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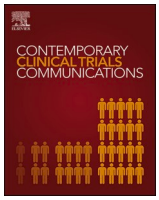

A pilot randomized clinical trial of tDCS for increasing exercise engagement in individuals with elevated depressive symptoms: Rationale, design, and baseline characteristics

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A B S T R A C T

Regular exercise protects against overweight/obesity as well as numerous chronic diseases. Yet, less than half of Americans exercise sufficiently. Elevated levels of depressive symptoms have been identified as an important correlate of physical inactivity as well as poor adherence to exercise programs. Individuals with depression are less sensitive to rewards and demonstrate an attentional bias toward negative stimuli. These, and other features of depression, may place them at increased risk for effectively managing the affective experience of exercise. Lower baseline levels of activation of the left (vs right) frontal cortex, an area implicated in affect regulation, have also been found in depression, potentially pointing to this region as a potential target for intervening on affect regulation during exercise. Transcranial direct current stimulation (tDCS) has shown promise in impacting a variety of cognitive and affective processes in a large number of individuals, including people with depression. Some findings have suggested that tDCS targeting the left dorsolateral prefrontal cortex (DLPFC), specifically, may improve emotion regulation. Transcranial direct current stimulation could theoretically be a novel and potentially promising approach to improving the affective experience of exercise, thereby increasing exercise adherence among individuals with depressive symptoms. Here we present the rationale, design, and baseline characteristics of a pilot randomized controlled trial of tDCS versus sham delivered 3x/week for 8 weeks in the context of supervised aerobic exercise (AE) program among 51 low-active individuals with elevated depressive symptoms (86.3% female; mean age = 49.5). Follow-up assessments were conducted at end of treatment, and three and six months after enrollment to examine changes in levels of objectively-measured moderate-to-vigorous physical activity (MVPA). If effective, this approach could have high public health impact on preventing obesity and chronic diseases among these at-risk individuals.

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1. Introduction

1.1. Physical inactivity is a significant public health problem

Regular exercise is associated with a longer, healthier life and protects against many health conditions including cardiovascular disease, certain cancers, type 2 diabetes, metabolic syndrome, bone loss, and overweight/obesity [1]. The estimated financial burden of physical *in*activity– due to direct medical care, workers' compensation, and productivity loss– is >$93 billion per year in the U.S [2]. Despite the risks associated with inactivity and numerous benefits of regular

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exercise, less than half of the U.S. population is sufficiently active to meet public health recommendations [3]. Importantly, there is a dose-response relationship between exercise and these physical and mental health benefits [1]. Yet, without regular adherence to exercise, these benefits are limited. To date, relatively little is known about how to help inactive individuals beginning an exercise program to sustain an increased level of physical activity long-term. Below, we discuss the background and rationale for a study investigating the potential of tDCS delivered over left dorsolateral prefrontal cortex (DLPFC) in combination with an aerobic exercise intervention, to increase adherence to exercise in individuals with elevated depressive symptoms (conceptual model presented in Fig. 1.)

1.2. Depressive symptoms relate to exercise adherence

Depression (either elevated symptoms or symptoms that meet full criteria for a major depressive episode) is an important risk factor for obesity [4] as well for the development of other serious/debilitating physical health problems such as heart disease [4], diabetes [5], and chronic back pain [6]. One likely contributor toward these medical comorbidities is the low levels of physical activity (PA) among individuals with depression [7,8]. Indeed, depression has consistently emerged as an important predictor of declining levels of physical activity over time [9] and of poor exercise adherence across prospective and intervention studies [10]. Prospective studies with varied populations such as heart disease patients [11,12] or those with type 2 diabetes [13] have also found baseline levels of depressive symptoms predict dropout and lower levels of physical activity two to five years later. Similarly, in intervention studies, baseline depression consistently predicts poorer adherence to suggested PA levels. Exercise intervention studies with older adults [14,15] young sedentary women [16], cardiac and pulmonary rehabilitation patients [17,18], hypertensive patients [19], overweight/obese individuals [20] and breast cancer patients [21] have found that baseline levels of depressive symptoms predict fewer attended exercise sessions and/or lower levels of engagement in prescribed exercise – a relationship that appears to hold even after controlling for other key variables such education, smoking, percent body fat, motivation [21], and health status [15].

A cardinal symptom of depression is dysregulated affect – i.e., lower levels of positive affect and higher levels of negative affect [22,23]. Positive affect has been consistently identified as a significant correlate of physical activity levels [24,25]. Indeed, it has been proposed that positive affect enhances the pursuit of physical activity goals, including greater intention to engage in PA, prioritizing PA, and willingness to try PA [26]. On the other hand, negative affect has been found to be inversely related to PA [27–29]. If positive emotional states facilitate physical activity engagement, individuals with elevated depressive symptoms may be at a disadvantage with regard to maintaining engagement in regular physical activity in the long-term. Taken together, these studies suggest that individuals with depression may experience unique depression-specific barriers which interfere with both the adoption and maintenance of regular physical activity.

1.3. Affective responses to exercise can influence exercise adherence

While individuals almost universally "feel good" after engaging in PA (Reed & Ones, 2006), there is a fair amount of variability in affective experience *during* exercise. That is, while engaging in exercise, some individuals experience a positive shift in affective valence, others experience a negative shift [30]. In a review of studies examining the affective response to exercise and future PA engagement, positive shifts in affect experienced during exercise was consistently found to predict greater subsequent PA [31]. For example, in a study of 127 men and women, those with the greatest positive shifts in affective valence during a submaximal exercise test also had the highest level of exercise participation 3 months later [32]. Similarly, Williams et al. [33] found that positive shifts in affect during a single bout of moderate intensity exercise predicted PA levels 6 and 12-months later in sedentary women. More recently, baseline affective response to PA of over 200 inactive participants beginning a 16-week exercise intervention was positively associated with minutes of exercise at follow-up [34,35]. These findings can be explained in the context of psychological hedonism which states that people are more likely to do what they find pleasurable or what feels good (approach behavior) while avoiding behaviors that feel bad [36,37].

While research on the affective experiences of exercise in those with depression has been limited, one study compared individuals with and without a history of depression and found that those with a depression history did not experience the same positive shift in affect following PA in their daily life as those without a depression history [38]. Further, any mood benefit of PA quickly dissipated among those with a history of depression while those without depression continued to experience a positive shift in affect up to 3 h after exercise. Individuals with higher levels of depressive symptoms have also reported greater perceived physical exertion with exercise [39]. In our own work [40], we found an inverse relationship between level of depressive symptoms and PA enjoyment among smokers with elevated depressive symptoms. If those with depression experience exercise as more challenging and less rewarding than nondepressed individuals, it may impact their likelihood of maintaining PA in the long-term.

1.4. Factors that influence the affective response during exercise

Research has identified several factors that may contribute to affective experience during bouts of PA and how these may, in turn, influence PA behaviors (see Refs. [34,35] for review). For example, higher exercise intensity levels are associated with physiological changes that produce inherently unpleasant interoceptive cues (e.g., increased heart rate, muscle pain, shortness of breath) [41]. The extent to which individuals can tolerate these cues can determine whether they are able to "stay positive" during exercise [30]. Indeed, vigorous intensity exercise has been associated with negative affective experiences [34,35]. Moreover, higher ratings of *perceived* exertion during exercise have been associated with lower levels of physical activity engagement 6- to 12-months later [33–35,42]. Also, higher levels of exercise intensity are predictive of drop-out from exercise programs [43]. Engaging in

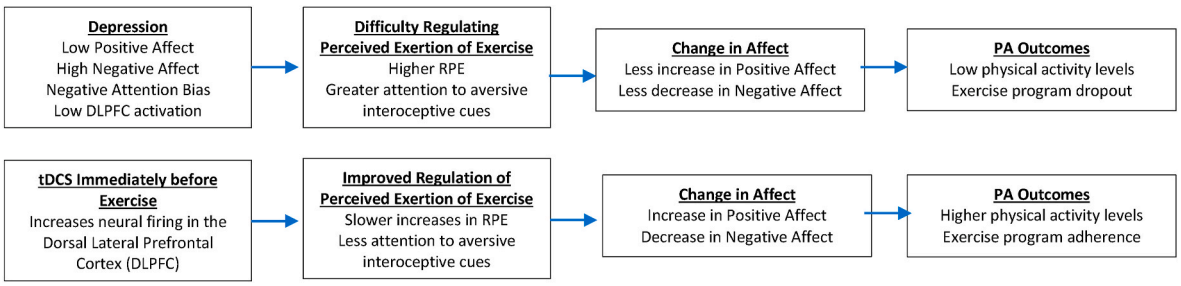

Fig. 1. Theoretical framework.

exercise at a lower intensity may be one approach to increase the likelihood of maintaining physical activity; however, sedentary individuals have particular difficulty accurately gauging intensity levels [44], so this may not necessarily align with improved affective response.

While physiological cues overwhelm the affective experience at higher exercise intensities, cognitive factors (e.g., self-regulation, attentional bias) influence affect at lower intensities (dual mode theory; [44]). The inability to direct attention away from unpleasant stimuli (i.e., attentional bias; [45]) is a hallmark of depression [46] and individuals with affective disturbances experience difficulty with attentional bias toward unpleasant emotions during exercise [47]. In non-depressed individuals, efforts to shift attention away from the sensory experience of exercise (e.g., with music and videos) have improved the affective experience of exercise [48]. Taken together, these findings suggest that strategies targeting the known cognitive-affective features of depression may help depressed individuals improve their affective experience of exercise and, in turn, maintain physical activity levels long-term.

Additionally, there is growing neurophysiological evidence that lateralization of brain activation in response to exercise may play a role in the affective experience of exercise [49]. Specifically, a number of exercise studies have shown that higher levels of activation in the left prefrontal cortex, evidenced by reduced alpha signals in that region on electroencephalography (EEG) relative to the right side, predict a more positive affective response to a single session of aerobic exercise. On the other hand, greater alpha activity in right prefrontal cortex is associated with negative affective responses to exercise [49,50]. Various lines of evidence implicate left-versus right-frontal brain activity in the processes underlying behavioral activation and avoidance, respectively [51,52]. This is particularly relevant for individuals with depression who, in both EEG and fMRI studies, have been found to show greater relative activity in right (vs. left) dorsolateral prefrontal cortex (DLPFC) [53,54]. Given inherent affect regulation difficulties associated with depression, it may be that individuals with depression may be less able to positively experience exercise, which may in turn contribute to their lower levels of physical activity. Ultimately, interventions designed to enhance activation in the left prefrontal cortex may help improve the affective experience of exercise among individuals with depression.

1.5. Transcranial direct current stimulation (tDCS) as a novel approach toward regulating cognitive and affective processes

tDCS is a form of noninvasive brain stimulation that involves the delivery of low-intensity electrical current (typically 1–2 mA) to the brain using electrodes placed on the scalp. As the current penetrates cortical regions, neuronal excitability in targeted brain regions can be modulated [55] through slight alterations to membrane potentials in areas underlying electrodes, leading to an increased likelihood of neuronal firing under the anode and decreased likelihood of firing under the cathode. Stimulation with tDCS is thought to shift the likelihood of neuronal firing but only impact the firing of action potentials in the context of endogenous brain activity, so it may be particularly promising in combination with behavioral interventions to enhance or diminish activity in neural circuits already in use. Effects of tDCS have been investigated in a broad range of populations [56], from healthy individuals to those with pain, movement disorders, psychiatric disorders, stroke, and many others. Under standard parameters, it has proven to be relatively safe with the vast majority of reported side effects being mild and transient (e.g., headache, fatigue; [57,58]). Though findings across populations and cognitive functions have been mixed, with a number of both positive and negative studies, research on tDCS has suggested the potential to impact a wide variety of cognitive and affective processes, such as working memory (e.g. Refs. [59,60], motor learning (e.g. Ref. [61]) and emotion regulation (e.g., Refs. [62,63]).

1.6. tDCS targeting the left dorsolateral prefrontal cortex has shown promise in improving emotion regulation

Meta-analyses and systematic reviews of tDCS delivered to DLPFC as an intervention for major depressive disorder have found superior treatment outcomes for active versus sham stimulation [64–66]. Though, it should be noted that many individual studies investigating tDCS have shown mixed results and are limited by small sample sizes [67]. Relatedly, a number of studies have found that tDCS to DLPFC improves cognitive control over emotional information [68–73]. In healthy individuals, Pena-Gomez et al. [74] found that (anodal) stimulation over left DLPFC was associated with lower perceived emotional valence for negative emotional stimuli when compared with sham stimulation; cathodal stimulation did not show this effect. Similarly, Boggio et al. [75] found that during anodal stimulation over left DLPFC, healthy participants rated negative images (of human pain) as less unpleasant and experienced less emotional discomfort than they did prior to stimulation or during sham tDCS. In a separate study using a cognitive control and frustration tolerance task (Paced Auditory Serial Addition Task), tDCS over DLPFC was associated with less reported frustration and improved task performance [70]. tDCS has similarly been found to affect the cognitive reappraisal of emotional stimuli [68]. Consistent with these findings, reduced attentional bias to emotional stimuli has been found following anodal tDCS to DLPFC [72] in depressed patients. Overall, these findings suggest that tDCS to DLPFC can be associated with improved cognitive control over emotional stimuli and corresponding reductions in emotional valence of negative stimuli and support testing its use when applied during physically and mentally challenging activities.

1.7. Combining tDCS with an exercise program may increase exercise engagement

The evidence base for tDCS is growing rapidly and the potential role of tDCS in exercise training has begun to emerge in the past decade. Most of these studies have involved delivering tDCS to motor cortex, resulting in improved mobility and physical functioning in patients with conditions such as chronic pain [76] and stroke [77], as evidenced by small-to-moderate effect sizes in these meta-analyses of studies. In addition, in a recent systematic review of 31 acute intervention studies, primarily in healthy individuals, anodal tDCS over primary motor cortex (M1) significantly increased muscle strength and aerobic endurance [78]. While far fewer, a number of emerging exercise studies have delivered tDCS to the DLPFC [79–83]. Outcomes of these studies varied greatly. For example, in one study [82], tDCS over DLPFC was associated with increased oxygen consumption (i.e., VO_2) following 30 min of exercise. In another study [83], overweight participants who received tDCS to the DLPFC experienced significantly less hunger and greater satiety after a bout of exercise, compared to those who received sham. More recently, in a sham-controlled study, Angius and colleagues [79] found that active tDCS over left DLPFC prior to cycling to exhaustion at 70% of maximal endurance resulted in significant improvements on task measures of inhibitory control and lower ratings of perceived exertion relative to the sham condition. Thus, while tDCS has been successfully implemented within the context of exercise protocols, to our knowledge, no work has yet been done to test potential effects of tDCS on improving the affective experience of exercise or on long-term exercise engagement in individuals particularly vulnerable to negative affect – i.e., those with depressive symptoms. Given the central role of the affective experience of exercise to long-term PA and given experimental findings relating tDCS of DLPFC to improved emotion regulation, the combination of tDCS (over DLPFC) with an exercise program may be a promising approach to improve exercise adherence.

1.8. Study aims

The purpose of this project was to conduct a pilot randomized controlled trial of tDCS to DLPFC versus sham delivered in the context of supervised aerobic exercise (AE) program among low-active individuals with elevated depressive symptoms, with a focus on both acute i.e., after 8-weeks of AE, and longer-term (3- and 6-month) outcomes. Given the pilot nature of the study, we were particularly interested in examining feasibility, acceptability, and preliminary efficacy of study procedures. Primary aims involved examining preliminary efficacy of tDCS for increasing exercise adherence by testing the hypotheses that, compared to those randomized to AE + sham, participants receiving AE + tDCS will have higher levels of objective-measured MVPA at follow-up assessments (Hypothesis 1a) as well as greater AE session attendance during the 8-week intervention (Hypothesis 1b). Secondary aims were to examine whether active tDCS, relative to sham, resulted in greater increases in positive affect (Hypothesis 2a), greater decreases in negative affect (Hypothesis 2b), and lower increases in rating of perceived exertion during exercise (Hypothesis 2c). Lastly, changes in motivation for exercise and depressive symptoms as well as adverse events were compared between conditions, with the hypotheses that those in the AE + tDCS condition would have greater motivation for exercise and lower levels of depression at follow-up.

2. Methods

2.1. Overview of study design

The goal of the proposed study was to test the preliminary efficacy of tDCS in the context of an 8-week AE intervention for increasing adherence to exercise in individuals with elevated depressive symptoms. Participants were randomized to receive the 8-week exercise intervention plus anodal tDCS to DLPFC (AE + tDCS) or sham tDCS to DLPFC (AE + sham). Outcomes were assessed at end-of-treatment (EOT) as well as at 3-and 6-month follow-up.

2.2. Study setting

Exercise sessions took place at the Butler Hospital Fitness Facility (BHFF). The facility contains commercial quality exercise equipment and is used exclusively by Butler Hospital researchers. tDCS was delivered immediately prior to exercise sessions in Butler Hospital's Neuromodulation Research Facility, which is approximately a 5-min walk from the BHFF.

2.3. Participants

Eligible participants (a) were between 18 and 65 years of age, (b) had low levels of physical activity (i.e., less than 90 min of moderate-intensity exercise/week for the past 6 months), (c) had elevated levels of depressive symptoms (i.e., Center for Epidemiological Studies Depression Scale score $\geq$10), and (d) indicated interest in starting an exercise program in the next month.

Exclusion criteria included: (a) a history of mania or hypomania, (b), history of psychotic disorder, (c) current DSM-5 diagnosis of anorexia nervosa, bulimia nervosa, or other eating disorder for which an exercise intervention would be contraindicated, (d) moderate or severe substance use disorder, (e) suicidality or homicidality at the time of enrollment, (f) presence of *untreated* major depressive disorder (MDD), (g) physical disabilities or medical problems that precluded participation in moderate intensity exercise (i.e., physician denied medical clearance), were contraindicated with tDCS (e.g., seizure disorder), or that might otherwise have interfered with study procedures (e.g., contagious skin disease), (h) pregnancy or breastfeeding at the time of enrollment, or intent to become pregnant during the subsequent 8 weeks, (i) presence of a pacemaker or metal implanted within the cranial cavity, (j) psychiatric medication changes within 6 weeks prior to study entry.

2.4. Recruitment and enrollment

Recruitment strategies included social media advertisements (e.g., Facebook) and brochures in the community. Interested individuals were phone screened for their current level of physical activity and depressive symptoms. Participants appearing to meet study criteria were scheduled for a more comprehensive baseline assessment. Research staff obtained informed consent and evaluated potential participants using the diagnostic and screening measures detailed below to confirm eligibility. A release of information form was obtained to contact participants' primary care providers (PCP) to request medical clearance. Medically cleared participants underwent a 1-mile Rockport treadmill walk test to obtain a baseline measure of cardiorespiratory fitness. Upon completion of all baseline procedures, participants were randomly assigned to AE + tDCS or AE + sham with MDD diagnosis (yes/no) as a stratification variable.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board (IRB) of Butler Hospital in Providence, Rhode Island, USA. This study was registered in ClinicalTrials.gov (NCT03178903).

2.5. Randomization to intervention conditions

After the medical clearance, participants were randomly assigned to AE + tDCS or AE + sham using stratified randomization procedures with current major depression disorder (MDD) diagnosis (yes/no) as the stratification variable.

2.6. Retention and follow-up

To reduce attrition, participants were paid $200 for assessments: $50 each for baseline, end of treatment (8 weeks), 3- and 6-month follow-ups. Participants were not paid for other study visits.

3. Intervention conditions

Conditions differed only in whether active or sham tDCS was delivered. Participants, evaluators, and those delivering the tDCS were all blinded to group assignment. Each intervention session began with 20 min of either active or sham stimulation, followed by supervised aerobic exercise. Participants were invited to attend 3 sessions per week for 8 weeks.

3.1. tDCS procedures

During each stimulation session, participants received 20 min of either active or sham tDCS with an intensity of 1 mA for active tDCS. Each carbon rubber anode and cathode insert was contained in a 5 $\times$ 5cm (25 cm^2) rectangular saline-soaked sponge. The anode was placed over left DLPFC (F3 on the EEG 10–20 system) and the reference electrode (cathode) over the contralateral (right) supraorbital region. Stimulation was delivered by a battery-driven, constant current stimulator (NeuroConn DC Stimulator Plus) which included a blinded study option such that subject-specific codes were entered into the device to deliver active or sham stimulation without unblinding the administrator. Sham stimulation used a "ramp up/ramp down" approach, with delivery of current starting (gradually ramped up) and then ending (gradually ramped down) over 30 s. This sham method has been found to be effective in previous studies using tDCS at 1–2 mA and is based on the fact that many of the sensations arising from active tDCS occur during the period of change in current intensity at the start of a session. For example, a recent review and meta-analysis of double-blind tDCS for depression studies found no difference between sham and active tDCS

groups in guessing their group assignment [84]. Immediately following the 20-min tDCS period, participants engaged in a supervised moderate-intensity aerobic exercise session.

3.2. Aerobic exercise (AE) component

After having received either tDCS or sham, participants engaged in an AE session at Butler Hospital's Fitness Facility. Exercise sessions were 20–30 min of moderate-intensity aerobic exercise on a treadmill, supervised by an exercise physiologist who monitored their heart rate and blood pressure to ensure safety and to make sure that physical activity occurred at moderate intensity (i.e., 64–76% of age predicted maximal heart rate). Participants were asked to rate their affect and rating of perceived exertion (RPE; [85]) during each exercise session. Sessions also included a 5-min warm-up and a 5-min cool-down to promote safe exercise procedures. In the later weeks of the study, participants were instructed to gradually increase their physical activity outside of these supervised sessions toward a goal of 150 min of moderate-intensity aerobic exercise per week, consistent with public health guidelines [1]. Participants were provided with resources for increasing their physical activity at home (e.g., lists of local walking trails, Youtube exercise videos, etc.).

4. Study design considerations

4.1. Stimulation location and electrode placement

We selected anodal stimulation of left DLPFC based on findings suggesting that tDCS over left DLPFC may enhance emotion regulation [70,71]. We were also unaware of support for similar effects in other regions, which would suggest an alternate neural target. We considered extracephalic cathode placement, as some studies have used [70,72], but chose the contralateral supraorbital location (as in Refs. [71,75] to avoid the potential for current flow across the brain stem.

4.2. Length and intensity of stimulation

tDCS parameters (20 min at 1.0 mA) were chosen based published data and for consistency with parameters used in tDCS studies of cognitive control of emotion [68–73]. Moreover, at these parameters, tDCS appears to produce after-effects of up to 60 min [86] which would be sufficiently durable for overlap with our AE intervention, as desired.

4.3. Intervention frequency

We selected a frequency consistent with a typical exercise intervention used with depressed individuals (i.e., 3x/week supervised sessions of moderate-intensity exercise ranging from 4 to 12 weeks in length) [87]. While there is some research suggesting that more frequent tDCS sessions may lead to greater cortical excitability [88], we anticipated that daily interventions may would not be feasible for our sample, and such a regimen would have a low likelihood of successful dissemination if found to be efficacious.

4.4. Center for Epidemiological Studies depression scale (CES-D) cutoff of 10 for determining elevated levels of depressive symptoms

Whereas 16 or higher on the CES-D is typically considered the threshold score for clinically significant level of depression, there is evidence that even lower levels of depressive symptoms (i.e., subclinical levels) can be predictive of poor exercise adherence. For example, in a study [13] of 624 patients with Type 2 diabetes beginning a 6-month exercise program, depressive symptoms of CES-D $\geq$10 were significantly associated with exercise session attendance and program dropout. Thus, we decided to set the CES-D cutoff for the current study at 10, as well.

5. Measures

A list of the complete assessment battery is presented in Table 1. Additional details regarding the assessment of physical activity and affective experience during exercise are presented below.

5.1. Assessment of depressive symptoms

The Structured Clinical Interview for DSM – (SCID-P), selected modules [90] was administered at baseline by trained research staff to assess for a diagnosis of current major depressive disorder. The Center for Epidemiological Studies-Depression scale (CES-D) [91] is a self-report, 20 item measure of depression symptoms experienced for the last week. Item responses include: rarely or none of the time, some or little of the time, occasionally or moderate amount of time, and most or all of the time. Scores range between 0 and 60, with higher scores reflecting greater depression. The CES-D was utilized to identify eligible individuals (i.e., those score 10 or above) and will be the depression outcome measure for determining intervention effects at follow-up timepoints. The Quick Inventory of Depression Symptoms: Self Report (QIDS) [99] is a 16-item self-administered measure that captures DSM-IV criteria for MDD. The QIDS was administered during the 8-week intervention period to monitor changes in MDD symptoms to ensure any experiences of clinical deterioration were identified and clinically addressed.

5.2. Assessment of primary outcome

The primary outcome for the RCT was objectively measured MVPA minutes/wk. At each timepoint, participants were given an Actigraph (GT3X) accelerometer with instructions for wearing the accelerometer on their hip for seven days. MVPA was estimated using the widely used Freedson cut point of 1952 counts•min^{-1} [102]. Only days of eight or

Table 1
Assessment measures.

	Time Point
Diagnostic and Screening Measures	
Physical Activity Screen	Pre-Baseline
Short-form Health Survey (SF-36) [89]	B, 3 M, 6 M
Structured Clinical Interview for DSM – (SCID-P), selected modules [90]	Baseline
Center for Epidemiological Studies-Depression scale (CES-D) [91]	Pre-Baseline, EOT, 3 M, 6 M
Feasibility and Safety	
Intervention Attendance (Documented by Staff)	Wks
Intervention Feedback Questionnaire	EOT
Modified Systematic Assessment of Treatment-Emergent Events – Specific Inquiry (SAFTEE-SI) (adverse events) [92]	Wks
Probe of tDCS Participant Blind	EOT
Physical Activity Related Measures	
Accelerometry-based MVPA	B, EOT, 3 M, 6 M
Rockport 1-Mile Walk Test (VO_{2peak}) [93]	B, EOT, 6 M
International Physical Activity Questionnaire (IPAQ) [94]	B, EOT, 3 M, 6 M
Benefits/Barriers to Exercise [95]	B, EOT, 3 M, 6 M
Affective Measurements	
Positive and Negative Affect Schedule (PANAS) [96]	B, EOT, 3 M, 6 M
Physical Activity Affect Scale (PAAS) [97]	B, Wks, EOT, 3 M, 6 M
Physical Activity Enjoyment Scale (PACES) [98]	B, EOT, 3 M, 6 M
Physical and Mental Health Outcomes	
Body Composition (BMI, %Body Fat)	B, EOT, 3 M, 6 M
Resting Heart Rate, Blood pressure	B, EOT, 3 M, 6 M
Quick Inventory of Depression Symptoms: Self Report (QIDS) [99]	B Wks, EOT, 3 M, 6 M
Behavioral Regulation in Exercise Questionnaire (BREQ-2) [100]	B, EOT, 3 M, 6 M
Concurrent Treatment – Treatment History Interview [101]	B, EOT, 3 M, 6 M

B=Baseline, EOT = End of Treatment, Mid = Midway through the 8-week intervention; 3 M&6 M = 3- and 6-month follow-ups; Wks = At weekly exercise.

more hours of Actigraph use, using Choi's algorithm [103]were considered valid days and included in analyses. MVPA minutes/week were calculated for participants with at least 3 days of validated wear time data.

5.3. Assessment of affective experience during exercise

The Physical Activity Affect Scale (PAAS) [97] is a 12-item self-report measure administered during exercise for measuring positive and negative affect (as well as fatigue and tranquility) and has demonstrated good reliability and validity. Participants responded to items on a 5-point Likert scale (0 = do not feel to 4 = feel very strongly). During weekly, supervised exercise sessions, participants were asked the PAAS questions immediately before the exercise bout and at 5, 15, 25 min during the bout and immediately after the bout. At each of these assessment points, RPE was also queried.

6. Participants enrolled and baseline characteristics

A total of 274 individuals were screened for the study. Two hundred and twenty-three were found to be ineligible for following reasons: 90 people were unable to attend the exercise sessions (40%), 50 people lost interest in the study (22%), 24 people ruled out for a psychiatric diagnosis (e.g. current mania) (11%), 16 people had medical contraindications to exercise (7%), 11 people had too low of a CES-D score (5%), 11 people had contraindications to tDCS (5%), 4 people were too active (2%), and the remaining 17 people (8%) ruled out for a variety of other reasons (e.g., outside of inclusion age criteria, PCP denied medical clearance, etc.). While the specific reasons interested individuals were not able to attend the exercise sessions were not recorded, in general, the most common explanation was due to conflicting work or family obligations prohibiting the attendance of 3x/week in-person exercise sessions during daytime hours at the study facility.

We enrolled a total of 51 participants. Twenty-five (n = 25) participants were randomized to AE + tDCS, and n = 26 were randomized to AE + sham. The entire sample was 86.3% female and was 49.5 (SD = 10.4) years of age. The sample reported being 90% White, 4% Black or African American, 4% another race, and 2% more than one race; 8% reported Hispanic or Latinx ethnicity. Mean baseline levels of depression were above the CES-D clinical threshold of 16 with a mean of 22.3 (SD = 10.7). Self-reported average exercise per week in the 3 months prior to enrollment was 25.9 min (SD = 48.4). In the 7-days prior to study enrollment, participants wearing the accelerometer for at least 3 days averaged 116.9 (SD = 96.9) minutes of MVPA for that week.

7. Data analytic plan

7.1. Sample size and power considerations

In selecting a target sample size, we balanced power considerations and feasibility given the exploratory and pilot nature of this trial. We aimed to have a total of 60 participants complete the study (~30 per group), estimating this would provide adequate power to detect medium to large effects. Specifically, we anticipated power to detect the condition by time interaction of our primary outcome at EOT to be 0.24, 0.87, 0.99 for small (f = 0.10), medium (f = 0.25), and large (f = 0.40) effects, respectively (assuming r = 0.25 between repeated measurements; α = 0.05). Based on our previous work, we expected 10–20% attrition. Thus, our goal was to enroll 72 total participants to obtain our desired sample size of 60 completers.

7.2. Primary hypotheses

We will first examine patterns of missing data to determine possible mechanisms of missingness and will explore different techniques to impute missing data values, as appropriate [104,105]. To test our first primary hypothesis, we will conduct a repeated-measures ANOVA (rmANOVA) via mixed modeling framework testing a condition by time interaction in MVPA across all time-points (EOT, 3- and 6-month follow-up). We then will conduct a between-groups *t*-test to assess whether session attendance differs between groups during the 8-week intervention.

7.3. Secondary hypotheses

To examine differences between conditions in affect and RPE change during exercise, we will use mixed effects models using pre- and all mid-exercise ratings from all sessions. To test for differences in motivation and depressive symptoms, we will again conduct rmANOVAs via a mixed modeling framework to test for condition by time interactions in motivation for exercise and depressive symptoms across follow-up time-points. Finally, we will test for differences (chi-square) in frequency of side effects reported between groups.

8. Conclusion

This report describes the study protocol and baseline characteristics of a sample of individuals with elevated depressive symptoms who participated in a preliminary randomized controlled trial of a non-invasive brain stimulation plus aerobic exercise intervention. While the goal of the study was to enroll 72 participants, we succeeded in enrolling approximately 70% (n = 51) of this intended target during the time allocated for completion of the project. It is possible we may be underpowered to find significant treatment effects when we conduct our primary outcome analyses. Therefore, in addition to statistical testing of our hypotheses, we will also plan to examine effect sizes to determine the strength and direction of these relationships. If these effect sizes prove worthy of pursing a larger, fully powered trial (i.e., at least moderate effect sizes), additional resources should be devoted to helping facilitate higher levels of recruitment. For example, employing the assistance of a marketing specialist who can effectively advertise for a complex study involving both brain stimulation and exercise may help attract greater number of interested individuals. In addition, future studies may consider testing intervention protocols that combine at-home tDCS plus exercise to help decrease the burden of in-person study visits.

Exercise adherence is a significant public health problem. Affective experiences during exercise predict long-term PA levels. Therefore, approaches to improving the affective experience of exercise are both important and likely to have high impact. This may be particularly true among individuals with elevated depressive symptoms due to their tendency toward more negative and less positive affect. Transcranial direct current stimulation is an approach with a growing body of literature supporting its effects on cognitive and emotional processing in varied populations, including those with depression. In addition, there is recent, increased interest in utilizing tDCS in the context of exercise (see above) and in obesity prevention [106]. While our understanding of the effects of tDCS on behavioral and cognitive functioning is still developing, promising findings have emerged for tDCS used in repeated combination with a behavioral or cognitive intervention [107–111]. Given that tDCS is relatively safe, inexpensive, and portable, individuals who struggle with enjoying exercise could be afforded a practical option for increasing and maintaining physical activity levels.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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