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## PROCEEDINGS #51: 4 MA ADAPTIVE TRANSCRANIAL DIRECT CURRENT STIMULATION FOR TREATMENT-RESISTANT DEPRESSION: EARLY DEMONSTRATION OF FEASIBILITY WITH A 20-SESSION COURSE

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### 1. Abstract

**Background**: Evidence supporting the use of transcranial direct current stimulation (tDCS) as a treatment for major depressive disorder (MDD) remains inconclusive. One suggested reason is that commonly used treatment protocols fail to deliver enough current to adequately modulate the neural targets.
**Methods**: Single-blind clinical trial of high-dose (4 milliamp) tDCS targeting the prefrontal cortex to assess for safety, tolerability, and efficacy.
**Results**: tDCS was safely applied to two patients with medication-resistant MDD. Both patients experienced significant improvements in depressive symptoms.
**Conclusions**: Based on a short case series, this paper is the first to demonstrate that 4 mA tDCS can be safe, well-tolerated, and potentially efficacious in the treatment of MDD. We present some promising preliminary findings of safety and treatment efficacy for two patients who failed multiple antidepressant medications.

### 2. Introduction

Major depressive disorder (MDD) is a worldwide problem, afflicting 1 in 23 people with a lifetime prevalence of 20.6%[1]. It is the leading causes of disability in the world[1]. New treatment options are desperately needed, as approximately 1/3 of patients fail to respond even after numerous pharmacotherapeutic trials[2]. Neuromodulation therapies have grown in popularity with the FDA approval of transcranial magnetic stimulation for MDD in 2008. Another form of neuromodulation, transcranial direct current stimulation (tDCS), has been studied extensively for the treatment of MDD with mixed results[3]. tDCS involves the application of low-intensity electrical stimulation to different targets on the scalp. Usually the current delivered is in the range of 1 to 2.5 mA, with application for 20-30 minutes daily for several weeks. Some studies have suggested that higher current intensities, on the order of 4.5 mA or more, are needed to adequately modulate neuronal activity in the brain, whereas those 3 mA and lower failed to do so[4]. Similarly, a meta-analysis of tDCS studies for MDD has proposed that higher tDCS "doses" would lead to greater clinical effects[5]. To date, no studies have attempted to apply currents greater than 2.5 mA to the prefrontal cortex of patients with MDD[6]. This dose has been demonstrated safe in other populations, such as stroke patients[7–9]. This trial aimed to investigate the safety, tolerability, and efficacy of 4 mA tDCS applied to the prefrontal cortex of subjects suffering from a major depressive episode.

### 3. Methods

**Subjects:** This was a single-blind (rater blinded) clinical trial conducted with IRB approval at Washington University in St. Louis and registered with Clinicaltrials.gov. Patients were recruited from the Washington University Treatment Resistant Depression Registry and advertisements placed around the hospital campus. Patients were screened by phone and then by expert psychiatric interview using the Mini-International Neuropsychiatric Interview (MINI) prior to enrollment, and met criteria for a DSM-5 diagnosis of major depressive disorder. Other medications were continued with treatment as usual.
**Device and Stimulation:** The tDCS device used was a tDCS 1x1 model 1300A (Ybrain, Republic of Korea) and the headband and stimulation pads (5x5 cm) were Soterix Medical SNAPstraps and SNAPpads (Soterix Medical, New York, NY). Anode was placed over the left dorsolateral prefrontal cortex (DLPFC) scalp region, and cathode was placed over the right DLPFC region. The stimulation protocol was 4mA current delivered for 20 minutes duration with a brief 30-second ramp-up and ramp-down for tolerability. Subjects had continuous access to the Ybrain Android-based tablet software that gave them the ability to temporarily ramp down ("RELAX") the stimulation intensity by pressing a button if it became uncomfortable. Stimulation was delivered 5 days per week for 4 weeks. Task engagement was standardized - all patients were given adult coloring books and instructed to color for the duration of stimulation.
**Evaluations:** Evaluations were conducted by trained, blinded psychiatrists at the following time points: pre-stimulation; post-10 stimulations (halfway point); post-20 stimulations; 1-week follow-up; 2-week follow-up. The raters were not told the specifics of the study and led to believe that some patients may receive sham treatments during the trial. The primary outcome measure was a change in Montgomery-Asberg Depression Rating Scale (MADRS) scores. Additional outcome measures included the Hamilton Depression Rating Scale (HAMD-17), the Hamilton Anxiety Rating Scale (HAM-A), the Clinical Global Impression Scale (CGI), the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR), the Montreal Cognitive Assessment (MOCA), the NIH Toolbox Cognitive and Emotional Batteries, the Temperament and Character Inventory (TCI), and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), amongst other tests. Physical and neurologic exams were conducted weekly, and patients were assessed daily by a physician to monitor for side effects. Pain visual analog scales (VAS) were recorded six times during each stimulation session to ensure safety and tolerance of the treatments (baseline, 2 mins, 5 mins, 10 mins, 15 mins, and 18 mins into stimulation).

### 4. Results

No statistical analyses were conducted as this is an ongoing clinical trial. At the time of this writing, two patients (n=2) had successfully completed the tDCS protocol

| Demographics | Pt. 1 | Pt. 2 |
|---|---|---|
| Age | 56 | 58 |
| Gender | M | M |
| Failed Medication Trials | 4 | 5 |
| MADRS Change (Pre to Post, %) | ↓100% | ↓61% |
| Change in Q-LES-Q (Pre to Post) | ↑59% | ↑37% |
| Average Pain VAS | 1.1 | 1.6 |
| Max Pain VAS | 3 | 3 |
| Total Uses of "RELAX" Feature | 0 | 0 |
| NIH Toolbox Z-Score Change, Fluid Intelligence | ↑1.1 | ↑0.8 |
| NIH Toolbox Z-Score Change, Crystallized Intel. | ↑0.2 | ↔0 |
| HAM-D Change (Pre to Post, %) | ↓100% | ↓41% |
| QIDS-SR Change (Pre to Post, %) | ↓100% | ↓64% |
| HAM-A Change (Pre to Post, %) | ↓100% | ↓50% |
| CGI-S Baseline to Final Score | 4 → 1 | 4 → 3 |

**Table 1. Demographics & outcome measures.** Changes are represented as a percentage change from the baseline score to the immediate post-stimulation score. Green boxes indicate an improvement in symptoms. Orange boxes highlight measures related to tolerability of the stimulus.

(Table 1). Both patients were diagnosed with unipolar major depressive disorder, and neither had any psychiatric comorbidities. Both patients tolerated the treatment well, noting scalp pain and tingling during the stimulation, but otherwise no headaches, scalp burns, or other side effects. There were no changes on serial physical or neurologic exams. The patients on average complained of VAS scales of pain ranging from 1-3 out of 10 (Table 1). Notably, neither patient had to press the "RELAX" button to decrease stimulus intensity at any point (Table 1).

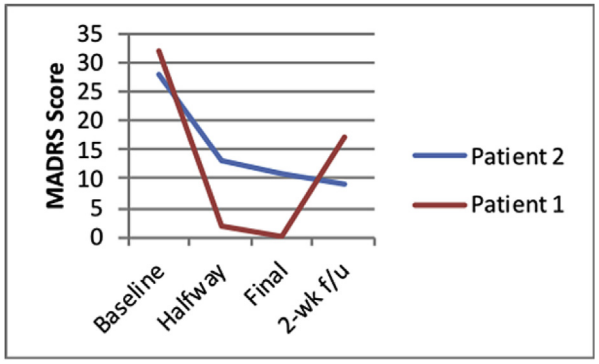


**Figure 1. MADRS scores.** Both patients met response criteria (MADRS score decreased >50%) by the halfway point (2 weeks into treatment). Patient 1 had a partial relapse by the 2-week follow-up, whereas patient 2 continued to improve.

On all depression measures (MADRS, HAMD-17, QIDS-SR, CGI) patients demonstrated improvement from baseline to week 4 (Table 1 & Figure 1), with robust responses as early as week 2. Patient 2 maintained these benefits out to the 2-week follow-up visit, but patient 1 did not (Figure 1). Also notably, improvements were seen in anxiety (HAM-A), quality of life (Q-LES-Q), and a cumulative measure of cognitive flexibility and reasoning on the NIH Toolbox termed Fluid Intelligence (Table 1). Other measures of cognition (MOCA and NIH Toolbox Crystallized Intelligence) did not change significantly.

## 5. Discussion and Conclusion

Use of 4 mA tDCS appears to be safe, well-tolerated, and potentially efficacious in the treatment of major depressive disorder. Considering the equivocal results often found with meta-analyses of 1-2 mA tDCS for MDD, as well as the suggestions in the literature that higher "doses" of tDCS may lead to improved efficacy of treatment, this represents a significant finding which should prompt further investigation of higher-dose tDCS for MDD and other neuropsychiatric illnesses. The improvements in anxiety and cognitive functioning seen as well in this single-blind study warrant further investigation with larger study samples and sham-controlled protocols.

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## PROCEEDINGS #52: DEVELOPMENT OF SURFACE EMG- TRIGGERED CLOSED LOOP STIMULATION FOR INDIVIDUALS WITH SPINAL CORD INJURY

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## 1. Abstract

**Object:** To develop surface EMG-triggered closed loop stimulation for individuals with spinal cord injury. The system can detect muscles' EMG signals and trigger transcranial magnetic stimulation (TMS) and peripheral nerve stimulation (PNS)
**Method:** We utilized a data acquisition board to collect muscles' EMG and exertion force in real-time. The data acquisition board connects to an Arduino micro-controller which sends analog output to TMS and PNS machine to generate the stimulation. One user graphic interface (GUI) was developed to allow researchers to configure the trigger properties including the threshold of EMG/force to activate the trigger and the interstimulus interval between TMS and PNS. This GUI also provides visual feedback to study participants to guide them to perform the anticipated movement exertion to trigger TMS and PNS.
**Results:** The system can reliably deliver stimuli with 20-25 milliseconds latency when triggered by EMG/pinch force between the range of 5 and 100 percent of maximal voluntary contraction. The straightforward user graphic interface provides clear and easy to follow instructions for the participants to complete the hand pinch task and trigger the stimulation successfully.
**Conclusion:** This working prototype system has been applied in our ongoing human study to test different combinations of TMS and PNS triggered by EMG signals to improve hand function after cervical SCI. We anticipate that EMG-triggered stimulation will provide significant improvement in motor neuron excitability compared with passively delivered stimulation.

## 2. Introduction

The spike timing-dependent plasticity (STDP) or Hebbian synaptic learning rule has been widely studied for inducing long term potentiation (LTP) or long term depression (LTD)[1,2]. This type of plasticity illustrates that synapses in the central nervous system can be strengthened or weakened by repeatedly paired presynaptic and postsynaptic action potentials that are fired synchronously or asynchronously[3]. These concepts have mostly been demonstrated in model systems such as in brain slices or dissected sea slugs[1,4].

Several experiments have been performed in humans using paired external stimulation such as transcranial magnetic stimulation (TMS) or peripheral nerve stimulation (PNS) in attempts to strengthen synapses. In persons with SCI, Bunday and Perez[5] utilized supra-threshold TMS over the hand motor cortex paired with high-intensity back- propagating ulnar nerve PNS to target the synapses at the cervical spinal level. They synchronized repetitive pairs of TMS pulses to arrive at cervical motor neurons 1-2 ms before arriving antidromic PNS pulses (STDP), and compared that to repetitive pairs of PNS pulses timed to reach motor neuron dendrites 5 ms before TMS (control). After 100 pairs of stimuli at 0.1 Hz, the size of the MEP of the first dorsal interosseous (FDI) increased in both spinal cord injured and healthy participants, and the manual dexterity