.e., two time-points). We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.2. Participants

Inclusion criteria included (1) consensus diagnosis of MCI due to AD based on 2011 NIA-AA diagnostic criteria (Montreal Cognitive Assessment version 2 education-adjusted total score of $18 \leq x \leq 26$; one standard deviation below age- and/or education-corrected population norms for Rey's Auditory Verbal Learning Test (Lists C&D); preserved activities of daily living via self-report version of the Activities of Daily Living-Prevention Instrument total score ≤ 30 ; and absence of dementia); (2) presence of two neuropsychiatric symptoms with

informant-rated Neuropsychiatric Inventory Questionnaire (NPI-Q) severity sum score ≥ 3 , rated by comparing to 6 months ago to capture a worsening trajectory (David et al., 2016). Each participant was required to have an informant who was 18+ years old, English-speaking, maintained regular (weekly) contact with the participant, and informed about the participant's current or past well-being and mood. Participants with MRI (e.g., pacemaker) or tDCS (e.g., history of seizures, repetitive motor conditions, skin condition or sensitivity) contraindications were excluded. Participant baseline data are presented in Table 1.

2.3. Intervention

We implemented an online (during task performance as opposed to offline performed at rest) tDCS design, following an established protocol (see review (Zhao et al., 2017) for protocol details), in which participants in both groups completed an MOT task. Participants could choose to have the intervention administered at home or any suitable alternative location, including in the lab.

tDCS set-up: Soterix Medical 1×1 transcranial Electrical Stimulation (1x1-tES) device was used to administer tDCS. The anodal electrode was placed over C3 (LSMC) and the cathodal electrode over Fp2 (orbitofrontal), according to the International 10–20 electrode placement system. Stimulation was delivered via a pair of leads attached to two surface sponge electrodes (30 cm² each), dampened with approximately 6 ml of saline and held against the scalp with the

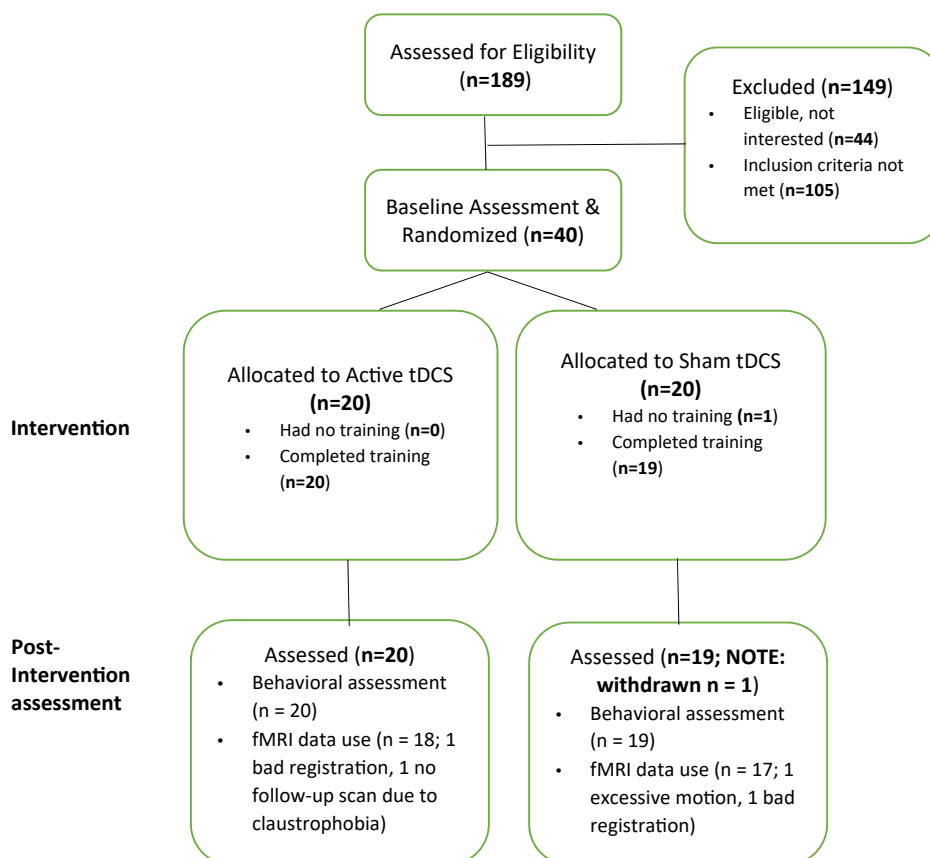


Fig. 1 – CONSORT form.

Table 1 – Baseline characteristics (N = 40).

Variable	Total	Intervention	Control	Statistics
Age, mean (SD)	71 (7.0)	70 (6.6)	73 (7.1)	$t = -1.47, p = .15$
White, n (%)	39 (97.5)	20 (100)	19 (95)	$\chi^2 = 1.03, p = .31$
Female, n (%)	24 (60)	14 (70)	10 (50)	$\chi^2 = 1.67, p = .20$
Years of education, mean (SD)	16 (2.9)	16 (3.3)	16 (2.6)	$t = -.99, p = .33$
MoCA, mean (SD)	23.33 (2.57)	22.80 (2.33)	23.70 (2.68)	$t = -1.05, p = .30$
Neurodegeneration, mean (SD)	2.77 (.14)	2.75 (.12)	2.78 (.16)	$t = -.74, p = .47$
Participant reported mood composite, mean (SD)	.13 (.76)	.20 (.78)	.06 (.75)	$t = .57, p = .58$
NPI-Full total-raw, mean (SD)	14.57 (13.74)	13.90 (11.64)	15.25 (15.84)	$t = -.31, p = .76$
NPI-Full total-adjusted for caregiving distress, mean (SD)	2.48 (2.18)	2.64 (2.34)	2.34 (2.07)	$t = -.41, p = .68$

MoCA=Montreal cognitive assessment; NPI=Neuropsychiatric Inventory-full; neurodegeneration was calculated as the Alzheimer's disease cortical thickness score from structural MRI using a previously described procedure (Lin et al., 2017).

Soterix Medical Elastic Fastener set. In the intervention condition, stimulation of 1.5 mA current was administered for 20 min, with ramp up and down periods of 30 sec each at the start and end of each session, respectively. In the sham condition, stimulation of 1.5 mA current was ramped up for 30 sec and then ramped down within 10 sec. Sham tDCS served as the control condition; 30 sec stimulation minimizes physiological effects of tDCS while inducing similar sensations to active tDCS, namely tingling and itching that are typically only pronounced at the beginning of the stimulation. The goal of sham tDCS is to equate participant sensation between experimental and control conditions.

MOT task was administered to both groups while receiving real or sham tDCS. In each trial, a set of 8 identically sized circles, consisting of blue targets (2 or 3) and yellow distractors, were displayed within a fixed circular field on the screen. Participants were required to track the target stimuli. Stimuli moved in Brownian motion for 2 sec, then the targets turned yellow to match distractors. After 4 sec, the stimuli stopped moving, and a randomly selected stimulus displayed a visual cue. Participants indicated with a key press whether the selected stimulus was a target. Each session lasted 20 min, using 1-sec fixation, 2-sec inter-stimulus interval, and 6-sec response window. Trials that timed out defaulted as an incorrect response. The first 7 intervention sessions used 2-target MOT (“low-demanding”), and the remaining 7 sessions used 3-target MOT (“high-demanding”). Code for the MOT task can be found at https://github.com/adamgeorgeturnbull/BEEM/tree/main/BEEM_MOT_task.

2.4. Measures

We collected two types of data: behavioral and brain imaging data immediately before and after a 4-week intervention period, as well as intervention process-related behavioral data across all intervention sessions within the 4-week intervention period.

2.4.1. NPS

Due to discrepancies between patient- and informant-reported NPS in the literature (Moye et al., 1993; Votruba et al., 2015), we considered both patient and informant measures as primary outcomes. Patient-reported NPS was measured using three mood-related questionnaires that probed mood within the past week: depression (Geriatric Depressive Scale; GDS-30

(Dunn & Sacco, 1989)); anxiety (State-Trait-Anxiety-Inventory; STAI-state (Kvaal et al., 2001)); and apathy (Apathy Evaluation Scale; AES (Resnick et al., 1998)). Total scores were z-transformed across timepoints and averaged to create a composite mood score. Informant-reported NPS was measured using the 12-domain Neuropsychiatric Inventory (NPI-Full) (Cummings, 1997), including both frequency and severity (based on present symptoms) during the past week. NPI-Full total score was calculated as the summed frequency \times severity for all present NPS. Additionally, we treated NPI-Full caregiver mean distress score across all domains as a confounder in later analyses. Higher mood or NPI scores indicated worse NPS. The correlation between NPI and mood was $r = .34$ at baseline and $r = .22$ at post-intervention. The NPS questionnaires can be found at https://github.com/adamgeorgeturnbull/BEEM/tree/main/NPS_questionnaires.

2.4.2. Neuroimaging

2.4.2.1. DATA ACQUISITION. The MRI protocol was conducted using a Siemens 3T Prisma (VE11C) scanner equipped with a 64-channel head coil. Each MRI session began with a scout image, followed by a single-shot EPI MPRAGE scan (TR/TE = 1400/2.34 msec, slice thickness = 1 mm, resolution = 1 mm isotropic, 192 slices, PE acceleration = GRAPPA, FA = 70°, fat suppression = OFF, orientation = sagittal, echo spacing = 7 msec, FOV = 256 mm) to provide high-resolution structural-weighted anatomical images. Anterior-to-posterior and posterior-to-anterior field maps were acquired to correct for distortions in echo-planar imaging sequences. Resting-state (TR/TE = 1010/44 msec, slice thickness = 2 mm, resolution = 2 mm isotropic, R = 1, SMS/MB acceleration factor = 8, FA = 70°, fat suppression = ON, orientation = transversal, echo spacing = .56 msec, FOV = 256 mm, acquisition matrix = 128 \times 128, 80 slices, 253 volumes) and task-related (TR/TE = 1010/44 msec, slice thickness = 2 mm, resolution = 2 mm isotropic, R = 1, SMS/MB acceleration = 8, FA = 70°, fat suppression = ON, orientation = transversal, echo spacing = .56 msec, FOV = 256 mm, acquisition matrix = 128 \times 128, 80 slices, 250 volumes). BOLD functional data were collected using a gradient echo-planar imaging sequence. An in-scanner camera was used to ensure compliance. Slice acquisition order was interleaved. Visual attention task: Participants completed a visual attention “Eyes for Detail” task during which they identified, as accurately and quickly as possible, whether a target stimulus (“申”) was displayed among

a set of distractors (“由”) that were presented in different orientations (e.g., “由”, “甲”, “由”). The task began with a 12-sec fixation period during which participants viewed a white fixation cross centered against a black background. In each trial, a set of six white stimuli were presented against a black background, followed by an interstimulus interval of 1 sec. The stimulus display lasted for 5.5 sec, within which participants were required to respond before the trial timed out and defaulted to an incorrect response. A block design was implemented and consisted of six blocks, with four trials per block (24 trials total). Each block was followed by a 12-sec fixation period. Task duration was 4 min and 10 sec.

Of note, the task here was different from the MOT task used in the tDCS intervention and therefore is not expected to be affected by practice effects.

2.4.2.2. DATA PROCESSING. Resting state fMRI: Data were analyzed using scripts adapted from previous research using multiband resting-state fMRI (Risk et al., 2021) (scripts publicly available at <https://github.com/adamgeorgeturnbull/BEEM>), using functions from FSL v6.0.5.1 and AFNI v21.1.07. The first four volumes were dropped to allow for signal stabilization. fMRI preprocessing consisted of motion correction (FSL MCFLIRT), distortion correction (FSL topup), slice-timing correction (FSL slicetimer), co-registration and normalization to MNI space (FSL FLIRT and FNIRT). fMRI timeseries underwent simultaneous nuisance regression (9p nuisance regression model: six rigid body realignment parameters, global signal, average CSF, and average WM signal (Ciric et al., 2017)) and temporal filtering (bandpass .009–.08 Hz), followed by spatial smoothing (FWHM 6 mm), using AFNI 3dTproject. Timeseries extraction and FC matrix generation (including r-to-z transformation) were performed using Python 3 and the Nilearn package (Version .9.1), using the AAL3 atlas (Rolls et al., 2020). Co-registration and normalization, as well as connectivity matrices, were visually inspected for artifacts or poor quality. One participant was excluded for motion exceeding 1 mm mean RMS. Two participants were excluded for consistently poor co-registration and normalization.

Task fMRI: Task fMRI data were analyzed using FSL. Individual subject data underwent motion correction (MCFLIRT) and distortion correction (topup). FSL FEAT (template fsf file available at <https://github.com/adamgeorgeturnbull/BEEM>) was used to perform slice-time correction, brain extraction, co-registration, normalization to MNI space, high-pass filtering (100 sigma), and spatial smoothing (FWHM 5 mm). A GLM was fit using FLAME 1 with one explanatory variable (EV) defined by the start of each task trial lasting for 5.5 sec (trial duration) convolved with a Double-Gamma HRF, and 6 motion parameters as confounds. A single contrast was modelled with the task EV, given a value of 1, to model task over baseline (fixation periods at the start of each scan and in between task blocks). Mean regional percent signal change (from baseline to task) was extracted using featurquery with masks generated with the AAL3 atlas for L-precentral and L-postcentral gyri (AAL3 labels “Precentral_L” and “Postcentral_L”). Co-registration and normalization, as well as connectivity matrices, were visually inspected for artifacts or poor quality. One participant was excluded for motion exceeding 1 mm mean RMS. Two participants were excluded for consistently

poor co-registration and normalization. These participants were the same as those excluded from resting state analyses.

2.4.2.3. REGIONS OF INTEREST. We focused on three variables: (1) LSMC activation during task (percent signal change from baseline to task); (2) LSMC resting FC with ventromedial prefrontal cortex (using left medial orbitofrontal gyrus; AAL3 label “OFC_med_L”); (3) LSMC resting FC with left amygdala (AAL3 label “Amygdala_L”). Variables (2) and (3) represent cortical and subcortical circuits, respectively, of emotional regulation (Andrewes & Jenkins, 2019). In terms of LSMC, as the effects of tDCS are relatively diffuse, we used the mean value of left precentral and postcentral gyri as the primary measure for C3, and the two gyri separately as secondary measures in exploratory follow-up analyses. Due to the diffuse nature of stimulation from our sponge electrodes, dorsolateral pre-frontal cortex (IDLFFC: AAL3 atlas region: “Frontal Mid L”) was used for specificity analysis, to assess whether effects on brain activity extended to this region. This region is adjacent to our target region (precentral gyrus) and is commonly used as a target in tDCS experiments.

2.4.2.4. VALENCE AND AROUSAL. Self-Assessment Manikin (SAM), a non-verbal pictographic Likert scale, was used to measure the affective dimensions of valence and arousal (Bradley & Lang, 1994). Immediately before and after each intervention session, participants were instructed to rate their current levels of pleasantness (valence) and activation (arousal) by pointing to one of five pictures for each dimension. Self-report pictorial ratings were coded according to a 5-point Likert scale, with 0 = not at all and 5 = very much.

2.5. Data analysis

AR (1) covariance matrix with Generalized Estimating Equation (GEE) model was applied in all main analyses: (1) within-group intervention effect was analyzed using $y = Time + error$; (2) between-group intervention effect was analyzed using $y = Group + Time + Group \times Time + error$; (3) relationships between time-correspondent brain-behavioral change or intervention process-outcome: $y = Group + Time + x$ (with x being brain data or intervention process, and y being behavior or intervention outcome). Across all analyses, *Time* was either a dichotomous variable for post-intervention compared to baseline or a continuous variable for 14 intervention sessions. To reduce type 1 error, we only compared between-group effect if within-intervention group effect reached a $p \leq .10$. For analyses where task fMRI or resting state fMRI values were the independent variable, task or rest motion (respectively) were included as covariates of no interest. For analyses where caregiver-reported NPS was the independent variable, caregiver distress was included as a covariate of no interest.

2.6. Sensitivity analysis

Given the exploratory nature of a Stage 0 mechanistic study, we proposed the sample size based on practicability (i.e., budget and length of an R21). Based on degree of freedom at 1, power at .80, and alpha at .05 for the GEE models, we were able to detect Wald's χ^2 (Victoroff et al., 2018) at 3.85.

3. Results

3.1. Intervention feasibility

Study attrition rate was 2.5% throughout the entire study period: one participant in the sham group withdrew from the study immediately after baseline assessment due to repeated changes in medication. Intervention adherence rate was 97.5%: all participants, except the drop-out, completed all 14 intervention sessions. Side effects were measured in both groups immediately following each intervention session. Side effect related to tDCS was minimal: Throughout the sessions, participants reported on average .22 adverse symptoms related to tDCS (range: 0–3 symptoms); control group reported significantly more symptoms ($B = .20$, $SE = .08$, $p = .009$) than the intervention group. There was no evidence of blinding violations based on study notes, however, we did not measure blinding efficacy directly (see Discussion).

3.2. Intervention effect on NPS (Fig. 2)

Data from 39 subjects (20 from intervention and 19 from control) were included in the data analysis on NPS (one participant withdrew from the control group).

Intervention ($B = -.22$, $SE = .11$, Wald's $\chi^2 = 3.80$, $p = .051$), but not control ($B = -.04$, $SE = .10$, Wald's $\chi^2 = .16$, $p = .69$), showed improvement in participant-reported mood immediately after intervention from baseline. The sample size might have been too small to detect a significant between-group effect ($B = -.18$, $SE = .15$, Wald's $\chi^2 = 1.45$, $p = .23$). To better understand these effects, we also analyzed clinically significant improvement, defined as an improvement from pre-to post-intervention assessment of at least one standard error of measurement (Copay et al., 2007). A higher proportion of the intervention group (75%) showed clinically significant improvement compared to the control group (47.3%) ($\chi^2 = 3.14$, $p = .076$). There were no within- or between-group effects for caregiver-reported NPI, controlling for caregiver distress. In the following analyses, we focused on understanding mechanistic or intervention processes related to participant-reported mood.

3.3. Intervention effect on LSMC (Fig. 2)

Data from 35 subjects (18 from intervention and 17 from control) were included in the data analysis on LSMC: in addition to the one participant that withdrew, one participant's data was excluded for excessive motion during MRI scanning, two for issues with co-registration and normalization, and one did not complete MRI scanning at timepoint 2 due to claustrophobia.

When examining LSMC activation during task fMRI as an outcome, intervention ($B = -.15$, $SE = .09$, Wald's $\chi^2 = 2.93$, $p = .087$), but not control ($B = .03$, $SE = .07$, Wald's $\chi^2 = .20$, $p = .65$), showed a decrease in LSMC activation after intervention from baseline. The between-group ($B = -.18$, $SE = .12$, Wald's $\chi^2 = 2.34$, $p = .13$) effects on LSMC activation was relatively weak. When examining left precentral and postcentral gyri separately, within-intervention group (precentral:

$B = -.12$, $SE = .09$, Wald's $\chi^2 = 1.64$, $p = .20$; postcentral: $B = -.18$, $SE = .09$, Wald's $\chi^2 = 4.26$, $p = .039$) and between-group (precentral: $B = -.17$, $SE = .13$, Wald's $\chi^2 = 1.81$, $p = .18$; postcentral: $B = -.19$, $SE = .12$, Wald's $\chi^2 = 2.60$, $p = .11$) effects on left postcentral gyrus were stronger.

Specificity analysis, using IDLPFC as a comparison showed no significant interaction effect ($B = -.11$, $SE = .11$, Wald's $\chi^2 = .13$, $p = .33$) or within-intervention effect ($B = -.04$, $SE = .09$, Wald's $\chi^2 = .19$, $p = .66$) of tDCS on IDPFC activation. This region is often used in tDCS experiments and is adjacent to the precentral gyrus region. This finding suggests that despite the relatively diffuse nature of stimulation from our tDCS electrodes, the effect of intervention on activation was stronger at the C3 target region, and appears to be strongest for the postcentral gyrus.

In a model for understanding the relationship between LSMC activation and mood, decrease in LSMC activation was significantly related to decrease in mood symptoms (LSMC: $B = .42$, $SE = .14$, Wald's $\chi^2 = 9.20$, $p = .002$; precentral: $B = .38$, $SE = .14$, Wald's $\chi^2 = 7.88$, $p = .005$; postcentral: $B = .39$, $SE = .14$, Wald's $\chi^2 = 7.83$, $p = .005$).

When examining LSMC's FC with amygdala as an outcome, intervention ($B = .11$, $SE = .06$, Wald's $\chi^2 = 3.13$, $p = .077$), but not control ($B = -.12$, $SE = .07$, Wald's $\chi^2 = 2.64$, $p = .10$), had increased LSMC-amygdala FC after intervention from baseline, consistent with a significant between-group effect ($B = .20$, $SE = .09$, Wald's $\chi^2 = 4.45$, $p = .035$). When examining left precentral and postcentral gyri separately, within-intervention group (precentral: $B = .06$, $SE = .07$, Wald's $\chi^2 = .87$, $p = .35$; postcentral: $B = .15$, $SE = .06$, Wald's $\chi^2 = 6.45$, $p = .011$) and between-group (precentral: $B = .20$, $SE = .11$, Wald's $\chi^2 = 3.54$, $p = .060$; postcentral: $B = .20$, $SE = .09$, Wald's $\chi^2 = 4.52$, $p = .033$) effects on left postcentral gyrus were stronger.

In a model for understanding the relationship between LSMC-amygdala FC and mood, increased LSMC-amygdala FC was significantly related to decrease in mood symptoms (LSMC: $B = -.51$, $SE = .23$, Wald's $\chi^2 = 4.72$, $p = .030$; precentral: $B = -.47$, $SE = .24$, Wald's $\chi^2 = 3.75$, $p = .053$; postcentral: $B = -.44$, $SE = .20$, Wald's $\chi^2 = 4.89$, $p = .027$).

There was no within-intervention group effect of LSMC-vmPFC FC (Wald's χ^2 (Victoroff et al., 2018) < 1.33 , $p > .25$ for LSMC, precentral gyrus, and postcentral gyrus), therefore, we did not further pursue analyses on between-group effect or brain–mood relationships.

3.4. Changes of behaviors during one-month intervention period (Fig. 3)

There was no significant change of valence or arousal from immediately before to immediately after each 20-min session in either group. In the following analyses, we used valence/arousal measured before session only. There was an increase in positive valence ($B = .06$, $SE = .03$, Wald's $\chi^2 = 4.50$, $p = .034$), which differed by the type of MOT task (high vs. low demanding) ($B = -.50$, $SE = .19$, Wald's $\chi^2 = 6.89$, $p = .009$). Follow-up analyses suggested the increase in valence was evident in 2 target MOT task only ($B = .12$, $SE = .03$, Wald's $\chi^2 = 14.68$, $p < .001$), driven by an improvement in valence in the intervention group only ($B = .09$, $SE = .02$, Wald's $\chi^2 = 23.38$, $p < .001$). There were no effects related to arousal.

Using across timepoint data, improvement in valence was related to participant-reported reduction in mood symptoms ($B = -.31$, $SE = .13$, Wald's $\chi^2 = 5.70$, $p = .017$). A follow-up analysis in each group separately showed that higher valence was related to better mood in the intervention group only ($B = -.33$, $SE = .07$, Wald's $\chi^2 = 22.92$, $p < .001$).

4. Discussion

We found tentative evidence that anodal tDCS to LSMC in older adults with MCI during MOT improves emotion dysregulation and NPS. There were improvements in patient-reported mood following intervention in the intervention

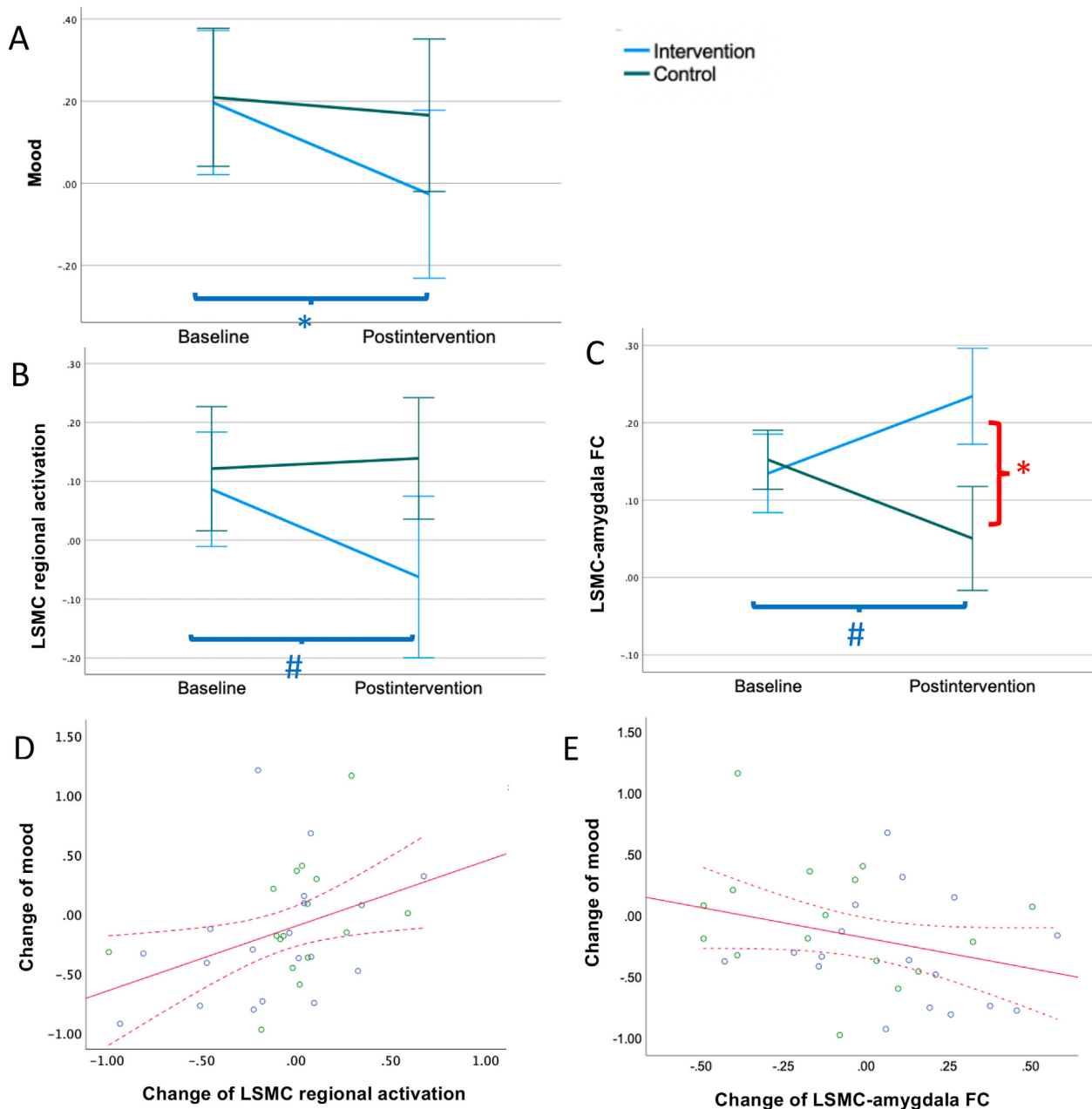


Fig. 2 – Intervention effect on NPS and LSMC related neural efficiency: (A) Intervention effect on mood symptoms; (B) intervention effect on LSMC regional activity; (C) intervention effect on LSMC-amygdala FC; (D) association between change of LSMC regional activity and change of mood symptoms from baseline to postintervention; (E) association between change of LSMC-amygdala FC and change of mood symptoms from baseline to postintervention; Plots were adjusted for baseline group difference; LSMC was calculated based on averaging AAL3 precentral and postcentral gyri. Red = between-group or across sample effect. Blue = intervention group or within-intervention group effect. Green = control group or within-control group effect. # = p-range .05–.1; * = p-range .01–.05.

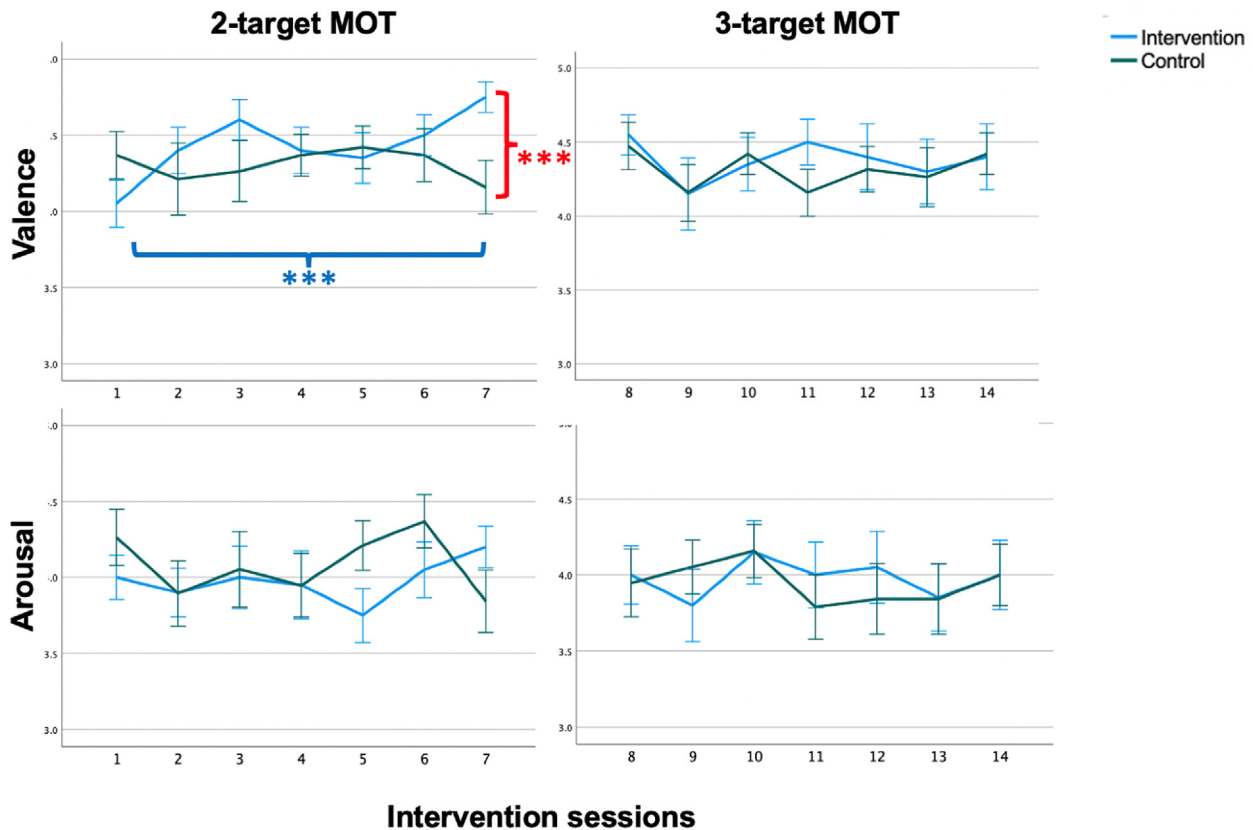


Fig. 3 – Valence (upper) and arousal (bottom) status during intervention period (left: 2-target MOT during the first 7 sessions; and right: 3-target MOT during the last 7 sessions). Red = between-group effect. Blue = intervention group or within-intervention group effect. Green: control group or within-control group effect. * = p-range < .001.**

group but not the control group, but there were no significant group-by-time interactions. Session-by-session increases in patient-reported valence were significantly associated with improvements in NPS in the intervention group. No effects were identified for caregiver-reported NPS. Importantly, we found that our tDCS training paradigm resulted in changes in LSMC activation and FC to the left amygdala; these changes were related to improvements in mood, identifying a potential neural mechanism for improving NPS in MCI. Results were stronger for the left postcentral gyrus than the left precentral gyrus. We suggest that larger scale trials should be performed to better understand the promise of this intervention for improving NPS in older adults with MCI/AD.

Anodal tDCS was found to decrease LSMC activity. While early studies suggested that anodal tDCS may be “excitatory” and cathodal tDCS “inhibitory”, recent research suggests this is an oversimplification (Bradley et al., 2022). Long term plasticity resulting from tDCS engages complex homeostatic mechanisms (Bradley et al., 2022). There is also inconsistency in the literature when interpreting decreased fMRI activity; some studies suggest it reflects increased efficiency (Lin et al., 2012; Pascual-Leone et al., 1994), others reduced engagement (Machulda et al., 2003). Therefore, we suggest caution in attempting to interpret the direction of this effect. Future studies are needed to better understand the physiological basis of tDCS-associated plasticity underlying this

mechanism. Increased LSMC-amygdala FC may reflect improved emotion regulation (Berboth & Morawetz, 2021; Toschi et al., 2017), and we found no effects for LSMC-vmPFC. vmPFC is important for higher-level emotion regulation, integrating sensory signals with schemas from previous knowledge to help determine subjective value and guide decision-making (Vaidya & Badre, 2020). The significance of LSMC-amygdala rather than LSMC-vmPFC FC in our study may suggest that the mechanisms by which tDCS plus MOT works to improve mood is via lower-level, bottom-up processes that are less likely to recruit prefrontal cortex (Casey et al., 2019). This non-prefrontal SMC-amygdala pathway may be particularly important in MCI/AD as prefrontal regions (including vmPFC) accumulate AD pathology relatively early in comparison to SMC (Braak et al., 1998, 2011).

There are several open questions from this research. First, we found evidence to suggest that the low demanding MOT task (2 targets) alongside tDCS was especially beneficial. Given our specific design (2 targets for 2 weeks followed by 3 targets for 2 weeks), it is difficult to disentangle this effect from time effects. States with low attentional demands may enhance plasticity to a greater extent than those with high attentional demands (Kamke et al., 2012), a potential mechanism for the benefits of 2 target MOT plus tDCS that should be investigated in future studies. We also found results for patient- but not caregiver-reported NPS. Patient-reported measures may be

more sensitive to subtle changes following short-term intervention. Alternatively, research has found that patient-reported depression symptoms were more strongly related to clinical outcomes than caregiver-reports (Votruba et al., 2015), and correspondence between participant- and caregiver-reports is particularly poor for internal aspects of patient experience (Moye et al., 1993) such as mood (Gómez-Gallego et al., 2012). Finally, there is a need to understand the regional specificity of our effects. Due to the relatively widespread effects of tDCS, it is likely that most subjects in our study experienced tDCS-dependent changes in both left precentral and postcentral gyri, and surrounding areas. While effects were stronger for left postcentral gyrus, it is unclear whether this is due to this region being more reliably targeted or for mechanistic reasons. Follow-up research that targets tDCS using individual-specific brain anatomy (using MRI or TMS) is needed. Studies using a different active control site (e.g., dorsolateral prefrontal cortex, stimulation of which can also improve emotional symptoms (Cash et al., 2021)) is also needed to understand whether stimulating these brain regions has differential effects on mood/NPS in MCI/AD, and whether these stimulation targets act via different or overlapping mechanisms.

Firstly, the use of sponge electrodes means that our stimulation may have been relatively diffuse, potentially reducing the effect of stimulation as well as the specificity of our findings. Specificity analysis using an adjacent IDLPFC region suggested that results on brain activity were stronger for our target C3 region (precentral gyrus and especially postcentral gyrus). However, future designs using more modern tDCS approaches with more focal stimulation will help to improve on this study. Secondly, although we collected adverse events immediately after each intervention session, we did not measure blinding efficacy directly as suggested in recent literature (Sheffield et al., 2022). Although the use of a double-blinded design with an active control sham group where participants had to engage with a task during tDCS may improve blinding efficacy, research suggests that blinding is still not always effective for tDCS studies using similar sham procedures (Sheffield et al., 2022). It is unclear how these findings generalize to individuals with MCI, however, future studies should actively measure and report blinding efficacy and find ways to further improve sham procedures.

5. Conclusions

In summary, tDCS during MOT training is safe and feasible among older adults with MCI. Our study failed to identify significant group by time interactions in favor of an effect of tDCS on either measure of NPS when compared to active control sham, however tDCS did improve patient-reported NPS in the intervention group specifically. Improvements were related to reduced LSMC-related activation during visual attention and strengthened LSMC-L-amygdala FC. Effects were stronger in left postcentral gyrus, and for tDCS applied during low-demand MOT. There were no improvements in caregiver-reported NPS. This work opens avenues for more precise mechanistic investigation.

Open practices

The study in this article earned Open Materials and Preregistered badges for transparent practices. Materials or the study are available at <https://github.com/adamgeorgeturnbull/BEEM> and <https://clinicaltrials.gov/ct2/show/NCT04099524>.

Credit author statement

Conceptualization: FVL; Methodology: FVL, MA; Software: AT; Formal analysis: AT, FVL; Investigation: FVL, MA; Resources: FVL, KH, DT; Data Curation: AT, MA, FVL; Writing – Original Draft: AT, FVL; Writing – Review & Editing: AT, MA, DT, APP, KH, FVL; Visualization: FVL; Supervision: FVL; Project administration: FVL, MA; Funding acquisition: FVL.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability statement

Data are available via the NIMH Data Archive (NDA), miNDAR package 1205214, Host: mindarvpc.cqahbwk3l1mb.us-east-1.rds.amazonaws.com. See: <https://nda.nih.gov/nda/access-data-info.html#cloud> for instructions on how to access data. Raw fMRI data are not available due to an institutional policy aimed at protecting vulnerable populations (in this case individuals with MCI and NPS). Researchers that want to access raw fMRI data will need to obtain institutional IRB and data user agreement approval.

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Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cortex.2022.10.015>.

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