Transcranial Direct Current Stimulation for Affective Symptoms and Functioning in Chronic Low Back Pain: A Pilot Sham-Controlled RCT

Timothy Mariano, MD, PhD, MSc

Instructor, Harvard Medical School
Medical Director, Sage Therapeutics, Inc.

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Disclosures

• Past Consulting
  – Janssen Pharmaceuticals, Inc.
  – Ad Scientiam SAS

• Current employee of Sage Therapeutics, Inc.

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Overview

• The affective component of pain
• CLBP: unmet need for non-opioid treatments
• Dorsal anterior cingulate cortex as a noninvasive brain stimulation target
• Pilot study: repeated sessions of tDCS in a CLBP population
• Future directions
  – At-home treatment
  – Multimodal treatment
“Pain and Suffering”

“An unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage.”

International Association for the Study of Pain (IASP)

(http://www.iasp-pain.org/Taxonomy)
Affective Symptoms and Disability

• Sensory
  – Major component of acute pain shortly after an injury
  – What most of us commonly think of as “pain”

• Emotional (affective, mood) “suffering”
  – Increasingly severe as pain “chronifies”
  – Psychiatric manifestations: fear avoidance, catastrophizing, depression
  – Imaging evidence suggests associated cortical changes
  – Treatment resistant

• Most current treatments only address the sensory component
Chronic Low Back Pain (CLBP)

- **Epidemiology**
  - Low back pain affects up to 80% of Americans (Manchikanti 2000)
  - Annual CLBP prevalence is 15%-45% (Manchikanti et al. 2009)

- **Current Treatments**
  - Opioid analgesics, NSAIDs, steroid injections, surgery: target the *sensory* component
  - Cognitive behavioral therapy (CBT) and biofeedback: target the *affective* component but access challenges

There is a critical need for novel *non-opioid* treatments addressing all components of chronic pain.
Neuromodulation: Electrical Stimulation

• Sensory pain relief
  – TENS
  – Spinal cord stimulation

• *Can noninvasive electrical stimulation of the brain treat both components of chronic pain?*
Transcranial Direct Current Stimulation

- tDGS is noninvasive
- Can increase or decrease excitability of brain regions
- Improves cognition, pattern recognition
- Used by military, video gamers
- Prior tDGS studies
  - Depression
  - Targeting primary motor cortex (M1) modulates nociception
Research tDCS Technique

- Carbon rubber electrodes in saline-soaked sponge pockets placed on scalp
- 10-20 EEG system for consistent placement
  - Stimulating electrode over region of interest (e.g. FC₁ for left dACC, F₃ for left DLPFC)
  - Return electrode elsewhere on head (e.g. mastoid process)

Dorsal Anterior Cingulate Cortex and Pain

• One of the highest densities of opioid receptors in the brain
• Surgical lesion of dACC (cingulotomy) used to treat intractable chronic pain since the 1960s
  – Patients reported unchanged pain intensity
  – Were less “bothered” by it

Foltz and White 1962
dACC as Neuromodulation Target

• Bilateral deep brain stimulation (DBS) of dACC created durable relief of the affective component of pain (Boccard et al. 2014, Boccard et al. 2017)

• Our prior work in healthy individuals suggested that tDCS may modulate pain-related distress (Mariano et al. 2015)

http://www.nature.com/nrn/journal/v13/n6/fig_tab/nrn3231_F1.html
Experimental Pain in Healthy Controls
Transcranial Direct Current Stimulation for Affective Symptoms and Functioning in Chronic Low Back Pain: A Pilot Double-Blinded, Randomized, Placebo-Controlled Trial

Timothy Y. Mariano, MD, PhD, MSc,*,† Frederick W. Burgess, MD, PhD,‡ Marguerite Bowker, RN,‡ Jason Kirschner,*+,§ Mascha van’t Wout-Frank, PhD,+,§ Richard N. Jones, ScD,*,†,§ Christopher W. Halladay, ScM,‡ Michael Stein, MD,*,† and Benjamin D. Greenberg, MD, PhD*,†,§
Clinical Study Methods

• Multi-site, double-blinded, placebo (sham) controlled RCT

• Participants
  – Structured interview to rule out major bipolar, psychotic, substance dependence disorders or tDCS contraindications
  – Stratify by Rx opioid status
  – **30 consented**
    • >18 years old
    • CLBP ≥6 mo with intensity ≥4/10 (VAS)
    • Stable medications ≥1 month
  – **21 completed** at Providence VAMC (N=17) and Butler Hospital (N=4)
  – 9 ineligible, withdrew, or lost to contact before first tDCS session

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[http://www.neuroconn.de/dc-stimulator_plus_en/]
“Targeting” tDCS to Left dACC

• 5 × 7 cm electrodes: cathode at FC\textsubscript{1} and anode at contralateral mastoid
• 10 in-clinic tDCS sessions on consecutive weekdays: 20 min, 2 mA
• Six week post-treatment follow-up
• Questionnaires to assess pain intensity, pain acceptance, disability, mood, satisfaction

Coronal Slice  Sagittal Slice  Axial Slice

L R F B L R

tDCS-Explore v. 4.0 (Soterix Medical, New York, New York, USA)
Results: Pain Disability, Interference

- Roland-Morris Disability Questionnaire: back-pain-specific disability
- Westhaven-Yale Multiphasic Pain Inventory (General Activity Subscale): perceived pain interference in daily functioning

Week 8 stim\times day interaction: $p = .001$

Week 8 stim\times day interaction: $p = .002$

Error bars are ±1 standard deviation
Results: Mood, Treatment Expectations

- Patient Health Questionnaire, 9-item
- Credibility/Expectancy Questionnaire: linearly transformed total score

![Graphs showing PHQ-9 Score and Transformed CEQ Score](image)

**Week 8 stim×day interaction: p = .003**

**Week 8 stim×day interaction: p = .038**

Error bars are ±1 standard deviation
## Results: Summary Table

|                      | Mean (Standard Deviation) Score | $|z|$ | $p$  |
|----------------------|---------------------------------|------|------|
|                      | Active tDCS                     | Sham tDCS |      |      |
| WHY-MPI-C            |                                 |      |      |
| Day 1                | 31.3 (16.1)                     | 36.9 (13.3) | 0.75 | .451 |
| Day 5                | 39.9 (23.0)                     | 40.8 (18.9) | 0.83 | .408 |
| Day 10               | 41.6 (21.9)                     | 41.0 (15.8) | 1.12 | .262 |
| 6-wk Follow-Up       | 48.4 (21.2)                     | 35.3 (17.7) | 3.11 | .002*|
| RMDQ                 |                                 |      |      |
| Day 1                | 13.8 (5.4)                      | 12.5 (4.9) | 0.74 | .460 |
| Day 5                | 13.2 (6.0)                      | 12.5 (5.3) | 0.61 | .539 |
| Day 10               | 12.5 (5.6)                      | 12.8 (4.1) | 1.50 | .133 |
| 6-wk Follow-Up       | 12.7 (5.6)                      | 15.4 (5.5) | 3.23 | .001*|
| PHQ-9                |                                 |      |      |
| Day 1                | 11.0 (7.8)                      | 8.1 (5.2)  | 1.10 | .272 |
| Day 5                | 10.0 (8.3)                      | 7.0 (4.7)  | 0.14 | .886 |
| Day 10               | 8.9 (7.1)                       | 6.8 (4.9)  | 0.46 | .645 |
| 6-wk Follow-Up       | 7.4 (6.1)                       | 8.9 (6.0)  | 2.96 | .003*|
| CEQ                  |                                 |      |      |
| Day 1                | 35.9 (7.8)                      | 38.5 (7.6) | 0.70 | .486 |
| Day 10               | 38.8 (9.7)                      | 33.7 (9.0) | 2.08 | .038*|

**DVPRS, CPAQ-8, GAD-7, PASS-20, CSQ-8:** all $|z| < 1.51$, all $p > 0.132$
Maximizing tDCS Effects

• tDCS may have a delayed or cumulative effects (Sampaio-Junior et al. 2018, Bikson et al. 2018, Mariano et al. 2018)

• Since tDCS could be done remotely, can it be combined with evidence-based psychotherapy? (Sathappan et al. 2019)
Current Work: CBT Group Teletherapy for CLBP

- Manualized and validated 8-session paradigm for chronic pain (Jamison 1996)
- Virtual groups delivered via
- Smartphone app assessments
- Encouraging results
  - > 40 participants enrolled
  - High retention, satisfaction

Summary and Future Work

• In CLBP patients, pain-related functioning and distress (WHY-MPI-C and RMDQ) may improve after repeated daily tDCS sessions intended to target dACC
• Post-hoc tests suggest WHY-MPI-C, RMDQ, and PHQ-9 improvements were not merely driven by group baseline differences
• Repeated tDCS (10 in-clinic daily sessions) was well-tolerated with high satisfaction
• tDCS effects may not fully manifest until after the acute treatment phase ends
• Future larger RCTs must explore the tDCS parameter space and target engagement more thoroughly
• Multimodal approaches may have synergistic effects: e.g. using tDCS to enhance evidence-based psychotherapy
• We are only beginning to scratch the surface of emerging non-opioid treatments leveraging portable, mobile, and remote technologies
Thank You!

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Michael Stein, MD
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Selected References


Questions?
Extra Slides
Bilateral Cingulotomy
(Foltz and White, 1962)
Hypotheses

• Both anodal and cathodal tDCS will modulate the affective dimension of pain in healthy volunteers
• Cathodal tDCS over dACC will increase tolerance to distress from acute painful stimuli
• Simultaneously, there will be no change in a visual analog pain rating scale

This will demonstrate selective targeting of the affective dimension of pain.
Research tDCS Technique

- Battery-powered device delivers direct current stimulation
- Some user-adjustable parameters
  - Electrode location
  - Treatment duration (typically ≤ 30 min)
  - Stimulation amplitude (typically ≤ 2 mA)

Soterix 1×1 tDCS Device and Accessories
Methods

• Subjects: $n = 40$ right-handed healthy controls without contraindications for tDCS
• Within-subjects design
• Stimulation targeting left dACC at 2 mA
Methods

- Validated non-harmful tasks, randomized and counterbalanced, to assess tolerance to pain-related distress as measure of the affective dimension of pain
  - Cold pressor to right hand/arm
  - Pressure algometer to left hand
  - Breath holding

- Pain ratings at baseline and after each task with the Defense and Veterans Pain Rating Scale (DVPRS)
DVPRS
Pressure Algometer

• Applies fixed amount of pressure to index finger of left hand
• Non-damaging, feels like dull butter knife
• Measures
  – Time to report pain
  – Time to removal of hand (tolerance)
But...what about DLPFC?

- Left dorsolateral prefrontal cortex is the target for 10 Hz “excitatory” TMS for MDD
- DLPFC implicated in affective, cognitive, and attentional aspects of pain

What would happen if we repeated the prior study in another 40 healthy volunteers, but targeted left DLPFC instead of left dACC?
DLPFC Results

Mixed ANOVA, All DLPFC Subjects
(error bars are ±1 standard error of the mean)

$p = 0.024$
Preliminary Results

- Direction of effect consistent with our hypothesis of cathodal stimulation increasing mean cold pressor tolerance \( (p = .064) \) vs. anodal stimulation.
- Improves if we exclude five subjects who reached cold pressor 5-minute time limit during both anodal and cathodal stimulation \( (p = .055) \).
- Mean pressure algometer tolerance demonstrated significant order effect regardless of stimulation polarity \( (all \ p < .01) \) with shorter tolerance in the second testing block.
- Breath holding tolerance unchanged with cathodal vs. anodal stimulation.
- tDCS had no effect on DVPRS pain ratings \( (all \ p > .067) \), but cold pressor and pressure algometer increased pain intensity \( (all \ p < .01) \).
Summary and Limitations

• tDCS targeting left dACC
  – Trend towards increased pain distress tolerance in the cold pressor (CP) task
  – Pressure algometer had strong sensitization effect
• tDCS targeting left DLPFC
  – Smaller CP DVPRS rise with anodal vs. cathodal stimulation
  – Stimulation polarity did not affect CP or BH tolerability
  – May suggest modulated attention or affective valence of DVPRS
• Likely underpowered given difficulty of performing power analysis with novel approach
• Comparing two active stimulation conditions without a sham control
• Only two sessions total per participant
Conclusions

• Chronic pain is a significant clinical problem
• Current treatments target nociception and are often inadequate
• tDCS is a non-invasive neuromodulation technique that has been used for analgesia
• dACC and DLPFC are implicated in the affective dimension of pain
• tDCS targeting these regions may modulate the affective dimension of pain
• A pilot clinical study is underway
• Much work remains...
tDCS Pilot Studies: Healthy Volunteers

Mixed ANOVA: Left dACC and DLPFC
(error bars are ±1 standard error of the mean)

Cold Pressor

dACC: dorsal anterior cingulate cortex
DLPFC: dorsolateral prefrontal cortex

(Mariano et al. 2015; Mariano et al. 2016)
Cold Pressor Pressure Algometer Breath Holding

Anodal Cathodal

$p = 0.064$

$p = 0.81$

$p = 0.19$
Change in DVPRS Pain Rating

- Cathodal
- Anodal

Cold Pressor Breath Holding

\[ p = 0.024 \]