Transcranial Direct Current Stimulation (tDCS) for the Treatment of Depression in HIV: A Mixed Methods Safety and Feasibility Study

Disclosures

- Edith L. Fisch Award for Innovation in Neurostimulation, New York University, School of Medicine
- NYU College of Nursing Pless Center for Nursing Research
- CTSI Grant # 5UL1RR029893. Supported in part by grant 1UL1RR029893 from the National Center for Research Resources, National Institutes of Health

Objectives

1. Identify barriers and facilitating factors for treating MDD in an HIV-infected patient population.
2. Examine tDCS as an alternative non-invasive treatment MDD.
3. Analyze how quantitative and qualitative methods are combined in an open-label pilot feasibility study and inform future research (e.g., recruitment strategies and study design).
New Populations: HIV-infected Persons with MDD

- Up to 48% of HIV patients have MDD comorbidity (Rabkin et al, 2008)
- Use of antidepressants + MH therapy, or MH therapy alone, associated with increased HAART utilization (N = 1,371; Cook, et al, AIDS Care, 2006)
- Depression significantly worsens HAART adherence and HIV viral control. Compliant SSRI use is associated with improved HIV adherence and laboratory parameters (CD4 cell count and viral load). (N= 3,359; Horberg, et al, JAIDS, 2008)

Limitations of Antidepressant Meds in HIV Population

- Fluoxetine (Prozac)* 10 - 60 mg/day
- Paroxetine (Paxil)* 10 - 60 mg/day
- Venlafaxine (Effexor) XR 75-300 mg qd
  - useful in SSRI nonresponders
  - extended release form preferable
  - may decrease indinavir levels - significance unknown
  
*More likely to cause drug interactions

American Psychiatric Association Practice Guidelines and other reference documents

www.psych.org

Common Underlying Pathways of Depression and Pain

- Dysregulation of Serotonin (5HT) and Norepinephrine (NE) in the brain are strongly associated with depression
- Dysregulation of 5HT and NE in the spinal cord may explain an increased pain perception among depressed patients
- Imbalances of 5HT and NE may explain the presence of both emotional and physical symptoms of depression
- Brain is an electrical and chemical organ, constantly converts electrical information, to chemical signals, and then back again into more electrical information

Adapted from References:

### Brain Areas Involved in Pain Processing “Pain Matrix”

The most commonly activated cortical and sub-cortical regions in pain processing are:

- The primary and secondary somatosensory cortices (S1, S2)
- Anterior cingulate cortex (ACC)
- Insular cortex
- Prefrontal cortex (PFC)
- Thalamus
- Basal Ganglia (BG)
- Cerebellum

*(From Schweinhardt & Bushnell, 2010)*

### Understanding a Possible Common Pathophysiology to Pain and Neuropsychiatric Symptoms

- Central sensitization is implicated in a number of chronic pain disorders including whiplash, TMJ pain, chronic low back pain, osteoarthritis, fibromyalgia, chronic fatigue syndrome and chronic tension headaches
- There is a possible role of central sensitization in rheumatoid arthritis and migraine headaches
- Central sensitization encompasses:
  - Altered sensory processing in the brain
  - Malfunctioning descending anti-nociception mechanisms
  - Increased pain facilitating pathways
  - Pain windup (repeated painful stimulation at peripheral nerves group C fibers leading to increasing electrical response in corresponding spinal posterior horn neurons)

### Hypotheses

- “Vulnerable” individuals
- Limitations in limbic “top down” regulation (e.g., those with limited emotional processing such as persons diagnosed with borderline personality disorder)
- There is likely a continuum of vulnerability
  - Experience a significant physical or emotional event and this leads to a central sensitization disorder (e.g., neuropathic pain, tinnitus, fibromyalgia)
- Those disorders may respond to targeted brain treatments (medications, brain stimulation such as TMS or transcranial direct current stimulation) or psychotherapy (e.g., CBT or DBT)
- Cytokines exert neuromodulatory effects through sensitization so targeted brain stimulation treatments can influence the expression of proinflammatory cytokines
- Proinflammatory Cytokines involved in both the pathogenesis of depression and altered pain processing
Early Electric Treatments

- Ancient Greeks and Romans used electric ray fish to treat pain from headaches, childbirth, gout, and other conditions.
- Electric rays generate electrical currents up to 220 V, 10 A, and pulse repetition rates of 0.6 Hz -> pretty good electrical stimulators.

Modern Electric & Magnetic Therapies in Psychiatry

- Deep Brain Stimulation (DBS)
- Transcranial Magnetic Stimulation (TMS)
- Transcranial Direct/Alternating Current Stimulation (TDCS/TACS)
- Vagus Nerve Stimulation (VNS)
- Craniocaudal Electrical Stimulation (CES)
- Magnetic Seizure Therapy (MST)
- Electroconvulsive Therapy (ECT)

- All interventions stimulate the brain and/or cranial nerves with induced electric fields (= induced electrical currents).
- What differentiates them are the parameters of stimulation:
  - electrode/coil configuration
  - electrical current waveform parameters
<table>
<thead>
<tr>
<th>Technique</th>
<th>Clinical Utility</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECT</td>
<td>Severe depression and schizophrenia</td>
<td>Highly effective (76-80% remission rate)</td>
<td>General anesthesia, seizure induction, cognitive side effects</td>
</tr>
<tr>
<td>TMS</td>
<td>FDA approved for depression, studies in other disorders</td>
<td>Non-invasive, no significant side effects</td>
<td>Modest efficacy: 24% response, 17% remission after 6 weeks</td>
</tr>
<tr>
<td>MST</td>
<td>Under study for depression</td>
<td>Reduced cognitive side effects compared to ECT</td>
<td>General anesthesia, seizure induction</td>
</tr>
<tr>
<td>VNS</td>
<td>Medication-resistant depression (FDA approved)</td>
<td>Less invasive than DBS</td>
<td>Requires surgery, limited efficacy, slow response: 16% remission after 12 months</td>
</tr>
<tr>
<td>DBS</td>
<td>Under study for treatment-resistant depression</td>
<td>Focal targeting of deep brain structures, works in some patients</td>
<td>Requires brain surgery, effectiveness under study</td>
</tr>
<tr>
<td>tDCS</td>
<td>Under study for depression, etc.</td>
<td>Non-invasive, no significant side effects, neuromodulatory effects</td>
<td>Randomized controlled trials support efficacy</td>
</tr>
<tr>
<td>CES</td>
<td>Claimed wide range of conditions</td>
<td>Non-invasive, no significant side effects</td>
<td>Efficacy &amp; mechanisms unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric Drugs</th>
<th>Brain Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic mechanisms</strong></td>
<td><strong>Biochemical</strong></td>
</tr>
<tr>
<td><strong>Focality</strong></td>
<td>Unfocal (delivered through bloodstream)</td>
</tr>
<tr>
<td></td>
<td>=&gt; side effects</td>
</tr>
<tr>
<td><strong>Speed of acute physiological response</strong></td>
<td>Slow (minutes to hours)</td>
</tr>
<tr>
<td></td>
<td>=&gt; alters baseline concentration of chemicals</td>
</tr>
<tr>
<td><strong>Ease of administration</strong></td>
<td>Easy (pills)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Basic Bioelectric Mechanisms of Brain Stimulation**

- **Electric Stimulation**
  - Electrical current
  - Electodes
  - Electric field
  - Change in neural activity

- **Magnetic Stimulation**
  - Electrical current
  - Coil
  - Magnetic field
  - Electric field
  - Change in neural activity
Why are some patients more prone to ongoing symptoms, pain, depression, generalized distress and more refractory to treatment? What can we do to help them?

A Treatment Wish List

- An evidence-based treatment for depression and pain
- Focus and dose that can be personalized
- Faster onset than medications
- Acceptable to those who cannot tolerate medications due to side effects, med interactions and comorbidities
- Adjunct treatment for those reporting partial relief from other treatments (safely combined/optimizing response)
- Feasible for patients with low performance status (minimal patient effort or attention)
- Clinically tested in racial and ethnic minorities
- Well tolerated, brief, safe, easy to administer and inexpensive

Noninvasive Brain Stimulation: Transcranial Direct Current Stimulation (tDCS)

- Noninvasive technique for modulation of cortical excitability
- Low intensity direct current applied with 2 electrodes penetrates the scalp to the brain influencing neuronal excitability and modulating firing rates of individual neurons
- Influences dopaminergic, adrenergic and serotonergic neural circuits
Transcranial Direct Current Stimulation: The Change in Cortical Excitability Depends on Polarity of the Current

It is well accepted that:

1. Anodal tDCS increases cortical excitability since cortical neurons are depolarized at the subthreshold level
2. Cathodal tDCS decreases cortical excitability, as cortical neurons are hyperpolarized

Nitsche and Paulus, 2001; Nitsche et al., 2003

---

tDCS for Depression

(Rigonnati et al., 2008 & Fregni et al., 2006)

Figure 2: Effects of tDCS over DLPFC as compared with sham and antidepressant fluoxetine on depression relief in 42 patients with Major Depression.

Legend: Effects of fluoxetine were substantially delayed. tDCS had immediate effect that was stable for the entire observed period (6 weeks). T1: 2 weeks after tDCS delivered (5 sessions) in one study group or fluoxetine started in another study group. T2: 4 weeks. T3: 6 weeks after the study treatment.

---

Safety of Transcranial Direct Current Stimulation in 815 Sessions of 100 Chronic Patients

Knotkova, Nafissi, Das, Rosedale, Strauss, Leuschner & Cruciani, 2010

---
Safety Tolerability and Feasibility of tDCS for HIV+ Persons Racial and Ethnic Minorities with MDD

- Open-label study using 2 week block of stimulation (10 sessions, consisting of 20 min of 2 mA tDCS over DLPFC
- Phoressor II 850 PM using 2 electrodes (36cm²) placed over F3 position of EEG 10-20 system and the contralateral supraorbital region.
- Recruit racial/ethnic minorities
- HamD24 and MADRAS
- Cytokine assays
- Analyze characteristics of completers/ non-completers
- Conduct qualitative interviews to incorporate subject input in future patient-centered treatment

To Recruit Racial and Ethnic Minorities: An Evidence-based Intervention to Minimize Racial/Ethnic Disparities in HIV/AIDS Clinical Trials: The ACT2 Project

Marya Viorst Gwadz, Ph.D.
Noelle Leonard, Ph.D.
Angela Banfield, MPH & the ACT2 Collaborative Research Team

Supported by:
- National Institute of Allergy and Infectious Diseases (NIAID: AI070005); Center for Drug Use and HIV Research (NIDA; P30 DA011041) at NYU College of Nursing; and the Center for AIDS Research (CFAR) at NYU School of Medicine

AIDS clinical trials (ACT) disparities (males and females)

NIAID, 2008
ACT2 intervention key characteristics

- Peer-driven intervention (PDI)
  - 6 hours total structured intervention
  - Interactive exercises
  - Not boring, not too didactic
  - Videotaped presentations
  - Peer education experiences

- Repetition of core messages
  - Including peer-to-peer interactions

- Brief individual session on clinical trials unit

- Liaison (navigation) through screening process

- Primary endpoint: Screening for ACTs

ACT Eligibility & Enrollment - in progress
(of those completed screening ACT2 arm, N=160; %)

Understanding Cytokine Assays as Safety and Potentially Efficacy Biomarkers

- Cytokines are soluble protein or peptide molecules that are secreted by lymphoid cells and act as communicators of defense processes against pathogens with inflammatory and anti-inflammatory effects.

- Types of cytokines include:
  - Interferons (IFN) (Induce antiviral resistance in uninfected tissue)
  - Interleukins (IL) (Direct other cells to divide and differentiate)
  - Colony stimulating factors (Direct the division and differentiation of bone-marrow stem cells and precursors of blood leukocytes)
  - Tumor necrosis factors (TNF) (Mediate inflammation and cytotoxic reactions)
Cytokines and HIV Infection

- Infection with HIV causes dysregulation of cytokines. In general, the cytokines with pro-inflammatory effects are increased, while the ones with anti-inflammatory effects are decreased.
- Specific cytokines which are increased in level include:
  - TNF-α, TNF-β, IL-1 and IL-6, IL-2, IL-7 and IL-1
- Specific cytokines which are decreased in level include:
  - IFN-α, IFN-β and IL-16, IL-10 and IL-13
  - IL-6 also increased in non-HIV, MDD

Cytokines and Depression

- Depression causes the body to be in a state of chronic stress which leads to overactivity of the sympathetic nervous system resulting in increased levels of cortisol and pro-inflammatory cytokines.
- Specific cytokines which are increased in level include:
  - IL-1, IL-6, IL-8, and TNF
- Profiling immune markers in saliva could potentially be used as a noninvasive diagnostic test for tracking progression of infection and depression and/or identifying treatment responders.

- Using a TH1/TH2 panel to detect cytokines and also Meso Scale Discovery (MSD) with
  - Electrochemiluminescence detection using sulfo-tag labels to emit light upon electrochemical stimulation by electrodes on the surface of the microplate, we found that cytokine levels were consistently higher in saliva versus plasma. For the cytokines detected in both fluids, the patterns in plasma and saliva were comparable.
Participant Characteristics

- 8 of the 10 seropositive patients initially enrolled completed the study (3 male; 5 female)
- On average, 54.1 years of age (SD=4.2yrs) (range=47-59)
- 7 of 8 identified as African American and 1 was nonhispanic white
- 4 were living with partners
- 3 had attended some college
- None of 8 were currently employed (including 3 who were disabled)
- Pre-tDCS administration, scores on mini-mental status exam ranged from 20 to 30 (mean=27.9) indicating (at most), mild cognitive impairment
- MADRAS, baseline scores ranged from 14 to 34 (mean=26.8; s.d.=6.7).
- HamD baseline scores ranged 17-34 (mean 26.3; s.d.=6.7)
Tests of Within-Subjects Contrasts for MADRAS

<table>
<thead>
<tr>
<th>Source</th>
<th>Contrast</th>
<th>Type III Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRAS</td>
<td>Pre-tDCS vs. Post-tDCS and 2 weeks later</td>
<td>2485.125</td>
<td>1</td>
<td>2485.125</td>
<td>59.600</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>Post-tDCS and 2 weeks later</td>
<td>144.500</td>
<td>1</td>
<td>144.500</td>
<td>7.692</td>
<td>.028</td>
</tr>
<tr>
<td>Error (MADRAS)</td>
<td>Pre-tDCS vs. Post-tDCS and 2 weeks later</td>
<td>291.875</td>
<td>7</td>
<td>41.696</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-tDCS and 2 weeks later</td>
<td>131.500</td>
<td>7</td>
<td>18.786</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Occurrence of Side Effects

- Unpleasant tingling/prickling sensation under electrode during one tDCS session: 2
- Mild dizziness: 1
- Restlessness: 1
- Swollen/painful ankles: 1
- Muscle spasm in thigh: 1
- Worsening of seasonal allergy: 1
- Disturbed GI (diarrhea and nausea): 1
- Tightness in chest due to asthma: 1
- Pain in left hip: 1

Sample Cytokine Concentration (pg/ml) (Based on Linear Regression Standard Curves)

<table>
<thead>
<tr>
<th>Pg/ml</th>
<th>Visit 1</th>
<th>Visit 10</th>
<th>2 Week F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>25.2</td>
<td>30.5</td>
<td>15.6</td>
</tr>
<tr>
<td>IL-4</td>
<td>77.1</td>
<td>30.6</td>
<td>15.5</td>
</tr>
<tr>
<td>IL-5</td>
<td>67.5</td>
<td>23.9</td>
<td>-</td>
</tr>
<tr>
<td>IL-6</td>
<td>10.3</td>
<td>9.2</td>
<td>-</td>
</tr>
<tr>
<td>IL-8</td>
<td>56.8</td>
<td>26.0</td>
<td>-</td>
</tr>
<tr>
<td>IL-10</td>
<td>18.9</td>
<td>6.8</td>
<td>-</td>
</tr>
<tr>
<td>IL-13</td>
<td>8.8</td>
<td>4.2</td>
<td>-</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>11.7</td>
<td>7.2</td>
<td>-</td>
</tr>
<tr>
<td>IFNγ</td>
<td>61.8</td>
<td>31.4</td>
<td>-</td>
</tr>
<tr>
<td>TNFa</td>
<td>50.6</td>
<td>31.4</td>
<td>-</td>
</tr>
</tbody>
</table>
RayBiotech Array Analysis

Meso Scale Discovery (MSD)

- Electrochemiluminescence detection: sulfo-tag labels emit light upon electrochemical stimulation by electrodes on the surface of the microplate
- Minimal background signals as only labels bound near the electrode surface are detected.
- 6 log-order dynamic detection range

MSD Sulfo-TAG™ Label
**Preliminary Themes for HIV-Depressed Persons Treated with TDCS**

**Treatment Was Cumulative**

My kids said: "Wow mommy, you really, really are coming back to being you. You know I feel wild, just think, once I get it all done, and I'll be better.

**Altruism**

You get HIV and a lot of people turn away, your family and even at your church. Being in the study helps me to feel less guilty and to give back to people who need help for depression like I did. What do they say: "Pay it forward!"

**Clearer Thinking with Reduced Perseveration, Rigidity of thinking and Drug cravings**

My mind wasn't cloudy, it was like I could see clearer, and I, I would, like I said earlier, if I would go to the kitchen and have coffee on my mind, I would forget, but when I was having treatment, I didn't forget, and I was on top of everything, you know. I was able to really function, in life you know. It helped to reduce my cocaine cravings.

---

**ECT Effects on Major Depression and Pain: Inflammatory molecules, Odor Acuity, Resting Neuroconnectivity (3T MRI) and Neurogenesis in the Dentate Gyrus (7 T MRI)**

- Psychopathology is associated with gabanergic deficits
- ECT helps inhibit high frequency gamma oscillation
- Olfaction is most primitive sense and first to phylogenetically older portions of cerebral cortex
- Most primitive sense and first to phylogenetically older portions of cerebral cortex
- The amygdala, hippocampus and orbitofrontal cortex receive projections from the piriform cortex and are key secondary olfactory areas and are key areas in olfactory processing

---

**Olfactory Pathway**
Future Aims

• To determine clinical effectiveness of a 2 week antidepressant tDCS treatment vs. sham, added to ongoing conventional antidepressant treatment of each participant with a follow-up period up to 3 months dependent on duration of treatment effects, and a two week open label tDCS treatment after follow up;
• Establish the correlation of the clinical antidepressant tDCS outcomes with:
  a) serum and salivary cytokine assays
  b) 3T and 7T MRI
  c) Additional qualitative analysis of the characteristics of responders vs. non-responders and patient experience with treatment
  d) Additional cue-provoked craving measures
  e) Olfaction acuity

Sequencing and combining current interventions and neuromodulation treatments using biological predictors of response will expand the range of therapeutic options for treatment-resistant patients.
**Life Long Neurogenesis:**

Olfactory System

- Olfactory Epithelium
- Culture Olfactory Neurons
- Gene Expression Studies
- Potential for Stem cells

Hippocampus

- Hippocampal Dentate Gyrus
- Coronal and sagittal 7T
- 100 micron cell layer

**Translational Neuroscience Research**

- Clinical Research
- Epidemiology
- Basic Science
- Animal Models
- Clinical Research
- Epidemiology
- Basic Science
- Animal Models