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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Disclosures

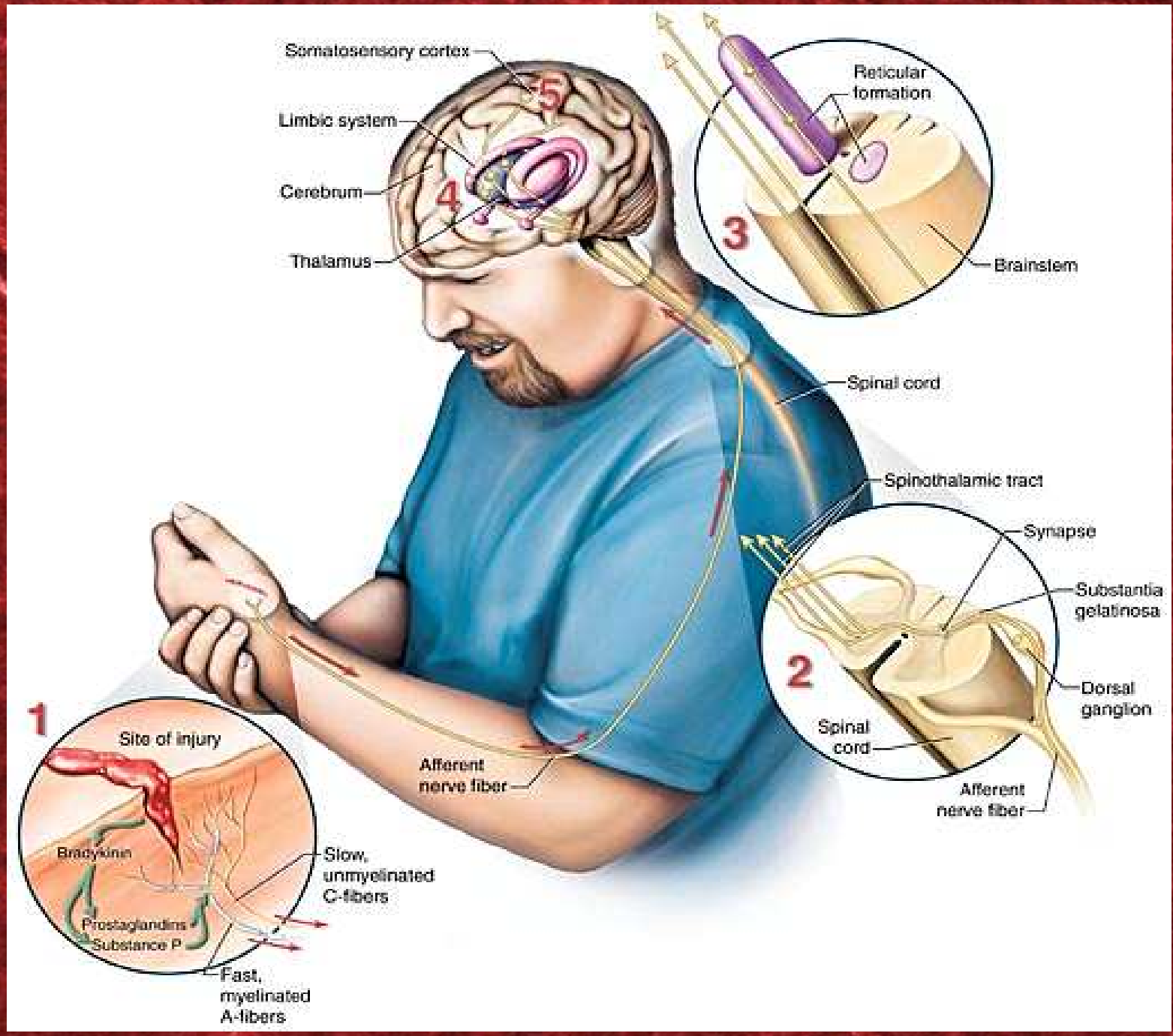
- My research is funded through NINDS, NIDA, NIMH & NIAMS at NIH, the North American Spine Society, the American Society for Gastrointestinal Endoscopy, Covidien and The Obesity Society
- I hold patents (pending and actual) for the use of VNS-induced changes in pain perception to dose VNS for depression, 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


Somatosensory cortex
5
Limbic system
Cerebrum
4
Thalamus
Reticular formation
3
Brainstem
Spinal cord
Spinothalamic tract
Synapse
Substantia gelatinosa
2
Dorsal ganglion
Spinal cord
Afferent nerve fiber
Afferent nerve fiber
1
Site of injury
Bradykinin
Prostaglandins
Substance P
Slow, unmyelinated C-fibers
Fast, myelinated A-fibers

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?"

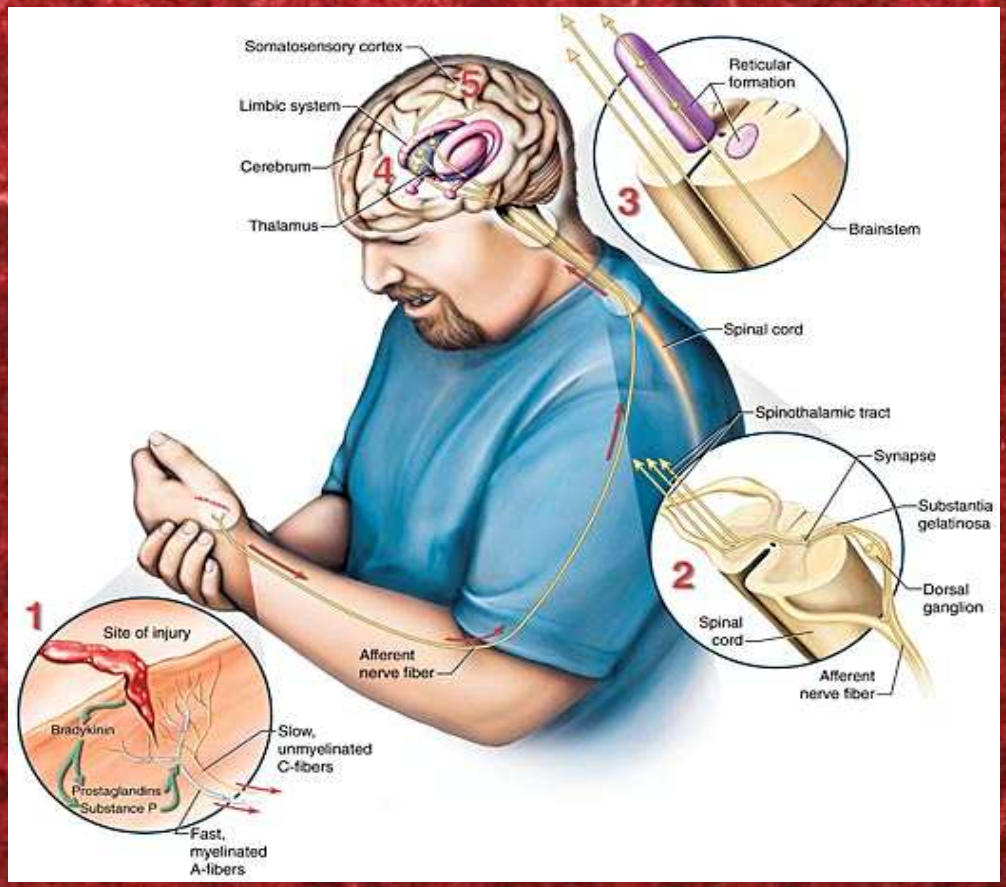
Chronic Pain

- 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

"Mr Trombly has cancelled his appointment. The Dow is up and he's feeling no pain."

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)

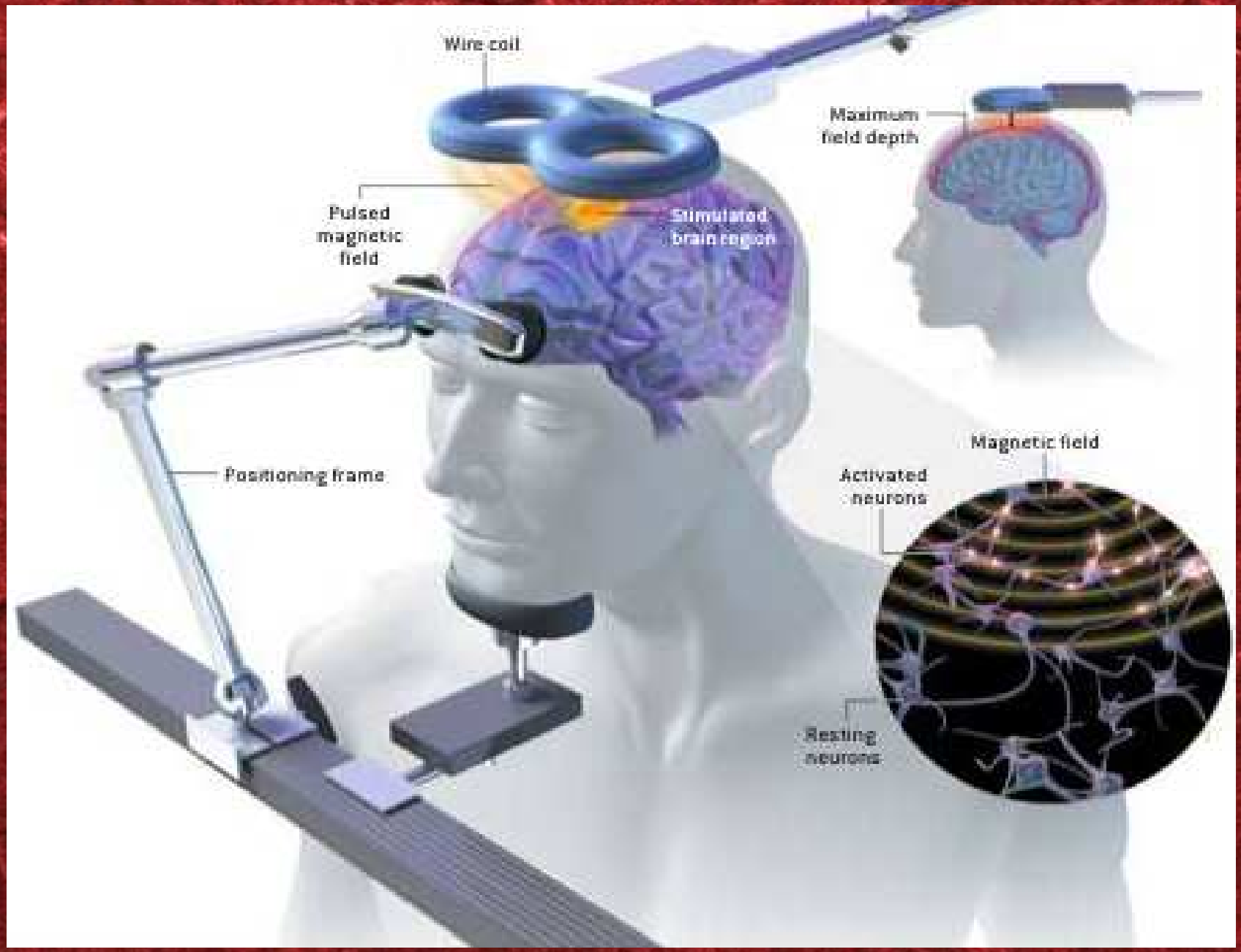


Motor Cortex Stimulation

- 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

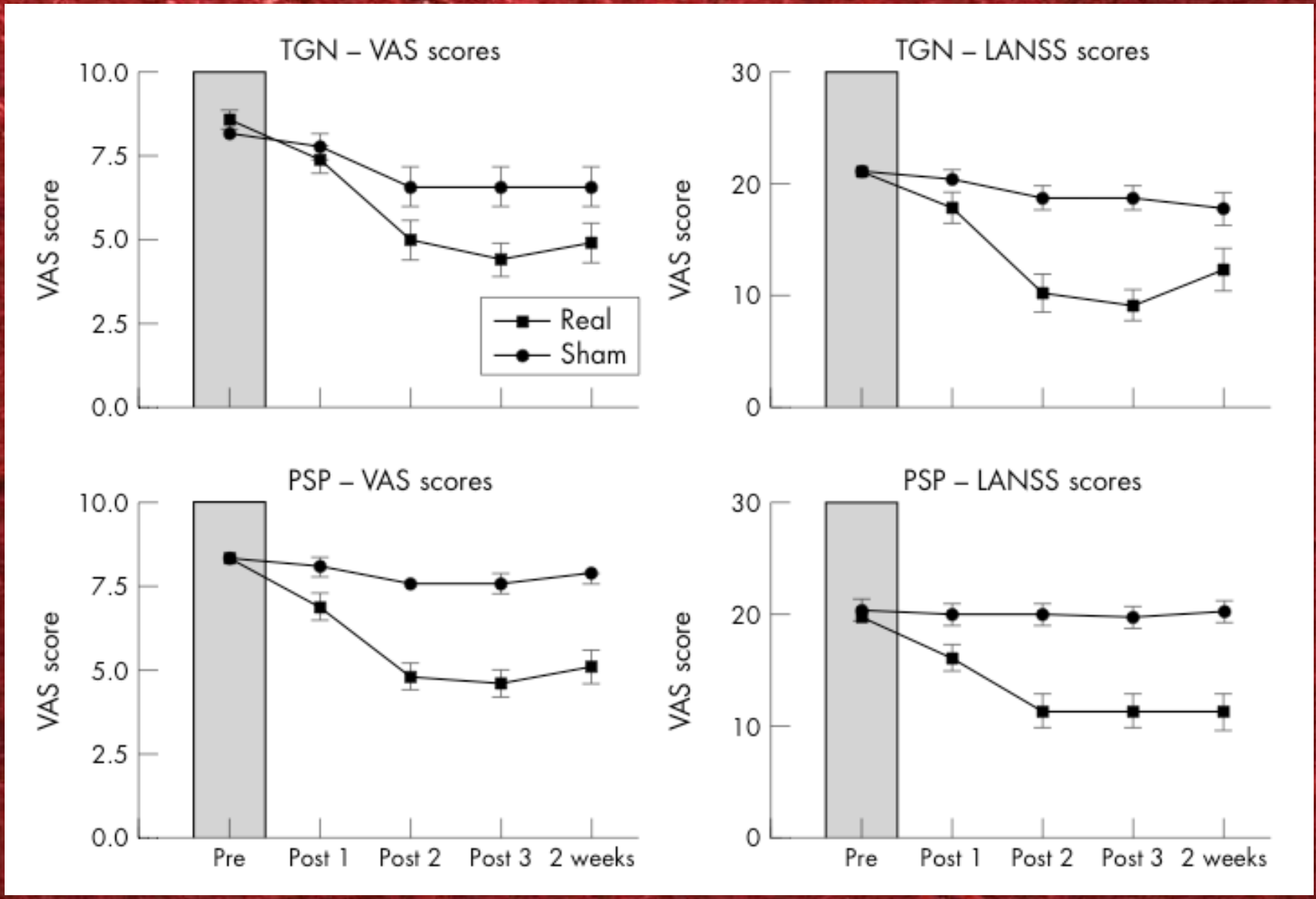
Transcranial Magnetic Stimulation

- 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-aminobuteric 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)



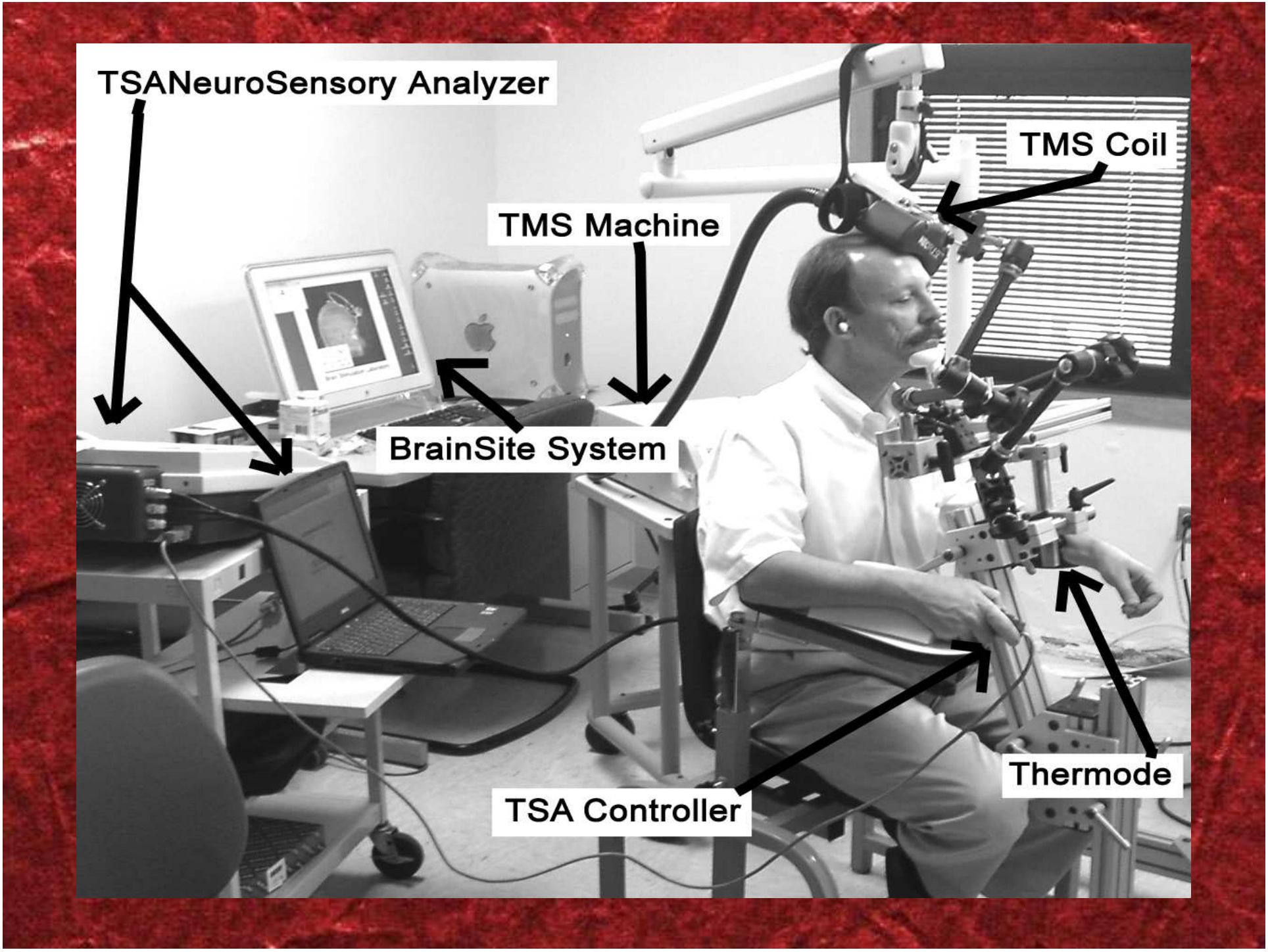
(George, 2003 Scientific American)

Motor cortex TMS effects on Neuropathic Pain
5-days; 20 minutes 20Hz 80%
(Khedr et al, 2005)

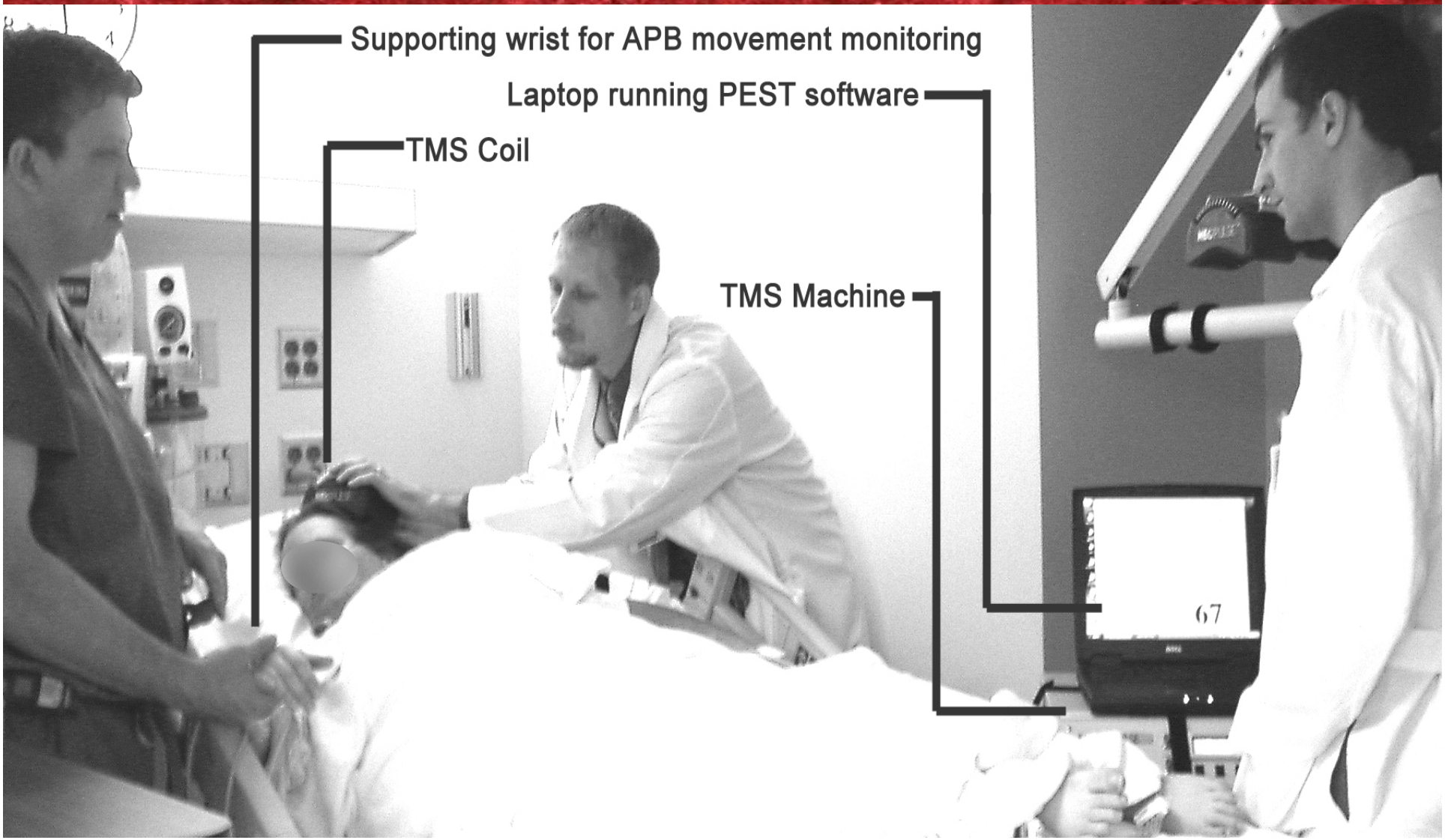


TMS for Pain

- 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)

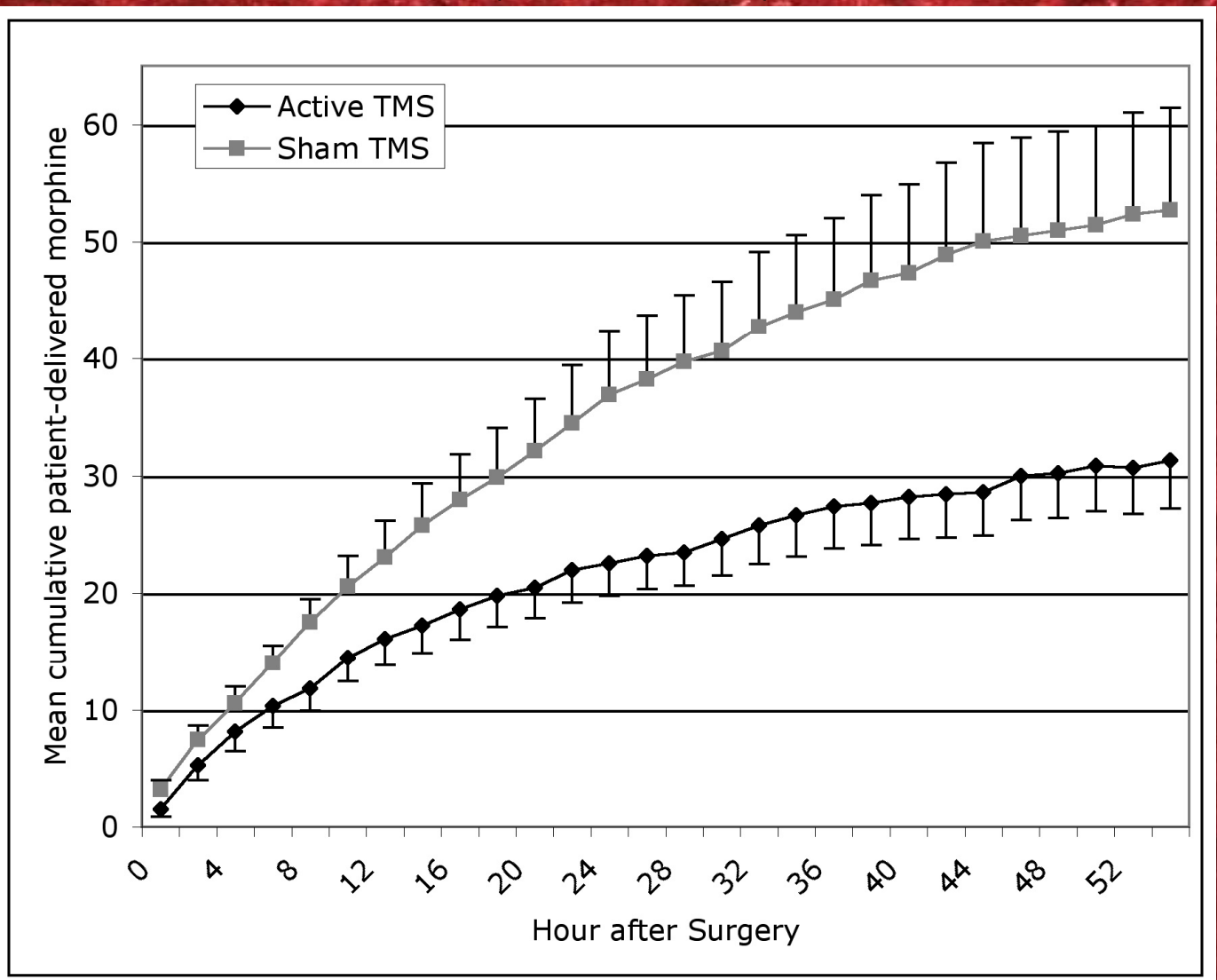

TSANeuroSensory Analyzer
TMS Coil
TMS Machine
BrainSite System
TSA Controller
Thermode

Perioperative TMS?

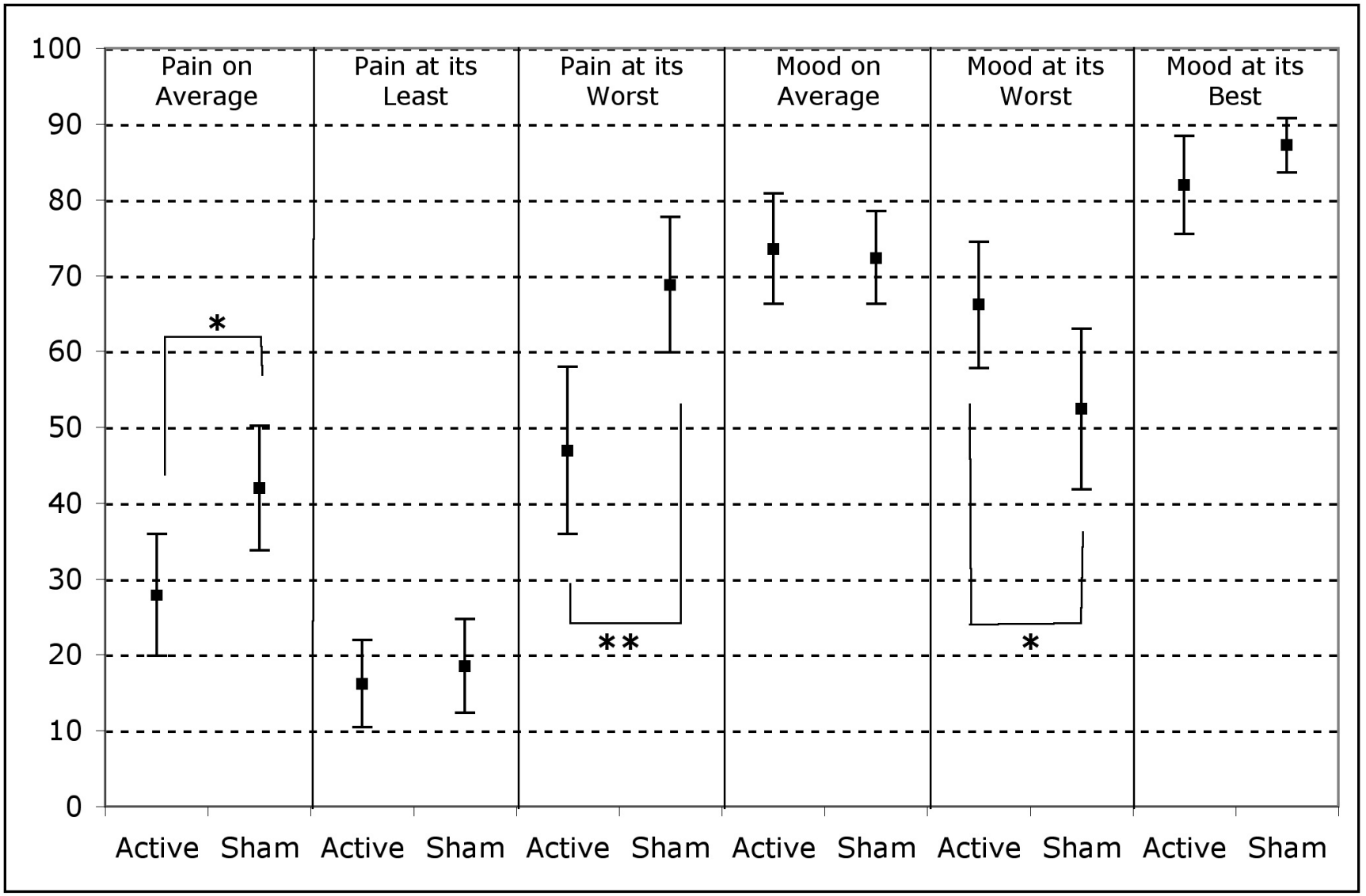


Effects of prefrontal TMS on patient-controlled analgesia During the postoperative period Among bariatric surgery patients

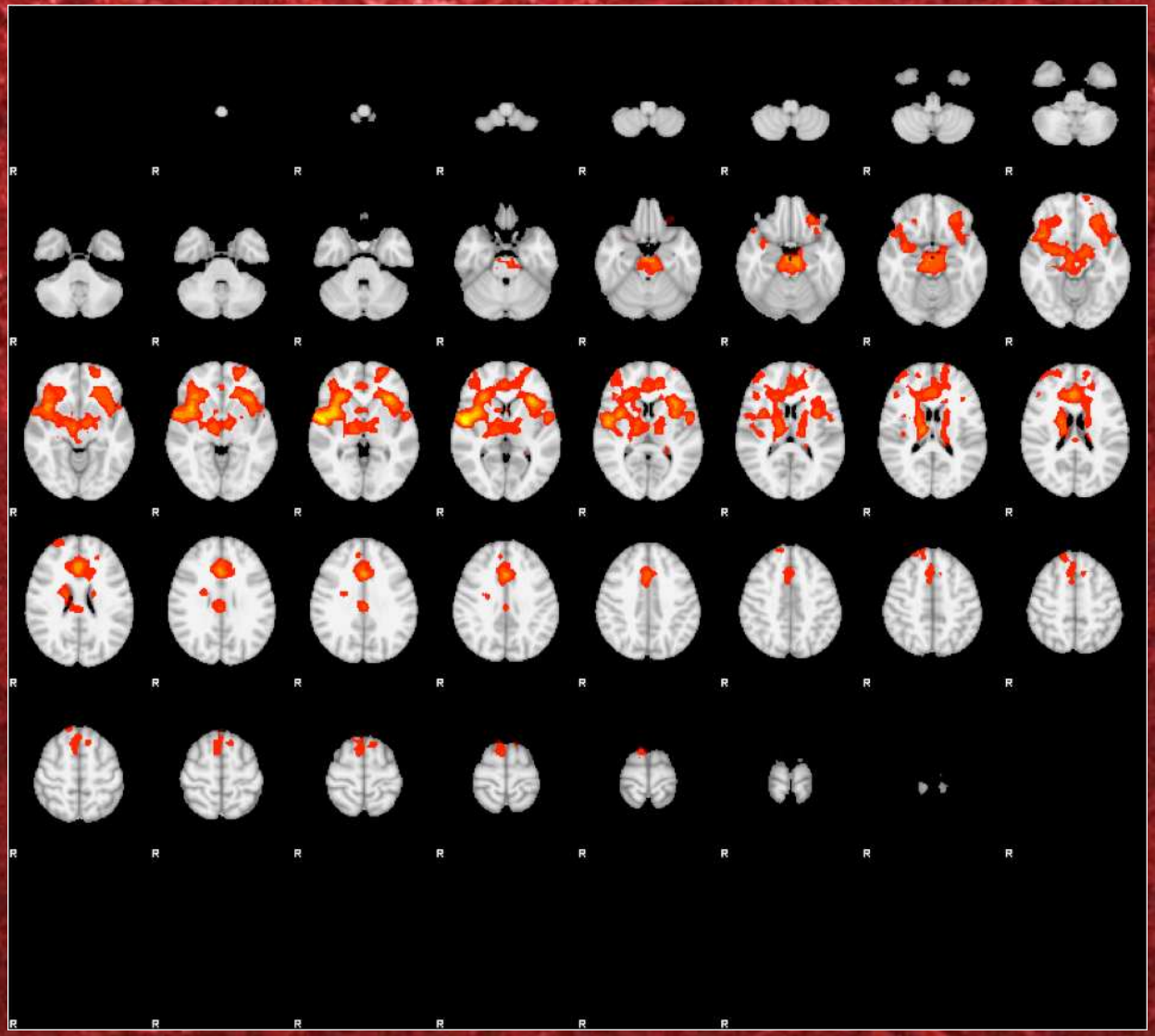
(Borckardt et al, 2006)



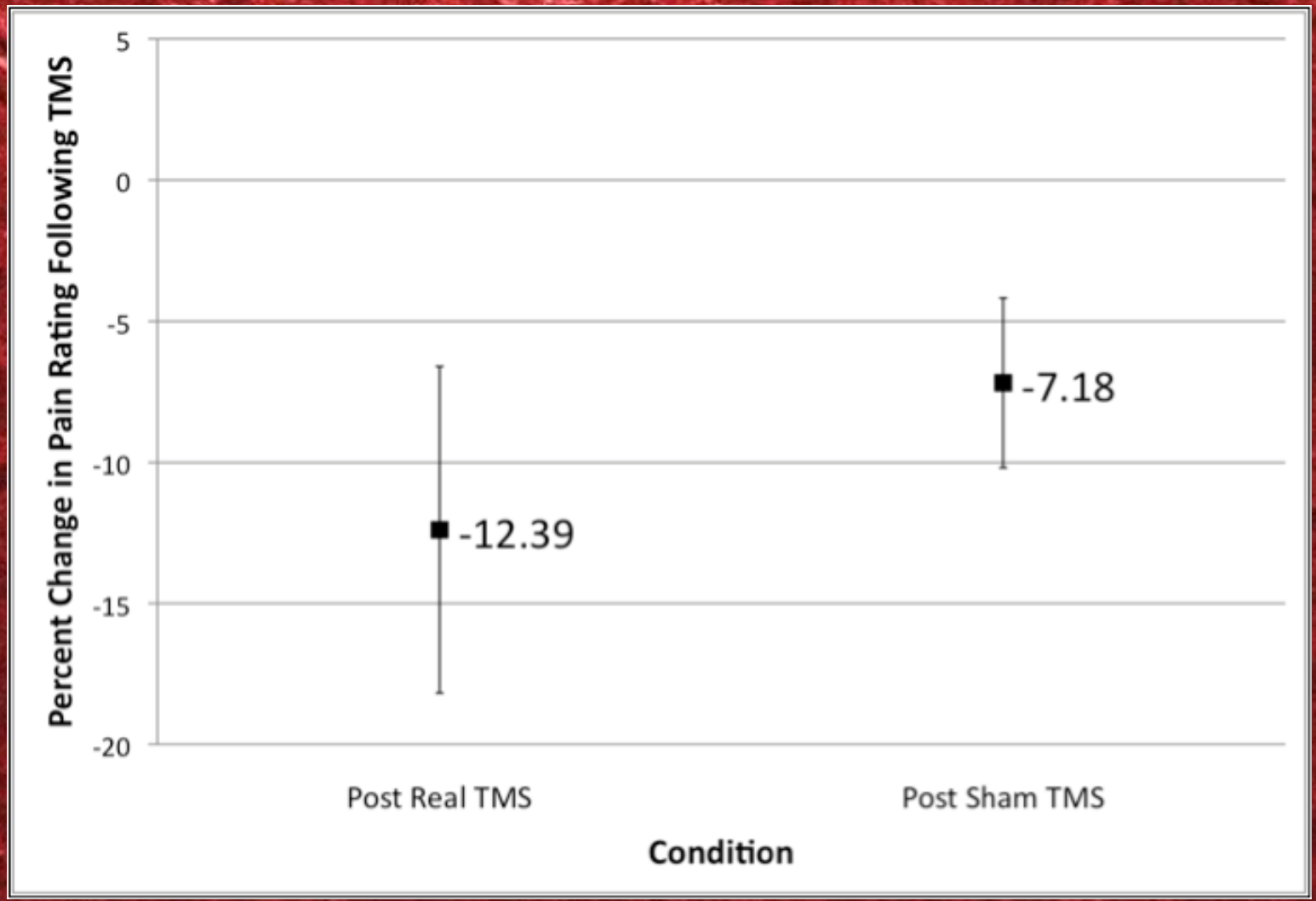
Effects of prefrontal TMS on pain and mood ratings During the postoperative period



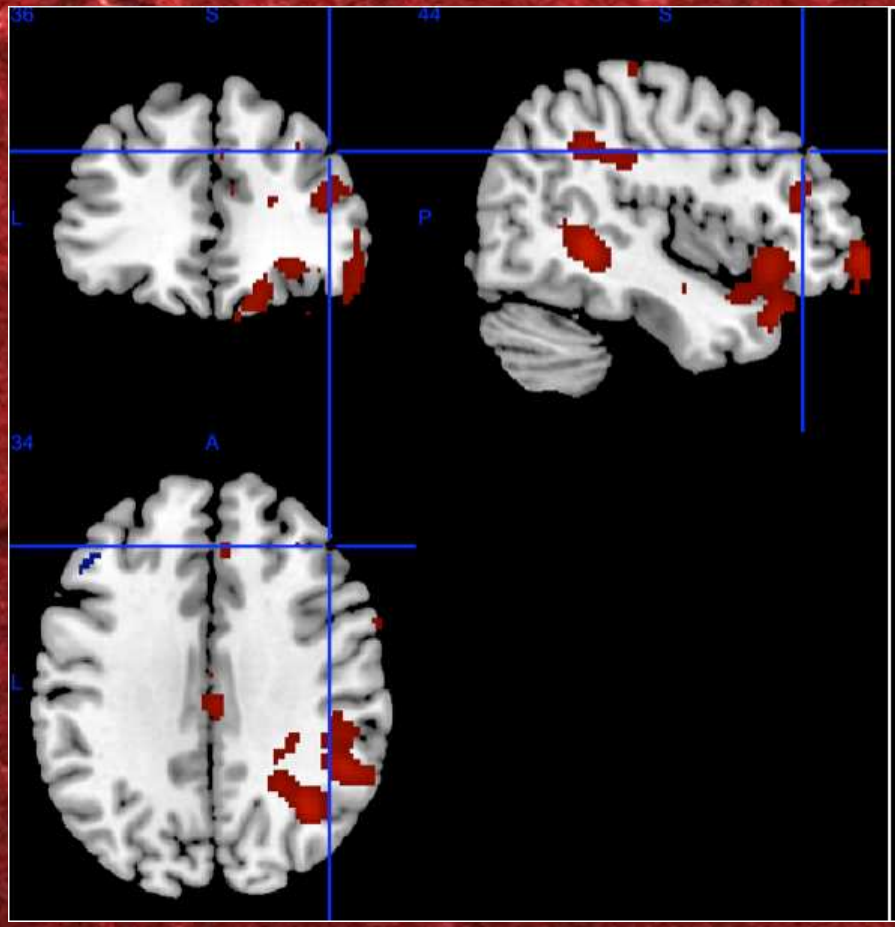
fMRI pre-treatment pain signal

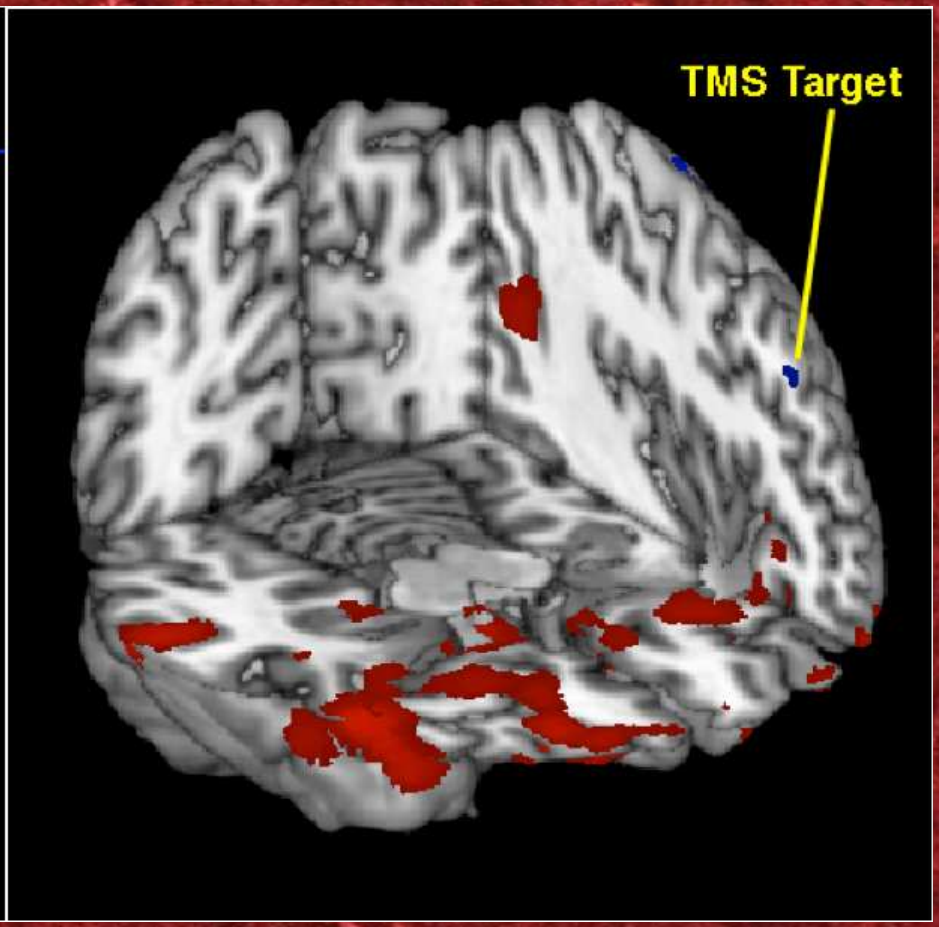


TMS Effects on Pain Ratings

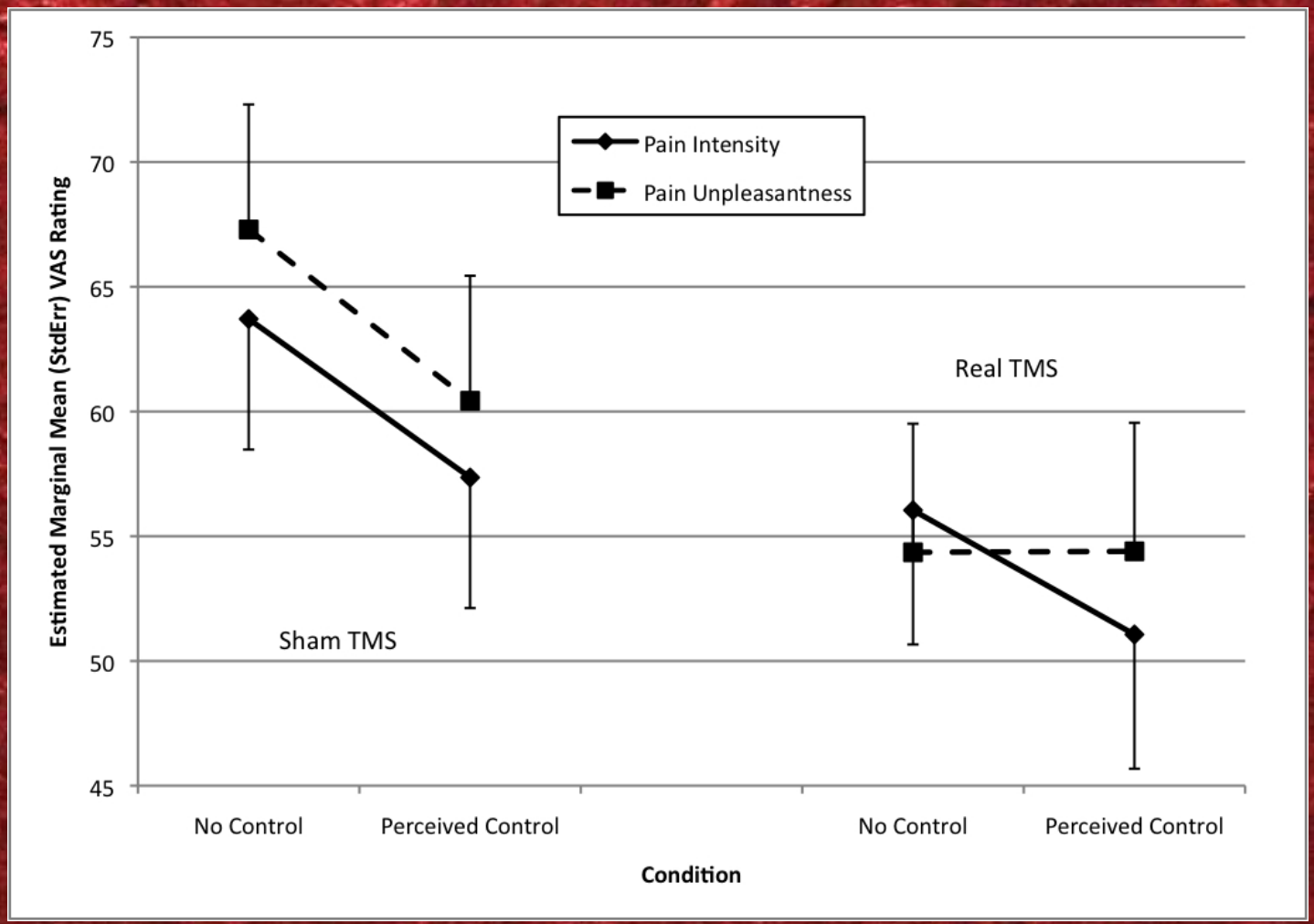


Contrast: Real>Sham, Post>Pre

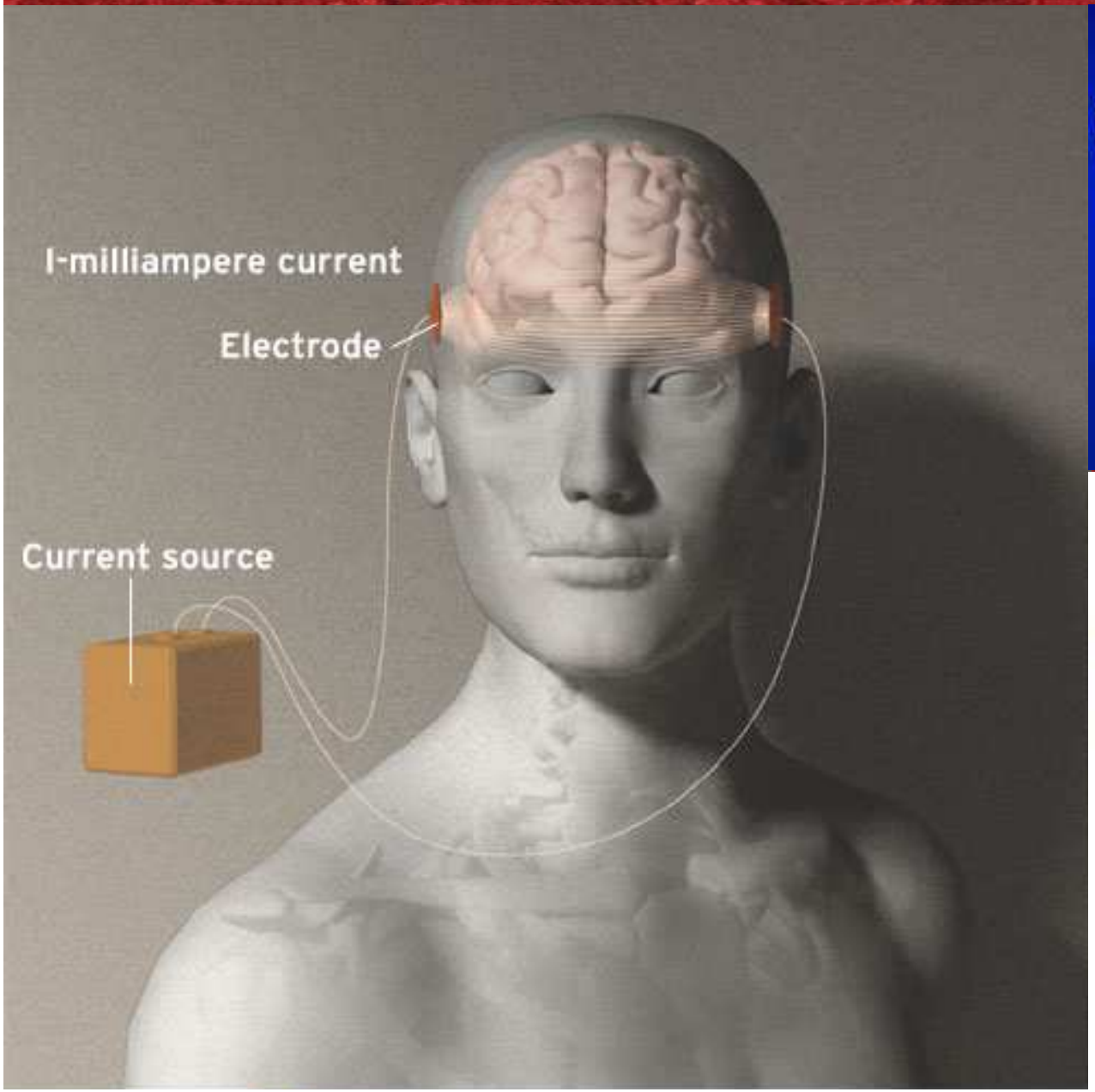




Perceived Control and Prefrontal Stimulation



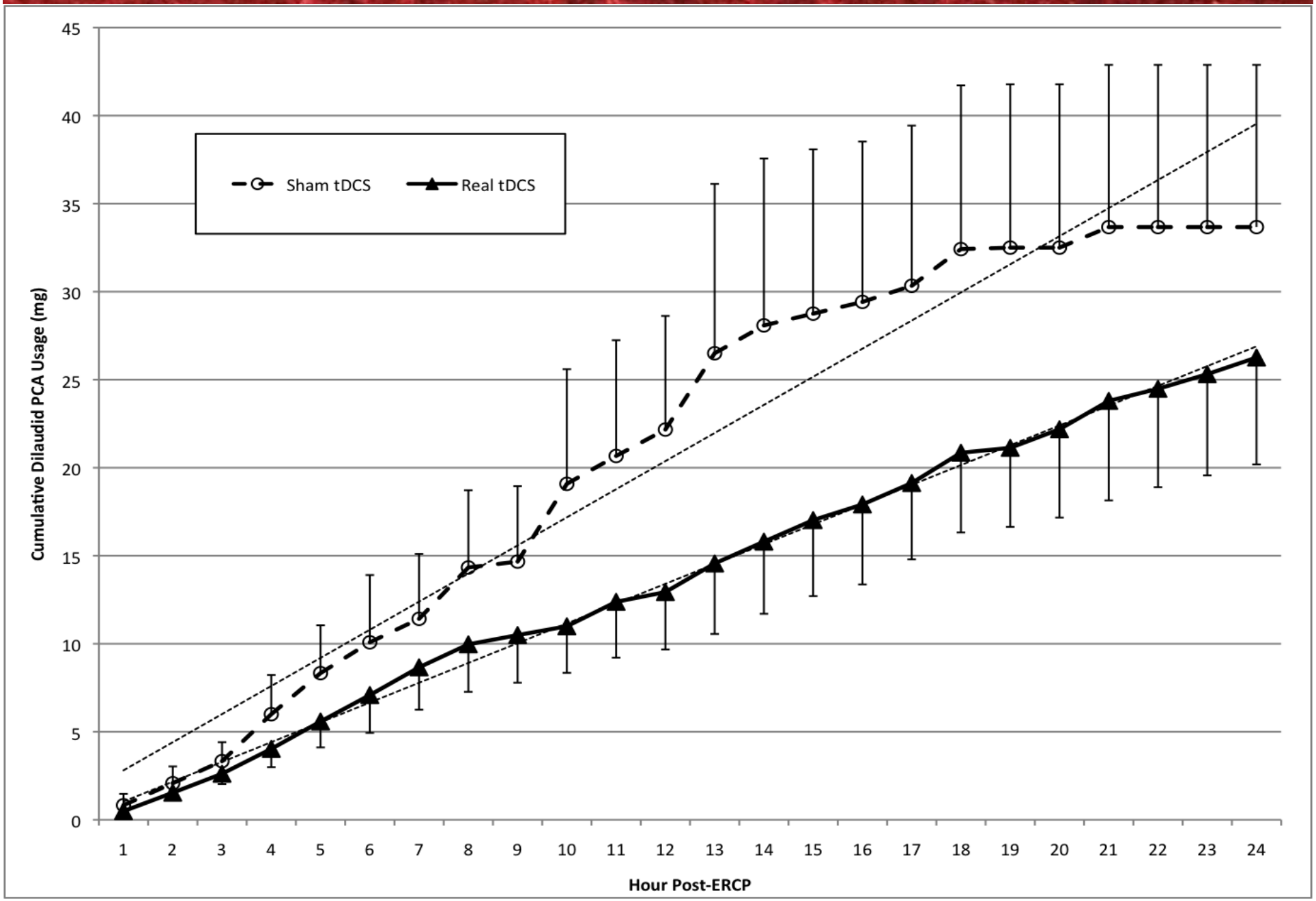
Transcranial Direct Current Stimulation (tDCS)



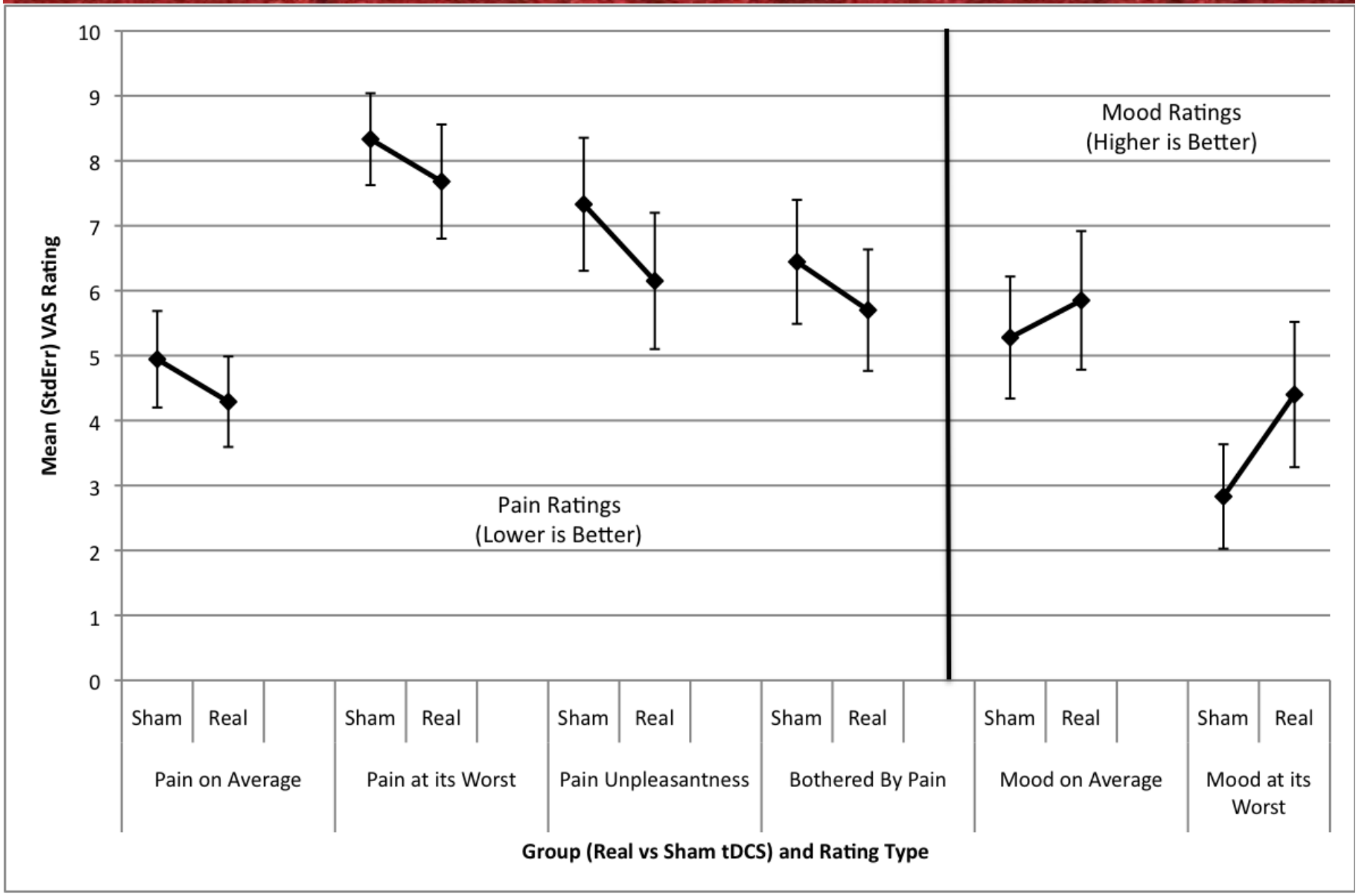
tDCS-ERCP Pilot Study

- 21 Females (Mean age = 37.2; SE=2.4)
- ERCP for pancreatits-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



VAS Pain Ratings 4-hours post tDCS



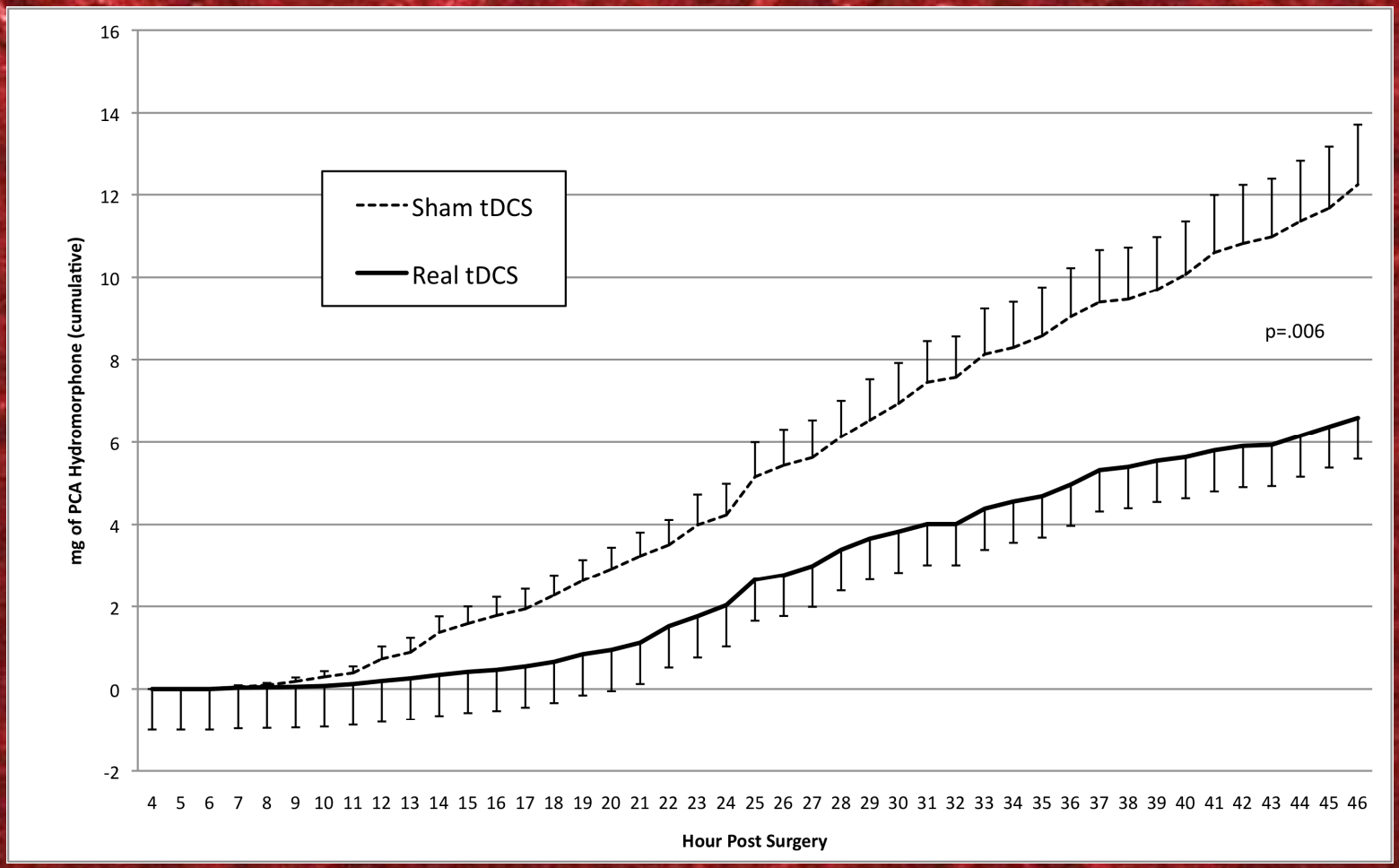
TKA Background

- 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



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

Thank-You to all of the wonderful collaborators with whom I have been lucky enough to work on developing and testing these technologies:

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