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NEUROMODULATION:

STATE OF THE ART IN NON-INVASIVE BRAIN STIMULATION

J. DONALD DISHMAN, D.C., M.SC., DIBCN, FIACN, FIBE

PROFESSOR AND DEAN OF GRADUATE CLINICAL NEUROSCIENCE PROGRAMS

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DISCLOSURES

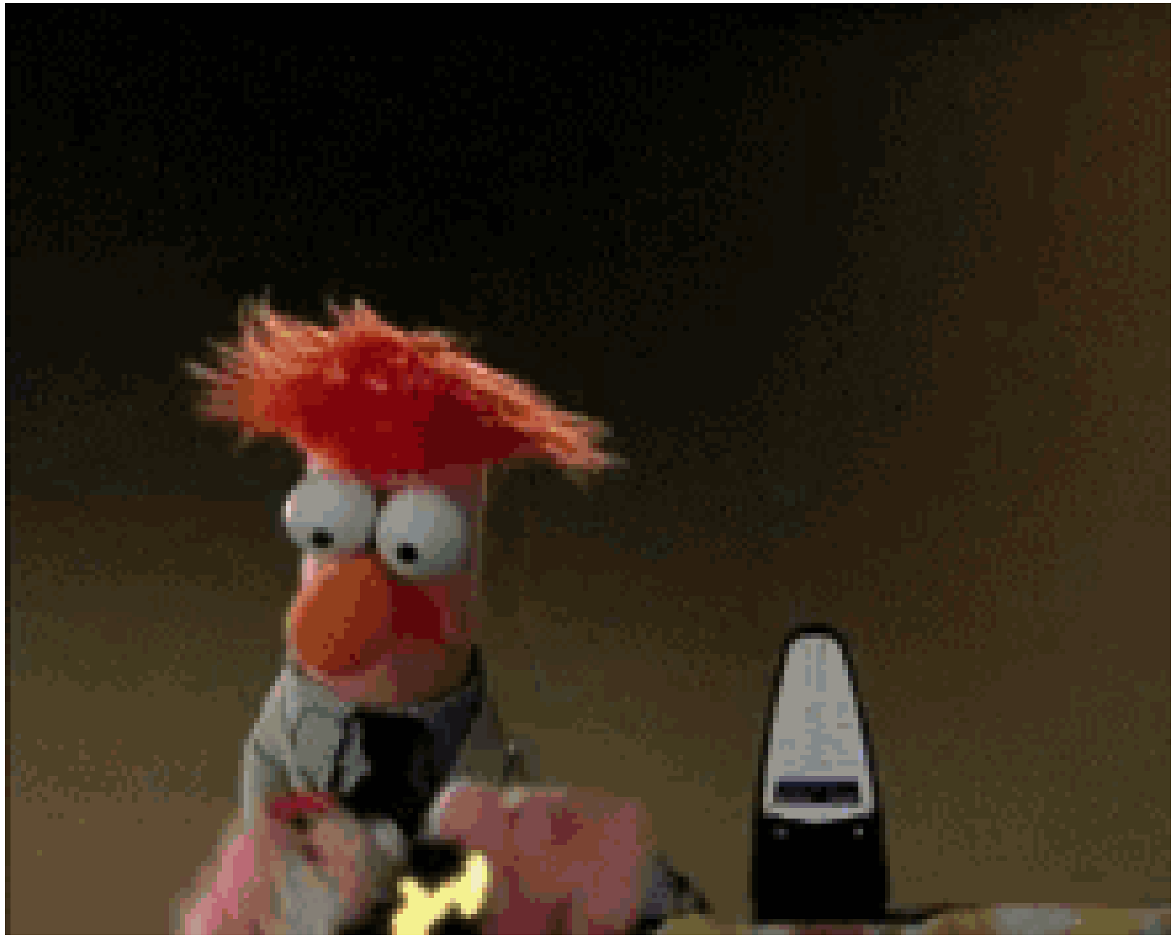
Financial interest in Helius medical technologies – PoNS device

Clinical consultant to Neuromod

No other financial interest in any company or product discussed in this presentation

Compensated employee of Parker University

-viewpoints and opinions are solely those of the presenter



WHAT IS NEUROMODULATION?

WHAT IS NEUROMODULATION?

"Neuromodulation is the alteration of nerve activity through targeted delivery of a stimulus, such as electrical or chemical agents, to specific neurological sites in the body."

A field focused on modulating nervous tissue function to improve an individual's quality of life and overall functioning, especially for those with neurological or psychiatric disorders.

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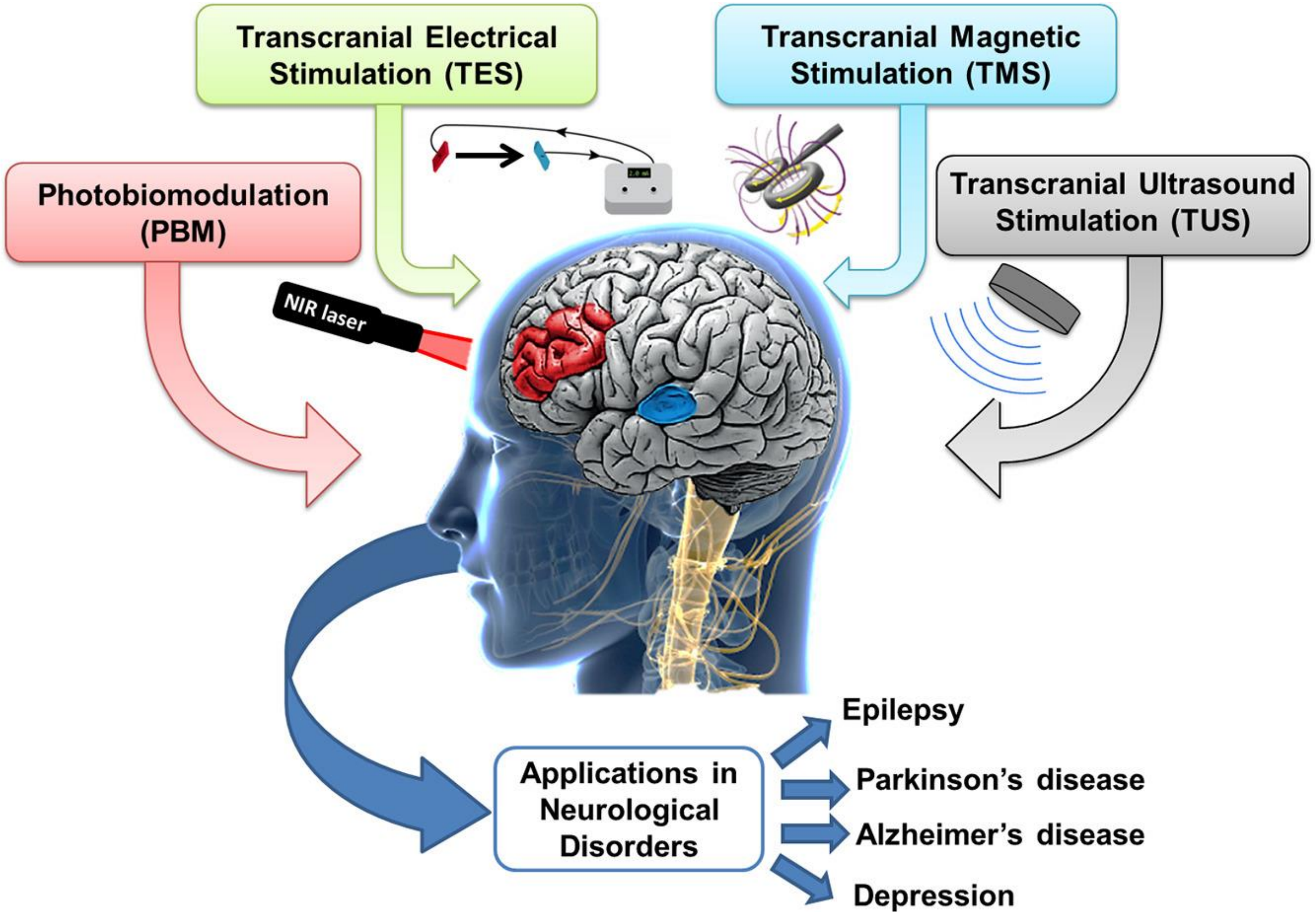
MOST COMMON NEUROMODULATION TECHNIQUES

- Transcranial magnetic stimulation (TMS)
- Transcranial direct current stimulation (tDCS)
- Photobiomodulation (PBM)
- Transcranial ultrasonic stimulation (TUS)



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IS NEUROMODULATION "FDA APPROVED"?

- FDA approved is for class III devices - typically devices that are implanted, sustain life, or present a potential significant risk of harm.

- The FDA does not seek out clinical trials and make decisions based on the literature, the USA FDA only responds to "marketing" requests made by specific companies.

- The FDA typically does not regulate non-medical use of devices, which includes uses for "wellness". In this sense, it is important to note that *most neuromodulation is broadly considered by researchers and experts to be low-risk.*

- For example, tDCS, is not FDA approved, but "cleared" as it is low risk.

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IS NEUROMODULATION "FDA APPROVED"?

- TMS, on the other hand is FDA approved for several psych and neuro conditions.
- TUS is not FDA cleared nor approved.
- Focused US is FDA approved for essential tremor and tremor predominate PD.
- The FDA does not regulate the practice of health care.
- Many Clinicians provide treatments that are "off-label" - things that doctors think work but do not have a "marketing" label from the FDA to the company.
- Clear Informed consent using off label devices is recommended.

WHY IS NEUROMODULATION NOT SO WELL KNOWN IN THE USA?

PHARMACEUTICAL REVENUE IN USA ALONE IN 2025 IS PROJECTED TO BE 1,296.9 BILLION

ONE TRILLION, TWO-HUNDRED NINETY-SIX BILLION, NINE - HUNDRED MILLION DOLLARS

WHY IS NEUROMODULATION NOT SO WELL KNOWN IN THE USA?

Top 5 revenue generators in the USA for 2025

1. Health & Medical Insurance: $1,542.2B
2. Hospitals: $1,517.3B
3. Commercial Real Estate: $1,483.6B
4. Commercial Banking: $1,418.0B
5. Drug, Cosmetic & Toiletry Wholesaling: $1,416.1B

EU – NETHERLANDS, GERMANY

AUSTRALIA

tES & tDCS Devices

Stimulators for clinical practice and research in tDCS, tACS and tRNS. Compatible with advanced EEG and Neuroimaging.

Neurofeedback Systems

Neurofeedback systems with optional Biofeedback extensions and precision artefact control.

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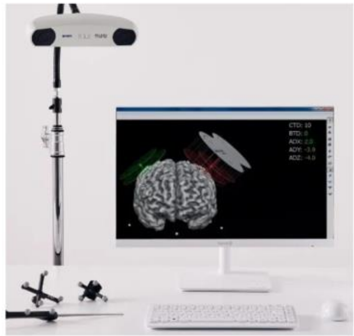
Leading Clinical & Research Technologies

Our products

TMS Systems

Systems for Transcranial Magnetic Stimulation applied in clinical and research settings.



TMS Neuronavigation Systems

Leading Neuronavigation systems for advanced practice and research of Transcranial Magnetic Stimulation.

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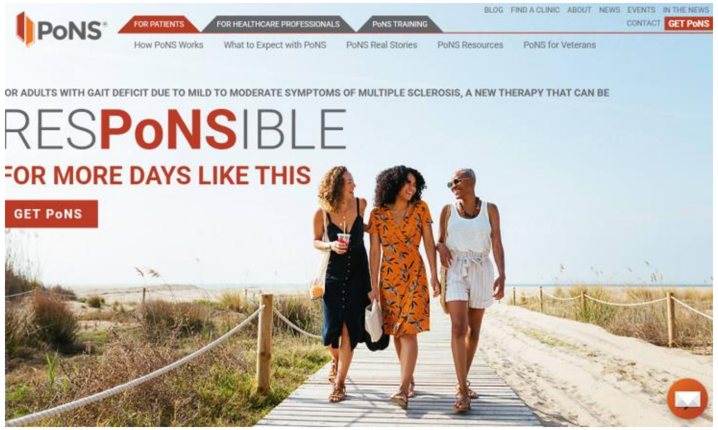
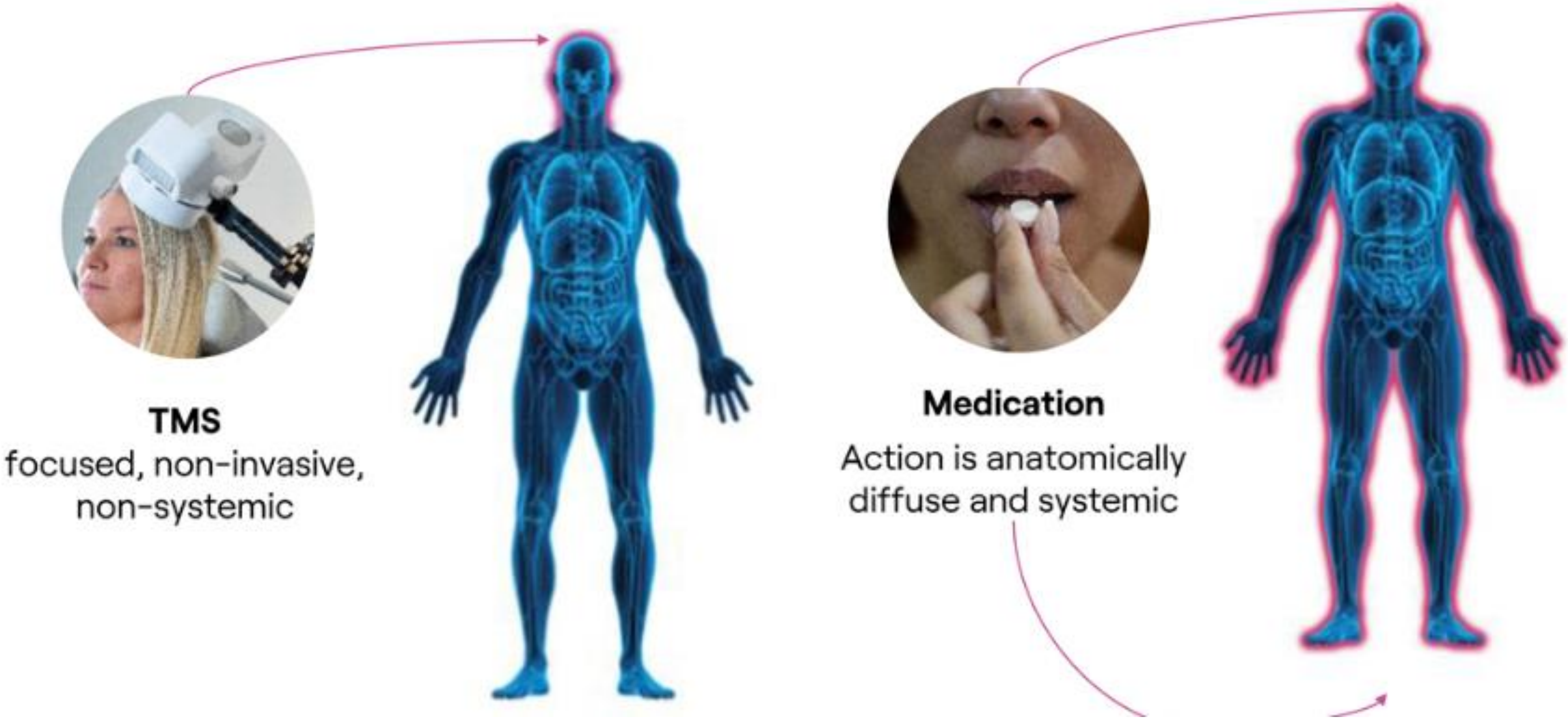
NEUROMODULATION IN PUBLIC REALM



THE BRAIN IS AN ELECTRO-CHEMICAL ORGAN

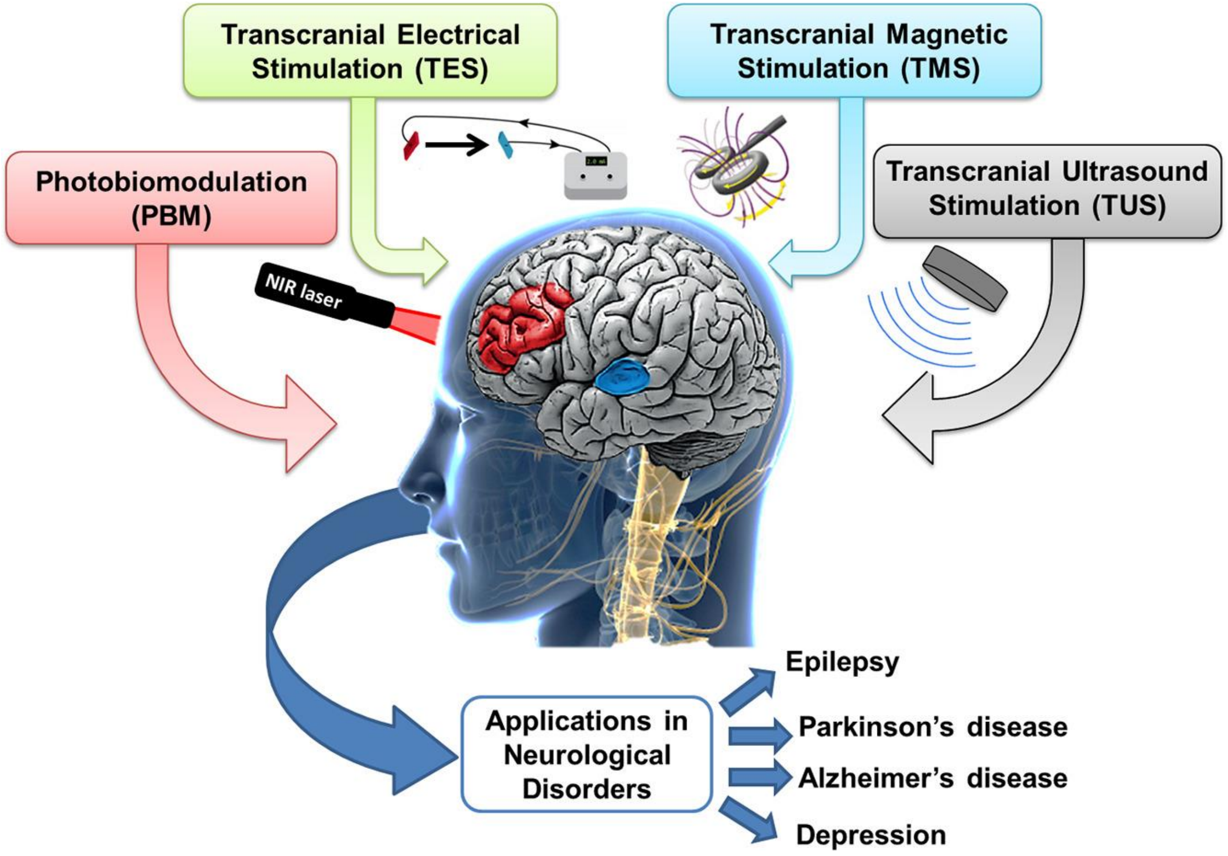
- Until recent times, most neuropsychiatric treatment has been based on the chemical
- Other brain disorders and dysfunction also treated pharmaceutically
- Failure to address the electrical deficits of the brain



OBJECTIVES

Discuss the foundations of modern neuromodulation and provide updates on latest techniques and clinical uses:

- Transcranial magnetic stimulation (TMS)
- Transcranial direct current stimulation (tDCS)
- Photobiomodulation (PBM)
- Transcranial ultrasonic stimulation (TUSS)



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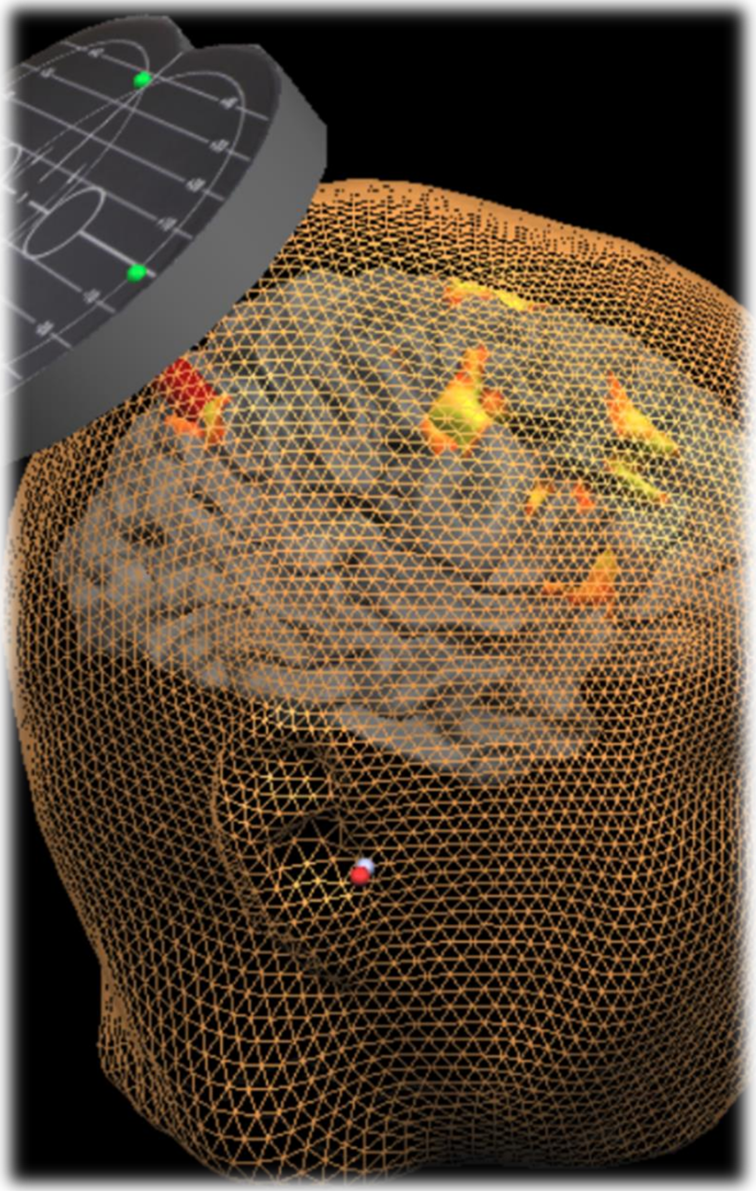
TMS – INTRODUCTION – PRIMARY USES



Treatment-Resistant Depression – FDA approved

- TMS is a well-established treatment for individuals who haven't found sufficient relief from depression through medication or therapy.

Obsessive-Compulsive Disorder – FDA approved

- TMS can be effective in reducing OCD symptoms, particularly when other treatments have been unsuccessful.

Smoking Cessation – FDA cleared

- TMS has been approved for short-term smoking cessation in adults who haven't responded to other treatments.

Migraine Headache – FDA approved

- Approved for acute pain of migraine with aura

Anxious Depression – FDA cleared

- TMS has received FDA clearance for the treatment of anxious depression, which involves both anxiety and depressive symptoms.

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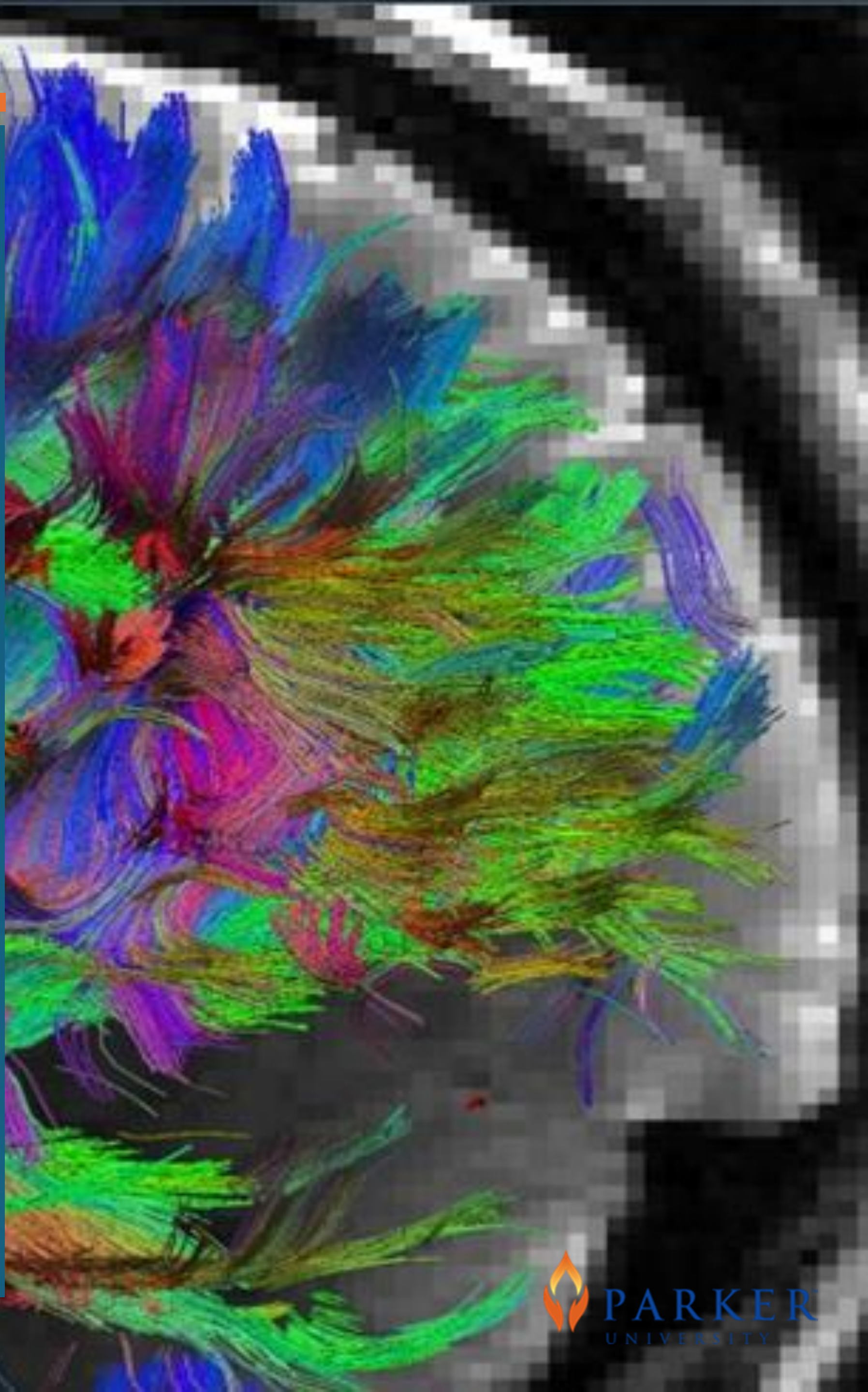
OBJECTIVES: TMS

- History of TMS
- Putative physiology of mechanisms
- Contraindications and potential risks of TMS
- Review of literature support rTMS for depression
- TMS applications for refractory Depression
- Review of literature for the role of TMS in traumatic brain injuries
- Overview of applications of TMS in the management of traumatic brain injuries
- Use of TMS in post-stroke rehabilitation
- Use of TMS in management of post-traumatic stress disorder
- Use of TMS for tinnitus



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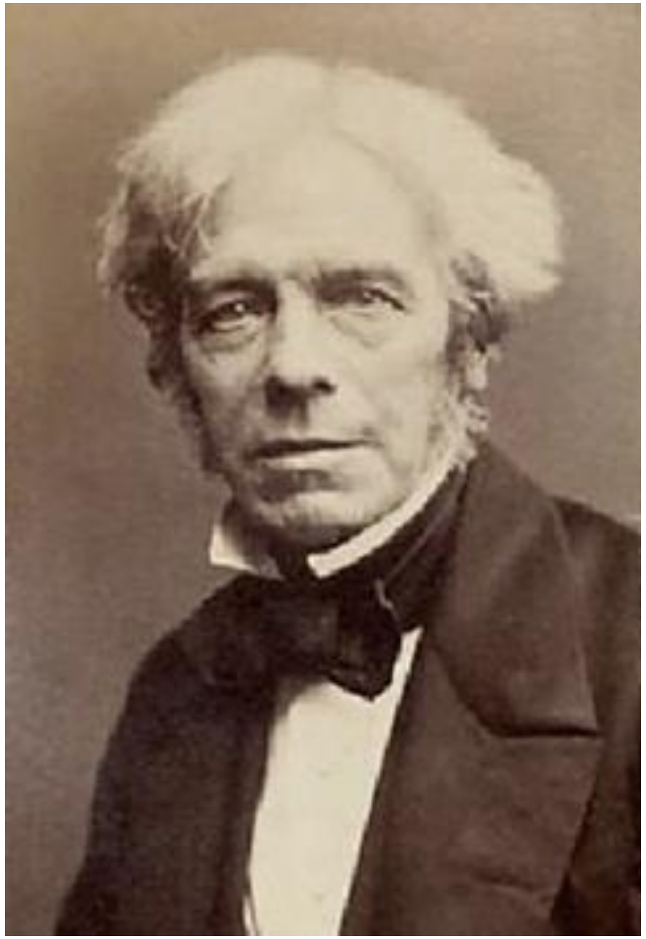
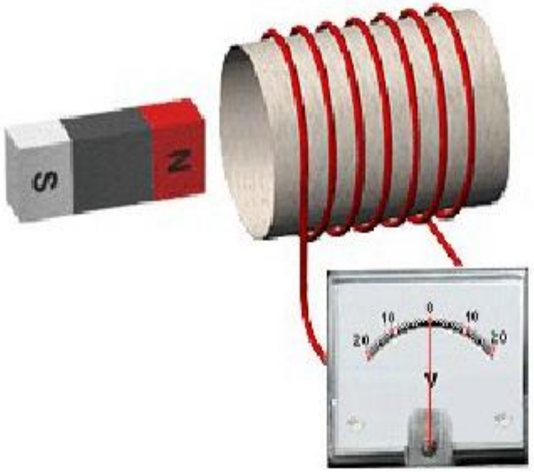
HISTORY OF TRANSCRANIAL MAGNETIC STIMULATION (TMS)

- Michael Faraday in 1831 – Faraday's Law :

"The induced electromotive force (EMF) in
any closed circuit is equal to the time rate of
change of the magnetic flux through the
circuit."





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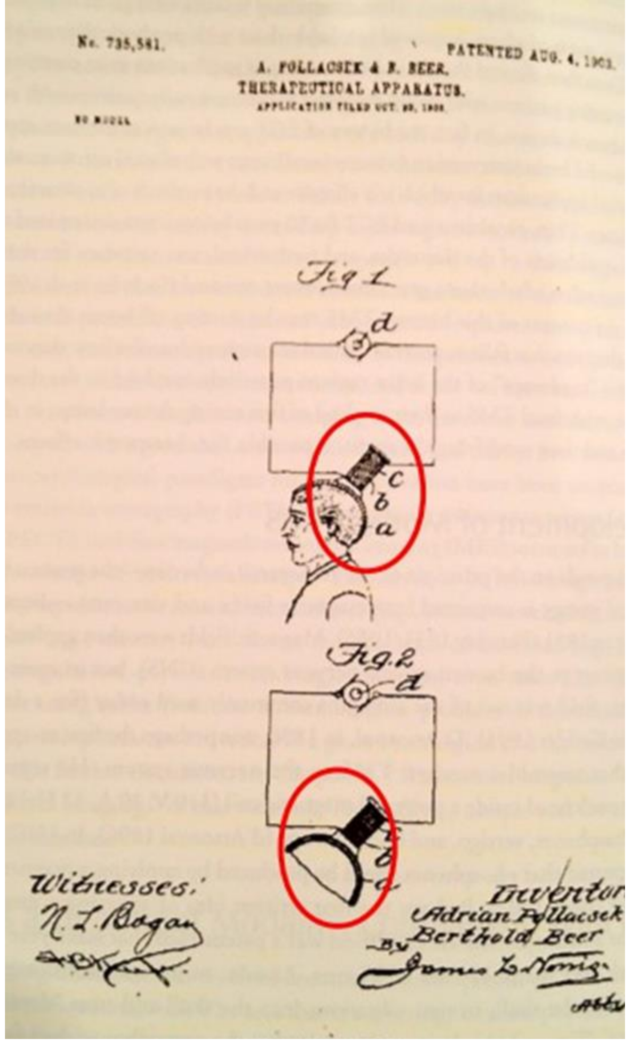
TMS: HISTORY

- R. Bartholomew (1874) – Stimulation of exposed cortex of patient with cranial defect
- Jacques-Arsène d'Arsonval (1892) – Phospenes and vertigo induced inside magnetic coil
- Sylvanus P. Thomson (1910)- new type of magnetic stimulation

TMS: HISTORY

- 1902 Adrian Pollacsek and Berthold Beer - Vienna, Austria patent for a “therapeutical apparatus”

Electromagnetic coil placed over the skull was noted to “pass vibrations into the skull and treat depression and neuroses”



TMS: HISTORY

- **First "modern" TMS device – 1985 – Dr. Anthony Barker**

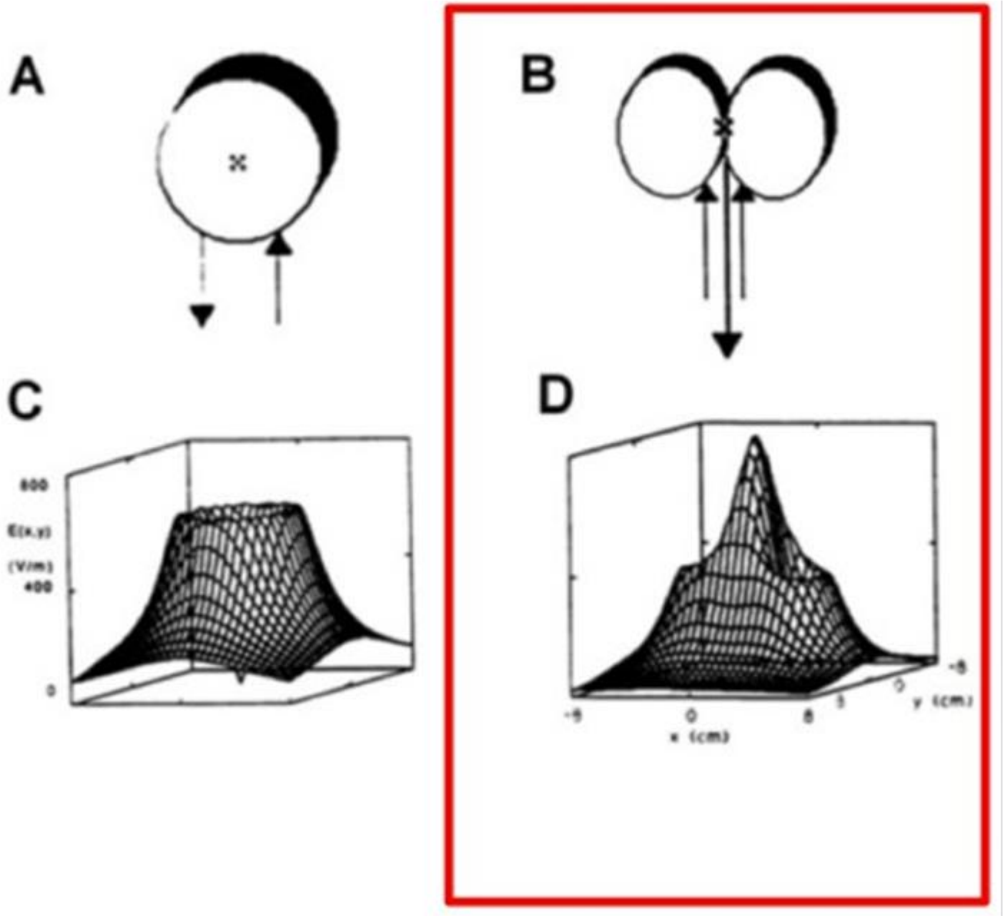
Barker, AT – "Non-invasive Magnetic Stimulation of the Human Cortex

The Lancet 1:1106-1107,
1985.

EARLY TMS DEVICES – MOTOR CONTROL RESEARCH TOOL – SINGLE PULSE

COIL TYPES AND RATIONALE

- <u>Single coil</u>: maximal magnetic field around the edge.
- <u>Figure-of-eight coil</u>: edges combine to create a focal point
  - Capable of depolarizing **1cc** of neurons
  - Focal point **only penetrates 2-3cm** into cortex



From Matt Edwardson, MD - Research Fellow and Acting Instructor, Dept. of Neurology, Univ. of WA

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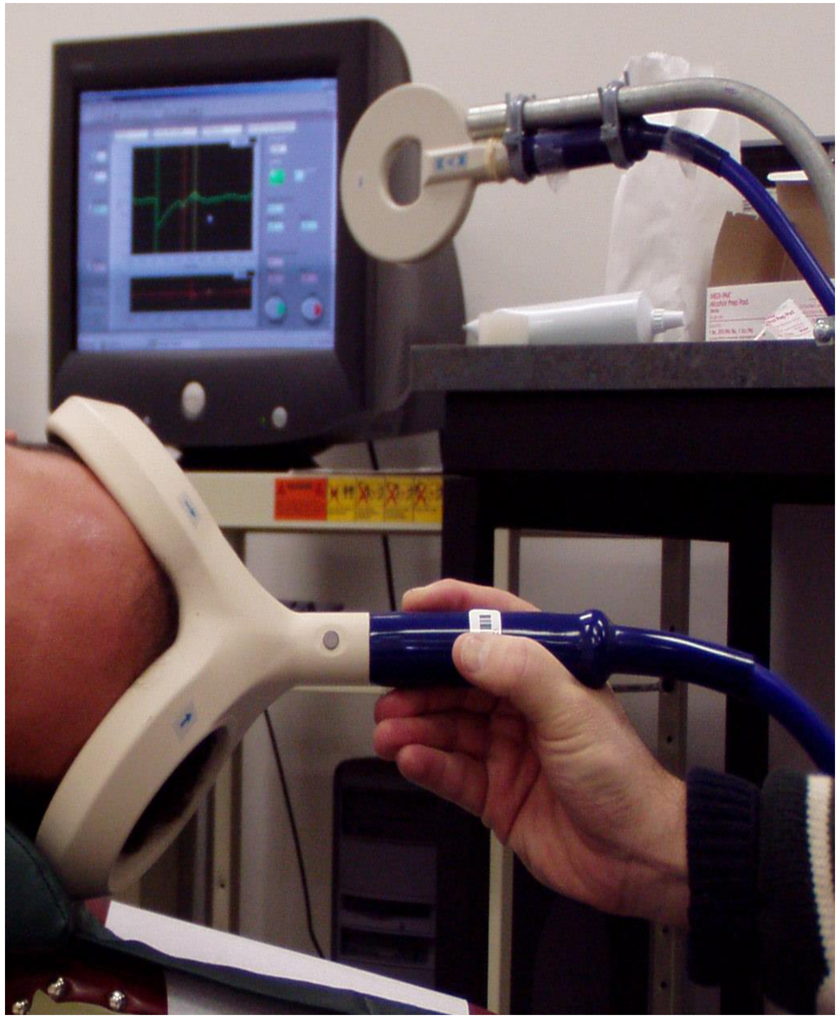
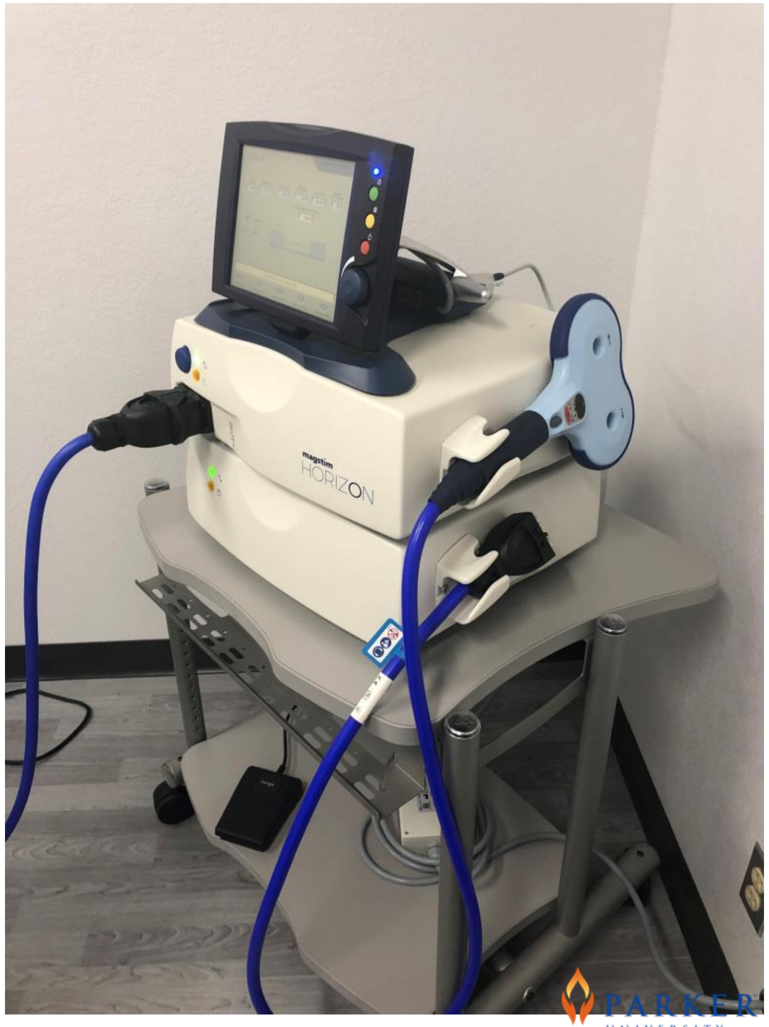
EARLY TMS DEVICES – MOTOR CONTROL RESEARCH TOOL

- "Figure of Eight" Coil





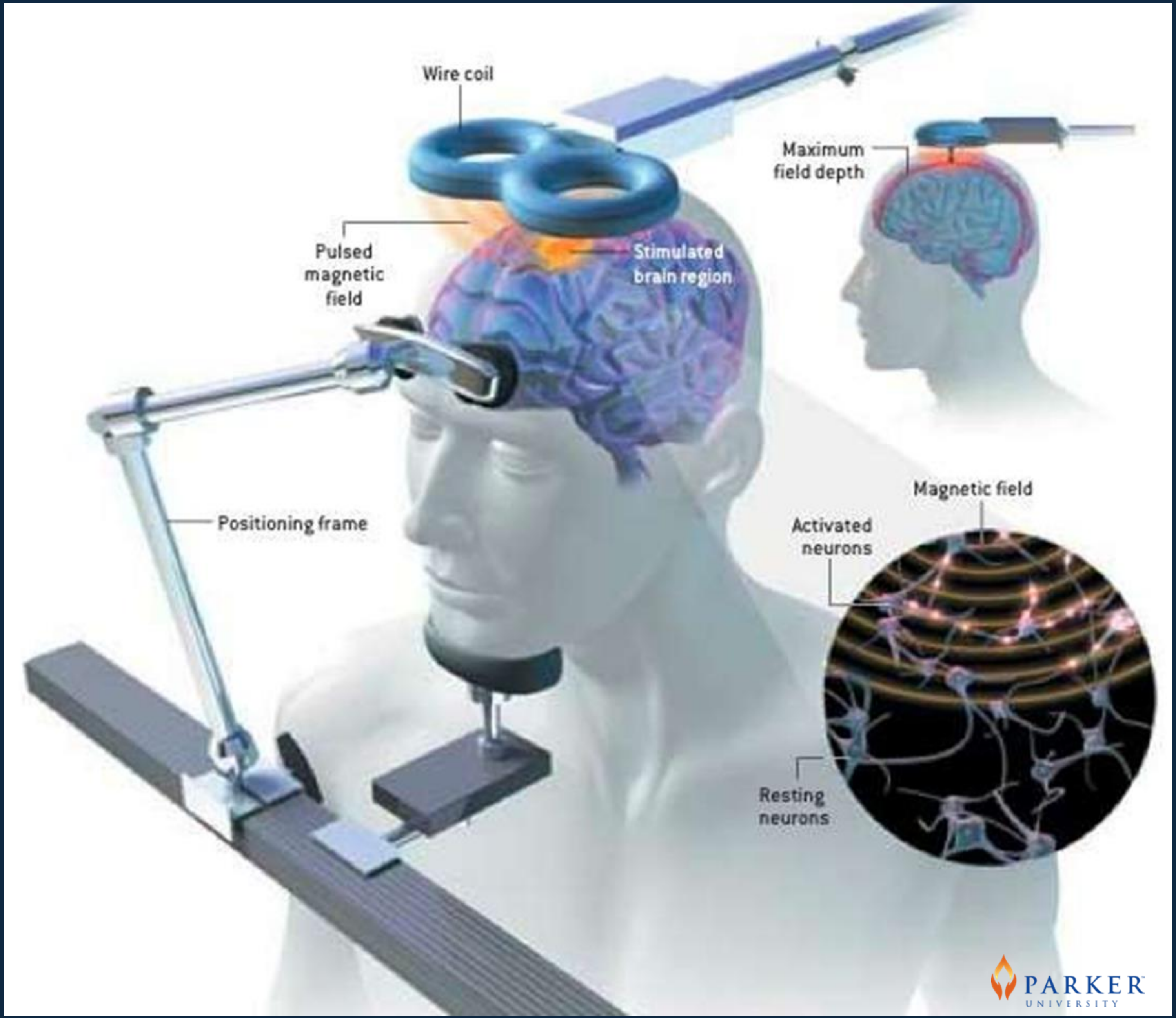
CLINICAL TMS DEVICE

TMS: MECHANISM

- Electrical current flowing through a coil induces a magnetic field
- Pass a current through a hand-held coil, whose shape determines the properties and the size of the field
- The coil is driven by a machine - switches the large current necessary in a very precise / controlled way – heat intensive
- The coil is held on the scalp and the magnetic field (2 Tesla) passes through the skull and into the brain
- Alternating (pulsating) magnetic fields induce electrical current in underlying brain tissue
- Small induced currents influence targeted areas of the brain

TMS: MECHANISM

George MS. Sci Am. 2003;289:66-73.



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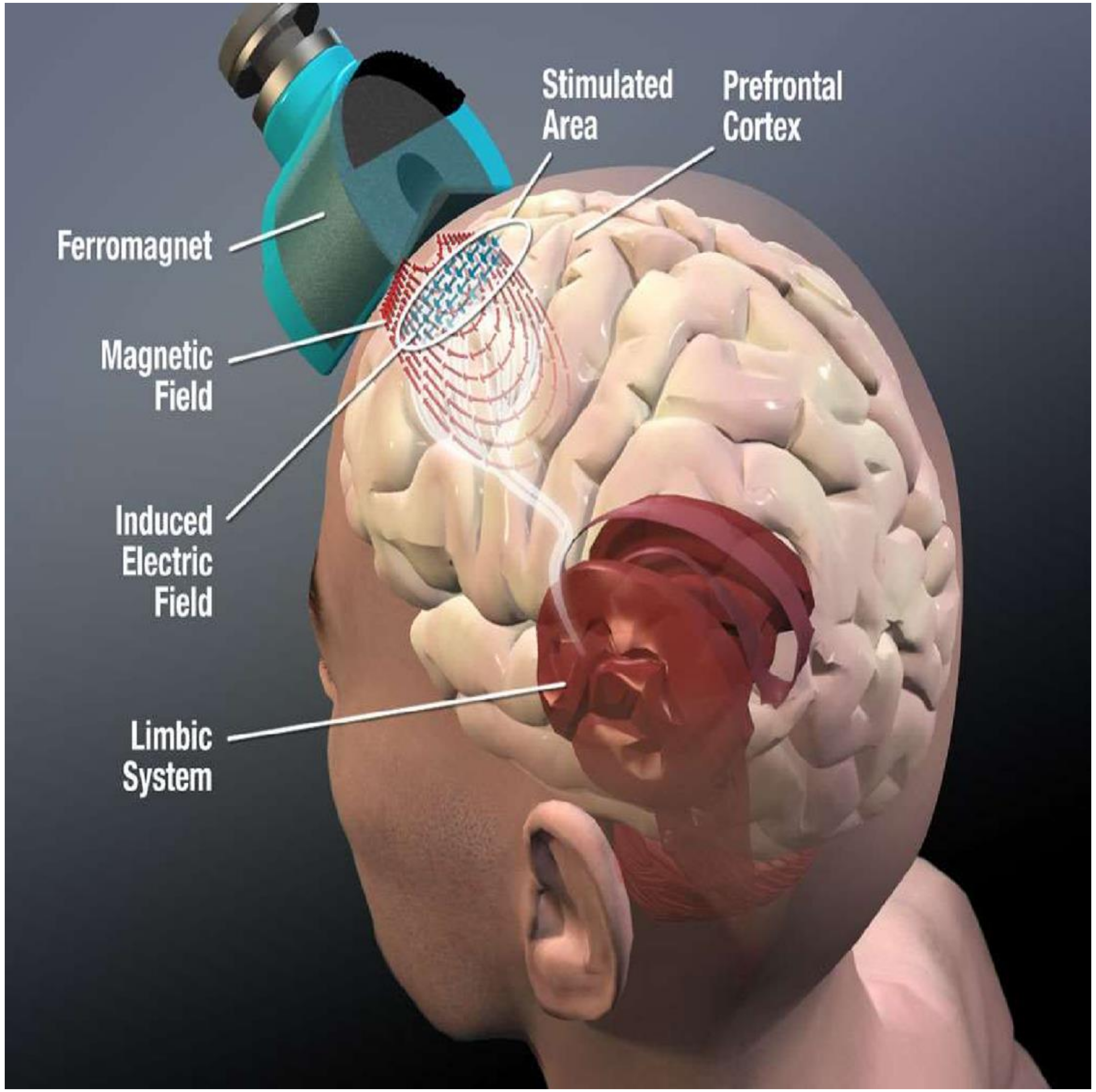
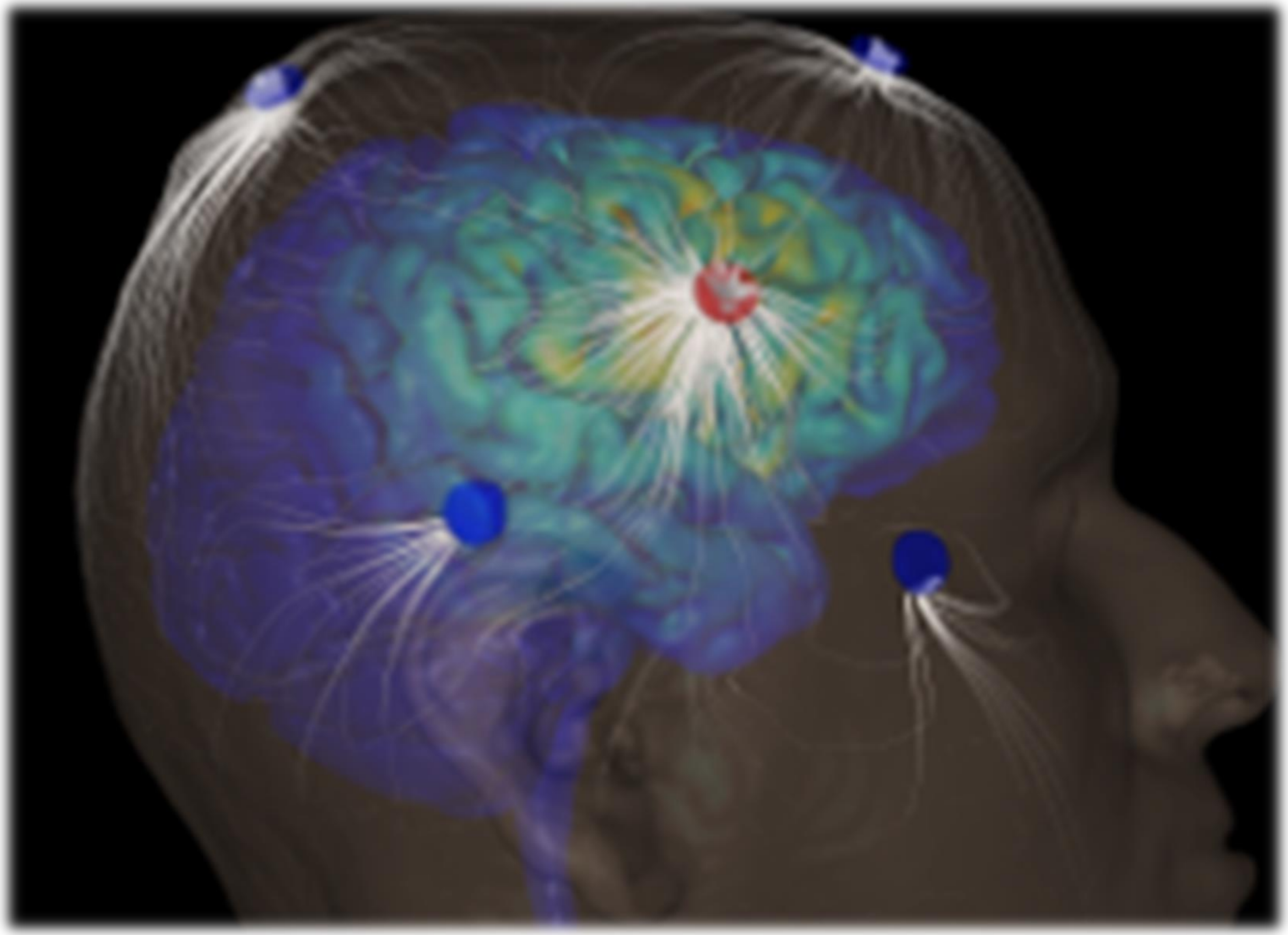


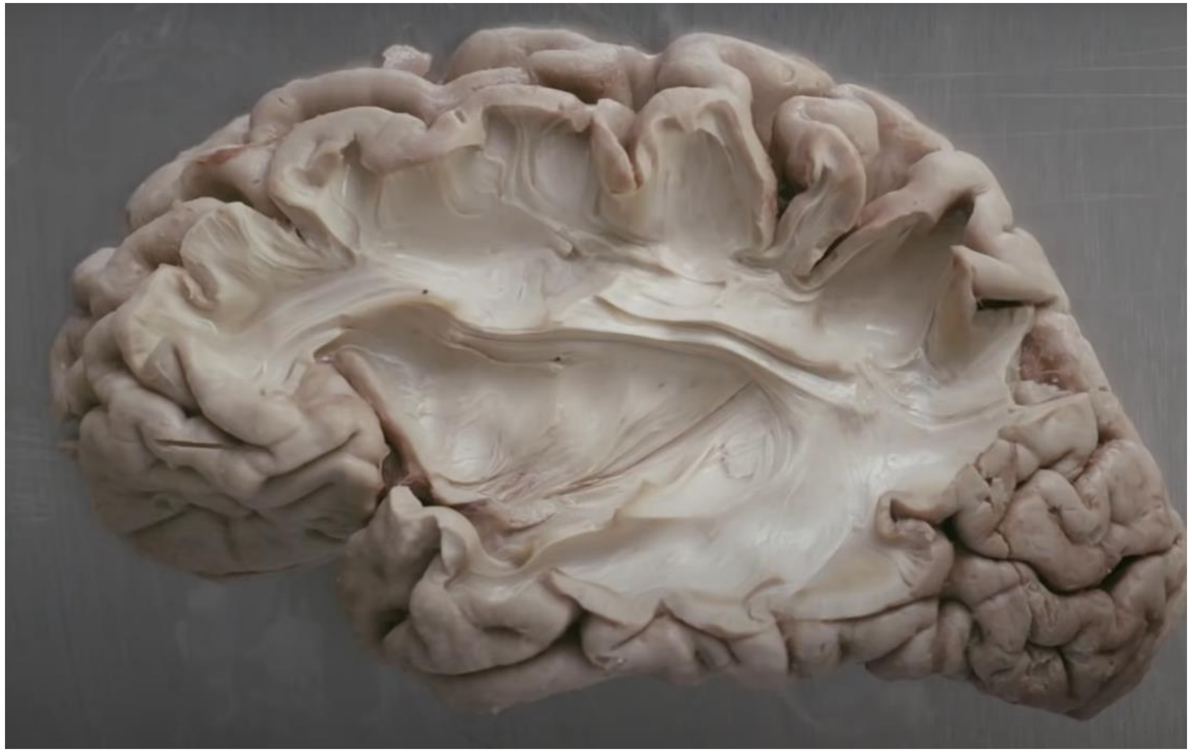
TMS: MECHANISM

- Electrical energy in insulated coil on the scalp induces pulsed magnetic field of about 1.5 – 2.0 Tesla in strength
- Passes through the cranium for 2-3 cm
- In turn induces a focal electrical current in the brain
- Get desired local and distal effects on the target neural circuitry
- Delivered as single pulses or repeated trains (rTMS)

TMS - MECHANISMS

- Some disorders show improvement with focal stimulation (MDD – DLPFC)
- Others respond to more regional stim (aphasia-tinnitus)
- Potentially the greatest use of TMS in neurorehab may be its ability to cause increased cortical excitability
- *An excited cortex undergoes neuroplasticity more efficiently*





TMS – MECHANISMS

MODULATION OF NEURAL CIRCUITS: TMS AFFECTS THE FUNCTIONAL CONNECTIVITY WITHIN AND BETWEEN LARGE-SCALE NEURAL NETWORKS, SUCH AS THE DEFAULT MODE NETWORK (DMN) AND THE CENTRAL EXECUTIVE NETWORK (CEN)

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TMS: SAFETY AND CONTRAINDICATIONS

- rTMS technique is contraindicated for use in patients who have *implanted ferromagnetic devices or other magnetic-sensitive metal implants* ***close*** *to the magnetic coil*
- *Seizures* – estimated at 1 per 30,000 – typically encountered with higher frequency stim and in those with stimulation over the motor cortex (M1)
- Most recent studies indicate .0075%
- Short-lived *headache* in a band-like distribution (10% of patients)
- *Auditory risk* with newer devices is low – earplugs still used but sound is much lower in new generation

(Wassermann and Lisanby 2001, Jennum and Klitgaard 1996 Pascual-Leone et al., 1993; Wassermann et al., 1996; Lisanby et al.,2001)

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TMS-INDUCED SEIZURES IN HUMANS –**LOW RISK**

- Seizure induction w/ single pulse TMS - Healthy subjects: No cases reported to date.*

- Seizure induction w/ single pulse TMS - Patients: Approximately 20 cases reported.*

- Seizure induction w/ repetitive TMS - Healthy subjects: Approximately 6 cases when parameters are outside of safety guidelines. 1 case when parameters are within safety guidelines.*

- Seizure induction w/ repetitive TMS - Patients: 3 cases.*

- Presenter's experience of over 2,000 cases – 0 seizures

*(Berenson-Allen Center for Noninvasive Brain Stimulation, Harvard Medical School – 2008)

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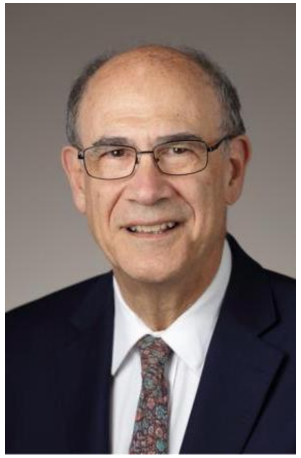
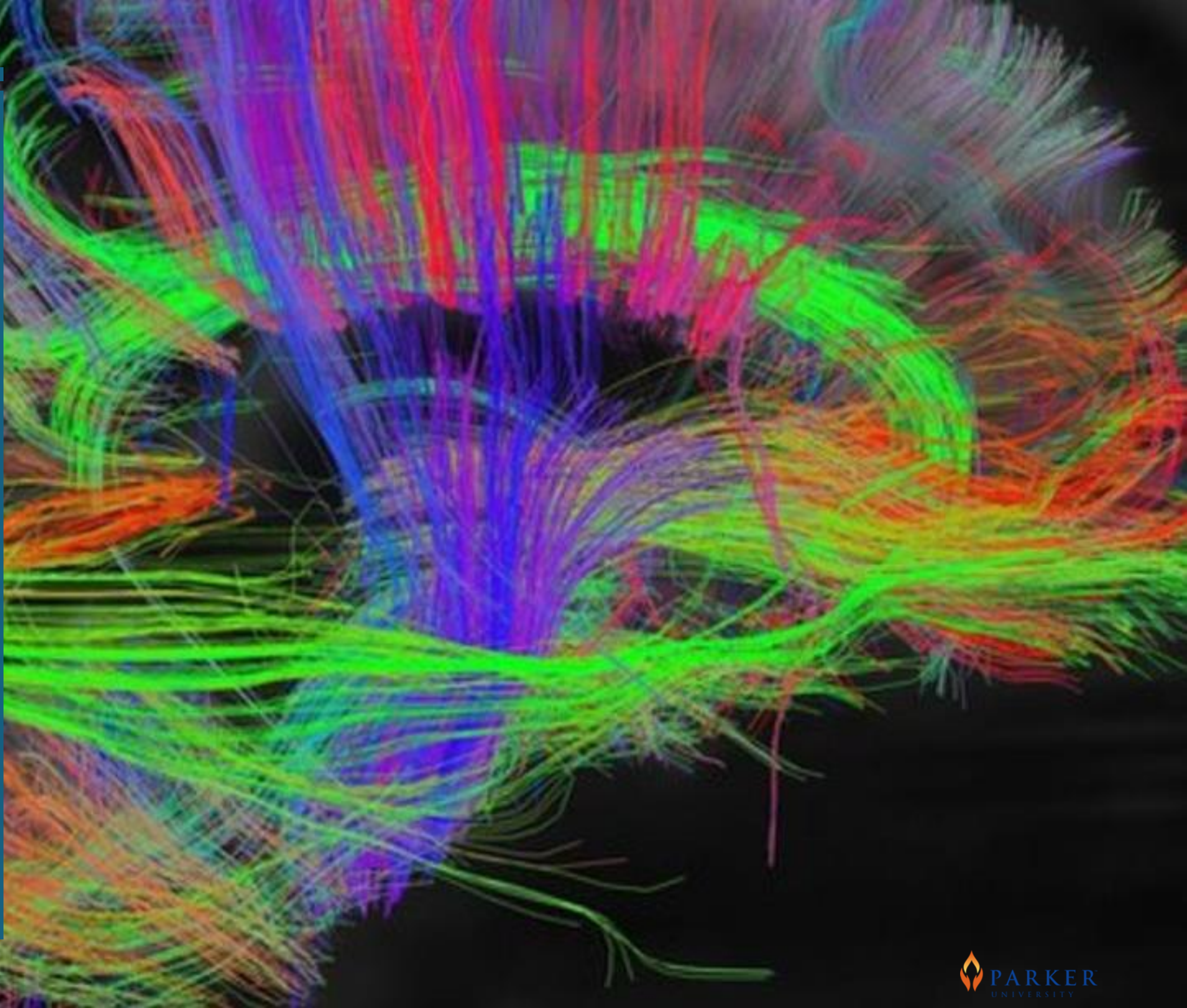
FOUNDERS IN NORTH AMERICA



- Initially developed as a motor control research tool – much credit to Dr. Mark Hallet –NIH
- Research participants reported positive mood and emotional impact
- First prominent promotor of TMS for neuropsychiatric use – Dr. Mark George – MUSC

TMS: PHYSIOLOGY

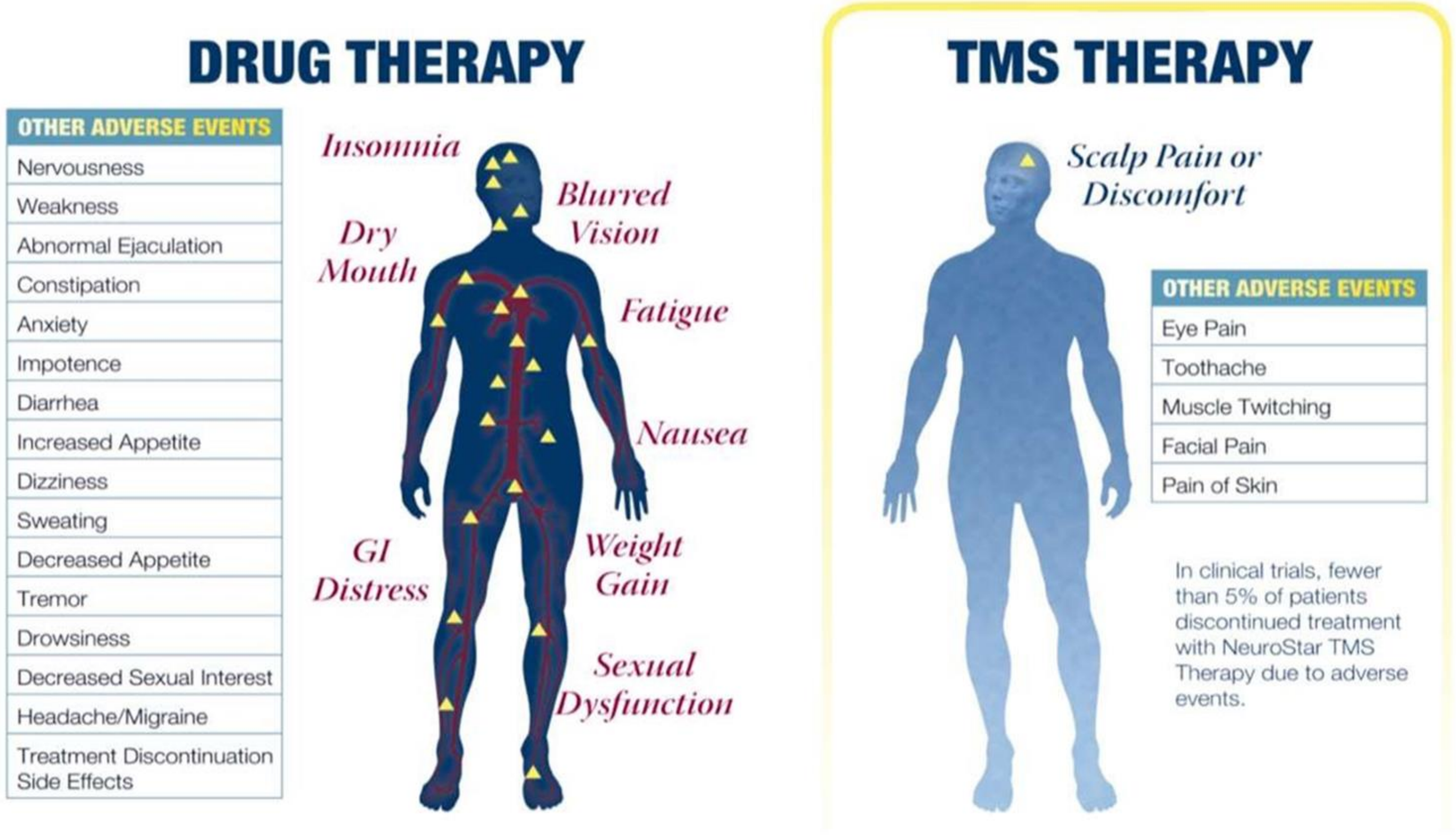
- Neurons are electrochemical cells that respond to *chemical* and *electrical* stimulation
- Pulsed TMS leads to depolarization of neurons and release of neurotransmitters
- Evidence that neurons in the dorsolateral prefrontal cortex (DLPFC) release neurotransmitters and change mood



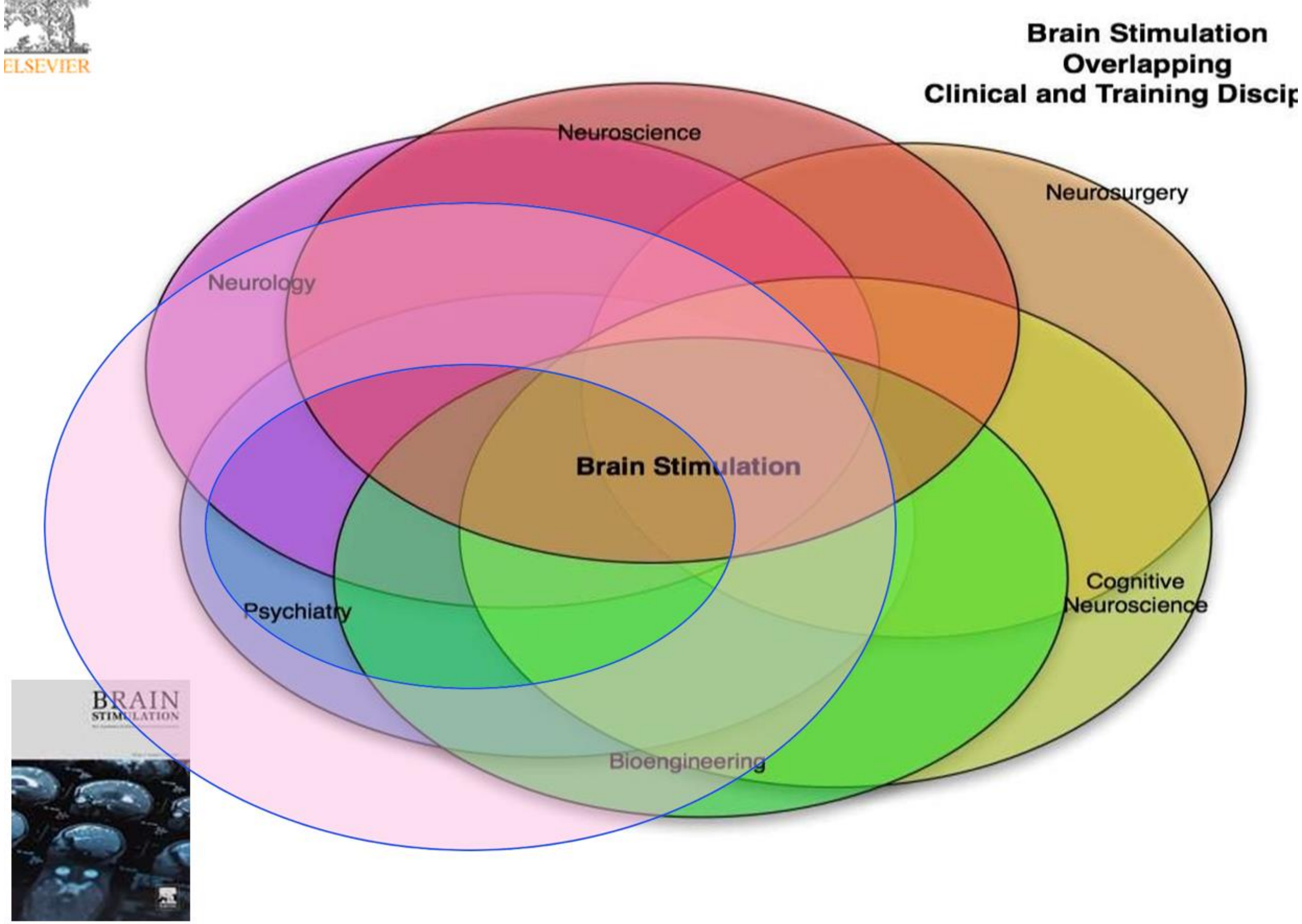
INITIAL CLINICAL APPLICATION - NEUROPSYCHIATRY

- Underlying premise of neuromodulation is that the brain is an electrochemical organ that can be modulated by pharmacotherapy or devise-based (TMS) approaches or their combination
- There is an explosion of new techniques for electrically, magnetically or ultrasonically stimulating the brain, primarily focally
- ***These new tools are changing neuroscience research, neurorehabilitation and neuropsychiatric therapies***
- They validate and inform us about functional neuroanatomy

ADVERSE EVENTS WITH DRUG THERAPY- ***SUICIDE***



From product labeling for currently marketed antidepressant medications; adverse events occurring at an incidence >5% incidence and 2x the rate of placebo treatment (Neuronetics, Inc, data on file)



TMS: MULTIDISCIPLINARY APPROACH

FDA APPROVAL FOR MAJOR DEPRESSIVE DISORDER (MDD) – 2008

LEFT DLPFC

A Controlled Trial of Daily Left Prefrontal Cortex TMS for Treating Depression*

Mark S. George, Ziad Nahas, Monica Molloy, Andrew M. Speer, Nicholas C. Oliver, Xing-Bao Li, George W. Arana, S. Craig Risch, and James C. Ballenger

Background: *Transcranial magnetic stimulation (TMS) is a new technology for noninvasively stimulating the brain. Several studies have suggested that daily stimulation of the left prefrontal cortex with TMS for 2 weeks has probable antidepressant effects. We conducted a parallel-design, double-masked, sham-controlled study to address whether 2 weeks of daily TMS over the left prefrontal cortex has antidepressant activity greater than sham.*

Methods: *Thirty medication-free adult outpatients with nonpsychotic, major depressive (n = 21) or bipolar (n = 9) (depressed phase) disorder who were in a current major depression (Hamilton Rating Scale for Depression [HRSD] 21-item score of >18) were treated each weekday for 2 weeks. Subjects were randomly assigned to receive either daily active (20 subjects) or sham (10 subjects) stimulation. Additionally, the 20 active subjects were equally divided between slower (5 Hz) and faster (20 Hz) frequency treatment. Antidepressant response was defined as greater than a 50% improvement in the baseline HRSD.*

Results: *Active TMS resulted in significantly more responders (9/20) than did sham (0/10) (χ^2 = 6.42, p < .01). The number of responders did not differ significantly between the two active cells (3/10 faster and 6/10 slower). Expressed as a percent change from baseline, active TMS subjects had significantly greater improvement on the Beck Depression Inventory as well as the Hamilton Anxiety Rating Scale than did those who received sham.*

Conclusions: *Daily left prefrontal TMS for 2 weeks significantly reduced depression symptoms greater than did sham. The two forms of active TMS treatment did not differ significantly.* Biol Psychiatry 2000;48:962–970 *© 2000 Society of Biological Psychiatry*

Key Words: Transcranial magnetic stimulation, depression, prefrontal cortex, treatments, mood, emotion, clinical trials

*See accompanying Editorial, in this issue.

Introduction

Transcranial magnetic stimulation (TMS) is a new method for noninvasively stimulating the brain (George and Belmaker 2000; George et al 1999a). A brief but powerful electric current is passed through a small coil of wires on the scalp. This generates a powerful but local magnetic field, which passes unimpeded through the skull and induces a weaker focal electric current in the brain (Barker et al 1985; Roth et al 1991; Saypol et al 1991). The highly localized TMS magnetic field typically has a strength of about 1–1.5 T (or 30,000 times the earth's magnetic field, or about the same intensity as the static magnetic field used in clinical magnetic reonance imaging [MRI]) (Bohning 2000). Although different coil designs allow for a focal or more diffuse stimulation, current technology is not able to stimulate deep brain structures directly. Transcranial magnetic stimulation can be performed in outpatient laboratory settings and, unlike electroconvulsive therapy (ECT), does not cause a seizure or require anesthesia. Subjects usually notice no adverse effects except for occasional mild headache and discomfort at the site of the stimulation. Recent technologic advances led to the development of magnetic stimulators that could repeatedly stimulate faster than once per second (1 Hz). This, by convention, is called repetitive transcranial magnetic stimulation (rTMS). There is some evidence from work in animals (Post et al 1997) and humans (Pascual-Leone et al 1991, 1994) that stimulation at different frequencies may have divergent and even antagonistic effects on neuronal activity (Kimbrell et al 1999; Wassermann et al 1998), with higher frequencies exciting the brain and slower frequencies inhibiting activity.

Clinical depressions are very common, with one out of five Americans having an episode during their life (Kessler et al 1994). Many depressions can be treated

From the Brain Stimulation Laboratory, Department of Psychiatry (MSG, ZN, MM, NCO, X-BL, SCR, JCB) and Departments of Radiology (MSG) and Neurology (MSG), Medical University of South Carolina, and the Department of Psychiatry, Ralph H. Johnson Veterans Affairs Hospital (MSG, ZN, GWA), Charleston, South Carolina; Biological Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland (AMS); and the Department of Psychiatry, Shangdong Medical University, Jinan, China (X-BL).
Address reprint requests to Mark S. George, M.D., Director, Functional Neuroimaging Division, Psychiatry, Associate Professor of Psychiatry, Radiology and Neurology, Medical University of South Carolina, Department of Radiology, 171 Ashley Avenue, Charleston SC 29425.
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Acute Left Prefrontal Transcranial Magnetic Stimulation in Depressed Patients Is Associated with Immediately Increased Activity in Prefrontal Cortical as well as Subcortical Regions

Xingbao Li, Ziad Nahas, F. Andrew Kozel, Berry Anderson, Daryl E. Bohning, and Mark S. George

Background: *Focal prefrontal cortex repetitive transcranial magnetic stimulation (rTMS) was originally investigated as a potential antidepressant under the assumption that in depressed patients, prefrontal cortex stimulation would produce changes in connected limbic regions involved in mood regulation.*

Methods: *Fourteen adult patients with depression were scanned in a 1.5-T scanner using interleaved rTMS (1 Hz) applied on the left prefrontal cortex over 7.35 min. Images were analyzed with Statistical Parametric Mapping 2b and principal component analysis.*

Results: *Over the left prefrontal cortex, 1-Hz TMS was associated with increased activity at the site of stimulation as well as in connected limbic regions: bilateral middle prefrontal cortex, right orbital frontal cortex, left hippocampus, mediodorsal nucleus of the thalamus, bilateral putamen, pulvinar, and insula ($t = 3.85$, $p < .001$). Significant deactivation was found in the right ventromedial frontal cortex.*

Conclusions: *In depressed patients, 1-Hz TMS at 100% motor threshold over the left prefrontal cortex induces activation underneath the coil, activates frontal–subcortical neuronal circuits, and decreases activity in the right ventromedial cortex. Further work is needed to understand whether these immediate changes vary as a function of TMS use parameters (intensity, frequency, location) and whether they relate to neurobiologic effects and antidepressant mechanisms of TMS.*

Key Words: Brain networks, depression, fMRI, limbic system, prefrontal cortex, transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a neuroscience research tool with potential as a treatment for several neuropsychiatric illnesses (George et al 1999a; Lisanby et al 2000; Wassermann and Lisanby 2001). It involves the use of a wire coil through which brief pulses of electrical current are passed, leading to the generation of magnetic fields that pass through the skull (George et al 1999a). Changes in superficial cortical neuronal activity can thus be achieved when the coil is placed close to the scalp.

Focal prefrontal repetitive TMS (rTMS) was initially tested in the early 1990s as an antidepressant treatment based on functional neuroimaging studies of patients with depression that showed prefrontal and limbic abnormalities (George and Wassermann 1994; Nobler et al 1999, 2000a, 2000b, 2001; Sackeim et al 1996; Teneback et al 1999). Additionally, a series of studies suggested that changes in prefrontal cortex activity predict antidepressant response to ECT (Nobler et al 1994, 2000a, 2000b, 2001; Sackeim et al 1996). Thus, daily prefrontal rTMS was initially tried as an antidepressant based on the assumption that rTMS might produce changes in these dysfunctional areas associated with mood regulation and that had been linked to antidepressant response (George et al 1994; George and Wassermann 1994). Since its initial use in 1995 (George et al 1995), there have been more than 20 randomized controlled clinical trials of repeated daily prefrontal rTMS as an antidepressant. Although not all studies have found antidepressant effects greater than sham, most have (for reviews and meta-analyses, see Burt et al 2002; Gershon et al 2003; Holtzheimer et al 2001; Kozel and George 2002; Martin et al 2002).

In contrast to the rapidly growing literature concerning the clinical therapeutic antidepressant effects, there have been fewer studies examining potential neurobiological mechanisms. Ironically, there is still incomplete evidence that prefrontal TMS actually affects limbic regions in depressed patients, which was the theory that lead to its development, although there have been several attempts to address this important question.

The first fluorodeoxyglucose positron emission tomography (PET) study with rTMS in a depressed patient suggested that 2 weeks of daily rTMS was associated with increased brain metabolism in many brain regions occurring over the course of treatment (George et al 1995). Since that time, several studies have used functional imaging (Kimbrell et al 2002; Loo et al 2003; Mottaghy et al 2002; Paus and Wolforth 1998; Speer et al 2000; Teneback et al 1999) to detect brain metabolism or flow changes during or following focal prefrontal TMS (30 min) and longer term (Cohen et al 1999). At least eight studies have been performed with PET, single photon emission computed tomography (SPECT), or functional magnetic resonance imaging (fMRI) in healthy subjects during or immediately following focal prefrontal TMS (Mottaghy et al 2003; Nahas et al 2001; Paus 1999). The majority of these studies found that prefrontal TMS produces brain activity changes in both cortical and subcortical regions. Previous SPECT (George et al 1999b) and fMRI (Nahas et al 2001) studies by our group in healthy subjects have also suggested that prefrontal rTMS can produce activation both underneath the coil and in connected limbic regions. These immediate changes have also been supported by TMS/PET studies in healthy subjects (Kimbrell et al 2002; Strafella et al 2001).

In depressed patients, the majority of studies have been performed with PET and SPECT examining the changes produced over several weeks of daily rTMS treatment (Speer et al

From the Brain Stimulation Laboratory, Department of Psychiatry (XL, ZN, FAK, BA, MSG), Center for Advanced Imaging Research (XL, ZN, FAK, BA, MSG), and Department of Radiology (DEB, MSG), Medical University of South Carolina; and Mental Health Service (FAK, MSG), Ralph H. Johnson Department of Veterans Affairs Medical Center, Charleston, South Carolina.

Address reprint requests to Dr. Xingbao Li, Brain Stimulation Laboratory, MUSC IOP, Room 502 North, 67 President Street, Charleston, SC 29425.

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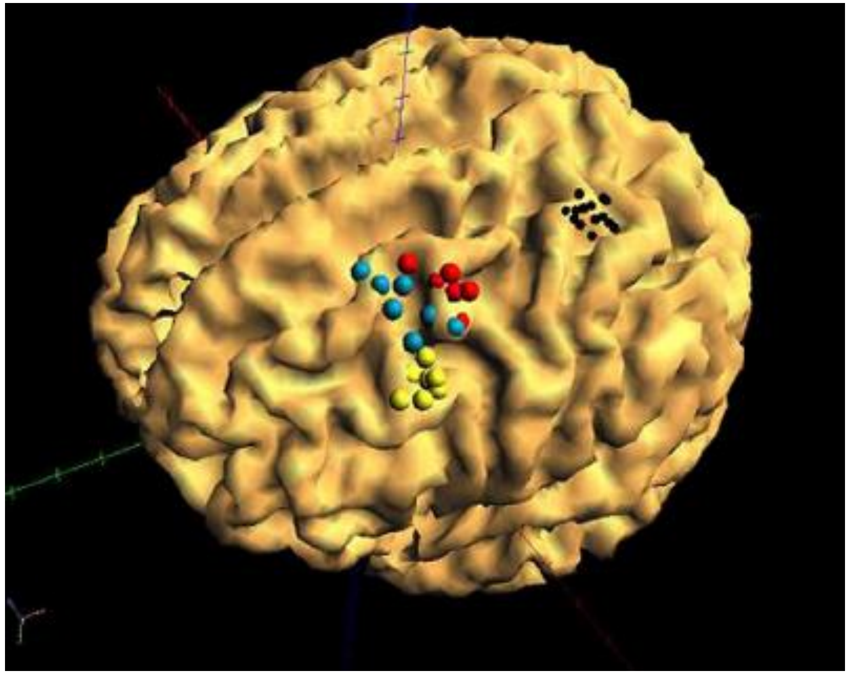

INCREASED PREFRONTAL CTX ACTIVITY POST TMS

HOW DOES TMS COMPARE TO PHARMACEUTICALS?

- George et al, Arch Gen Psychiatry, May 2010 – 30% remission, vs. 16% Lithium augmentation
- Carpenter et al, 2012 – n=307 – 58% responded, 37% remission

WITH NO SIDE EFFECTS

HOW DOES TMS COMPARE TO PHARMACEUTICALS?

rTMS as a Next Step in Antidepressant Nonresponders: A Randomized Comparison With Current Antidepressant Treatment Approaches

Iris Dalhuisen, Ph.D. ✉, Iris van Oostrom, Ph.D., Jan Spijker, M.D., Ph.D., Ben Wijnen, Ph.D., Eric van Exel, M.D., Ph.D., Hans van Mierlo, M.D., Ph.D., Dieuwertje de Waardt, M.D., Ph.D., Martijn Arns, Ph.D., Indira Tendolkar, M.D., Ph.D., and Philip van Eijndhoven, M.D., Ph.D. | AUTHORS INFO & AFFILIATIONS

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The study's findings revealed a significant advantage for TMS over traditional medication. "After 8 weeks of treatment, we found that the group that received TMS had significantly lower depression rates than the group that received medication during these 8 weeks," says Dr. van Oostrom.

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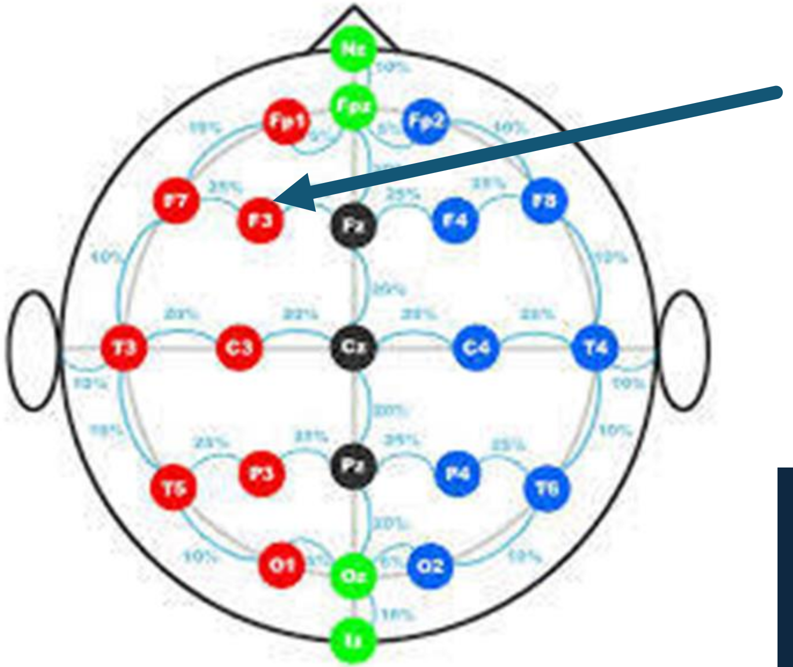
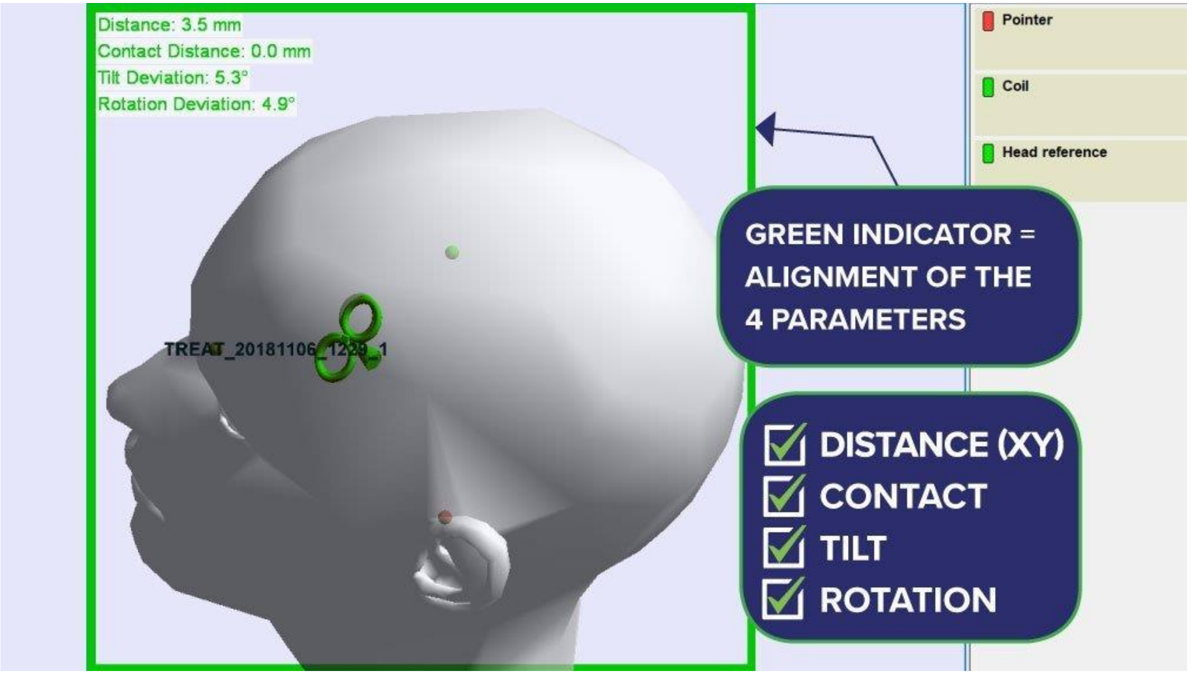




TMS PROCEDURE FOR DEPRESSION – F3 DLPFC

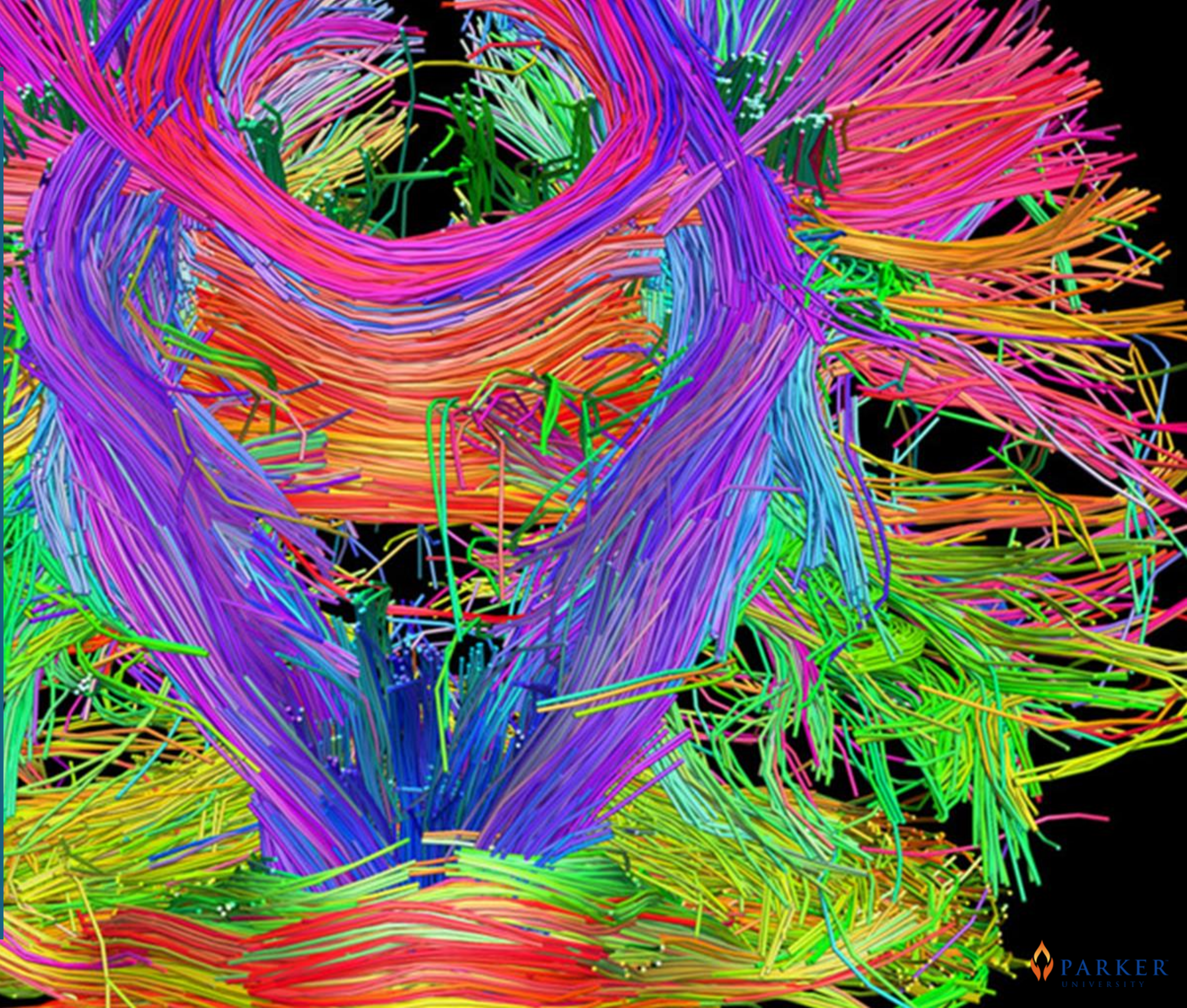
COIL PLACED OVER F3 ON LEFT SIDE (DLPFC) ON THE INTERNATIONAL 10-20 EEG MONTAGE

TYPICAL PROTOCOLS FOR DEPRESSION

- Daily sessions lasting 20-30 minutes
- 4-6 weeks trial
- If no response in 1 week modify protocol or d/c – 20% chance of improvement
- If no positive response in 2 weeks modify protocol or d/c – 10% chance of improvement
- Motor threshold is obtained and recorded
- Most protocols use stimulus 20% above motor threshold or patient comfort
- Patient comfort MUST be considered for compliance - <4% on average do not complete 6 week protocol

“OFF LABEL” USE OF TMS – NON-FDA APPROVED

- Traumatic brain injury (TBI)
- Stroke rehabilitation
- Post-traumatic stress disorder (PTSD)
- Tinnitus



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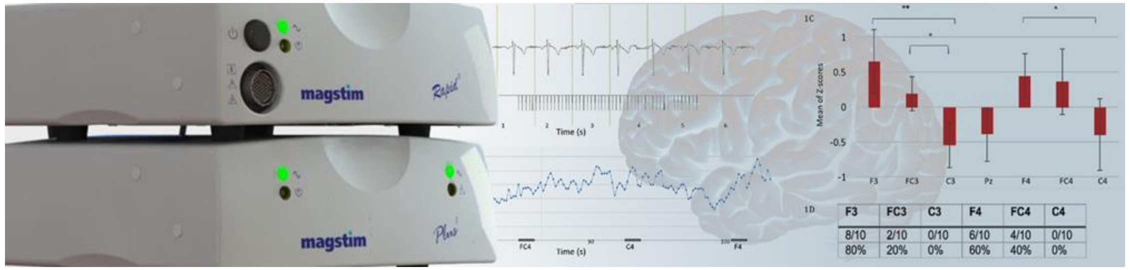

TMS APPLICATIONS IN TRAUMATIC BRAIN INJURY

- Currently not FDA approved

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR CONCUSSION

2017 CMBEC40 Conference
Winnipeg MB
May 23–26, 2017

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) AS A TREATMENT FOR POST-CONCUSSION SYNDROME

Grant Rutherford[1], Brian Lithgow[12], Behzad Mansouri[1], Abed Sulieman[1], Omid Ranjbar Pouya[1], Zeinab Dastgheib[1], Xikui Wang[1], Weijia Zhang[1], Jennifer Salter[2], Zahra Moussavi[12]

[1]University of Manitoba, Canada, [2]Riverview Health Centre, Canada

ABSTRACT

As part of an ongoing study, a small group of volunteers with post-concussion syndrome (PCS) were given either real or sham rTMS treatment. Thirteen treatment sessions over three weeks applied 20 Hz rTMS to the left dorsolateral prefrontal cortex. Assessments to determine cognitive ability, memory, depression symptoms, and PCS symptom burden were done before and after treatment, and twice following up at one and two months post-treatment. Significant improvements were found at two months post-treatment in the measurement of symptom burden using the Rivermead Post Concussion Symptoms Questionnaire. This result suggests that rTMS may be an effective treatment for some of the symptoms of post-concussion syndrome.

INTRODUCTION

Repetitive Transcranial Magnetic Stimulation (rTMS) is a technology that may have the potential to help improve the symptoms of post-concussion syndrome (PCS). rTMS technology has already been shown to be effective in the treatment of various neurological and psychiatric disorders, such as depression, schizophrenia, and Parkinson's disease [1]. There are several reports of case studies that show beneficial effects of rTMS treatment on patients with severe traumatic brain injury (TBI) [2, 3]. Also, a pilot study by our lab has shown encouraging improvements in cognitive and memory deficits of Alzheimer's patients [4]. The ongoing study presented here evaluates a similar rTMS treatment protocol as that used in our Alzheimer's treatment study for people with PCS.

Concussion or mild TBI (mTBI) is the most common form of traumatic brain injury. Concussion is more frequent in teenagers, young adults, males and people who are engaged in high impact physical activities [5, 6]. Individuals who usually sustain mTBI develop neuropathological, neurophysiological, and neurocognitive changes, which result in physical, cognitive, and emotional symptoms. If these symptoms persist long after the mTBI, it is referred to as PCS. These symptoms, if not treated, can last for months and years and may be permanent and cause disabilities [7, 8].

Given that TBI imposes substantial medical and socio-economic burden on patients and the healthcare system [9-11], there is an urgent need to develop an effective treatment strategy. The current treatments for PCS include medications [12] and psychological treatments [13-15]. However, the effectiveness of these treatments is still in dispute [16].

The principle behind rTMS is the application of a rapidly changing magnetic field to the brain [17], which induces electrical fields and ion currents. This causes neurons within a limited area on the surface of the brain to either depolarize or hyperpolarize. When applied over the cortex, depending on the frequency of pulses, rTMS can affect the excitability of the region. It is believed that high frequency (>5 Hz) pulses of rTMS are able to increase cortical excitability in a similar way to the effects of Long-Term Potentiation [18, 19]. The procedure is non-invasive and easy for patients to tolerate.

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TRANSCRANIAL MAGNETIC STIMULATION (RTMS)

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A Pilot Randomised Double-Blind Study of the Tolerability and efficacy of repetitive Transcranial Magnetic Stimulation on Persistent Post-Concussion Syndrome

Zahra Moussavi[1,2], Abdelbaset Suleiman[1], Grant Rutherford[1], Omid Ranjbar Pouya[1], Zeinab Dastgheib[1], Weijia Zhang[3], Jennifer Salter[2], Xikui Wang[3], Behzad Mansouri[1,4] & Brian Lithgow[1,2,5]

This study investigates the effect of Repetitive Transcranial Magnetic Stimulation (rTMS) on persistent post-concussion syndrome (PCS). The study design was a randomized (coin toss), placebo controlled, and double-blind study. Thirty-seven participants with PCS were assessed for eligibility; 22 were randomised and 18 completed the study requirements. Half the participants with PCS were given an Active rTMS intervention and the other half given Sham rTMS over 3 weeks. Follow ups were at the end of treatment and at 30 and 60 days. The primary outcome measure was the Rivermead Post-Concussion Symptoms Questionnaire (RPQ3 & RPQ13). The results indicate participants with more recent injuries (<12 month), who received Active rTMS, showed significant improvements compared to those of: 1) the same subgroup who received Sham, and 2) those with a longer duration of injury (>14 months) who received Active rTMS. This improvement predominantly manifested in RPQ13 in the follow up periods 1 and 2 months after the intervention (RPQ13 change (mean ± SD): at 1 month, Active = −21.8 ± 6.6, Sham = −2.2 ± 9.8; at 2 months, Active = −21.2 ± 5.3, Sham = −5.4 ± 13.7). No improvement was found in the subgroup with longer duration injuries. The results support rTMS as a tolerable and potentially effective treatment option for individuals with a recent (<1 year) concussion.

In most cases of mild traumatic brain injury (mTBI), also called concussion, the symptoms disappear in the first 2 to 4 weeks[1,2]. However, the symptoms can also persist for months or years following the injury; in that case, they are referred to as persistent post-concussion syndrome (PCS)[3,4]. Many authors consider symptoms lasting more than one month as PCS[2,5], however, the more conservative DSM-IV guideline defines symptoms lasting more than 3 months as PCS[6]. The PCS symptoms include somatic symptoms (i.e., headache, blurry vision, anxiety, etc.) and cognitive (i.e., confusion, memory) deficits[1,7,8]. In 20–40% of mTBI cases symptoms are still reported at 6 months post-injury[9], and in 10–20% of cases symptoms are still present at 1 year and beyond[10]. It should be noted that some of the symptoms reported in[9] may have other causes besides mTBI.

Given that PCS imposes substantial medical and socio-economic burdens on patients and the healthcare system[11–13], there is an urgent need to develop an effective treatment strategy as well as quantitative methods to monitor PCS recovery. The current treatments for PCS include medications[14] and psychological treatments[15–17]. However, the effectiveness of these treatments is still in dispute[1]. In recent years a few studies have considered applying repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment for PCS/mTBI[18–21].

rTMS treatment involves the repetitive application of a quickly changing magnetic field pulse to the brain[22]. The rapidly changing magnetic field induces an electric field and causes ions to flow in the brain tissue. These current flows cause neurons in the area of effect to either depolarize or hyperpolarize. Depending on the frequency

[1]Biomedical Engineering, University of Manitoba, Winnipeg, Canada. [2]Riverview Health Centre, Winnipeg, Canada. [3]Statistics Department, University of Manitoba, Winnipeg, Canada. [4]Neurology Department, University of Manitoba, Winnipeg, Canada. [5]Monash Alfred Psychiatry Research Center, Melbourne, Australia. Correspondence and requests for materials should be addressed to Z.M. (email: Zahra.Moussavi@umanitoba.ca)

TMS AND TBI

172 Transcranial Magnetic Stimulation Improves Post Concussive Syndrome Scores and DTI Metrics for Traumatic Brain Injury

Liker, Jakob; Liker, Mark A. MD; Bierling, Tasha

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INTRODUCTION:

According to the CDC, there were approximately 214,110 TBI related hospitalizations in 2020, many continue to be burdened by post-concussive symptoms affecting many aspects of their lives. Current treatments involve symptomatic interventions only, thus a need to provide adequate treatment for long lasting concussion symptoms. Transcranial magnetic stimulation (TMS) has been shown to be effective in treating PTSD and depression in a Veterans Administration population.

METHODS:

Nineteen patients who were diagnosed with ongoing symptoms of PCS at least 3 months after injury underwent repetitive bifrontal TMS for a total of 50 sessions. Rivermead Post Concussive Questionnaire (RPQ) and Diffusion Tensor Imaging (DTI) metrics were obtained before and after treatment.

RESULTS:

The average RPQ score for the pretreatment group was 32 while the post treatment group's average RPQ score was 22. A paired T-test was used to analyze the difference in RPQ scores before and after treatment for each patient. The T-Test was significant ($p<.05$), indicating that there is a difference between the pre and post treatment concussion symptoms.

CONCLUSIONS:

In conclusion, TMS significantly decreased late RPQ score and improved DTI metrics, thus improving delayed post concussive syndrome symptoms.

TMS AND TBI

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TYPE Brief Research Report
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Efficacy of transcranial magnetic stimulation treatment in reducing neuropsychiatric symptomatology after traumatic brain injury

Gianna Carla Riccitelli[1,2]*, Riccardo Borgonovo[1†], Mariasole Villa[1†], Emanuele Pravatà[2,3] and Alain Kaelin-Lang[1,2,4]

[1]Non-Invasive Brain Stimulation Research Unit, Neurocenter of Southern Switzerland, EOC, Lugano, Switzerland, [2]Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland, [3]Neuroradiology Research Unit, Neurocenter of Southern Switzerland, EOC, Lugano, Switzerland, [4]Department of Neurology, Inselspital, Bern University Hospital, Bern, Switzerland

Discussion: These findings suggest that guided, alternating neurostimulation of the DLPFC may modulate activity within cortico-striato-thalamo-cortical circuits, providing a promising alternative for managing neuropsychiatric symptoms in TBI patients who are resistant to traditional treatments.

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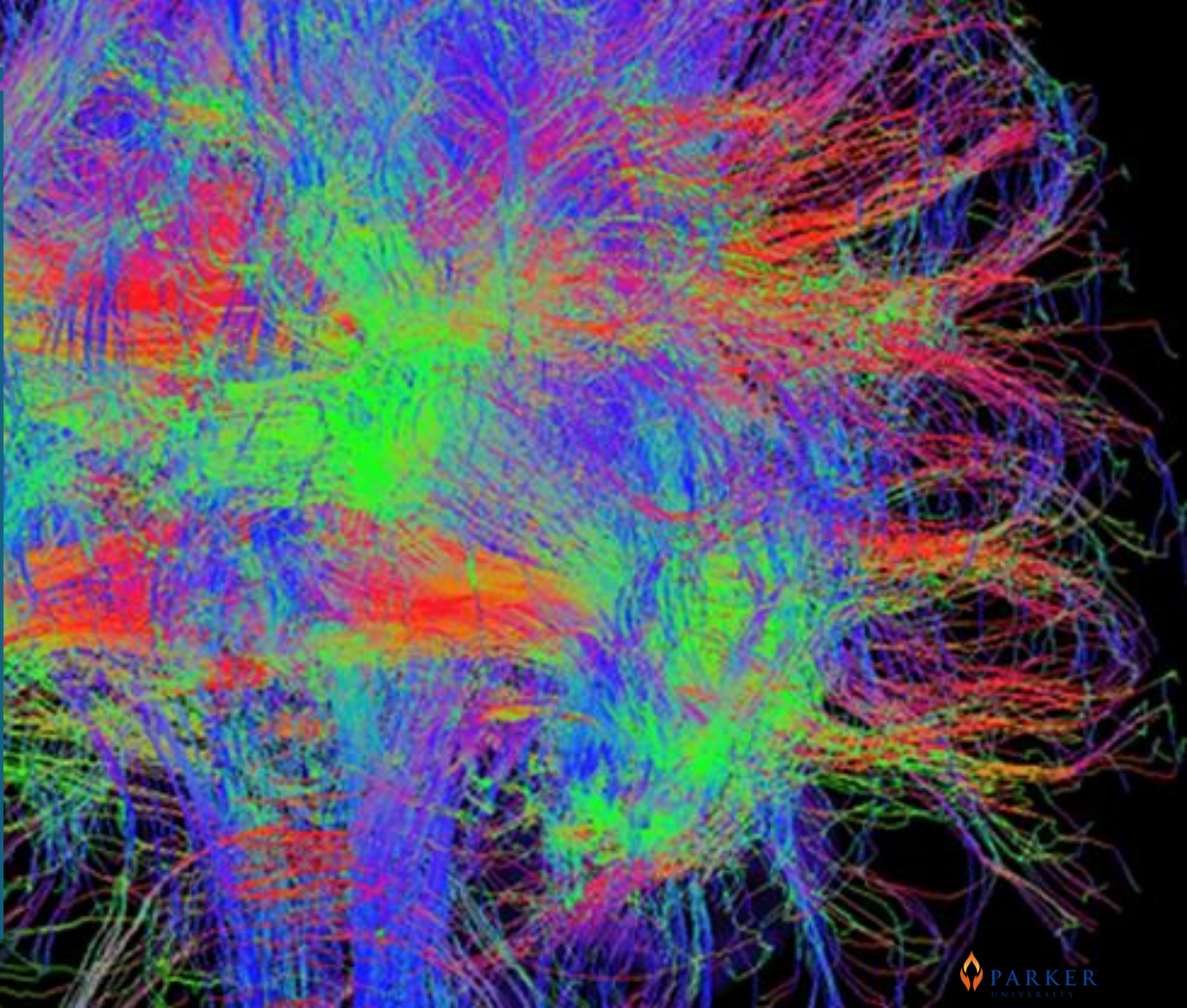
TMS FOR STROKE REHABILITATION

- Stroke recovery - usually subacute (after 2-3 mo): either high frequency ipsilateral or low frequency contralateral, combined w/rehab
- Typically, low-frequency rTMS (<5 Hz) is characterized by decreased cortical excitability, whereas high-frequency rTMS (≥5 Hz) is characterized by enhanced excitability (Pascual-Leone et al., 1998; Fitzgerald et al., 2006)

TMS FOR STROKE REHABILITATION

- Recently, a new rTMS protocol, theta burst stimulation (TBS), was introduced which can produce longer-lasting and more stable changes in cortical excitability compared to standard rTMS (Huang et al., 2005).

- AN EXCITED CORTEX UNDERGOES NEUROPLASTICITY MORE READILY



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TMS FOR STROKE REHABILITATION

frontiers in HUMAN NEUROSCIENCE

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5 Hz repetitive transcranial magnetic stimulation over the ipsilesional sensory cortex enhances motor learning after stroke

Sonia M. Brodie[1], Sean Meehan[2], Michael R. Borich[1] and Lara A. Boyd[1]*

[1] Department of Physical Therapy, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[2] School of Kinesiology, University of Michigan, Ann Arbor, MI, USA

Edited by:
Srikantan S. Nagarajan, University of California, San Francisco, USA

Reviewed by:
Theodore Zanto, University of California San Francisco, USA
Sandro M. Krieg, Technical University Munich, Germany
Phiroz E. Tarapore, University of California, San Francisco, USA

***Correspondence:**
Lara A. Boyd, Department of Physical Therapy, University of British Columbia, 212-2177 Wesbrook Mall, Vancouver, BC V6T 1Z3, Canada
e-mail: lara.boyd@ubc.ca

Sensory feedback is critical for motor learning, and thus to neurorehabilitation after stroke. Whether enhancing sensory feedback by applying excitatory repetitive transcranial magnetic stimulation (rTMS) over the ipsilesional primary sensory cortex (IL-S1) might enhance motor learning in chronic stroke has yet to be investigated. The present study investigated the effects of 5 Hz rTMS over IL-S1 paired with skilled motor practice on motor learning, hemiparetic cutaneous somatosensation, and motor function. Individuals with unilateral chronic stroke were pseudo-randomly divided into either Active or Sham 5 Hz rTMS groups ($n = 11$/group). Following stimulation, both groups practiced a Serial Tracking Task (STT) with the hemiparetic arm; this was repeated for 5 days. Performance on the STT was quantified by response time, peak velocity, and cumulative distance tracked at baseline, during the 5 days of practice, and at a no-rTMS retention test. Cutaneous somatosensation was measured using two-point discrimination. Standardized sensorimotor tests were performed to assess whether the effects might generalize to impact hemiparetic arm function. The active 5 Hz rTMS + training group demonstrated significantly greater improvements in STT performance {response time [$F_{(1, 286.04)} = 13.016$, $p < 0.0005$], peak velocity [$F_{(1, 295.95)} = 4.111$, $p = 0.044$], and cumulative distance [$F_{(1, 285.92)} = 4.076$, $p = 0.044$]} and cutaneous somatosensation [$F_{(1, 21.15)} = 8.793$, $p = 0.007$] across all sessions compared to the sham rTMS + training group. Measures of upper extremity motor function were not significantly different for either group. Our preliminary results suggest that, when paired with motor practice, 5 Hz rTMS over IL-S1 enhances motor learning related change in individuals with chronic stroke, potentially as a consequence of improved cutaneous somatosensation, however no improvement in general upper extremity function was observed.

Keywords: repetitive transcranial magnetic stimulation, stroke, hemiparesis, primary sensory cortex, upper extremity, motor learning

INTRODUCTION

Motor recovery typically plateaus by 6 months after stroke (Hendricks et al., 2002), leaving 55–75% of individuals with chronic functional impairments of the hemiparetic arm (Gresham et al., 1995). Despite the neurological deficits after stroke, the capacity for motor learning persists (Boyd et al., 2009; Vidoni and Boyd, 2009; Meehan et al., 2011a). This has led to an interest in adjunct interventions to positively augment motor learning and further enhance functional recovery in chronic stroke.

Repetitive transcranial magnetic stimulation (rTMS)[1] is a non-invasive technique used to modulate local cortical excitability in a frequency-dependent manner (Maeda et al., 2000), for a period of time that outlasts the duration of stimulation (Chen et al., 2003). Immediately following stimulation, the aftereffects may be capitalized on by pairing it with skilled motor practice to promote use-dependent neuroplastic change (Cohen et al., 1998). As such, rTMS is a promising adjunct therapy for enhancing the sensorimotor benefits of motor skill practice. Past work has primarily considered the application of rTMS over the primary motor cortex (M1) in individuals with stroke. However, to date findings have been inconclusive, both when rTMS is delivered in isolation (Boggio et al., 2006; Fregni et al., 2006; Carey et al., 2010), and when it is paired with rehabilitation (Seniow et al., 2012; Talelli et al., 2012). Inconsistent results may stem from a number of factors, including non-standardized stimulation location within and across experimental sessions, a failure to pair rTMS with a well-controlled motor learning task, and an

[1] **Abbreviations:** rTMS, repetitive transcranial magnetic stimulation; M1, primary motor cortex; S1, primary sensory cortex; cTBS, continuous theta-burst stimulation; CL, contralesional; IL, ipsilesional; MoCA, Montreal Cognitive Assessment; FM, Fugl Meyer score; STT, serial targeting task; 2PD, 2 point discrimination; WMFT, Wolf Motor Function Test; BBT, box and blocks test; RMT, resting motor threshold; EMG, electromyography; MEP, motor evoked potential; ECR, extensor carpi radialis.

TMS FOR STROKE REHABILITATION

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HUMAN NEUROSCIENCE

REVIEW ARTICLE
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Induction of neuroplasticity and recovery in post-stroke aphasia by non-invasive brain stimulation

Priyanka P. Shah[1,2], Jerzy P. Szaflarski[3], Jane Allendorfer[3] and Roy H. Hamilton[1,2]*

[1] Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA
[2] Laboratory for Cognition and Neural Stimulation, Center for Cognitive Neuroscience, University of Pennsylvania, Philadelphia, PA, USA
[3] Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA

Edited by:
Edward Taub, University of Alabama at Birmingham, USA

Reviewed by:
Victor W. Mark, University of Alabama at Birmingham, USA
Gitendra Uswatte, University of Alabama at Birmingham, USA

***Correspondence:**
Roy H. Hamilton, Department of Neurology, Center for Cognitive Neuroscience, University of Pennsylvania, 518 Goddard Building, 3710 Hamilton Walk, Philadelphia, PA 19104, USA
e-mail: roy.hamilton@uphs.upenn.edu

Stroke victims tend to prioritize speaking, writing, and walking as the three most important rehabilitation goals. Of note is that two of these goals involve communication. This underscores the significance of developing successful approaches to aphasia treatment for the several hundred thousand new aphasia patients each year and over 1 million stroke survivors with chronic aphasia in the U.S. alone. After several years of growth as a research tool, non-invasive brain stimulation (NBS) is gradually entering the arena of clinical aphasiology. In this review, we first examine the current state of knowledge of post-stroke language recovery including the contributions from the dominant and non-dominant hemispheres. Next, we briefly discuss the methods and the physiologic basis of the use of inhibitory and excitatory repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) as research tools in patients who experience post-stroke aphasia. Finally, we provide a critical review of the most influential evidence behind the potential use of these two brain stimulation methods as clinical rehabilitative tools.

Keywords: TMS, rTMS, fMRI, tDCS, rehabilitation, aphasia

INTRODUCTION

Aphasia, defined as an impaired ability to communicate, is one of the most feared symptoms of stroke. About 21–38% of acute stroke survivors suffer from aphasia (Berthier, 2005), a devastating neurological condition affecting a person's ability to communicate and, thus, reintegrate into the society. It is a consequence of damage in a widely distributed and complex language network involving the fronto-temporal areas in the dominant hemisphere (typically left). Aphasia usually impacts all areas of communication including language formulation and comprehension as well as the ability to read and write. These deficits are attributed to damage in higher cognitive areas involved in language processing rather than to areas involved in motor control of the articulatory structures (Allendorfer et al., 2012a), although aphasia and disorders of speech articulation often coincide.

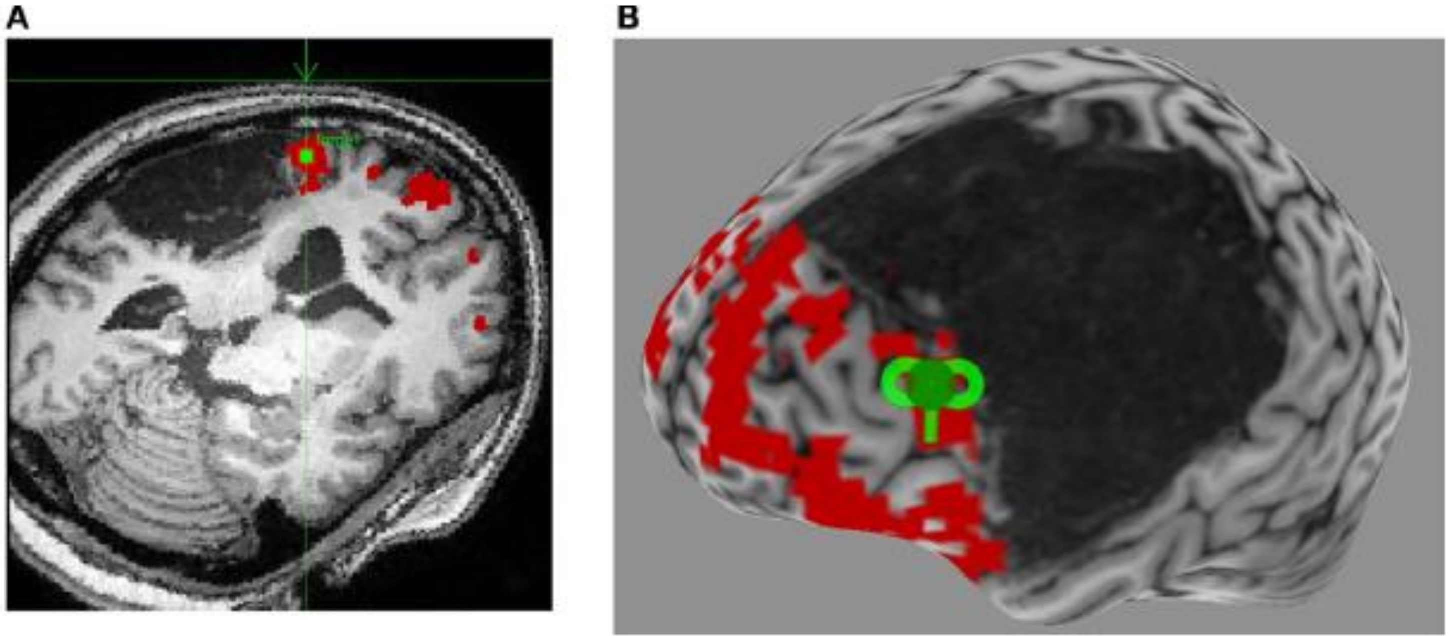
The first 2 to 3 months after stroke are crucial for spontaneous neuroplasticity, which refers to the natural course of neurophysiological repair and cortical reorganization of language functions (Robertson and Fitzpatrick, 2008). During this period, restoration of some language functions is common and usually fairly rapid (Lazar et al., 2008). However, the slope of spontaneous recovery tends to level off within the first year of stroke (Pedersen et al., 1995; Berthier, 2005), resulting in chronic impairments in language processing in many patients.

Despite availability of pharmacological treatments and professionally-administered speech-language therapy (SLT), new strategies e.g., adjuvant therapies, are required to boost recovery, especially in the chronic stages of stroke. While SLT is the most commonly employed treatment of aphasia, its therapeutic effects are quite variable and are generally modest (Berthier, 2005; Brady and Enderby, 2010). Recently, non-invasive brain stimulation (NBS) techniques, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have shown promise as potential approaches for enhancing aphasia recovery. A number of research studies employing these techniques, especially repetitive rTMS, have reported lasting improvement in specific language functions in patients with chronic post-stroke aphasia. In addition to behavioral improvement, evidence of induced neuroplasticity has further validated the efficacy of these interventions. However, application of therapeutic NBS within few days after stroke i.e., in sub-acute and acute phase, is still in its infancy.

In this article, we will explore the neuroplastic processes that underlie spontaneous recovery in patients with aphasia, and present the methods and discuss the physiologic basis of NBS techniques. Next, we will discuss recently published and influential work in which NBS has been used to enhance recovery from post-stroke aphasia. Lastly, we will review studies that investigate the effect that NBS has on neuroplasticity in patients with aphasia; specifically, we will examine studies that address the functional neuroimaging and electrophysiologic correlates of neuroplastic changes after brain stimulation.

NEUROPLASTICITY IN SPONTANEOUS RECOVERY OF POST-STROKE APHASIA

Converging evidence indicates that recovery in post-stroke aphasia is supported by compensatory changes in the representation of language functions, either involving recruitment of



Repetitive peripheral magnetic stimulation alone or in combination with repetitive transcranial magnetic stimulation in poststroke rehabilitation: a systematic review and meta-analysis

Yong Wang[1,2†], Kenneth N. K. Fong[1,3†], Youxin Sui[1†], Zhongfei Bai[4] and Jack Jiaqi Zhang[1*]

Journal of NeuroEngineering and Rehabilitation

Abstract

Objective This study aimed to comprehensively review the effects of repetitive peripheral magnetic stimulation (rPMS) alone or in combination with repetitive transcranial magnetic stimulation (rTMS) on improving upper limb motor functions and activities of daily living (ADL) in patients with stroke, and to explore possible efficacy-related modulators.

Methods A literature search from 1st January 2004 to 1st June 2024 was performed to identified studies that investigated the effects of rPMS on upper limb motor functions and ADL in poststroke patients.

Results Seventeen studies were included. Compared with the control, both rPMS alone or rPMS in combination with rTMS significantly improved upper limb motor function (rPMS: Hedge's $g = 0.703$, $p = 0.015$; rPMS + rTMS: Hedge's $g = 0.892$, $p < 0.001$) and ADL (rPMS: Hedge's $g = 0.923$, $p = 0.013$; rPMS + rTMS: Hedge's $g = 0.923$, $p < 0.001$). However, rPMS combined with rTMS was not superior to rTMS alone on improving poststroke upper limb motor function and ADL (Hedge's $g = 0.273$, $p = 0.123$). Meta-regression revealed that the total pulses ($p = 0.003$) and the number of pulses per session of rPMS ($p < 0.001$) correlated with the effect sizes of ADL.

Conclusions Using rPMS alone or in combination with rTMS appears to effectively improve upper extremity functional recovery and activity independence in patients after stroke. However, a simple combination of these two interventions may not produce additive benefits than the use of rTMS alone. Optimization of rPMS protocols, such as applying appropriate dosage, may lead to a more favourable recovery outcome in poststroke rehabilitation.

Keywords Stroke, Upper extremity, Peripheral magnetic stimulation, Transcranial magnetic stimulation, Cortical excitability

Conclusions Using rPMS alone or in combination with rTMS appears to effectively improve upper extremity functional recovery and activity independence in patients after stroke. However, a simple combination of these two interventions may not produce additive benefits than the use of rTMS alone. Optimization of rPMS protocols, such as applying appropriate dosage, may lead to a more favourable recovery outcome in poststroke rehabilitation.

TMS AND PTSD

- Repetitive transcranial magnetic stimulation(rTMS) has been found to be effective for treating PTSD, but whether different frequencies have different effects remains controversial.
- LF rTMS can reduce overall PTSD and depression symptoms. HF rTMS can improve the main and related symptoms of PTSD

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ELSEVIER

Different frequency repetitive transcranial magnetic stimulation (rTMS) for posttraumatic stress disorder (PTSD): A systematic review and meta-analysis

CrossMark

Tingting Yan, M.D., Ph.D. [a, *], Qinglian Xie [b], Zhong Zheng, M.D., Ph.D. [c], Ke Zou [c], Lijuan Wang, M.D., Ph.D. [d]

[a] Department of Disaster Medical Science, Sichuan University, Institute for Disaster Management and Reconstruction, Sichuan University, Chengdu, 610041, PR China
[b] Department of Psychiatry, West China Hospital, Sichuan University, Chengdu, 610041, PR China
[c] Department of Neurobiological Examine Centre, West China Hospital, Sichuan University, Chengdu, 610041, PR China
[d] Department of Neurology, Sichuan Academy of Medical Sciences & Sichuan Provincial Peoples Hospital, Chengdu, 610041, PR China

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A B S T R A C T

Posttraumatic stress disorder (PTSD) is a psychiatric disorder. Repetitive transcranial magnetic stimulation (rTMS) has been found to be effective for treating PTSD, but whether different frequencies have different effects remains controversial. We conducted this systematic review and meta-analysis to address this question. We searched the literature for studies written in English or Chinese in 9 electronic databases from the databases' inception to August 1, 2016. Additional articles were identified from the reference lists of identified studies and from personal reference collections. Eighteen articles were included, and 11 were suitable for the meta-analysis (Combined sample size was 377 (217 in active rTMS groups, 160 in sham-controlled groups)). Low-frequency (LF) rTMS resulted in a significant reduction in the PTSD total score and the depression score (1. PTSD total score: pooled SMD, 0.92; CI, 0.11–1.72; 2. Depression: pooled SMD, 0.54; CI, 0.08–1.00). High-frequency (HF) rTMS showed the following results: 1. PTSD total score: pooled SMD, 3.24; CI, 2.24–4.25; 2. re-experiencing: pooled SMD, −1.77; CI, −2.49-(-1.04); 3. Avoidance: pooled SMD, −1.57; CI, −2.50-(-0.84); 4. hyperarousal: pooled SMD, −1.32; CI, −2.17-(-0.47); 5. depression: pooled SMD, 1.92; CI, 0.80–3.03; and 6. Anxiety: pooled SMD, 2.67; CI, 1.82–3.52. Therefore, both HF and LF rTMS can alleviate PTSD symptoms. Although the evidence is extremely limited, LF rTMS can reduce overall PTSD and depression symptoms. HF rTMS can improve the main and related symptoms of PTSD. However, additional research is needed to substantiate these findings.

1. Introduction

Posttraumatic stress disorder (PTSD) is a chronic psychiatric disorder that commonly occurs among trauma survivors. In recent years, researchers have started to recognize the characteristics of this complicated mental disorder. According to Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), PTSD is characterized by three main symptom clusters: re-experiencing, avoidance and hyperarousal (APA, 1994). In the United States, PTSD has a 12-month prevalence of 3.5% and a lifetime prevalence of 7% (Kessler et al., 2005a, 2005b, 1995). For the affected person's family, PTSD is a huge economic burden (Thomas et al., 2010).

In two-thirds of patients, PTSD symptoms can be alleviated with commonly used treatment methods (APA, 2004; D. G. Baker et al., 2009; Cloitre M., 2009; Kessler et al., 1995; Institute of Medicine Committee on the Treatment of Posttraumatic Stress Institute of Medicine Committee on Treatment of Posttraumatic Stress Disorder, 2007). However, the symptoms of the remaining one-third of patients are very difficult to treat (Bisson and Andrew, 2007; Kessler et al., 1995; Stein et al., 2006).

Repetitive transcranial magnetic stimulation (rTMS) is a new, noninvasive technique that alters brain activity through repeated changes of the coil's magnetic field. This modulation effect can

* Corresponding author.
E-mail address: tingting.yan84@qq.com (T. Yan).

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Trends
in Psychiatry and Psychotherapy

Brief Communication

Transcranial magnetic stimulation for posttraumatic stress disorder: an updated systematic review and meta-analysis

Estimulação magnética transcraniana para transtorno de estresse pós-traumático: revisão sistemática de literatura e metanálise

Alisson Paulino Trevizol,[1] Mirna Duarte Barros,[1] Paula Oliveira Silva,[1] Elizabeth Osuch,[2] Quirino Cordeiro,[1] Pedro Shiozawa[1]

Abstract

Introduction: Transcranial magnetic stimulation (TMS) is a promising non-pharmacological intervention for posttraumatic stress disorder (PTSD). However, randomized controlled trials (RCTs) and meta-analyses have reported mixed results.
Objective: To review articles that assess the efficacy of TMS in PTSD treatment.
Methods: A systematic review using MEDLINE and other databases to identify studies from the first RCT available up to September 2015. The primary outcome was based on PTSD scores (continuous variable). The main outcome was Hedges' g. We used a random-effects model using the statistical packages for meta-analysis available in Stata 13 for Mac OSX. Heterogeneity was evaluated with I^2 (> 35% for heterogeneity) and the χ^2 test ($p < 0.10$ for heterogeneity). Publication bias was evaluated using a funnel plot. Meta-regression was performed using the random-effects model.
Results: Five RCTs (n = 118) were included. Active TMS was significantly superior to sham TMS for PTSD symptoms (Hedges' g = 0.74; 95% confidence interval = 0.06-1.42). Heterogeneity was significant in our analysis (I^2 = 71.4% and p = 0.01 for the χ^2 test). The funnel plot shows that studies were evenly distributed, with just one study located marginally at the edge of the funnel and one study located out of the funnel. We found that exclusion of either study did not have a significant impact on the results. Meta-regression found no particular influence of any variable on the results.
Conclusion: Active TMS was superior to sham stimulation for amelioration of PTSD symptoms. Further RCTs with larger sample sizes are fundamental to clarify the precise impact of TMS in PTSD.
Keywords: Meta-analysis, posttraumatic stress disorder, transcranial magnetic stimulation, non-pharmacological therapies, systematic review.

Resumo

Introdução: A estimulação magnética transcraniana (EMT) é uma intervenção não farmacológica promissora no tratamento de transtorno de estresse pós-traumático (TEPT). No entanto, estudos controlados e metanálises apresentaram resultados conflitantes até o momento.
Objetivo: Revisar os artigos sobre a eficácia da EMT para o tratamento de TEPT.
Métodos: Conduzimos uma revisão sistemática da literatura no MEDLINE para identificar estudos controlados e randomizados publicados até setembro de 2015. O desfecho primeiro foi baseado nas escalas de gravidade de TEPT como variáveis contínuas. O desfecho principal foi o g de Hedges. Utilizamos o modelo de efeito randômico com as análises estatísticas para metanálise do Stata 13 para Mac OSX. A heterogeneidade foi avaliada com o I^2 (> 35% para heterogeneidade) e o teste do χ^2 ($p < 0{,}01$ para heterogeneidade). Viés de publicação foi avaliado utilizando-se o gráfico do funil. Realizamos metarregressões com modelo de efeito randômico.
Resultados: Cinco estudos foram incluídos. A EMT ativa foi superior ao placebo para o tratamento de TEPT (g de Hedges = 0,74; intervalo de confiança 95% = 0,06-1,42). A heterogeneidade entre os estudos foi significativa em nossa análise (I^2 = 71,4% e p = 0,01 para o teste do χ^2). O gráfico do funil nos mostrou estudos simetricamente distribuídos, com apenas um estudo localizado marginalmente ao gráfico e um estudo localizado fora do funil. Encontramos que a exclusão de cada estudo não alterou significativamente o resultado final. A metarregressão não mostrou influência de nenhuma variável no resultado.
Conclusões: A estimulação ativa de EMT foi superior à estimulação simulada para melhora dos sintomas de TEPT. Novos estudos randomizados e controlados por simulação são necessários para esclarecer com melhor precisão o impacto da EMT no TEPT.
Descritores: Metanálise, transtorno de estresse pós-traumático, estimulação magnética transcraniana, terapias não farmacológicas, revisão sistemática.

[1] Centro Interdisciplinar de Neuromodulação Clínica, Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo, SP, Brazil. [2] Department of Psychiatry, University of Western Ontario, Schulich School of Medicine and Dentistry, London, Ontario, Canada.

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TMS AND PTSD

ACTIVE TMS WAS SUPERIOR TO SHAM STIMULATION FOR AMELIORATION OF PTSD SYMPTOMS

RESEARCH ARTICLE

Explore the durability of repetitive transcranial magnetic stimulation in treating post-traumatic stress disorder: An updated systematic review and meta-analysis

Guobin Xu, Geng Li, Qizhang Yang, Chao Li, Chengzhen Liu

First published: 15 July 2023 | https://doi.org/10.1002/smi.3292 | Citations: 1

TMS AND PTSD

Abstract

The objective was to synthesize results from studies that assessed symptom relief after repetitive transcranial magnetic stimulation (rTMS) treatment for post-traumatic stress disorder (PTSD) and investigate the long-term effectiveness of rTMS for treating PTSD. We searched multiple databases for relevant randomized controlled trials of rTMS for PTSD treatment up to 1 January 2023. Two researchers evaluated the studies and focused on the CAPS and PCL as outcome indicators. We used STATA17 SE software for the data analysis. Eight articles involving 309 PTSD patients were analysed in a meta-analysis, which found that rTMS had a significant and large effect on reducing core post-traumatic symptoms [Hedges'g = 1.75, 95% CI (1.18, 2.33)]. Both low and high-frequency rTMS also significantly reduced symptoms, with the latter having a greater effect. rTMS was shown to have a long-term effect on PTSD, with all three subgroup analyses demonstrating significant results. Interestingly, no significant difference in symptom relief was found between the follow-up and completion of treatments [Hedges'g = 0.01, 95% CI (−0.30, 0.33)], suggesting that the treatment effect of rTMS is stable. The meta-analysis provides strong evidence that rTMS is effective in reducing the severity and symptoms of PTSD in patients, and follow-up studies confirm its long-term stability.

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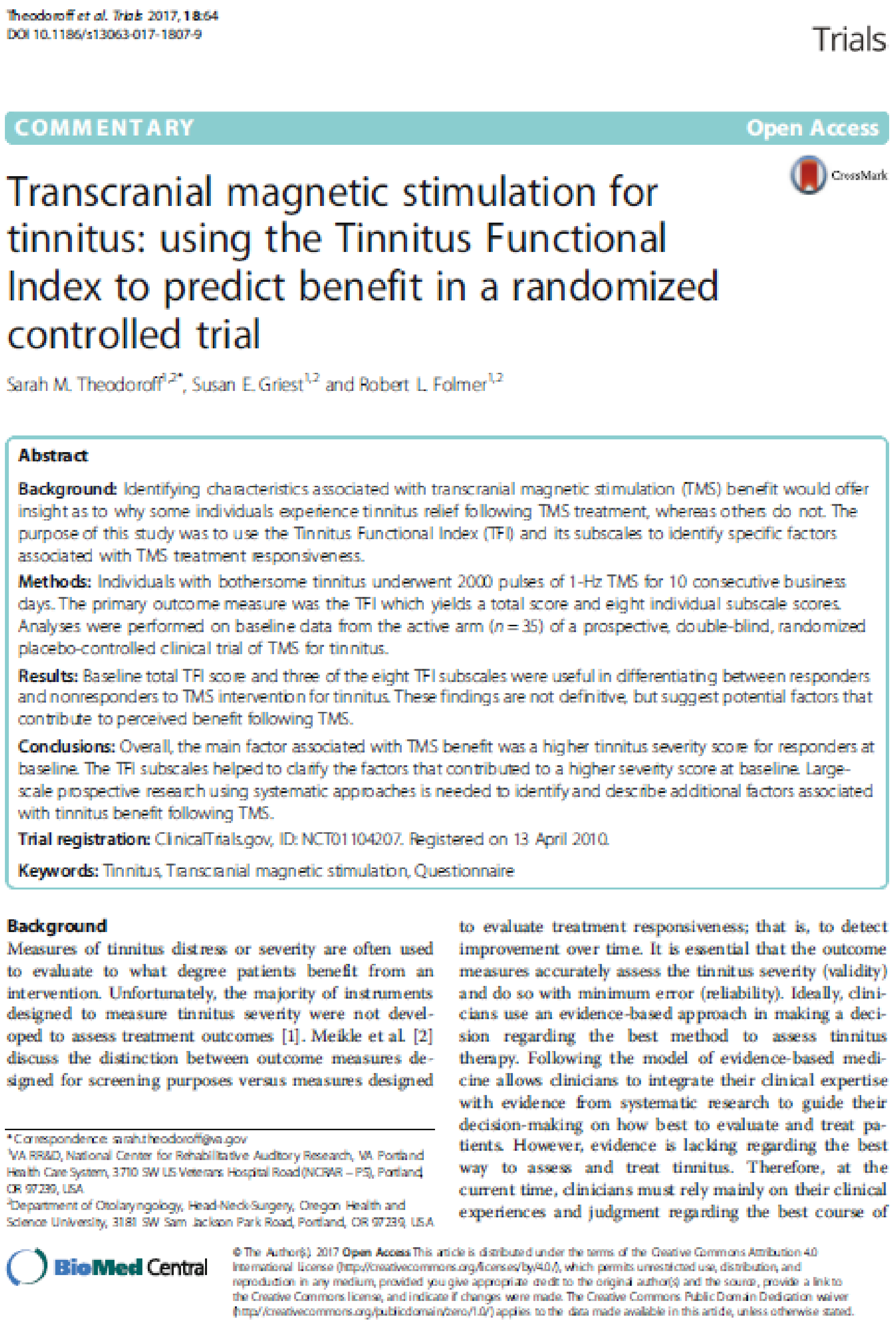


Theodoroff et al. Trials 2017, 18:64
DOI 10.1186/s13063-017-1807-9

Trials

COMMENTARY — Open Access

Transcranial magnetic stimulation for tinnitus: using the Tinnitus Functional Index to predict benefit in a randomized controlled trial

Sarah M. Theodoroff[1,2*], Susan E. Griest[1,2] and Robert L. Folmer[1,2]

Abstract

Background: Identifying characteristics associated with transcranial magnetic stimulation (TMS) benefit would offer insight as to why some individuals experience tinnitus relief following TMS treatment, whereas others do not. The purpose of this study was to use the Tinnitus Functional Index (TFI) and its subscales to identify specific factors associated with TMS treatment responsiveness.

Methods: Individuals with bothersome tinnitus underwent 2000 pulses of 1-Hz TMS for 10 consecutive business days. The primary outcome measure was the TFI which yields a total score and eight individual subscale scores. Analyses were performed on baseline data from the active arm ($n = 35$) of a prospective, double-blind, randomized placebo-controlled clinical trial of TMS for tinnitus.

Results: Baseline total TFI score and three of the eight TFI subscales were useful in differentiating between responders and nonresponders to TMS intervention for tinnitus. These findings are not definitive, but suggest potential factors that contribute to perceived benefit following TMS.

Conclusions: Overall, the main factor associated with TMS benefit was a higher tinnitus severity score for responders at baseline. The TFI subscales helped to clarify the factors that contributed to a higher severity score at baseline. Large-scale prospective research using systematic approaches is needed to identify and describe additional factors associated with tinnitus benefit following TMS.

Trial registration: ClinicalTrials.gov, ID: NCT01104207. Registered on 13 April 2010.

Keywords: Tinnitus, Transcranial magnetic stimulation, Questionnaire

Background

Measures of tinnitus distress or severity are often used to evaluate to what degree patients benefit from an intervention. Unfortunately, the majority of instruments designed to measure tinnitus severity were not developed to assess treatment outcomes [1]. Meikle et al. [2] discuss the distinction between outcome measures designed for screening purposes versus measures designed to evaluate treatment responsiveness; that is, to detect improvement over time. It is essential that the outcome measures accurately assess the tinnitus severity (validity) and do so with minimum error (reliability). Ideally, clinicians use an evidence-based approach in making a decision regarding the best method to assess tinnitus therapy. Following the model of evidence-based medicine allows clinicians to integrate their clinical expertise with evidence from systematic research to guide their decision-making on how best to evaluate and treat patients. However, evidence is lacking regarding the best way to assess and treat tinnitus. Therefore, at the current time, clinicians must rely mainly on their clinical experiences and judgment regarding the best course of

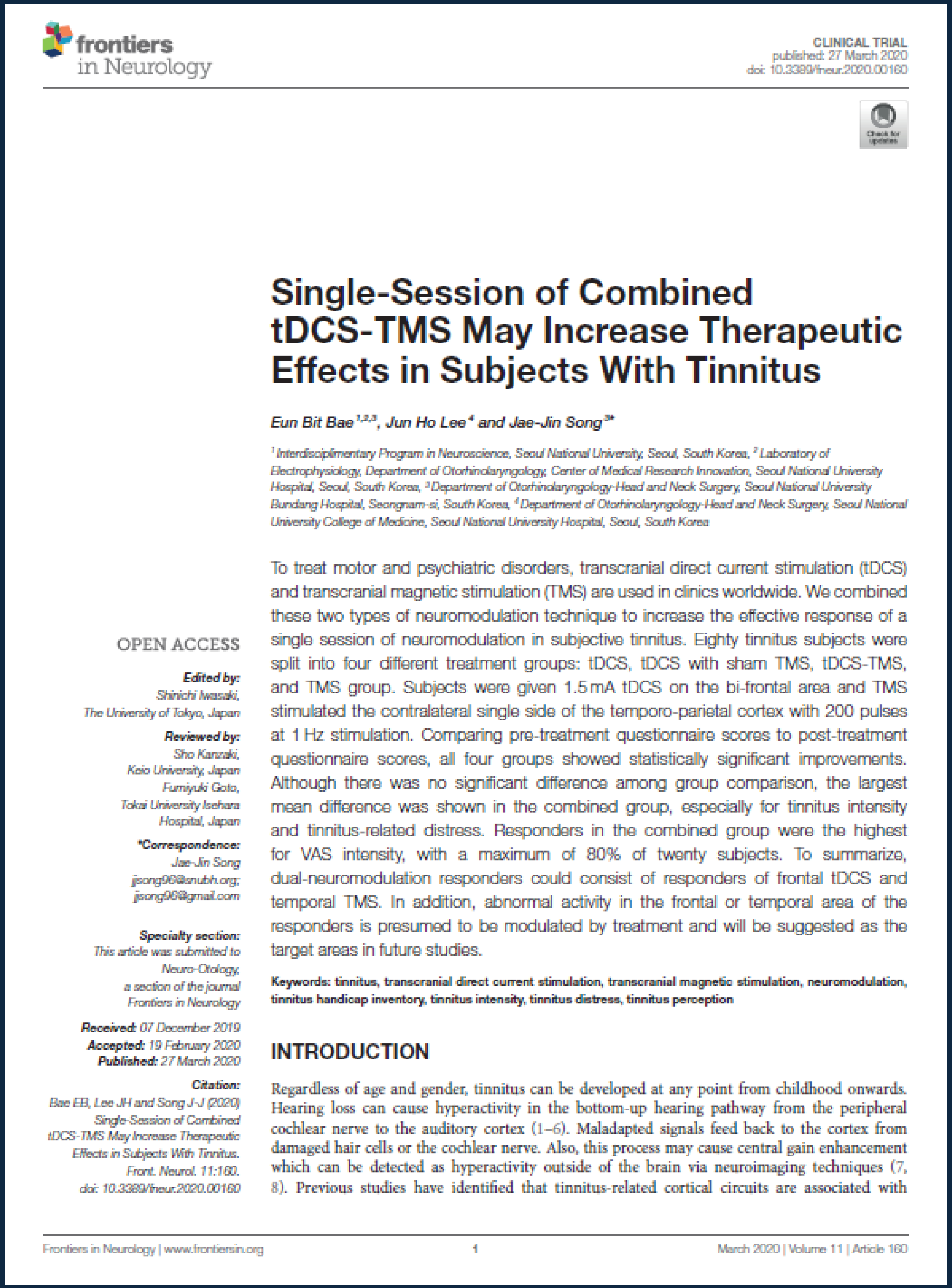
*Correspondence: sarah.theodoroff@va.gov
[1]VA RR&D, National Center for Rehabilitative Auditory Research, VA Portland Health Care System, 3710 SW US Veterans Hospital Road (NCRAR – P5), Portland, OR 97239, USA
[2]Department of Otolaryngology, Head-Neck-Surgery, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA

TMS IN TINNITUS

- Higher severity leads to better response
- Overall response good but largest change noted in higher indicies

TMS IN TINNITUS

- rTMS alone and rTMS combined with tDCS
- Combo group 80% response
- Frontal tDCS and temporal rTMS



frontiers in Neurology

CLINICAL TRIAL
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doi: 10.3389/fneur.2020.00160

Single-Session of Combined tDCS-TMS May Increase Therapeutic Effects in Subjects With Tinnitus

Eun Bit Bae[1,2,3], Jun Ho Lee[4] and Jae-Jin Song[3*]

[1] Interdisciplimentary Program in Neuroscience, Seoul National University, Seoul, South Korea, [2] Laboratory of Electrophysiology, Department of Otorhinolaryngology, Center of Medical Research Innovation, Seoul National University Hospital, Seoul, South Korea, [3] Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seongnam-si, South Korea, [4] Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, South Korea

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Shinichi Iwasaki,
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***Correspondence:**
Jae-Jin Song
jjsong96@snubh.org;
jjsong96@gmail.com

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Bae EB, Lee JH and Song J-J (2020) Single-Session of Combined tDCS-TMS May Increase Therapeutic Effects in Subjects With Tinnitus. Front. Neurol. 11:160. doi: 10.3389/fneur.2020.00160

To treat motor and psychiatric disorders, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are used in clinics worldwide. We combined these two types of neuromodulation technique to increase the effective response of a single session of neuromodulation in subjective tinnitus. Eighty tinnitus subjects were split into four different treatment groups: tDCS, tDCS with sham TMS, tDCS-TMS, and TMS group. Subjects were given 1.5 mA tDCS on the bi-frontal area and TMS stimulated the contralateral single side of the temporo-parietal cortex with 200 pulses at 1 Hz stimulation. Comparing pre-treatment questionnaire scores to post-treatment questionnaire scores, all four groups showed statistically significant improvements. Although there was no significant difference among group comparison, the largest mean difference was shown in the combined group, especially for tinnitus intensity and tinnitus-related distress. Responders in the combined group were the highest for VAS intensity, with a maximum of 80% of twenty subjects. To summarize, dual-neuromodulation responders could consist of responders of frontal tDCS and temporal TMS. In addition, abnormal activity in the frontal or temporal area of the responders is presumed to be modulated by treatment and will be suggested as the target areas in future studies.

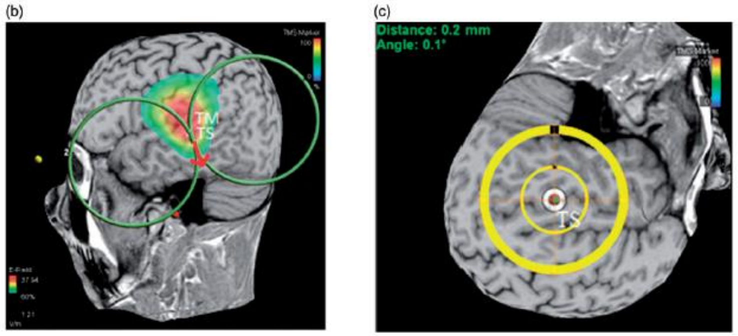
Keywords: tinnitus, transcranial direct current stimulation, transcranial magnetic stimulation, neuromodulation, tinnitus handicap inventory, tinnitus intensity, tinnitus distress, tinnitus perception

INTRODUCTION

Regardless of age and gender, tinnitus can be developed at any point from childhood onwards. Hearing loss can cause hyperactivity in the bottom-up hearing pathway from the peripheral cochlear nerve to the auditory cortex (1–6). Maladapted signals feed back to the cortex from damaged hair cells or the cochlear nerve. Also, this process may cause central gain enhancement which can be detected as hyperactivity outside of the brain via neuroimaging techniques (7, 8). Previous studies have identified that tinnitus-related cortical circuits are associated with

TMS IN TINNITUS

- TMS very effective – responder rates 35-85%
- Coil position appears to not be of significance



Trends in Hearing
Volume 23: 1–14

DOI: 10.1177/2331216518822198
journals.sagepub.com/home/tia
SAGE

Neuronavigated Versus Non-navigated Repetitive Transcranial Magnetic Stimulation for Chronic Tinnitus: A Randomized Study

Hanna Sahlsten[1], Anu Holm[2], Esa Rauhala[2], Mari Takala[2], Eliisa Löyttyniemi[3], Max Karukivi[4,5], Johanna Nikkilä[4,5], Kirsi Ylitalo[6], Janika Paavola[7], Reijo Johansson[8], Tero Taiminen[9], and Satu K. Jääskeläinen[10]

Abstract

Repetitive transcranial magnetic stimulation (rTMS) has shown variable effect on tinnitus. A prospective, randomized 6-month follow-up study on parallel groups was conducted to compare the effects of neuronavigated rTMS to non-navigated rTMS in chronic tinnitus. Forty patients (20 men, 20 women), mean age of 52.9 years (standard deviation [SD] = 11.7), with a mean tinnitus duration of 5.8 years (SD = 3.2) and a mean tinnitus intensity of 62.2/100 (SD = 12.8) on Visual Analog Scale (VAS 0–100) participated. Patients received 10 sessions of 1-Hz rTMS to the left temporal area overlying auditory cortex with or without neuronavigation. The main outcome measures were VAS scores for tinnitus intensity, annoyance, and distress, and Tinnitus Handicap Inventory (THI) immediately and at 1, 3, and 6 months after treatment. The mean tinnitus intensity (hierarchical linear mixed model: $F_3 = 7.34$, $p = .0006$), annoyance ($F_3 = 4.45$, $p = .0093$), distress ($F_3 = 5.04$, $p = .0051$), and THI scores ($F_4 = 17.30$, $p < .0001$) decreased in both groups with non-significant differences between the groups, except for tinnitus intensity ($F_3 = 2.96$, $p = .0451$) favoring the non-navigated rTMS. Reduction in THI scores persisted for up to 6 months in both groups. Cohen's d for tinnitus intensity ranged between 0.33 and 0.47 in navigated rTMS and between 0.55 and 1.07 in non-navigated rTMS. The responder rates for VAS or THI ranged between 35% and 85% with no differences between groups ($p = .054$–1.0). In conclusion, rTMS was effective for chronic tinnitus, but the method of coil localization was not a critical factor for the treatment outcome.

Keywords

tinnitus, transcranial magnetic stimulation, TMS, rTMS, neuronavigated

Date received: 17 August 2018; revised: 26 November 2018; accepted: 5 December 2018

Introduction

Tinnitus is the perception of sound in the absence of an external sound source. Its prevalence is 10% to 15% in the general population, increasing with age and after noise exposure (De Ridder et al., 2014). Tinnitus severely impairs the quality of life in 1% to 2% of people and is frequently associated with depression, anxiety, and insomnia (Langguth, Kreuzer, Kleinjung, & De Ridder, 2013; Langguth, Landgrebe, Kleinjung, Sand, & Hajak, 2011).

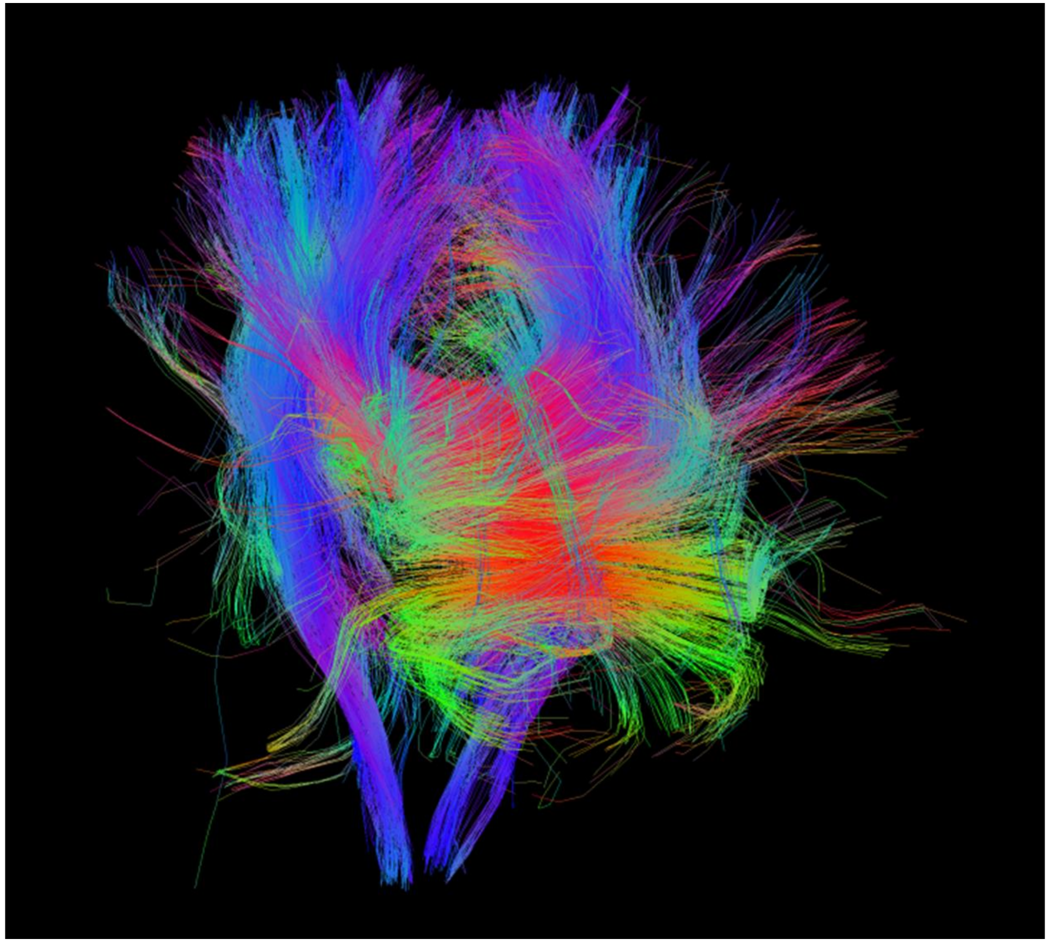
The exact pathophysiology of tinnitus remains unclear. Neuroplastic changes occurring in the brain following auditory sensory deafferentation alter neural

[1]Faculty of Medicine, University of Turku, Finland
[2]Department of Clinical Neurophysiology, SataDiag, Satakunta Hospital District, Pori, Finland
[3]Department of Biostatistics, University of Turku, Finland
[4]Unit of Adolescent Psychiatry, Satakunta Hospital District, Pori, Finland
[5]Department of Psychiatry, University of Turku and Turku University Hospital, Finland
[6]Department of Ear, Nose and Throat, Satakunta Hospital District, Pori, Finland
[7]Department of Medical Physics, Turku University Hospital, Finland
[8]Department of Ear, Nose and Throat, Turku University Hospital, Finland
[9]Department of Psychiatry, Turku University Hospital, Finland
[10]Department of Clinical Neurophysiology, Division of Medical Imaging, Turku University Hospital and University of Turku, Finland

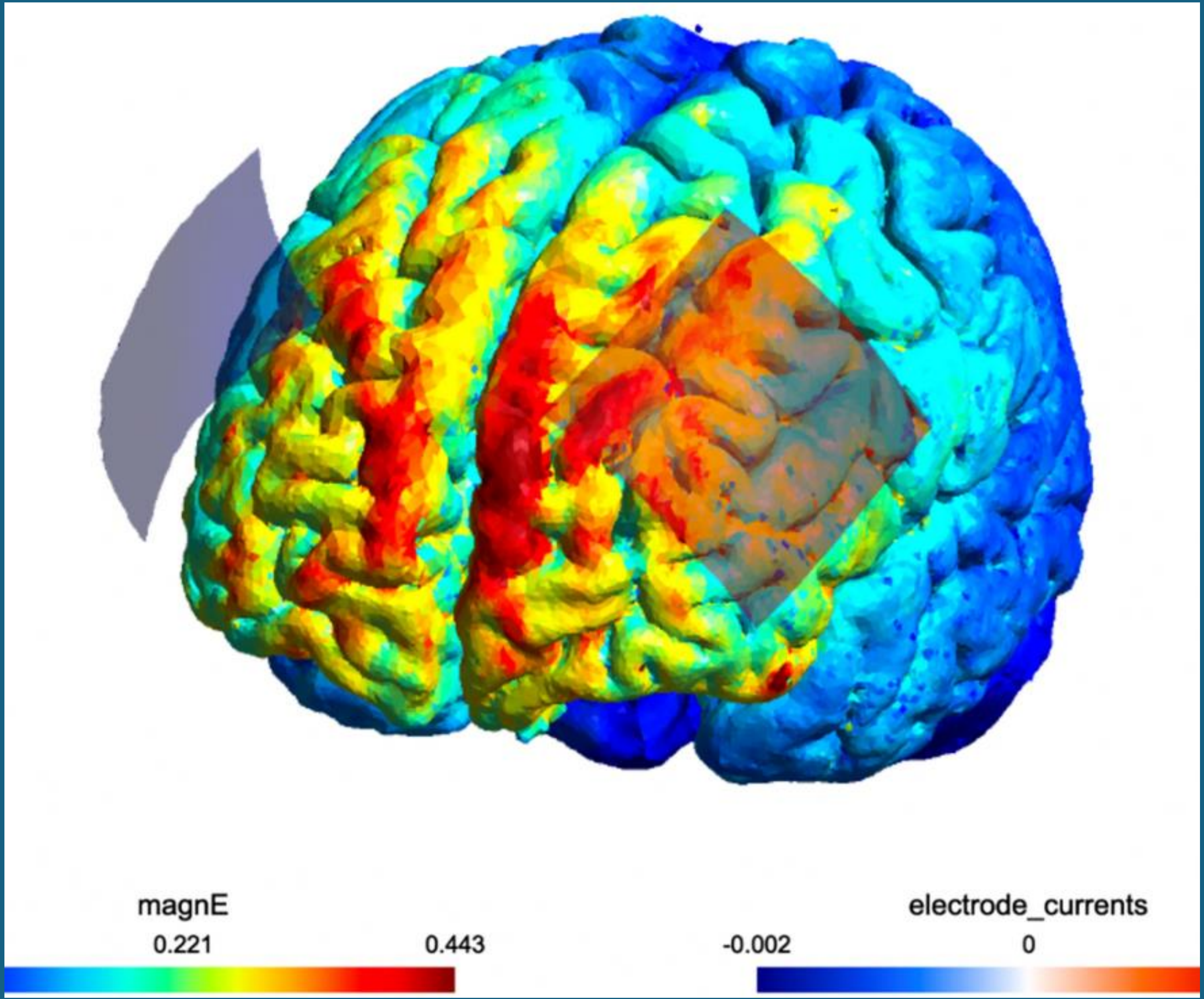
Corresponding author:
Hanna Sahlsten, Department of Clinical Neurophysiology, Division of Medical Imaging, Turku University Hospital, Postal Box 52, 20521 Turku, Finland.
Email: hanna.sahlsten@hotmail.fi

SUMMARY OF TMS

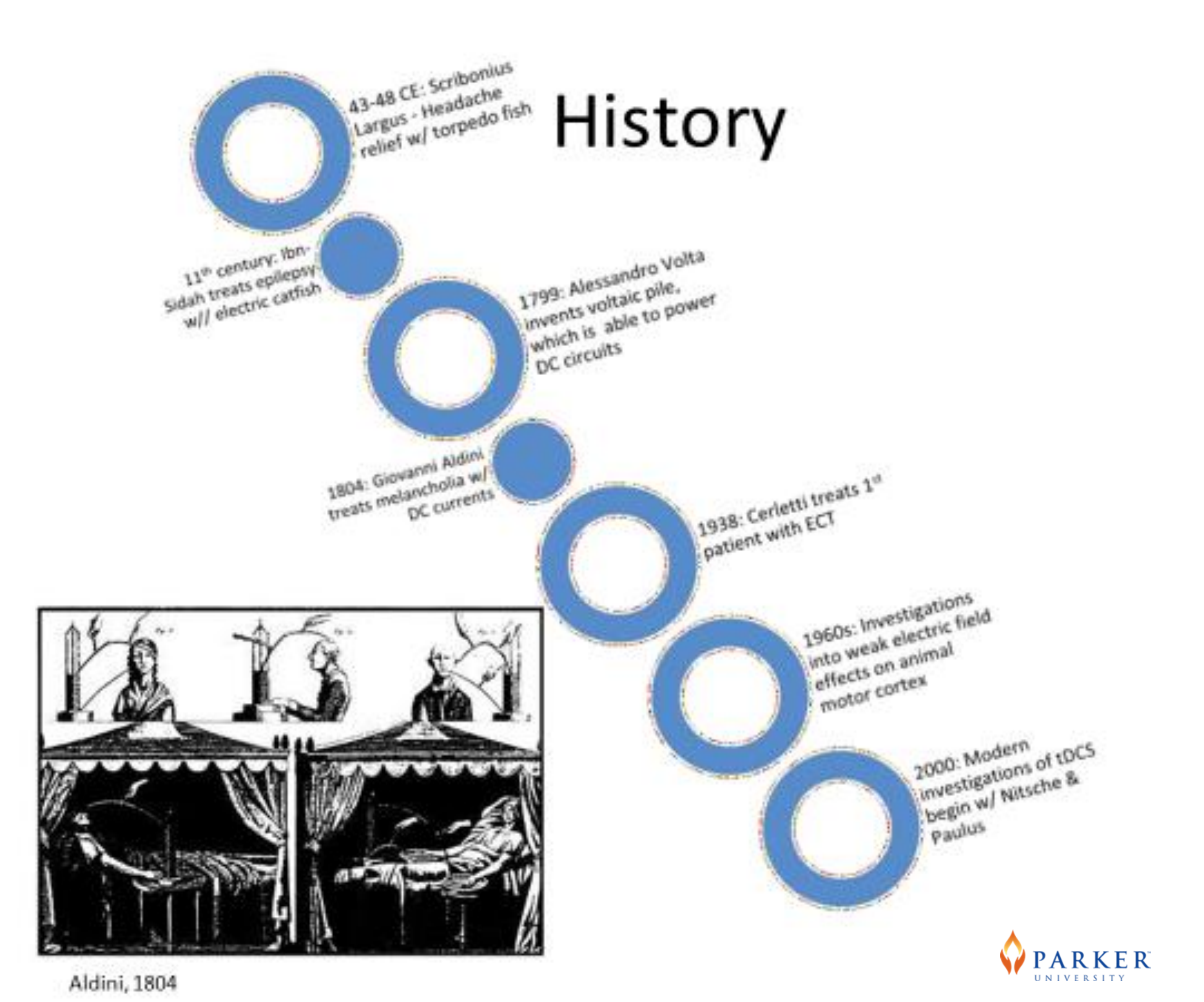
- TMS is a very safe and effective tool for major depression disorder (MDD) without the side effects of pharmaceuticals
- TMS is FDA approved currently for MDD and OCD
- TMS is an evidence-based tool to assist in the management of Stroke patients with motor deficits and aphasia
- TMS is an evidence-based tool for treatment of those with PTSD (FDA soon?)
- TMS is showing great promise as a treatment option for those with tinnitus



TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS)

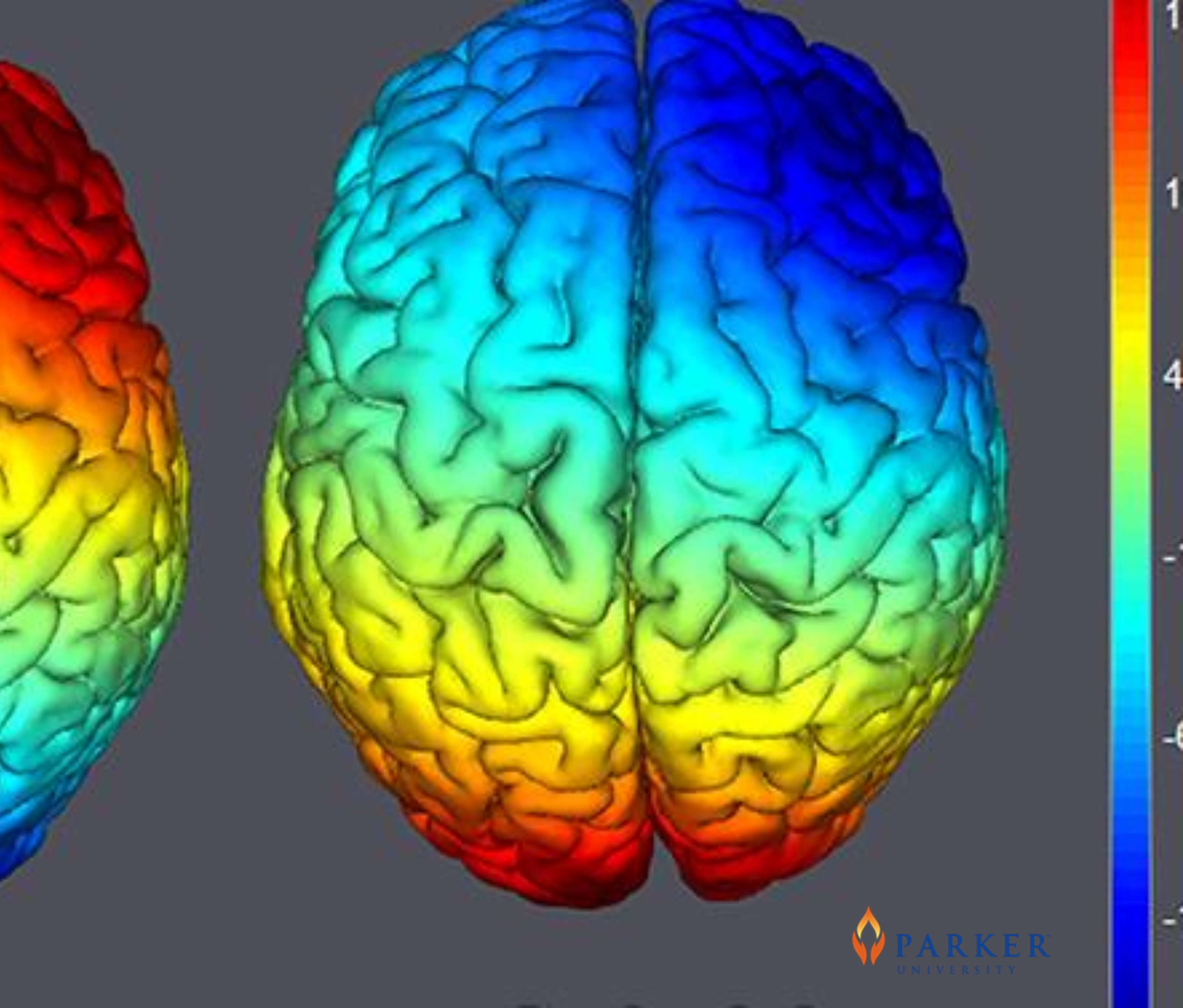


TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) - HISTORY



OBJECTIVES: TDCS

- History of tDCS
- Putative physiology of mechanisms
- Contraindications and potential risks of tDCS
- Review of literature for the role of tDCS in traumatic brain injuries
- Overview of applications of tDCS in the management of traumatic brain injuries
- Use of tDCS for depression
- Use of tDCS for insomnia
- Off label uses of tDCS



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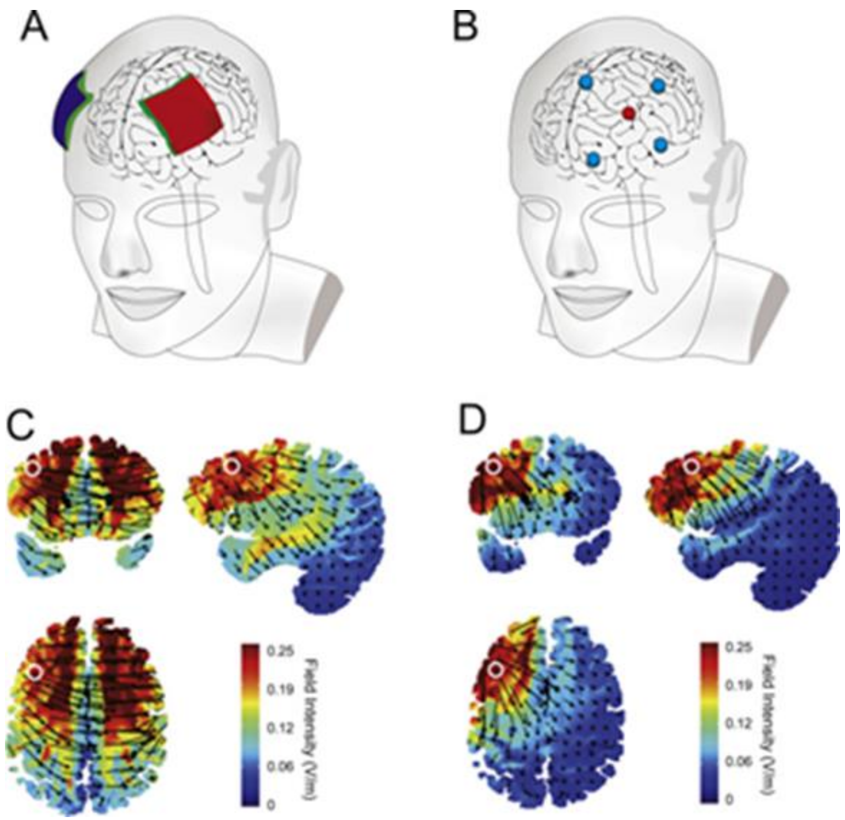
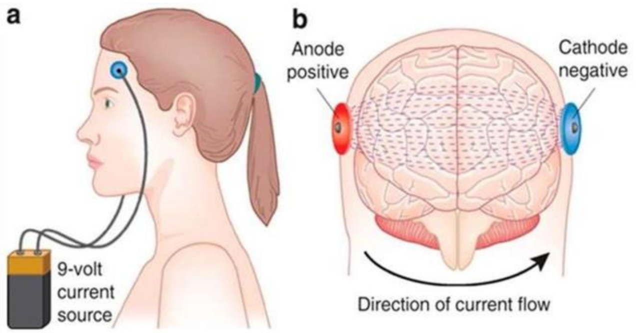
THE DEVICE



TDCS



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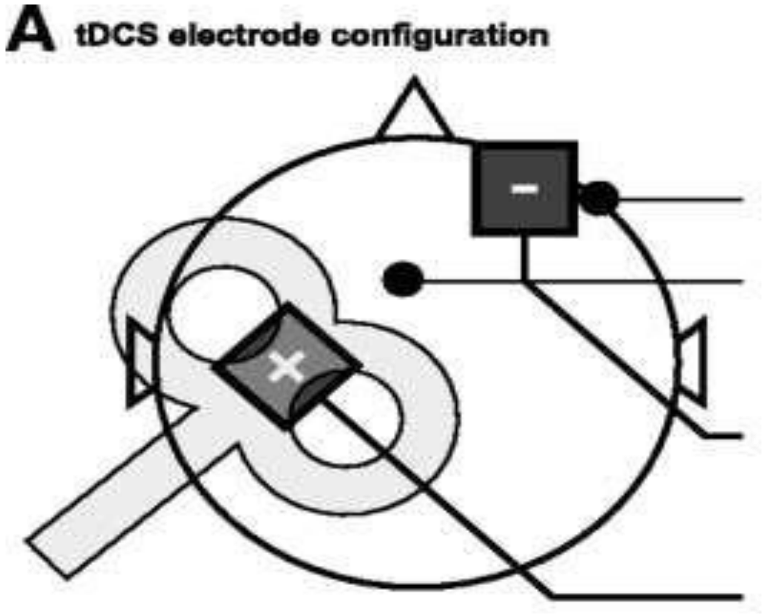
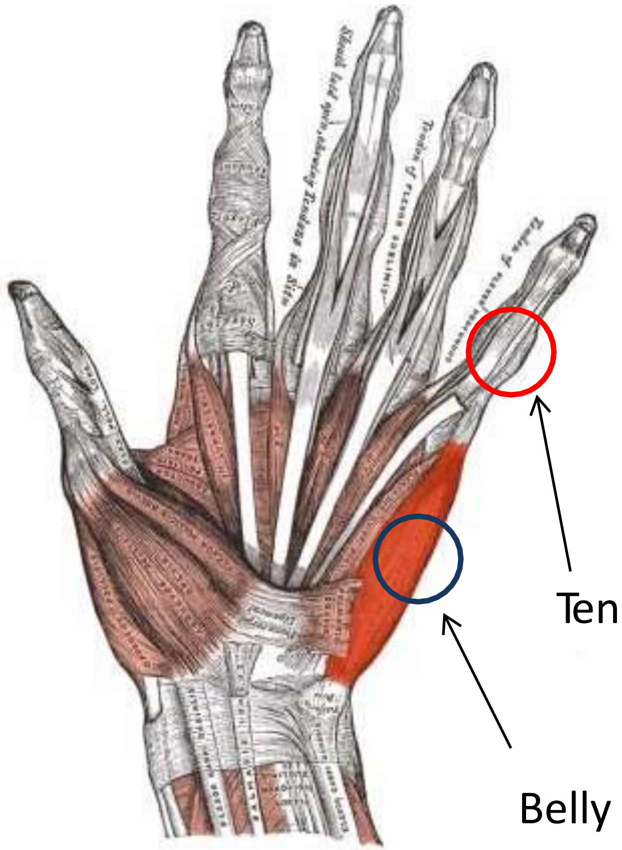
PUTATIVE PHYSIOLOGY: METHODOLOGY

Surface EMG Recordings of TMS induced Motor Evoked Potentials (MEPs)





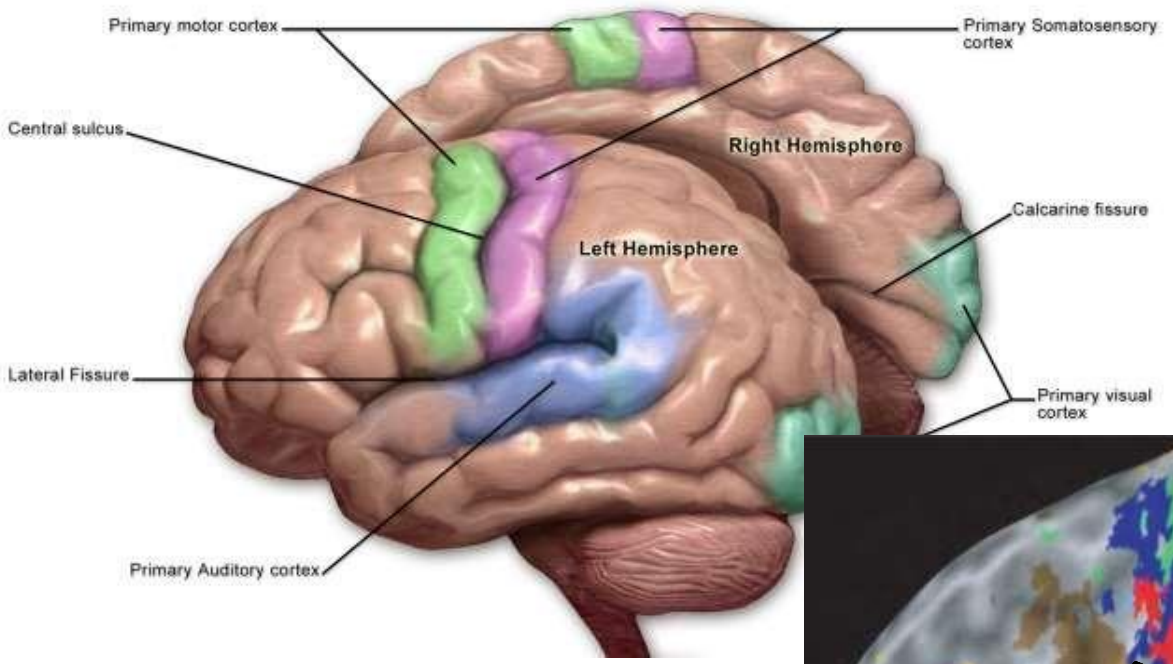
Abductor digiti minimi muscle of the hand (ADM)

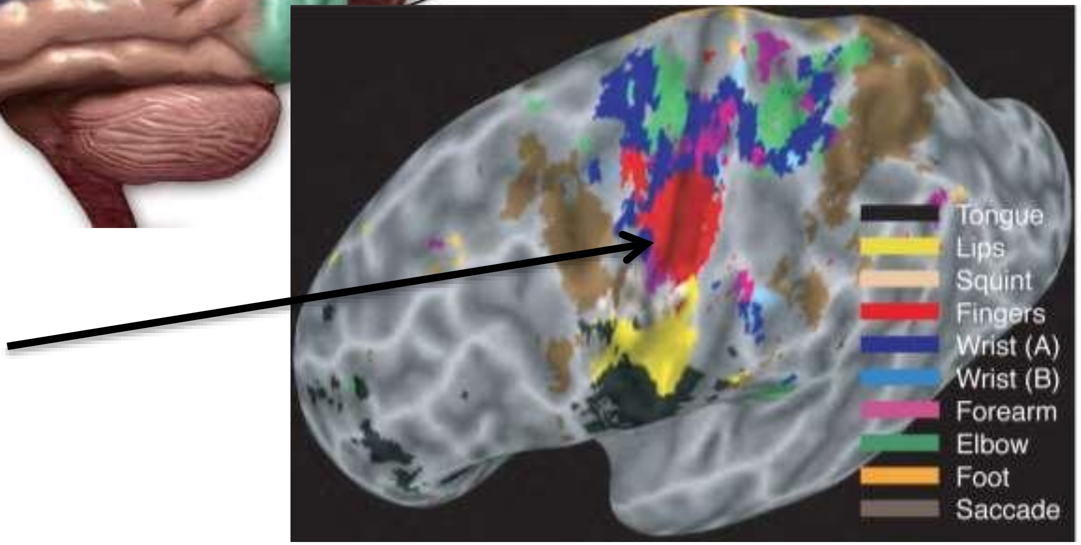
Tendon

Belly

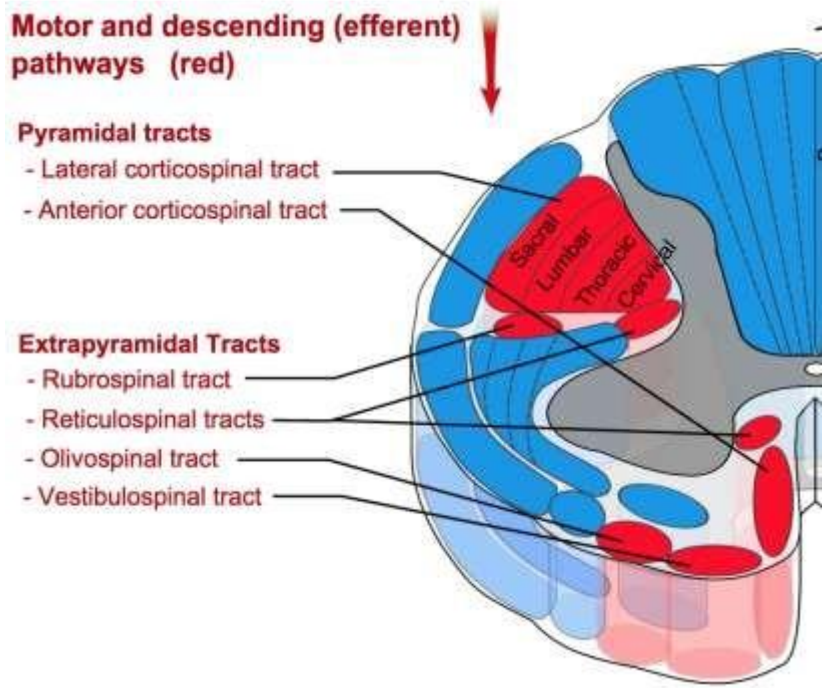
Ag-AgCl electrodes are placed in a "belly-tendon montage"

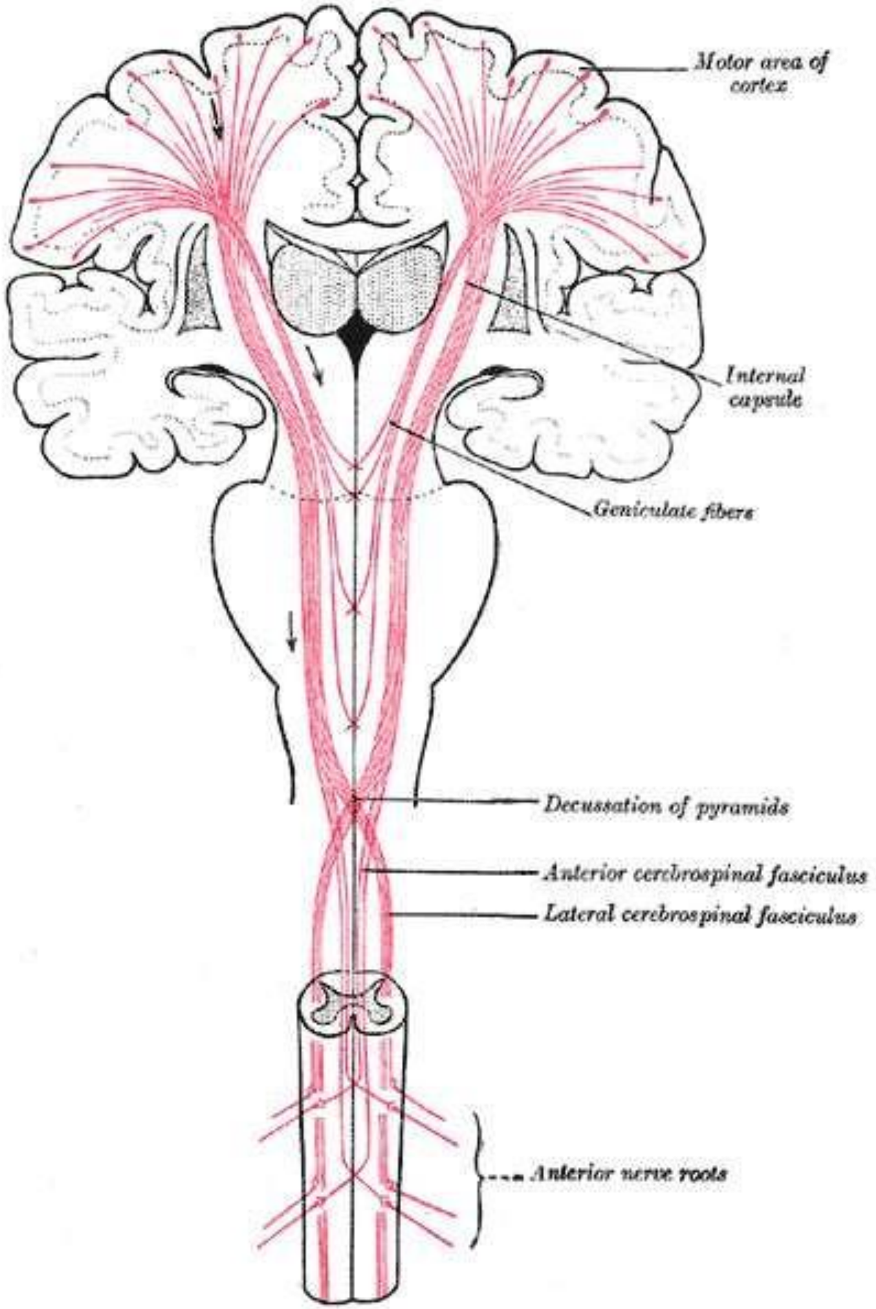
PRIMARY MOTOR CORTEX





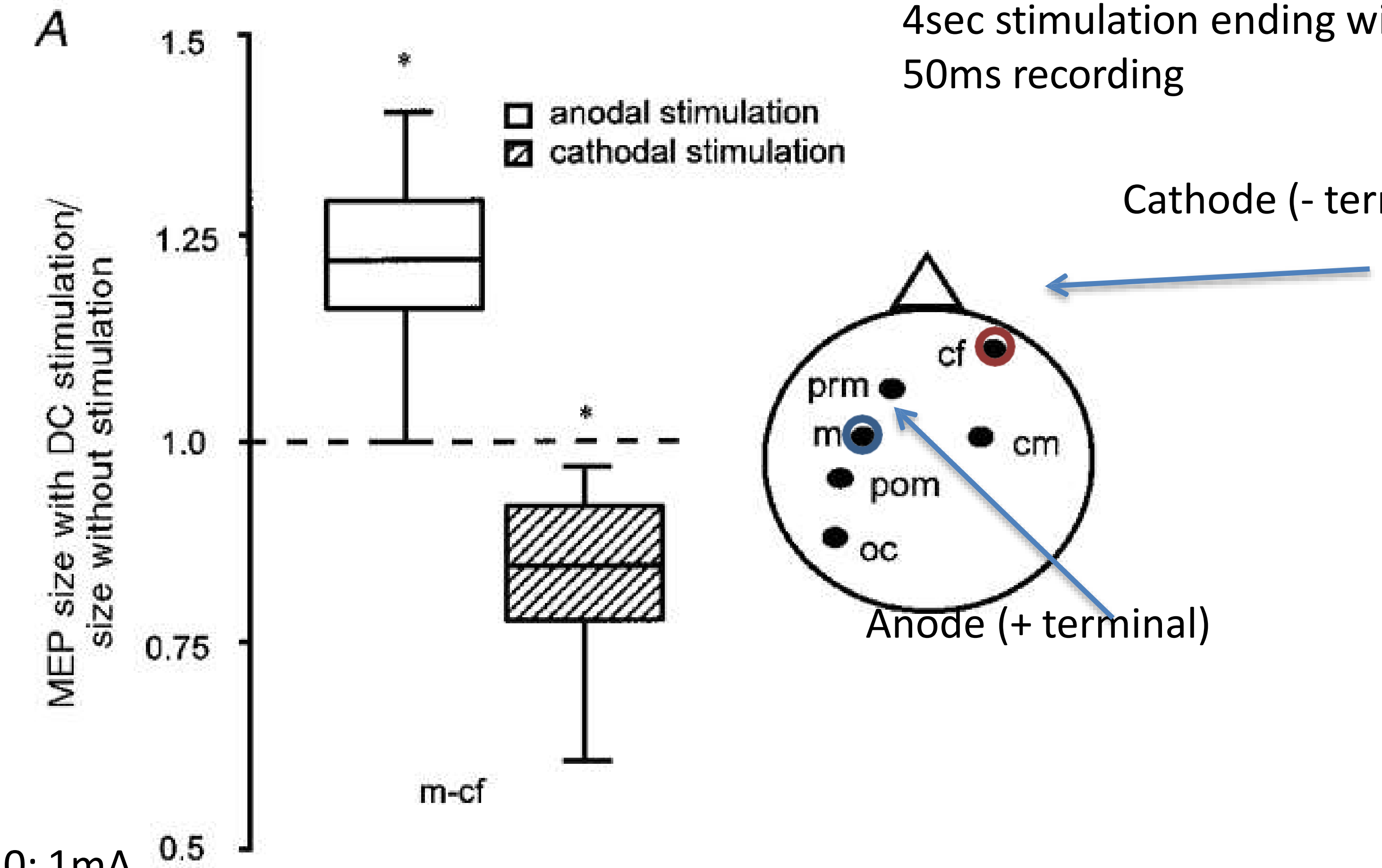
Pyrimidal Tract Neurons:
Corticospinal-Upper motor neurons originating in layer 5 of the cortex terminate in spinal cord and innervate lower motor neuron
Corticobulbular-terminate in brainstem





TDCS MODIFIES 'CORTICAL EXCITABILITY'

4sec stimulation ending with 50ms recording



N=10; 1mA

Nitsche & Paulus. (2000) *J Physiology 527.3*: 633-639

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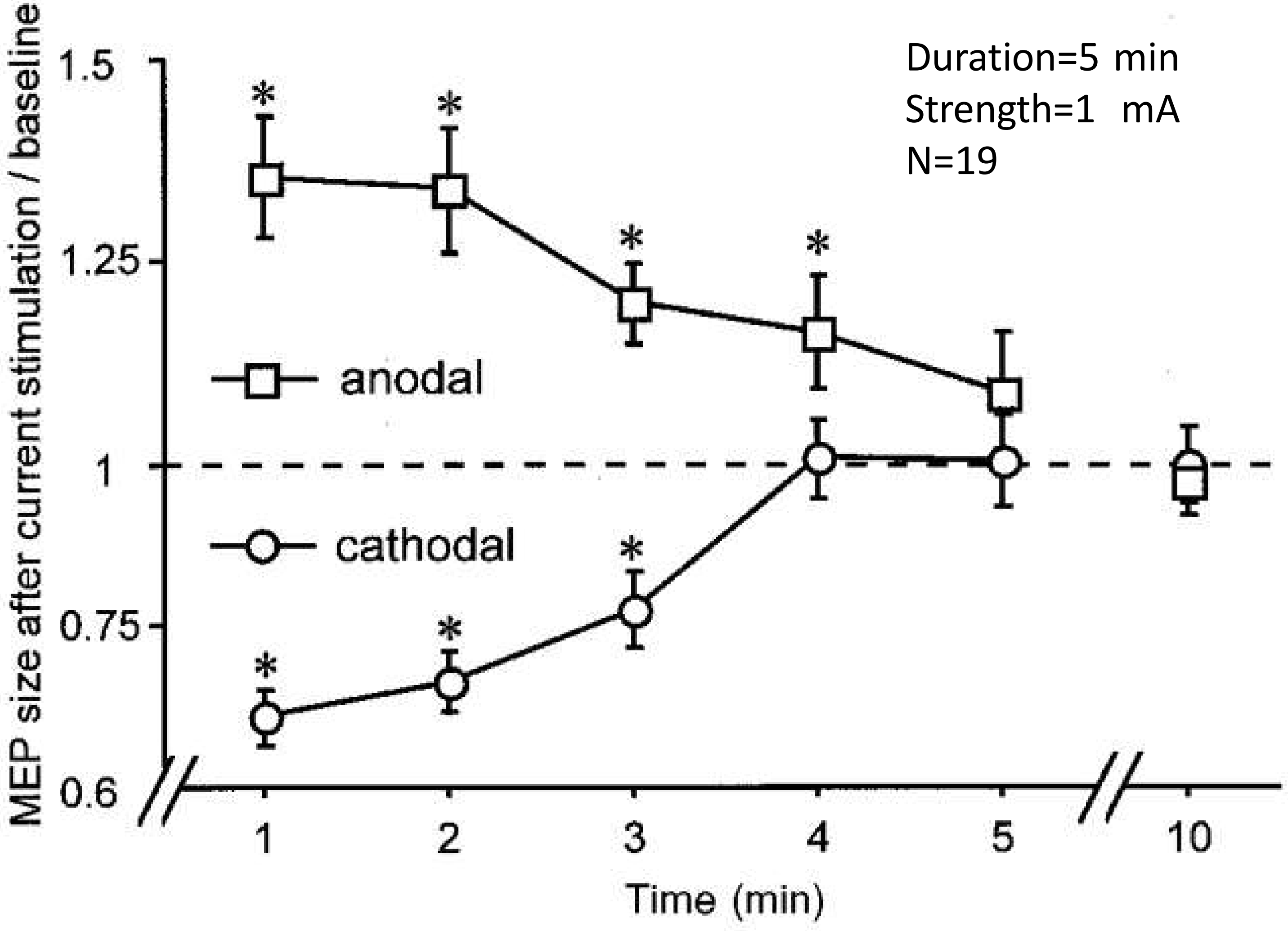
EFFECTS LAST AFTER STIMULATION



Duration=5 min
Strength=1 mA
N=19

Nitsche & Paulus. (2000) *J Physiology 527.3*: 633-639

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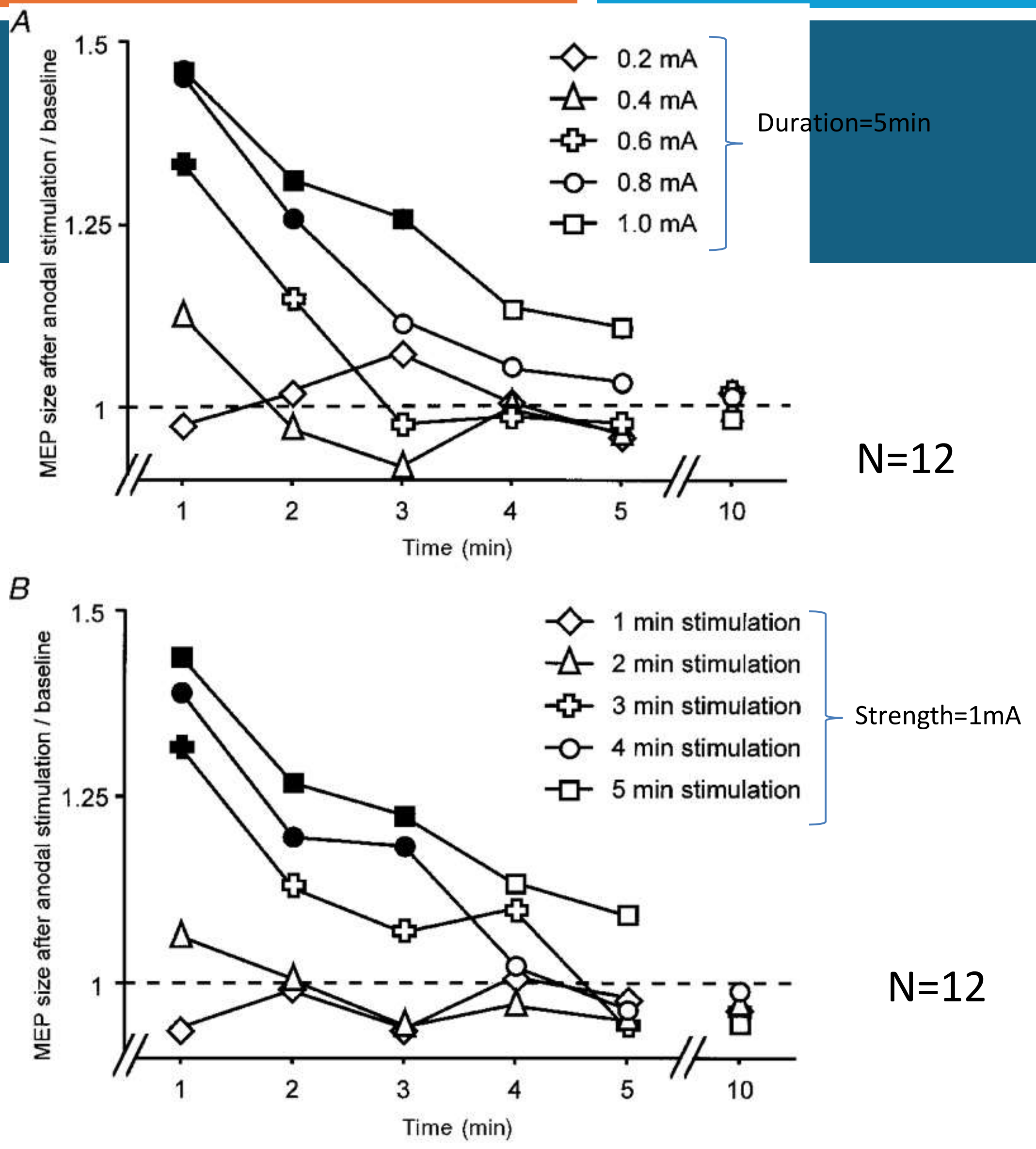
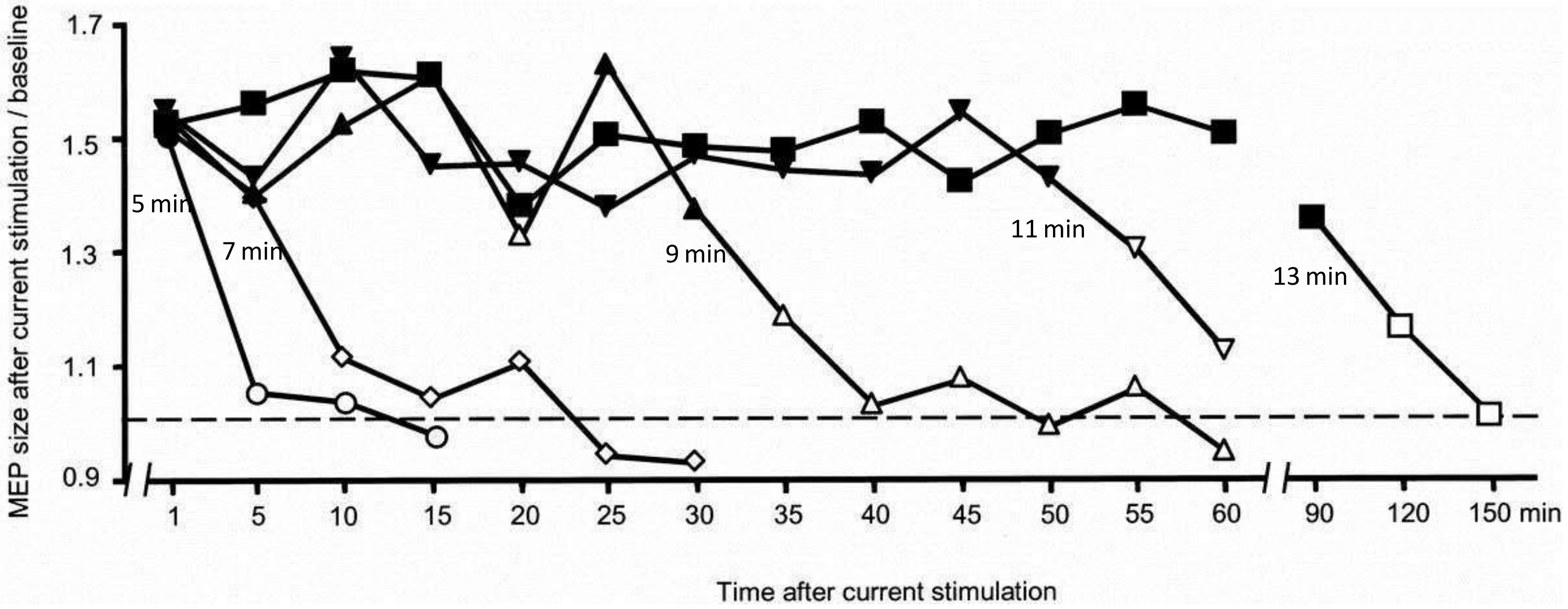
EFFECTS ARE DEPENDENT ON DURATION & STRENGTH



Filled shapes are Significant p>0.5

Nitsche & Paulus. (2000) *J Physiology 527.3*: 633-639

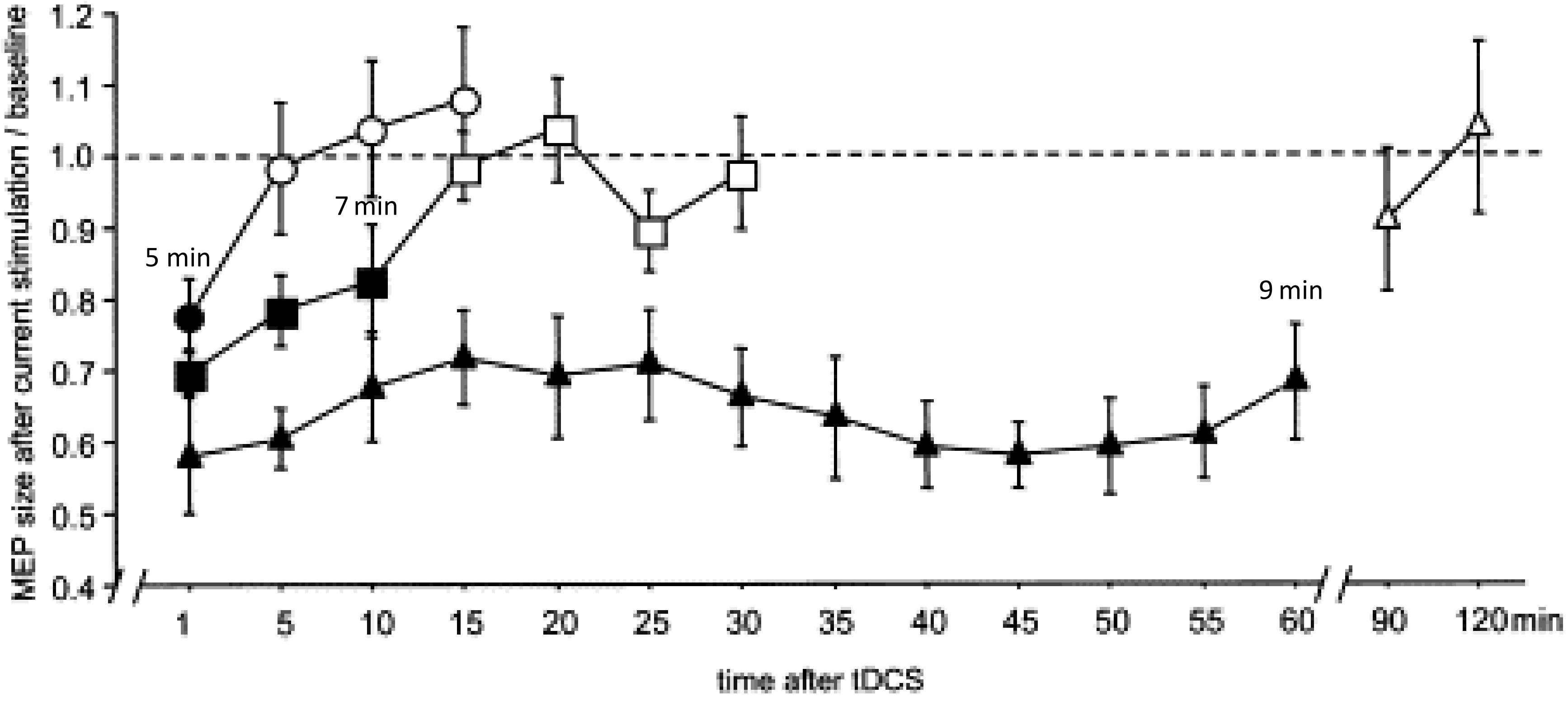
PROLONGED EFFECTS OF ANODAL TDCS



Strength=1mA
N=12

Nitsche & Paulus. (2001) *Neurology 57*: 1899-1901

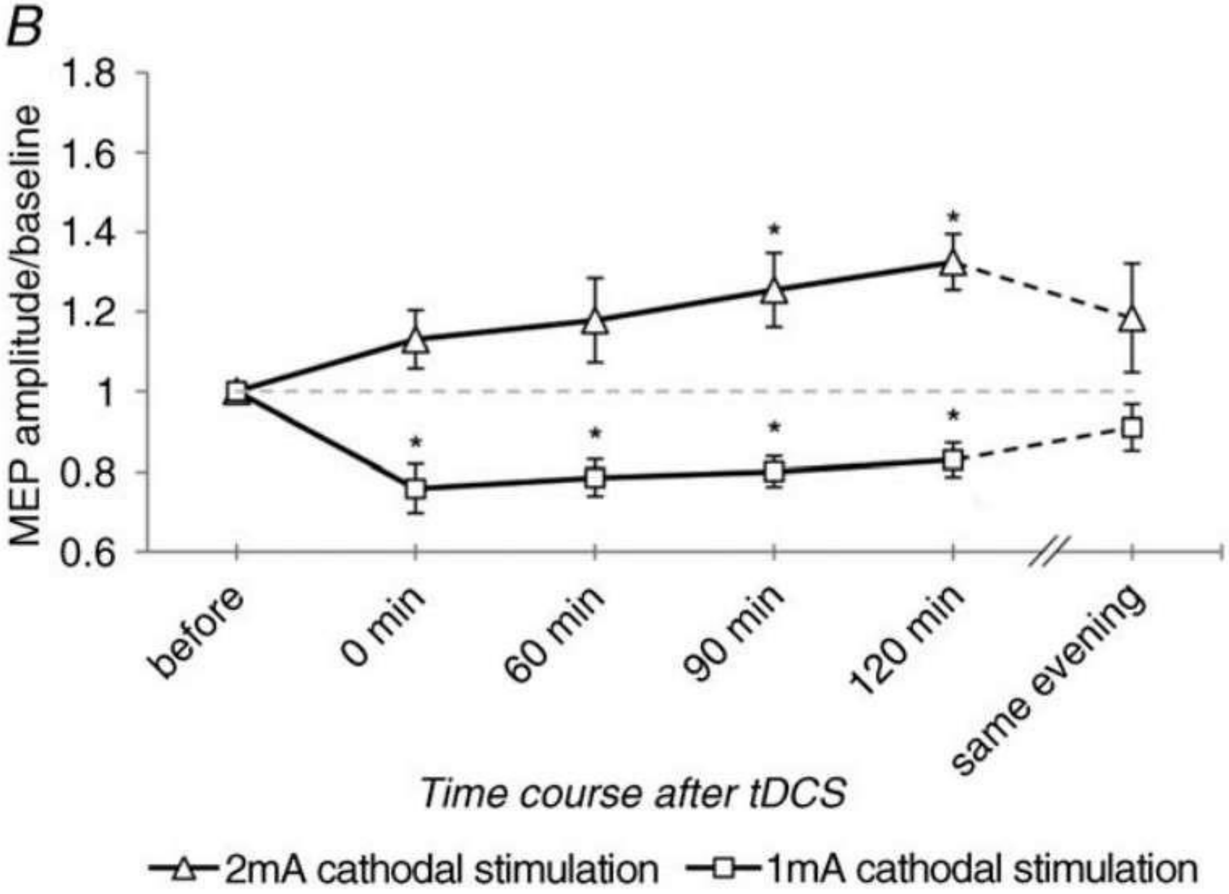
PROLONGED EFFECTS OF CATHODAL TDCS



Strength=1mA
N=12

Nitsche et al. (2003) *Clinical Neurophysiology 114*(4): 600-604

NON-LINEAR EFFECT OF CATHODAL TDCS



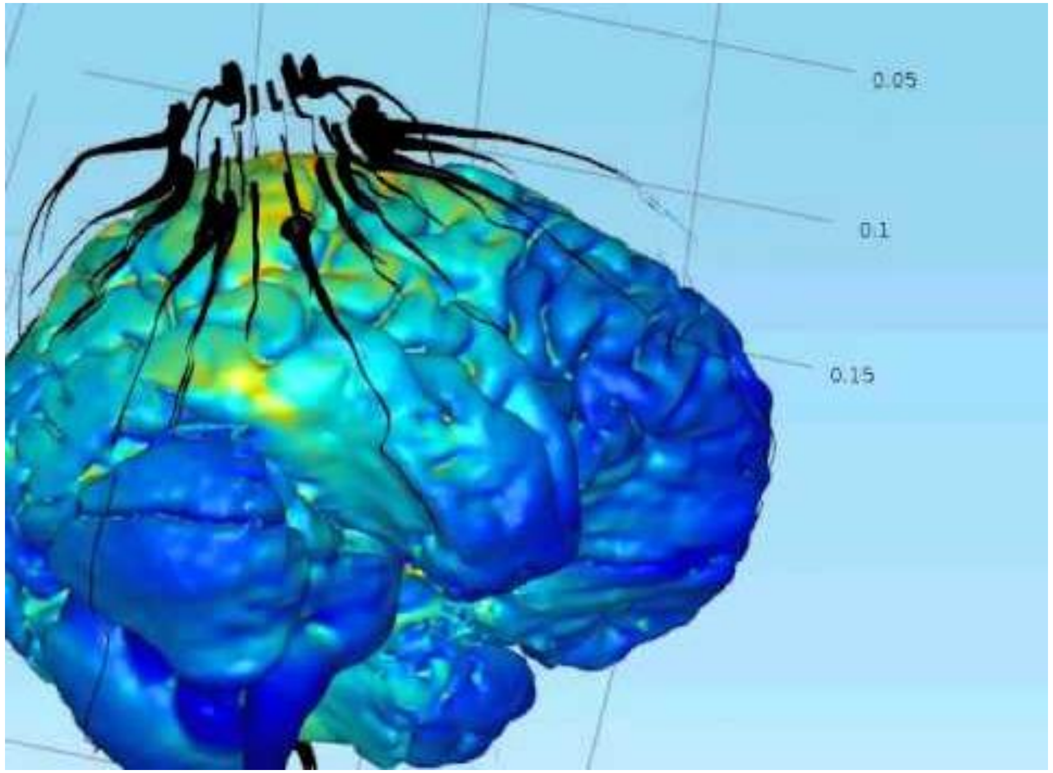
Duration=20min

N_{2mA}=14

N_{1mA}=9

Batsikadze, et al. (2013). *J Physiol 591*(7): 1987-2000

SAFETY OF TDCS



- 63% of studies report 1 mild 'adverse effect'
- Itching, tingling, headache, burning sensation, discomfort
- However:
- Active tDCS Rate = Sham Rate
- Except:
- Skin reddening (Tx w/ Ketoprofen)

Fregni et al. (2014). Clinical Research and Regulatory Affairs, [Early Online]: 1-14.

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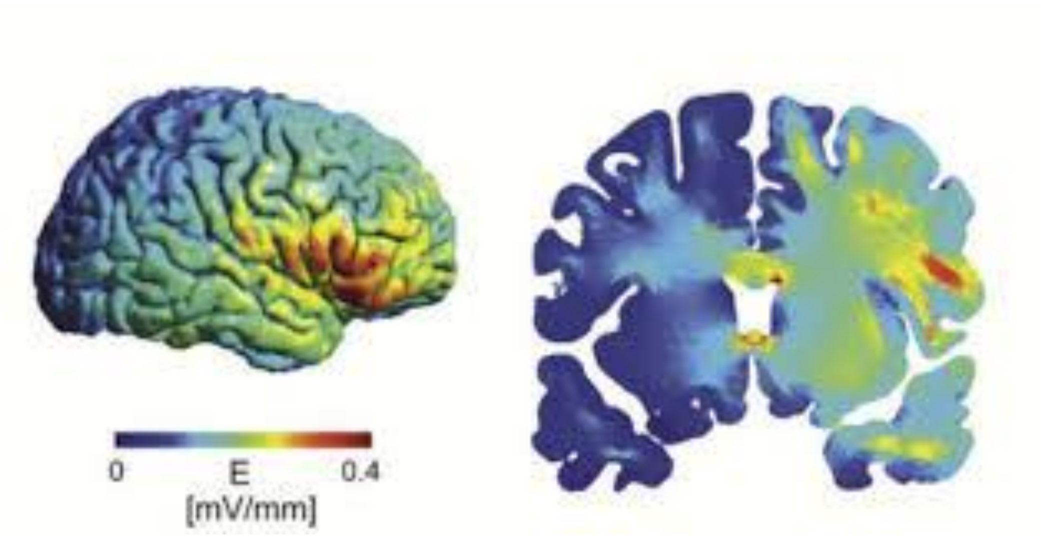
SAFETY: SERIOUS ADVERSE EFFECTS

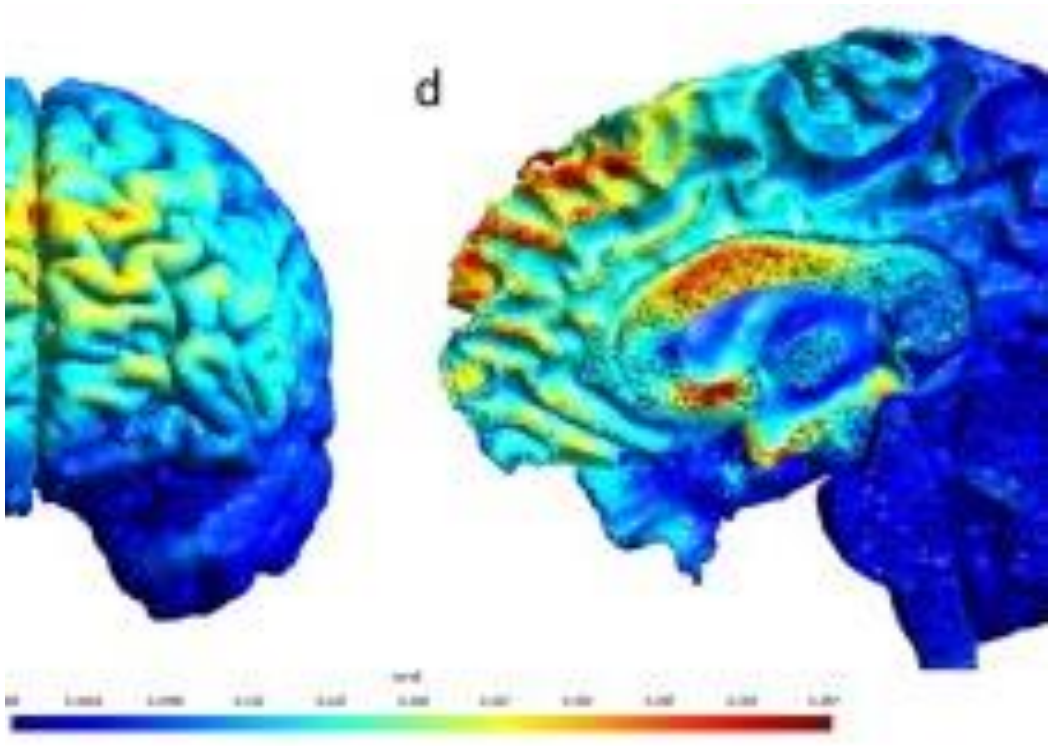
- Review: No “serious adverse events” since 1998 in >10,000 subjects
- 1964 study: “respiratory and motor paralysis”
- Bifrontal anodal electrodes with leg cathode
- 10x intended current strength (likely ~3mA)
- DIY-tDCS concerns



Fregni et al. (2014). Clinical Research and Regulatory Affairs, [Early Online]: 1-14.

Lippold O. C. J., & Redfearn, J. W. T. (1964). Mental changes resulting from the passage of small direct currents through the human brain. 110(469): 768-772

SAFETY: PHYSIOLOGICAL EVIDENCE



No pathological changes in:

- Serum enolase (marker of neuronal damage)
- HRV
- EEG

100x the charge density used in humans is required to cause brain damage in rats

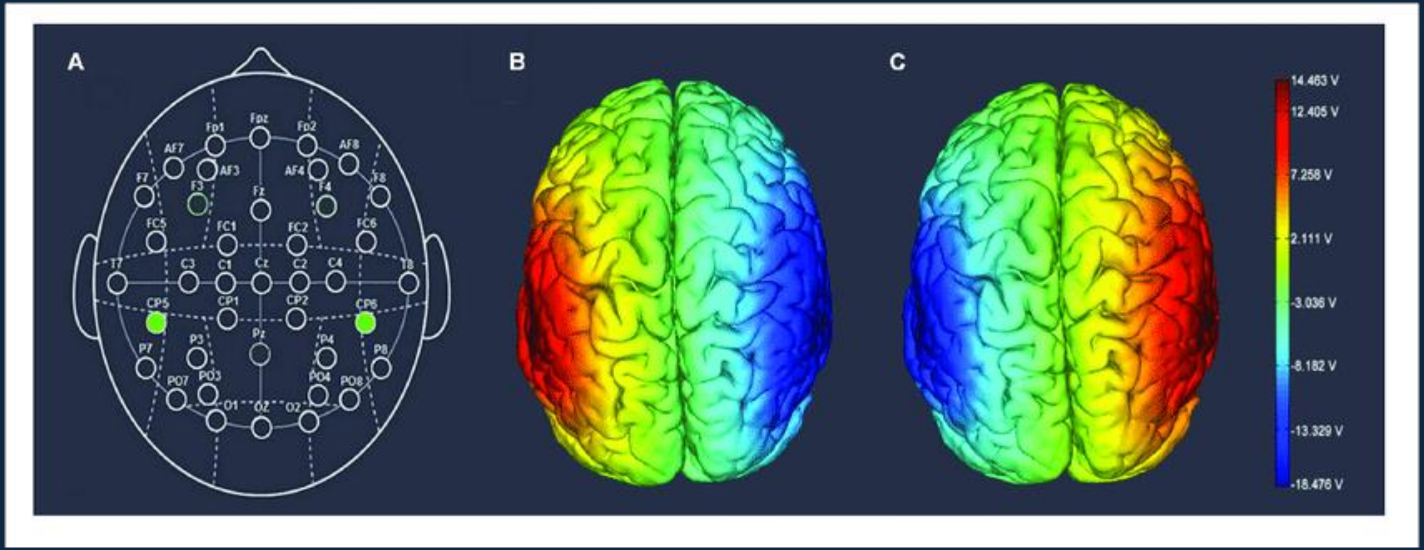
- Discomfort in humans starts at 2-3x

Fregni et al. (2014). Clinical Research and Regulatory Affairs, [Early Online]: 1-14.

SAFETY: STANDARD PARAMETERS

- Current strength <2.5mA
- Duration <60min
- ≤2 sessions per day

- This does not imply going beyond these parameters is not safe



Fregni et al. (2014). Clinical Research and Regulatory Affairs, [Early

Online]: 1-14.

SAFETY: UNKNOWNS

Long term usage

Need for more studies on safety

Fregni et al. (2014). Clinical Research and Regulatory Affairs, [Early

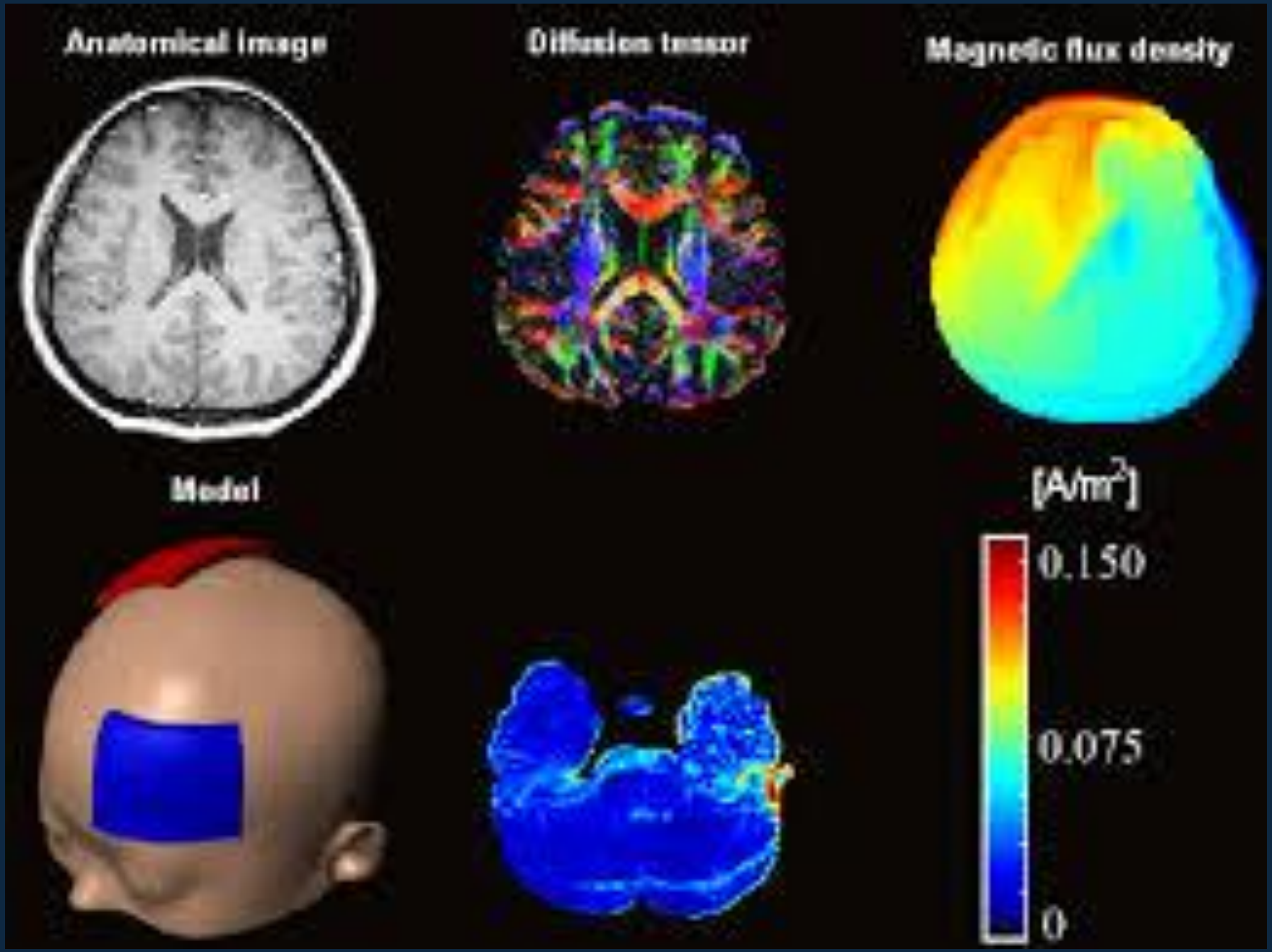
Online]: 1-14.

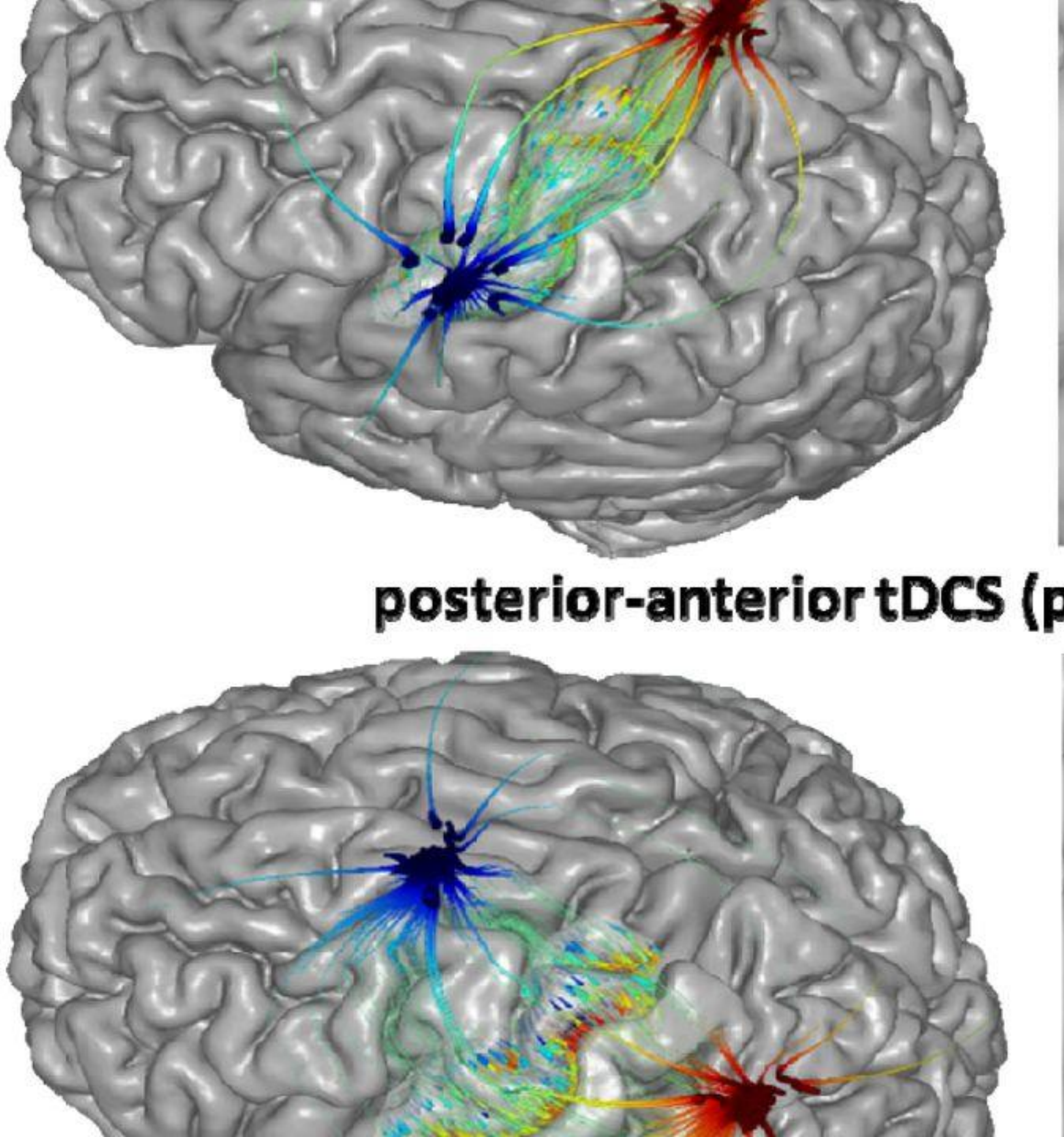
FDA REGULATIONS

- "Medical device"
- Most stimulators are Class II
- "Investigational Device Exception" approval
- "non-significant risk" exception "expedited IDE"
- NSR overwhelmingly applied
- "Minimal Risk"
- "not approved" for any specific condition but is FDA low risk and allowable for off label use

TDCS: OFF LABEL USES

- Traumatic brain injury (TBI)
- Depression
- Insomnia
- PTSD
- Tinnitus
- Stroke Rehabilitation





TDCS: TRAUMATIC BRAIN INJURY

- Not FDA approved – EU approved
- Commonly used off label to increase cortical excitability for rehabilitation
- Used in TBI frequently
- Research using tDCS has been growing exponentially
- TBI research expanding as well and results are very promising

TDCS: TRAUMATIC BRAIN INJURY

Kim et al. Journal of NeuroEngineering and Rehabilitation (2019) 16:14
https://doi.org/10.1186/s12984-019-0489-9

Journal of NeuroEngineering and Rehabilitation

REVIEW Open Access

Transcranial direct current stimulation for the treatment of motor impairment following traumatic brain injury

Won-Seok Kim[1], Kiwon Lee[2], Seonghoon Kim[2], Sungmin Cho[3] and Nam-Jong Paik[1*]

Abstract

After traumatic brain injury (TBI), motor impairment is less common than neurocognitive or behavioral problems. However, about 30% of TBI survivors have reported motor deficits limiting the activities of daily living or participation. After acute primary and secondary injuries, there are subsequent changes including increased GABA-mediated inhibition during the subacute stage and neuroplastic alterations that are adaptive or maladaptive during the chronic stage. Therefore, timely and appropriate neuromodulation by transcranial direct current stimulation (tDCS) may be beneficial to patients with TBI for neuroprotection or restoration of maladaptive changes.

Technologically, combination of imaging-based modelling or simultaneous brain signal monitoring with tDCS could result in greater individualized optimal targeting allowing a more favorable neuroplasticity after TBI. Moreover, a combination of task-oriented training using virtual reality with tDCS can be considered as a potent tele-rehabilitation tool in the home setting, increasing the dose of rehabilitation and neuromodulation, resulting in better motor recovery.

This review summarizes the pathophysiology and possible neuroplastic changes in TBI, as well as provides the general concepts and current evidence with respect to the applicability of tDCS in motor recovery. Through its endeavors, it aims to provide insights on further successful development and clinical application of tDCS in motor rehabilitation after TBI.

Keywords: Traumatic brain injuries, Transcranial direct current stimulation, Recovery of function, Rehabilitation, Neuronal plasticity, Electroencephalography, Functional near infrared spectroscopy, Virtual reality

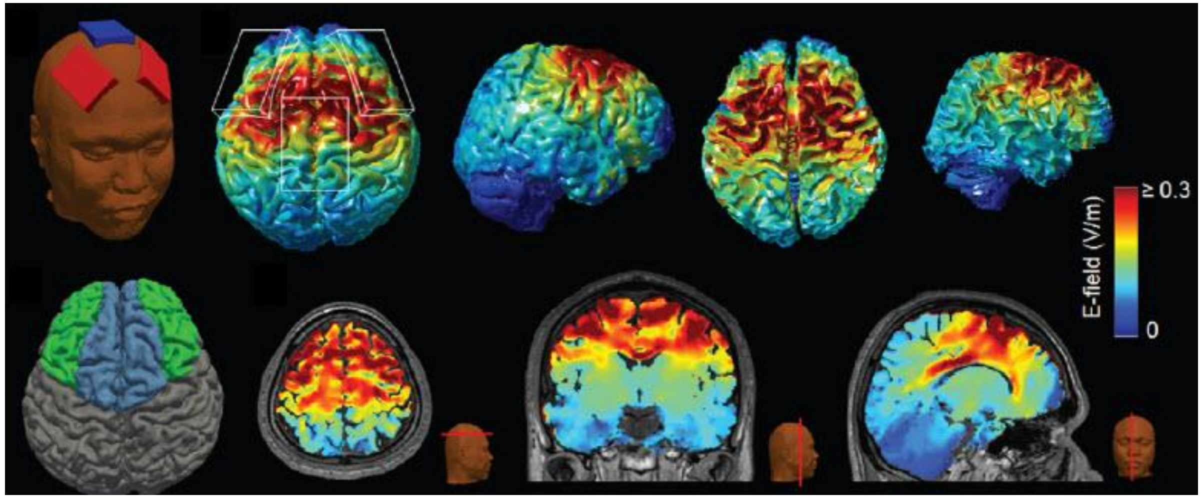
Background

Traumatic brain injury (TBI) is defined as "an alteration in brain function (loss of consciousness, post-traumatic amnesia, and neurologic deficits) or other evidence of brain pathology (visual, neuroradiologic, or laboratory confirmation of damage to the brain) caused by external force" [1]. The incidence and prevalence of TBI are substantial and increasing in both developing and developed countries. TBI in older age groups due to falling has been on the rise in recent years, becoming the prevalent condition in all age groups [2, 3]. TBI causes broad spectrum of impairments, including cognitive, psychological, sensory or motor impairments [4, 5], which may increase the socioeconomic burdens and reduce the quality of life [6, 7]. Although motor impairment, such as limb weakness, gait disturbance, balance problem, dystonia or spasticity, is less common than neurocognitive or behavioral problems after TBI, about 30% of TBI survivors have reported motor deficits that severely limited activities of daily living or participation [8].

Motor impairment after TBI is caused by both focal and diffuse damages, making it difficult to determine the precise anatomo-clinical correlations [9, 10]. According to previous clinical studies, recovery after TBI also seems worse than that after stroke, although the neuroplasticity after TBI may also play an important role for recovery [11]. Therefore, a single unimodal approach for motor recovery, including conventional rehabilitation, may be limiting, and hence, requiring a novel therapeutic modality to improve the outcome after TBI.

* Correspondence: njpaik@snu.ac.kr
[1] Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Republic of Korea
Full list of author information is available at the end of the article

TDCS: TRAUMATIC BRAIN INJURY



HHS Public Access

Author manuscript

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Cerebral Hemodynamics after Transcranial Direct Current Stimulation (tDCS) in Patients with Consequences of Traumatic Brain Injury

Alexey O. Trofimov[1], George Kalentiev[1], Michael Karelsky[1], Cristina Ksenofontova[1], Alevtina Ruzavina[1], Michail Yuriev[1], and Denis E. Bragin[2]

[1]Department of Neurosurgery, Nizhniy Novgorod State Medical Academy, 10/1, Minin Str., Nizhniy Novgorod, 603950, Russia

[2]Department of Neurosurgery, University of New Mexico School of Medicine, 1 University of New Mexico, MSC 10 5615 Neurosurgery, Albuquerque, NM 87131, USA

Abstract

In recent years, hopes for better treatment of traumatic brain injury (TBI) have focused on non-pharmacologic transcranial electrical brain stimulation; however, studies of perfusion changes after stimulation are few and contradictory. Therefore, the aim of this study was to assess cerebral perfusion after high-definition transcranial direct current stimulation (HD-tDCS) in patients with posttraumatic encephalopathy (PTE).

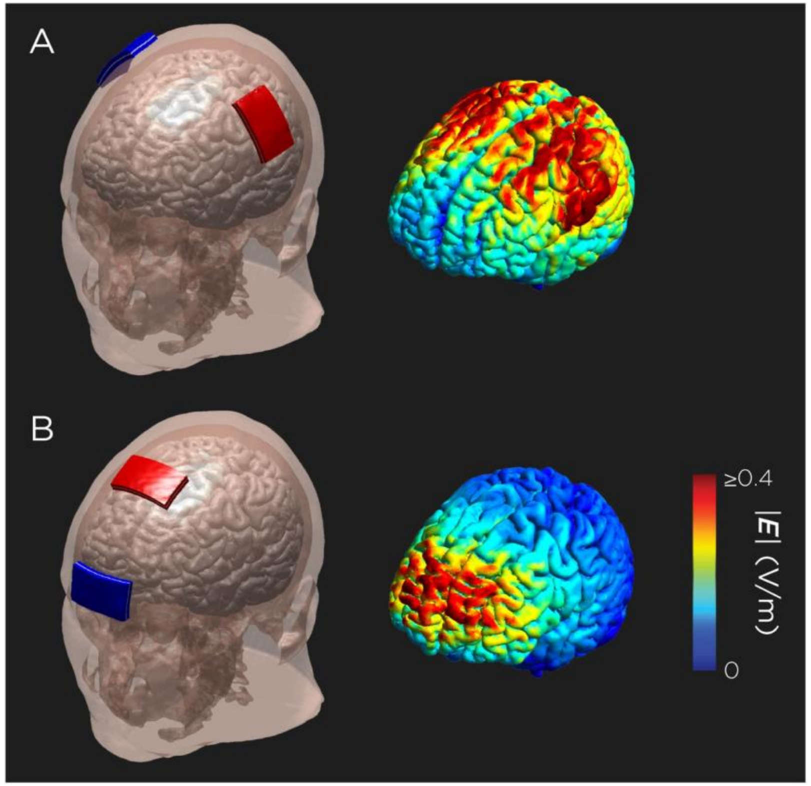
Methods.—Twenty patients with PTE (16 men and 4 women, aged 35.5 ± 14.8 years) underwent perfusion computed tomography (PCT), followed by anodal HD-tDCS and post-stimulation tomography at 21 days after TBI. The Westermark perfusion maps were constructed and quantitative per-fusion parameters calculated. Significance was preset to $P < 0.05$.

Results.—Qualitative analysis revealed that all patients had areas with reduced cerebral blood flow (CBF) and increased average mean transit time (MTT). HD-tDCS was accompanied by a significant decrease in the number of zones of both hypoperfusion and ischemia ($p < 0.05$). Quantitative analysis showed that, in all patients, HD-tDCS caused a significant increase in CBF ($p < 0.001$), cerebral blood volume (CBV) ($p < 0.01$) and MTT shortening ($p < 0.05$) in the frontotemporal region on the anode side. In the basal ganglia, a significant increase in CBF was found only in the 5 patients in whom this was initially reduced ($p < 0.01$) and only with an anode placed on the same side.

Conclusions.—In patients with complications due to PTE TBI, HD-tDCS causes a significant increase in CBV, CBF and a decrease in the average MTT, suggesting better oxygen delivery to tissue.

PARKER UNIVERSITY

TDCS: TRAUMATIC BRAIN INJURY



Transcranial direct current stimulation (tDCS) effects on traumatic brain injury (TBI) recovery

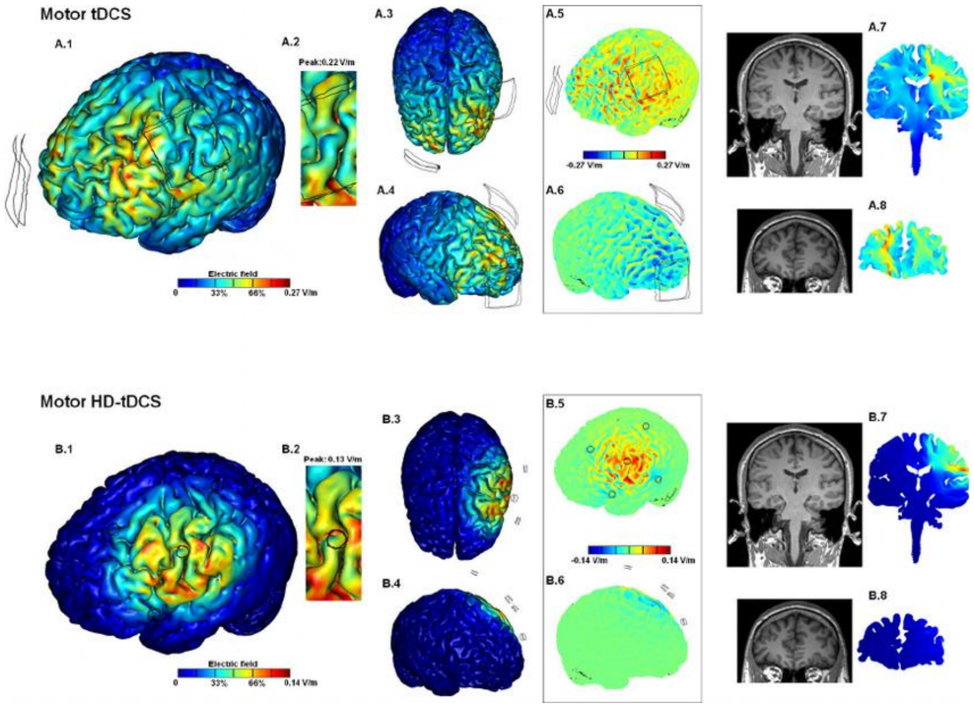
A systematic review

Ana Luiza Zaninotto[1], Mirret M. El-Hagrassy[2], Jordan R. Green[1], Maíra Babo[3], Vanessa Maria Paglioni[3], Glaucia Guerra Benute[4], Wellingson Silva Paiva[3]

ABSTRACT. Traumatic brain injury (TBI) is a major cause of chronic disability. Less than a quarter of moderate and severe TBI patients improved in their cognition within 5 years. Non-invasive brain stimulation, including transcranial direct current stimulation (tDCS), may help neurorehabilitation by boosting adaptive neuroplasticity and reducing pathological sequelae following TBI. **Methods:** we searched MEDLINE/PubMed and Web of Science databases. We used Jadad scale to assess methodological assumptions. **Results:** the 14 papers included reported different study designs; 2 studies were open-label, 9 were crossover randomized clinical trials (RCTs), and 3 were parallel group RCTs. Most studies used anodal tDCS of the left dorsolateral prefrontal cortex, but montages and stimulation parameters varied. Multiple studies showed improved coma recovery scales in disorders of consciousness, and improved cognition on neuropsychological assessments. Some studies showed changes in neurophysiologic measures (electroencephalography (EEG) and transcranial magnetic stimulation (TMS), correlating with clinical findings. The main methodological biases were lack of blinding and randomization reports. **Conclusion:** tDCS is a safe, non-invasive neuromodulatory technique that can be given as monotherapy but may be best combined with other therapeutic strategies (such as cognitive rehabilitation and physical therapy) to further improve clinical cognitive and motor outcomes. EEG and TMS may help guide research due to their roles as biomarkers for neuroplasticity.

Key words: traumatic brain injury, neuronal plasticity, rehabilitation, non-invasive brain stimulation, transcranial direct current stimulation.

TDCS: TRAUMATIC BRAIN INJURY



Hindawi
Neural Plasticity
Volume 2017, Article ID 1372946, 7 pages
https://doi.org/10.1155/2017/1372946

Research Article

Anodal Transcranial Direct Current Stimulation Provokes Neuroplasticity in Repetitive Mild Traumatic Brain Injury in Rats

Ho Jeong Kim[1] and Soo Jeong Han[2]

[1]*Department of Rehabilitation Medicine, Seonam Hospital, Ewha Womans University Medical Center, Seoul, Republic of Korea*
[2]*Department of Rehabilitation Medicine, School of Medicine, Ewha Womans University, Seoul, Republic of Korea*

Correspondence should be addressed to Soo Jeong Han; ocrystal@ewha.ac.kr

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Academic Editor: Andrea Turolla

Repetitive mild traumatic brain injury (rmTBI) provokes behavioral and cognitive changes. But the study about electrophysiologic findings and managements of rmTBI is limited. In this study, we investigate the effects of anodal transcranial direct current stimulation (tDCS) on rmTBI. Thirty-one Sprague Dawley rats were divided into the following groups: sham, rmTBI, and rmTBI treated by tDCS. Animals received closed head mTBI three consecutive times a day. Anodal tDCS was applied to the left motor cortex. We evaluated the motor-evoked potential (MEP) and the somatosensory-evoked potential (SEP). T2-weighted magnetic resonance imaging was performed 12 days after rmTBI. After rmTBI, the latency of MEP was prolonged and the amplitude in the right hind limb was reduced in the rmTBI group. The latency of SEP was delayed and the amplitude was decreased after rmTBI in the rmTBI group. In the tDCS group, the amplitude in both hind limbs was increased after tDCS in comparison with the values before rmTBI. Anodal tDCS after rmTBI seems to be a useful tool for promoting transient motor recovery through increasing the synchronicity of cortical firing, and it induces early recovery of consciousness. It can contribute to management of concussion in humans if further study is performed.

TDCS AND TBI

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Original Investigation

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Published Online: 13.02.2024

Effects of Transcranial Direct Current Stimulation on Motor and Cognitive Dysfunction in an Experimental Traumatic Brain Injury Model

Guven AKCAY[1], Filiz DEMIRDOGEN[2], Tuba GUL[3], Ali YILMAZ[4], Dilcan KOTAN[5], Esra KARAKOC[6], Huseyin Emre OZTURK[6], Cagla CELIK[7], Haydar CELIK[8], Yavuz ERDEM[8]

[1]Hitit University, Faculty of Medicine, Department of Biophysics, Çorum, Türkiye
[2]Binali Yildirim University, Mengücek Gazi Education and Research Hospital, Department of Neurology, Erzincan, Türkiye
[3]Ordu University, Faculty of Medicine, Department of Neurology, Ordu, Türkiye
[4]Ordu University, Faculty of Medicine, Department of Neurosurgery, Ordu, Türkiye
[5]Sakarya University, Training and Research Hospital, Department of Neurology, Sakarya, Türkiye
[6]Hitit University, Medicine Student, Çorum, Türkiye
[7]Hitit University, Vocational School of Health Services, Pharmacy Services Program, Çorum, Türkiye
f Neurosurgery, Ankara, Türkiye

ɣibu@gmail.com

ABSTRACT

AIM: To investigate the therapeutic and neuroprotective effects of transcranial direct current stimulation (tDCS) application on the traumatic brain injury (TBI)-induced glutamate and calcium excitotoxicity and loss of motor and cognitive functions.

MATERIAL and METHODS: Forty rats were equally divided in the sham, TBI, tDCS + TBI + tDCS, and TBI + tDCS groups. Mild TBI was induced by dropping a 450-g iron weight from a height of 1 m onto the skull of the rats. The tDCS + TBI + tDCS group was prophylactically administered 1 mA stimulation for 30 min for 7 days starting 5 days before inducing TBI. In the TBI + tDCS group, tDCS (1 mA for 30 min) was administered 2 h after TBI, on days 1 and 2. Cognitive and locomotor functions were assessed using the novel object recognition and open field tests. The calcium, glutamate, and N-methyl-D-aspartate receptor 1 (NMDAR1) levels in the hippocampus were measured using enzyme-linked immunosorbent assay.

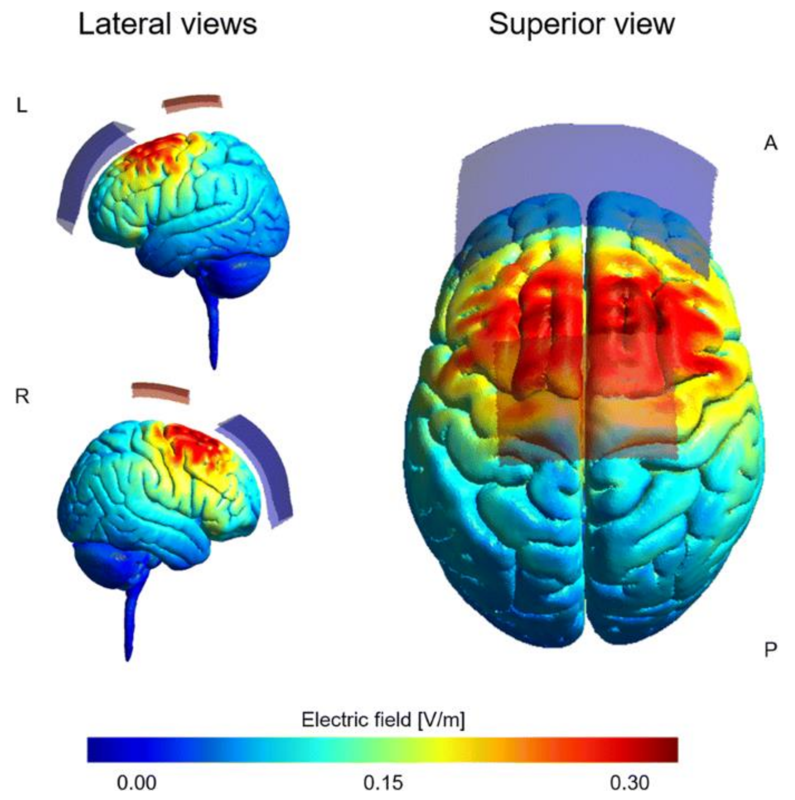
RESULTS: Although the motor and cognitive functions were substantially reduced in the TBI group when compared with the sham, they improved in the treatment groups ($p<0.05$). The calcium, glutamate, and NMDAR1 levels were considerably higher in the TBI group than in the sham ($p < 0.001$). However, they were considerably lower in the tDCS + TBI + tDCS and TBI + tDCS groups than in the TBI groups ($p < 0.05$). In particular, the change in the tDCS + TBI + tDCS group was higher than that in the TBI + tDCS group.

CONCLUSION: Application of tDCS before the development of TBI improved motor and cognitive dysfunction. It demonstrated a neuroprotective and therapeutic effect by reducing the excitotoxicity via the regulation of calcium and glutamate levels.

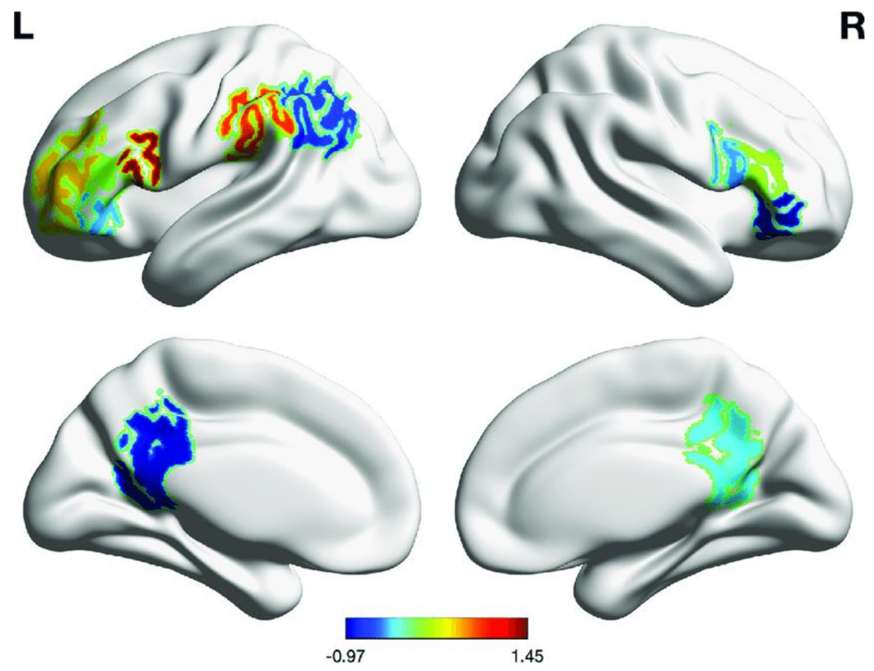
KEYWORDS: Calcium, Glutamate, N-methyl-d-aspartate receptor, Transcranial direct current stimulation, Traumatic brain injury, Rat

TDCS FOR DEPRESSION

- Clinical depression is at an all time high in the USA and the world
- Billions of dollars in pharmaceutical costs and lost workdays/productivity
- ECT and r TMS have been shown to be effective
- ECT and rTMS are both FDA approved
- tDCS has great promise for ease of use, safety and costs



TDCS:DEPRESSION



Brain Stimulation 12 (2019) 1475–1483

Contents lists available at ScienceDirect

Brain Stimulation

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Transcranial direct current stimulation (tDCS) for depression in pregnancy: A pilot randomized controlled trial

Simone N. Vigod [a, b, *], Kellie E. Murphy [a, c], Cindy-Lee Dennis [a, d], Tim F. Oberlander [e], Joel G. Ray [a, d], Zafiris J. Daskalakis [a, f], Daniel M. Blumberger [a, f]

[a] University of Toronto, Toronto, Ontario, Canada
[b] Women's College Hospital and Research Institute, Toronto, Ontario, Canada
[c] Sinai Health System, Toronto, Ontario, Canada
[d] St. Michael's Hospital, Li Ka Shing Knowledge Translation Institute, Toronto, Ontario, Canada
[e] BC Children's Hospital Research Institute, University of British Columbia, Vancouver, BC, Canada
[f] Temerty Centre for Therapeutic Brain Intervention and Campbell Family Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

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Keywords:
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Pregnancy
Antenatal depression
tDCS
Antidepressive agents

A B S T R A C T

Background: Depression in pregnancy negatively affects maternal-child health. Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation treatment for depression, has not been evaluated in pregnancy.
Objective: To conduct a pilot randomized controlled trial (RCT) to evaluate tDCS for antenatal depression.
Methods: In this pilot RCT in Toronto, Ontario (October 2014 to December 2016), adult pregnant women 14–32 weeks gestation with major depressive disorder who had declined antidepressant medication were considered for inclusion. Participants were randomly assigned 1:1 to tDCS or sham-control. Active tDCS comprised 30-min sessions of 2 mAmp direct current delivered over the dorsolateral prefrontal cortex, 5 days per week, for 3 weeks. Sham was administered similarly, but with current turned off after 30 s. Main outcomes were feasibility, acceptability, and protocol adherence. Maternal Montgomery Asperg Depression Rating Scale (MADRS) was measured post-treatment and at 4 and 12 weeks postpartum.
Results: Of 20 women randomized, 16 completed treatment and provided data (124 tDCS, 122 sham sessions). Views of treatment were positive with no serious adverse events. Post-treatment estimated marginal mean MADRS scores were 11.8 (standard error, SE 2.66) for tDCS and 15.4 (SE 2.51) for sham ($p = 0.34$). At 4 weeks postpartum, 75.0% of tDCS women were remitted versus 12.5% sham-control ($p = 0.04$).
Conclusions: Results support proceeding to a definitive RCT to evaluate tDCS for antenatal depression. The preliminary efficacy estimates immediately post-treatment and in the postpartum, are encouraging with respect to the potential use of tDCS to improve treatment rates in this population. The trial was registered at: clinical trials.gov (NCT02116127).

PARKER UNIVERSITY

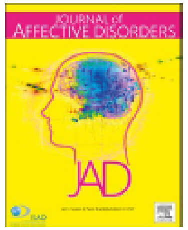
TDCS:DEPRESSION

Journal of Affective Disorders 252 (2019) 475–483

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad



Research paper

Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression

Angelo Alonzo[a,*], Joanna Fong[a], Nicola Ball[a], Donel Martin[a], Nicholas Chand[a], Colleen Loo[a,b]

[a] *School of Psychiatry, University of New South Wales/Black Dog Institute, Hospital Road, Randwick, NSW 2031, Australia*
[b] *St George Hospital, South Eastern Sydney Health, Level 2, James Laws House, Gray St, Kogarah, NSW 2217, Australia*

ARTICLE INFO

Keywords:
Major depressive disorder
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Clinical trial
Safety
Psychiatric somatic therapies

ABSTRACT

Background: Transcranial Direct Current Stimulation (tDCS) is a non-invasive, neuromodulation approach with promising efficacy for treating depression. To date, tDCS has been limited to clinical or research centre settings with treatment administered by staff. The aim of this study is to examine the efficacy, tolerability and feasibility of home-administered, remotely-supervised tDCS for depression.

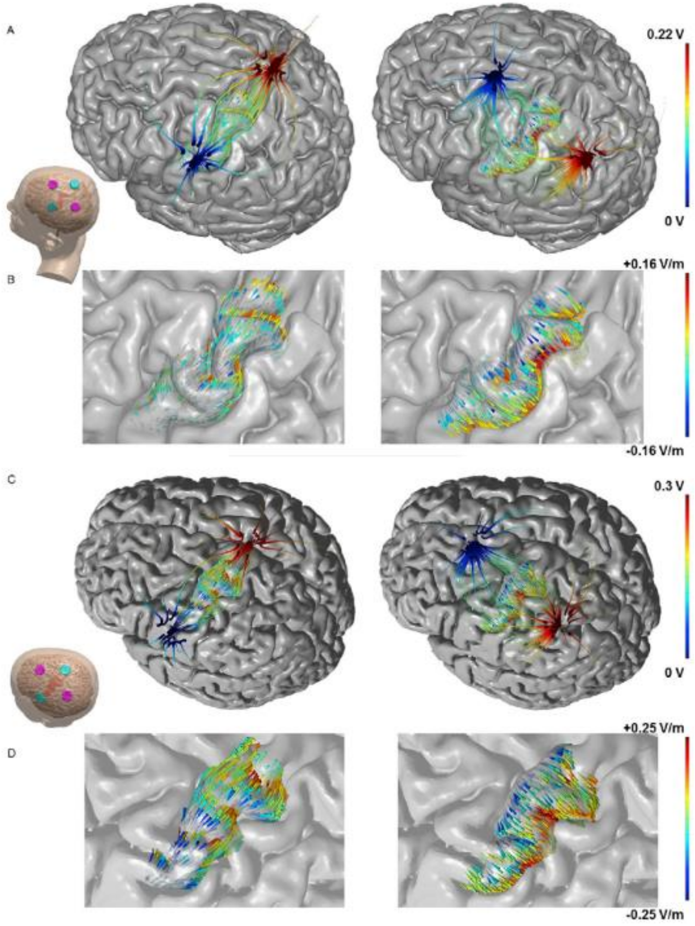
Methods: In an open label trial, 34 participants used a Soterix 1 × 1 mini-CT device to self-administer 20–28 tDCS sessions (2 mA, 30 min, F3-anode and F8-cathode montage according to 10–20 EEG placement) over 4 weeks followed by a taper phase of 4 sessions 1 week apart. Participants were initially monitored via video link and then through completion of an online treatment diary. Mixed effects repeated measures analyses assessed change in mood scores.

Results: Mood improved significantly from baseline (27.47 on Montgomery–Asberg Depression Rating Scale) to 1 month after the end of acute treatment (15.48) ($p < 0.001$). Side effects were largely transient and minor. Outcomes were comparable to those reported in clinic-based trials. Protocol adherence was excellent with a drop-out rate of 6% and 93% of scheduled sessions completed.

Limitations: The tDCS and remote monitoring procedures employed in this study require a level of manual dexterity and computer literacy, which may be challenging for some patients. This study did not have a control condition.

Conclusions: This study provides initial evidence that home-based, remotely-supervised tDCS treatment may be efficacious and feasible for depressed patients and has high translational potential.

TDCS:DEPRESSION



Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Transcranial Direct-Current Stimulation (tDCS) Versus Venlafaxine ER In The Treatment Of Depression: A Randomized, Double-Blind, Single-Center Study With Open-Label, Follow-Up

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

Martin Bares[1,2]
Martin Brunovsky[1,2]
Pavla Stopkova[1,2]
Martin Hejzlar[1,2]
Tomas Novak[1,2]

[1]NIMH Clinical Center, National Institute of Mental Health Czech Republic, Topolova 748, Klecany, Czech Republic; [2]The Department of Psychiatry and Medical Psychology, 3rd Faculty of Medicine, Charles University, Prague, Czech Republic

Objective: Transcranial direct-current stimulation (tDCS), a relatively new neuromodulation approach, provides some evidence of an antidepressant effect. This randomized, 4-week, double-blind study with 8-week, open-label, follow-up compared the efficacy and tolerability of left anodal tDCS with venlafaxine ER (VNF) in the treatment of depression and prevention of early relapse.

Methods: Subjects (n = 57) received tDCS (2 mA, 20 sessions, 30 mins) plus placebo (n = 29) or VNF plus sham tDCS (n = 28). Responders to both interventions entered the open-label follow-up. The primary outcome was score change in the Montgomery–Åsberg Depression Rating Scale (MADRS) at week 4 of the study. Secondary outcomes were response, remission, dropout rates and relapse rates within the follow-up.

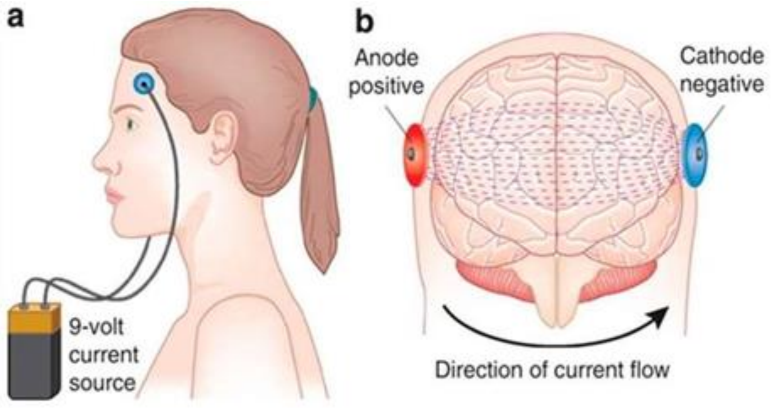
The mean change in the MADRS score from baseline to week for patients treated with tDCS was 7.69 (95% CI, 5.09–10.29) points and 9.64 (95% CI, 6.20–13.09) points for patients from the VNF group, a nonsignificant difference (1.95, 95% CI −2.25–6.16; t (55) = 0.93, p= 0.36, Cohen´s d = 0.24). There were no significant between-group differences in the MADRS scores from baseline to endpoint (intention-to-treat analysis). The response/remission rate for tDCS (24%/17%) and VNF (43%/32%) as well as the dropout rate (tDCS/VNF; 6/6) did not differ significantly between groups. In the follow-up, relapse (tDCS/VNF; 1/2) and dropout (tDCS/VNF; 2/3) rates were low and comparable.

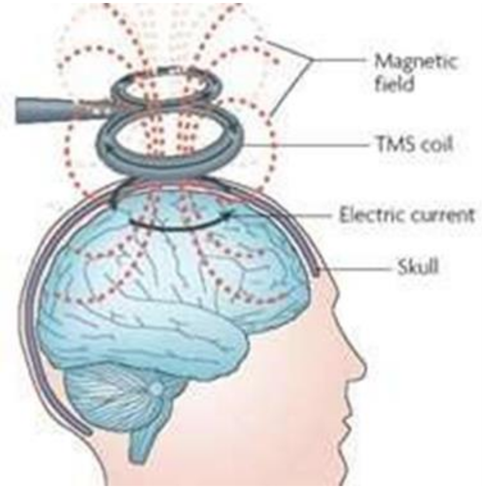
Limitations: A relatively small sample size and short duration of the antidepressant treatment; no placebo arm.

Conclusion: Overall, this study found a similar efficacy of tDCS and VNF in the acute treatment of depression and prevention of early relapse. The real clinical usefulness of tDCS and its optimal parameters in the treatment of depression should be further validated.

Keywords: transcranial direct-current stimulation, tDCS, depression, venlafaxine ER,

TDCS:DEPRESSION





rTMS and tDCS are both effective in the treatment of depression

frontiers in Psychology

OPINION
published: 13 January 2020
doi: 10.3389/fpsyg.2019.02923

The Reason Why rTMS and tDCS Are Efficient in Treatments of Depression

Milena Čukić [1,2]*

[1] Department for General Physiology and Biophysics, University of Belgrade, Belgrade, Serbia, [2] Instituto de Tecnologia del Conocimiento, Complutense University of Madrid, Madrid, Spain

Keywords: physiological complexity, rTMS, tDCS, depression, efficiency of treatment, neuromodulation

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*Correspondence:
Milena Čukić
micu@3ega.nl;
micukic@ucm.es

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INTRODUCTION

The exact neurophysiological mechanisms of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) for treating patients diagnosed with depression are still not clear. Results of previous structural and functional MRI studies showed an aberated functional connectivity in major depressive disorder (MDD) (Vederine et al., 2011; de Kwaasteniet et al., 2013). Those, as well as several connectivity studies (Bluhm et al., 2009; Berman et al., 2011; Zhang et al., 2011; Kim et al., 2013; Chen et al., 2015) seem to support the hypothesis that aberrant functional connectivity within fronto-limbic system underlies the pathophysiology of depression. It should be noted that antidepressant application of both rTMS and tDCS is based on previous findings that these two methods help in the case of hypoactivity of the left dorsolateral prefrontal cortex (DLPFC) (Grimm et al., 2006). Those structural and functional differences probably introduce abnormal physiological complexity demonstrated in electroencephalographic (EEG) (Ahmadlou et al., 2012; Bachmann et al., 2013; Hosseinifard et al., 2014; De la Torre-Luque and Bornas, 2017; Jaworska et al., 2018; Lebiecka et al., 2018) as well as in electrocardiographic (ECG) signals in depression (Migliorinni et al., 2012; Rossi et al., 2016; Iseger et al., 2019).

TDCS is low-intensity modality of transcranial electrical stimulation (TES) which induces very mild sensations in the skin (Stagg and Nitsche, 2011). Much later developed TMS primarily uses a strong magnetic field to induce an electric field in the cortex painlessly, initiating optimally focused activation of neural structures (Barker et al., 1985). Some of its modalities used in psychiatry are repetitive TMS (rTMS) and intermittent theta burst TMS (iTBS). In the present abundant literature about both rTMS and tDCS, there is scarce evidence of *why* these two techniques are capable of ameliorating depressive symptoms. We still don't know what precise mechanisms behind them are. Only a fraction of published research (Amassian et al., 1989; Maccabee et al., 1990; Wassermann and Grafman, 2005; Miranda et al., 2009; Ilmoniemi and Kičić, 2010; Alam et al., 2016) describe the theoretical background of those mechanisms from electromagnetics/physics point of view. The majority of published studies are based on multi-centric comparisons of clinical efficiency (Brunoni et al., 2016; Antal et al., 2017; Mutz et al., 2018) and computational methods-or simulations (Miranda et al., 2001, 2006; Wagner et al., 2007; Huang et al., 2017). Recently, a team of leading researchers in low intensity electrical transcranial stimulation reviewed clinical outcomes for 8,000 people (Antal et al., 2017) confirming its safety and effectiveness, and defined the regulatory and application guidelines for future research.

A term "non-invasive" (attached to both rTMS and tDCS) stems from obsolete medical point of view that the stimulating electrodes do not enter the crania (and the stimulation is performed either via small electrical charges in case of tDCS or via Faraday's induction). The real effect of "non-invasive" electromagnetic stimulation (rTMS and tDCS) cannot be measured directly due to their non-invasive nature. Opitz stated in recent research, that the important point is in interpretability of stimulation effects (Opitz et al., 2015): "if electric fields are delivered inconsistently, but effects are observed nevertheless, the results are more difficult to interpret

TDCS:DEPRESSION

RESEARCH ARTICLE Open Access

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Delayed effect of bifrontal transcranial direct current stimulation in patients with treatment-resistant depression: a pilot study

Min-Shan Li[5], Xiang-Dong Du[2,3], Hsiao-Chi Chu[5], Yen-Ying Liao[5], Wen Pan[2,3], Zhe Li[2,3*] and Galen Chin-Lun Hung[1,4,5*]

Abstract

Background: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique, which has yielded promising results in treating major depressive disorder. However, its effect on treatment-resistant depression remains to be determined. Meanwhile, as an emerging treatment option, patients' acceptability of tDCS is worthy of attention.

Methods: This pilot study enrolled 18 patients (women = 13) with treatment-resistant unipolar ($n = 13$) or bipolar ($n = 5$) depression. Twelve sessions of tDCS were administered with anode over F3 and cathode over F4. Each session delivered a current of 2 mA for 30 min per ten working days, and at the 4th and 6th week. Severity of depression was determined by Montgomery–Åsberg Depression Rating Scale (MADRS); cognitive performance was assessed by a computerized battery.

Results: Scores of MADRS at baseline (29.6, SD = 9.7) decreased significantly to 22.9 (11.7) ($p = 0.03$) at 6 weeks and 21.5 (10.3) ($p = 0.01$) at 8 weeks. Six (33.3%) participants were therapeutically responsive to tDCS. MADRS scores of responders were significantly lower than those of non-responders at the 6th and 8th week. Regarding change of cognitive performance, improved accuracy of paired association ($p = 0.017$) and social cognition ($p = 0.047$) was observed at the 8th week. Overall, tDCS was perceived as safe and tolerable. For the majority of patients, it is preferred than pharmacotherapy and psychotherapy.

Conclusions: TDCS can be a desirable option for treatment-resistant depression, however, its efficacy may be delayed; identifying predictors of therapeutic response may achieve a more targeted application. Larger controlled studies with optimized montages and sufficient periods of observation are warranted.

Trial registration: This trial has been registered at the Chinese Clinical Trial Registry (ChiCTR-INR-16008179).

Keywords: Transcranial direct-current stimulation, Treatment-resistant depression, Cognitive ability

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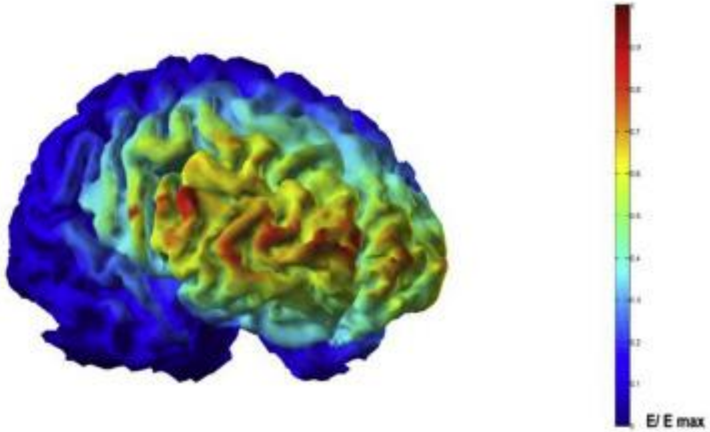
TDCS:DEPRESSION AND INSOMNIA



Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

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sleepmedicine

Original Article

The effects of repeated transcranial direct current stimulation on sleep quality and depression symptoms in patients with major depression and insomnia

Check for updates

Qi Zhou [a,1], Chang Yu [a,1], Haihang Yu [a,1], Yuanyuan Zhang [a], Zhiwang Liu [a], Zhenyu Hu [a], Ti-Fei Yuan [b,c,*], Dongsheng Zhou [a,**]

[a] *Ningbo Kangning Hospital, Ningbo, Zhejiang, China*
[b] *Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, China*
[c] *Co-innovation Center of Neuroregeneration, Nantong University, Nantong, Jiangsu, China*

A R T I C L E I N F O

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Keywords:
Major depression
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A B S T R A C T

Importance: Although several strategies using transcranial direct current stimulation (tDCS) have been investigated to treat major depressive disorder (MDD), the efficacy of this treatment for patients with MDD who also have insomnia is unclear.
Objective: To observe the effects of tDCS on sleep quality and depressive symptoms in patients with MDD who have insomnia.
Methods: We conducted a randomized, double-blinded study involving adults with major depression and insomnia. We randomly assigned patients to either add tDCS or to sham tDCS to their regular treatment. After randomization, we treated a total of 90 patients at the Kangning Hospital, Ningbo, China. We allocated 47 patients to the tDCS group and 43 to the sham tDCS group. The tDCS treatment procedure included 20 sessions of 2-mA stimulation of the dorsolateral prefrontal cortex (DLPFC) for 30 min, which was followed by four weekly treatments. The anode and cathode electrodes were placed on the left and right DLPFC, respectively. We recorded the Self-rating Depression Scale (SDS), Self-rating Anxiety Scale (SAS), Pittsburgh Sleep Quality Inventory (PSQI), and Polysomnography (PSG) at Day 1 and Day 28.
Results: Compared with the sham tDCS group, the active tDCS group showed improved total scores of SAS and SDS. PSQI total score and all PSQI sub-divisions, except for "sleep duration and sleep efficiency," significantly improved after treatment. We also observed that tDCS affected sleep architecture, by increasing total sleep time and improving sleep efficiency through PSG.
Conclusions: Our study demonstrated the effect of tDCS on sleep quality and depressive symptoms in patients with MDD and insomnia. These results suggested that tDCS stimulation not only improved symptoms of depression and anxiety but also had a positive effect on sleep quality in patients with MDD. For patients with depression and insomnia, tDCS stimulation could be a good supplement to drugs.

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TDCS AND INSOMNIA

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

The effects of non-invasive brain stimulation on sleep disturbances among different neurological and neuropsychiatric conditions: A systematic review

Alberto Herrero Babiloni [a, b, *], Audrey Bellemare [b], Gabrielle Beetz [b], Sophie-A. Vinet [b], Marc O. Martel [a, c, d], Gilles J. Lavigne [b, c, e], Louis De Beaumont [b, f]

[a] Division of Experimental Medicine, McGill University, Montreal, Quebec, Canada
[b] Sacré-Coeur Hospital, University of Montreal, Montreal, Quebec, Canada
[c] Faculty of Dentistry, McGill University, Montreal, Quebec, Canada
[d] Department of Anesthesia, McGill University, Montreal, Quebec, Canada
[e] Faculty of Dental Medicine, University of Montreal, Montreal, Quebec, Canada
[f] Department of Surgery, University of Montreal, Montreal, Quebec, Canada

A R T I C L E I N F O

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Sleep disorders
Circadian rhythm
Brain

S U M M A R Y

Sleep disturbances (e.g., difficulty to initiate or maintain sleep) and poor sleep quality are major health concerns that accompany several neurological and neuropsychiatric clinical conditions where different brain circuitries are affected (e.g., chronic pain, Parkinson's disease or depression), having a great impact in the individual's well-being, quality of life, and the socioeconomic system. Sleep disturbances in absence of breathing or neurological disorders are mainly treated with medications (e.g., benzodiazepines, hypnotics, etc.) and cognitive behavioral therapy, which are associated with side-effects and adherence issues, respectively. Moreover, these therapies do not seem to work effectively for some individuals. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are non-invasive stimulation techniques used to treat several conditions and symptoms. Results from this systematic review indicate that rTMS and tDCS are safe and have potential to improve insomnia symptoms and sleep disturbances across different types of neurological and neuropsychiatric diseases. However, uncontrolled and quasi experimental studies with high risk of bias were included. Thus, although these results can help developing the field, caution in interpreting them is advised. Additional research efforts are needed to reduce bias, improve quality, and characterize optimal brain stimulation parameters to promote their efficacy on sleep related outcomes.

TDCS AND PTSD

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Brain Research Bulletin

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Transcranial direct current stimulation (tDCS) for post-traumatic stress disorder (PTSD): A randomized, double-blinded, controlled trial

Mohammad Javad Ahmadizadeh[a,*], Mehdi Rezaei[a], Paul B. Fitzgerald[b]

[a] Behavioral Science Research Center, Life Style Institute, Baqiyatallah University of Medical Science, Tehran, Iran

[b] Epworth Centre for Innovation in Mental Health, The Epworth Clinic, Camberwell, Victoria, Australia, 3124 and Monash University Central Clinical School, Commercial Rd, Melbourne, Victoria, Australia

A R T I C L E I N F O

Keywords:
Post-traumatic stress disorder (PTSD)
Transcranial direct current stimulation (tDCS)

A B S T R A C T

Currently, there is not definitive information regarding the efficacy of transcranial direct current stimulation (tDCS) for Post-traumatic stress disorder (PTSD). This study aimed to examine the efficacy of tDCS for PTSD and its sub-symptoms. In a double-blind, controlled randomized clinical trial, 40 participants with PTSD were randomly assigned to receive either 10 tDCS sessions delivered at 2 mA to the right (cathode) and left (anode) dorsolateral prefrontal cortex (DLPFC) or 10 sham tDCS sessions to the same area. A blinded rater assessed PTSD, depressive, and anxiety symptoms before treatment, following it, and after a 1-month follow-up period. According to the results: i) PTSD patients demonstrated a significant reduction in PTSD symptoms, hyper-arousal and negative alterations in cognition and mood sub-symptoms as well as depressive and anxiety symptoms in the active stimulation compared to the sham stimulation at post-treatment and follow-up; ii) active stimulation when compared to sham stimulation revealed greater reductions in re-experiencing sub-symptoms from baseline to post-test. However, follow-up differences did not reach significance; iii) With respect to avoidance sub-symptoms, there were no significant differences between the active and sham stimulation at post-test and follow-up. This study supported the efficacy of 10 sessions of bilateral DLPFC tCDS delivered at 2 mA for the treatment of PTSD symptoms. Taken together, these findings suggest that although tDCS can reduce PTSD symptoms, researchers should consider the different types of PTSD and use strategies to ensure sufficient power to detect a potential effect of tDCS on various types of PTSD.

TDCS AND PTSD

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International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Variable symptomatic and neurophysiologic response to HD-tDCS in a case series with posttraumatic stress disorder

Benjamin M. Hampstead[a,b,*], Nathan Mascaro[c,d], Stephen Schlaefflin[b], Arijit Bhaumik[e], Julia Laing[b], Scott Peltier[f,g], Brian Martis[a]

[a] Mental Health Service, VA Ann Arbor Healthcare System, Ann Arbor, MI, USA
[b] Neuropsychology Section, Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA
[c] Trauma Recovery Program, Atlanta VAMC, Decatur, GA, USA
[d] Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, USA
[e] Department of Neurology, University of Michigan, Ann Arbor, MI, USA
[f] Functional MRI Laboratory, University of Michigan, Ann Arbor, MI, USA
[g] Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

ARTICLE INFO

Keywords:
fMRI
tDCS
Connectivity
Graph theory
Anxiety
Mood
Neuromodulation

ABSTRACT

Chronic Posttraumatic stress disorder (PTSD), characterized by symptoms of re-experiencing, hyperarousal, and avoidance, is challenging to treat as a significant proportion of patients remain symptomatic following even empirically supported interventions. The current case series investigated the effects of up to 10 sessions of high definition transcranial direct current stimulation (HD-tDCS) on symptoms of PTSD. Participants received HD-tDCS that targeted the right lateral temporal cortex (LTC; center cathode placed over T8), given this region's potential involvement in symptoms of re-experiencing and, possibly, hyperarousal. Five of the six enrolled patients completed at least 8 sessions. Of these five, four showed improvement in symptoms of re-experiencing after HD-tDCS. This improvement was accompanied by connectivity change in the right LTC as well as a larger extended fear network but not a control network that consisted of visual cortex regions; however, the nature of the change varied across participants as some showed increased connectivity whereas others showed decreased connectivity. These preliminary data suggest that HD-tDCS may be beneficial for treatment of specific PTSD symptoms, in at least some individuals, and warrants further investigation.

TDCS AND PTSD

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Effectiveness of Transcranial Direct Current Stimulation (tDCS) on Depression, Anxiety and Rumination of Patients with Post-traumatic Stress Disorder Symptoms (PTSD)

Mohammadjavad Ahmadizadeh [1*], Mehdi Rezaei [2]

[1] *Assistant Professor, Department of Psychology, Behavioral Science Research Center, Life Style Institute, Baqiyatallah University of Medical Science, Tehran, Iran*
[2] *Assistant Professor, Department of Psychology, Sahryar Branch, Islamic Azad University, Sahryar, Iran*

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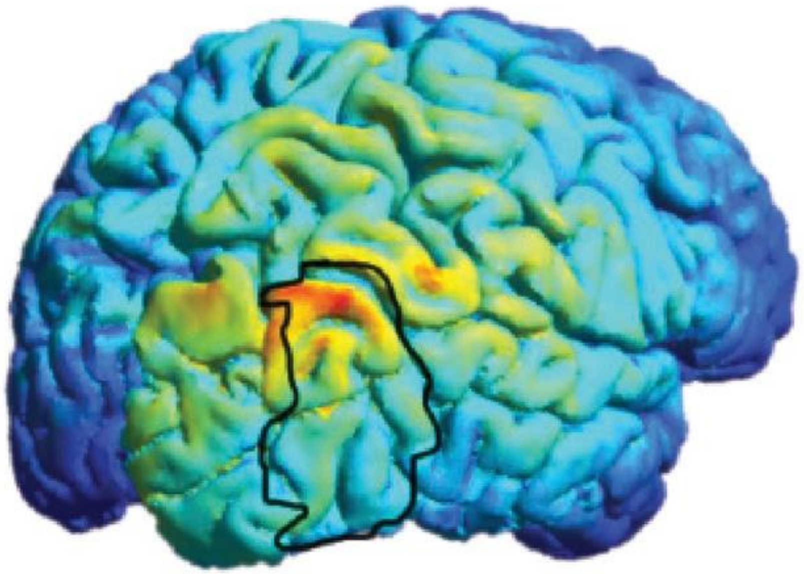
Abstract

Background and Aim: Transcranial direct current stimulation (tDCS) is a potential non-invasive treatment for psychiatric disorders. The aim of this study was to investigate the efficacy of bilateral tDCS on depression, anxiety and rumination of patients with post-traumatic stress disorder (PTSD).

Methods: This was a double-blind interventional study with pretest – posttest design and one month follow-up. This study was carried out in 2018 with statistical population of PTSD patients from Tehran, Iran. In this study 20 patients with PTSD symptoms were selected using convenience sampling and randomly divided to interventional (n=10) and control groups (n=10). The interventional group received real 2.0 mA tDCS over dorsolateral prefrontal cortex (DLPFC) lasting 20 min in 10 sessions and the control group received sham tDCS. Structured Clinical Interview, the Beck Depression and Anxiety Inventory and Nolen-Hoeksema Ruminative Response Scale were used in pretest, posttest and follow-up.

Results: Patients demonstrated significant reduction of depression and anxiety symptoms in the interventional group compared to the control group. There were significant differences between the two groups in rumination at post-test but there were no significant differences between the interventional and control groups in rumination at follow-up.

Conclusion: tDCS improved depressive and anxiety symptoms in patients with PTSD. However, there was no significant reduction in rumination at follow-up course. Further studies may determine optimal stimulation parameters for maximal mood benefit in patients with PTSD.



TDCS AND TINNITUS

tDCS and Tinnitus: A meta-analytic exploration into efficacy and optimization

Alexander Cates
Northwestern University

Evan Davies
University of Wisconsin

Millions of Americans suffer from tinnitus, or ringing of the ears. Despite its prevalence, treatment for tinnitus is limited, with most approaches focusing on making the symptoms tolerable, instead of treating the underlying neurological causes. Recently however, brain stimulation techniques, such as transcranial direct current stimulation (tDCS), have emerged offering a new method to interact with the brain and offering hope as a new approach to treating the underlying causes of tinnitus, not just making the symptoms tolerable. In the present meta-analysis, we analyzed the results from 17 controlled trials and 5 uncontrolled case studies to determine the efficacy of tDCS for treating tinnitus. Additionally, we performed sub-analyses to test how different tDCS parameters may alter the efficacy of treatment. Overall, we found a small but significant effect (Overall Hedges g of 0.17 (95% CI 0.09-0.25)) of tDCS on tinnitus symptoms. However, mechanistically we found that targeting the DLPFC improved symptoms significantly more than other targets, including targeting the auditory cortex directly. This along with the subjective outcome measures currently available, suggest that while tDCS does offer a benefit to treating the symptoms, it does not appear to treat any underlying causes. It is the opinion of the authors therefore that tDCS should be used in addition to traditional interventions to make the symptoms more tolerable. As covered in the discussion, future research should explore more objective measures of tinnitus in order to better assess the efficacy of tDCS and other brain stimulation methods, with the hope of developing a causal treatment of tinnitus.

Practical significance: tDCS offers a small but significant benefit for treating subjective tinnitus and should therefore be considered in addition to traditional therapies as a method to manage tinnitus symptoms..

Data, analysis code, supplementary material: https://osf.io/zsca4/

Keywords: tinnitus, tDCS, brain stimulation, auditory disorders

Journal of Motor Behavior, Vol. 52, No. 4, 2020

TDCS AND STROKE REHABILITATION

RESEARCH ARTICLE

OPEN ACCESS Check for updates

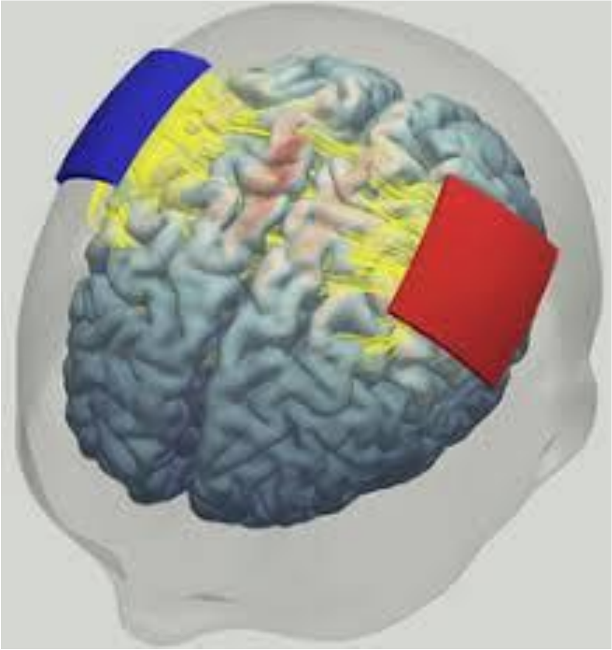
Effect of tDCS on Fine Motor Control of Patients in Subacute and Chronic Post-Stroke Stages

E. L. Pavlova[1], R. V. Semenov[2], A. B. Guekht[2,3]
[1]Department of Clinical Sciences Karolinska Institute, Danderyd University Hospital, Stockholm, Sweden. [2]Moscow Research and Clinical Center for Neuropsychiatry of the Healthcare Department of Moscow, Moscow, Russian Federation. [3]Russian National Research Medical University, Moscow, Russian Federation.

ABSTRACT. In this study we compared the effects of transcranial direct current stimulation (tDCS) in the subacute and chronic stages of post-stroke recovery. Anodal/sham tDCS was applied to the primary motor cortex of stroke patients in these stages of recovery in a cross-over design. The Jebsen–Taylor hand function test was employed. The repeated-measure ANOVA showed significant influence of the stimulation type and test performance time (during/after tDCS) with no overall influence of recovery stage. The interaction TYPE*TIME*STAGE was significant. The effect after anodal tDCS in the subacute stage was significantly higher compared to the effects in all relevant conditions including the chronic stage. Therefore, tDCS treatment in the subacute stage of recovery can be superior, at least for some patients, to treatment in the chronic stage.

Keywords: tDCS, stroke, Jebsen–Taylor Hand Function Test, timing

Kerkhoff, 2010). Direct current results in subthreshold polarity-specific polarization of neuronal membranes (Bikson et al., 2004; Nitsche & Paulus, 2000; Purpura & McMurtry, 1965). After several minutes of stimulation, excitability changes last after the end of the session (Nitsche & Paulus, 2000, 2001; Nitsche et al., 2003b). These changes are related to glutamatergic plasticity (Nitsche et al., 2003a), presumably gated by GABAergic downregulation (Stagg et al., 2009). This plasticity is considered to be similar to neurophysiological correlate of learning – long-term potentiation (LTP) and long-term depression (LTD) – since it is associated with N-methyl-D-aspartate (NMDA) receptors, calcium channels and protein synthesis (Fritsch et al., 2010; Nitsche et al., 2003a). In addition to inducing changes to brain regions under the electro-



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Journal of the Neurological Sciences

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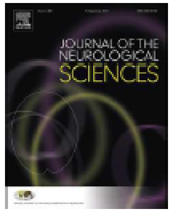

Timing-dependent interaction effects of tDCS with mirror therapy on upper extremity motor recovery in patients with chronic stroke: A randomized controlled pilot study

Minxia Jin[a,b], Ziwei Zhang[a,b], Zhongfei Bai[a,b], Kenneth N.K. Fong[a,*]

[a] *Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR*
[b] *Shanghai Sunshine Rehabilitation Centre, Shanghai, China*

ARTICLE INFO

Keywords:
Transcranial direct current stimulation
Motor priming
Mirror therapy
Stroke
Upper extremity
Motor recovery

ABSTRACT

This study was a randomized, controlled pilot trial to investigate the timing-dependent interaction effects of dual transcranial direct current stimulation (tDCS) in mirror therapy (MT) for hemiplegic upper extremity in patients with chronic stroke. Thirty patients with chronic stroke were randomly assigned to three groups: tDCS applied before MT (prior-tDCS group), tDCS applied during MT (concurrent-tDCS group), and sham tDCS applied randomly prior to or concurrent with MT (sham-tDCS group). Dual tDCS at 1 mA was applied bilaterally over the ipsilesional M1 (anodal electrode) and the contralesional M1 (cathodal electrode) for 30 min. The intervention was delivered five days per week for two weeks. Upper extremity motor performance was measured using the Fugl-Meyer Assessment-Upper Extremity (FMA-UE), the Action Research Arm Test (ARAT), and the Box and Block Test (BBT). Assessments were administered at baseline, post-intervention, and two weeks follow-up. The results indicated that concurrent-tDCS group showed significant improvements in the ARAT in relation to the prior-tDCS group and sham-tDCS group at post-intervention. Besides, a trend toward greater improvement was also found in the FMA-UE for the concurrent-tDCS group. However, no statistically significant difference in the FMA-UE and BBT was identified among the three groups at either post-intervention or follow-up. The concurrent-tDCS seems to be more advantageous and time-efficient in the context of clinical trials combining with MT. The timing-dependent interaction factor of tDCS to facilitate motor recovery should be considered in future clinical application.

TDCS AND STROKE REHABILITATION

TDCS AND TINNITUS

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Journal of Motor Behavior, Vol. 52, No. 4, 2020

TDCS AND STROKE REHABILITATION

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Effect of tDCS on Fine Motor Control of Patients in Subacute and Chronic Post-Stroke Stages

E. L. Pavlova[1], **R. V. Semenov**[2], **A. B. Guekht**[2,3]
[1]Department of Clinical Sciences Karolinska Institute, Danderyd University Hospital, Stockholm, Sweden. [2]Moscow Research and Clinical Center for Neuropsychiatry of the Healthcare Department of Moscow, Moscow, Russian Federation. [3]Russian National Research Medical University, Moscow, Russian Federation.

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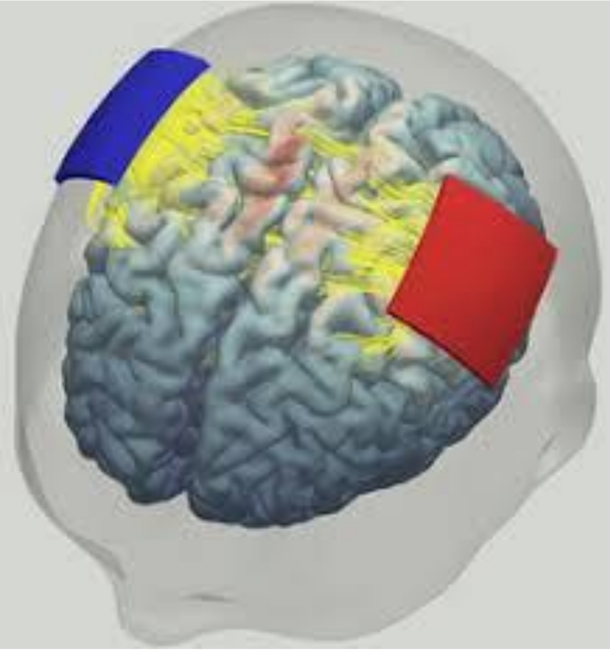

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Minxia Jin[a,b], Ziwei Zhang[a,b], Zhongfei Bai[a,b], Kenneth N.K. Fong[a,*]

[a] *Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR*
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A R T I C L E I N F O

Keywords:
Transcranial direct current stimulation
Motor priming
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Upper extremity
Motor recovery

A B S T R A C T

This study was a randomized, controlled pilot trial to investigate the timing-dependent interaction effects of dual transcranial direct current stimulation (tDCS) in mirror therapy (MT) for hemiplegic upper extremity in patients with chronic stroke. Thirty patients with chronic stroke were randomly assigned to three groups: tDCS applied before MT (prior-tDCS group), tDCS applied during MT (concurrent-tDCS group), and sham tDCS applied randomly prior to or concurrent with MT (sham-tDCS group). Dual tDCS at 1 mA was applied bilaterally over the ipsilesional M1 (anodal electrode) and the contralesional M1 (cathodal electrode) for 30 min. The intervention was delivered five days per week for two weeks. Upper extremity motor performance was measured using the Fugl-Meyer Assessment-Upper Extremity (FMA-UE), the Action Research Arm Test (ARAT), and the Box and Block Test (BBT). Assessments were administered at baseline, post-intervention, and two weeks follow-up. The results indicated that concurrent-tDCS group showed significant improvements in the ARAT in relation to the prior-tDCS group and sham-tDCS group at post-intervention. Besides, a trend toward greater improvement was also found in the FMA-UE for the concurrent-tDCS group. However, no statistically significant difference in the FMA-UE and BBT was identified among the three groups at either post-intervention or follow-up. The concurrent-tDCS seems to be more advantageous and time-efficient in the context of clinical trials combining with MT. The timing-dependent interaction factor of tDCS to facilitate motor recovery should be considered in future clinical application.

TDCS AND OBESITY

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Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

Repeated net-tDCS of the hypothalamus appetite-control network enhances inhibitory control and decreases sweet food intake in persons with overweight or obesity

Theresa Ester-Nacke [a,c,*], Ralf Veit [a,c], Julia Thomanek [a,c], Magdalena Book [a,c], Lukas Tamble [a,c], Marie Beermann [a,c], Dorina Löffler [a,b,c], Ricardo Salvador [d], Giulio Ruffini [d], Martin Heni [a,b,c,e,f], Andreas L. Birkenfeld [a,b,c], Christian Plewnia [g,h], Hubert Preissl [a,b,c,h,i], Stephanie Kullmann [a,b,c]

[a] Institute for Diabetes Research and Metabolic Diseases (IDM) of the Helmholtz Center Munich at the University of Tübingen, Tübingen, Germany
[b] Department of Internal Medicine, Division of Endocrinology, Diabetology and Nephrology, Eberhard Karls University Tübingen, Tübingen, Germany
[c] German Center of Diabetes Research (DZD), Tübingen, Germany
[d] Neuroelectrics Barcelona, Barcelona, Spain
[e] Institute for Clinical Chemistry and Pathobiochemistry, Department for Diagnostic Laboratory Medicine, Eberhard Karls University Tübingen, Tübingen, Germany
[f] Division of Endocrinology and Diabetology, Department of Internal Medicine 1, University Hospital Ulm, Ulm, Germany
[g] Department of Psychiatry and Psychotherapy, Neurophysiology & Interventional Neuropsychiatry, University Hospital Tübingen, Tübingen, Germany
[h] German Center for Mental Health (DZPG), Partner Site Tübingen, Tübingen, Germany
[i] Institute of Pharmaceutical Sciences, Department of Pharmacy and Biochemistry, Interfaculty Centre for Pharmacogenomics and Pharma Research at the Eberhard Karls University Tübingen, Tübingen, Germany

Highlights

- Active net-tDCS groups showed better inhibitory control compared to the sham group.
- Stronger increase in hypothalamic functional connectivity associated with better inhibitory control after active net-tDCS.
- No differences were found between the active net-tDCS and sham groups for total kilocaloric intake.
- Anodal net-tDCS showed lower sweet food intake compared to the sham group.

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TRANSLINGUAL NEURAL STIMULATION

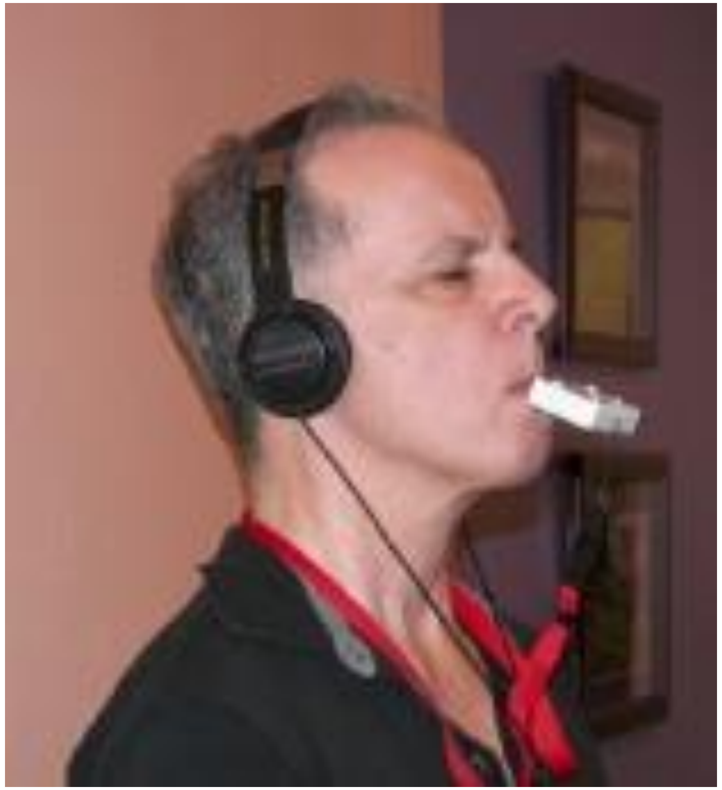
TONGUE STIMULATION (TRIGEMINAL) – "PONS DEVICE"

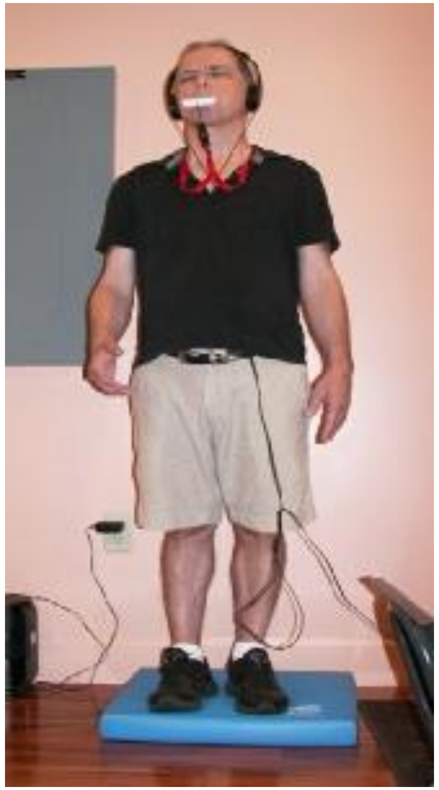
- Trigeminal afferents to cortex are vast
- Cortical excitability as a result of tongue stimulation – fMRI, TMS MEP, and EEG evidence
- An excited cortex - neuroplasticity
- Minimal intensity required
- Stimulation is performed concurrently with other rehabilitation procedures

BALANCE/PROPRIOCEPTION DEFICITS

PONS Device™ - Portable Oral Neuro Stimulator

A type of superficial neuromodulation of the trigeminal system via the tongue





PONS – INDUCING NEUROPLASTICITY

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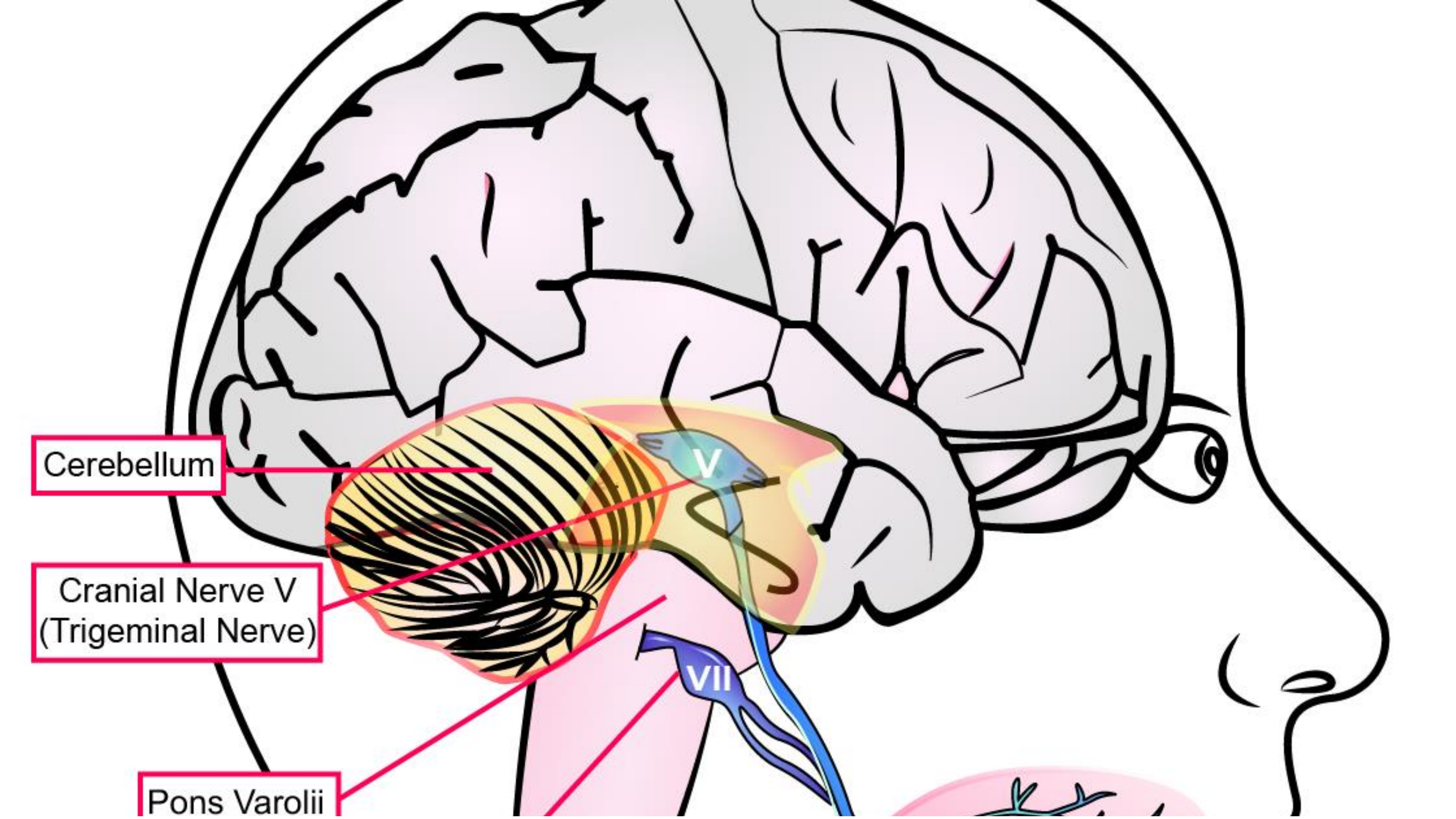
Cerebellum
Cranial Nerve V
(Trigeminal Nerve)
Pons Varolii
V
VII

PONS DEVICE


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PONS DEVICE – LEADS TO STRUCTURAL CHANGES IN TBI

Translingual Neural Stimulation With the Portable Neuromodulation Stimulator (PoNS®) Induces Structural Changes Leading to Functional Recovery In Patients With Mild-To-Moderate Traumatic Brain Injury

Authors: Jiancl
Yuri D
*Vivel
1. Dep
Wisc
2. Dep
Wisc
3. Dep
Wisc
*Corres

Abstract

Traumatic brain injury (TBI) of varying severity can result in balance and movement disorders, for which the benefits of treatment with physical therapy has limits. In this study, patients with post-TBI balance issues received translingual neural stimulation (TLNS) in concert with physical therapy

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and the effects on the grey matter volume (GMV) were evaluated. TBI-related balance and movement impairments were also assessed through Sensory Organization Test (SOT) and Dynamic Gait Index (DGI) scoring. When comparing pre- and post-intervention results, the most prominent GMV changes were increases within the cerebellum, and temporal regions, which are involved in automatic processing of gait, balance, motor control, and visual-motion. Decreases of GMV in frontal, occipital lobes (involved in less automatic processing or more conscious/effortful processing of gait, balance, motor control, and vision) positively correlated to increases in SOT/DGI scores. These results indicate that TLNS can produce brain plasticity changes leading to positive changes in functional assessments. Overall, these data indicate that TLNS delivered in conjunction with physical therapy, is a safe, effective, and integrative way to treat TBI.

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PONS DEVICE – LEADS TO EEG CHANGES

Frehlick *et al. Journal of NeuroEngineering and Rehabilitation* (2019) 16:60
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Journal of NeuroEngineering and Rehabilitation

RESEARCH **Open Access**

Check for updates

Human translingual neurostimulation alters resting brain activity in high-density EEG

Zack Frehlick[1], Bimal Lakhani[1], Shaun D. Fickling[1], Ashley C. Livingstone[1], Yuri Danilov[2], Jonathan M. Sackier[3,4] and Ryan C. N. D'Arcy[1*]

Abstract

Background: Despite growing evidence of a critical link between neuromodulation technologies and neuroplastic recovery, the underlying mechanisms of these technologies remain elusive.

Objective: To investigate physiological evidence of central nervous system (CNS) changes in humans during translingual neurostimulation (TLNS).

Methods: We used high-density electroencephalography (EEG) to measure changes in resting brain activity before, during, and after high frequency (HF) and low frequency (LF) TLNS.

Results: Wavelet power analysis around Cz and microstate analysis revealed significant changes after 20 min of stimulation compared to baseline. A secondary effect of exposure order was also identified, indicating a differential neuromodulatory influence of HF TLNS relative to LF TLNS on alpha and theta signal power.

Conclusions: These results further our understanding of the effects of TLNS on underlying resting brain activity, which in the long-term may contribute to the critical link between clinical effect and changes in brain activity.

Keywords: Cranial nerve stimulation, Neuromodulation, Neuroplasticity, EEG

Archives of Rehabilitation Research and Clinical Translation (2019) 1, 100026

ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Rehabilitation Research and Clinical Translation

Archives of Rehabilitation Research and Clinical Translation 2019;1:100026

Available online at www.sciencedirect.com

Original Research

Translingual Neurostimulation for the Treatment of Chronic Symptoms Due to Mild-to-Moderate Traumatic Brain Injury

Mitchell Tyler, MS [a,b], Kim Skinner, DPT [b], Vivek Prabhakaran, MD, PhD [c], Kurt Kaczmarek, PhD [b], Yuri Danilov, PhD [b]

[a] *Department of Biomedical Engineering, University of Wisconsin-Madison, Madison, Wisconsin*
[b] *Department of Kinesiology, University of Wisconsin-Madison, Madison, Wisconsin*
[c] *Department of Radiology, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin*

Abstract *Objective:* To compare the efficacy of high- and low-frequency noninvasive translingual neurostimulation (TLNS) plus targeted physical therapy (PT) for treating chronic balance and gait deficits due to mild-to-moderate traumatic brain injury (mmTBI).
Design: Participants were randomized 1:1 in a 26-week double-blind phase 1/2 study (NCT02158494) with 3 consecutive treatment stages: in-clinic, at-home, and no treatment. Arms were high-frequency pulse (HFP) and low-frequency pulse (LFP) TLNS.
Setting: TLNS plus PT training was initiated in-clinic and then continued at home.
Participants: Participants (N=44; 18-65y) from across the United States were randomized into the HFP and LFP (each plus PT) arms. Forty-three participants (28 women, 15 men) completed at least 1 stage of the study. Enrollment requirements included an mmTBI ≥1 year prior to screening, balance disorder due to mmTBI, a plateau in recovery with current PT, and a Sensory Organization Test (SOT) score ≥16 points below normal.
Interventions: Participants received TLNS (HFP or LFP) plus PT for a total of 14 weeks (2 in-clinic and 12 at home), twice daily, followed by 12 weeks without treatment.
Main Outcome Measures: The primary endpoint was change in SOT composite score from baseline to week 14. Secondary variables (eg, Dynamic Gait Index [DGI], 6-minute walk test [6MWT]) were also collected.
Results: Both arms had a significant ($P<.0001$) improvement in SOT scores from baseline at weeks 2, 5, 14 (primary endpoint), and 26. DGI scores had significant improvement ($P<.001$-.01) from baseline at the same test points; 6MWT evaluations after 2 weeks were significant. The SOT, DGI, and 6MWT scores did not significantly differ between arms at any test point. There were no treatment-related serious adverse events.
Conclusions: Both the HFP+PT and LFP+PT groups had significantly improved balance scores, and outcomes were sustained for 12 weeks after discontinuing TLNS treatment. Results between arms did not significantly differ from each other. Whether the 2 dosages are equally effective or whether improvements are because of provision of PT cannot be conclusively established at this time.

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PONS DEVICE

frontiers | Frontiers in Human Neuroscience

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Translingual neural stimulation induced changes in intra- and inter-network functional connectivity in mild-moderate traumatic brain injury patients

Daniel Y. Chu[1†], Jiancheng Hou[2†], Thomas Hosseini[1], Veena A. Nair[1], Nagesh Adluru[1], Yuri Danilov[3], Kurt A. Kaczmarek[3], Mary E. Meyerand[4], Mitchell Tyler[3,4] and Vivek Prabhakaran[1]*

[1]Department of Radiology, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, United States, [2]Research Center for Cross-Straits Cultural Development, Fujian Normal University, Fuzhou, Fujian, China, [3]Department of Kinesiology, University of Wisconsin-Madison, Madison, WI, United States, [4]Department of Biomedical Engineering, University of Wisconsin-Madison, Madison, WI, United States

Introduction: Mild-to-moderate traumatic brain injury (mmTBI) that lead to deficits in balance and gait are difficult to resolve through standard therapy protocols, and these deficits can severely impact a patient's quality of life. Recently, translingual neural stimulation (TLNS) has emerged as a potential therapy for mmTBI-related balance and gait deficits by inducing neuroplastic changes in the brain gray matter structure. However, it is still unclear how interactions within and between functional networks in brain are affected by TLNS. The current study aimed to extend our previous resting-state functional connectivity (RSFC) study investigating the effects of TLNS intervention on outcome measures related to gait and balance.

Methods: An experimental PoNS device was utilized to deliver the TLNS. The 2-week TLNS intervention program, specifically stimulation during focused physical therapy focused on recovery of gait and balance, included twice-daily treatment in the laboratory and the same program at home during the intervening weekend. The resting-state fMRI datasets at pre- and post-interventions were collected by 3T MRI scanner with nine mmTBI patients. All participants also received both Sensory Organization Test (SOT) and Dynamic Gait Index (DGI) testing pre- and post-intervention as part of the behavioral assessment.

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PONS DEVICE

Translingual neural stimulation induced changes in intra- and inter-network functional connectivity in mild-moderate traumatic brain injury patients

Daniel Y. Chu[1†], Jiancheng Hou[2†], Thomas Hosseini[1], Veena A. Nair[1], Nagesh Adluru[1], Yuri Danilov[3], Kurt A. Kaczmarek[3], Mary E. Meyerand[4], Mitchell Tyler[3,4] and Vivek Prabhakaran[1*]

[1]Department of Radiology, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, United States, [2]Research Center for Cross-Straits Cultural Development, Fujian Normal University, Fuzhou, Fujian, China, [3]Department of Kinesiology, University of Wisconsin-Madison, Madison, WI, United States, [4]Department of Biomedical Engineering, University of Wisconsin-Madison, Madison, WI, United States

Results: Compared to baseline, TLNS intervention led to statistically significant improvements in both the SOT [$t_{(8)} = 2.742$, $p = 0.028$] and the DGI [$t_{(8)} = 2.855$, $p = 0.024$] scores. Moreover, significant increases in intra- and inter-network RSFC were observed, particularly within the visual, default mode, dorsal attention, frontoparietal (FPN), and somatosensory (SMN) networks. Additionally, there were significant correlations between the SOT and inter-network FC [between FPN and SMN, $r_{(9)} = -0.784$, $p = 0.012$] and between the DGI and intra-network FC [within SMN, $r_{(9)} = 0.728$, $p = 0.026$].

Discussion: These findings suggest that TLNS intervention is an effective in increasing somatosensory processing, vestibular-visual interaction, executive control and flexible shifting, and TLNS may be an effective approach to inducing brain network plasticity and may serve as a potential therapy for mmTBI-related gait and balance deficits.

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PHOTOBIOMODULATION

PHOTOBIOMODULATION (PBM)

What is PBM?

- A category of non-invasive treatment that uses specific wavelengths of light, typically red and near-infrared, to stimulate cells and promote tissue repair, reduce inflammation, and alleviate pain

PHOTOBIOMODULATION

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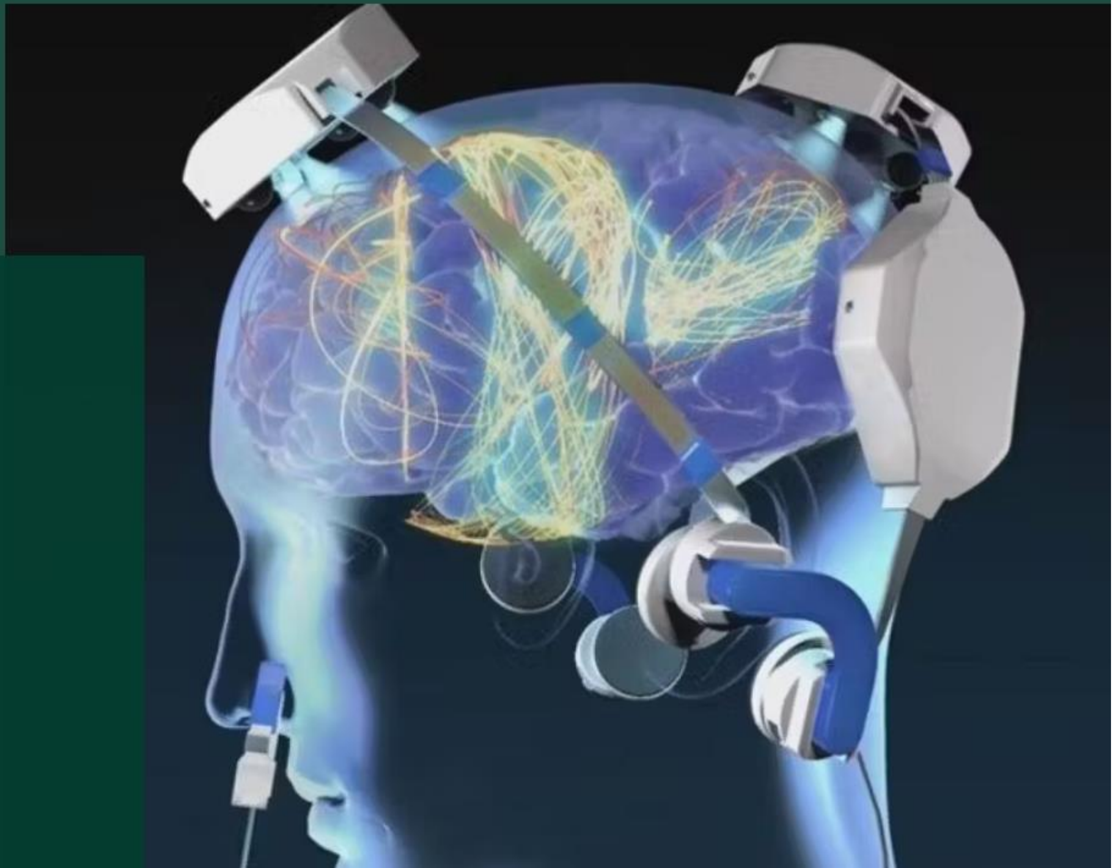
Home > Patient Care > Therapies > Neuromodulation Th... > Photo-Bio-Modulation...

NEUROMODULATION THERAPIES

Photo-Bio-Modulation (PBM)

The latest technology for treating the Central Nervous System and particularly suitable for children, which uses increased cerebral blood flow to stimulate brain metabolism and promote neuroplasticity processes.



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PBM – MECHANISMS

- PBM uses characteristics of artificial light or sunlight, including infrared, ultraviolet, visible light, and laser to modulate biological activity.
- PBM with infrared light penetrates the tissue to stimulate mitochondria, thereby increasing cellular respiration and *adenosine triphosphate (ATP) production*.
- PBM up-regulates complex IV of the respiratory chain to modulate cytochrome c oxidase (CCO), leading to *increased ATP formation*.
- Increased availability of energy in the form of ATP leads to cellular growth and repair.
- More active mitochondria support higher oxygen / glucose consumption supporting *increased cerebral blood flow.*
- When delivered to the brain, transcranial PBM (tPBM) with low-level laser in the near-infrared range can penetrate the skin and skull and have neurostimulation effects.

PBM - MECHANISMS

- There is encouraging evidence that tPBM can have beneficial effects on traumatic events (stroke, traumatic brain injury, and global ischemia), degenerative diseases (dementia, Alzheimer's and Parkinson's), psychiatric disorders (depression, anxiety, post traumatic stress disorder), and lead to cognitive enhancement.
- tPBM is also appealing because it has a good safety profile and is easy to administer. (children)

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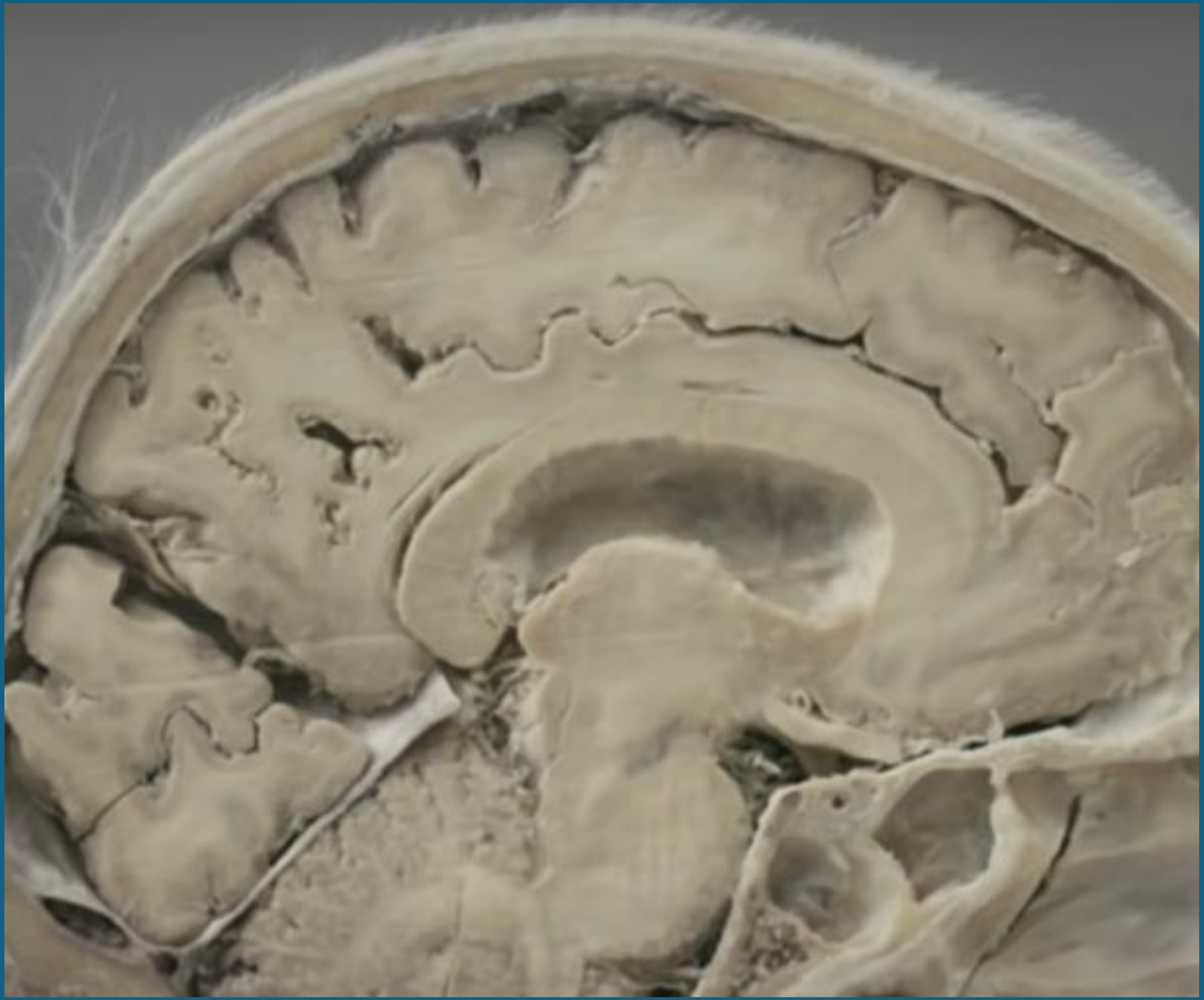
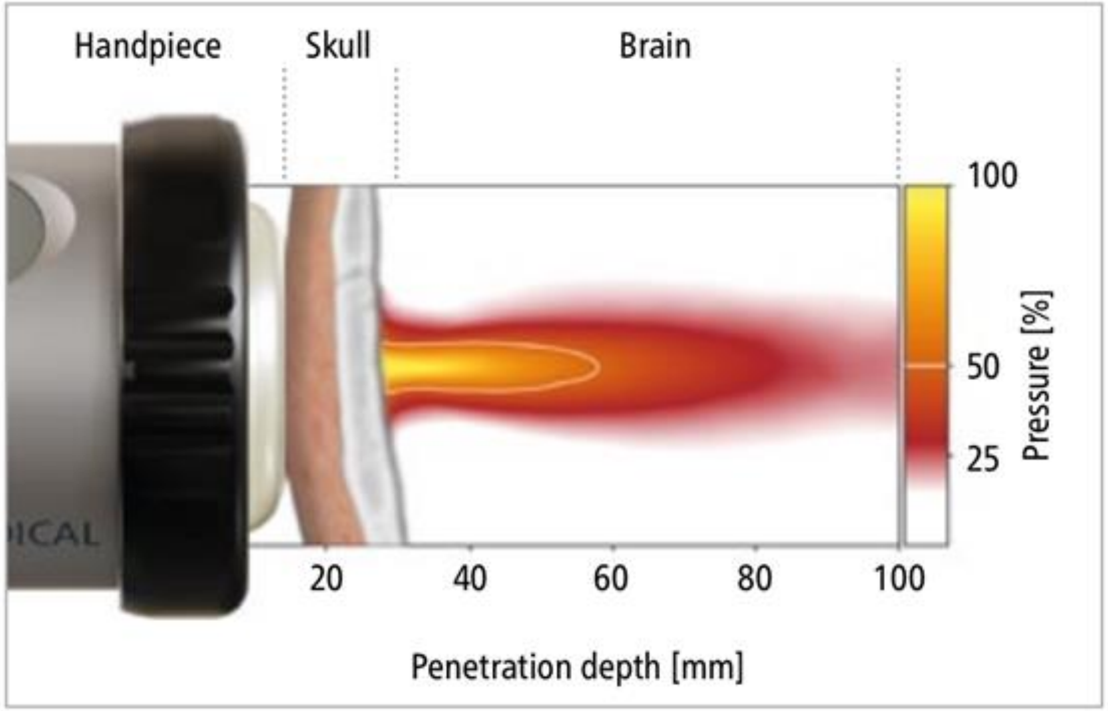
PBM – CAN LIGHT ENERGY REACH THE BRAIN?



PBM – CAN LIGHT ENERGY REACH THE BRAIN?



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PBM – CAN LIGHT ENERGY REACH THE BRAIN?

Rationale and Objectives

Transcranial photobiomodulation (tPBM) has emerged as a promising noninvasive therapeutic technique for neurological diseases, such as Alzheimer's Disease and Stroke. However, the optimal incidence site for precise stimulation remains unclear. To address this, we aimed to employ the high-resolution Visible Chinese Human (VCH) dataset and Monte Carlo simulation to identify the most suitable incidence site.

Materials and Methods

Monte Carlo model for photon migration in voxelized media (MCVM) was applied to visualize and compare the photon distribution across different incidence sites. We selected four representative incidence sites in the frontal, parietal, occipital, and temporal lobes and simulated photon propagation at four wavelengths commonly used in tPBM studies: 660nm, 810nm, 980nm, and 1064nm.

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Academic Radiology

Available online 26 May 2025

In Press, Corrected Proof ⓘ What's this?

Metabolic Imaging and Spectroscopy

Effect of Incidence Sites on Light Distribution at Different Wavelengths During Transcranial Photobiomodulation

Bowen Zhang [a 1], Songqi Yang [a 1], Meihua Piao [b], Polun Chang [c], Ting Li [a]

PBM – CAN LIGHT ENERGY REACH THE BRAIN?

Results

For each wavelength, the light source incident from prefrontal lobe had the deepest penetration depth (7cm, 7cm, 5cm, 5cm for 660cm, 810nm, 980nm, 1064nm, respectively) and the widest irradiation range (15%, 20%, 13%, 14% of brain for 660cm, 810nm, 980nm, 1064nm, respectively), while that incident from temporal lobe ensured the highest photon fluence reaching brain parenchyma. When the same light source (the input power was normalized to 1) was respectively applied at four incidence sites, $\sim 1 \times 10^{-3}$ 1/cm^2 of photon fluence reached brain parenchyma for prefrontal lobe, $\sim 7.5 \times 10^{-5}$ 1/cm^2 for parietal lobe, $\sim 1.5 \times 10^{-3}$ 1/cm^2 for occipital lobe, and $\sim 2.8 \times 10^{-2}$ 1/cm^2 for temporal lobe. To achieve similar photon fluence reaching brain parenchyma across all brain regions during whole-brain tPBM stimulation, we recommended setting the input power ratios of light source at four sites as ~17:280:20:1 (prefrontal: parietal: occipital: temporal) for 660nm light, ~22:250:18:1 for 810nm, ~60:1450:20:1 for 980nm, and ~54:830:17:1 for 1064nm.

Conclusion

From the perspective of photon delivery to the brain, the prefrontal and temporal lobes were two more optimal locations for light source placement. This study provided a theoretical strategy for optimizing incidence sites in tPBM.

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PBM AND TBI

Article | Open access | Published: 11 January 2025

Remote photobiomodulation ameliorates behavioral and neuropathological outcomes in a rat model of repeated closed head injury

Chongyun Wu, Meng Li, Zhe Chen, Shu Feng, Qianting Deng, Rui Duan, Timon Cheng-Yi Liu & Luodan Yang

Translational Psychiatry **15**, Article number: 8 (2025) | Cite this article

Repeated closed-head injuries (rCHI) from activities like contact sports, falls, military combat, and traffic accidents pose a serious risk due to their cumulative impact on the brain. Often, rCHI is not diagnosed until symptoms of irreversible brain damage appear, highlighting the need for preventive measures. This study assessed the prophylactic efficacy of remote photobiomodulation (PBM) targeted at the lungs against rCHI-induced brain injury and associated behavioral deficits. Utilizing the "Marmarou" weight-drop model, rCHI was induced in rats on days 0, 5, and 10. Remote PBM, employing an 808 nm continuous wave laser, was administered daily in 2-min sessions per lung side over 20 days. Behavioral deficits were assessed through three-chamber social interaction, forced swim, grip strength, open field, elevated plus maze, and Barnes maze tests. Immunofluorescence staining and 3D reconstruction evaluated neuronal damage, apoptosis, degeneration, and the morphology of microglia and astrocytes, as well as astrocyte and microglia-mediated excessive synapse elimination. Additionally, 16S rDNA amplicon sequencing analyzed changes in the lung microbiome following remote PBM treatment. Results demonstrated that remote PBM significantly improved depressive-like behaviors, motor dysfunction, and social interaction impairment while enhancing grip strength and reducing neuronal damage, apoptosis, and degeneration induced by rCHI. Analysis of lung microbiome changes revealed an enrichment of lipopolysaccharide (LPS) biosynthesis pathways, suggesting a potential link to neuroprotection. Furthermore, remote PBM mitigated hyperactivation of cortical microglia and astrocytes and significantly reduced excessive synaptic phagocytosis by these cells, highlighting its potential as a preventive strategy for rCHI with neuroprotective effects.

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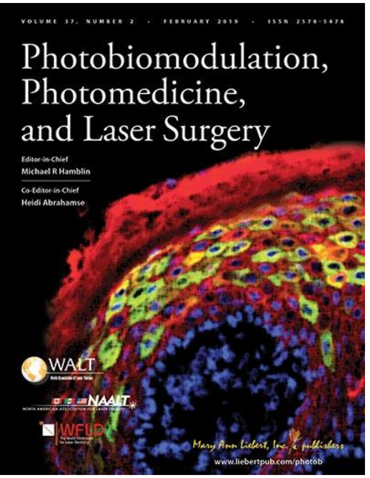

Photobiomodulation, Photomedicine, and Laser Surgery
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DOI: 10.1089/photob.2018.4489

Pulsed Transcranial Red/Near-Infrared Light Therapy Using Light-Emitting Diodes Improves Cerebral Blood Flow and Cognitive Function in Veterans with Chronic Traumatic Brain Injury: A Case Series

S. Gregory Hipskind, MD, PhD,[1,2] Fred L. Grover, Jr., MD,[3] T. Richard Fort, PhD,[4] Dennis Helffenstein, PhD,[5]
Thomas J. Burke, PhD,[6] Shane A. Quint, BS,[4] Garrett Bussiere, BS,[4]
Michael Stone, MD,[7] and Timothy Hurtado, MD[8]

Abstract

Objective: This study explored the outcome of applying red/near-infrared light therapy using light-emitting diodes (LEDs) pulsed with three different frequencies transcranially to treat traumatic brain injury (TBI) in Veterans.

Background: Photobiomodulation therapy (PBMT) using LEDs has been shown to have positive effects on TBI in humans and animal models.

Materials and methods: Twelve symptomatic military Veterans diagnosed with chronic TBI >18 months post-trauma received pulsed transcranial PBMT (tPBMT) using two neoprene therapy pads containing 220 infrared and 180 red LEDs, generating a power output of 3.3 W and an average power density of 6.4 mW/cm^2 for 20 min, thrice per week over 6 weeks. Outcome measures included standardized neuropsychological test scores and qualitative and quantitative single photon emission computed tomography (SPECT) measures of regional cerebral blood flow (rCBF).

Results: Pulsed tPBMT significantly improved neuropsychological scores in 6 of 15 subscales (40.0%; $p < 0.05$; two tailed). SPECT analysis showed increase in rCBF in 8 of 12 (66.7%) study participants. Quantitative SPECT analysis revealed a significant increase in rCBF in this subgroup of study participants and a significant difference between pre-treatment and post-treatment gamma ray counts per cubic centimeter [$t = 3.77$, $df = 7$, $p = 0.007$, 95% confidence interval (95,543.21–21,931.82)]. This is the first study to report quantitative SPECT analysis of rCBF in regions of interest following pulsed tPBMT with LEDs in TBI.

Conclusions: Pulsed tPBMT using LEDs shows promise in improving cognitive function and rCBF several years after TBI. Larger, controlled studies are indicated.

PBM AND TBI

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BIOENGINEERING & TRANSLATIONAL MEDICINE

RESEARCH ARTICLE

Photobiomodulation improves functional recovery after mild traumatic brain injury

Andrew R. Stevens[1,2,3] | Mohammed Hadis[3,4] | Abhinav Thareja[1] | Freya G. Anderson[1] | Michael R. Milward[3,4] | Valentina Di Pietro[1,2,5] | Antonio Belli[1,2,5] | William Palin[3,4,5] | David J. Davies[1,2,3,5] | Zubair Ahmed[1,2,5]

Abstract

Mild traumatic brain injury (mTBI) is a common consequence of head injury but there are no recognized interventions to promote recovery of the brain. We previously showed that photobiomodulation (PBM) significantly reduced the number of apoptotic cells in adult rat hippocampal organotypic slice cultures. In this study, we first optimized PBM delivery parameters for use in mTBI, conducting cadaveric studies to calibrate 660 and 810 nm lasers for transcutaneous delivery of PBM to the cortical surface. We then used an in vivo weight drop mTBI model in adult rats and delivered daily optimized doses of 660, 810 nm, or combined 660/810 nm PBM. Functional recovery was assessed using novel object recognition (NOR) and beam balance tests, whilst histology and immunohistochemistry were used to assess the mTBI neuropathology. We found that PBM at 810, 660 nm, or 810/660 nm all significantly improved both NOR and beam balance performance, with 810 nm PBM having the greatest effects. Histology demonstrated no overt structural damage in the brain after mTBI, however, immunohistochemistry using brain sections showed significantly reduced activation of both $CD11b^+$ microglia and glial fibrillary acidic protein $(GFAP)^+$ astrocytes at 3 days post-injury. Significantly reduced cortical localization of the apoptosis marker, cleaved caspase-3, and modest reductions in extracellular matrix deposition after PBM treatment, limited to choroid plexus and periventricular areas were also observed. Our results demonstrate that 810 nm PBM optimally improved functional outcomes after mTBI, reduced markers associated with apoptosis and astrocyte/microglial activation, and thus may be useful as a potential regenerative therapy.

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RESEARCH ARTICLE

BIOENGINEERING & TRANSLATIONAL MEDICINE

Photobiomodulation improves functional recovery after mild traumatic brain injury

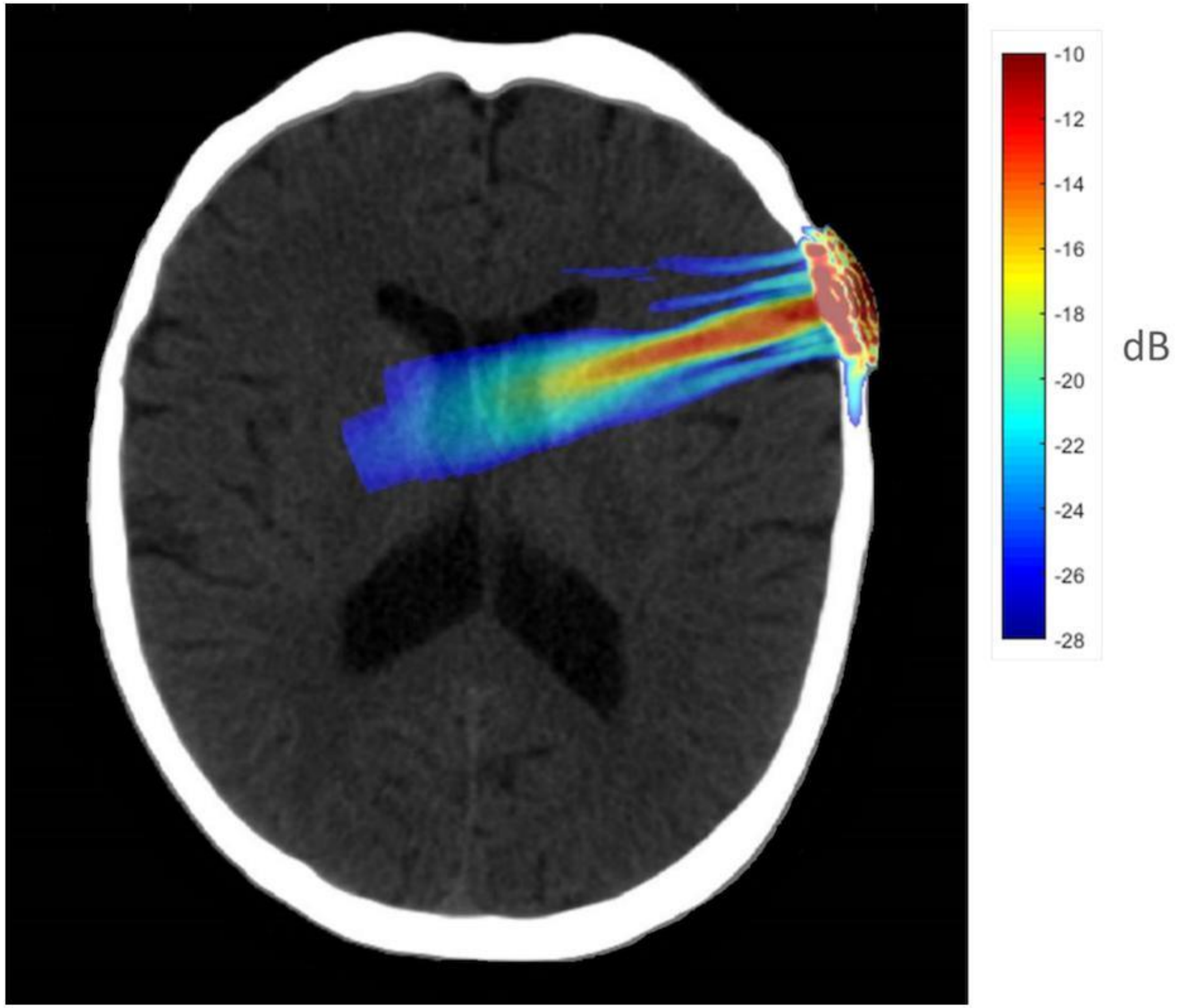
Andrew R. Stevens[1,2,3] | Mohammed Hadis[3,4] | Abhinav Thareja[1] | Freya G. Anderson[1] | Michael R. Milward[3,4] | Valentina Di Pietro[1,2,5] | Antonio Belli[1,2,5] | William Palin[3,4,5] | David J. Davies[1,2,3,5] | Zubair Ahmed[1,2,5]

Translational Impact Statement

Photobiomodulation (PBM) may stimulate neuroprotection after mild traumatic brain injury (mTBI). We show the development and use of transcutaneous PBM in preclinical models of mTBI. Our results demonstrated that transcutaneous PBM improved functional recovery, reduced astrocyte and microglial activation, reduced the apoptosis marker, cleaved caspase-3, after mTBI. PBM therefore has the potential to be neuroprotective and improve functional recovery in patients with mTBI.

TRANSCRANIAL ULTRASOUND STIMULATION

- Transcranial ultrasound stimulation (TUS) is a non-invasive brain stimulation technique that uses ultrasound waves to modulate neural activity.
- It offers the potential for *high spatial resolution and depth penetration*, allowing for targeted stimulation of specific brain regions, including deep structures that are difficult to reach with other non-invasive methods like transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS).



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TRANSCRANIAL ULTRASOUND STIMULATION

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Brain Stimulation

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Deep transcranial ultrasound stimulation using personalized acoustic metamaterials improves treatment-resistant depression in humans

David Attali[a,b,c,1], Thomas Tiennot[a,1], Thomas J. Manuel[a], Maxime Daniel[a], Alexandre Houdouin[a], Philippe Annic[a], Alexandre Dizeux[a], Alexandre Haroche[b,d], Ghita Dadi[b], Adèle Henensal[d], Mylène Moyal[d], Alice Le Berre[d,e], Cécile Paolillo[b,g], Sylvain Charron[d,e], Clément Debacker[d,e], Maliesse Lui[d,e], Sabrina Lekcir[f], Rosella Mancusi[f], Thierry Gallarda[b], Tarek Sharshar[c,h], Khaoussou Sylla[f], Catherine Oppenheim[d,e], Arnaud Cachia[d,g], Mickael Tanter[a], Jean-Francois Aubry[a,1,*], Marion Plaze[b,d,1]

[a] Institute Physics for Medicine Paris, Inserm U1273, ESPCI Paris, PSL University, CNRS UMR 8063, 75015, Paris, France
[b] S17-18 Adult Psychiatry Department, GHU Paris Psychiatrie & Neurosciences, Site Sainte-Anne, 75014, Paris, France
[c] Anesthesia and Intensive Care Department, GHU Paris Psychiatrie & Neurosciences, Pôle Neuro, Sainte-Anne Hospital, 75014, Paris, France
[d] Université Paris Cité, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, IMA-brain Team, 75014, Paris, France
[e] Department of Neuroradiology, GHU Paris Psychiatrie & Neurosciences, Site Sainte-Anne, 75014, Paris, France
[f] Clinical Research and Innovation Department, GHU Paris Psychiatrie & Neurosciences, Site Sainte-Anne, 75014, Paris, France
[g] Université Paris Cité, LaPsyDÉ, CNRS, F-75005, Paris, France
[h] Université Paris Cité, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, 75014 Paris, France

Highlights

- Neuromodulation of deep brain regions could be promising for drug-resistant depression.
- TUS spatial precision was limited by the defocusing effect of the skull.
- We developed a novel portable ultrasound device capable of millimeter precision.
- An intensive 5-day course of mTUS reduced depression severity by an average of 61 %.
- No serious adverse events occurred during this open label trial.

TRANSCRANIAL ULTRASOUND STIMULATION

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Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

Sustained reduction of essential tremor with low-power non-thermal transcranial focused ultrasound stimulations in humans☆

Thomas Bancel[a], Benoît Béranger[b], Maxime Daniel[a], Mélanie Didier[b], Mathieu Santin[b], Itay Rachmilevitch[c], Yeruham Shapira[c], Mickael Tanter[a], Eric Bardinet[b], Sara Fernandez Vidal[b], David Attali[a,d], Cécile Galléa[b], Alexandre Dizeux[a], Marie Vidailhet[b,f], Stéphane Lehéricy[b,e], David Grabli[f], Nadya Pyatigorskaya[b,e], Carine Karachi[g], Elodie Hainque[f], Jean-François Aubry[a,*]

[a] Physics for Medicine Paris, Inserm U1273, ESPCI Paris, CNRS UMR 8063, PSL University, Paris, France
[b] ICM-Paris Brain Institute, Centre de NeuroImagerie de Recherche-CENIR, Inserm U 1127, CNRS UMR 7225, Sorbonne Université, F-75013, Paris, France
[c] Insightec, Tirat Carmel, Israel
[d] Université Paris Cité, GHU-Paris Psychiatrie et Neurosciences, Hôpital Sainte Anne, F-75014, Paris, France
[e] Department of Neuroradiology, Hôpital de la Pitié Salpêtrière, Sorbonne Université, AP-HP, Paris, France
[f] Department of Neurology, Hôpital de la Pitié Salpêtrière, Sorbonne Université, AP-HP, Paris, France
[g] Department of Neurosurgery, Hôpital de la Pitié Salpêtrière, Sorbonne Université, AP-HP, Paris, France

Highlights

- Transcranial Ultrasound Stimulation induced more than 89 % reduction of essential tremor in 5 patients.
- A sustained effect (more than 23min) was observed in 3 patients.
- Stimulation was performed in the VIM and the DRT.
- No significant thermal rise was measured by MR Thermometry during stimulation.

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TRANSCRANIAL ULTRASOUND STIMULATION

Yi *et al. BMC Neuroscience* (2024) 25:8
https://doi.org/10.1186/s12868-024-00849-0

BMC Neuroscience

COMMENT Open Access

Multimodal evaluation of the effects of low-intensity ultrasound on cerebral blood flow after traumatic brain injury in mice

Huiling Yi[1], Shuo Wu[1], Xiaohan Wang[2], Lanxiang Liu[1,2*], Wenzhu Wang[3], Yan Yu[3], Zihan Li[3], Yinglan Jin[4], Jian Liu[5], Tao Zheng[1] and Dan Du[1]

Abstract
Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide, and destruction of the cerebrovascular system is a major factor in the cascade of secondary injuries caused by TBI. Laser speckle imaging (LSCI)has high sensitivity in detecting cerebral blood flow. LSCI can visually show that transcranial focused ultrasound stimulation (tFUS) treatment stimulates angiogenesis and increases blood flow. To study the effect of tFUS on promoting angiogenesis in Controlled Cortical impact (CCI) model. tFUS was administered daily for 10 min and for 14 consecutive days after TBI. Cerebral blood flow was measured by LSCI at 1, 3, 7 and 14 days after trauma. Functional outcomes were assessed using LSCI and neurological severity score (NSS). After the last test, Nissl staining and vascular endothelial growth factor (VEGF) were used to assess neuropathology. TBI can cause the destruction of cerebrovascular system. Blood flow was significantly increased in TBI treated with tFUS. LSCI, behavioral and histological findings suggest that tFUS treatment can promote angiogenesis after TBI.

Keywords Traumatic brain injury, Transcranial focused ultrasound stimulation, Angiogenesis Laser speckle imaging, Vascular endothelial growth factor

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TRANSCRANIAL ULTRASOUND STIMULATION

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Techniques and Methods

Transcranial focused ultrasound for the treatment of tremor: A preliminary case series

C.M. Deveney [a,1,*], J.R. Surya [a,1], J.M. Haroon [a], K.D. Mahdavi [a], K.R. Hoffman [a], K.C. Enemuo [a], K.G. Jordan [a], S.A. Becerra [a], T. Kuhn [c], A. Bystritsky [c], S.E. Jordan [a,b]

[a] The Regenesis Project, Santa Monica, CA, USA
[b] University of California Los Angeles, Department of Neurology, USA
[c] University of California Los Angeles, Department of Psychiatry and Biobehavioral Sciences, USA

Highlights

- Patients with Essential Tremor received eight, 10-minute LIFU treatments to the ventral intermediate thalamus.
- 8/10 patients reported significant improvement in tremor symptoms, with GRC score > 2 immediately post-treatment.
- Analysis of TETRAS scores demonstrated significantly decreased tremor severity for all patients following eight treatments.
- LIFU may represent an intermediate treatment for Essential Tremor prior to more invasive treatments.

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TUS - ADHD

NeuroImage 299 (2024) 120841

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NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Low-intensity transcranial ultrasound stimulation improves memory behavior in an ADHD rat model by modulating cortical functional network connectivity

Mengran Wang[a,b], Zhenyu Xie[a,b], Teng Wang[a,b], Shuxun Dong[a,b], Zhenfang Ma[c], Xiangjian Zhang[d], Xin Li[a,b,*], Yi Yuan[a,b,*]

[a] School of Electrical Engineering, Yanshan University, Qinhuangdao 066004, China
[b] Key Laboratory of Intelligent Rehabilitation and Neuromodulation of Hebei Province, Yanshan University, Qinhuangdao 066004, China
[c] Department of Rehabilitation, Hebei General Hospital, Shijiazhuang 050000, China
[d] Department of Neurology, Hebei Key Laboratory of Vascular Homeostasis and Hebei Collaborative Innovation Center for Cardio-cerebrovascular Disease, The Second Hospital of Hebei Medical University, Shijiazhuang 050000, China

Highlights

- The cortical functional network connectivity in ADHD rats are abnormal during memory tasks.
- TUS improved the global and local characteristics of the cortical functional network connectivity of ADHD rats during memory tasks.
- TUS improves memory behavior in ADHD by modulating cortical functional network connectivity.

TUS - ADHD

- The SNAP-IV is a rating scale used to assess symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) and related behavioral disorders in children. It gathers information from both parents and teachers to provide a comprehensive view of the child's behavior. The scale focuses on inattention, hyperactivity/impulsivity, and also includes Oppositional Defiant Disorder (ODD) symptoms

frontiers | Frontiers in Neurology

Efficacy and safety of transcranial pulse stimulation in young adolescents with attention-deficit/hyperactivity disorder: a pilot, randomized, double-blind, sham-controlled trial

Teris Cheung[1,2]*, Benjamin K. Yee[2,3], Bolton Chau[2,3], Joyce Yuen Ting Lam[1,2], Kwan Hin Fong[1], Herman Lo[4], Tim Man Ho Li[5], Albert Martin Li[6], Lei Sun[7], Roland Beisteiner[8] and Calvin Pak Wing Cheng[9]*

[1]School of Nursing, The Hong Kong Polytechnic University, Kowloon, Hong Kong SAR, China, [2]The Mental Health Research Centre, The Hong Kong Polytechnic University, Kowloon, Hong Kong SAR, China, [3]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Kowloon, Hong Kong SAR, China, [4]Department of Applied Social Sciences, The Hong Kong Polytechnic University, Kowloon, Hong Kong SAR, China, [5]Department of Psychiatry, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China, [6]Department of Paediatrics, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China, [7]Department of Biomedical Engineering, The Hong Kong Polytechnic University, Kowloon, Hong Kong SAR, China, [8]Department of Neurology, Vienna Medical University, Vienna, Austria, [9]Department of Psychiatry, The University of Hong Kong, Pokfulam, Hong Kong SAR, China

Background: This is the first study to evaluate the efficacy and safety of transcranial pulse stimulation (TPS) for the treatment of attention-deficit/hyperactivity disorder (ADHD) among young adolescents in Hong Kong.

Methods: This double-blind, randomized, sham-controlled trial included a TPS group and a sham TPS group, encompassing a total of 30 subjects aged 12–17 years who were diagnosed with ADHD. Baseline measurements SNAP-IV, ADHD RS-IV, CGI and executive functions (Stroop tests, Digit Span) and post-TPS evaluation were collected. Both groups were assessed at baseline, immediately after intervention, and at 1-month and 3-month follow-ups. Repeated-measures ANOVAs were used to analyze data.

Results: The TPS group exhibited a 30% reduction in the mean SNAP-IV score at postintervention that was maintained at 1- and 3-month follow-ups.

Conclusion: TPS is an effective and safe adjunct treatment for the clinical management of ADHD.

Clinical trial registration: ClinicalTrials.Gov, identifier NCT05422274.

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TUS – ANXIETY/TRAUMA RELATED

Low-intensity transcranial focused ultrasound amygdala neuromodulation: a double-blind sham-controlled target engagement study and unblinded single-arm clinical trial

Bryan R. Barksdale, Lauren Enten, Annamarie DeMarco, Rachel Kline, Manoj K. Doss, Charles B. Nemeroff & Gregory A. Fonzo

Molecular Psychiatry (2025) | Cite this article

Mood, anxiety, and trauma-related disorders (MATRDs) are highly prevalent and comorbid. A sizable number of patients do not respond to first-line treatments. Non-invasive neuromodulation is a second-line treatment approach, but current methods rely on cortical targets to indirectly modulate subcortical structures, e.g., the amygdala, implicated in MATRDs. Low-intensity transcranial focused ultrasound (tFUS) is a non-invasive technique for direct subcortical neuromodulation, but its safety, feasibility, and promise as a potential treatment is largely unknown. In a target engagement study, magnetic resonance imaging (MRI)-guided tFUS to the left amygdala was administered during functional MRI (tFUS/fMRI) to test for acute modulation of blood oxygenation level dependent (BOLD) signal in a double-blind, within-subject, sham-controlled design in patients with MATRDs ($N = 29$) and healthy comparison subjects ($N = 23$). In an unblinded treatment trial, the same patients then underwent 3-week daily (15 sessions) MRI-guided repetitive tFUS (rtFUS) to the left amygdala to examine safety, feasibility, symptom change, and change in amygdala reactivity to emotional faces. Active vs. sham tFUS/fMRI reduced, on average, left amygdala BOLD signal and produced patient-related differences in hippocampal and insular responses. rtFUS was well-tolerated with no serious adverse events. There were significant reductions on the primary outcome (Mood and Anxiety Symptom Questionnaire General Distress subscale; $p = 0.001$, Cohen's $d = 0.77$), secondary outcomes (Cohen's *d of* 0.43–1.50), and amygdala activation to emotional stimuli. Findings provide initial evidence of tFUS capability to modulate amygdala function, rtFUS safety and feasibility in MATRDs, and motivate double-blind randomized controlled trials to examine efficacy.

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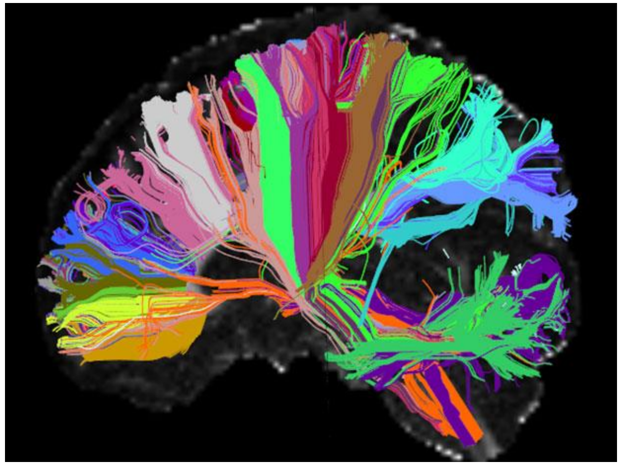
SUMMARY

- This was a cursory overview of the literature regarding the four most common neuromodulation techniques and how they may be of benefit in neurological and psychological dysfunction
- The field of neuromodulation is emerging and exploding
- rTMS and tDCS are safe and effective ways to manage many disorders in a drug-free safe manner
- Non-electrical neuromodulation such as PBM and TUS are emerging
- Presently, TMS and tDCS are most researched and supported for many neuro and neuropsych conditions
- Greatest patient access for tDCS and TMS currently

THANK YOU



ddishman@parker.edu