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Exploring the efficacy of a 5-day course of transcranial direct current stimulation (TDCS) on depression and memory function in patients with well-controlled temporal lobe epilepsy

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ABSTRACT

Introduction: Depression and memory dysfunction significantly impact the quality of life of patients with epilepsy. Current therapies for these cognitive and psychiatric comorbidities are limited. We explored the efficacy and safety of transcranial direct current stimulation (TDCS) for treating depression and memory dysfunction in patients with temporal lobe epilepsy (TLE).

Methods: Thirty-seven (37) adults with well-controlled TLE were enrolled in a double-blinded, sham-controlled, randomized, parallel-group study of 5 days of fixed-dose (2 mA, 20 min) TDCS. Subjects were randomized to receive either real or sham TDCS, both delivered over the left dorsolateral prefrontal cortex. Patients received neuropsychological testing and a 20-minute scalp EEG at baseline immediately after the TDCS course and at 2- and 4-week follow-up.

Results: There was improvement in depression scores immediately after real TDCS, but not sham TDCS, as measured by changes in the Beck Depression Inventory (BDI change: −1.68 vs. 1.27, $p < 0.05$) and NDDI-E (−0.83 vs. 0.9091, $p = 0.05$). There was no difference between the groups at the 2- or 4-week follow-up. There was no effect on delayed or working memory performance. Transcranial direct current stimulation was well-tolerated and did not increase seizure frequency or interictal discharge frequency. Transcranial direct current stimulation induced an increase in delta frequency band power over the frontal region and delta, alpha, and theta band power in the occipital region after real stimulation compared to sham stimulation, although the difference did not reach statistical significance.

Discussion: This study provides evidence for the use of TDCS as a safe and well-tolerated nonpharmacologic approach to improving depressive symptoms in patients with well-controlled TLE. However, there were no changes in memory function immediately following or persisting after a stimulation course. Further studies may determine optimal stimulation parameters for maximal mood benefit.

1. Introduction

Patients with focal epilepsy frequently suffer from comorbid mood and cognitive complaints. Depression is the most frequent psychiatric comorbidity of epilepsy, especially with patients with frontal or temporal lobe onset. The estimated prevalence of depression in this group of patients ranges between 20 and 50% [1], higher than rates in the general population [2–4]. Depression in epilepsy is an independent predictor of poor quality of life, increased suicidal risk, greater use of health services, and higher medical costs [5] and, therefore, important to recognize and manage. Epilepsy and depression have reciprocal relations with overlapping neuroanatomical and neurotransmitter abnormalities suggesting that treating depression may decrease seizure frequency [5].

Memory difficulty, slowed processing, and attention deficits are the most common complaints of patients with epilepsy [6]. Temporal lobe epilepsy affects memory as well as intelligence (IQ), executive functions, language, and sensorimotor function [7,8]. Similarly, instead of a

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localized deficit, functional imaging and MRI volumetric models reveal that patients with TLE display widespread dysfunction and atrophy in the bilateral frontal, temporal, and parietal lobes as well as the thalamus, basal ganglia, and cerebellum [9–11]. It is unclear whether treating more transient variables, such as seizure frequency and interictal activity, can improve cognition [12,13].

Current therapies for these cognitive and psychiatric comorbidities are limited. Currently, there are no proactive means of addressing memory dysfunction in patients with epilepsy. Pharmacologic approaches to enhance memory in patients have been unsuccessful [14,15]. Antidepressant medications may interact with antiepileptic medications, cause undesirable side effects, take time to reach therapeutic effect, or lower the seizure threshold. Finding safe, alternative methods of addressing the affective and cognitive aspects of epilepsy is of tremendous clinical significance.

1.1. Transcranial direct current stimulation (TDCS)

Transcranial direct current stimulation is a method of noninvasive brain stimulation which delivers low-amplitude (1–2 mA) direct current between scalp electrodes — the anode and cathode. Transcranial direct current stimulation has been shown to modulate brain activity and depending on stimulation parameters, can enhance or reduce cortical excitability [16]. Although there is substantial shunting of current in the scalp, modeling studies demonstrate that sufficient current penetrates the brain to modify the transmembrane neuronal potential [17,18]. Cortical excitability can be altered beyond the stimulation period and modulates firing rate for up to 90 min in humans [19].

Clinical advantages of TDCS include low cost, ease of administration, known safety profile, and noninvasive and painless nature. However, patients with epilepsy are typically excluded from TDCS studies because of a theoretical risk of seizure exacerbation.

Major depression has been associated with hypoactivity in the left dorsolateral prefrontal cortex (DLPFC) as demonstrated by PET, fMRI, and resting state EEG activity [20,21] as well as observations of greater incidence of depression in patients affected by stroke with damage to this region [22]. Hence, TDCS, with the anode over the left DLPFC, may help increase regional activity [23] as has been supported by numerous pilot studies for depression [24–28]. There has been an independent effect in enhancing working memory in healthy subjects [29,30] although the results have been variable [31,32].

In this pilot study, we explored whether treatment with TDCS, with the anode over the left DLPFC, can improve depressive symptoms and enhance memory function as compared with sham TDCS in patients with stable TLE. We examined two types of memory, including 1) working memory, the active maintenance of information in the mind that can be potentially manipulated to complete goal-directed tasks and is associated with frontal lobe function, and 2) verbal episodic memory, which is the longer-term storage of verbal information. As secondary aims, we explored the effect of TDCS on 1) seizure and interictal discharge frequency as well as 2) resting state EEG band power changes.

2. Methods

The study was conducted at Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA and the New York University Comprehensive Epilepsy Center, New York University School of Medicine, New York, NY, with a period of active recruitment from January 2012 to September 2014. Local institutional review board approvals were obtained, and all participants signed informed consents.

This was a prospective double-blind, sham-controlled, randomized, parallel-group study of fixed-dose TDCS in patients with well-controlled TLE. Well-controlled TLE was defined as a stable seizure frequency for 2 months prior to enrollment, measured by lack of changes in the patients' antiepileptic drug regimen for 2 months prior to enrollment. Patients provided consent, and were told that there would be a 50% chance of being randomized to receive real stimulation. After consent, subjects were asked to maintain a seizure diary for 28 ± 7 days prior to the stimulation week. Patients who were seizure-free for 2 months or more were exempted from this window between the first and second visits. Urine pregnancy tests were performed for women of childbearing potential at the baseline visit to exclude pregnancy.

During stimulation week, subjects were randomly assigned to receive active or sham stimulation using a block randomization scheme in a 1:1 manner. Treatment allocations were unknown to the subject, experimenter, and reviewer. Neuropsychological testing and symptom inventories (reviewed in detail below) and a 20-minute EEG were collected at baseline before the first session of stimulation, after the last stimulation session, as well as at the 2-week and 4-week follow-up intervals. The study design is reviewed in Fig. 1.

2.1. Participants

Thirty-seven patients were enrolled. Participants were included if they met the following criteria: 1) aged between 18 and 70 years; 2) diagnosis of temporal lobe epilepsy, with seizure focus defined by seizure semiology, EEG, brain MRI, PET, and/or ictal and interictal SPECT; 3) a stable seizure frequency in the two months prior to enrollment as verified by the patient's seizure log and/or clinic notes and without recent antiepileptic medication changes; 4) a score above 22/30 on the Montreal Cognitive Assessment (MOCA); and 5) capacity to provide informed consent. The exclusion criteria were the following: 1) progressive or unstable neurological or systemic disease; 2) an ictal focus over the F3 or F4 (DLPFC) field; 3) a history of severe depression, as determined by a screen inventory test such as the Beck Depression Inventory—II (score greater than 29 out of 63) or as determined by a psychiatrist, or suicidality at the time of screening; 4) a history of severe traumatic brain injury or prior brain surgery with a skull defect; 5) a contraindication to TDCS, including metal in the head or implanted brain medical devices; 6) pregnancy; 7) any implanted electrical medical device, including pacemakers and implanted cardiac defibrillators; 8) history of schizophrenia, schizoaffective disorder, other psychosis, rapid-cycling bipolar illness, and alcohol/drug abuse within the past year; or 9) history of dementia.

Patients were recruited by flyers, website advertisements, and physician referrals. They were prescreened by a brief telephone conversation, and those patients meeting general criteria were invited for an in-person screening and consent process.

2.2. Intervention

For each session, the TDCS montage consisted of the anodal electrode over the left DLPFC (F3 electrode position of the 10/20 international electrode system) and the cathode over the right supraorbital area. Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 cm^2 each) and delivered by the Chattanooga Ionto, which is a battery-driven, constant-current stimulator with a maximum output of 2 mA. For real stimulation, 2 mA of TDCS (current density: 0.57 A/m^2) was applied for 20 min over the left DLPFC for 5 consecutive sessions on consecutive days. Previously, more than 1 session has been used for sustained effects. In a review of randomized controlled studies using TDCS for depression [33], protocols that applied from 1 to 2 mA of current (current density: 0.28 to 0.57 A/m^2) for 20 min between 5 and 15 sessions have been demonstrated to be safe [24,25,28,33,34].

For subjects assigned to the sham condition, the same montage was used; however, the current was ramped up for 30 s and then ramped down. Such a protocol is a routinely used method of sham stimulation as sensations arising from TDCS treatment occur only at the beginning of application as also demonstrated by a randomized study [35].

Two research assistants administered the TDCS intervention. They completed a TDCS practical course and, thereafter, administered several TDCS applications under direct supervision. To ensure standardization

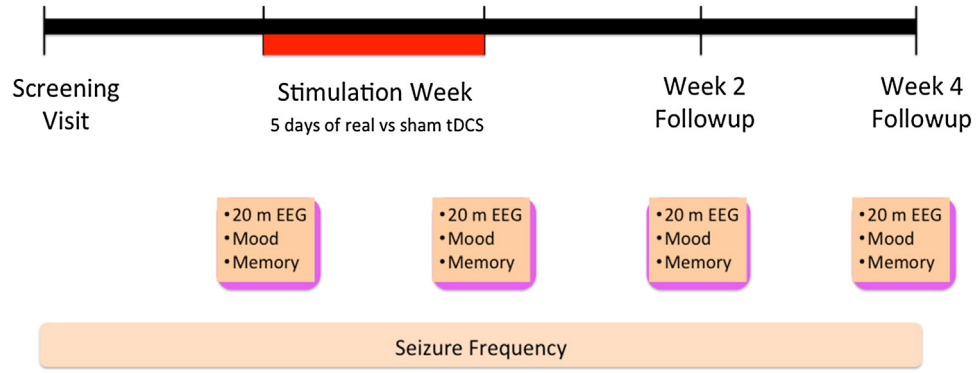

Fig. 1. Study design. Subjects with stable temporal lobe epilepsy were screened and consented on visit 1. They were then randomly assigned to receive either real or sham TDCS. Both the subject and the research investigator administering the TDCS were blinded to randomization condition. The subject first received a battery of mood (BDI, NDDI-E, QOLIE-31) inventories as well as tests of working and delayed memory (Digits, Letter–Number, RAVLT). The subjects were then administered a 20-minute EEG while awake with eyes closed. Finally, the subjects were given 20 min of either real or sham TDCS, with anodal TDCS delivered over F3 and cathodal TDCS delivered over the right supraorbital region. On days 2–5, the subjects continued to receive either real or sham TDCS. After the fifth and last session, they were administered a follow-up 20-minute EEG while awake with eyes closed. They were given similar mood inventories and memory testing. At week 2 and follow-up, the subjects only received 20 min of EEG and neuropsychological inventories. The subjects were monitored for side effects and seizure frequency throughout.

across montages and applications, each session was double-checked by the principal investigator (AL) or another trained research assistant.

2.3. Assessments

The assessments were administered by a research assistant blinded to subject treatment allocation. The primary efficacy outcome was the Beck Depression Inventory—II (BDI-II) after 5 days of stimulation. Secondary outcomes included 1) performance on working memory and delayed verbal recall measures, 2) seizure frequency, 3) interictal discharge frequency, and 4) change in regional EEG band power.

2.3.1. Depression

The primary efficacy outcome was the Beck Depression Inventory—II (BDI-II) score after 5 days of stimulation. Beck Depression Inventory—II is based on the DSM-IV diagnostic criteria for depression. It contains 21 questions, each answer being scored on a scale of 0 to 3. Higher scores indicated more depressive symptoms. A score of 0–13 is considered minimal depression, 14–19 is mild depression, 20–28 is moderate depression, and 29–63 is severe depression. Patients were screened to ensure that none met criteria for severe depression. If the subject endorsed suicidality with intent or plan as determined by BDI-II (Question 9), the subject was directed to emergency services or a psychiatrist.

The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) was a secondary outcome measure and six-question screening tool used to rapidly identify symptoms of major depression while excluding effects [36] of antiepileptic drugs which may be conflated with depressive feelings. Subjects respond to the questions “everything is a struggle”, “nothing I do is right”, “feel guilty, I'd be better off dead”, “frustrated”, and “difficulty finding pleasure” on a five-point Likert scale [37].

2.3.2. Tests of working memory

Secondary outcomes also included several measures of working memory and executive function, including (a) the Letters and Numbers Sequencing subtest, which is typically administered with the Wechsler Adult Intelligence Scale—III (WAIS-III) [38], in which the subject is presented combinations of letters and numbers between 2 and 9. Subjects must then repeat the sequence by presenting the numbers in ascending order, then the letters in alphabetical order (e.g., 7–N–3–D, the correct response is 3–7–D–N). (b) The Digits Span Test subtest (also from WAIS-III) [38] consists of two parts, digits forward and backward. Subjects were asked to repeat between 3- and 9-digit sequences forward, then backward.

2.3.3. Rey Auditory Verbal Learning Test (RAVLT)

Rey Auditory Verbal Learning Test (RAVLT) is a test of verbal encoding, consolidation, and retrieval [39]. Participants are asked to learn a set of 15 unrelated words, repeated over 5 times. Then, another list of 15 unrelated words is presented, and the subject must repeat the original list of 15 words and again after 20 min. Subjects receive a total of 3 scores, including RAVLT 1–5 (summed performance from 5 initial encoding trials of the original list, maximum performance: 75), RAVLT 6 (number of words out of 15 from the original list, tested after the interference list), and RAVLT 7 (number of words out of 15 remembered from the original list, after a 20-minute delayed recall). Higher scores correlate with more words remembered at the encoding and retrieval sessions.

2.3.4. Quality of Life in Epilepsy Inventory (QOLIE-31)

This is a 31-question inventory developed to measure health-related quality of life in epilepsy, measuring items such as emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life. Subjects can have a maximum raw score of 73 (with higher scores representing better quality of life) and a maximum adjusted score of 100 [40].

2.4. EEG

Spontaneous EEG was recorded while subjects sat upright in a comfortable chair, at 4 time points: before TDCS (baseline), immediately after the five-day course of TDCS (post-TDCS), and 2 and 4 weeks after stimulation. Sixteen-channel resting state EEG (awake, eyes closed, 20 min) was obtained. Electroencephalogram tracings were recorded with the BioSignal microEEG system, with a Cz reference. The BioSignal microEEG is an FDA-approved, miniature ($9.4 \times 4.4 \times 3.8$ cm, 88 g), wireless, battery-powered EEG device which samples at 1000 Hz and has a bandwidth between 0.15 and 500 Hz, A/D converter resolution of 16, and voltage resolution of 0.15 mV. The device has been validated against a standard EEG machine in several studies [41,42]. The cap electrodes were positioned using the 10–20 international system at the following locations: Fp1, Fp2, C3, F3, F7, A1, T7, P7, O1 C4, F4, F8, T8, A2, P8, and O2. Electrode impedances were kept less than 20 kΩ throughout the study.

On all days involving TDCS treatment, a side-effects questionnaire was completed before and after stimulation. Patients were asked to report if they experienced side effects of headache, neck pain, scalp pain, scalp burns, tingling, skin redness, sleepiness, difficulty with concentration, and mood changes and were asked to quantify the severity of side effects on a scale of 1–5. The EEG was evaluated offline for interictal

discharge frequency by a board-certified clinical neurophysiologist (SH) who was blinded to the randomization arm.

2.4.1. EEG preprocessing

Quantitative analysis was performed offline for EEG sessions performed before and after the 5-day course of stimulation. The MatLab FieldTrip toolbox (http://www.fieldtriptoolbox.org/) was used for further preprocessing of the data, including a 0.5-Hz high-pass filter, random segregation into consecutive trials of 3 s followed by line-noise removal (60 Hz and harmonics), and a combination of semiautomatic and visual artifact rejection for nonphysiological noise and muscle and eye movements. The power in each frequency band was computed using multitaper time–frequency analysis [43].

The average power was then calculated for common frequency bands [1–4 Hz (delta), 5–7 Hz (theta), 8–10 Hz (low alpha), 11–13 Hz (high alpha), 14–32 Hz (beta), and 33–55 Hz (low-gamma)] for the cleaned epochs. To offset the increased number of comparisons, we averaged raw power values across four regions of interest (ROIs), the frontocentral (Fp1, Fp2, F3, F4, C3, C4), left temporal (F7, T3, T5, A1), right temporal (F8, T4, T6, A2), and occipital (O1, O2) regions. To correct for the 1/f dependence, we performed a log transformation of the raw power values prior to statistical analysis, allowing for better evaluation of power changes at higher frequency bands.

2.5. Statistical analysis

All analyses were performed using SPSS version 22 statistical software with 2-sided significance tests at the 5% significance level. Analyses were conducted by intention to treat according to the randomization condition. Data were tested for missing and out-of-range values (defined as greater than ±2.5 SD from the mean).

Sample size was based on effect size from previous TDCS studies on depression. Sample size was based on the assumption that effect size should be 0.70 (moderate) to be able to achieve 80% power at 95% confidence level. Assuming a 10% dropout rate, we calculated needing 19 study subjects per group (38 total) to achieve, after attrition, a final sample size of 17 subjects per group (34 subjects total).

We compared demographic, clinical, and neuropsychological characteristics between groups at baseline by *T*-test for continuous and X^2 test for categorical variables. To analyze the primary outcome, we generated a repeated measures analysis of variance (ANOVA) model with one dependent within-subject variable (BDI-II score), one within-subject variable (time, 4 levels), and one between-subjects variable (group, 2 levels, real TDCS vs. sham TDCS). Post-hoc analysis was conducted using an independent *T*-test comparison of subject-level changes in BDI-II scores, comparing real and sham conditions.

Secondary outcomes were also evaluated by an ANOVA model, with NDDI-E, LNS raw, digits raw, RAVLT, and QOLIE scores treated as separate dependent variables. In a post-hoc analysis, independent *T*-test comparing of subject-level changes in scores were performed (including comparing post-TDCS to pre-TDCS (baseline), 2-week follow-up to pre-TDCS, and 4-week follow-up to pre-TDCS).

For EEG, a repeated measures ANOVA was performed, with condition (group, 2 levels, sham vs. real TDCS) as the between-subjects variable, time as the within-subject variable (2 levels, pre vs. post), and resting EEG power values for each frequency band for a given ROI as the dependent variables. Post-hoc analysis was conducted via an independent samples *T*-test for subject-level changes in resting power for each frequency band at each ROI, comparing real and sham conditions.

3. Results

3.1. Subjects

Of approximately eighty (80) patients screened, thirty-seven (37) subjects were enrolled in the study between two sites, New York University Comprehensive Epilepsy Center, New York, NY (30) and Beth Israel Deaconess Medical Center, Harvard Medical School (7). Thirty-three (33) subjects were randomized to receive real TDCS (N = 21) or sham TDCS (N = 12) and completed the study. Four subjects did not complete the study. One subject was excluded based on eligibility criteria (did not pass the MOCA screening); one subject randomized to sham TDCS dropped out because of perceived side effects; one subject randomized to real TDCS was lost to follow-up (before starting stimulation); and one subject randomized to sham TDCS was discontinued because of subject noncompliance (patient broke the blind). Dropouts were balanced between treatment groups. Patients randomized to either treatment arm were matched in baseline demographic characteristics, educational level, seizure frequency, and performance on memory and mood tasks, as shown in Table 1. Subjects who received TDCS did not differ in their baseline BDI scores (real: 7.81 ± 7.181 vs. sham: 10.17 ± 7.284) and NDDI-E scores (real: 11.95 ± 4.40 vs. sham: 12.91 ± 3.27).

3.2. Depression

The primary outcome was the change in BDI-II score. Outliers (BDI score changes greater than 2.5 SD from the mean) were removed (1 subject in the real and sham stimulation conditions). In the factorial analysis, there was no significant time × group interaction (F = 01.127, p = 0.356) when 4 time points were considered (pre, post, 2 weeks, and 4 weeks). However, on post-hoc analysis, after 5 TDCS sessions, subjects receiving real stimulation reported a greater decrease in their depressive symptoms compared to subjects who received sham TDCS (mean difference ± SD, BDI XX vs. YY, p = 0.048; NDDIE XX vs. YY, p = 0.050). However, this improvement did not persist to 2 weeks (BDI: −1.25 + 4.68 vs. −1.40 + 3.81, p = 0.931; NDDI-E: −0.300 ± 2.62 vs. 0.182 ± 2.40, p = 0.618) or 4 weeks (−1.00 + 3.55 vs. −.727 + 5.90, p = 0.315; NDDI-E: −0.3684 ± 2.54 vs. 0.7273 ± 2.55, p = 0.264) (Fig. 2). This corresponded to an immediate effect size on the NDDIE of g = 0.7576 (Hedges test), which is considered to be a moderate effect.

In a post-hoc analysis, subjects who received TDCS who had the most improvement on their BDI-II scores, or subjects who were in the top 50% of BDI-II improvement scores, appeared to have more depressive symptoms at baseline although this was not significant (BDI-II: 9.6 ± 7.34, 5.1 ± 6.30, p = 0.158). Subjects who responded to stimulation tended to have continuously lower BDI scores at 2 weeks and 4 weeks although this was not statistically significant (Fig. 3). Of note, decrease in BDI scores was limited by a floor effect in which further decrease may have been limited by the fact that the mean BDI score was 5.65 immediately after real TDCS.

3.3. Working memory

At baseline, subjects who received real TDCS did not differ in their performance scores on any of the working memory measures, including digit span forward (real vs. sham: 10.48 ± 1.94, 10.83 ± 2.2125), digit span backward (8.76 ± 1.947 vs. 8.67 ± 1.37, p = 0.626), or letter number sequence (19.33 ± 2.436 vs. 20.00 ± 3.516, p = 0.525). There was no significant time × group interaction for digits forward (F = 2.350, p = 0.94), digits backward (F = 1.302, p = 0.293), or letter number sequence (F = 0.411, p = 0.746),

3.4. Episodic verbal memory

There were no significant changes comparing across group and time for measures of verbal memory, including total learning (RAVLT 1–5, F = 0.422, p = 0.739), immediate recall (RAVLT 6, F = 2.450, p = 0.084), or delayed recall (RAVLT 7, F = 1.290, p = 0.297).

Table 1
Demographic and baseline clinical characteristics (N = 33). We compared demographic, clinical, and neuropyschological characteristics between groups at baseline by independent samples T-test for continuous and X^2 test for categorical variables.

Demographic characteristics	Sham TDCS (±SD)	Real TDCS (±SD)	t	P (2-tailed)
Number (N = 33)	12 (36.4%)	21 (63.6%)		
Age (years)	43.33 (±15.47)	43.29 (±15.29)	0.009	0.966
Gender (M/F)	6/6	13/8	0.443	0.716
Race/ethnicity			1.217	0.544
White/Caucasian	100%	90.5%		
African-American	0%	4.8%		
Asian	0%	4.8%		
Education level			0.051	0.975
High school	0	0		
Some college	2	4		
College graduate	5	9		
Graduate school	5	8		
Seizure laterality			9.314	0.097
Bilateral	3	1		
Left	3	7		
Right	2	10		
Unknown	4	3		
Seizure frequency	0.42 (±0.996)	0.00 (±0.655)	1.94	0.061
Number of seizure meds	1.82 (±1.168)	1.65 (±0.671)	0.512	0.612

Neuropsychiatric inventories	Sham TDCS (±SD)	Real TDCS (±SD)	t	P (2-tailed)
BDI	10.17 (±7.284)	7.81 (±7.181)	0.902	0.374
NDDI-E	12.91 (±3.270)	11.95 (±4.399)	0.349	0.730
MOCA	26.67 (±2.309)	25.76 (±2.488)	1.031	0.311
WTAR raw	43.08 (±7.342)	42.30 (±5.939)	0.331	0.743
WTAR scaled	115.42 (±11.866)	114.10 (±9.380)	0.348	0.730
Verbal IQ	111 (±8.707)	110.80 (±7.353)	0.070	0.945
RAVLT total	46 (±8.759)	47.48 (±24.985)	−0.197	0.845
RAVLT 6	8.58 (±3.476)	7.76 (±3.700)	0.627	0.535
RAVLT 7	6.67 (±4.097)	7.24 (±3.604)	−0.417	0.680
Digit span forward raw	10.83 (±2.125)	10.48 (±1.940)	0.492	0.626
Digit span forward scaled	10.50 (±2.431)	10.10 (±2.587)	0.442	0.662
Digit span backward raw	8.67 (±1.371)	8.76 (±1.947)	−0.149	0.882
Digit span backward scaled	9.92 (±1.730)	10.14 (±2.287)	−0.297	0.769
Letter number sequence raw	20.00 (±3.516)	19.33 (±2.436)	0.643	0.525
Letter number sequence scaled	10.42 (±3.204)	9.52 (±1.692)	1.053	0.300
QOLIE total	62.50 (±16.116)	65.33 (±16.366)	−0.481	0.634
QOLIE scaled	49.75 (±9.882)	51.43 (±10.127)	−0.462	0.647
QOLIE seizure worry	74.92 (±25.92)	68.45 (±22.34)	0.939	0.355
QOLIE overall	73.00 (±10.278)	72.65 (±19.704)	−0.152	0.880
QOLIE emotional	63.50 (±17.810)	69 (±18.117)	−0.927	0.361
QOLIE energy	48.33 (±16.697)	57.65 (±21.099)	−1.345	0.188
QOLIE cognitive	52.17 (±20.008)	55.40 (±22.139)	−0.436	0.666
QOLIE medication	54.00 (±33.109)	64.90 (±30.395)	−1.102	0.279
QOLIE social	73.42 (±27.427)	73.50 (±22.547)	0.053	0.953
QOLIE-31	69.09 (±12.004)	76.19 (±12.440)	−1.551	0.131

3.5. Quality of life

At baseline, subjects did not differ in their overall QOL, as measured on the QOLIE total (65.33 ± 16.37 vs. 62.50 ± 16.116, p = 0.634) or in any of the subscales (Table 1). There was no significant time × group interaction (F = 1.185, p = 0.333) when 4 time points were considered (pre, post, 2 weeks, and 4 weeks) (Table 2). After 5 sessions, there was no difference in improvement in QOLIE scores (F = 0.987, p = 0.328) or subscale scores (Table 3).

3.6. Seizure frequency

Subjects had well-controlled seizures, with average seizure frequency less than 1 seizure per month at baseline and verified by seizure diary (0.42 ± 0.996 vs. 0.00 ± 0.655, p = 0.061). There was no significant difference in seizure frequency by condition across time (F = 1.109, p = 0.402) (Table 1). After 5 days of stimulation, there was no difference in seizure frequency between real and sham TDCS point (F = 2.402, p = 0.133) (Table 2).

3.7. Interictal discharge frequency

Subjects had infrequent interictal discharges at baseline, with subjects receiving sham TDCS recording a mean of 8.9 ± 23.8 SD discharges over a 20-minute awake resting period (median: 0.0) and subjects receiving real TDCS recording a mean of 0.8 ± 3.1 SD interictal discharges per 20-minute EEG period (median: 0.0, Table 2). There was no change in interictal discharge frequency for either subjects who received real or sham stimulation directly after stimulation (F = 1.460, p = 0.239) or across the 2- or 4-week follow-up period (F = 0.329, p = 0.578).

3.8. EEG power

Of the 37 subjects included in the study, 23 subjects had high quality EEG data at both the baseline visit and immediately after the fifth stimulation session. After preprocessing, an average of 75.2% of the 3-second epochs were used for further analysis. There was an increase in delta, theta, and low alpha frequency spectral power seen over the frontocentral region, as well as the occipital region, although these differences did not

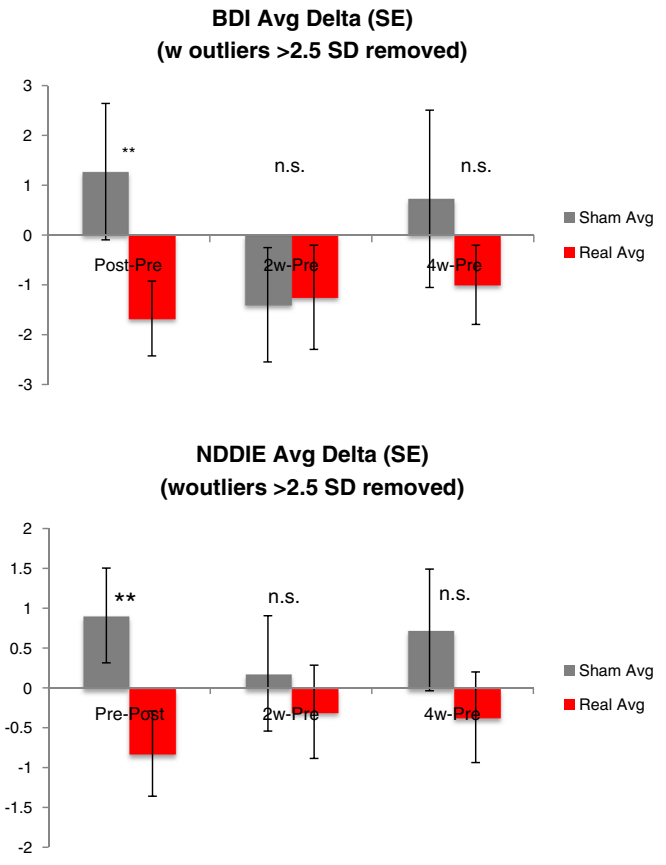

Fig. 2. Changes in depression scores. After 5 TDCS sessions, the subjects who received real stimulation (red bar) reported a greater improvement in their depression symptoms compared to subjects who received sham TDCS (gray bar), as measured by BDI (mean ± SD, −1.68 + 3.36 vs. 1.27 + 4.54, p = 0.048) (top) as well as NDDI-E (−0.8250 ± 2.39 vs. 0.9091 ± 1.973) (bottom). However, this improvement did not persist to 2 weeks (BDI: −1.25 + 4.68 vs. −1.40 + 3.81, p = 0.931; NDDI-E: −0.300 ± 2.62 vs. 0.182 ± 2.40, p = 0.618) or 4 weeks (BDI: −1.00 + 3.55 vs. −.727 + 5.90, p = 0.315; NDDI-E: −0.3684 ± 2.54 vs. 0.7273 ± 2.55, p = 0.264). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

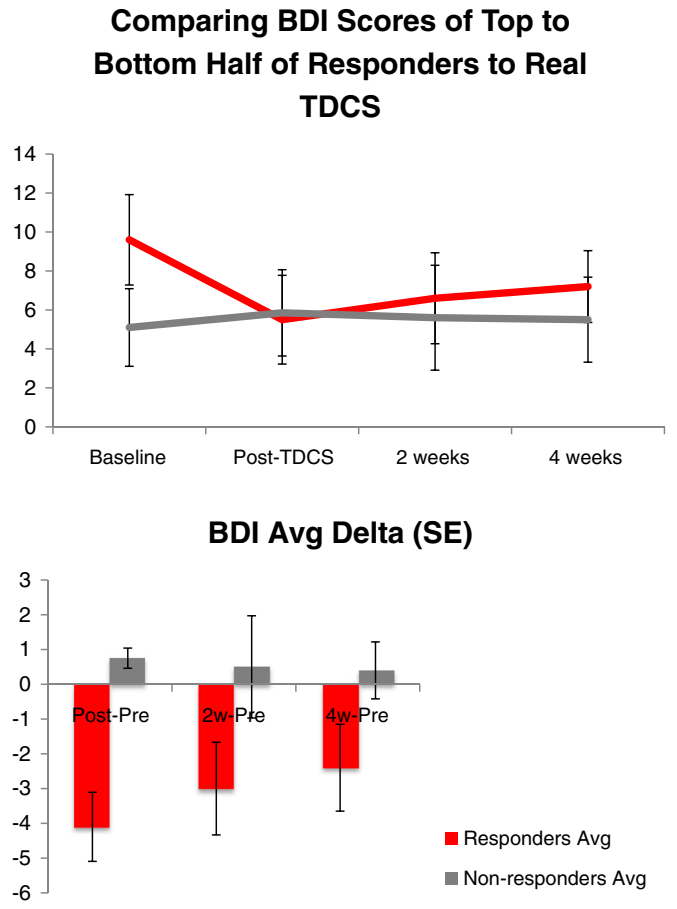

Fig. 3. Post-hoc analysis of Beck Depression Inventory (BDI). In a post-hoc analysis, the subjects who received real TDCS who had the most improvement on their BDI scores (red bar, in the top 50% of BDI improvement scores) appeared to have more depressive symptoms at baseline, compared to subjects who did not respond as well (gray bar, in the lower 50% of BDI improvement scores), although this was not significant (BDI: 9.6 ± 7.34, 5.1 ± 6.30, p = 0.158). Subjects who responded to stimulation tended to have continuously lower BDI scores at 2 weeks and 4 weeks although this was not statistically significant. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

reach statistical significance after Benjamini–Hochman correction for multiple comparisons (see Fig. 4).

To evaluate for more subtle localized and lateralized effects within these regions, post-hoc testing (*T*-test comparison) of power changes at single electrodes (F3, C3, F4, C4) was performed. Sham stimulation was associated with a decrease in delta power whereas real stimulation was associated with an increase in delta (F3: p = 0.082, C3: p = 0.074) and theta (C3: p = 0.072) power in the left frontocentral region although this did not reach significance. This suggests that modulation effects are localized to the cortical region underneath the anodal electrode.

3.9. Side effects

Subjects appeared to be effectively blinded to randomization condition, as their ability to guess whether they were assigned to receive real or sham stimulation was no greater than chance (X^2 = 0.14, p = 1.000). Subjects reported few side effects, with no difference in reported side effects between real and sham TDCS across any of the polled effects, including headache, neck pain, scalp pain, scalp burns, skin redness, sleepiness, concentration, acute mood change, or other effects.

4. Discussion

4.1. Depression

Subjects who received real, but not sham, TDCS administered at fixed dose at 2 mA for 20 min for five consecutive days demonstrated a modest but significant improvement in depressive symptoms immediately after the stimulation course. The effect was moderate, as measured by 2 independent measurements of mood, BDI-II and NDDI-E. At the group level, these improvements in depression scores did not persist to the 2- or 4-week follow-up point.

There was a large degree of heterogeneity in baseline BDI scores as well as variance in the degree of improvement. Post-hoc analysis revealed a trend for subjects receiving real TDCS who improved most on their BDI scores (defined as falling within the top 50% of BDI-II improvement scores) to have greater depressive symptoms at baseline. Furthermore, subjects who responded to stimulation tended to maintain lower BDI-II scores at 2 weeks and 4 weeks although this was not statistically significant (Fig. 3). Of note, the decrease in BDI scores among patients receiving real TDCS was possibly limited by a floor effect; a significant decrease in depression scores may have been seen as a main effect if the treatment was extended to patients with higher baseline BDI-II and NDDI-E scores. For reasons of safety, we excluded patients with severe depression or suicidality from the study, reasoning that these

Table 2
Changes in seizure characteristics and neuropsychological testing over time. Raw scores for seizure characteristics (monthly frequency and epileptiform discharge frequency for subjects who received sham and real TDCS). Subjects whose scores on any inventory changed more than 2.5 SD from the mean were removed from this analysis. Comparisons were made via a repeated measures analysis of variance (ANOVA) model with 2 factors, including one within-subject variable (time, 4 levels) and one between-subjects variable (condition, 2 levels, real vs. sham). F and p values for Wilks's lambda are reported.

	Sham TDCS (SD)				Real TDCS (SD)				F*	p
	Baseline	Post-TDCS	2 weeks	4 weeks	Baseline	Post-TDCS	2 weeks	4 weeks		
Seizure frequency	0.79 (1.75)	0.10 (0.316)	0.25 (0.622)	0.17 (0.39)	0.14 (0.65)	0.06 (0.24)	0.05 (0.22)	0.05 (0.22)	1.019	0.402
Interictal discharge frequency mean	8.89 (23.80)	4.3 (12.97)	0.123 (0.33)	0.0 (0.0)	0.76 (3.06)	0.24 (0.73)	0.29 (1.14)	0.06 (0.32)	0.319	0.578
RAVLT 1–5	46.00 (8.759)	50.08 (8.196)	49.25 (9.156)	50.08 (10.825)	47.71 (25.574)	44.75 (10.422)	44.60 (9.9986)	43.76 (9.767)	0.422	0.739
RAVLT 6	8.58 (3.476)	8.917 (3.704)	8.83 (3.95)	8.33 (3.60)	7.76 (3.700)	7.571 (3.710)	7.65 (3.760)	8.6 (3.575)	2.450	0.084
RAVLT 7	6.67 (4.097)	7.75 (2.927)	8.17 (4.239)	7.67 (4.292)	7.24 (3.660)	6.62 (3.891)	7.10 (3.386)	7.05 (4.236)	1.290	0.297
Digits forward raw	10.83 (2.125)	11.25 (2.633)	11.24 (2.633)	11.67 (2.103)	10.50 (1.987)	9.90 (2.245)	11 (2.052)	11.20 (2.167)	2.350	0.94
Digit span backward raw	8.67 (1.371)	8.92 (2.712)	9.83 (2.517)	10.50 (2.316)	8.80 (1.989)	9.15 (2.43)	9.15 (2.540)	9.62 (2.479)	1.302	0.293
Letter number sequence raw	20.00 (3.516)	20.58 (4.033)	19.83 (3.099)	21.25 (2.563)	19.33 (2.436)	19.95 (2.110)	19.85 (2.889)	20.60 (2.087)	0.411	0.746
BDI-II	9.09 (6.564)	10.36 (7.379)	7.1 (8.319)	9.82 (6.615)	7.35 (7.043)	5.675 (6.914)	6.10 (7.772)	6.35 (6.277)	1.127	0.356
NDDI-E	12.36 (3.2)	13.27 (2.76)	12.54 (2.81)	13.09 (2.43)	12.05 (4.249)	11.225 (4.48)	11.75 (4.153)	11.42 (3.990) (3.706)	1.407	0.263
QOLIE total	62.50 (16.116)	62.58 (13.621)	68.42 (14.829)	66.50 (16.003)	65.30 (16.327)	67.60 (15.916)	67.80 (16.108)	68.94 (14.482)	1.185	0.333

* F ratio for One-Way ANOVA, from which p-value is calculated.

patients should seek more traditional modalities of psychiatric therapy. However, other studies studying the effect of TDCS on depression have included patients with moderate to severe depression [24,28,33,34], suggesting that future iterations may include patients with epilepsy with greater depressive symptoms. Indeed, our post-hoc analysis, combined with other studies, suggests that patients with moderate or severe depression may benefit more from TDCS therapy. These benefits may be additive with pharmacologic therapies, with data supporting such synergistic effects [44].

Our behavioral findings are consistent with two recent meta-analyses published, which found that TDCS was significantly superior to sham TDCS for the treatment of major depressive disorders, as measured by both continuous and categorical outcomes [44,45]. One meta-analysis including only randomized controlled trials of TDCS found a weighted mean reduction of 32.3% (range: 14.6% [33] to 60% [25]). However, it should be noted that another meta-analysis which included categorical outcomes (response and remission rates) did not find a significantly positive effect of TDCS [46].

4.2. Memory

Ours was a negative study for the use of TDCS to enhance memory function. There were no significant improvements in any of the working memory tasks, including LNS or Digit Span. Likewise, there were no improvements in delayed verbal recall, as measured by the RAVLT. In fact, there was a suggestion that patients who received sham stimulation improved more on one measure of the delayed memory task (RAVLT 6) after 5 sessions compared to those who received real stimulation.

Lack of improvement in measures of working memory is consistent with several recent meta-analyses on the effect of TDCS on working memory function when applied to the DLPFC [31,47]. These meta-analyses employed a different measure of working memory, which is more widely used, the n-back task, and considered both an online and offline delivery of stimulation. One meta-analysis found a significant improvement in reaction time but not in accuracy [31]. This study also found a significant main effect of offline rTMS applied to the DLPFC in working memory [31].

4.3. Safety of TDCS in epilepsy

To our knowledge, our study was the first to apply TDCS stimulation in an attempt to enhance cortical (left DLPFC) function in a population with epilepsy. A 5-day course of TDCS stimulation was safe and well-tolerated in a group of patients with well-controlled partial epilepsy. Patients receiving stimulation did not experience an exacerbation of seizure frequency or an increase in interictal discharge frequency

Table 3
Changes in neuropsychological testing after 5-day stimulation.

	Sham TDCS (SD)		Real TDCS (SD)		F*	p
	Baseline	Post-TDCS	Baseline	Post-TDCS		
Seizure frequency (N = 28)	0.30 (0.949)	0.10 (0.316)	0.00 (0.000)	0.06 (0.236)	2.402	0.133
Interictal discharge frequency	0.0 (23.80)	0.0 (12.97)	0 (3.06)	0 (0.73)	1.460	0.239
RAVLT 1–5 (N = 33)	46.00 (8.759)	50.08 (8.196)	47.71 (25.574)	44.75 (10.422)	1.244	0.273
RAVLT 6	8.58 (3.476)	8.917 (3.704)	7.76 (3.700)	7.571 (3.710)	0.290	0.594
RAVLT 7	6.67 (4.097)	7.75 (2.93)	7.24 (3.604)	6.62 (3.892)	2.860	0.101
Digits forward raw	10.83 (2.125)	11.25 (2.633)	10.50 (1.987)	9.90 (2.245)	4.537	0.041
Letter number sequence raw	20.00 (3.516)	20.58 (4.033)	19.33 (2.436)	19.95 (2.110)	0.002	0.963
BDI-II	9.09 (6.564)	10.36 (7.379)	7.35 (7.04)	5.675 (6.914)	4.255	0.048**
NDDI-E	12.36 (3.2)	13.27 (2.76)	12.05 (4.249)	11.225 (4.48)	4.194	0.050**
QOLIE total (QOLIE-1)	62.50 (16.116)	62.58 (13.621)	65.30 (16.366)	67.95 (15.596)	0.987	0.328
QOLIE-31 (QOLIE-2)	69.09 (12.004)	73.73 (7.669)	76.19 (12.440)	75.24 (14.007)	3.243	0.082
QOLIE scaled (QOLIE-3)	49.75 (9.882)	49.75 (8.465)	51.43 (10.127)	53.10 (9.481)	1.091	0.304
QOLIE cognitive (N = 33)	46.58 (8.702)	46.83 (7.998)	48.10 (9.492)	49.14 (8.446)	0.175	0.679
QOLIE emotional (N = 33)	48.08 (9.307)	50.08 (8.670)	51.19 (9.234)	52.90 (9.016)	0.017	0.899
QOLIE energy (N = 33)	46.67 (7.924)	47.33 (7.935)	51.14 (9.794)	52.57 (9.389)	0.144	0.707
QOLIE medication	49.42 (11.098)	50.83 (9.980)	53.71 (10.036)	54.10 (9.695)	0.134	0.717
QOLIE social	52.25 (10.244)	51.08 (7.229)	52.05 (8.225)	53.10 (8.154)	1.234	0.275

* F ratio calculated from one-way ANOVA, from which p-value is calculated.

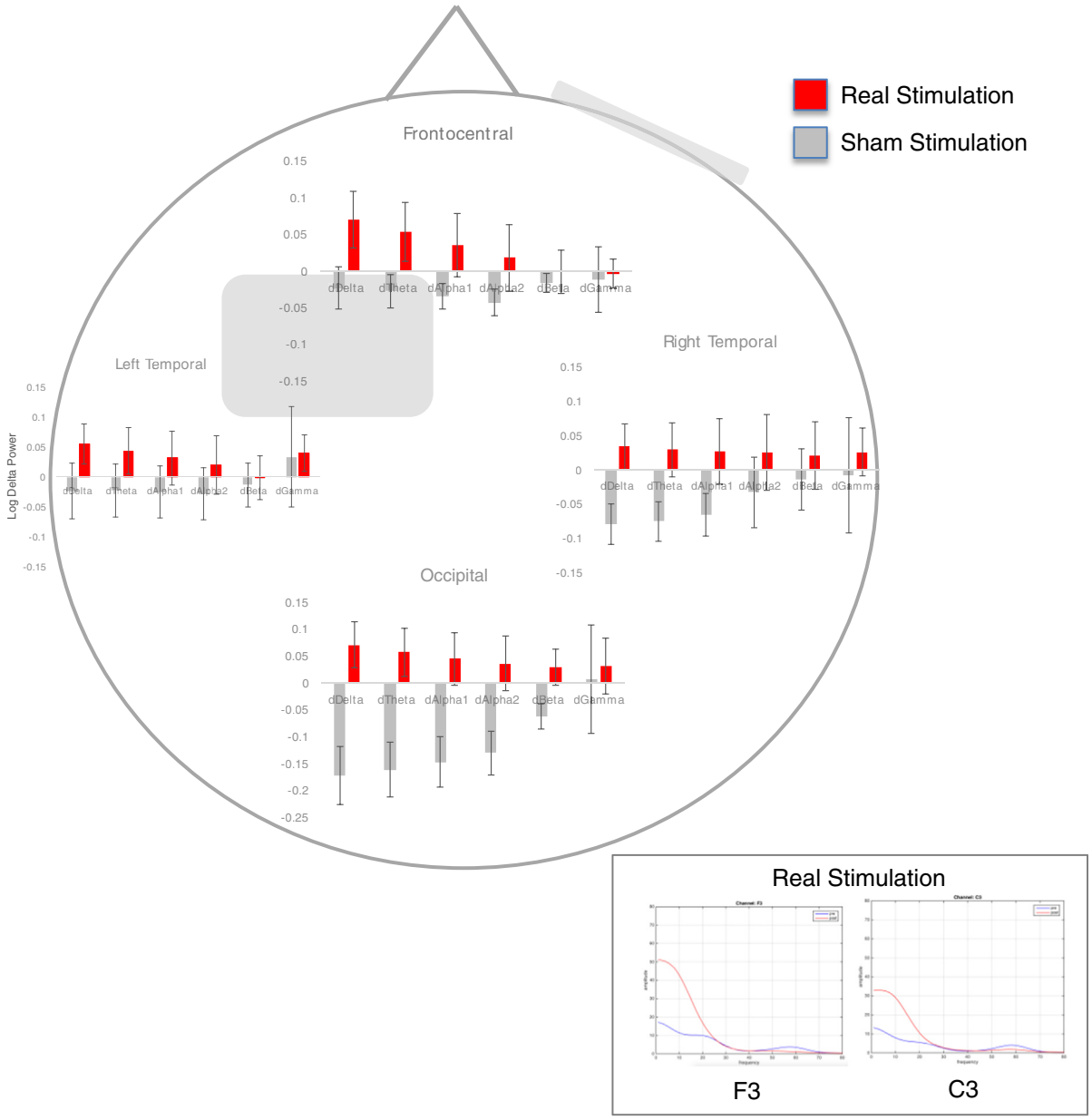

Fig. 4. Electroencephalogram regional power changes. Comparative changes in EEG spectral power. Real vs. TDCS induces changes in spectral power in the delta, theta, and low alpha frequency bands in the frontocentral and occipital regions. Average power was calculated for common frequency bands (delta: 1–4 Hz, theta: 5–7 Hz, low alpha: 8–10 Hz, high alpha: 11–13 Hz, beta: 14–32 Hz, and low gamma: 35–55 Hz). Power values were log transformed prior to statistical analysis. Four topographic regions of interest were created by averaging power values across several electrode sites: frontocentral (Fp1, Fp2, F3, F4, C3, C4), left temporal (F7, T3, T5, A1), right temporal (F8, T4, T6, A2), and occipital (O1, O2). Power values were log transformed prior to statistical analysis. A repeated measures ANOVA was performed, with condition (2 levels, sham vs. real TDCS) as the between-subjects variable, and time (2 levels, pre vs. post condition) as the within-subjects variable. Resting EEG power values for each frequency band for a given ROI (frontocentral, left temporal, right temporal, and occipital) was calculated as the dependent variable. An independent samples *T*-test was performed for delta power for each frequency band at each ROI. There was an increase in delta, theta, and low alpha frequency spectral power seen over the frontocentral region, as well as the occipital region, although this did not reach statistical significance. In post-hoc testing (*T*-test comparison of power changes at each electrode), the greatest effect was on delta and theta power in the left frontocentral region although this did not reach significance (delta F3, $p = 0.082$, C3, $p = 0.074$; theta C3, $p = 0.072$). On average, sham stimulation was associated with a decrease in delta and theta power whereas real stimulation was associated with an increase in delta and theta power over the left frontocentral region. The inset demonstrates a representative subject who received real TDCS, which demonstrated a broad increase in delta, theta, and low alpha frequency activity in F3/C3, corresponding to the region under the electrode.

as measured immediately after stimulation or during a 2- and 4-week follow-up.

Patients receiving real TDCS had an average rating between 1 (absent) and 2 (mild) for each of the polled side effects, including headache, neck pain, scalp pain, scalp burns, tingling, skin redness, sleepiness, concentration, and acute mood change. These reports did not differ significantly from patients who received sham stimulation. We do not believe that findings of safety or tolerability were biased by dropout rates as there were similar dropout rates between subjects receiving active and sham. Our findings are comparable to other published reports of safety and tolerability data [48].

Previous studies using TDCS in patients with epilepsy have sought to use cathodal stimulation over the epileptogenic cortex to dampen excess hyperexcitability [49]. In a randomized, sham-controlled study applying a single session of cathodal stimulation (1 mA, 20 min) over the epileptogenic zone, with the anode placed over an area without epileptiform activity, there was a significant reduction in the frequency of interictal epileptiform discharges, with a trend toward decrease in

seizure frequency [50]. Likewise, in another study involving 36 children with partial epilepsy, a single session of cathodal TDCS (1 mA, 20 min) suppressed epileptiform activity for 48 h and demonstrated a trend toward seizure reduction [51]. In addition, several case reports and small case series demonstrate safe and well-tolerated application of cathodal TDCS over the epileptogenic cortex [52], including transient reduction in spike frequency in continuous spike and slow wave during sleep [53].

Our study supports the conclusion that, with appropriate safety precautions, TDCS in patients with epilepsy is well-tolerated and safe [48]. Such tolerability and safety profile suggests that further investigation involving TDCS, including anodal stimulation, in patients with partial epilepsy would be safe, at least for patients with well-controlled seizures.

4.4. Changes in EEG spectral power

We found increased spectral power for real TDCS in the delta and theta frequency bands in the left frontocentral (F3/C3) region after anodal stimulation compared to baseline. The areas of significant spectral increase in the real TDCS condition in the delta and theta frequency bands may correspond to the region of greatest expected induced voltage intensity (frontocentral) although the differences did not reach significance. Changes in lower frequency oscillations (delta, alpha, and theta) may represent the integrated activity of large numbers of neurons [54].

Only a few studies measured the effect of TDCS on resting state EEG oscillatory power. For anodal stimulation, an increase in power of alpha and theta frequencies has been reported across a wide field (although no sham comparison was made) [55] while two other studies did not find any induced change of anodal stimulation on spectral power [56,57]. Regarding cathodal stimulation, there have been heterogenous reports of EEG changes, including a broad increase in delta oscillations compared to sham [58], a broad increase in alpha and theta oscillations (although this was similar in direction and magnitude of change with anodal stimulation) [55], a decrease in alpha activity [57], and no changes [56]. In a review of neurophysiological outcomes of TDCS, Horvath et al. comment on the lack of reliable and consistent findings across different spectral bands across studies, which may be partly due to the lack of consistency in protocols [47].

4.5. Summary

Our pilot study suggests that TDCS may be an effective, and safe, adjunctive treatment for patients with well-controlled partial epilepsy and mild to moderate depression. There is a suggestion that patients with higher depression scores at baseline may benefit most from TDCS. However, at this time, the modest antidepressant effects of TDCS, as demonstrated by this pilot study, do not currently make TDCS a viable clinical option for mood disorders. Rather, our findings suggest that TDCS may be safely explored for patients with epilepsy suffering from more significant depressive symptoms.

In the future, patients with epilepsy with moderate and even severe depression should be included in studies to assess the efficacy of TDCS for mood dysfunction. Further studies may explore how TDCS parameters (such as stimulation intensity, duration, and novel montages, using modeling guidance), alone and in combination with psychopharmacology and behavioral interventions, may be optimized for behavioral benefits.

Conflict of Interest

There is no conflict of interest.

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