Neurophysiological changes associated with combined transcranial direct current stimulation and cognitive emotional training for treatment-resistant depression

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ABSTRACT

Transcranial direct current stimulation (tDCS), a form of non-invasive brain stimulation, is a promising treatment for depression. Recent research suggests that tDCS efficacy can be augmented using concurrent cognitive emotional training (CET). However, the neurophysiological changes associated with this combined intervention remain to be elucidated. We therefore examined the effects of tDCS combined with CET using electroencephalography (EEG). A total of 20 participants with treatment resistant depression took part in the study and received 18 sessions over 6 weeks of tDCS and concurrent CET. Resting-state and task-related EEG during a 3-back working memory task were aquired at baseline and immediately following the treatment course. Results showed an improvement in mood and working memory accuracy, but not response time, following the intervention. We did not find significant effects of the intervention on resting-state power spectral density (frontal theta and alpha asymmetry), time-frequency power (alpha event-related desynchronization and theta event-related synchronisation), or event-related potentials (P3 component). There was weak evidence for an increase in P2 amplitude, suggesting an improvement to attentional processes, but this result did not survive correction for multiple comparisons. We therefore identified little evidence of neurophysiological changes associated with treatment using tDCS and concurrent CET, despite significant improvements in mood and near transfer effects of cognitive training to working memory accuracy. Further research incorporating a sham controlled group may be necessary to identify the neurophysiological effects of the intervention.

INTRODUCTION

Major depressive disorder (MDD) is a debilitating mental illness with a lifetime prevalence of 12-20% [1]. Transcranial direct current stimulation (tDCS), a mild, non-invasive method of brain stimulation, has shown promising therapeutic potential for the treatment of depression [2-5]; however, results from a recent large controlled trial suggested that such antidepressant effects of tDCS when given alone are modest [2], raising the need for research into improving tDCS clinical outcomes. Combining tDCS with concurrent cognitive training (e.g., cognitive emotional training, designed to activate brain regions associated with cognitive control and emotion processing) appears to be an effective method to further boost treatment efficacy [6]. However, the neural pathways by which this novel combined intervention improves mood remains unknown. An examination of the neurophysiological changes associated with this approach may shed light on its mechanisms of action and pave the way for further augmentation of the therapy.

tDCS for depression involves the delivery of an electrical current, typically between 1-2.5 mA, using a positively charged electrode placed on the scalp over the left dorsolateral prefrontal cortex (LDLPFC) and a negatively charged electrode on a contralateral frontal region [7]. Though research suggests that tDCS is an effective treatment in MDD in general [8], the results in treatment resistant depression appear less promising [9, 10]. Indeed, a meta-analysis of individual patient data found treatment resistance to be associated with reduced tDCS efficacy [5].

To improve therapeutic efficacy in people with treatment resistant depression, some trials have combined tDCS with cognitive training [11, 12]. It has been suggested that tDCS interacts with ongoing neuronal activity to boost synaptic plasticity within activated regions [13, 14]. The administration of behavioural tasks during tDCS may then be used to pre-activate relevant cortical regions and thus augment the neuromodulatory potential of tDCS by

69 improving the functional specificity of stimulation [15]. Cognitive emotional training (CET)
70 is a form of computerised cognitive training which was designed to activate cognition- and
71 emotion processing-circuits implicated in MDD to treat depressive symptoms [16, 17].
72 Specifically, it involves training using an emotional working memory paradigm which aims
73 to simultaneously activate brain regions in the cognitive control (i.e., prefrontal
74 cortex/DLPFC)) and affective networks (i.e., amygdala) to improve emotion regulation. A
75 recent pilot study by Martin [6] combined tDCS with concurrent CET, and reported a 41%
76 response rate in treatment resistant participants. The neurophysiological changes associated
77 with this intervention, however, remain to be elucidated. Determination of such changes may
78 provide insight into the mechanisms underlying the antidepressant response and inter-
79 individual predictors which can assist with the further development and targeting of
80 treatment.

81 Electroencephalography (EEG) allows for non-invasive assessment of brain activity and
82 has been used to gain further insights into the functional changes associated with
83 antidepressant response [18]. Electrophysiological markers acquired at rest can provide
84 valuable information regarding severity of depression symptomatology. For example, frontal
85 alpha asymmetry, in which higher alpha power is observed in the left compared to the right
86 prefrontal cortex [19-21], has been inversely correlated with depression scores [22]. Frontal
87 asymmetry in upper alpha has also been shown to correlate with increased blood oxygenation
88 level dependent (BOLD) activation in the amygdala during a task of emotion regulation [23].
89 Although recent research has questioned the diagnostic value of frontal alpha asymmetry as a
90 biomarker for depression [24], alpha asymmetry has been associated with response to
91 antidepressant medications, and may therefore have prognostic value [25]. In addition to
92 alpha band activity, resting-state frontal theta power may also provide a marker for
93 depression [18, 26]. Source localisation techniques have identified the generator of frontal

94 theta activity as the anterior cingulate cortex [27-29], a structure involved in emotion
95 processing [30, 31]. Several studies have reported elevated frontal theta as a positive
96 predictive factor for antidepressant response [32-36], although another study suggested that
97 mood changes are negatively correlated with frontal theta activity [37].

98 Due to its high temporal resolution, EEG has also been widely used to investigate task-
99 related responses to cognitive demands, such as those associated with working memory [38].
100 Task-related EEG measures, such as event-related potentials (ERPs) and time-frequency
101 power, have shown improved sensitivity to the neurophysiological effects of tDCS as
102 compared to behavioural outcomes on a working memory task [39]. ERPs reflect the activity
103 of a population of neurons time-locked to the onset of an event, such as the presentation of
104 stimuli [40]. Two ERP components, P2 and P3, have been found to be particularly sensitive
105 to the effects of tDCS during a task of working memory [41]. The P2 amplitude reflects
106 sustained attention and initiates context updating during working memory tasks [42-45], and
107 its amplitude has been observed to be positively correlated to working memory performance
108 [46]. The P3 component appears to reflect higher order executive processes within the
109 frontoparietal cortical network [47, 48], and has also been positively correlated with working
110 memory capacity and task performance [39, 49-51].

111 In addition to event-related potentials, time-frequency analysis can be used to investigate
112 task-related activity during a cognitive task. Frequency-specific increases in EEG amplitude
113 are referred to as event-related synchronisation (ERS); conversely, decreases in amplitude
114 lead to event-related desynchronization (ERD) [52]. ERS/ERD during working memory
115 cognitive processes have been mainly found in the theta and alpha band [53-56]. Alpha
116 desynchronisation is thought to reflect selective inhibition of irrelevant brain regions to
117 maintain functional engagement with regions necessary for task performance [57], and
118 becomes more pronounced with increasing cognitive load [58-61]. In healthy individuals,

anodal tDCS of the prefrontal cortex has been shown to improve working memory performance and increase event-related alpha and theta power [62]. Theta ERS may reflect a gating mechanism, integrating and coordinating activity between multiple brain structures to control working memory processes [63]. Specifically, frontal theta ERS during working memory has been linked to allocation of attention to task-relevant stimuli [53]. Like alpha ERD, theta ERS becomes more pronounced with increasing cognitive load [58-61], and frontal theta activity has been found to be reduced during memory retrieval in depressed participants [64].

We sought to examine the neurophysiological effects of tDCS combined with concurrent CET for participants with treatment resistant depression. EEG was acquired while participants were at rest, and during a working memory task, at baseline and at the end of the treatment course. We hypothesised that tDCS combined with CET would restore cognitive control network functioning, observable as an improvement in working memory performance and a reduction in frontal alpha asymmetry and frontal theta recorded during resting-state EEG. Additionally, we hypothesised that the intervention would increase the amplitude of event-related EEG components P2 and P3. Finally, we anticipated a reduction in alpha ERD and theta ERS during the working memory task, indicative of improved cognitive processing efficiency.

MATERIAL AND METHODS

Participants

We recruited twenty participants with treatment resistant depression. All participants were screened by a study psychiatrist and met DSM-IV criteria for a major depressive episode [65]. Additional inclusion criteria included: a score on the Montgomery-Asperg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) ≥ 20, treatment

resistance as defined by failure to respond to at least two adequate courses of antidepressant medications, and aged between 18 and 65 years old. Participants were excluded from the study if they had a neurological illness, were diagnosed with a psychotic disorder, had alcohol or illicit substance abuse, failed to respond to a course of electroconvulsive therapy in the current episode, were a high suicide risk, or regularly used benzodiazepines. Participants were not permitted to change medications or their dosages in the four weeks preceding the study and for the duration of the combined tDCS and CET intervention. Written informed consent was provided by all participants, and the study was approved by the UNSW Human Research Ethics Committee .

Procedure

Participants received a course of 18 sessions of tDCS combined with CET, delivered three times per week for six weeks. Neurophysiological outcomes were assessed pre-treatment (BASELINE) and at the completion of 18 sessions of the intervention (POST) in a within-subjects open label study design. EEG was recorded during 5 min of eyes closed resting-state activity, followed by 5 min of eyes open resting-state activity, and finally 7 min of task-related activity during a visual 3-back working memory task (Fig. 1A). During the eyes closed condition, participants were asked to close their eyes until the experimenter informed them that the EEG recording was complete. For the eyes open condition, participants were asked to focus their gaze on a fixation cross displayed on a computer screen.

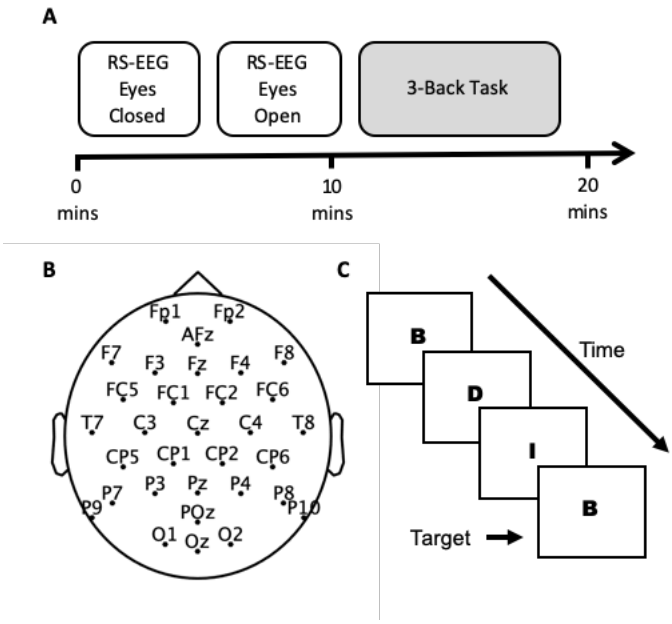


Figure 1. Experiment Details. A) Illustration of the EEG protocol and timeline. Participants completed EEG testing at baseline, and following 18 sessions of tDCS combined with CET; **B)** The EEG layout for 32 water-based electrode recording channels; **C)** For the 3-back task, participants were asked to respond when the letter currently on the screen matched the letter presented three trials previously. RS-EEG: resting-state EEG.

Transcranial direct current stimulation

An Eldith-DC Stimulator (NeuroConn GmbH, Germany) was used to deliver a 2 mA current for 40 minutes each session. Anodal tDCS was applied using a 5 × 7 cm (35 cm^2) rubber electrode placed on the scalp directly over the left DLPFC (F3 using the 10-20 EEG system). An extracephalic 10 × 10 cm (100 cm^2) return cathode was placed on the participant's right shoulder. This montage increases the activation of limbic regions, such as the anterior cingulate cortex, as compared to bifrontal tDCS electrode placements commonly used for depression [67]. Sponges soaked in saline were used improve conductivity between the electrodes and skin, and thereby minimise the risk of skin lesions [68].

Cognitive emotional training

The Emotional Faces Memory Task (EFMT) was used to provide CET, and is described in greater detail in Iacoviello et al. [17]. In EFMT, participants observe a series of faces depicting various emotions (sadness, happiness, surprise and disgust) on a computer screen and respond (yes/no) whether the emotion observed matched the emotion presented several (a set value, "n") trials previously, thus combining emotion processing and n-back working memory components. The task difficulty was adjusted according to participant performance by increasing or decreasing the number of emotional faces participants had to maintain in memory (n); task difficulty also progresses throughout an EFMT session as the emotional intensity observed on the faces decreases.

Electroencephalography data acquisition

Continuous EEG data was acquired using 32 water-based EEG recording channels and a TMSi Refa amplifier (TMS International, Oldenzaal, Netherlands). EEG processing and analysis was conducted using custom-developed MATLAB scripts (v.R2019a; MathWorks) and the Fieldtrip toolbox [69]. All scripts used for EEG processing and calculation of neurophysiological measures are available at the following link (https://github.com/snikolin/tDCSandCET).

EEG data were sampled at 1024Hz, and filtered using a bandpass filter (0.5–70 Hz) and a notch filter at 50 Hz to remove electrical line noise. Data were epoched in 2-second intervals and inspected using a semi-automated algorithm to remove epochs containing artefacts. Independent components analysis (ICA) was then used to remove eye blink and muscle artefacts. Following ICA, EEG data were re-referenced to the common average reference.

Behavioural measures

Mood was assessed using the MADRS, a validated clinician-rated scale of depression symptom severity (Montgomery and Asberg, 1979). The visual 3-back task, adapted from Mull and Seyal [70], was administered using Inquisit 4 software (Version 4, Millisecond

205 Software) to assess working memory. Participants were asked to observe a sequence of letter
206 stimuli presented on a computer screen in random order and respond (by pressing the
207 spacebar on a keyboard) when the target letter currently on the screen matched the letter
208 presented three trials previously. The 3-back task is therefore similar to the Emotional Faces
209 Memory Training task used for CET, but does not require processing of emotional content.
210 The 3-back task consisted of 40 target letters interspersed with 180 non-targets, with a 2-
211 second interval between successive letters. Prior to the start of each experiment, participants
212 practiced the task for approximately 5 minutes to ensure they understood task instructions.
213 The 3-back task was selected because it is considered challenging, requiring greater
214 attentional and executive resources, and so reduces the likelihood of ceiling effects for
215 participants that improved cognitively over the 6-week intervention. The primary working
216 memory outcome measures were response time (RT) for correct responses, and d-prime, a
217 measure of discriminate sensitivity [71].

218 Neurophysiological measures

219 *Resting-state power spectral density*

220 Power spectra were calculated for resting-state EEG under eyes open and eyes closed
221 conditions. Data from the first 15 seconds were discarded to ensure participants were
222 completely at rest in the time window being analysed and power spectral densities (PSD)
223 were estimated using 285 seconds of data. Log-normalised power spectral density values
224 ($\mu V^2/Hz$) were estimated for each EEG electrode over a range of 1 – 70Hz using the fast
225 Fourier transform with 2-second sliding Hamming windows with 50% overlap, as initially
226 described by Welch [72].

227 Frontal alpha asymmetry was obtained under the eyes closed resting-state EEG condition
228 [24]. To calculate this index, power in the alpha frequency band (8-13 Hz) was obtained at

EEG channels F3 and F4. We then divided the difference in alpha power between channels by the sum of alpha power between channels: (F4 − F3)/(F4 + F3).

Frontal theta was calculated as the average of power in the theta frequency band (4-8 Hz) at anterior EEG channels Fp1, Fp2, Afz, F3, Fz, and F4 under the eyes closed resting-state EEG condition.

Event-related potentials

Event related potentials (ERPs) were calculated by averaging across target and non-target trials from the 3-back task. Post-stimulus activity was baseline-corrected using the mean amplitude from 500 ms to 0 ms prior to stimulus onset. Average amplitudes for ERP components P2 and P3 were measured from frontal EEG channel Fz. The time-window for averaging was determined by computing the grand average ERP component across BASELINE and POST periods for all participants and isolating the mean latency for the P2 and P3 components. The average amplitude was then calculated for each participant in a time-window ±20 ms around the grand average latencies for P2 and P3 components from the previous step. The latency of the P2 component was identified as 145.5 ms post-stimulus (time window for averaging: 125.5 – 165.5 ms), and the latency for the P3 component was 373.0 ms (time window for averaging: 353.0 – 393.0 ms) following stimulus onset.

Time-frequency analysis

Similar to ERP measures, time-frequency power was calculated by averaging across target and non-target trials from the 3-back task. We used a Hanning taper with a fixed 500 ms time window. Power values were baseline-corrected using activity from 500 ms to 0 ms prior to stimulus onset and transformed into a decibel scale (10*log10 of the signal). Alpha event-related desynchronization (ERD) was operationalised as band power 200 – 700 ms from stimulus onset in the alpha frequency band (8 – 12Hz). Theta event-related

253 synchronisation (ERS) was defined as band power 0 – 500 ms from stimulus onset in the
254 theta frequency band (4 – 8 Hz).

255 Statistical analysis

256 Statistical analyses were performed using R statistical software version 3.5.1 [73] and the
257 Fieldtrip MATLAB toolbox [69]. Scripts used for statistical analysis are available at the
258 following link (https://github.com/snikolin/tDCSandCET). Two-tailed paired samples t-tests
259 were performed for mood, working memory, and EEG neurophysiological outcomes to
260 evaluate changes from BASELINE to POST. We applied a Bonferroni correction to
261 neurophysiological outcomes to reduce the false-positive (Type 1) error associated with
262 multiple comparisons. As such, the threshold for statistical significance for EEG measures
263 was set at $p = 0.008$ (i.e. 0.05/6).

264 *Equivalence tests*

265 A within-subjects study design of n = 20 allows for the detection of moderate-large effect
266 sizes of Cohen's $d \geq 0.65$ using $\alpha = 0.05$ and 80% statistical power. Therefore, lack of
267 statistical significance on a paired-samples t-test may be indicative of no effect or of
268 insufficient power to detect effects sizes smaller than this threshold. To statistically reject the
269 possibility of non-trivial effect sizes, we performed two one-sided t-test (TOST) equivalence
270 procedures using Cohen's $d = 0.3$ as the smallest effect size of interest. Thus, a significant
271 equivalence test result would suggest an effect size of $d < 0.3$. This procedure was performed
272 using the R package, TOSTER, and the *TOSTpaired* function [74].

273 *Non-parametric cluster-based permutation tests*

274 In additional to the previous analyses for single electrodes (or averages of a small number
275 of electrodes), we also conducted exploratory non-parametric cluster-based permutation
276 analyses on the entire EEG dataset for measures extracted using power spectral density, event

277 related potential, and time-frequency analyses. This method controls for multiple
278 comparisons while assessing global changes from BASELINE to POST across all EEG
279 channels, frequency ranges, and post-stimulus time points for event-related measures (i.e.
280 ERPs and ERS/ERD); changes that were not otherwise hypothesised *a priori* [75].

281 The Monte-Carlo method was used, whereby trials were randomly permuted in 3000
282 iterations and the resulting distributions were statistically compared using dependent samples
283 *t*-tests. A two-tailed significance threshold of $\alpha < 0.05$ was adopted as the cluster threshold
284 and significance threshold for all analyses. Cluster-based permutation tests commonly require
285 clusters of at least two neighbouring channels; however, due to the limited number of EEG
286 channels in the current experiment, we opted for a less conservative threshold of at least one
287 neighbouring channel.

288 For ERPs and ERS/ERD, the non-parametric cluster-based permutation tests were
289 performed on a time interval of interest 0 – 1000 ms from the onset of 3-back task letter
290 stimuli. For neurophysiological outcomes with frequency information, including resting-state
291 PSDs and ERS/ERD, permutation testing was conducted in the frequency band of 1 – 70Hz.

292 RESULTS

293 A total of twenty participants with treatment resistant depression completed 18 sessions
294 of tDCS combined with CET. Table 1 shows baseline demographic and clinical information
295 for the sample. Correlations between behavioural and neurophysiological measures are also
296 provided in Supplementary Materials (see Supplementary Tables 1 and 2).

297 **Table 1. Baseline demographic and clinical information.**

Variable	Mean (SD)
Sample (n)	20
Age (years)	45.1 (12.2)
Years of education	13.8 (2.17)
Age at onset (years)	23.2 (10.2)
Gender, females (n)	12
Concurrent antidepressants (yes)	15
SSRI or SSNRI	1
Number of antidepressant courses failed during the current episode	2.15 (1.81)
Number of lifetime antidepressant courses failed	4.65 (2.11)
Duration of current episode (months)	44.5 (68.7)
Duration of previous episodes (months)	54.2 (71.0)
Maudsley Treatment Resistance	6.85 (2.41)
Baseline MADRS	30.0 (5.15)

298 SSRI: selective serotonin reuptake inhibitor; SSNRI: selective serotonin-norepinephrine reuptake inhibitor; Maudsley
299 Treatment Resistance: Total score on the Maudsley Staging Method [76]; MADRS: Montgomery-Asperg Depression Rating
300 Scale [66].

301 Behavioural outcomes

302 A summary of statistical outcomes for behavioural measures is provided in Table 2. tDCS
303 combined with CET was found to significantly reduce symptoms of depression ($p < 0.001$).
304 Participants significantly improved on working memory d-prime ($p = 0.03$), but not response
305 time ($p = 0.45$).

306 **Table 2. Summary of statistical outcomes for behavioural and neurophysiological measures.** Baseline and post-intervention summary

307 measures are shown for mood, working memory, and EEG outcomes. Paired samples *t*-tests were used to examine changes from baseline to post.

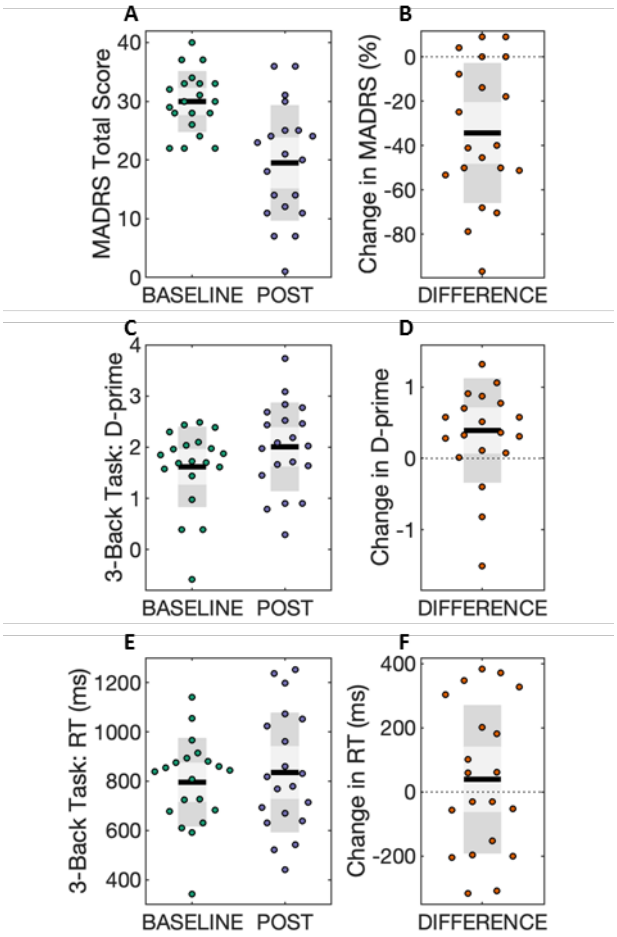
308 Equivalence tests were used to determine whether effects were significantly lower than the smallest effect size of interest i.e. an effect size of

309 Cohen's $d = 0.3$.

	Baseline		Post		Post – Baseline		Paired Samples T-Test			Equivalence Test	
Test	**Mean (SD)**		**Mean (SD)**		**Mean (95% CI)**		t_{19}	***p***	**Cohen's *d***	t_{19}	***p***
Mood Outcome											
MADRS	30.0	5.0	19.5	9.5	-10.5	-5.7 – -15.2	-4.61	<0.001	1.03	3.27	0.998
Working Memory											
D-prime	1.62	0.76	2.01	0.84	0.39	0.05 – 0.73	2.40	0.027	0.54	-1.06	0.848
RT (ms)	796	174	835	235	40	-68 – 148	0.77	0.452	0.17	0.57	0.287
Power Spectral Density											
Frontal Alpha Asymmetry	0.09	0.31	0.04	0.25	-0.05	-0.24 – 0.14	-0.55	0.591	0.12	-0.80	0.218
Frontal Theta	-0.18	1.00	-0.09	1.17	0.09	-0.44 – 0.62	0.35	0.729	0.08	0.99	0.167
Event-Related Potentials											
P2	1.64	1.27	2.06	1.46	0.42	-0.004 – 0.85	2.07	0.052	0.46	-0.73	0.763
P3	1.01	1.65	1.04	1.27	0.03	-0.41 – 0.47	0.31	0.888	0.03	1.20	0.123
Time-Frequency Representations											
Alpha ERD	-1.24	1.43	-1.35	1.31	-0.11	-0.51 – 0.29	-0.57	0.575	0.13	-0.77	0.225
Theta ERS	0.46	0.69	0.51	0.83	0.05	-0.18 – 0.29	0.47	0.641	0.11	0.87	0.198

310 MADRS: Montgomery-Asperg Depression Rating Scale [66]; ERD: Event-related desynchronization; ERS: Event-related synchronisation.

311



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313 **Figure 2. Behavioural outcomes.** Scatter plots for mood and working memory

314 performance scores are displayed at BASELINE and POST time points, in addition to change

315 scores (DIFFERENCE). Black lines show the mean, light grey shaded boxes indicate the

316 standard deviation, and dark grey regions indicate the 95% confidence interval. **A)** Total

317 MADRS scores; **B)** MADRS difference scores, calculated as the percentage change in

318 MADRS using the equation (POST – BASELINE)/BASELINE; **C)** 3-back task d-prime

319 scores; **D)** D-prime difference scores, calculated as POST – BASELINE; **E)** 3-back task

320 response time (RT) scores; **F)** RT difference scores, calculated as POST – BASELINE.

321

322 Neurophysiological outcomes

A summary of statistical outcomes for neurophysiological measures is provided in Table 2.

Resting-state power spectral density

There were no significant effects for frontal alpha asymmetry ($p = 0.59$) or frontal theta ($p = 0.73$) change from BASELINE to POST time periods. Equivalence testing for both measures was not significant, thus an effect size greater than $d = 0.3$ cannot be statistically rejected. Exploratory cluster-based permutation testing did not reveal any significant spectral power changes for any frequency band for eyes-closed or eyes-open resting-state EEG conditions (Fig. 3).

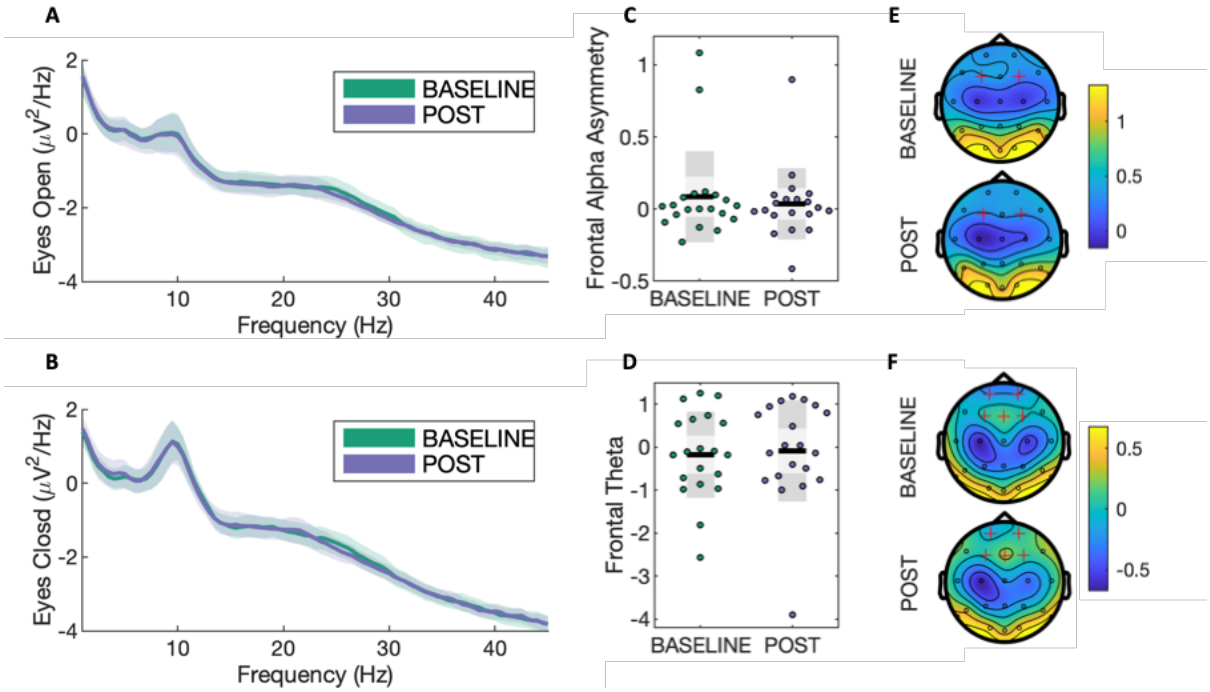

Figure 3. Resting-state power spectral density. **A)** Power spectra for eyes open resting-state EEG with bootstrapped 95% confidence intervals at channel Cz; **B)** Power spectra for eyes closed resting-state EEG with bootstrapped 95% confidence intervals at channel Cz; **C)** Frontal alpha asymmetry scatterplot during eyes-closed resting-state EEG, calculated as [F4 − F3]/[F4 + F3]. Black lines show the mean, light grey shaded boxes indicate the standard

deviation, and dark grey regions indicate the 95% confidence interval; **D)** Frontal theta during eyes-closed resting state; **E)** Topography for alpha (8-13Hz) power. Highlighted channels (F3 and F4) were used to calculate the frontal alpha asymmetry measure; **F)** Topography for theta (4-8Hz) power. Highlighted channels were averaged to calculate the frontal theta index.

Event-related potentials

There was no significant effect for the P3 ERP component ($p = 0.89$). There was a moderate increase in P2 amplitude ($p = 0.05$), however, this did not survive correction for multiple comparisons using the Bonferroni adjusted p-value threshold (i.e. $p < 0.008$). Equivalence testing for P2 and P3 components was not significant. No significant clusters were observed comparing ERP measures at BASELINE to POST (see Fig. 4).

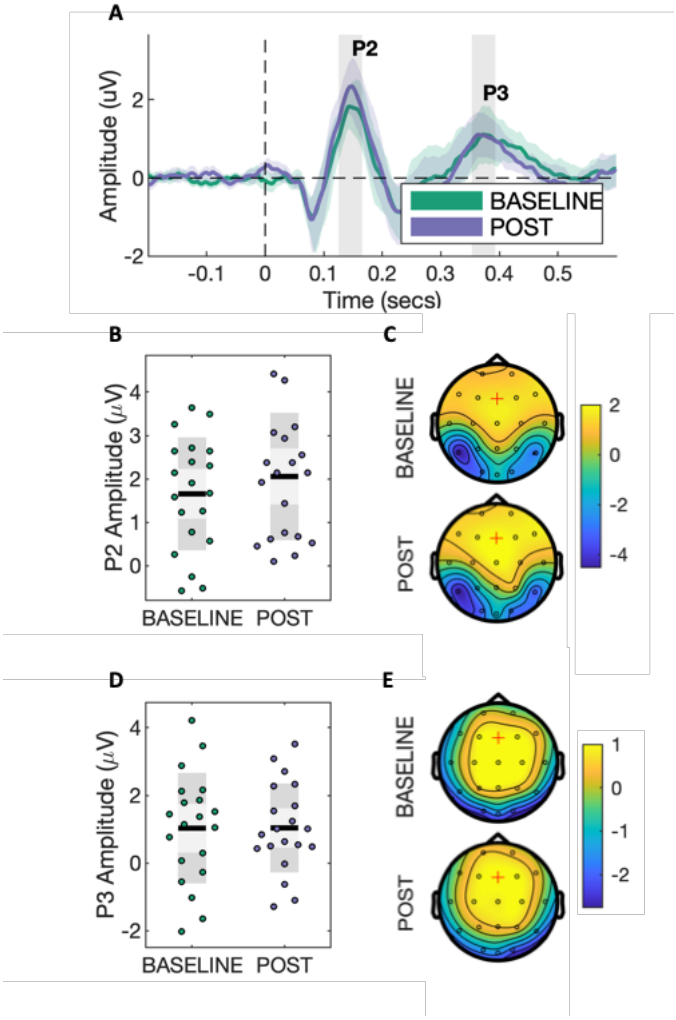

Figure 4. Event-related potentials during the 3-back task. **A)** ERPs with bootstrapped 95% confidence intervals at channel Fz; **B)** P2 component scatterplot. Black lines show the mean, light grey shaded boxes indicate the standard deviation, and dark grey regions indicate the 95% confidence interval; **C)** Topography for the P2 component (145.5 ms ± 20 ms); **D)** P3 component scatterplot; **E)** Topography for the P3 component (373 ms ± 20 ms).

Time-frequency analysis

There were no significant effects for alpha ERD ($p = 0.58$) or theta ERS ($p = 0.64$). Likewise, equivalence testing was not significant for both measures. No significant clusters were observed at any frequency bands, channels, or time points.

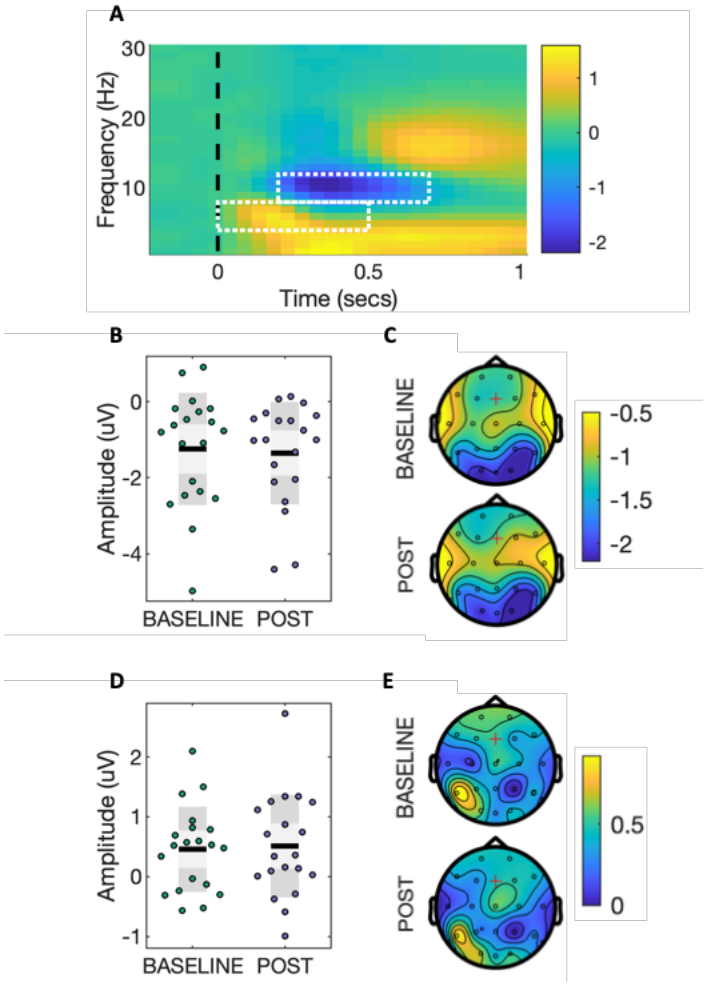

Figure 5. Time-frequency power during the 3-back task. **A)** EEG power at channel Fz. White boxes indicate regions of interest for alpha ERD and theta ERS; **B)** Alpha ERD scatterplot. Black lines show the mean, light grey shaded boxes indicate the standard deviation, and dark grey regions indicate the 95% confidence interval; **C)** Topography for alpha ERD; **D)** Theta ERS scatterplot; **E)** Topography for theta ERS.

DISCUSSION

This study investigated the neurophysiological effects of tDCS combined with CET in participants with treatment resistant depression. Following the intervention, participants improved in mood as well as working memory performance accuracy, but not response time,

374 on a visual 3-back task. Contrary to our hypotheses, for EEG outcomes, there was no
375 evidence of differences in resting-state measures (frontal alpha asymmetry and frontal theta),
376 or in task-related measures (alpha ERD, theta ERS, and the P3 ERP component). We found
377 weak evidence to suggest that P2 amplitude, a marker of attentional processes, increased, but
378 this result did not survive correction for multiple comparisons.

379 Combining tDCS with CET appears to be a promising augmentation strategy to improve
380 therapeutic efficacy in treatment resistant depression. Accompanying the observed
381 improvement in mood, there was a near transfer effect from CET to improved discriminate
382 sensitivity (i.e. d-prime) on the 3-back working memory task. In a similar study combining
383 five repeated sessions of tDCS with cognitive control training, Segrave [11] also noted
384 improved accuracy on an affective 2-back task. Our findings are in line with near transfer
385 effects following working memory training for improving cognition [77, 78]. A meta-analysis
386 by Schwaighofer [79] suggests that the near transfer effect of working memory training has
387 an effect size ranging between Hedge's g = 0.37-0.72, which encompasses the effect size for
388 d-prime observed in the present study (Cohen's d = 0.54). In the absence of a control
389 condition, however, it is difficult to determine whether working memory improvements
390 observed in the current study are due to the intervention (i.e. near transfer effects from CET),
391 or may be associated with mood improvement.

392 Although there were no significant changes in neurophysiological measures after
393 controlling for multiple comparisons, we found weak evidence that the intervention increased
394 the P2 ERP amplitude. The P2 component has been linked to attentional processes [42-45,
395 80]), whereas P3 is associated with higher-order cognitive functions such as target
396 identification and categorisation [81-83]. McEvoy [84] systematically investigated the impact
397 of working memory load and practice effects, and similarly observed changes in P2, but not
398 P3, amplitude. Our results therefore suggest that CET, which involves a working memory

component, may improve lower order processing and attentional capacity, observed as an increase in P2 amplitude, although the statistical evidence was only weak. In line with this interpretation, similar findings were obtained following 3 weeks of treatment for depression using transcranial magnetic stimulation, another form of non-invasive brain stimulation, which increased P2 ERP amplitudes during an oddball task [85]. Likewise, Spronk [86] observed a left lateralised increase in frontal P2 amplitude in depressed patients during an auditory oddball task following 20 treatment sessions of transcranial magnetic stimulation, providing additional support for improvements in sensory-attentional processes but not higher-order cognitive functions.

Resting-state EEG measures commonly associated with depression, such as frontal alpha asymmetry and frontal theta power, were not significantly altered by the treatment despite meaningful improvements in mood. These measures were hypothesised *a priori* to change with treatment because they had been linked to antidepressant response [25, 32, 34]. Recently, there have been some criticisms of the viability of alpha asymmetry as a relevant factor for depression [24]. Debener [21] challenge the notion that alpha asymmetry is a trait marker for depression, and report that increased variability, rather than increased alpha lateralisation, may be a more relevant measure. Similarly, frontal theta PSD may be better interpreted as a trait measure, reflecting structural or function abnormalities that contribute to the risk of developing depression, rather than a biomarker of the state of being depressed. Indeed, Hunter [87] found theta generated in the rostral anterior cingulate cortex to be a trait predictor of depression that does not change with treatment. Interestingly, supplementary analyses of change scores from the current study show correlations between frontal alpha asymmetry (p=0.012) and frontal theta (p=0.025), and mood scores (see Supplementary Table 2). However, these must be interpreted with caution as correlations using small samples have a low probability of replication and can result in exaggerated effects through

424 chance alone. Monte-Carlo simulations show that correlations converge, that is, produce
425 stable estimates close to the true effect, only as sample sizes approach n=250 [88].
426 Our lack of positive neurophysiological findings is generally consistent with the tDCS
427 literature for protocols using repeated sessions of stimulation. To the best of our knowledge,
428 only three studies have identified functional or structural changes associated with repeated
429 sessions of anodal tDCS to the LDLPFC. Previous work by our group found an increase in
430 neuroplasticity, quantified by probing motor cortex reactivity using transcranial magnetic
431 stimulation, following prefrontal tDCS treatment for depression [89]. In another clinical
432 application, Ulam [90] examined the neurorehabilitatory effects of 10 consecutive sessions of
433 LDLPFC tDCS for traumatic brain injury. They did not observe any significant effects from
434 baseline to the final session of stimulation on EEG measures, including an analysis of frontal
435 (F3) theta power, but did note a significant interaction effect compared to sham tDCS for
436 delta and alpha frequency bands. Mondino [91] delivered 10 sessions of anodal stimulation
437 over the LDLPFC, with cathodal stimulation over the temporo-parietal junction, for the
438 treatment of auditory verbal hallucinations in schizophrenia and showed increased resting-
439 state functional connectivity in the active tDCS group compared to sham. The present study
440 did not include a sham control group, and thus we were unable to examine interaction effects,
441 which may have revealed similar neurophysiological changes.
442 There may be several reasons why we did not observe significant neurophysiological
443 changes in the present study. Firstly, the modest sample size only allowed for detection of
444 moderate-large effects. The estimated effect sizes for the EEG measures were small (d = 0.03
445 – 0.13), with the exception of P2 amplitude (d = 0.46). Although the majority of these effects
446 were less than the smallest effect size of interest (d = 0.3), equivalence testing was non-
447 significant for all neurophysiological outcomes. This suggests that there was sufficient
448 variability in participant outcomes that the true effect could not be identified as less than our

threshold criteria for equivalence testing. Thus, we are also unable to rule out the possibility of effect sizes greater than Cohen's $d = 0.3$. Larger sample sizes are therefore required to overcome issues of heterogeneity, and associated variability, inherent in depressed samples, and to thereby improve the ability to draw conclusions from statistical testing.

Another potential reason for our null findings could be that the neurophysiological measures selected for hypothesis testing were suboptimal to detect treatment effects. To counteract this limitation, we examined resting-state PSD, as well as ERP and ERS/ERD during the 3-back task, using exploratory cluster-based non-parametric permutation tests to account for the possibility that an effect may lie beyond our *a priori* hypotheses, and found no significant clusters. Nevertheless, more sophisticated analyses, such as theta-gamma phase-amplitude coupling [92, 93], or dynamic causal modelling to determine changes in effective connectivity between brain regions [94-96], may reveal the effects of the intervention. For example, theta connectivity localised to the anterior cingulate cortex has been identified as a predictor of antidepressant response to treatment courses using transcranial magnetic stimulation [26, 97], and sertraline [98].

Lastly, depression has been linked to abnormal activity in the subgenual anterior cingulate cortex, an area of the limbic system associated with emotional information processing [33, 35, 99, 100]. The Emotional Faces Memory Training task used for CET in the current study was designed to concurrently activate the cognitive control network and increase brain activity in these deeper, limbic regions. Therefore, the effects of the intervention may be more readily observed within these subcortical structures. However, identification of changes at this depth may lie beyond the reach of the EEG setup used in this experiment. Though other EEG studies have successfully localised dysfunctional brain activity to sources within the anterior cingulate [101], this is typically achieved using EEG systems with a larger number of recording channels to better estimate source activity. It is

also possible that greater effects would have been observed using task-related electrophysiological measures during an emotional processing task similar to the CET, such as passive viewing of emotionally salient images [102]. Stewart [103] found that alpha asymmetry was a better predictor when measured during an emotional task rather than during resting-state EEG. Unfortunately, this data was not collected, but may be a valuable addition to future studies seeking to examine similar interventions in depression.

CONCLUSION

Combining tDCS with CET is a promising augmentation strategy for treatment resistant depression. Although behavioural measures identified improvements in mood and working memory accuracy, the neurophysiological mechanisms underlying these improvements remain elusive. EEG analyses of resting-state (i.e. PSD) and task-related activity (i.e. ERPs and ERS/ERD) did not reveal substantial changes from baseline to post-treatment. There is, however, tentative evidence of an increase in P2 amplitude, suggesting that tDCS and CET may improve attention modulation and context updating in depressed participants. These findings do not rule out the possibility that more sophisticated EEG analyses, such as phase-amplitude coupling or functional/effective connectivity, may uncover significant effects and better explain observed antidepressant and working memory changes. Further research is needed using a sham control condition and a larger sample of participants to better quantify the mechanisms of action for this promising new intervention.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Correlations between behavioural and neurophysiological measures. Repeated measures correlations were calculated using the *rmcorr* package on R software. The table displays the Pearson product-moment correlation coefficient (*r*), as well as *p*-values obtained from statistical testing.

	MADRS	RRS	D-prime	RT
Power Spectral Density (PSD)				
Frontal Alpha Symmetry	0.48	-0.17	-0.11	0.04
	(*p*=0.029)	(*p*=0.468)	(*p*=0.622)	(*p*=0.856)
Frontal Theta	-0.38	0.08	0.28	-0.30
	(*p*=0.087)	(*p*=0.729)	(*p*=0.213)	(*p*=0.186)
Event-related potentials (ERPs)				
P2	-0.42	-0.18	0.38	0.10
	(*p*=0.060)	(*p*=0.446)	(*p*=0.090)	(*p*=0.675)
P3	0.17	0.21	0.02	0.25
	(*p*=0.469)	(*p*=0.354)	(*p*=0.939)	(*p*=0.266)
Time-frequency power				
Alpha ERD	0.00	0.10	0.18	-0.18
	(*p*=0.993)	(*p*=0.671)	(*p*=0.440)	(*p*=0.445)
Theta ERS	0.09	0.03	0.17	-0.14
	(*p*=0.669)	(*p*=0.891)	(*p*=0.452)	(*p*=0.553)

MADRS: Montgomery-Asperg Depression Rating Scale (Montgomery and Asberg, 1979); RRS: Ruminative Response Scale; RT: response time; ERD: event-related desynchronization; ERS: event-related synchronisation.

505 **Supplementary Table 2. Correlations between behavioural and neurophysiological**

506 **change scores.** Change scores were calculated from BASELINE to POST (i.e. following the

507 final session of tDCS combined with CET) time points for all outcomes. The table displays

508 the Pearson product-moment correlation coefficient (*r*), as well as *p*-values obtained from

509 statistical testing.

	ΔMADRS	**ΔRRS**	**ΔD-prime**	**ΔRT**
Power Spectral Density (PSD)				
ΔFrontal Alpha Asymmetry	-0.55	0.43	-0.09	-0.21
	(*p*=0.012)	(*p*=0.056)	(*p*=0.715)	(*p*=0.368)
ΔFrontal Theta	0.50	-0.25	-0.10	0.47
	(*p*=0.025)	(*p*=0.297)	(*p*=0.666)	(*p*=0.039)
Event-related potentials (ERPs)				
ΔP2	0.14	-0.09	0.25	0.02
	(*p*=0.568)	(*p*=0.718)	(*p*=0.284)	(*p*=0.929)
ΔP3	-0.32	-0.30	0.23	-0.21
	(*p*=0.172)	(*p*=0.191)	(*p*=0.339)	(*p*=0.376)
Time-frequency power				
ΔAlpha ERD	0.16	0.10	-0.17	0.17
	(*p*=0.501)	(*p*=0.675)	(*p*=0.469)	(*p*=0.465)
ΔTheta ERS	-0.25	-0.07	0.01	0.11
	(*p*=0.296)	(*p*=0.770)	(*p*=0.959)	(*p*=0.656)

510 MADRS: Montgomery-Asperg Depression Rating Scale (Montgomery and Asberg, 1979); RRS: Ruminative Response

511 Scale; RT: response time; ERD: event-related desynchronization; ERS: event-related synchronisation.

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