Transcranial Direct Current Stimulation (tDCS) of the human motor and prefrontal cortices reduces pain and opioid use following total knee arthroplasty

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• I hold patents (pending and actual) for the use of VNS-induced changes in pain perception to dose VNS for depression, a portable electrical sham TMS system, and the use of TMS to localize cortical areas for neurosurgical intervention

• TMS and tDCS are investigational and are not approved by the FDA as treatments for pain
Pain: an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
Three levels

- **Sensory-Discriminatory**
  - Location, quality, intensity

- **Motivational-Affective**
  - Emotional/Limbic, depression, anxiety

- **Cognitive-Evaluative**
  - Thoughts about the cause and significance of the pain
Acute Pain

- Caused by noxious stimulation due to injury, disease process, or abnormal function of muscle or viscera.
- Serves to detect, localize and limit tissue damage.
- Involves: transduction, transmission, modulation and perception.
- Self-limited.
- Resolves in days to weeks.

"Tell me Mr. Jones. Does it hurt when I do this?"
Chronic Pain

- Pain that persists beyond the usual course of an acute disease or after a reasonable time for healing to occur
- Psychological and environmental factors often play major roles
Neurostimulation

- Transcutaneous Electrical Nerve Stimulation (TENS)
- Spinal Cord Stimulation (SCS)
- Vagus Nerve Stimulation (VNS)
- Motor Cortex Stimulation (MCS)
- Transcranial Magnetic Stimulation (TMS)
- Transcranial Direct Current Stimulation (tDCS)
Motor Cortex Stimulation

- Post Stroke Pain, Trigeminal Neuropathic Pain, Deafferentation Pain
- Subthreshold stimulation of the motor area leads to modulation of pain related areas like the medial thalamus, anterior cingulate, and upper brainstem
- 65% pass trial and get permanently implanted
- 47% of those permanently implanted show continued benefit ~3 years later
- Antidromic activation of large fiber reciprocal connections between motor and sensory cortices restores inhibitory control over nociceptive signaling (Tsubokawa et al, 1993).
- Amount of analgesia negatively correlates with limbic structure activity
Transcranial Magnetic Stimulation

- TMS is a minimally invasive brain stimulation technology that can focally stimulate the brain of an awake individual.
- A localized pulsed magnetic field transmitted through a figure-8 coil (lasting only microseconds) is able to focally stimulate the cortex by depolarizing superficial neurons inducing electrical currents in the brain.
- TMS can induce varying brain effects depending on:
  - 1) the cortical region stimulated,
  - 2) the activity that the brain is engaged in,
  - 3) the TMS device parameters (particularly frequency and intensity).
- Intermediate effects of TMS (seconds to minutes) likely arise from transient changes in local pharmacology (e.g., gamma-aminobutyric acid, glutamate).
- Repeated low-frequency stimulation of a single neuron in culture produces inhibition of cell-cell communication (LTD).
- High frequency stimulation can improve communication (LTP).
Motor cortex TMS effects on Neuropathic Pain
5-days; 20 minutes 20Hz 80%
(Khedr et al, 2005)
TMS for Pain

- Fast left prefrontal TMS increases thermal pain thresholds in healthy adults (Borckardt et al., 2007)
- Slow right prefrontal TMS decreases fibromyalgia pain (Sampson et al., 2006)
- Fast left prefrontal TMS reduces fibromyalgia pain (Short & Borckardt et al., 2007)
- Fast left prefrontal TMS reduces neuropathic pain (Borckardt et al., 2007)
- Misc. aches and pains reduced with fast left prefrontal TMS (Avery et al., 2007)
- Fast left prefrontal TMS decreases postoperative pain (Borckardt et al., 2006)
Perioperative TMS?
Effects of prefrontal TMS on patient-controlled analgesia
During the postoperative period
Among bariatric surgery patients
(Borckardt et al, 2006)
Effects of prefrontal TMS on pain and mood ratings
During the postoperative period
fMRI pre-treatment pain signal
TMS Effects on Pain Ratings

![Chart showing percent change in pain rating following TMS. The chart indicates a decrease in pain ratings post-real TMS and post-sham TMS. The values are -12.39 for post-real TMS and -7.18 for post-sham TMS.](chart.png)
Contrast: Real > Sham, Post > Pre
Perceived Control and Prefrontal Stimulation

![Graph showing the relationship between perceived control and pain intensity/unpleasantness with conditions (No Control, Perceived Control, Real TMS, Sham TMS). The graph displays a downward trend in estimated mean VAS ratings as perceived control increases, with clearer reductions in pain intensity and unpleasantness under real TMS compared to sham TMS conditions.](image-url)
Transcranial Direct Current Stimulation (tDCS)
tDCS-ERCP Pilot Study

- 21 Females (Mean age = 37.2; SE=2.4)
- ERCP for pancreatitis-related pain
- Randomly assigned to receive 20-mins of REAL or SHAM tDCS (2.0 mA) immediately after ERCP
- Anode over left prefrontal cortex
- Cathode over gut-representation of the sensory cortex
- Pain ratings and PCA usage tracked
Cumulative PCA Usage After 20-mins Real or Sham tDCS

Cumulative Dilaudid PCA Usage (mg) vs Hour Post-ERCP

- Sham tDCS
- Real tDCS
VAS Pain Ratings 4-hours post tDCS

Mood Ratings
(Higher is Better)

Pain Ratings
(Lower is Better)

Group (Real vs Sham tDCS) and Rating Type
TKA Background

- Total knee arthroplasty (TKA) is one of the most common orthopedic procedures performed.
- While knee pain is often a complaint that precedes TKA, the procedure itself is associated with considerable post-operative pain lasting days to weeks.
- Adequate postoperative pain control is an important factor in determining recovery time and hospital length of stay.
- Primary methods used to manage post-operative pain in general involve systemic opioid or other analgesic drug delivery, and regional blocks.
- Despite these pain-management strategies, patients still report considerable post-operative pain, and often struggle to complete post-operative physical therapy regimens.
tDCS for Total Knee Arthroplasty Pain

- 40 patients undergoing unilateral TKA
- Randomly assigned to receive a total of 80 minutes of real (n=20) or sham tDCS (n=20)
- Anode placed over the knee representation of the motor strip
- Cathode placed over the right dorsolateral prefrontal cortex
- Patient controlled analgesia (PCA; hydromorphone) use was tracked during the ~48-hours post-surgery.
Mean PCA Hydromorphone Usage following TKA

![Graph showing the usage of PCA Hydromorphone following TKA. The graph compares Sham tDCS and Real tDCS, with the cumulative mg of Hydromorphone plotted against the hour post-surgery. The p-value for the difference is 0.006.](image)
Pain Ratings

• Patients in the real tDCS group rated their pain unpleasantness significantly lower (mean=9 out of 100, SD=12) than those in the sham group (mean=34 out of 100, SD=25) after the last tDCS session (t(37)=4.01, p<.001)
Summary

- Minimally invasive brain stimulation (MIBS) technologies appear safe, and are developing rapidly.
- We now have the ability to directly modulate brain activity in targeted regions in awake humans.
- While it is unclear how to stimulate pain (and mood) modulating brain regions for optimal clinical benefit, several studies suggest that MIBS is a promising new approach for both acute and chronic pain management.
- Little is known about the effects of combined MIBS and psychotherapy.
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