



Pain, the Brain and Neuromodulation

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Disclosures

- My research is funded through the National Institutes of Health, the Duke Foundation, and the U.S. Department of Veterans Affairs.
- I hold patents, pending and actual for the use of several neurostimulation technologies in pain management and for optimizing neurostimulation treatment for psychiatric disorders.
- I will be discussing off-label use of neurostimulation technologies (TMS & tDCS) for pain management.



Major Pain Categories

- **Nociceptive Pain**

- Activation of specialized pain receptors
- Burns, sprains, fractures, bumps, bruises...
- Constant: “aching”, “throbbing”, “sharp”

- **Neuropathic**

- Injury or malfunction of peripheral or central nervous system
- Nerve compression, nerve injury, infection
- Intermittent: “burning”, “electric”, “tingling”, “shooting”

Three Dimensions of Pain

- **Sensory-Discriminatory**
 - Location, quality, intensity
- **Motivational-Affective**
 - Emotional Valence, Unpleasantness
- **Cognitive-Evaluative**
 - Thoughts about the cause and significance of the pain

Acute Pain



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

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

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

Chronic Pain



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

Epidemiology

- Chronic pain: prolonged and persistent pain lasting at least 3 months in duration
- Recurrent pain: recurrent episodes of pain interspersed with pain free periods
- AAPM: 57% of adult Americans reported experiencing chronic or recurrent pain in past year
 - 62% of them reported pain for more than one year
 - 40% reported constant pain
- Chronic pain impacts: **100 million** US adults
- Costs from **\$560 to \$635 billion** annually
- Pain accounts for 80% of all physician visits
- There are no solid data supporting the efficacy of long-term opioid therapy for chronic non-malignant pain management



The complexity of pain...

BIO

PSYCHO

SOCIAL

Central Processes

Biological

Cognitive

Social

Affective

Self-Enhancement Feedback

Attention Feedback

Peripheral Processes

Immune/Systems

Endocrine

Immune/
Systems

Genetic Predispositions

Activities of Daily Living

Environmental Stressors

Interpersonal Relationships

Family Environment

Social Support Isolation

Social Expectations

Cultural Factors

Medicolegal / Insurance Issues

Previous Treatment Experiences

Work History

Pain and Emotion

- Patients with chronic pain are over 4 times more likely to meet criteria for an anxiety disorder than people in the general population (McWilliams et al 2003)
- Fear of movement and fear of re-injury are better predictors of functional limitations than biomedical parameters or even pain severity and duration.
- 40% to 50% of chronic pain patients suffer from depressive disorders (Dersh et al, 2006)
- Depressive episodes often begin after the onset of pain (Magni et al, 1994)
- However, patients with depression are 2.3 times more likely to develop chronic pain within a 3-year period than those with no depression (Jarvik et al, 2005).

Pain and Emotion



Pain and Cognition



The Phuket Vegetarian Festival in Thailand is an annual event held during the ninth lunar month of the Chinese calendar. It is believed that its sacred rituals bestow good fortune upon those who religiously participate



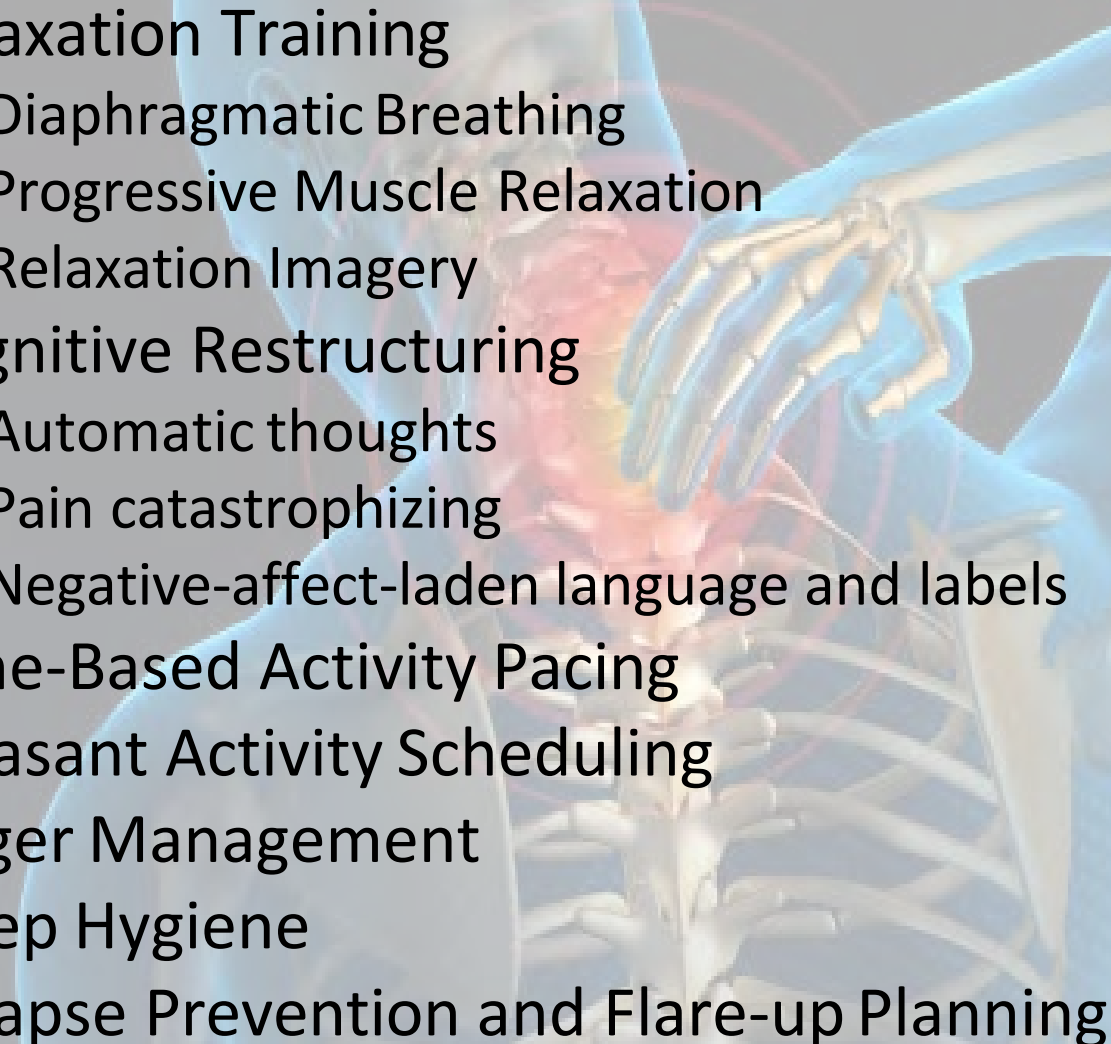
Pain and Cognition

- Pain appraisal refers to the meaning a patient ascribes to his/her pain
- A patient's beliefs about pain and its impact on his/her functioning shape how he/she interprets pain signals and pain-related events
- Maladaptive pain beliefs and pain catastrophizing significantly, negatively impact functioning and pain experience
- Controlled trials of CBT for chronic pain demonstrate significant decreases in pain, greater activity, better quality of life, better general health, and lower health care costs (Linton and Nordin, 2006)
- Experimental manipulation of perceived controllability of pain significantly effects neural response to pain as measured by fMRI (Salomons et al, 2004).

Some Empirically Supported Manualized CBT Treatments

- Murphy, J.L., McKellar, J.D., Raffa, S.D., Clark, M.E., Kerns, R.D., & Karlin, B.E. ***Cognitive behavioral therapy for chronic pain among veterans: Therapist manual***. Washington, DC: U.S. Department of Veterans Affairs.
- Otis, J. ***Managing Chronic Pain: A Cognitive Behavioral Approach***; Oxford University Press.
- Carlson, M. ***CBT for Chronic Pain and Psychological Well-Being***; Wiley Blackwell
- Thorn, B. ***Cognitive Therapy for Chronic Pain: A step-by-step guide***.
- Caudill, M. ***Managing Pain Before it Manages You, Fourth Edition***.

Common CBT-Pain Content

- Relaxation Training
 - Diaphragmatic Breathing
 - Progressive Muscle Relaxation
 - Relaxation Imagery
 - Cognitive Restructuring
 - Automatic thoughts
 - Pain catastrophizing
 - Negative-affect-laden language and labels
 - Time-Based Activity Pacing
 - Pleasant Activity Scheduling
 - Anger Management
 - Sleep Hygiene
 - Relapse Prevention and Flare-up Planning
- 

MUSC Pain Rehabilitation Program

A group of seven diverse adults, including men and women of various ages and ethnicities, are walking together on a paved path outdoors. They are all smiling and appear to be in good health and active. The background is a bright, sunny day with green grass and trees, creating a positive and energetic atmosphere.

South Carolina's only comprehensive chronic pain rehabilitation program

Program Description

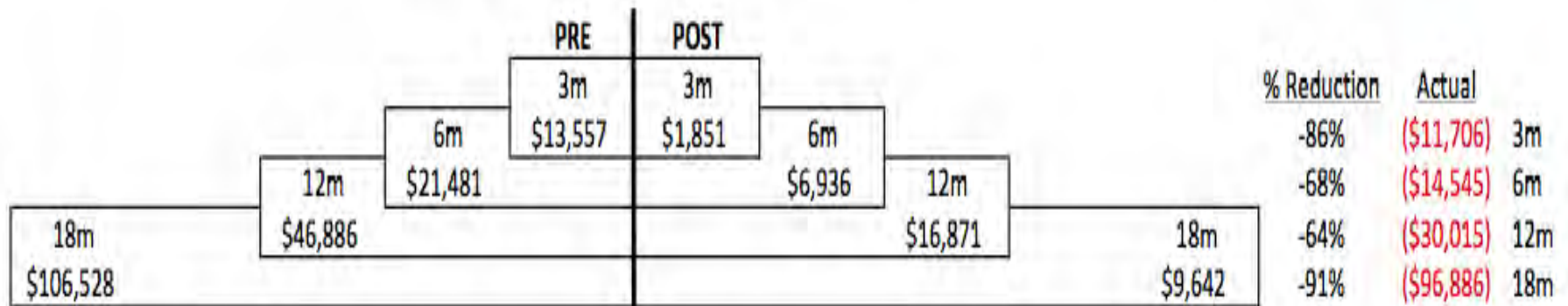
- Modeled after the highly successful Mayo Clinic Program
- Intensive outpatient program
 - 5 days/week for 3 weeks
 - 15 patients
- Emphasis on
 - Physical reconditioning
 - Reinstitution of activities of daily living
 - Cognitive-behavioral interventions
 - Complete weaning of opioid medications (& other controlled substances)

Cost of Chronic Pain

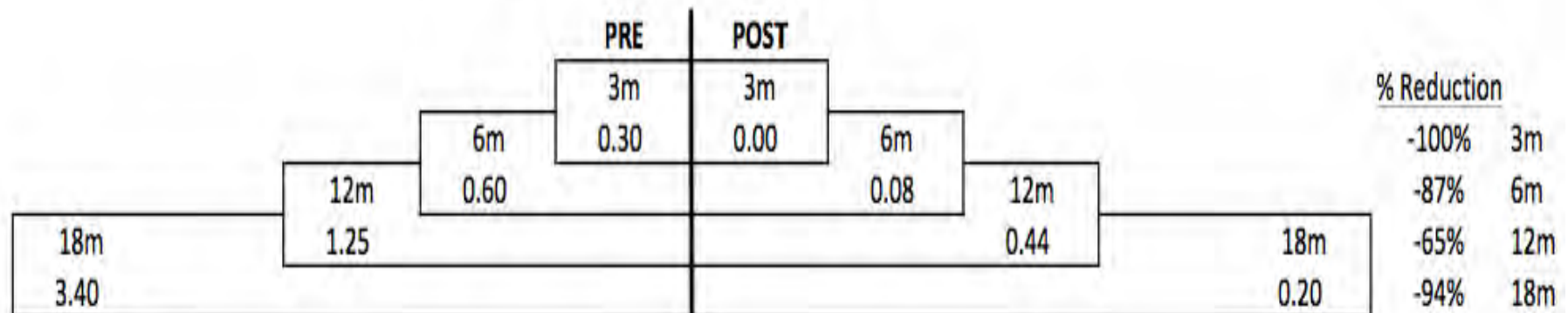
- Chronic pain impacts: **100 million** US adults
- Costs from **\$560 to \$635 billion** annually
 - Leading by a large margin:
 - Cardiovascular Diseases (\$309 billion)
 - Neoplasms (\$243 billion)
 - Injury and poisoning (\$205 billion)
 - Endocrine, nutritional, and metabolic diseases (\$127 billion)
 - Digestive system diseases (\$112 billion)
 - Respiratory system diseases (\$112 billion)

Cost-Effectiveness of the Pain Rehabilitation Program (Mayo Model)

Average Medical Cost per Patient

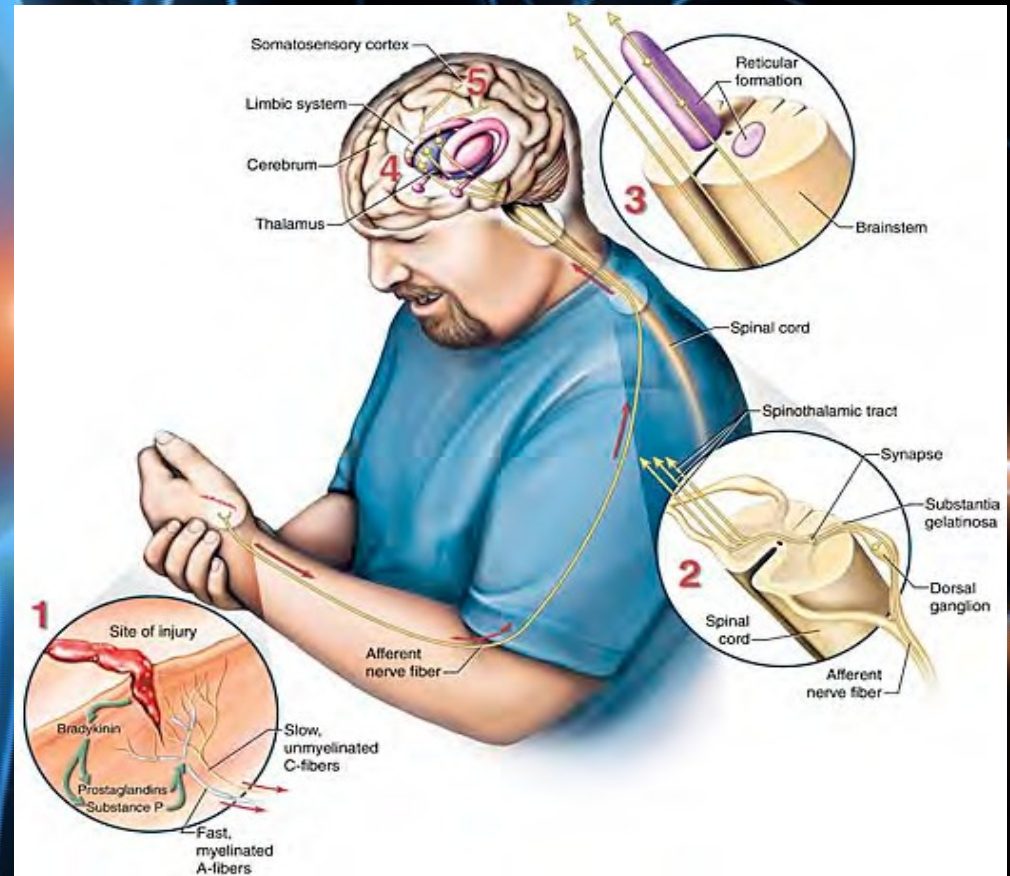


Average Number of ED Visits per Patient



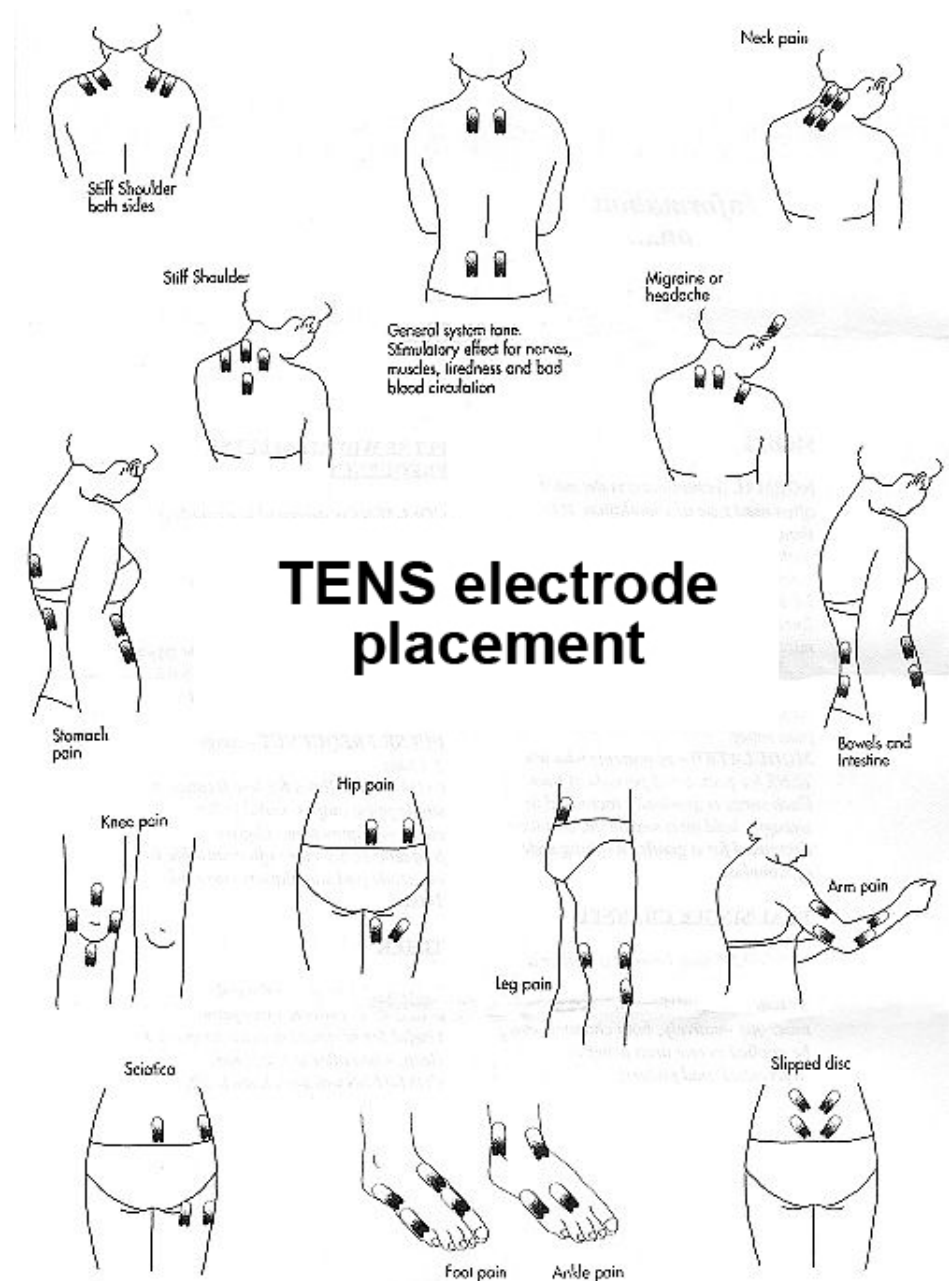
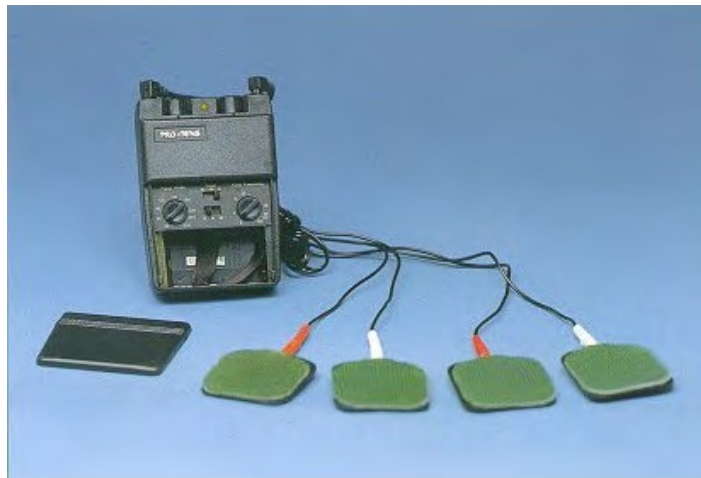
Neurostimulation

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



TENS

- In theory, involves stimulation of A β fibers (but not A δ fibers) in the painful area

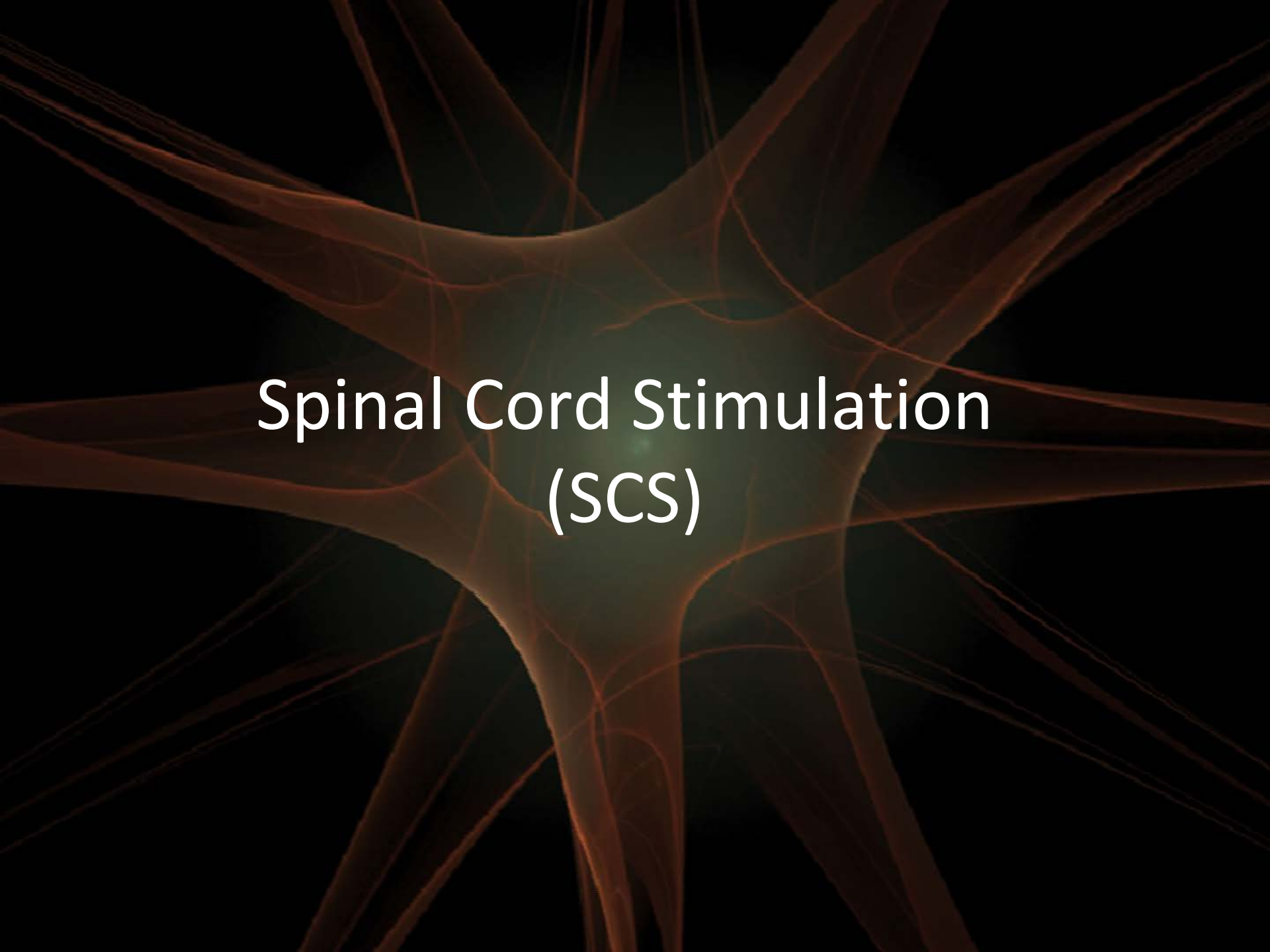


TENS

- Stimulation is applied at varying frequencies, intensities and pulse durations
- Pain relief is similar to that of morphine
- Primary mechanism is thought to involve the “Gate-Theory” of pain
- Stimulation intensity is typically set to just above sensory threshold

Interesting twists on TENS

- Analgesia lasts 8 to 24 hours after stimulation stops
- TENS effects appear to be opioid mediated
- Depletion of serotonin (primary neurotransmitter in the PAG-RVM pathway) decreases high frequency TENS analgesia
- TENS analgesia is enhanced by administration of L-5-hydroxytryptophan and blocked by methysergide (serotonin antagonist)



Spinal Cord Stimulation (SCS)



SCS Procedures and Results

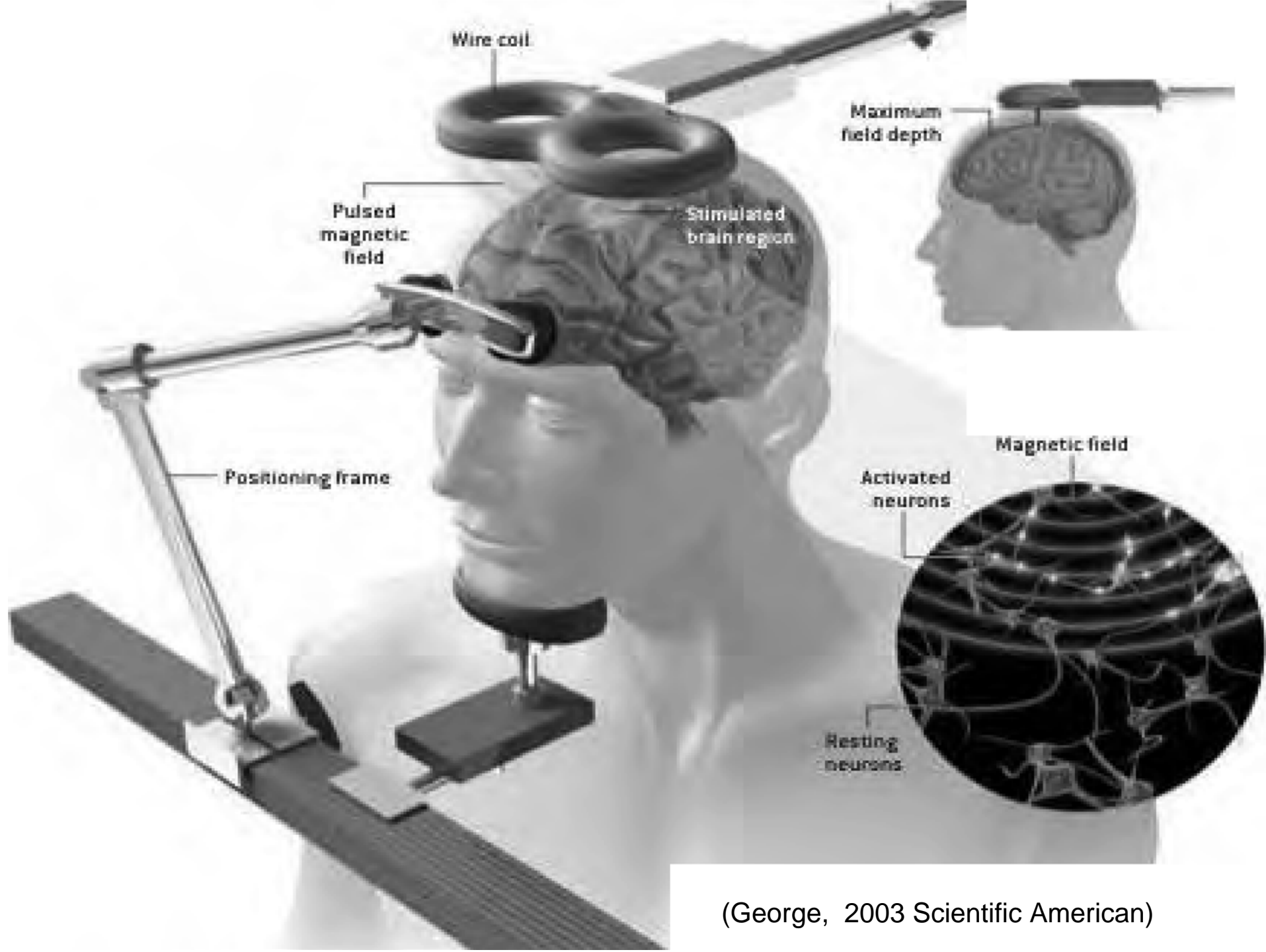
- Evaluation (medical and psychological)
- Trial (1-2 weeks)
- Implantation
- 2/3 of those selected pass the trial and get implanted
- 3/4 of those who get implanted experience excellent pain relief (>50%)
- At 7-years 52% maintained >50% relief



Transcranial Magnetic Stimulation (TMS)

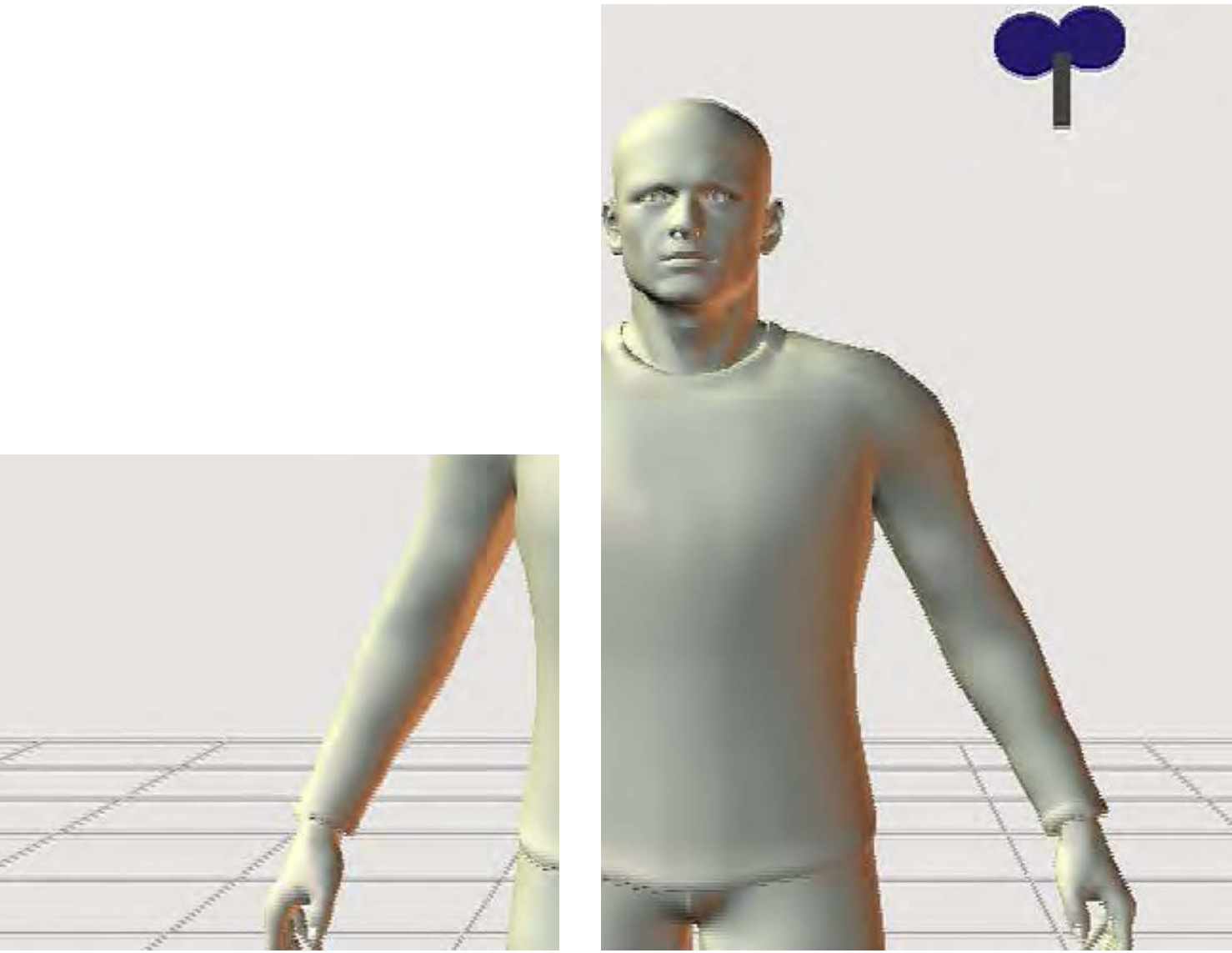
Transcranial Magnetic Stimulation

- 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).

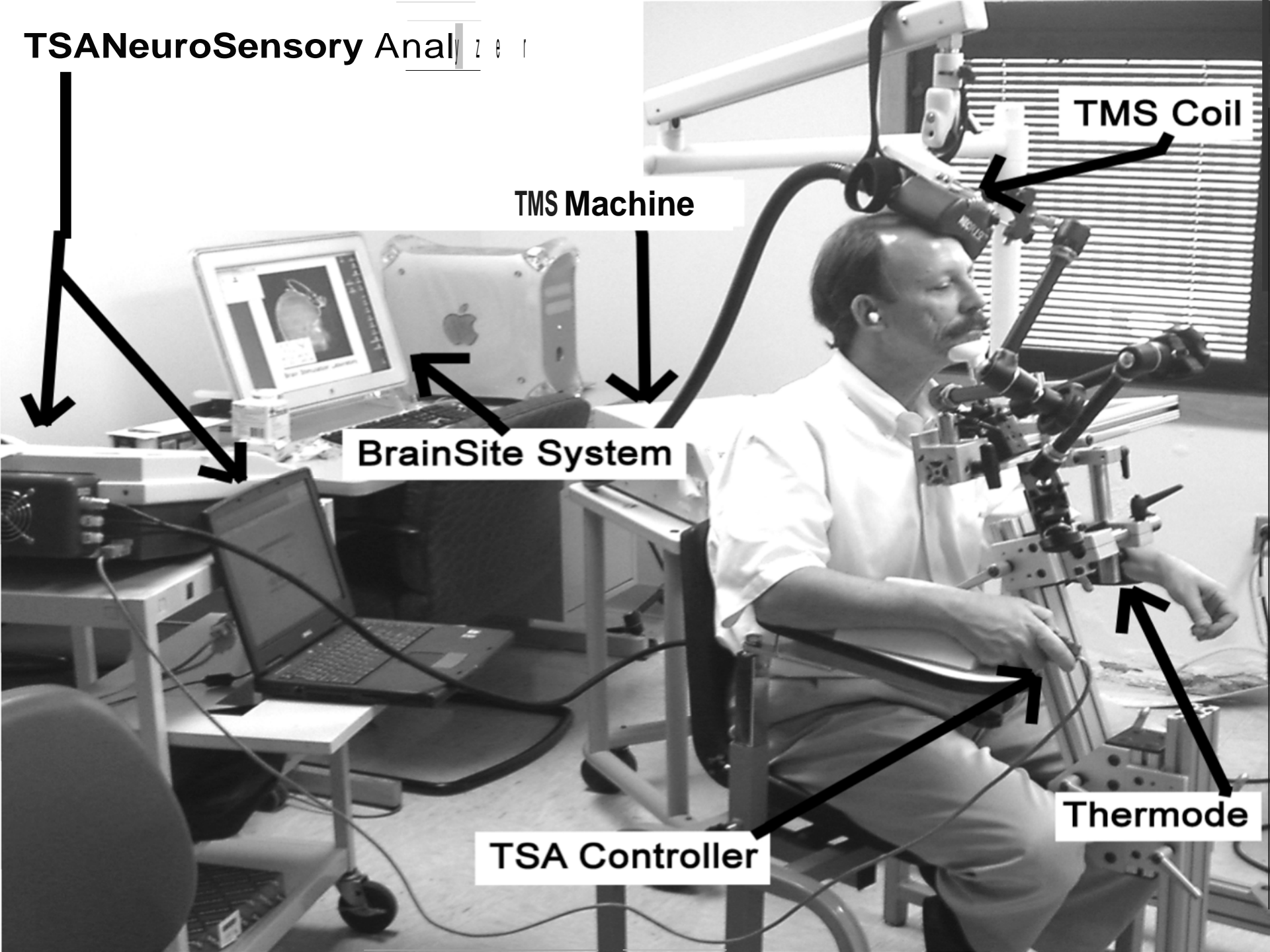


(George, 2003 Scientific American)

TMS Procedures: (1) Thumb Location (2) MT Determination, (3) Prefrontal Placement, (4) Stimulation



TSA NeuroSensory Analysis



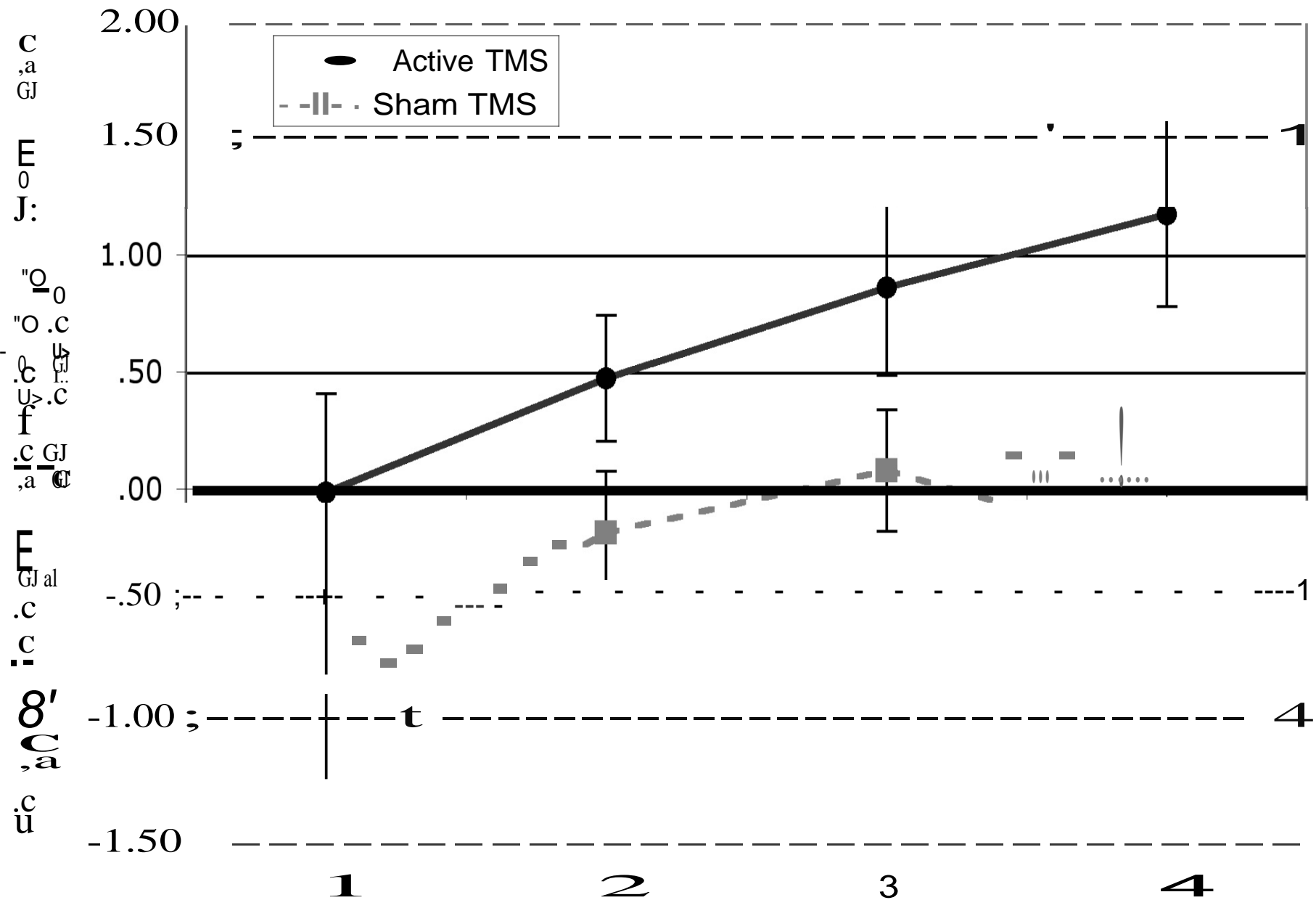
TMS Coil

TMS Machine

BrainSite System

TSA Controller

Thermode

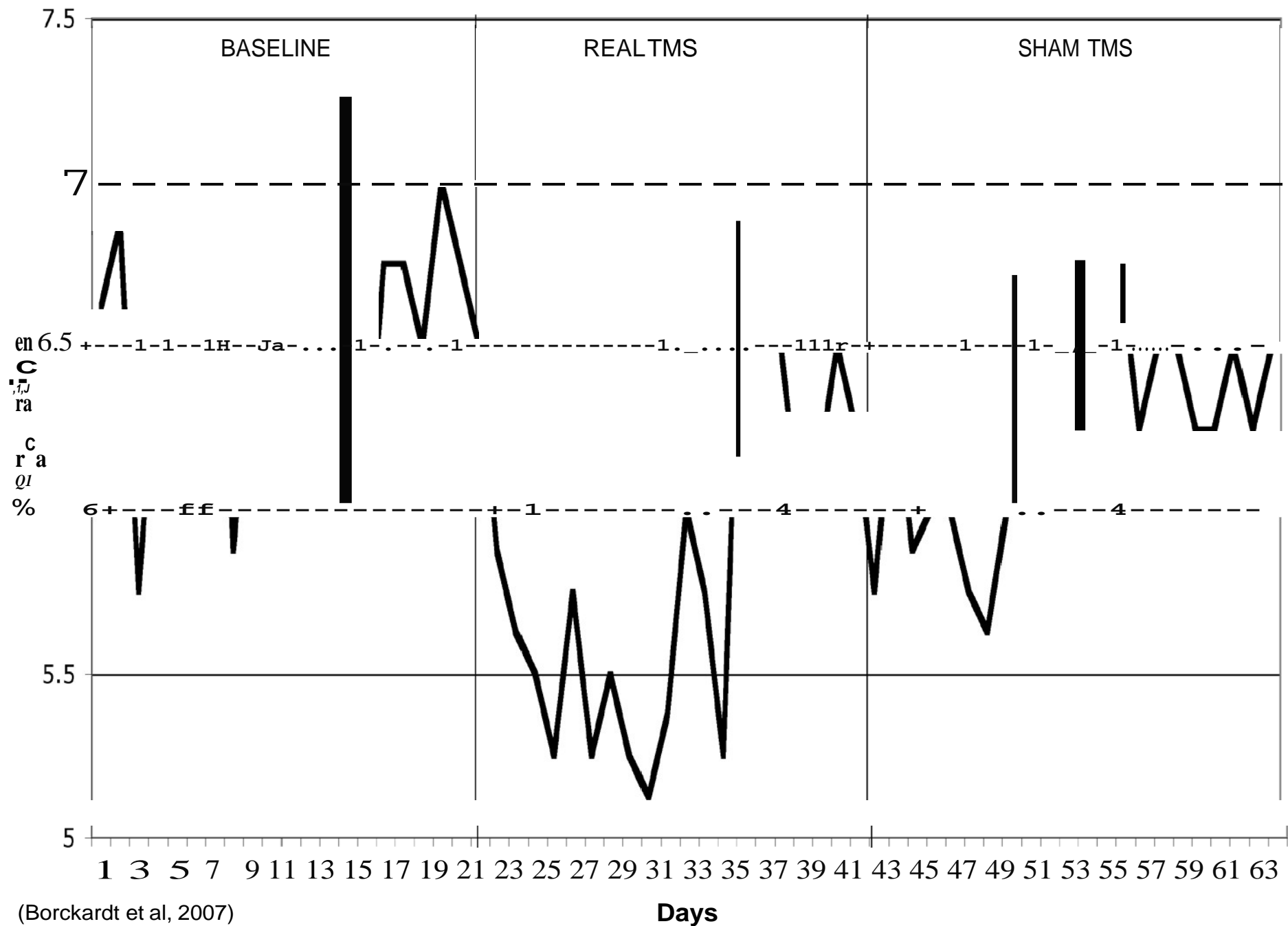


(Borckardt et al, 2007)

Thermal Threshold Trial Following rTMS

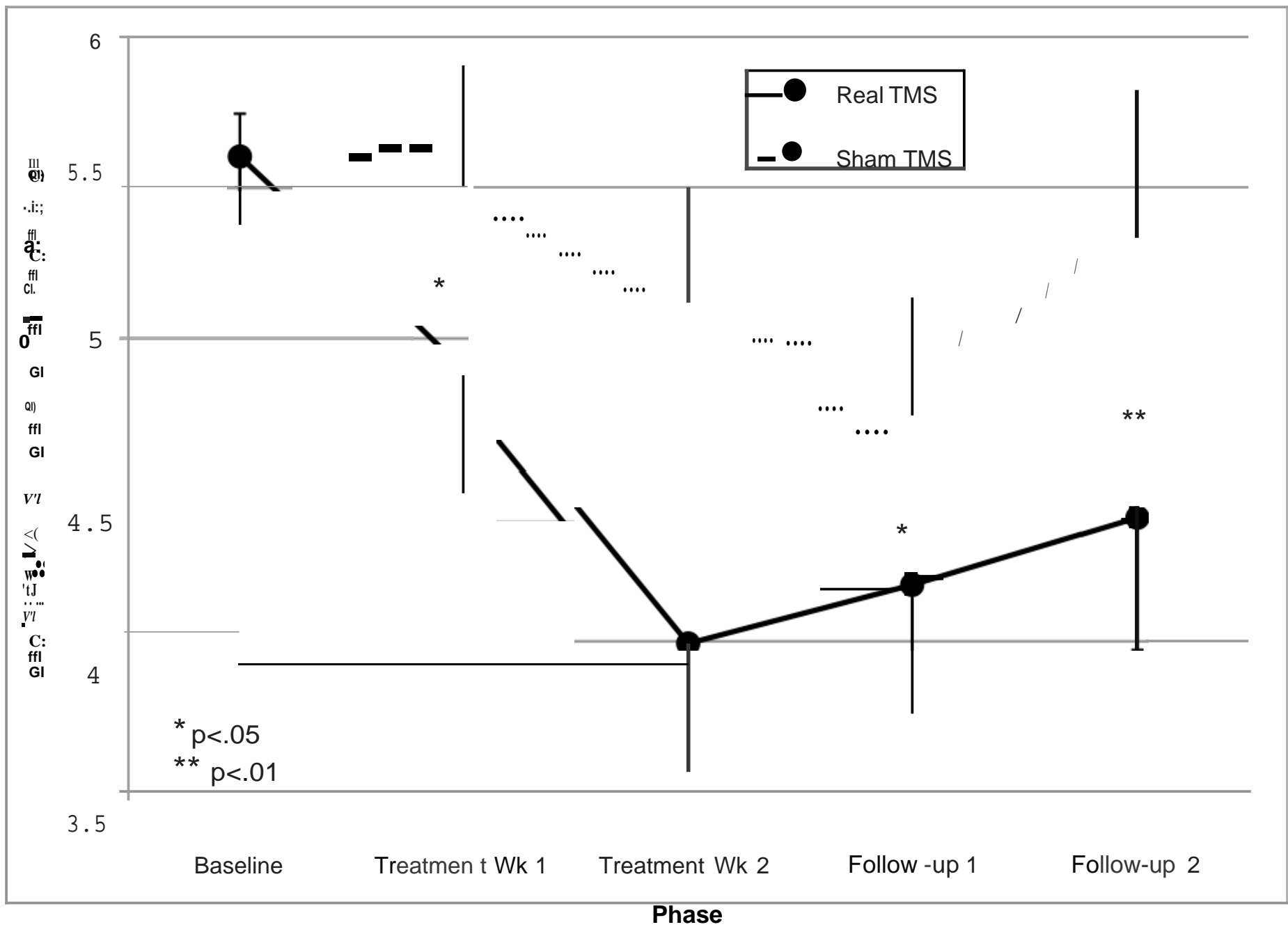
TMS for Neuropathic Pain

- Most clinical studies have examined motor cortex rTMS for neuropathic pain
- We conducted a small cross-over-controlled trial of fast rTMS (10Hz 100%rMT) over left DLPFC for neuropathy
- 3 treatments were conducted of both real and sham rTMS
- Daily pain-diaries were collected

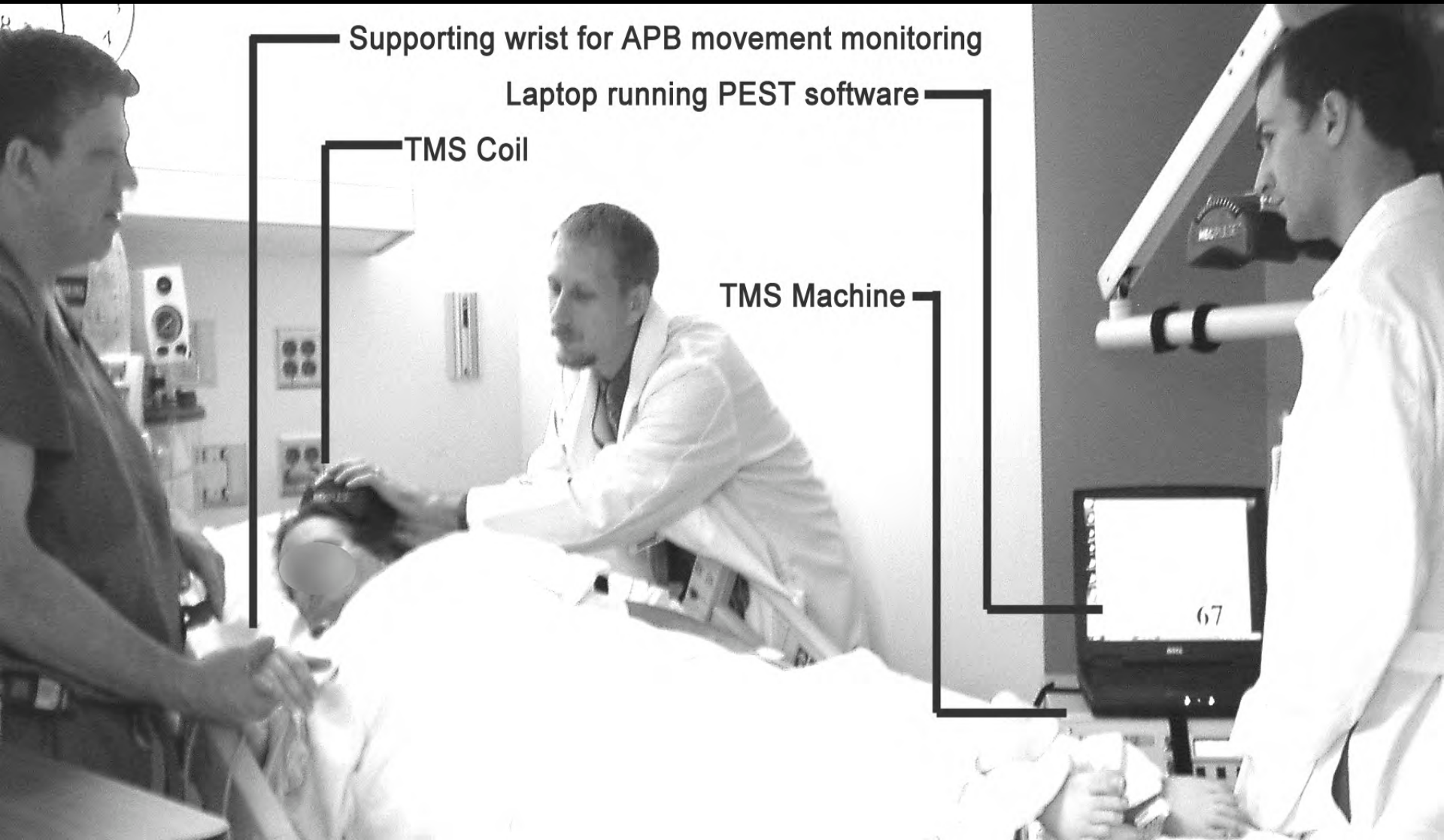


TMS for Fibromyalgia

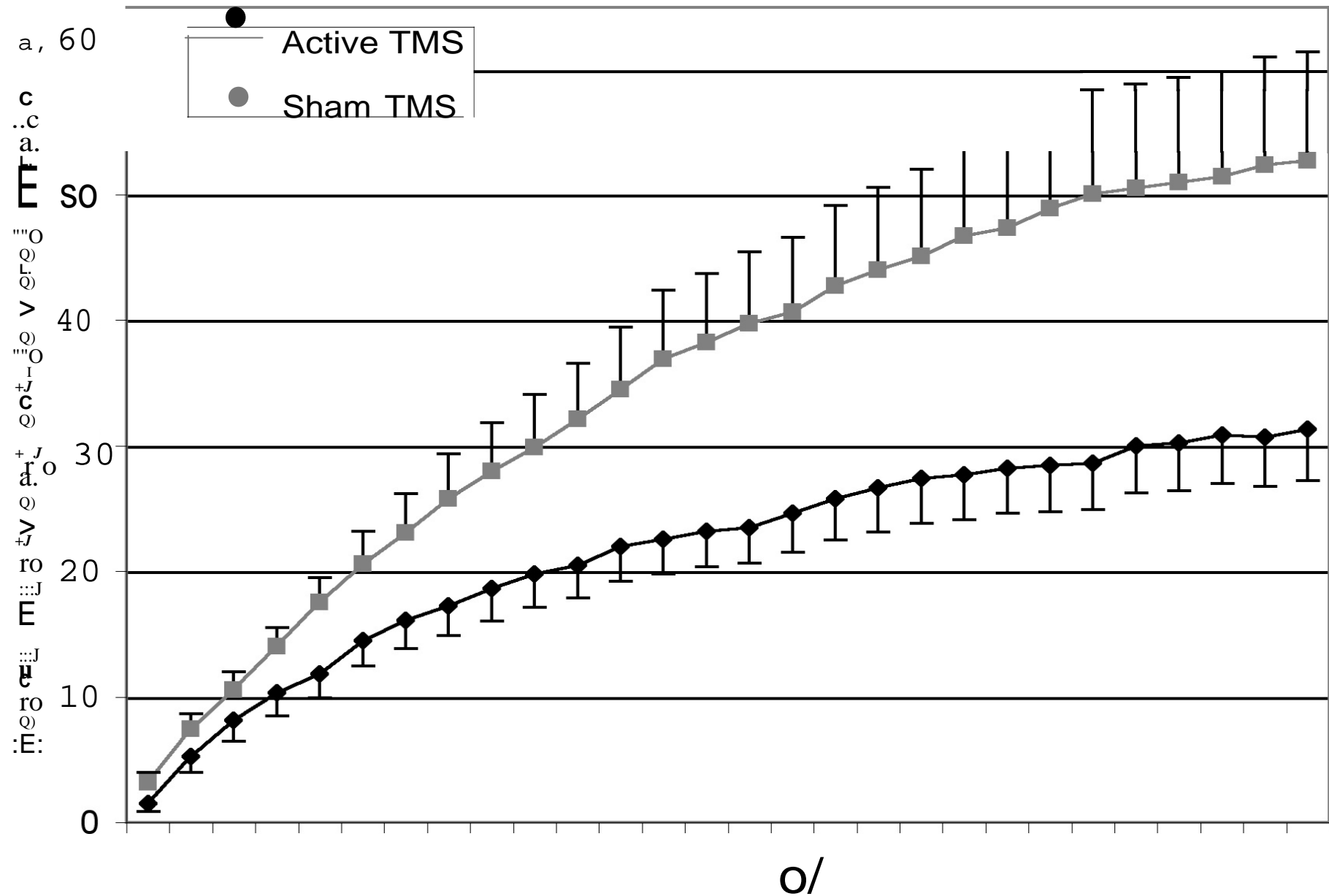
- 20 TMS-naïve subjects with FMS for >1 year
- 10 Sessions of real (n=10) or sham (n=10) 10Hz prefrontal rTMS of Left DLPFC (over 2-weeks)
- Daily pain diaries were completed



Perioperative TMS





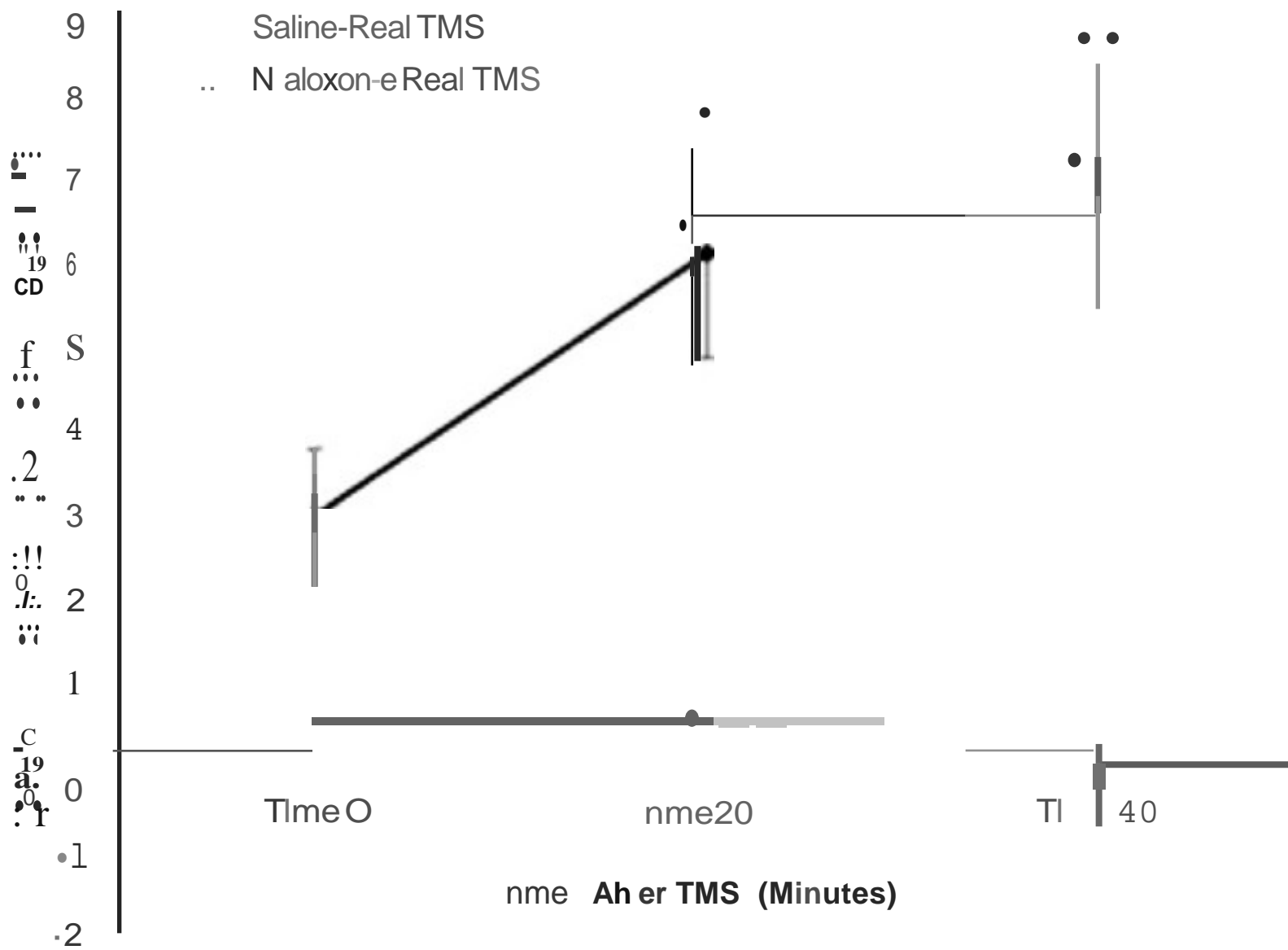


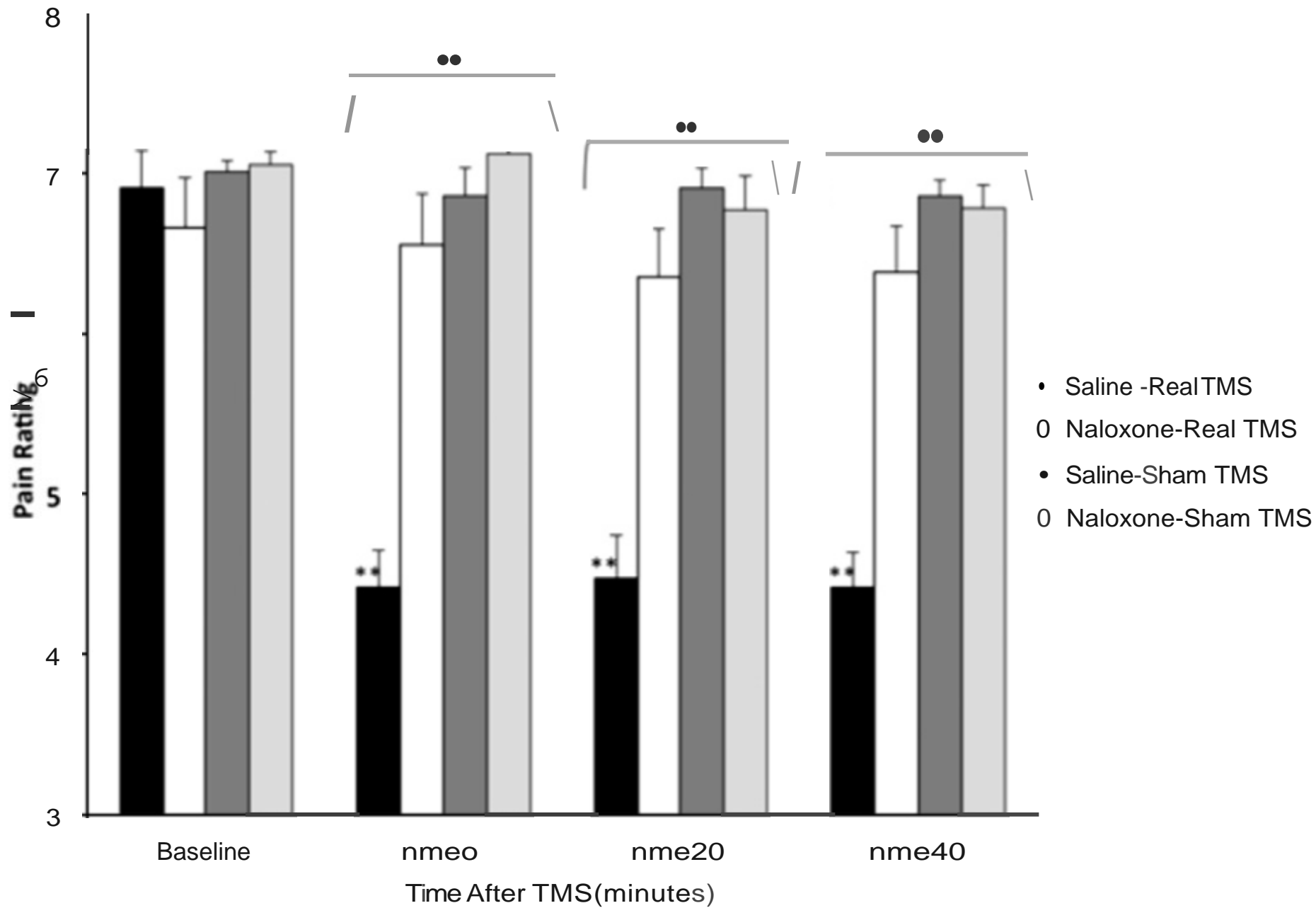
(Borckardt et al, 2006)

Hour after Surgery

TMS and μ -opioids

- 24 Healthy volunteers
- Real (n=12) or Sham (n=12) rTMS 10Hz
110%rMT of left DLPFC
- 2 visits... one involved IV naloxone bolus
(0.1mg/kg); one involved IV saline bolus
- Thermal pain thresholds measured via
method of limits using Pathway thermode

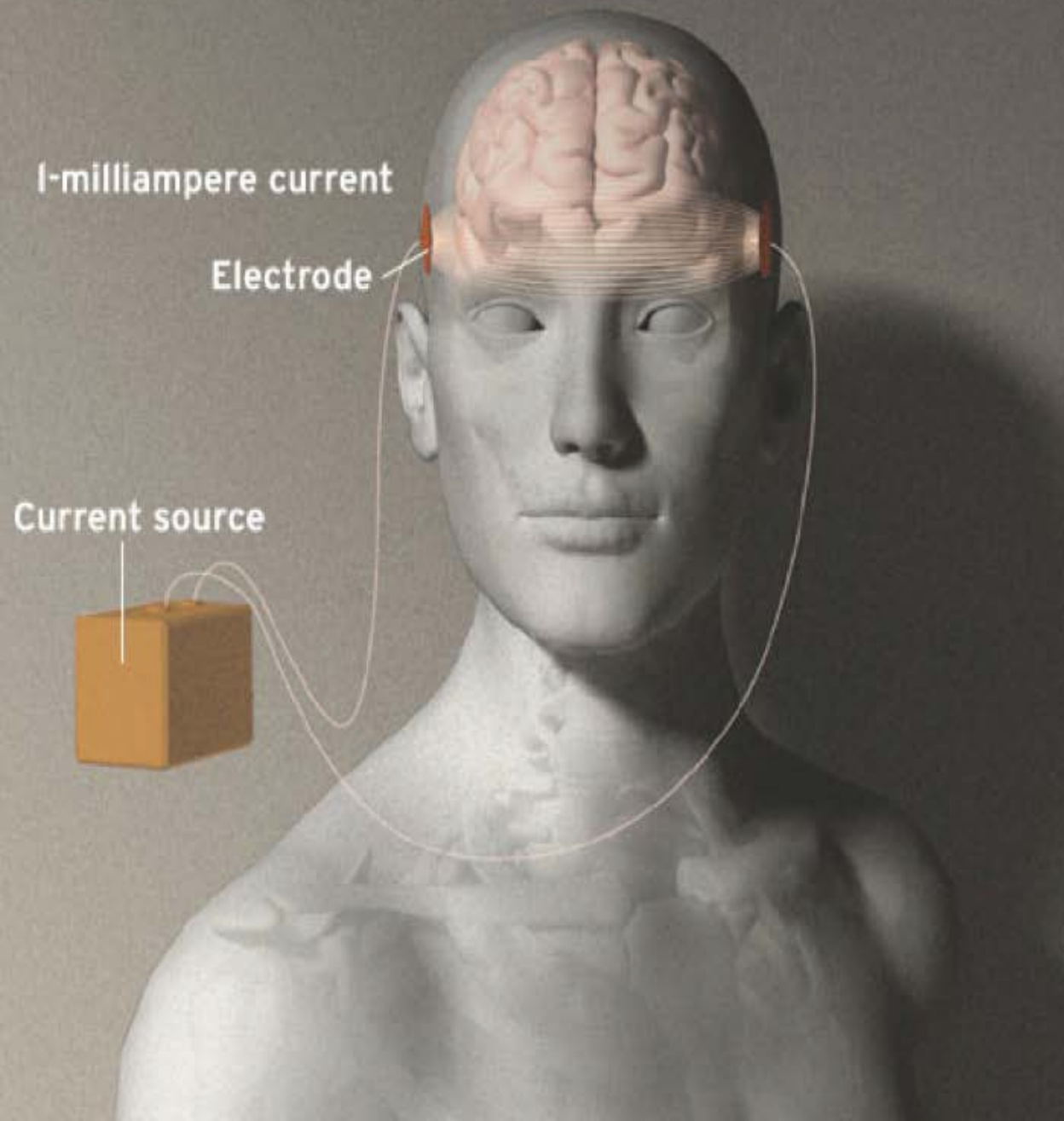




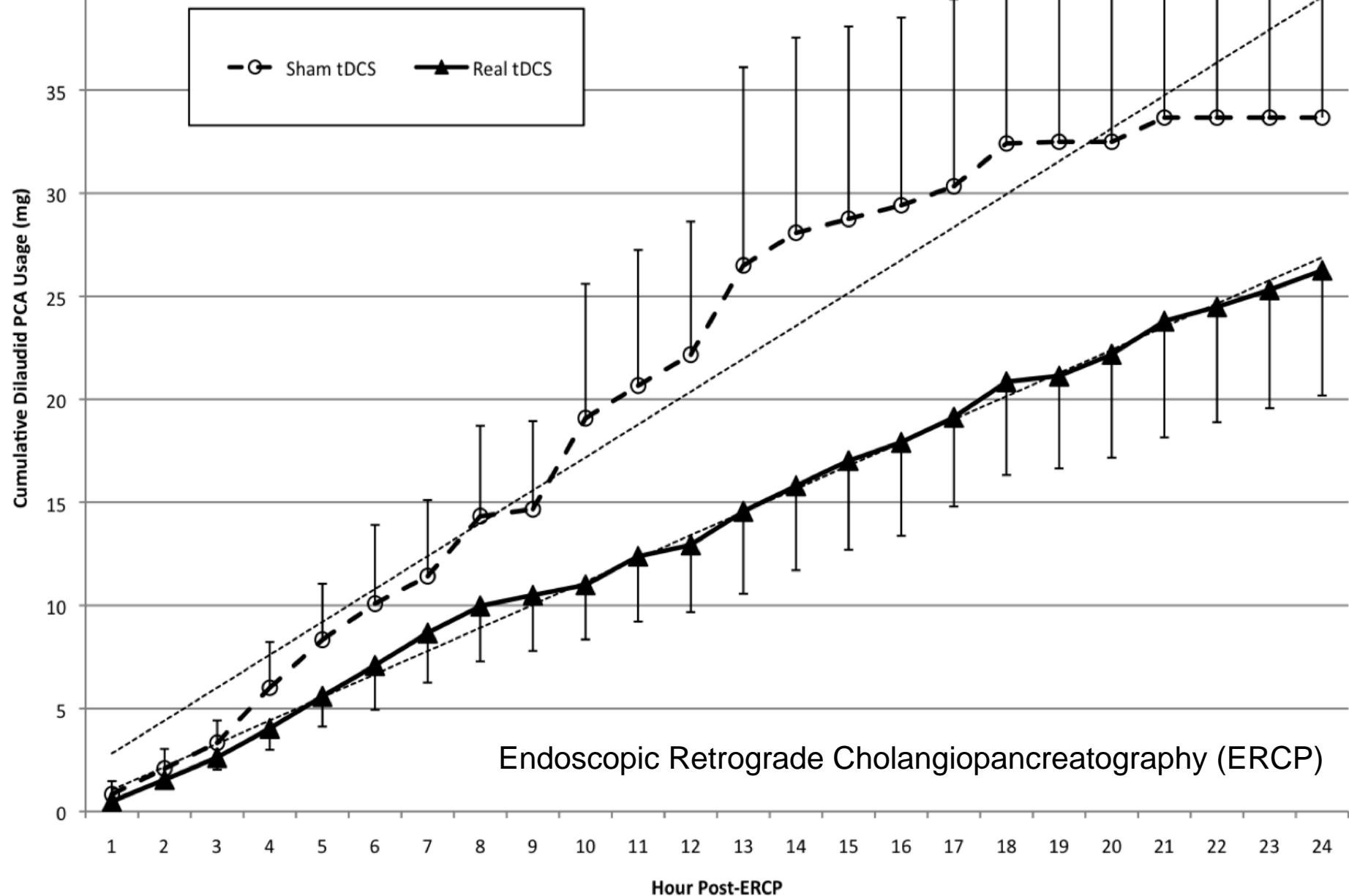


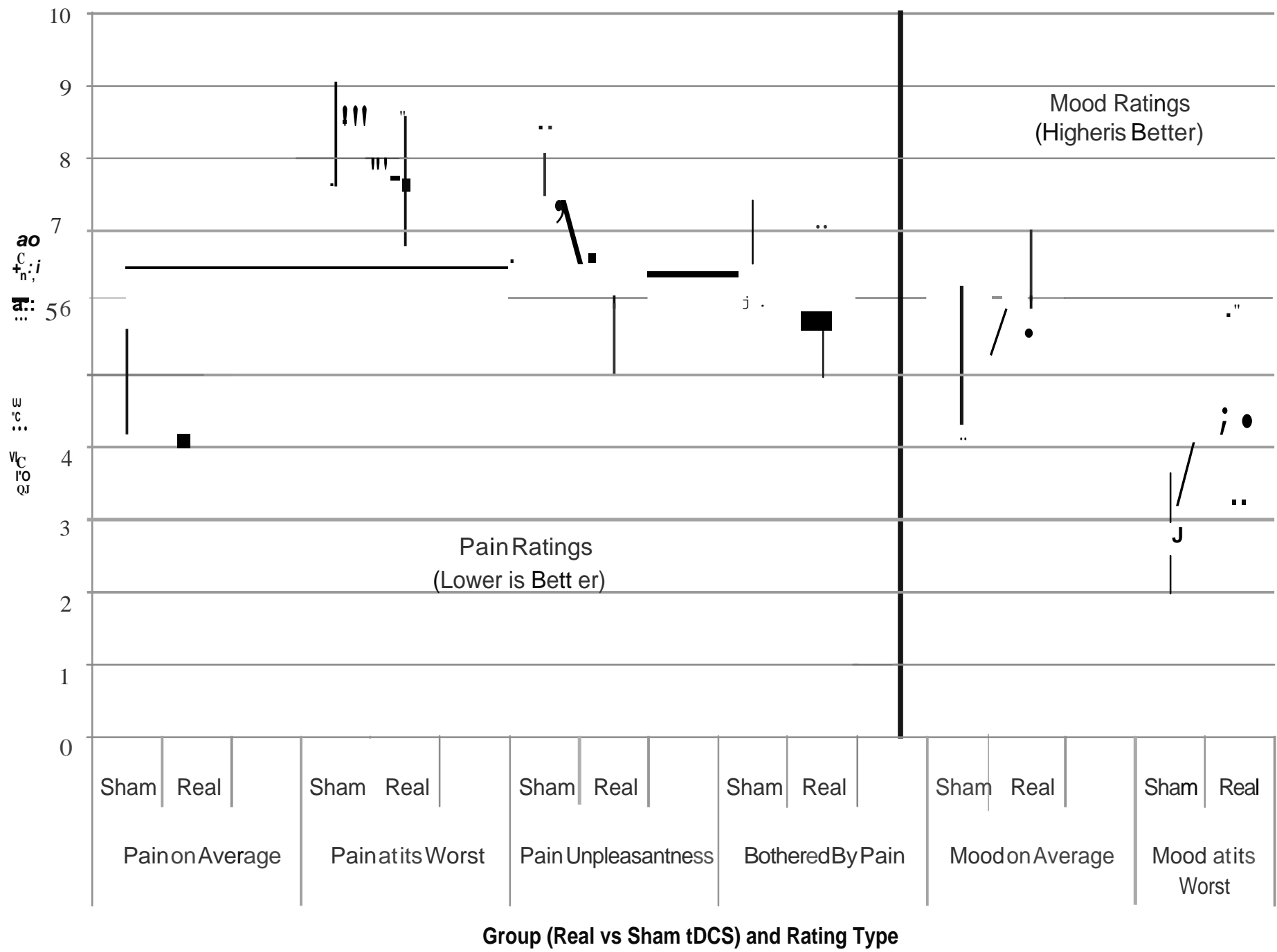
Transcranial Direct Current Stimulation (tDCS)

Transcranial Direct Current Stimulation (tDCS)

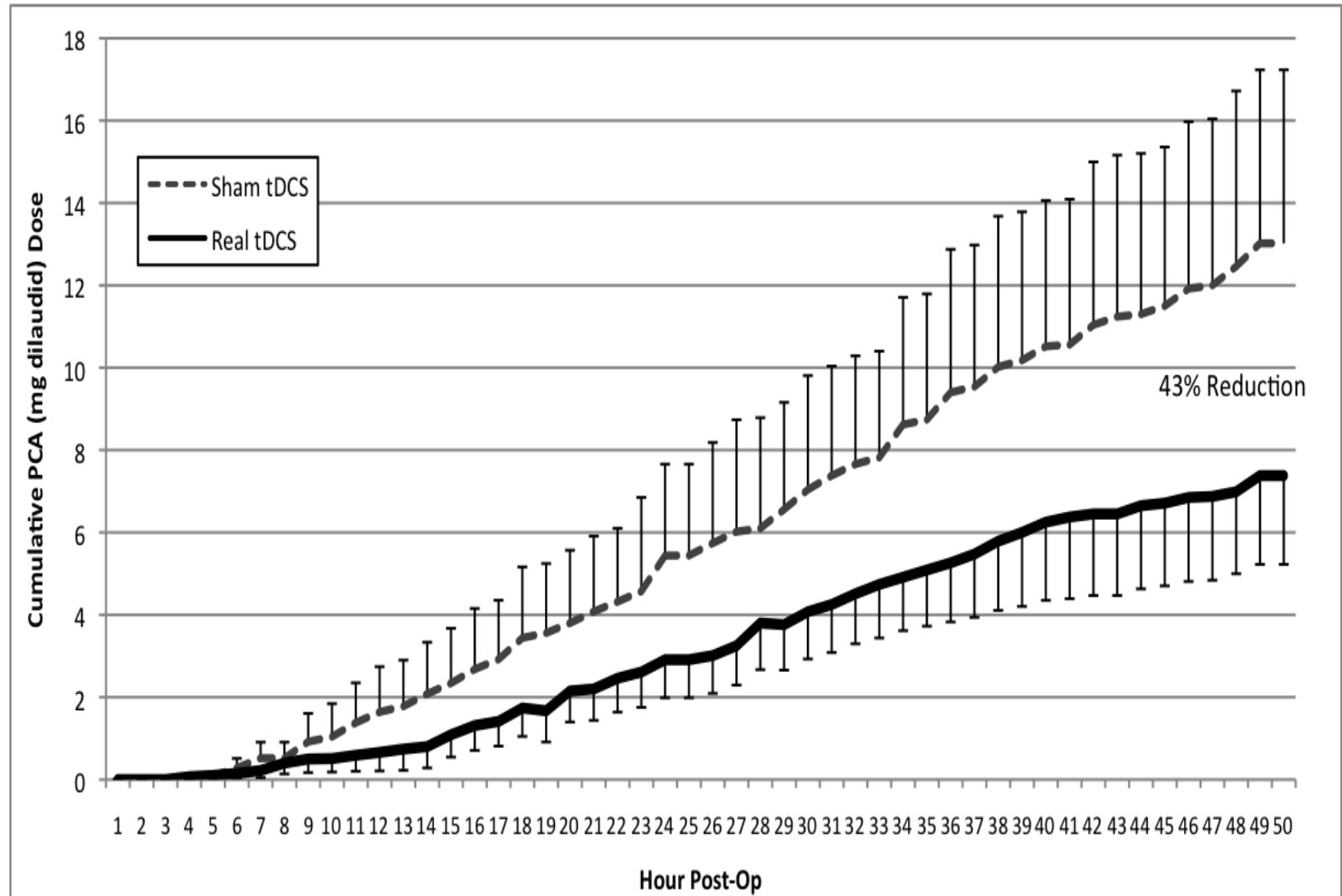


Anode - left dlPFC; Cathode - Gut representation of sensory cortex





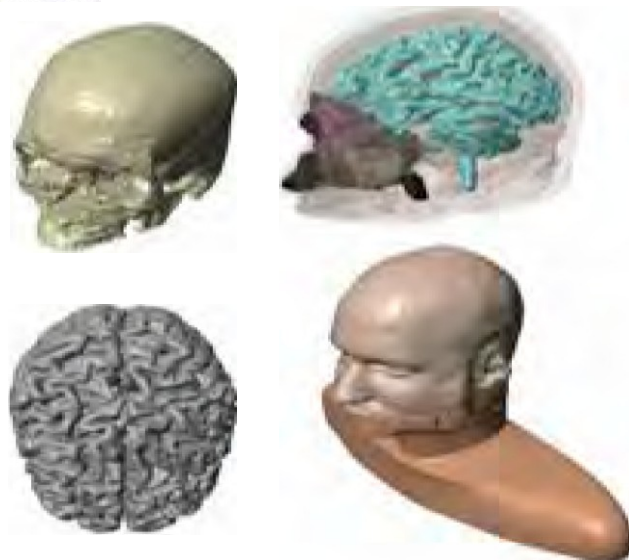
4-Sessions of Motor Cortex tDCS for TKA Pain



High Definition tDCS (HD-tDCS)



SEGMENTED TISSUE MASKS



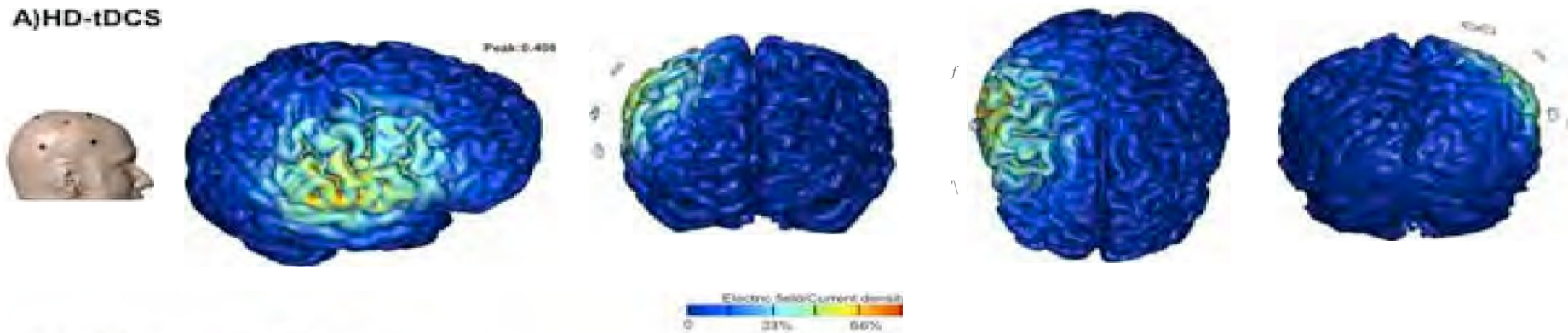
HIGH DEFINITION (HD) MONTAGE



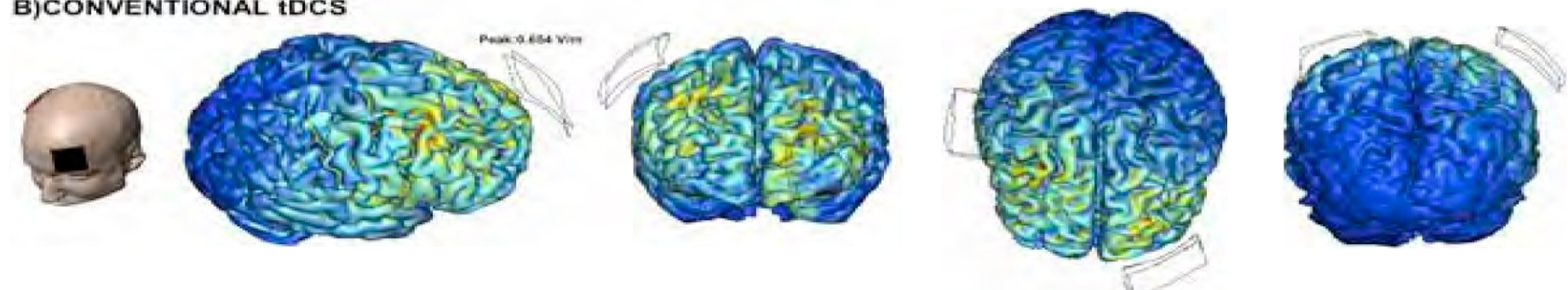
CONVENTIONAL SPONGE PAD MONTAGE



A) HD-tDCS



B) CONVENTIONAL tDCS

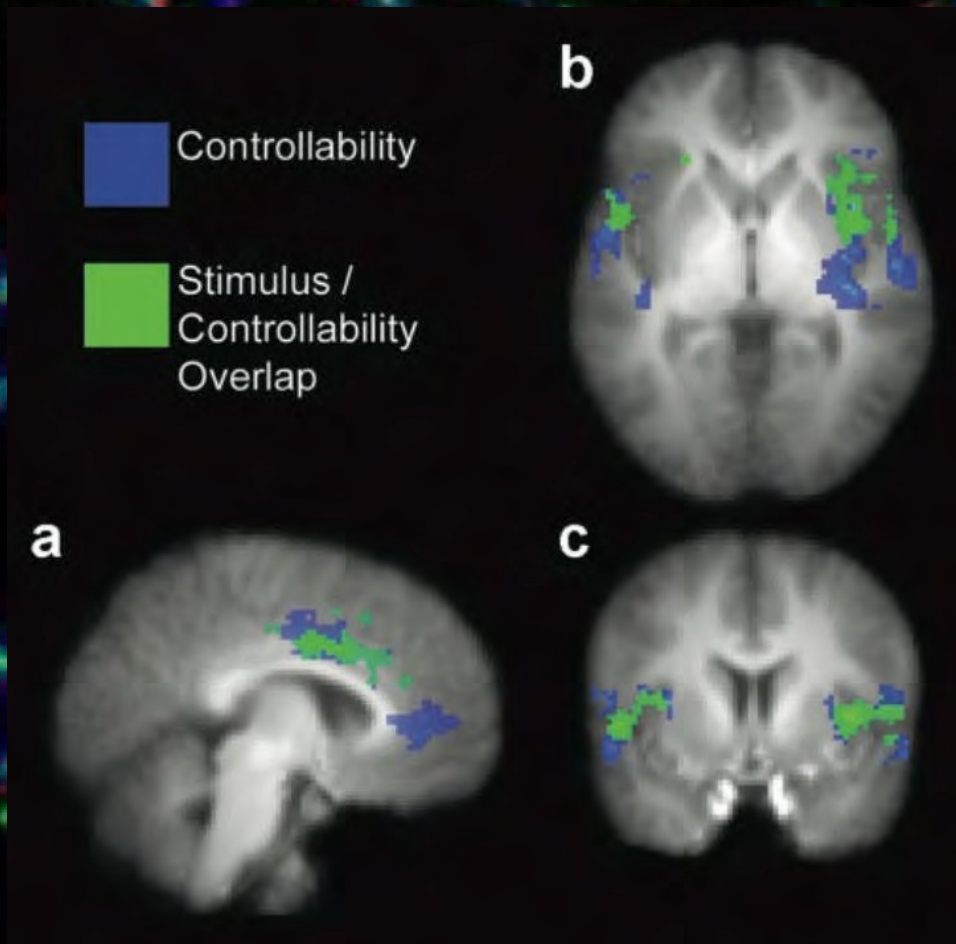




Neuro-Cognitive Mechanisms

Differences between TMS and tDCS

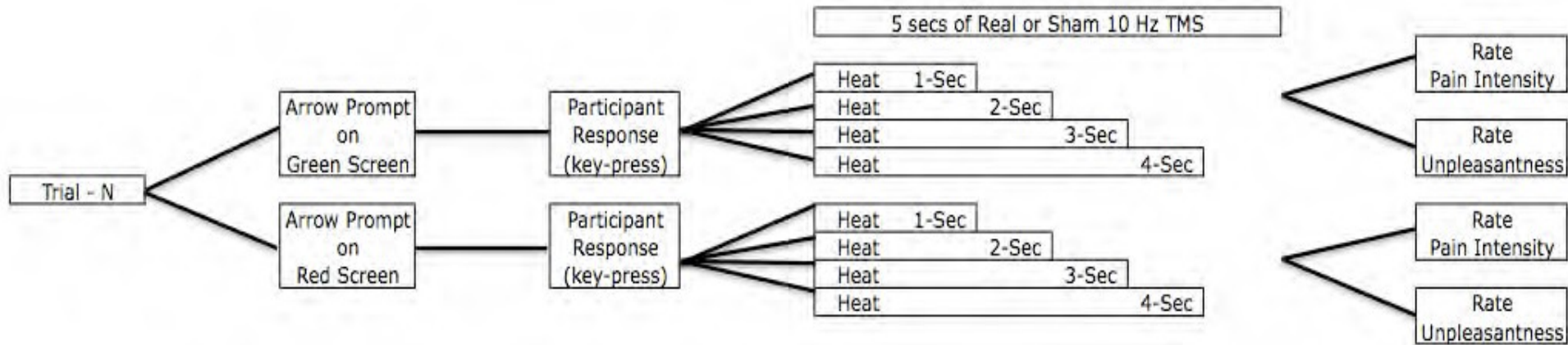
Pain and Perceived Control



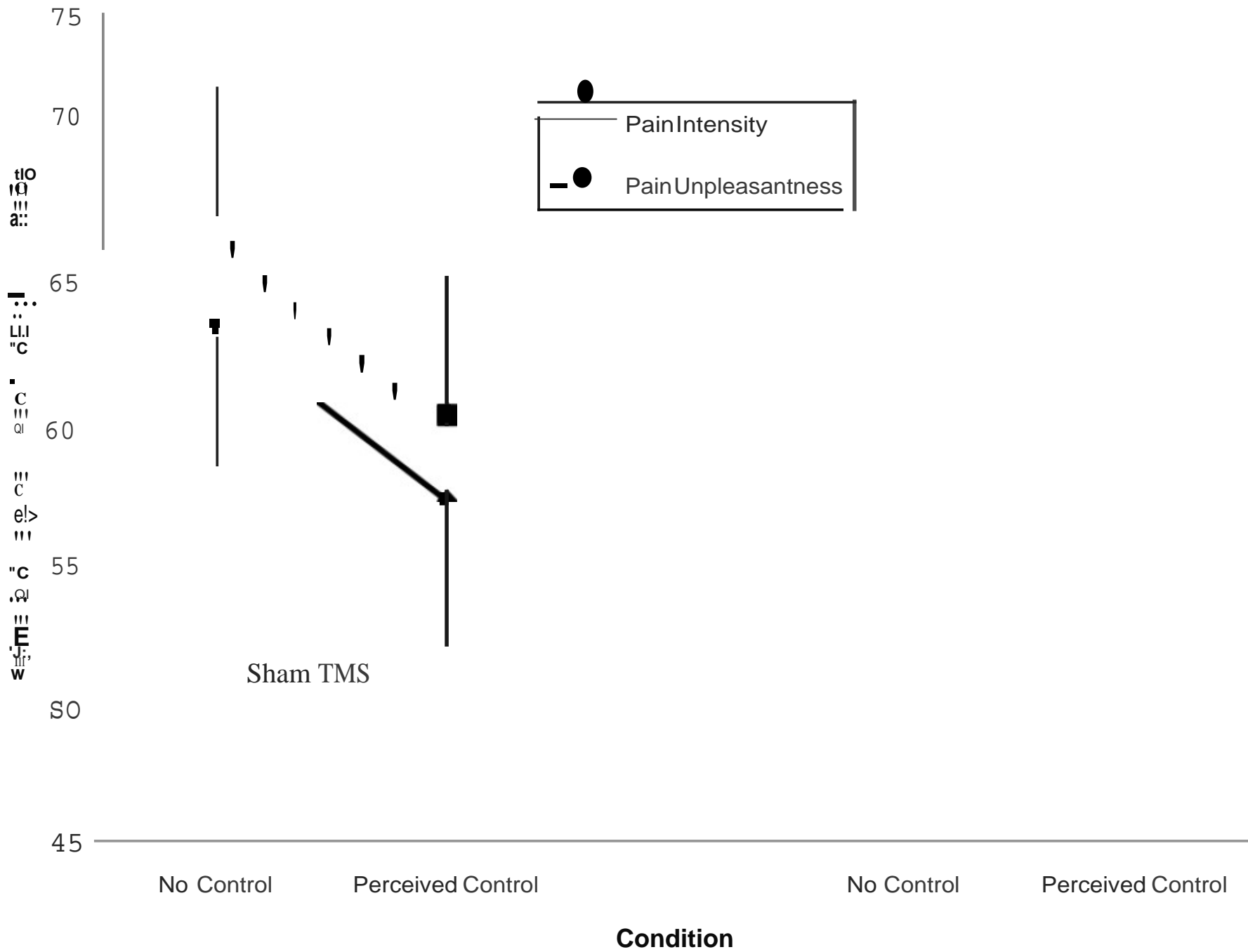
When pain stimulus-intensity is controlled-for, and when we manipulate perception of control, pain is rated as less intense, less bothersome, and unique areas of the brain appear to become involved.

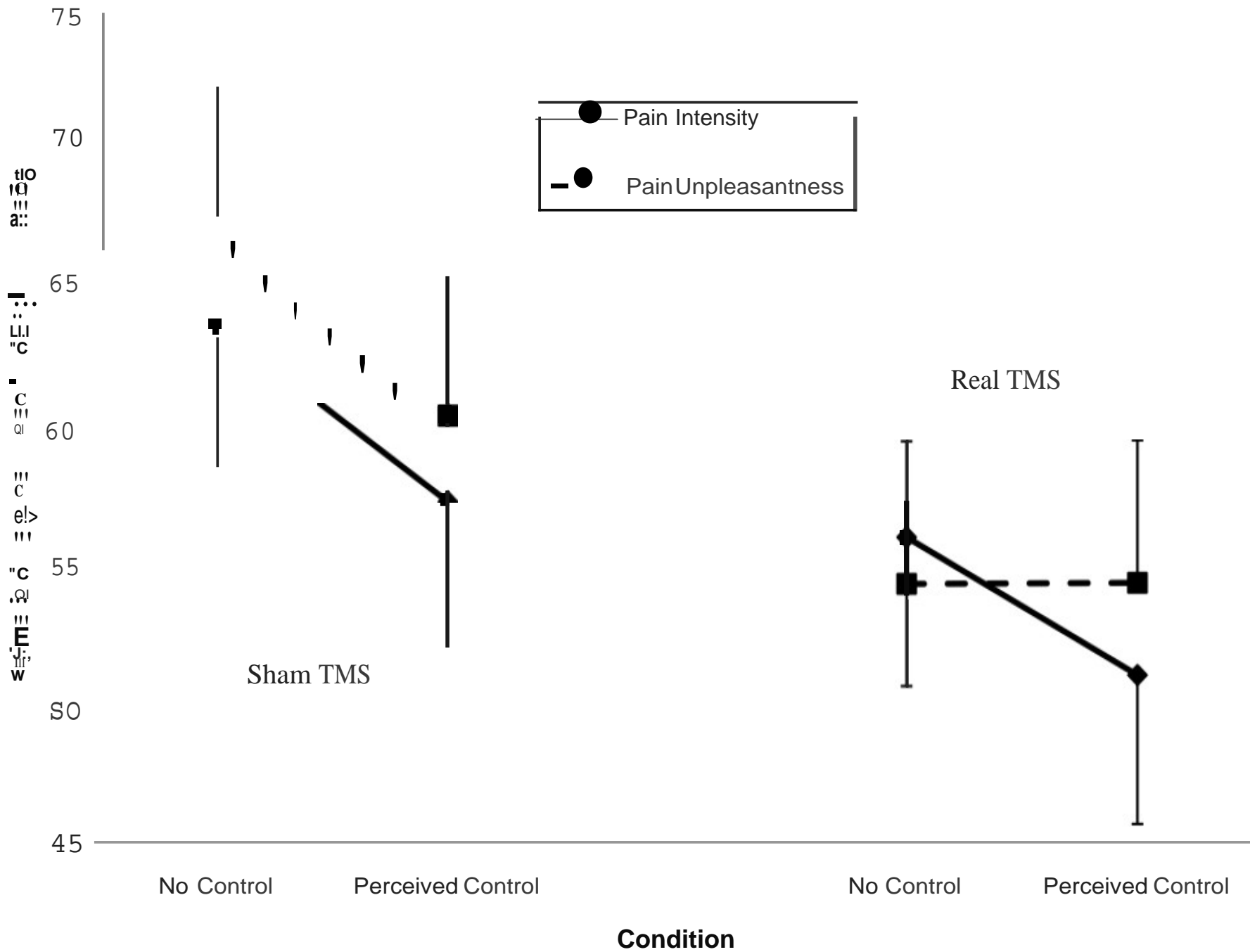
Figure 2. *a–c*, Significant activations in the ACC, insula, and SII. Areas shaded in blue were significantly more activated in response to identical pain stimuli when they were perceived to be uncontrollable rather than controllable ($UC - C$). Areas shaded in green were significantly activated in both the uncontrollable and controllable conditions but were significantly more activated when the pain was perceived to be uncontrollable [$(UC \text{ and } C)$ and $(UC - C)$].

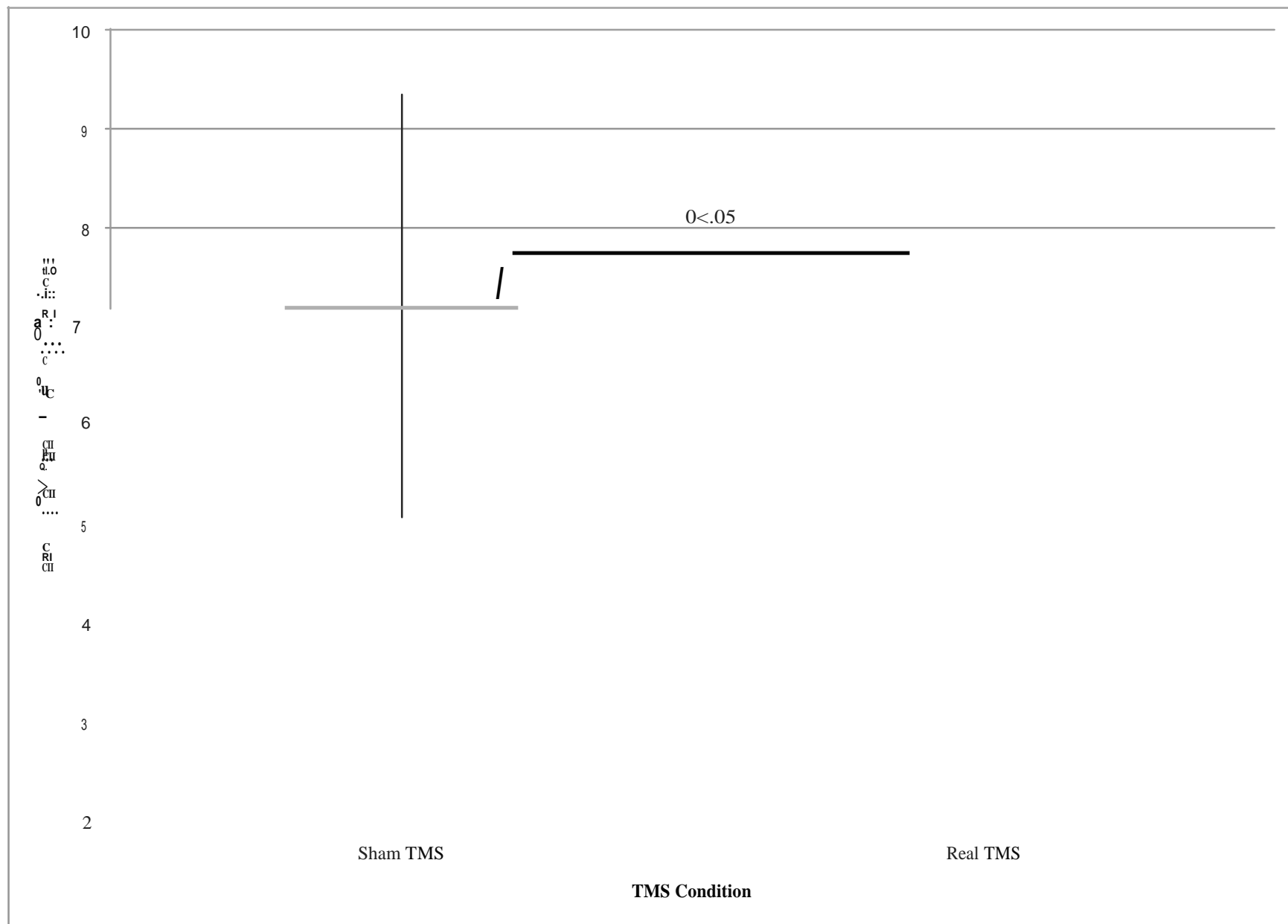
Perceived Pain Controllability Paradigm



Regardless of screen-color and participant performance, the thermal stimuli are all random and the durations are balanced between green and red screen conditions.

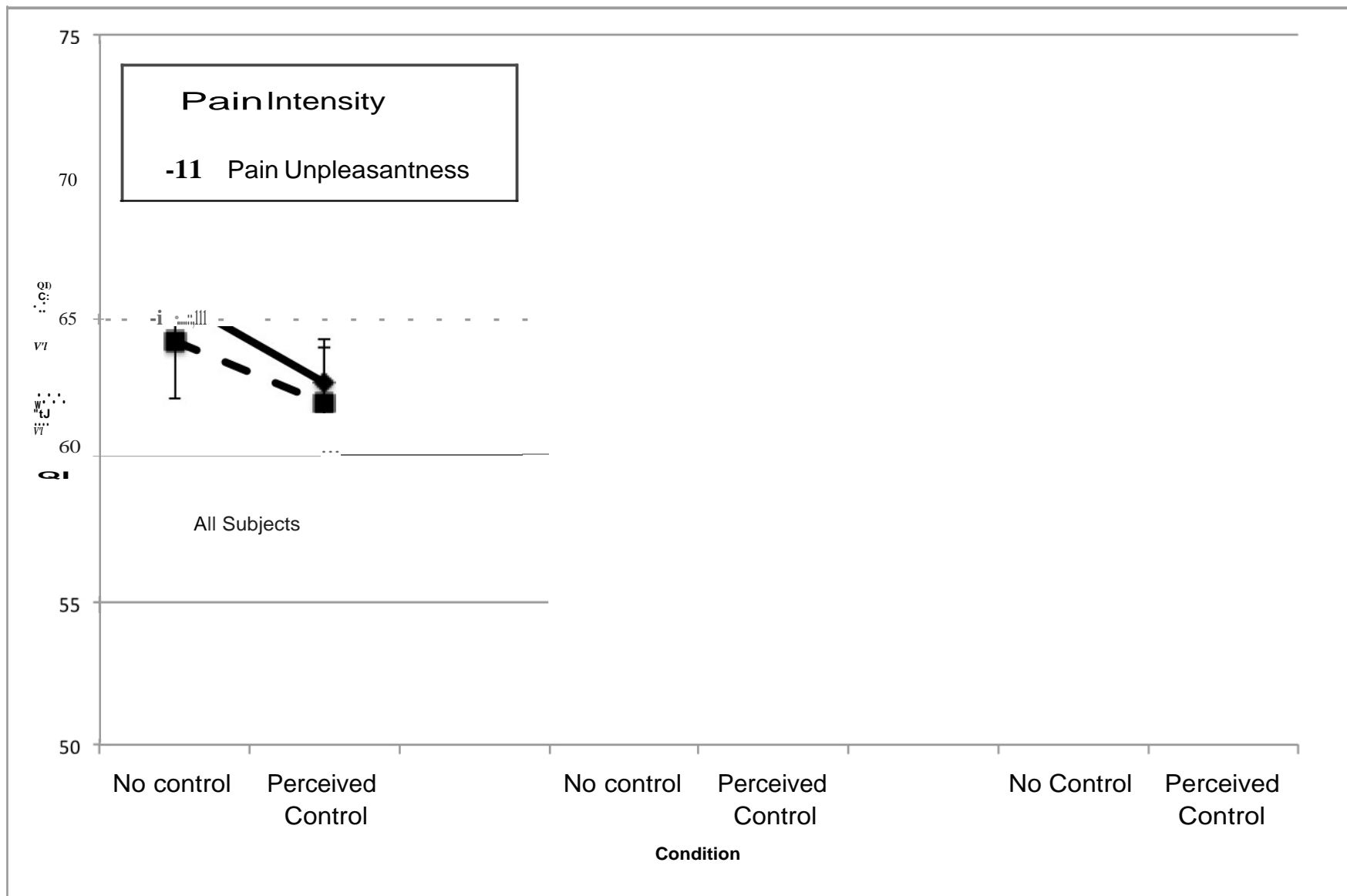


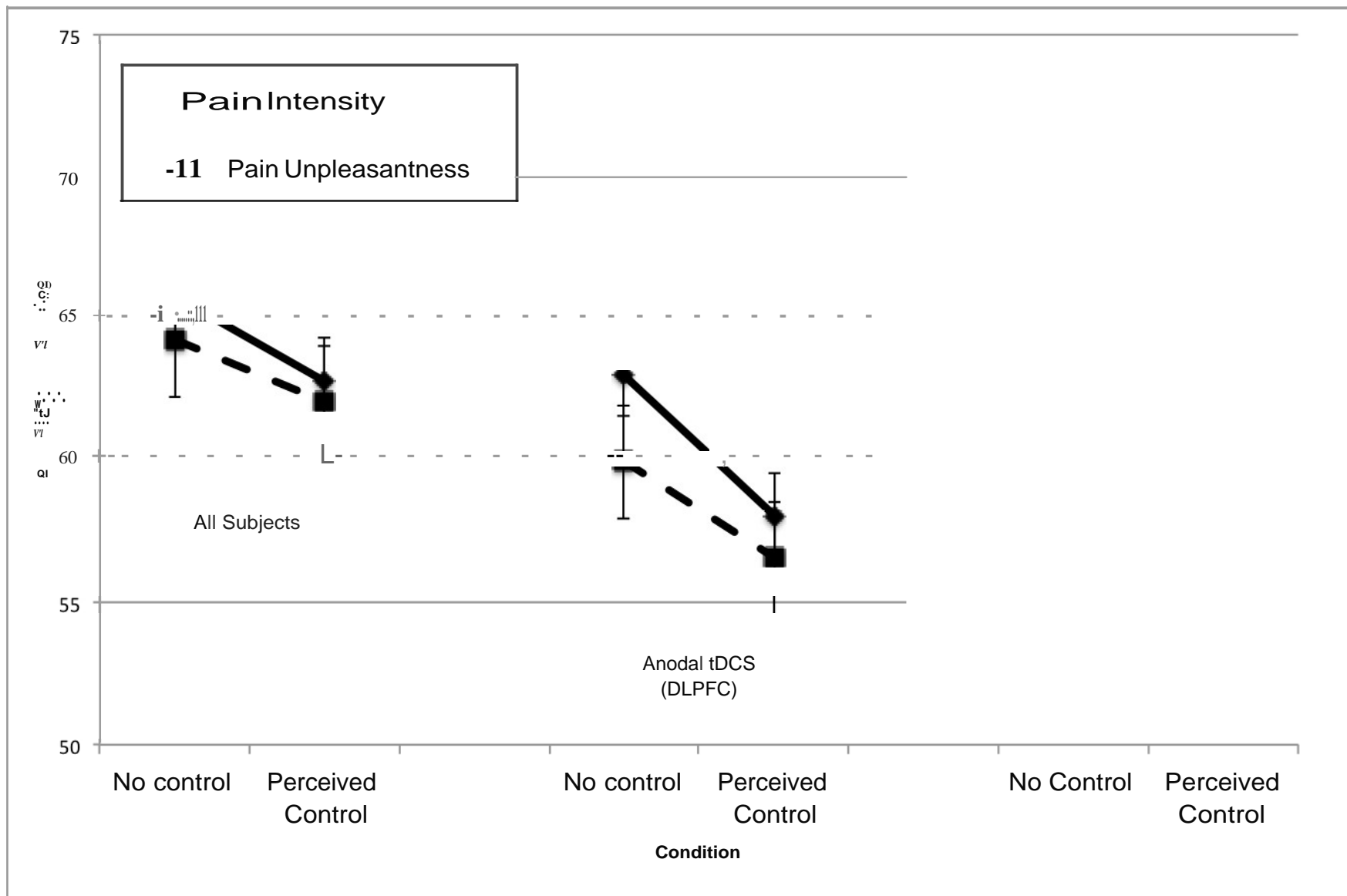


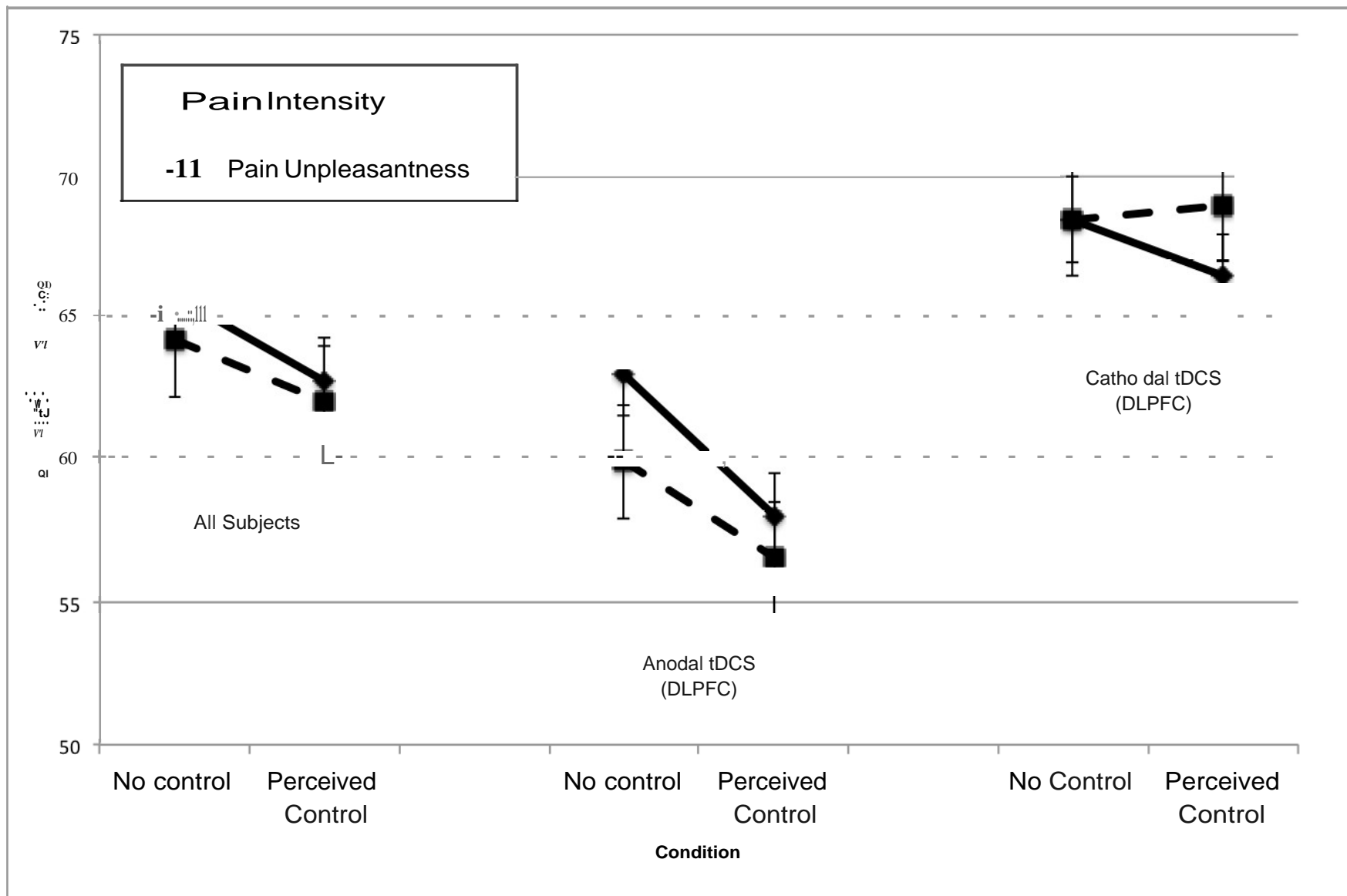


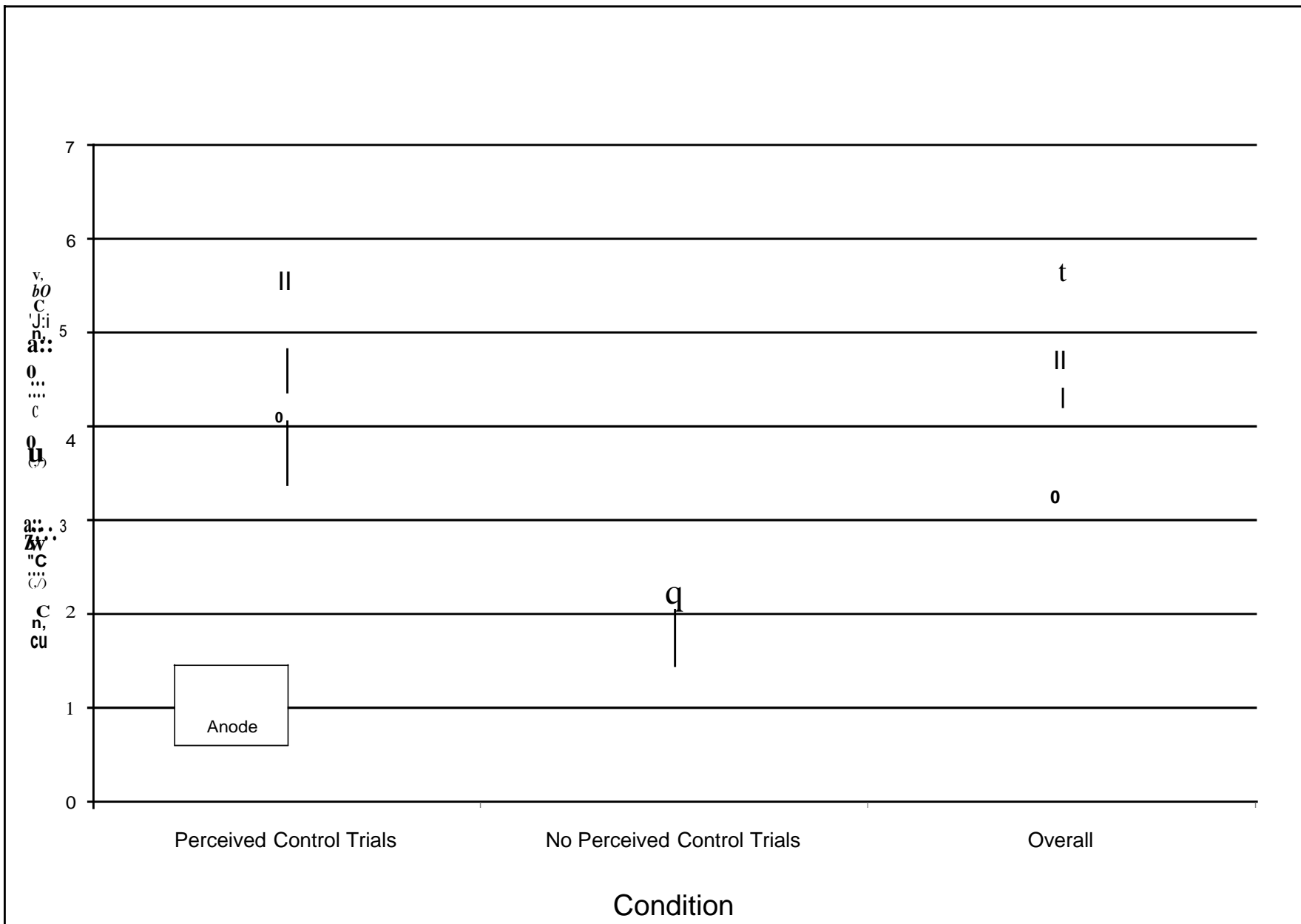
tDCS and Perceived Control

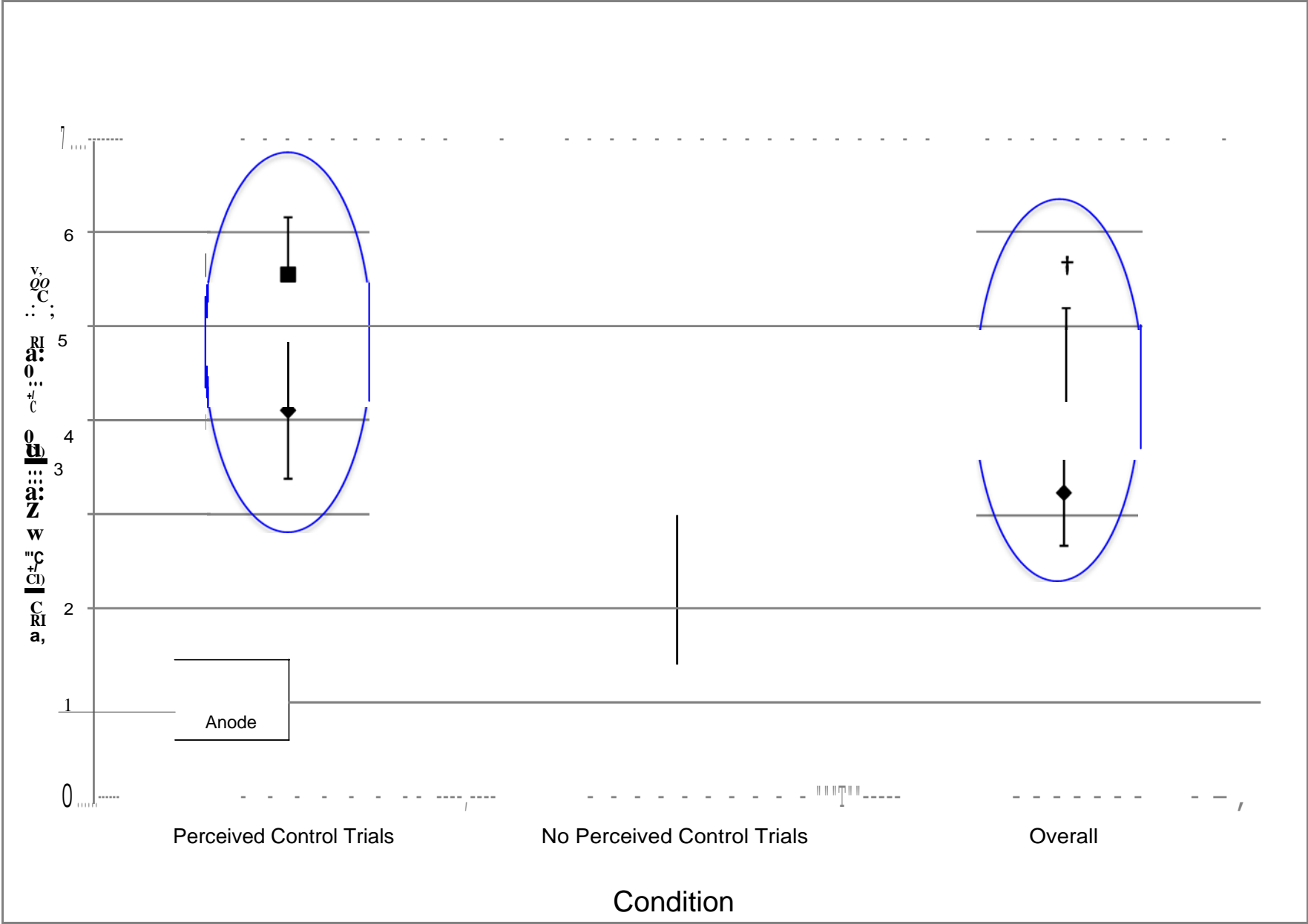
- 41 Healthy Adults
- Underwent pain perceived controllability task
- 20 mins of anodal (n=21) or cathodal (n=20) tDCS at 2mA over left DLPFC during pain controllability task
- Other electrode was attached to right shoulder







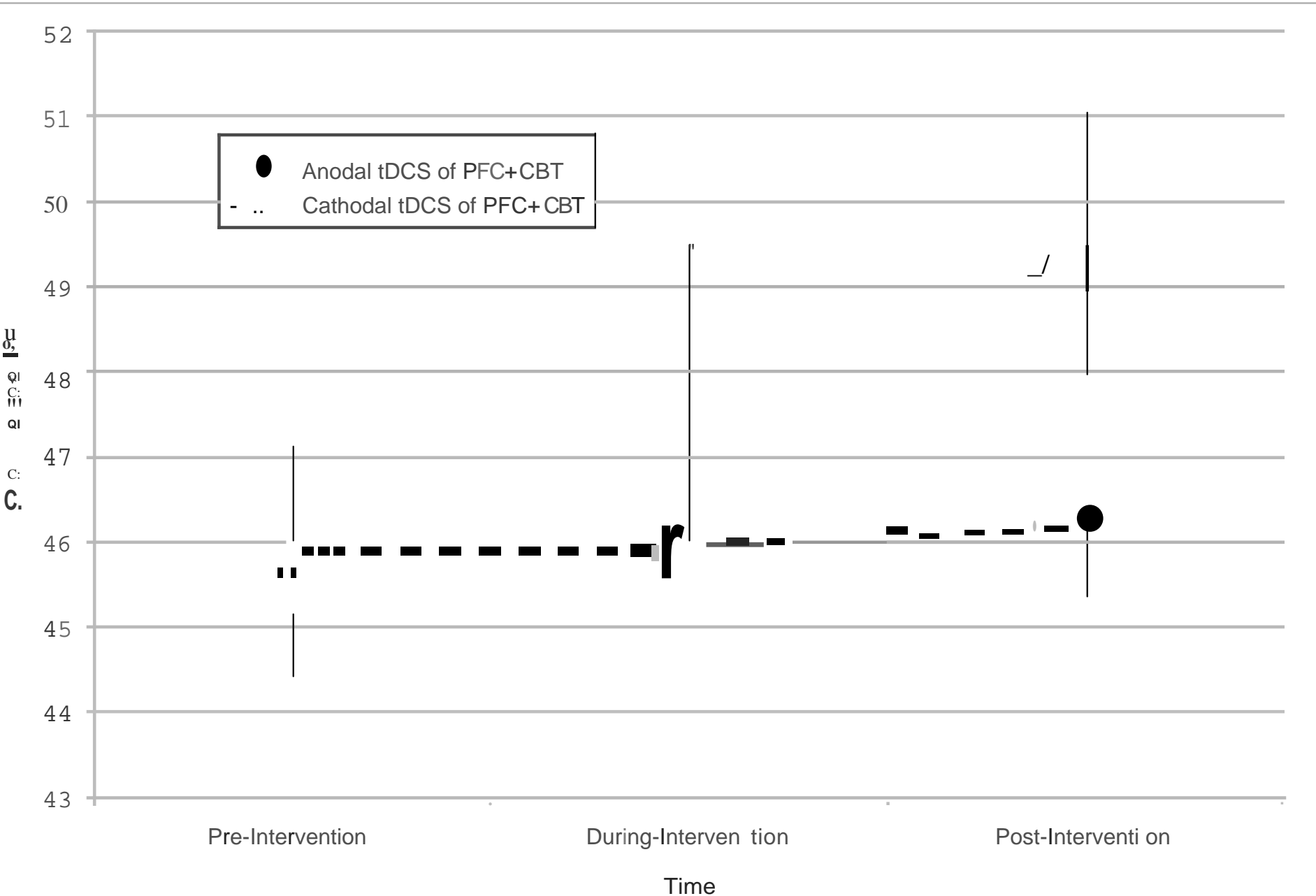


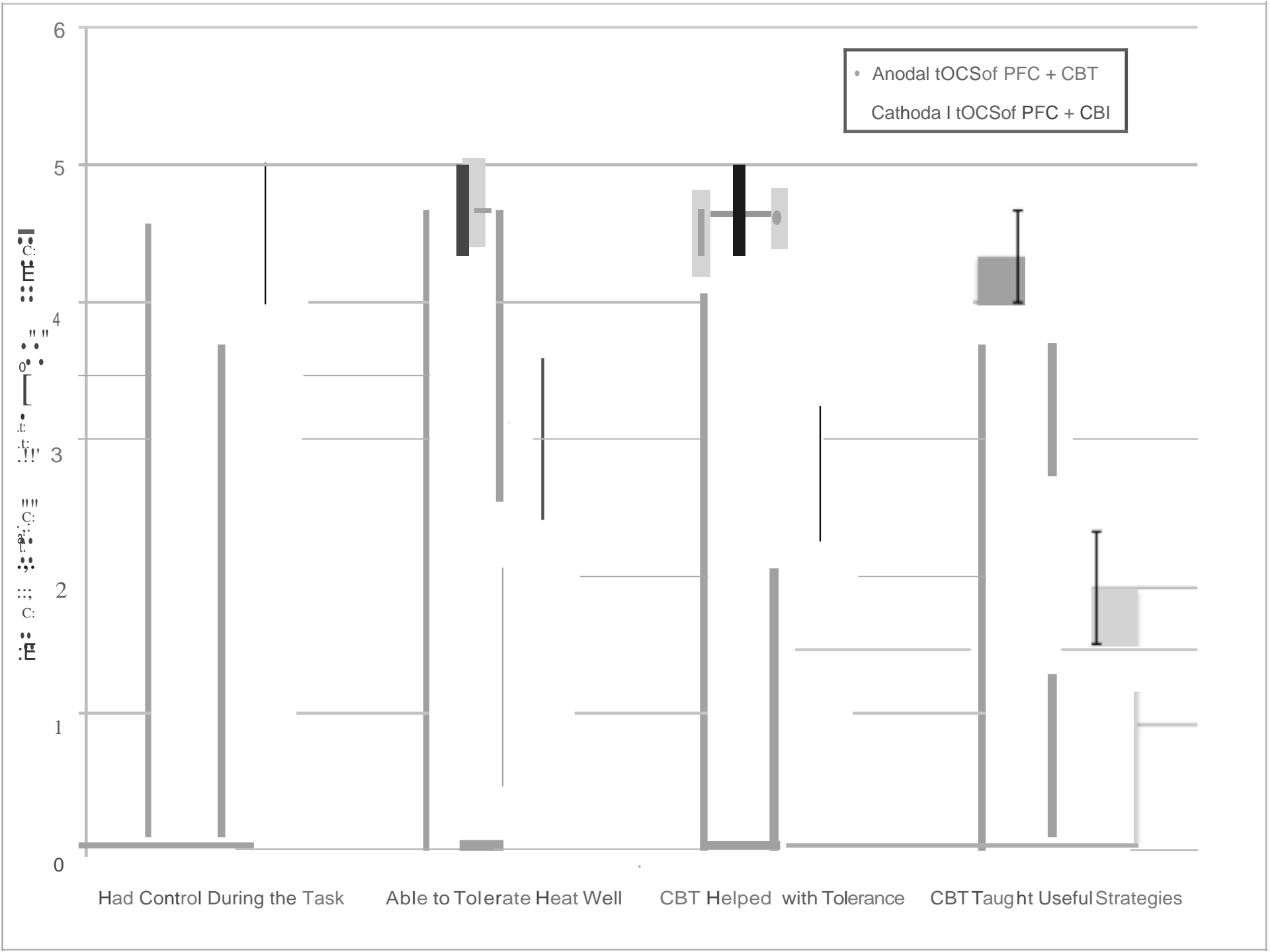


tDCS + CBT for Pain

- Pilot study (n=8) of healthy volunteer participants
- Thermal pain tolerance assessed pre-, during, and post- a laboratory CBT intervention
- tDCS applied to the left DLPFC (anodal versus cathodal) during the CBT intervention
- Post-task retrospective assessment administered to evaluate subjective perspectives

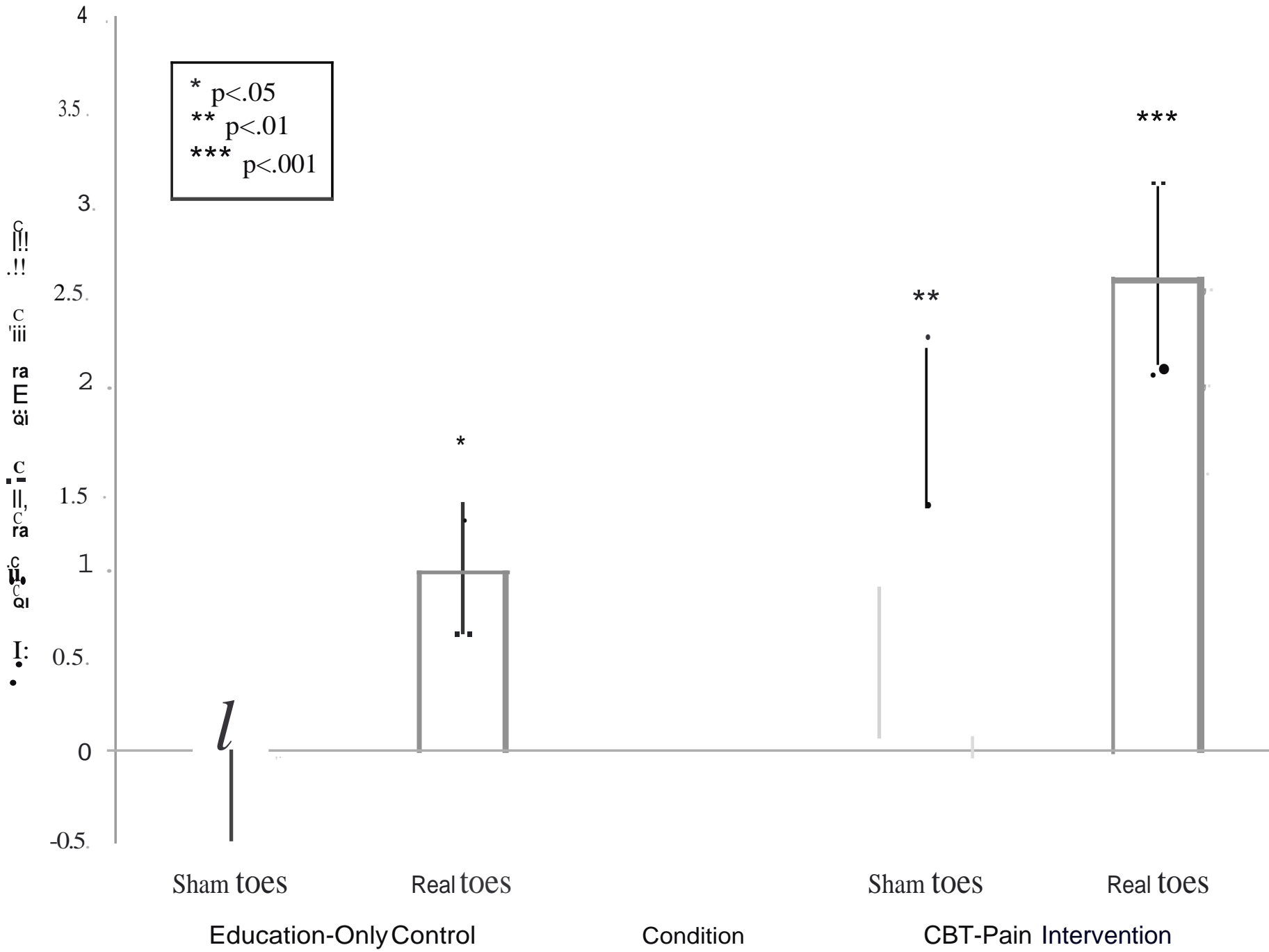
Laboratory CBT plus Anodal versus Cathodal toes of the left DLPFC



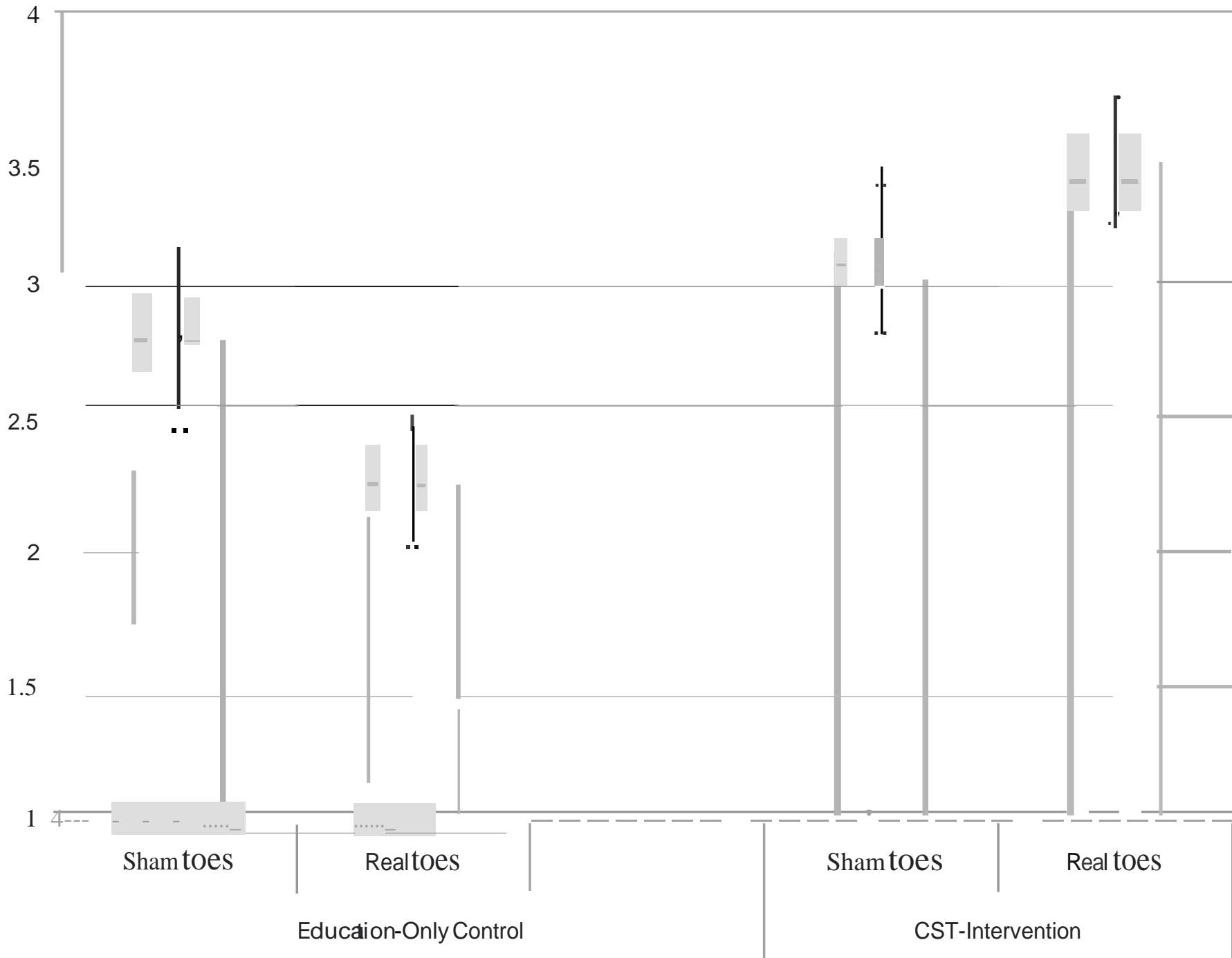


Study 2: CBT + tDCS for Pain

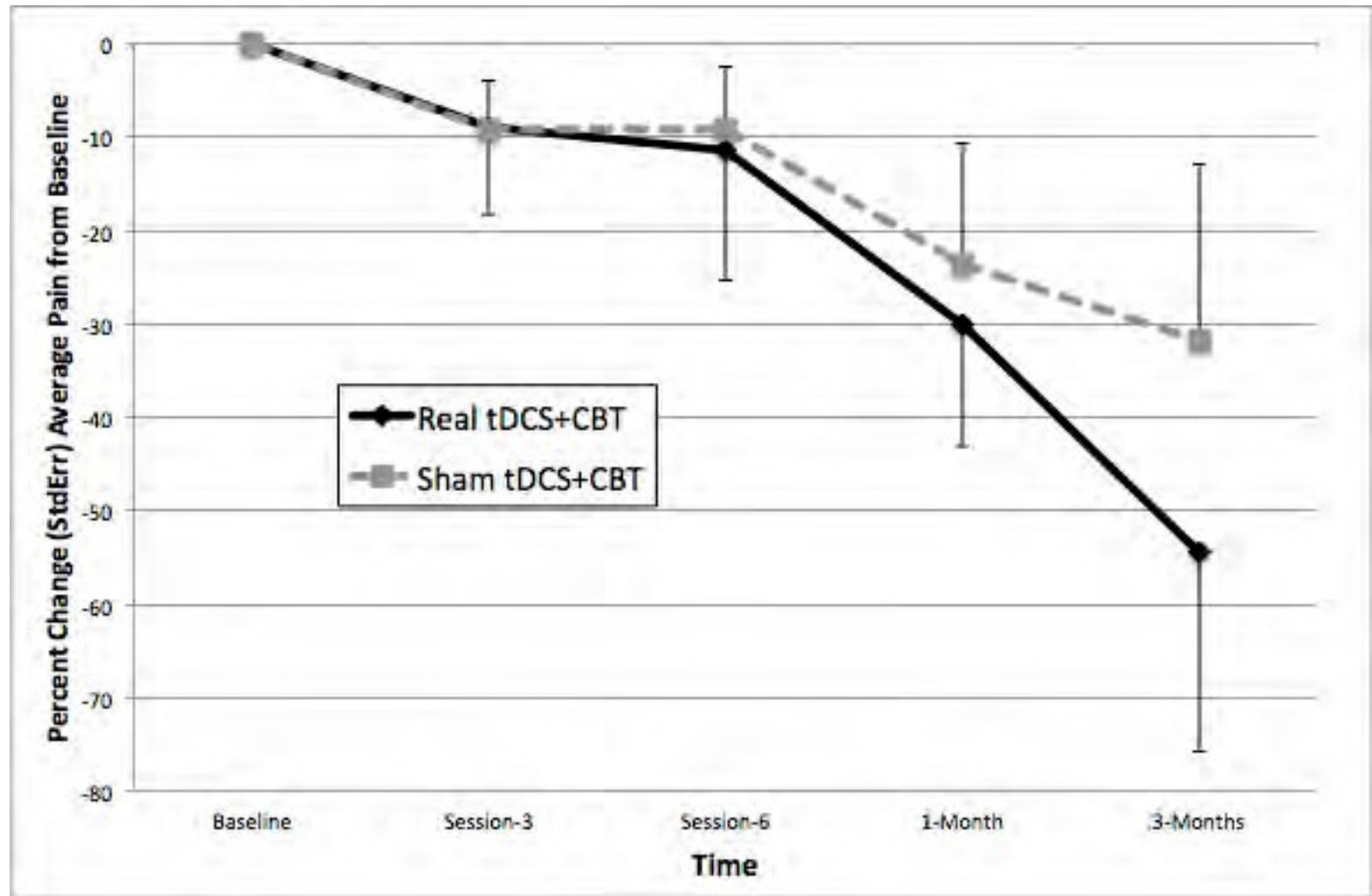
- Lab Pain Paradigm (thermal pain tolerance)
- n=86 healthy volunteers
- CBT versus Education-Only Control Intervention
- Left DLPFC tDCS versus Sham tDCS



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Clinical Pilot Trial: CBT + tDCS for Fibromyalgia (n=15)





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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
- Locating motor strip:
 - Anatomical
 - Functional MRI
 - Waking stimulation trial in OR



Melding of TMS technology and MCS

Can TMS be used to improve the effectiveness of motor cortex stimulator surgical procedures?

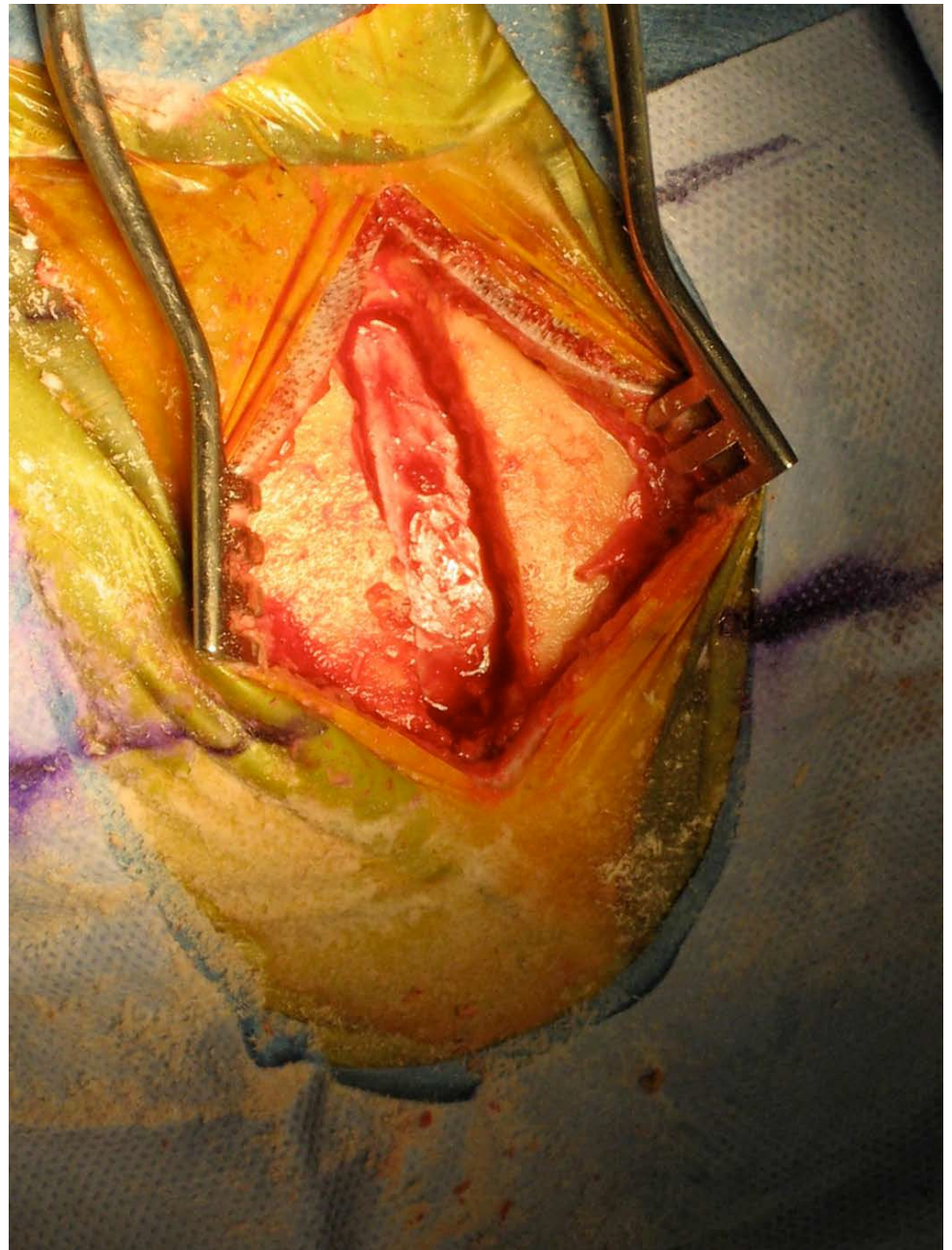


Melding of TMS technology and MCS at MUSC

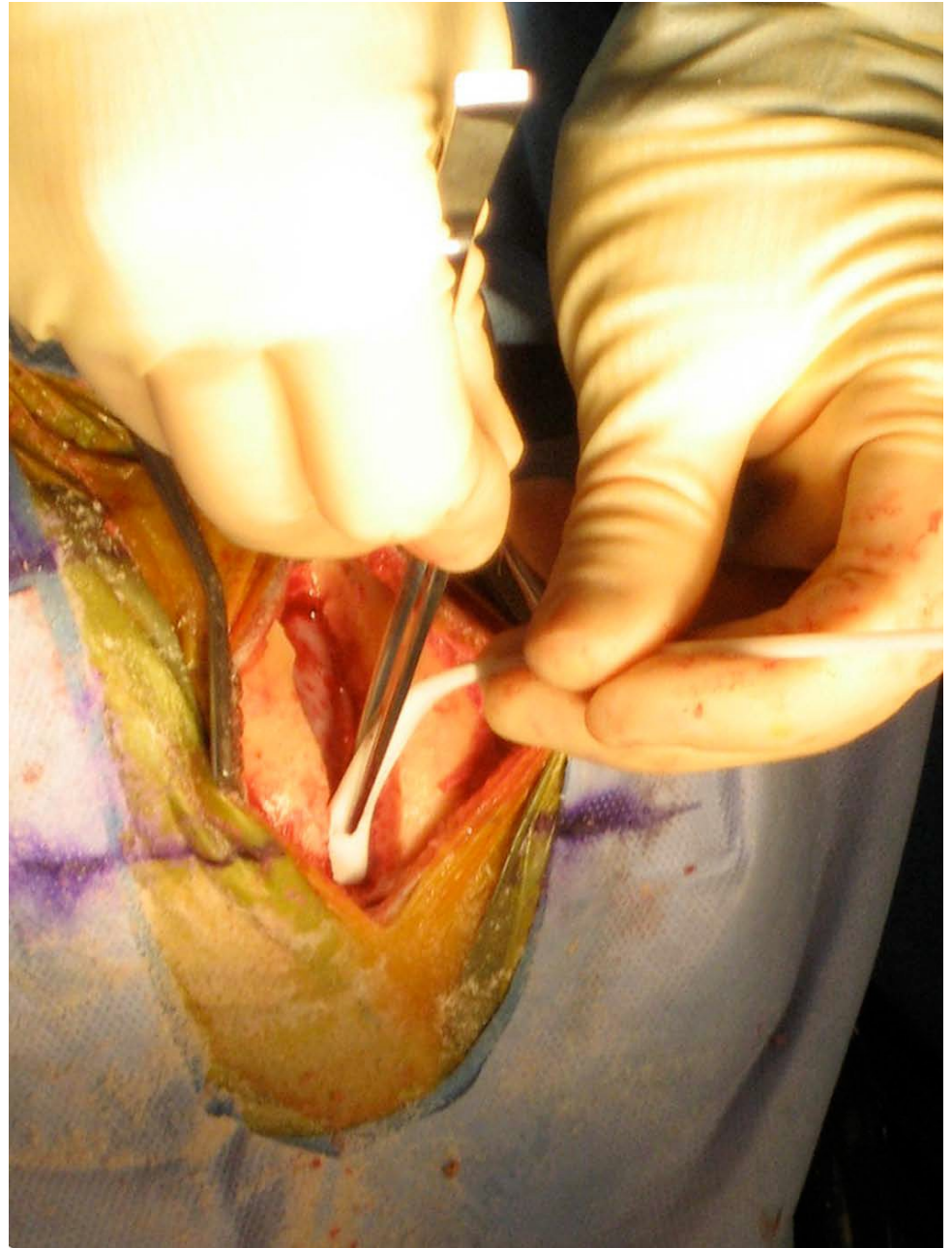
We used TMS to locate and map the motor strip in 24 patients the day before neurosurgical implantation of MCS



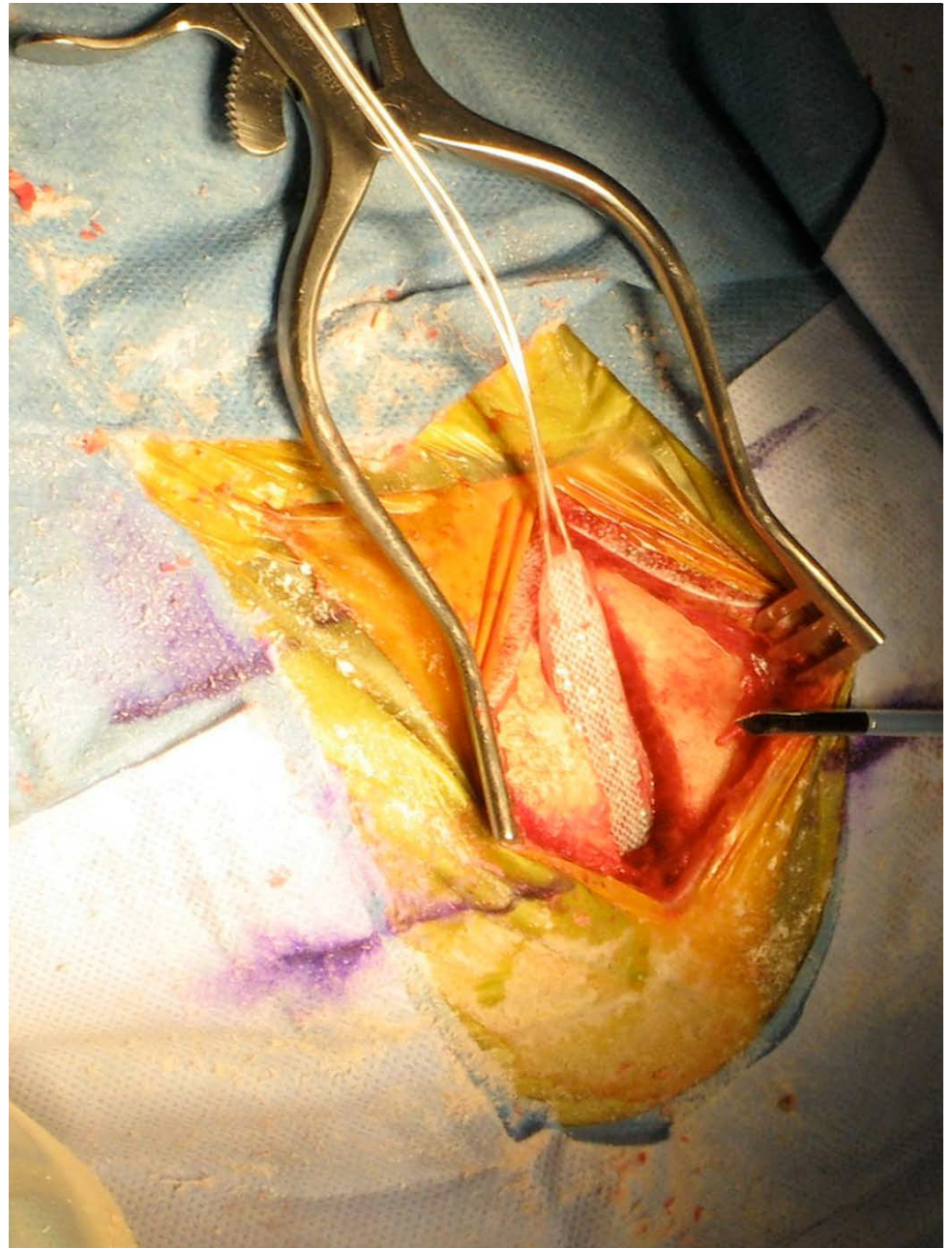
The skull is opened
over the motor strip
area identified via TMS



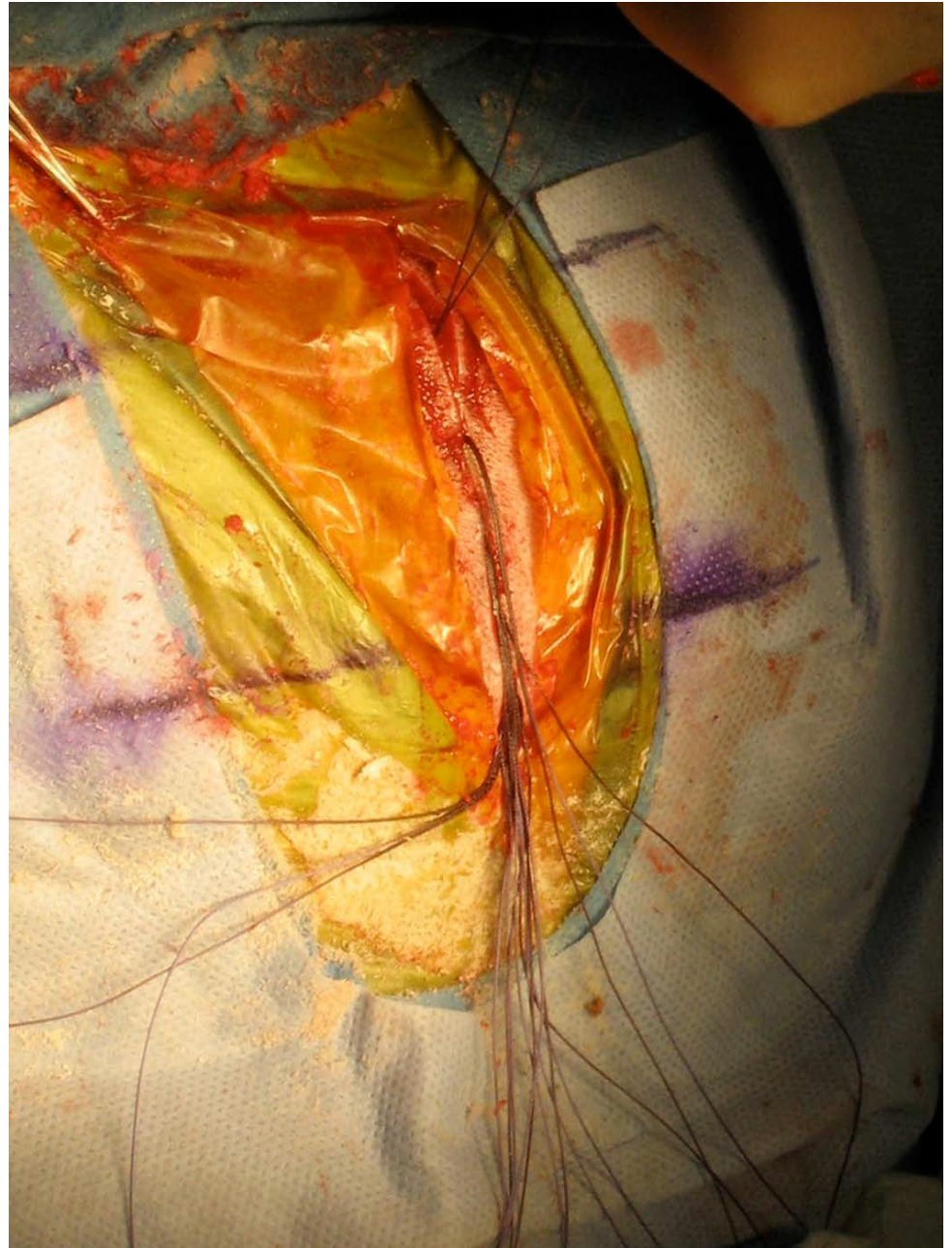
The opening is expanded to accommodate the MCS lead



The MCS lead is placed



The wires are guided through the scalp, the skull is rebuilt and the incision is sewed up.



The patient is awakened in the PACU and the stimulator is turned on. The benefits are often experienced immediately.



Pain Management: Psychological and Neurostimulation Approaches

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