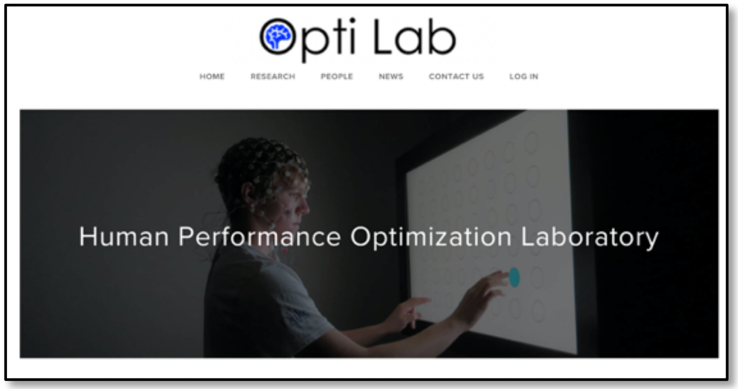
Introduction to Noninvasive Brain Stimulation (NIBS)

Greg Appelbaum, Ph.D

SSNAP 2021

Introduction

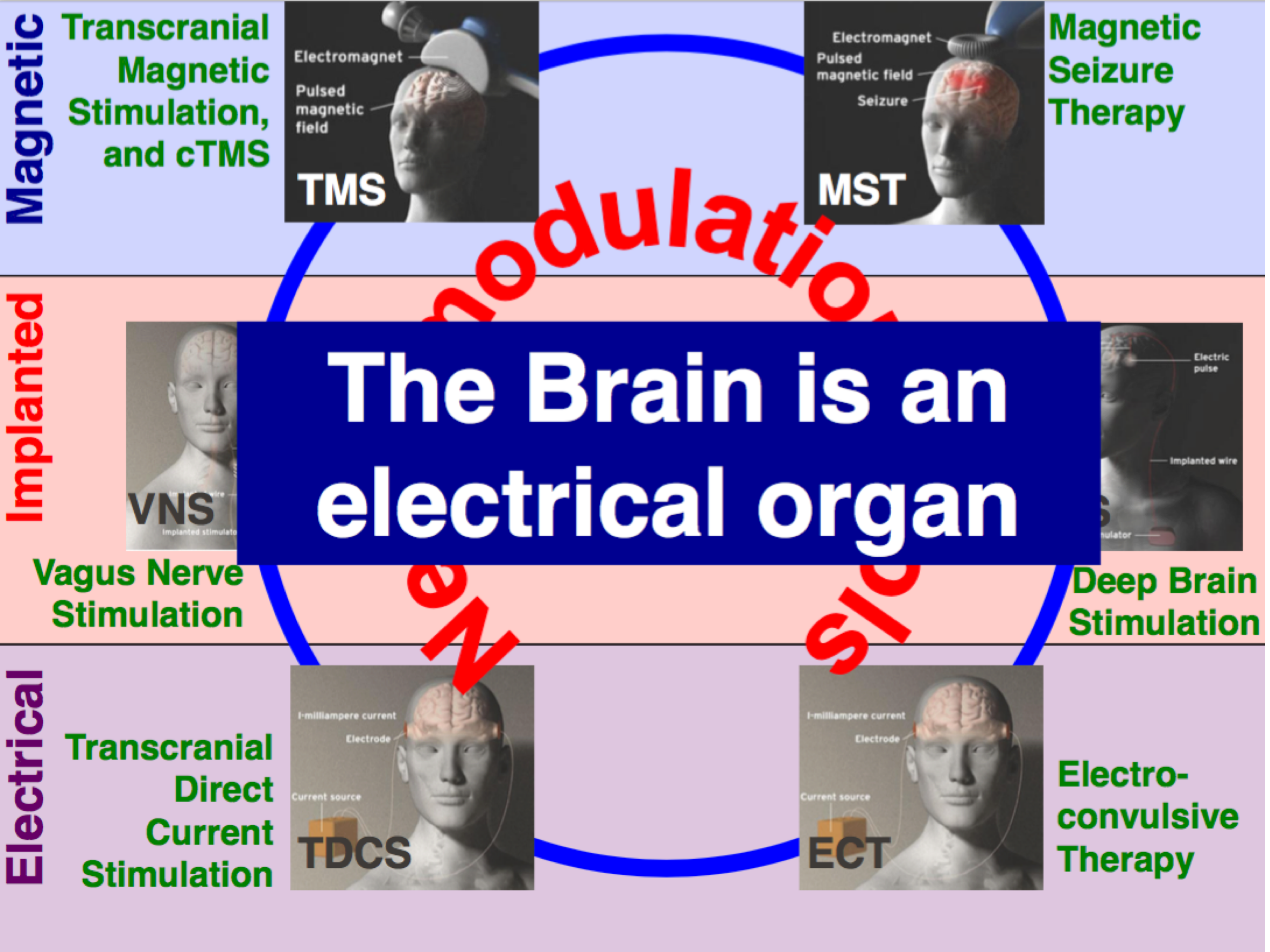
Greg is a cognitive neuroscientists who studies neuroplasticity and expertise



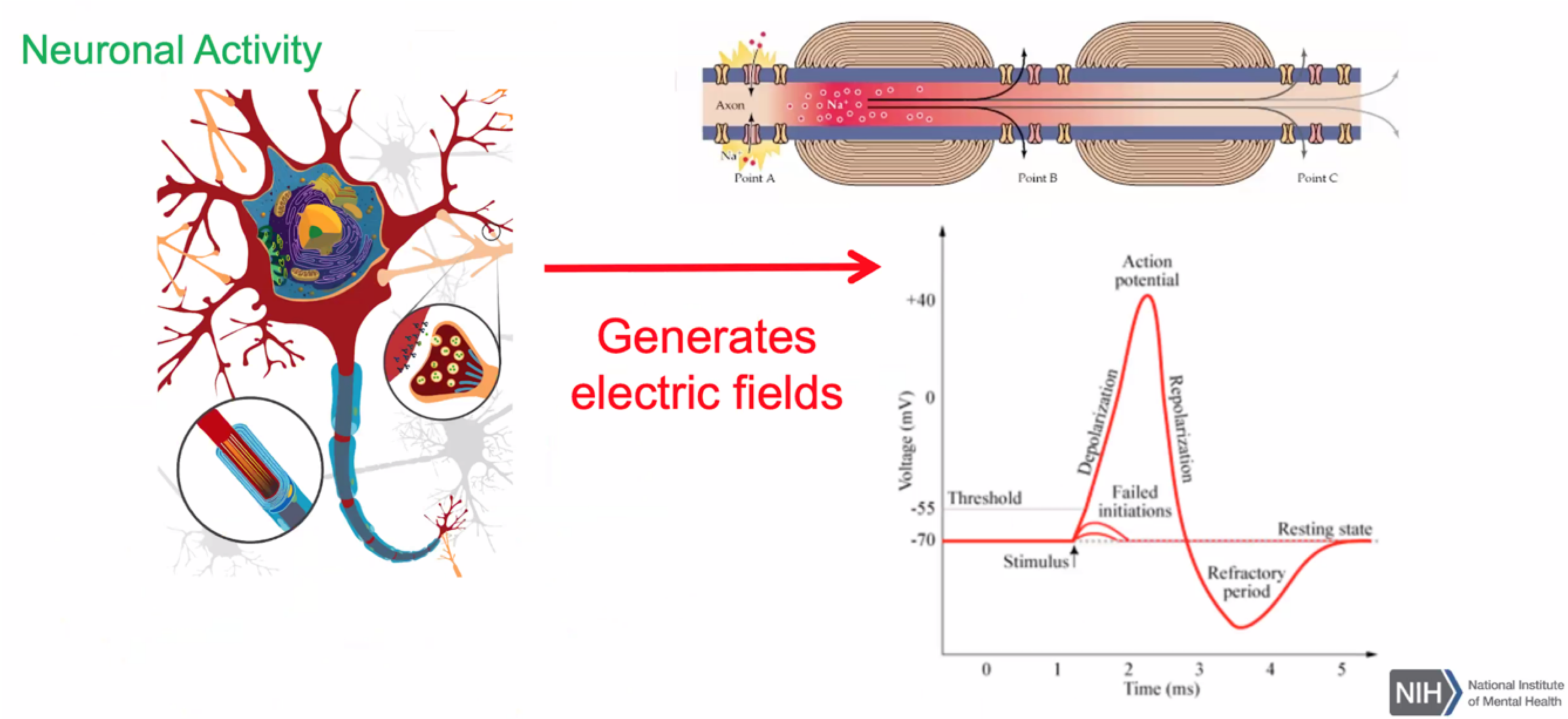
We use behavioral tasks combined with neuroscience approaches (EEG, fMRI, TMS…) to do applied research that attempts to optimize human performance

The plan for today

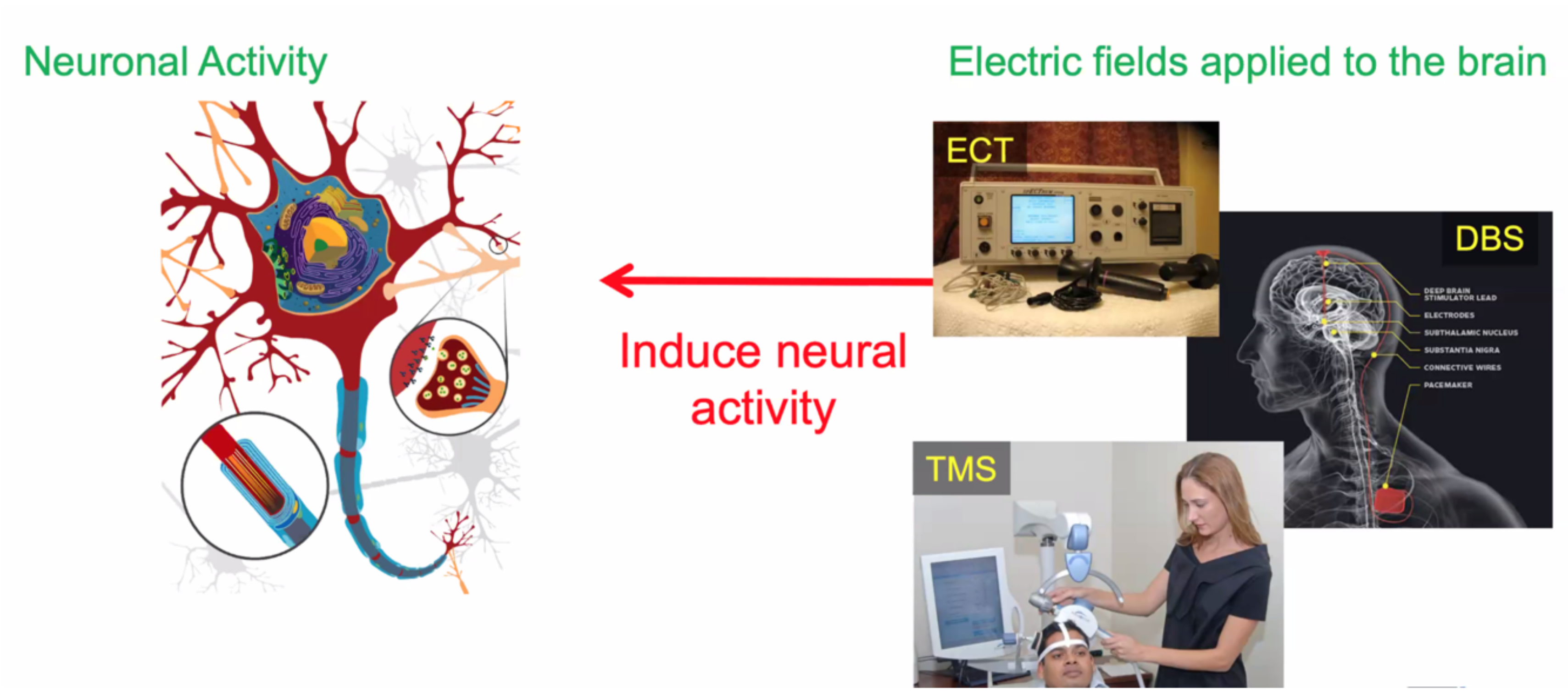
- Outline
  - The landscape of Brain Stimulation Techniques
  - Basic Principles of Brain Stim
    - Mechanisms of action; Dosing; Targeting;
  - TMS Applications –clinical; research
  - tDCS Applications – research; clinical
  - Demo
- Audience participation is encouraged! Ask questions at will.


Magnetic
Transcranial Magnetic Stimulation, and cTMS
Electromagnet
Pulsed magnetic field
TMS
Electromagnet
Pulsed magnetic field
Seizure
MST
Magnetic Seizure Therapy
The Brain is an electrical organ
Implanted
VNS
Vagus Nerve Stimulation
Electric pulse
Implanted wire
Deep Brain Stimulation
Electrical
Transcranial Direct Current Stimulation
1-milliampere current
Electrode
Current source
TDCS
1-milliampere current
Electrode
Current source
ECT
Electro-convulsive Therapy

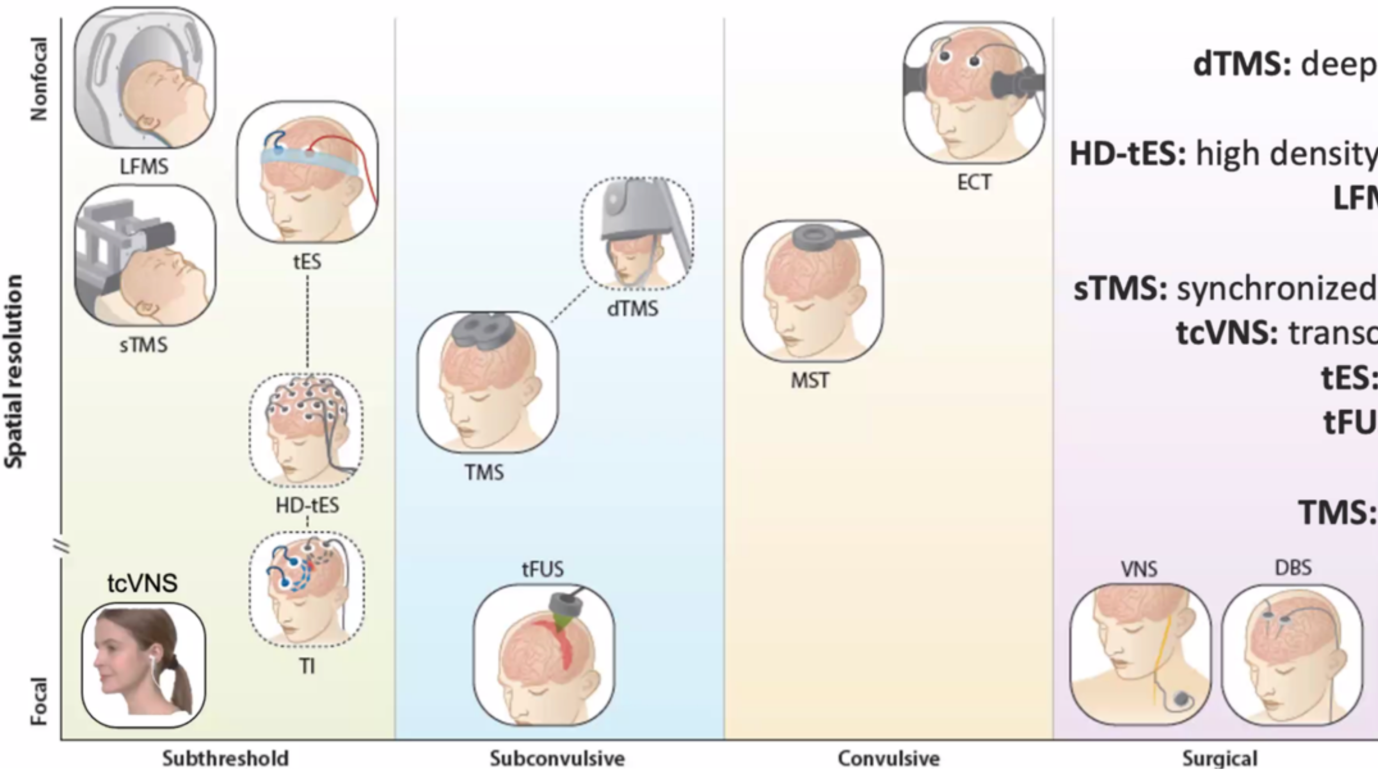
The electric brain



The electric brain



The Landscape of Brain Stimulation Techniques

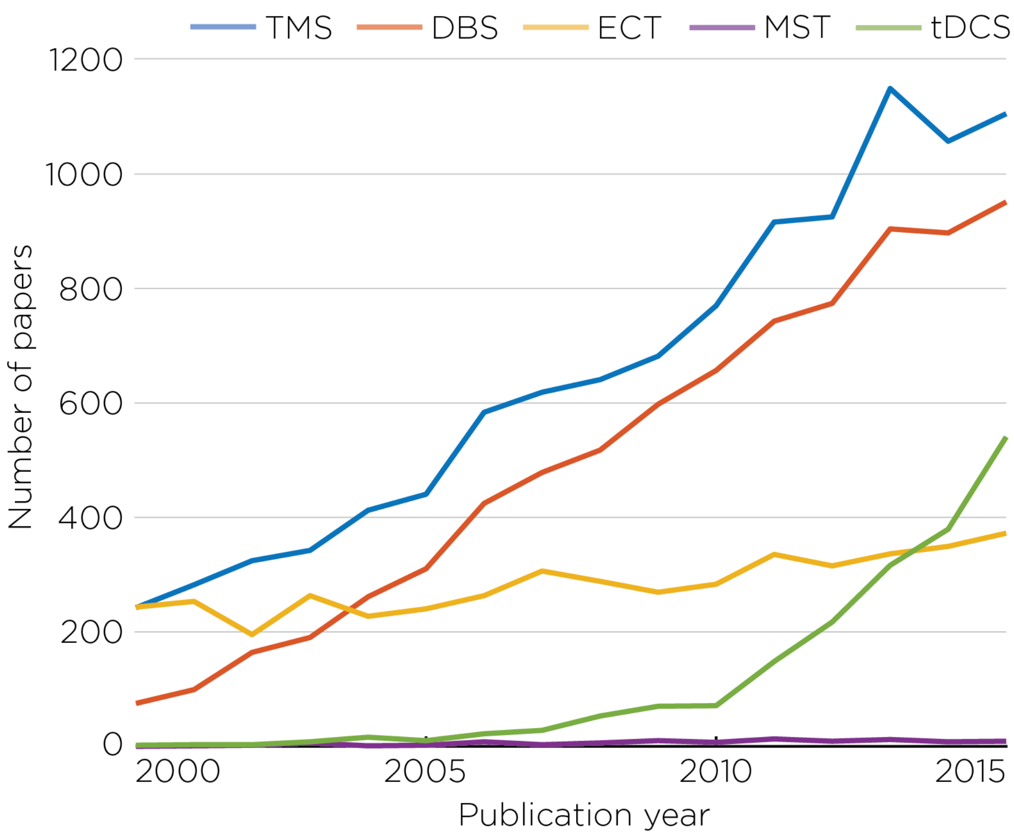


DBS: deep brain stimulation
dTMS: deep transcranial magnetic stimulation
ECT: electroconvulsive therapy
HD-tES: high density transcranial electrical stimulation
LFMS: low field magnetic stimulation
MST: magnetic seizure therapy
sTMS: synchronized transcranial magnetic stimulation
tcVNS: transcutaneous vagus nerve stimulation
tES: transcranial electrical stimulation
tFUS: transcranial focused ultrasound
TI: temporal interference
TMS: transcranial magnetic stimulation
VNS: vagus nerve stimulation

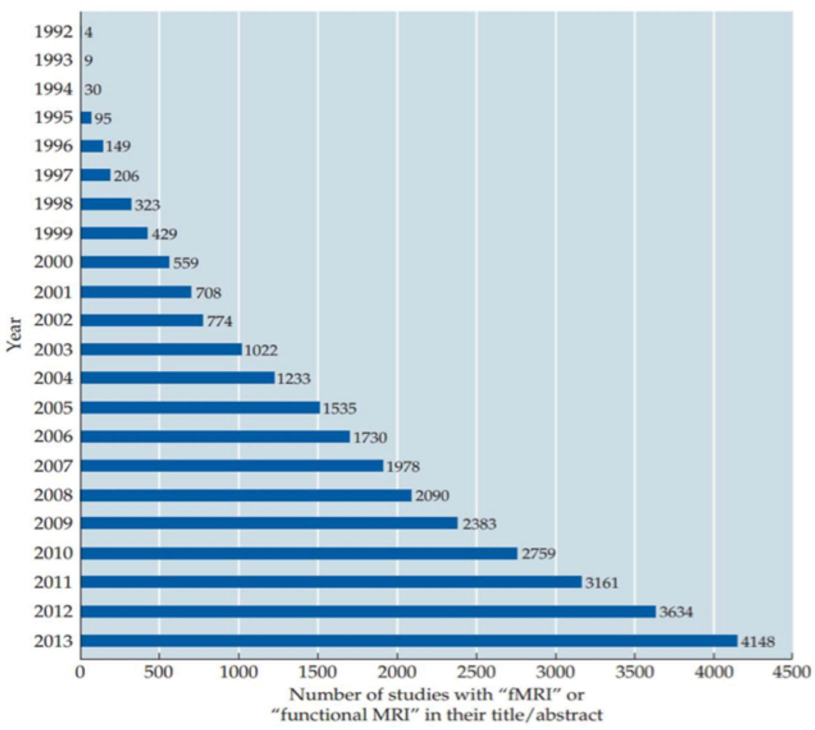
Deng et al 2019

invasiveness

Rapidly growing use of Brain Stimulation

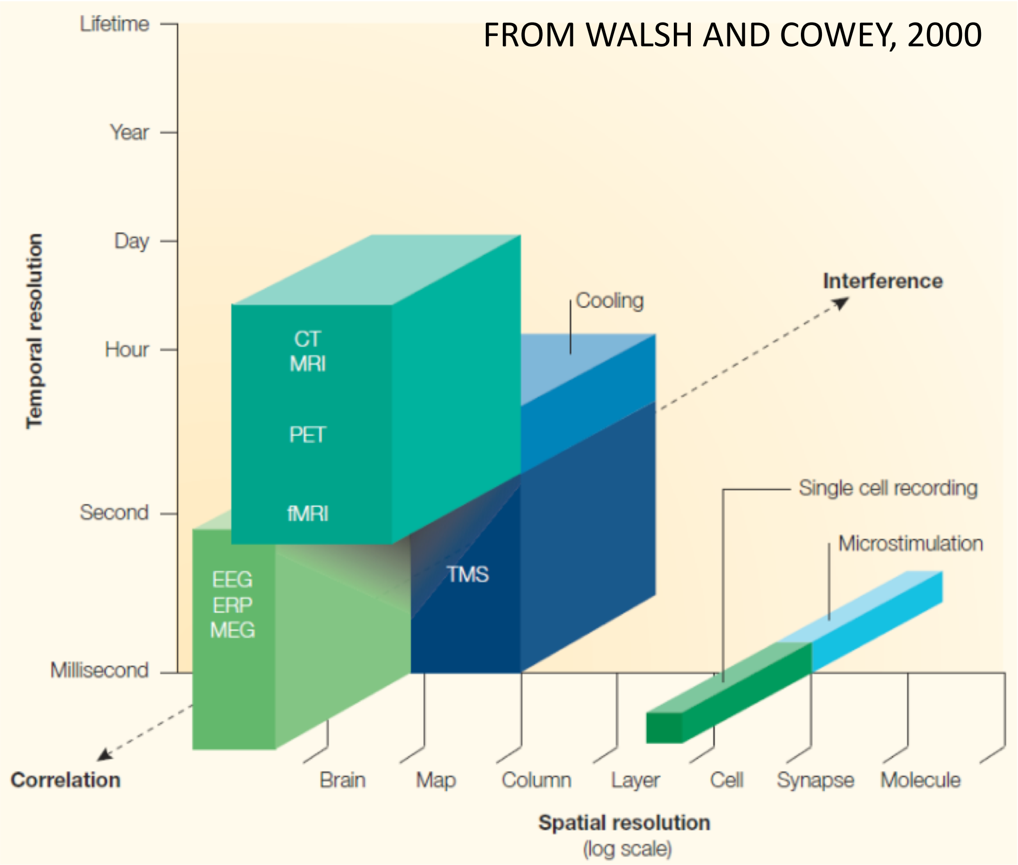


Pub Med hits



But still a fraction of fMRI

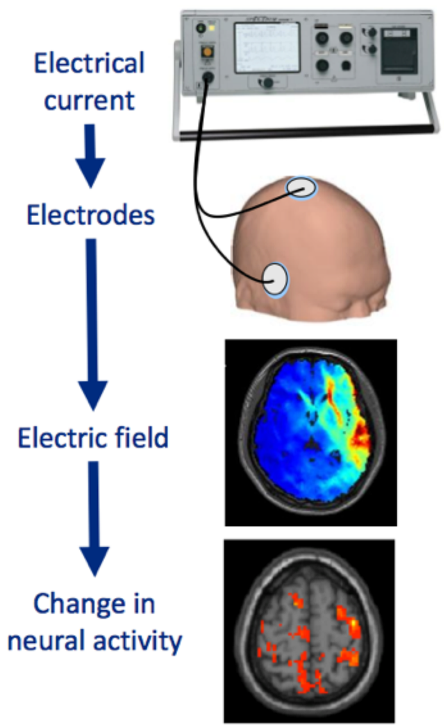
Brain Stimulation in the Context of other Neuroscience Techniques



Whereas most of the other techniques you have encountered in this course are correlational (there is a relationship between 2 or more variables), brain stimulation is causal (variable x is necessary for effect y).

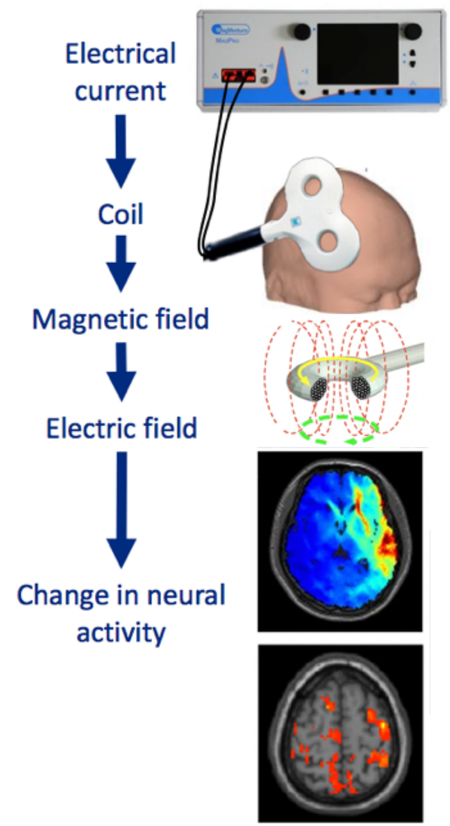
Basic Principles of Brain Stimulation

Transcranial Electrical Stimulation



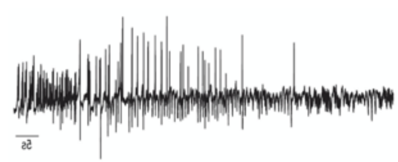
- Skin resistance
- Very weak; <1 mV/mm
- Slow; minutes
- Affects membrane potential

Transcranial Magnetic Stimulation



- No resistance
- Strong ~ 100 mV/mm
- Fast microsec
- Induces action potentials
- Therapeutic effects by modulating dysregulated neural circuits, e.g., MDD

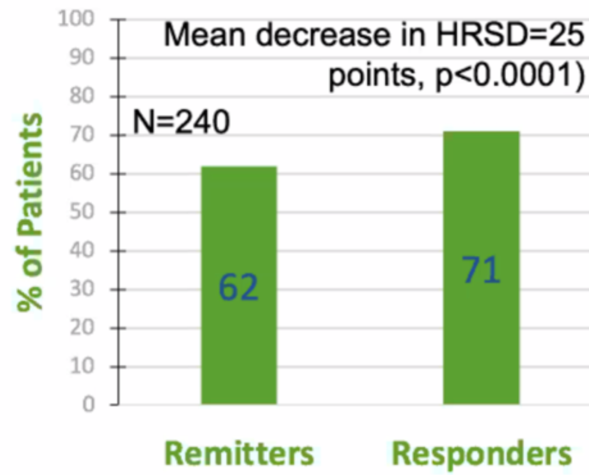
Therapeutic Seizure



Electroconvulsive Therapy (ECT)

- Unparalleled efficacy
  - Among FDA-approved antidepressants, ECT is the most potent (Effect size 0.8)

U01 MH084241 MPI: Lisanby/Weiner



Kellner…Lisanby Am J Psych 2016

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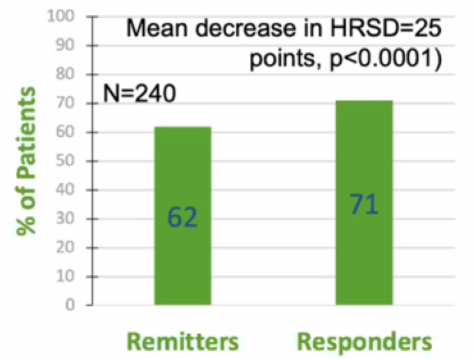
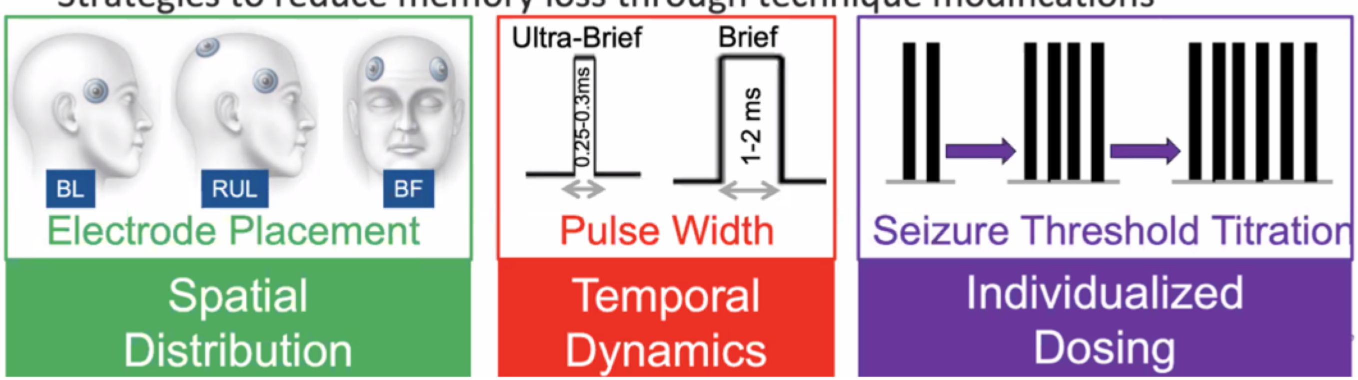
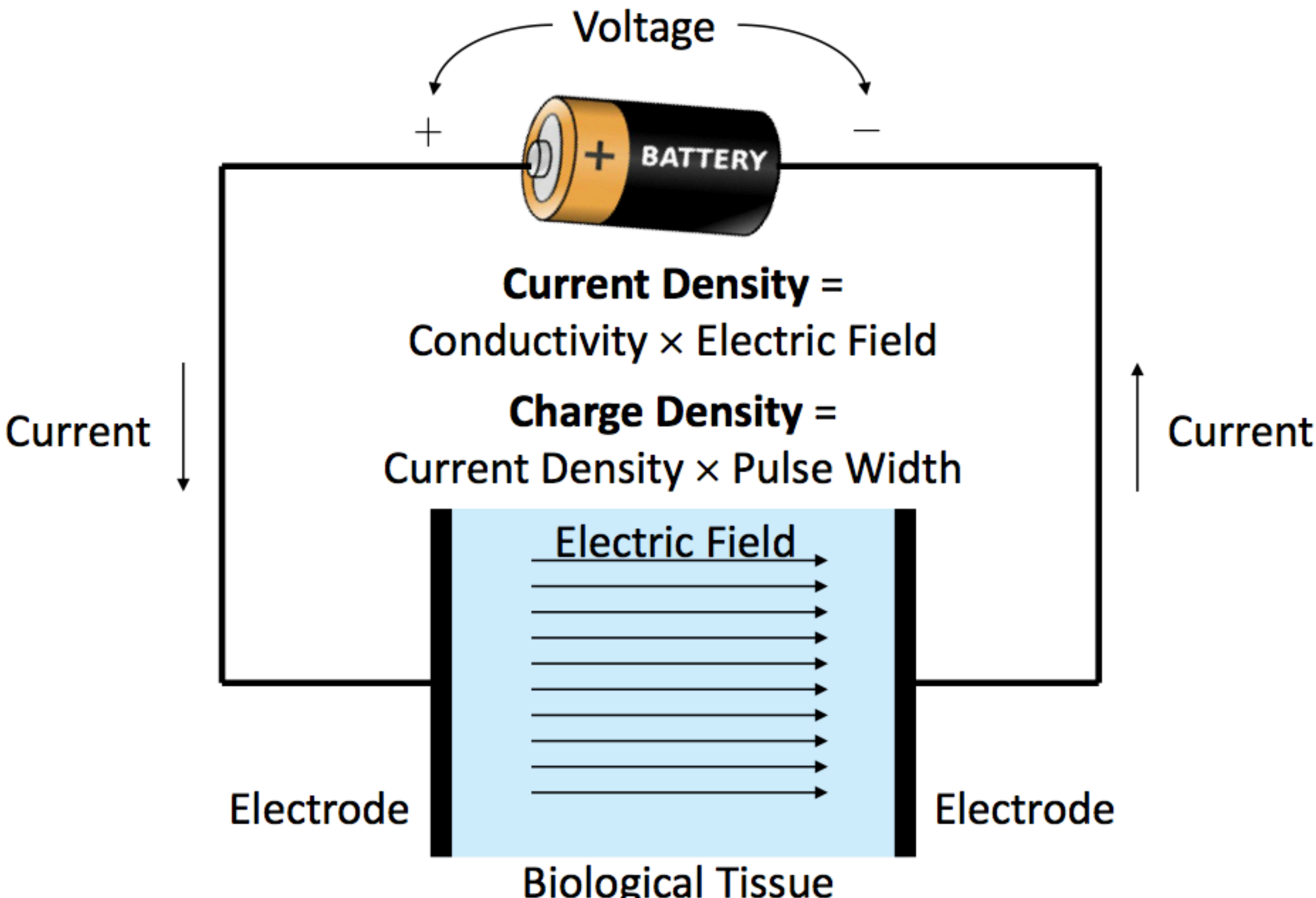


Kellner…Lisanby Am J Psych 2016

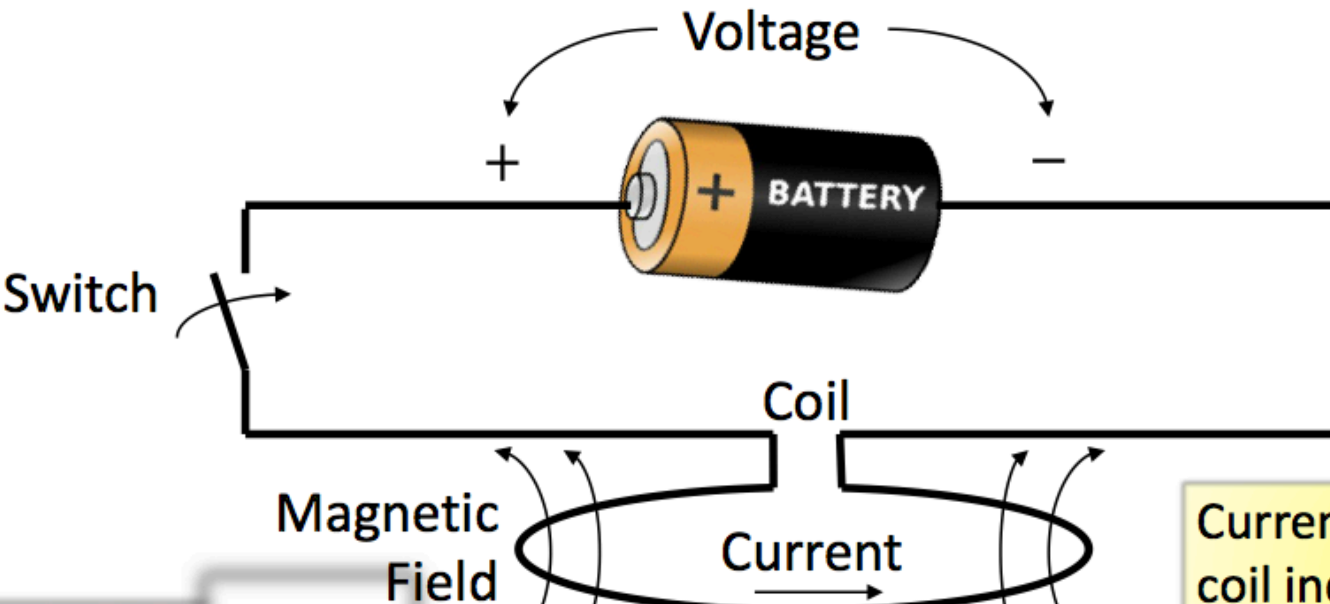
- Rapid onset of action
- Potent anti-suicidal action
- Strategies to reduce memory loss through technique modifications

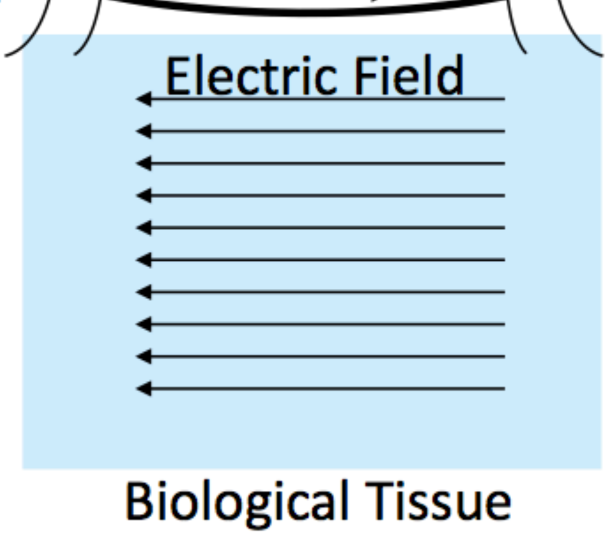


Basic Principles of Electric Stimulation



Basic Principles of Magnetic Stimulation

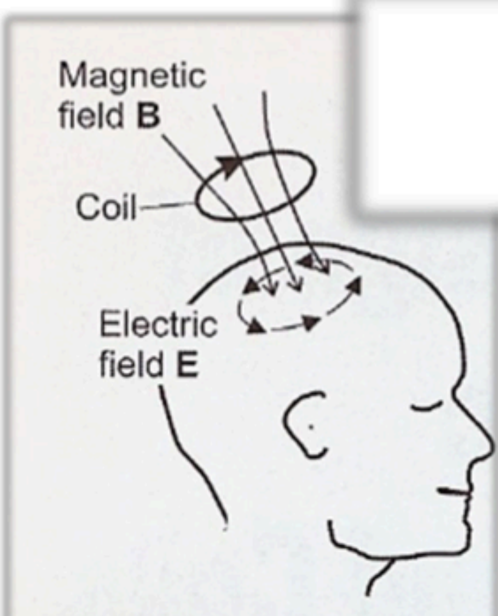




Principle of electromagnetic induction, also used in electrical transformers

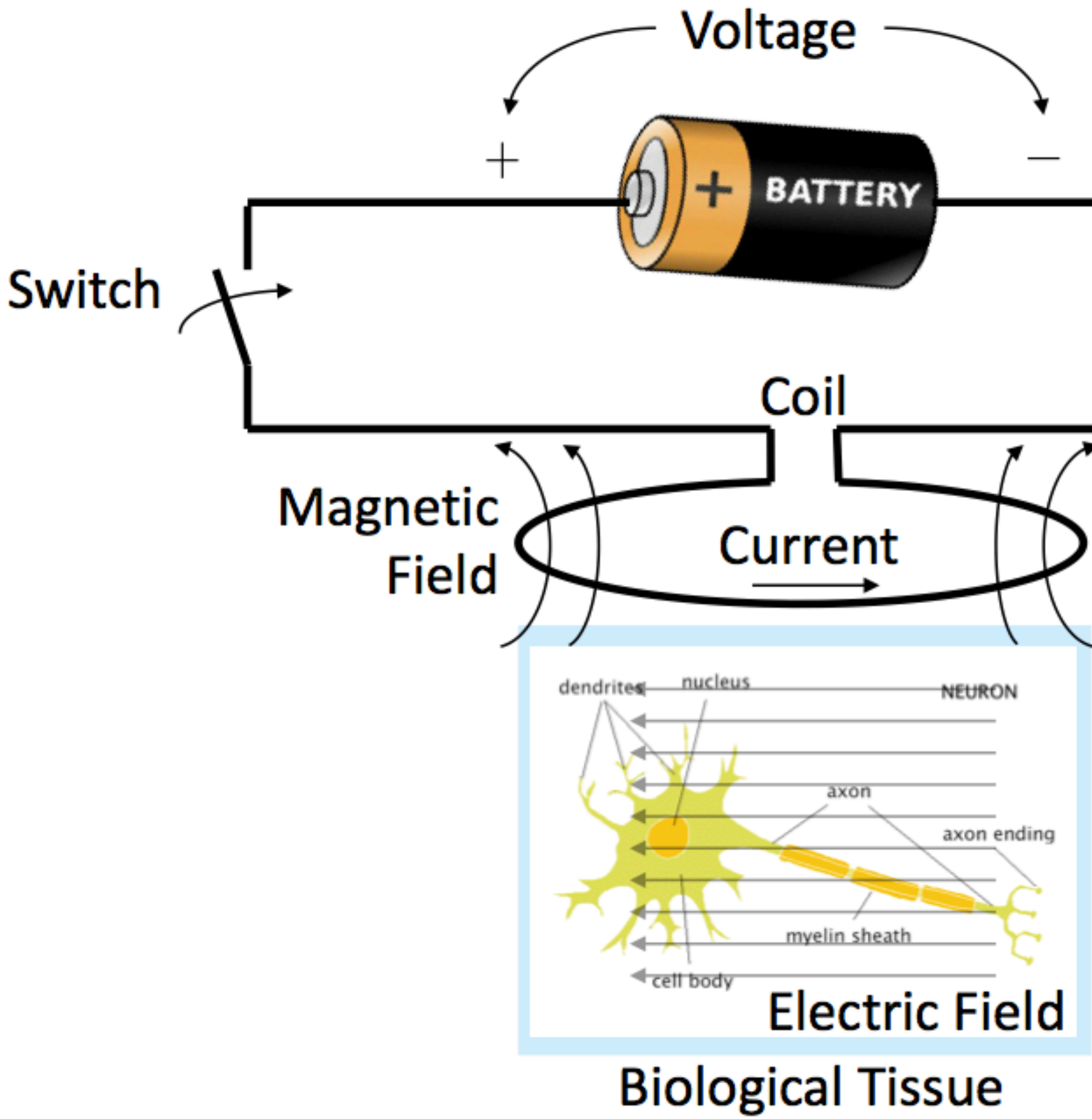
Current pulse in TMS coil induces changing magnetic field

Changing magnetic field induces electric field in tissue (e.g., brain)



[Ruohonen & Ilmoniemi, 2002]

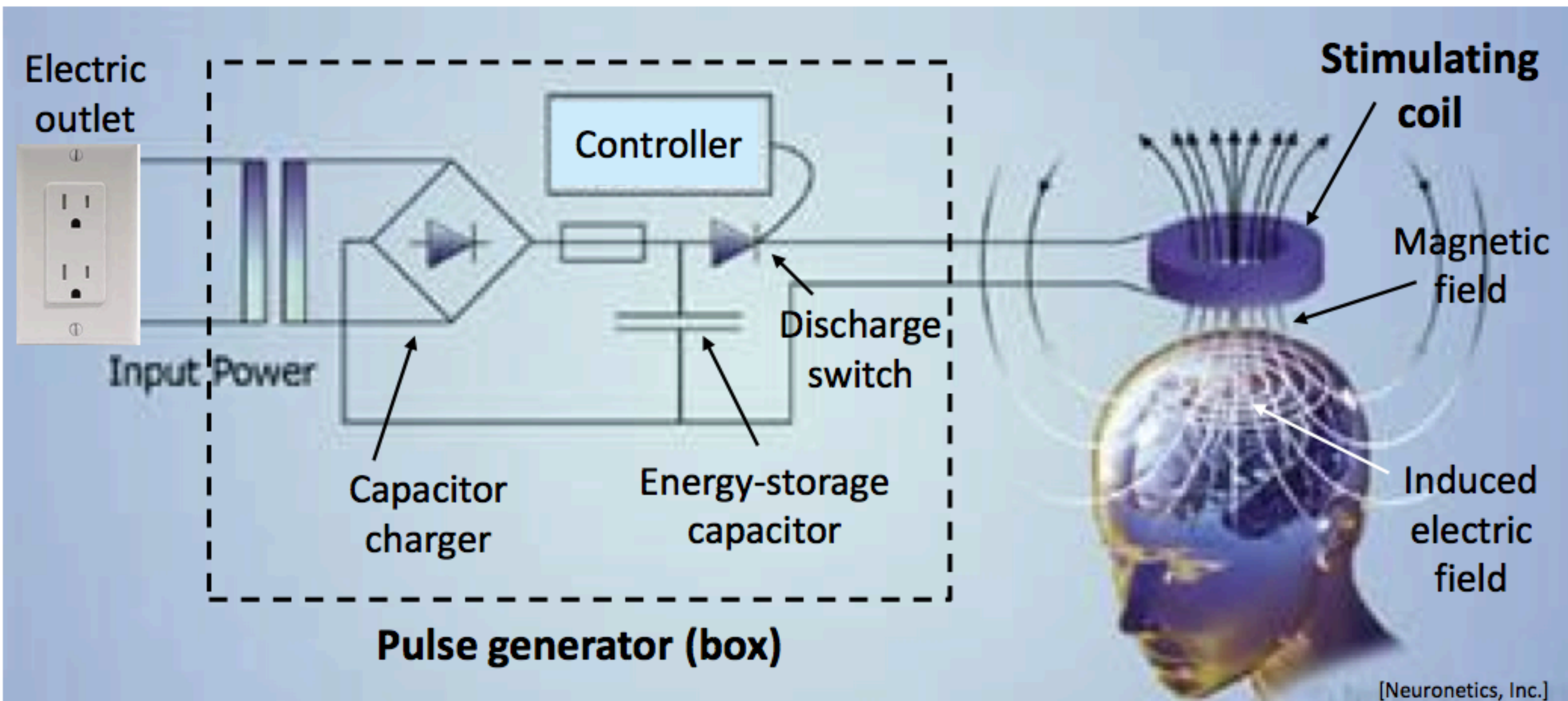
Neuron Depolarization by Electric Field



Electric field creates extracellular and intracellular currents that can depolarize (or hyperpolarize) axonal membrane

TMS Device Structure

- Two main components: **pulse generator (in box)** and **stimulation coil**
- Capacitor is charged to high voltage (up to 1,500–2,800 V)
- Capacitor is discharged into stimulation coil (up to 8,000 A)
- Magnetic field is induced around stimulation coil (up to 2.5 T)



What Do We Mean by “Dose” in Brain Stimulation?

- Medications have a physical quantity measured in milligrams

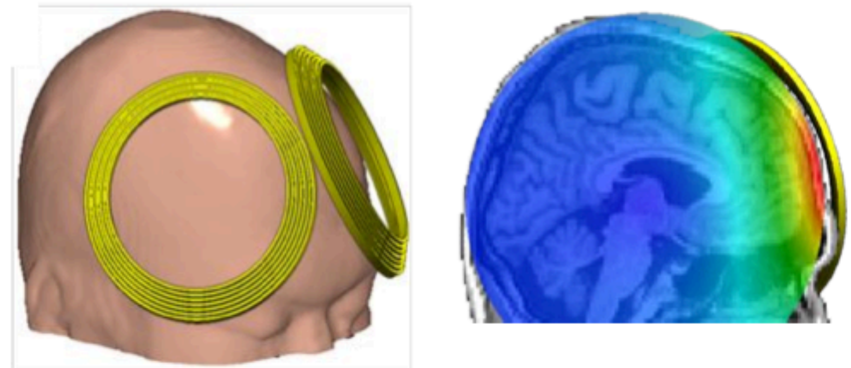
- Transcranial brain stimulation dose includes all stimulus parameters that affect the electric field induced in brain

- Like in pharmacology, TMS dose should always be completely known and documented by giving device model and settings, coil placement, and stimulation session number and frequency

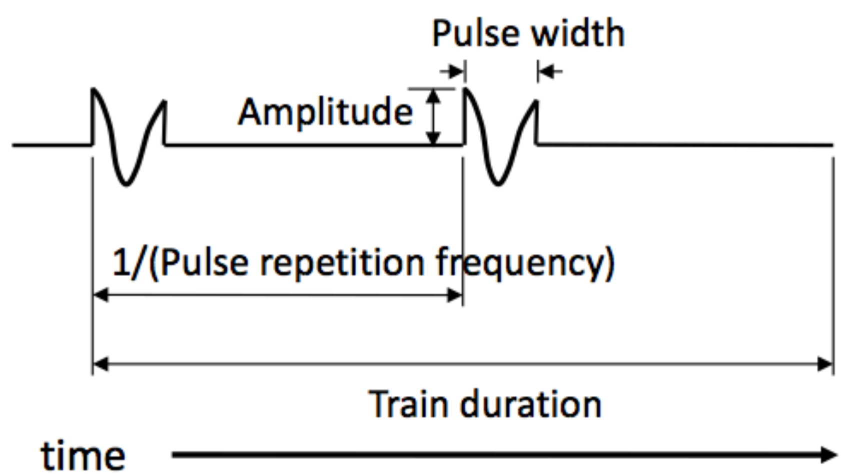
Spatial and Temporal Components of TMS Dose

- Stimulus parameters that control electric field can be segregated in **spatial** and **temporal**

- **Spatial** parameters control relative strength of electric field in various brain areas—shape, size, position, orientation of coil

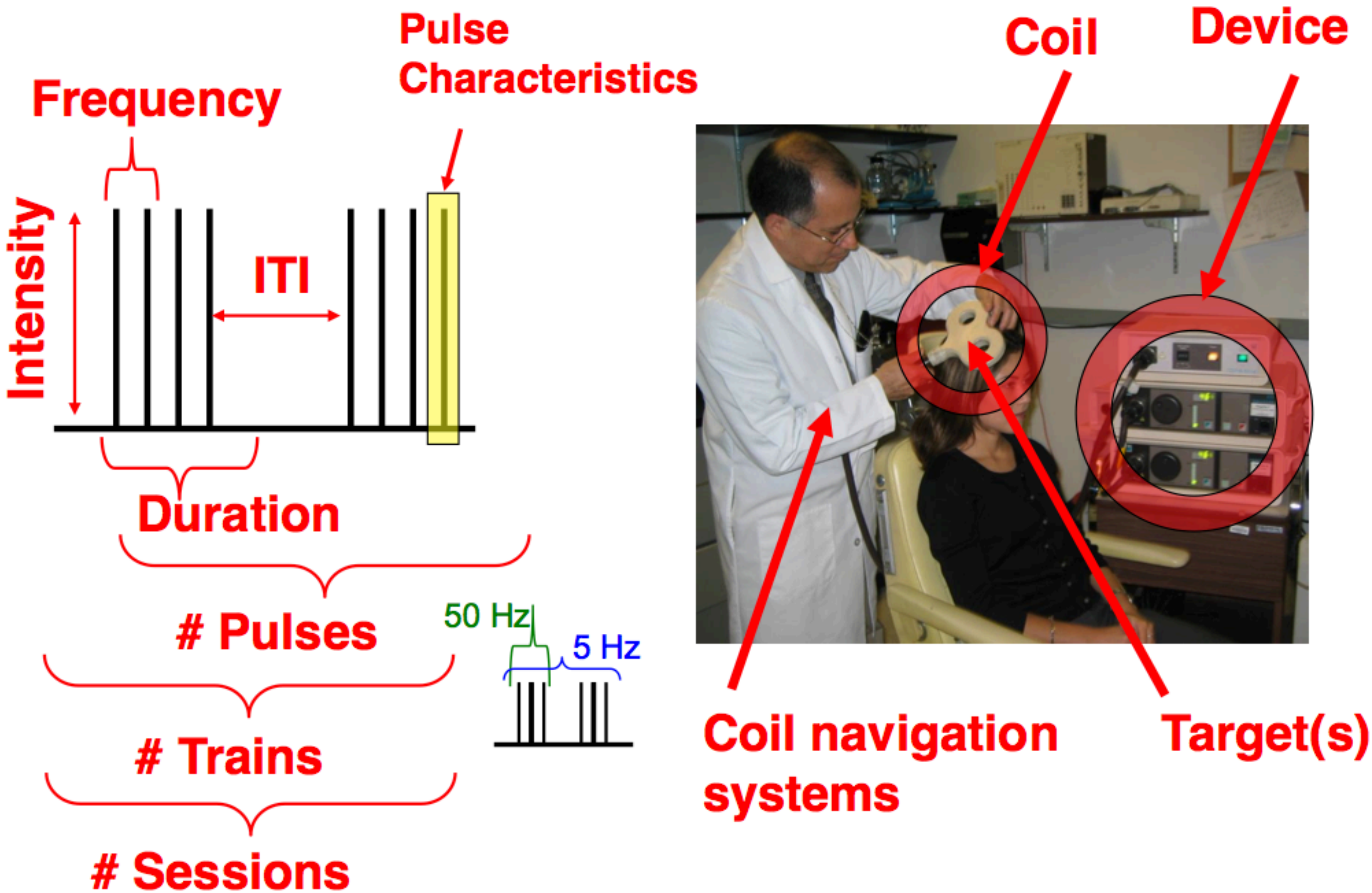


- **Temporal** parameters determine how electric field changes over time—pulse shape, amplitude, width, polarity, repetition frequency, and train duration; number and interval between stimulation sessions

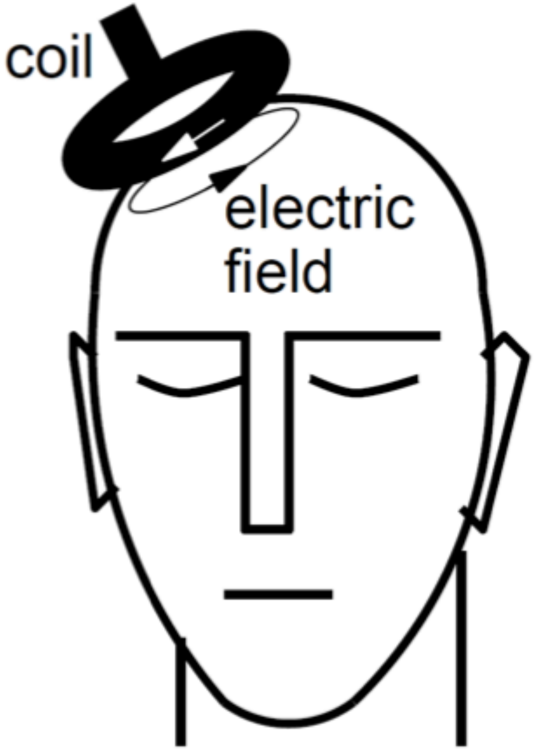


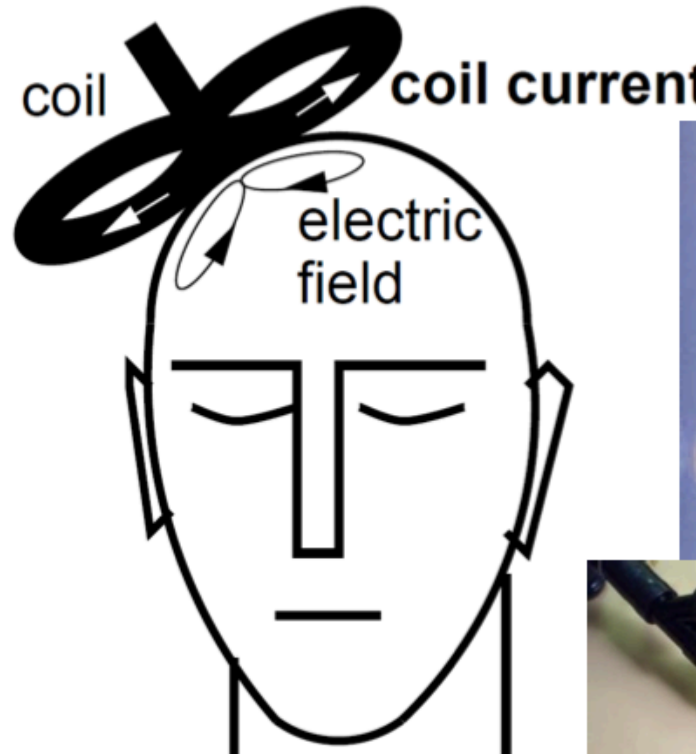
[Peterchev et al., Brain Stimulation, 2012]

The number of possible parameters for dosing is extremely large



TMS Coil Types





Circular (round) coil

- Non-focal

Figure-of-8 (double) coil

- Focal

Induced Electric Field Spatial Distribution

- Figure-8 coil stimulates focally under intersection of two loops
- Circular equally stimulates all structures under the loop

Round coil

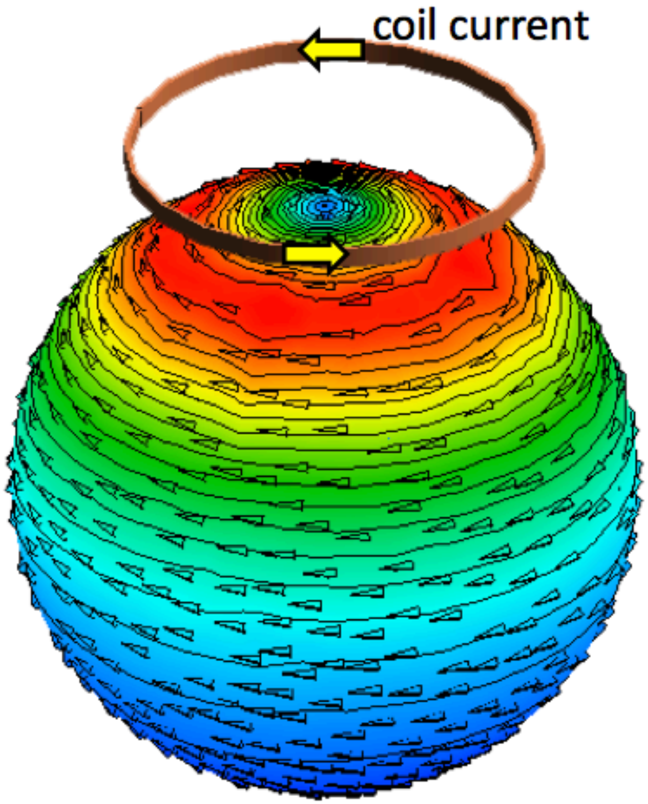
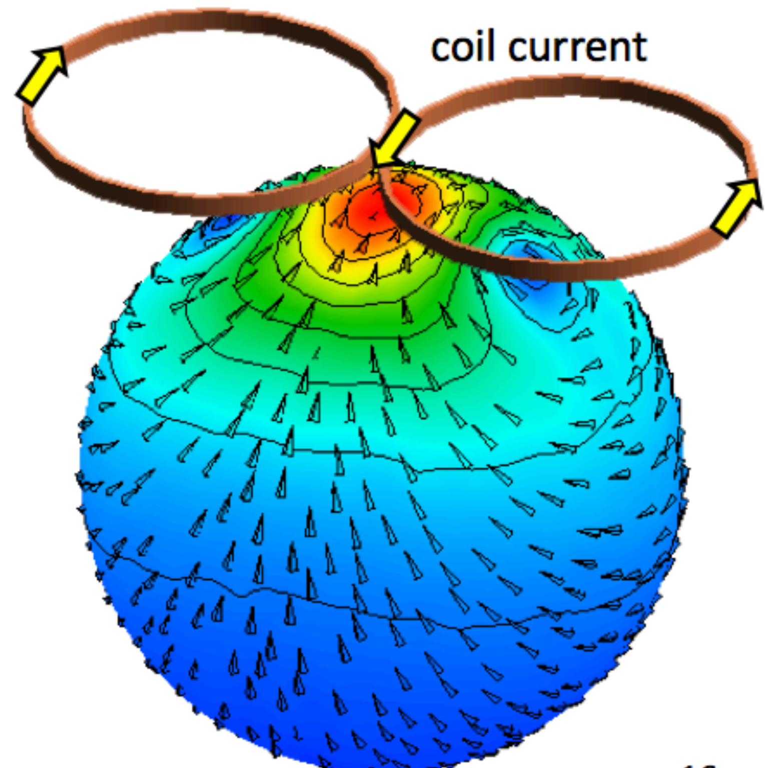


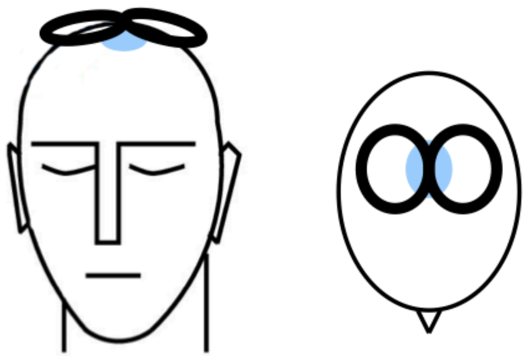
Figure-8 coil



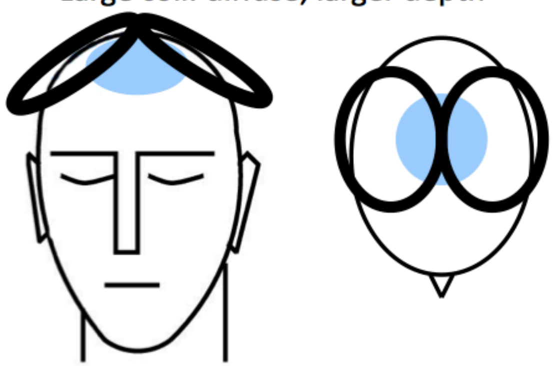
[Deng et al., 2013, 2014]

Coil Focality/Penetration Depth Tradeoff

Small coil: focal, small depth



Large coil: diffuse, larger depth



- Fundamental physics constraints:
- Larger coils can stimulate relatively deeper brain structures, but are less focal
- Smaller coils stimulate the cortex more focally, but cannot stimulate deeper structures

[Deng, Lisanby & Peterchev, Brain Stimul. 2012]

Magnetic Field Characteristics: Coil Shape

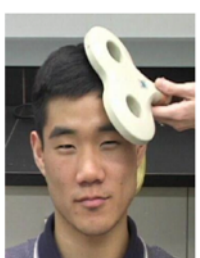
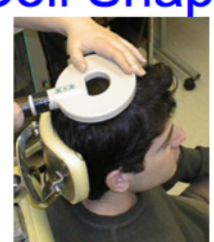


Figure 8

Double Cone

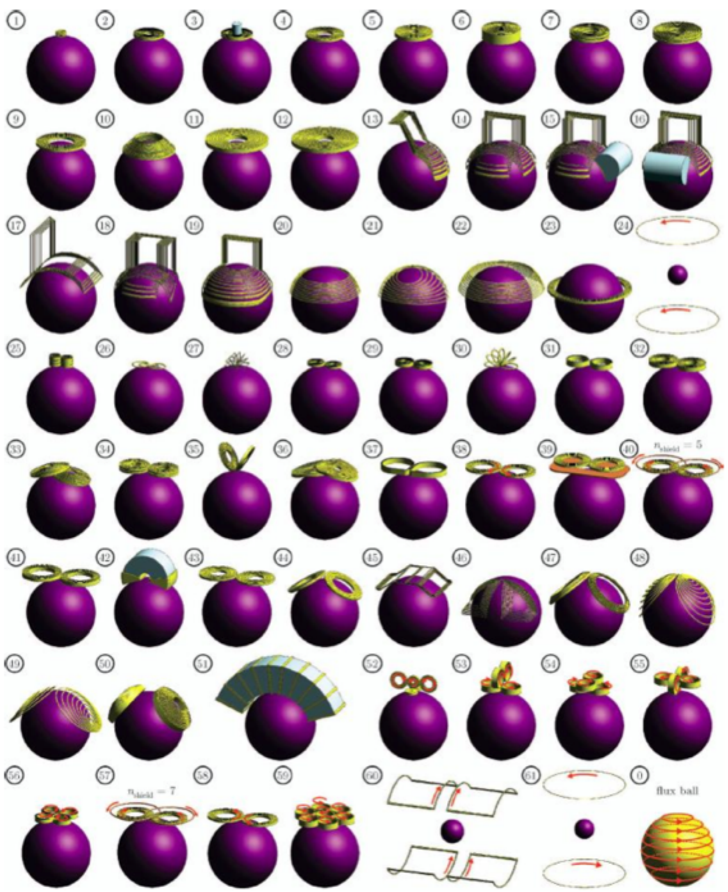


Round

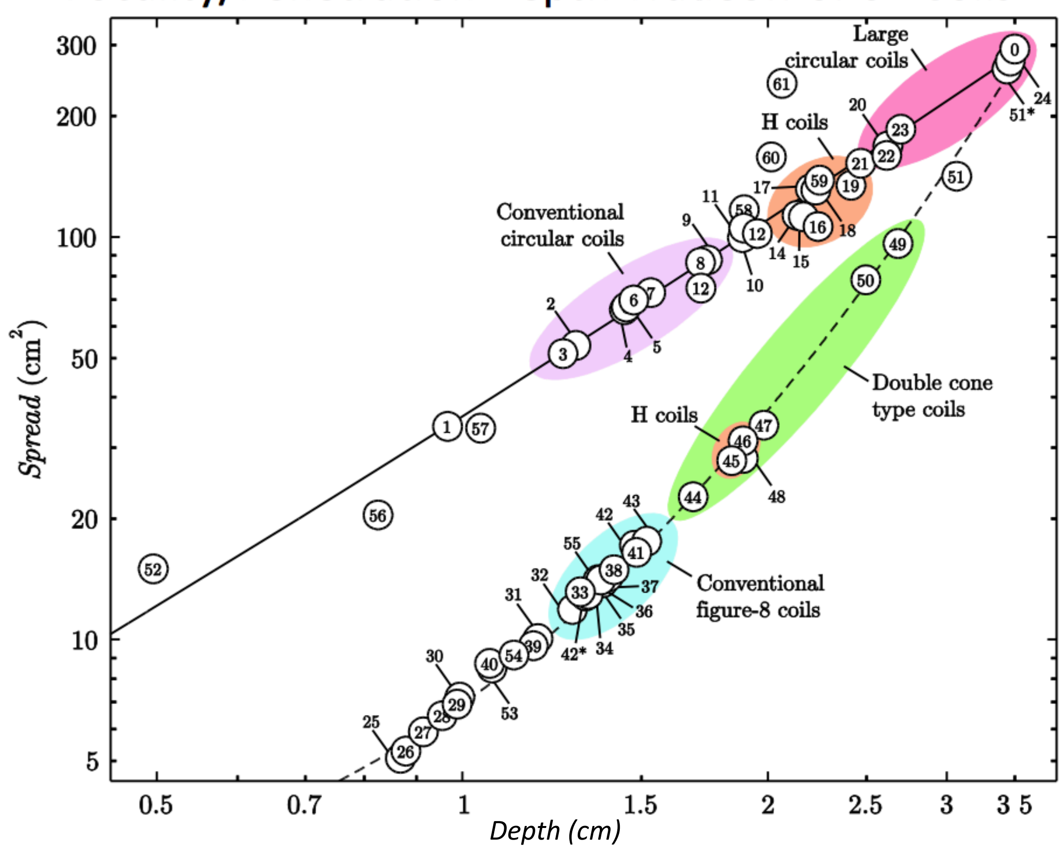
Metal Core

Comparison of Coil E-field

- Can depth of stimulation be increased while keeping coil focal?
- Modeled E-field characteristics of 61 conventional and experimental coils



Focality/Penetration Depth Tradeoff of 61 Coils

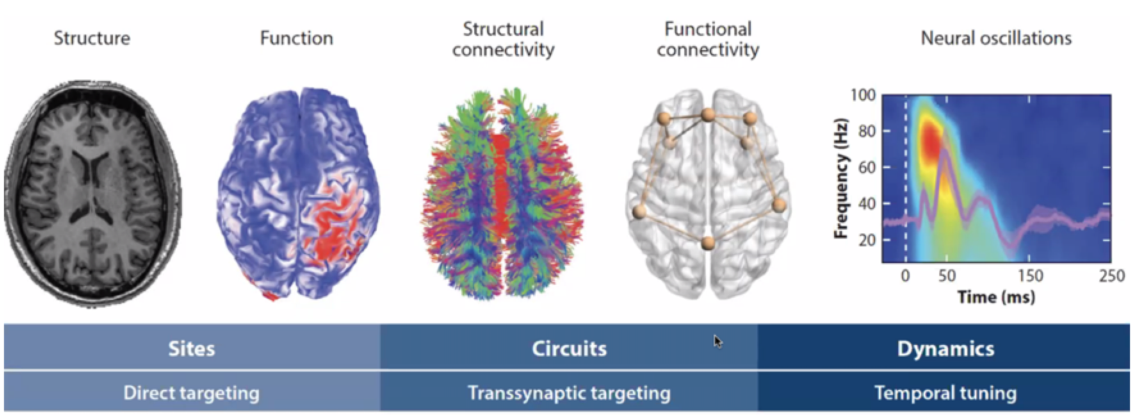


Deng, Lisanby & Peterchev, Brain Stim. 2013]

TMS Targeting

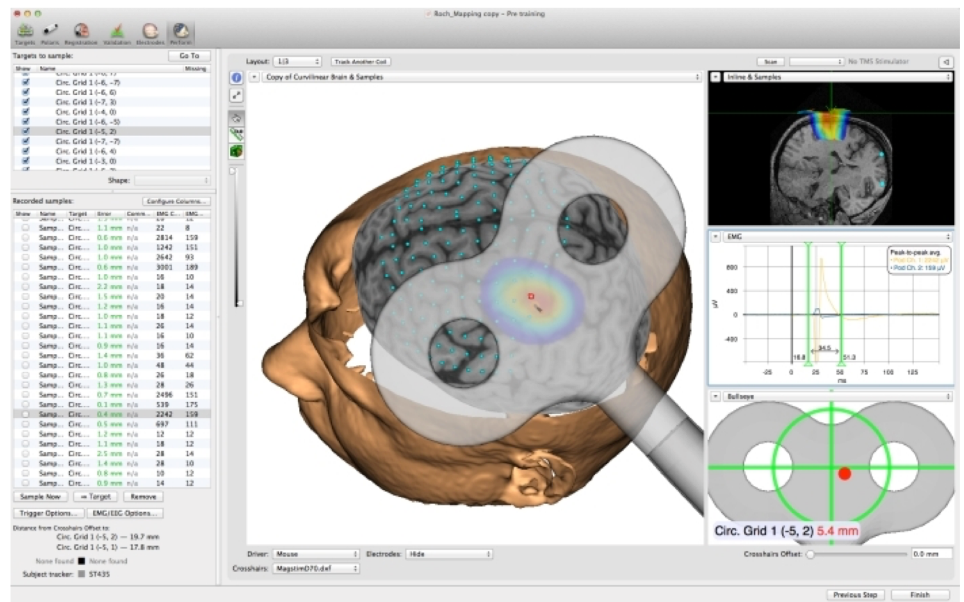
- **Scalp coordinate system**: 10-20 EEG system
- **Strict Anatomic**
  - Pick a spot based on a structural MRI
  - Problem: not functional location
- **Functional Behavioral**
  - Sweet spot search until behavior/perception occurs, e.g. motor or phosphene thresholds
- **Imaging Functional**
  - Do activation imaging (e.g. fMRI), find region, direct TMS there

Targeting with Brain Stimulation

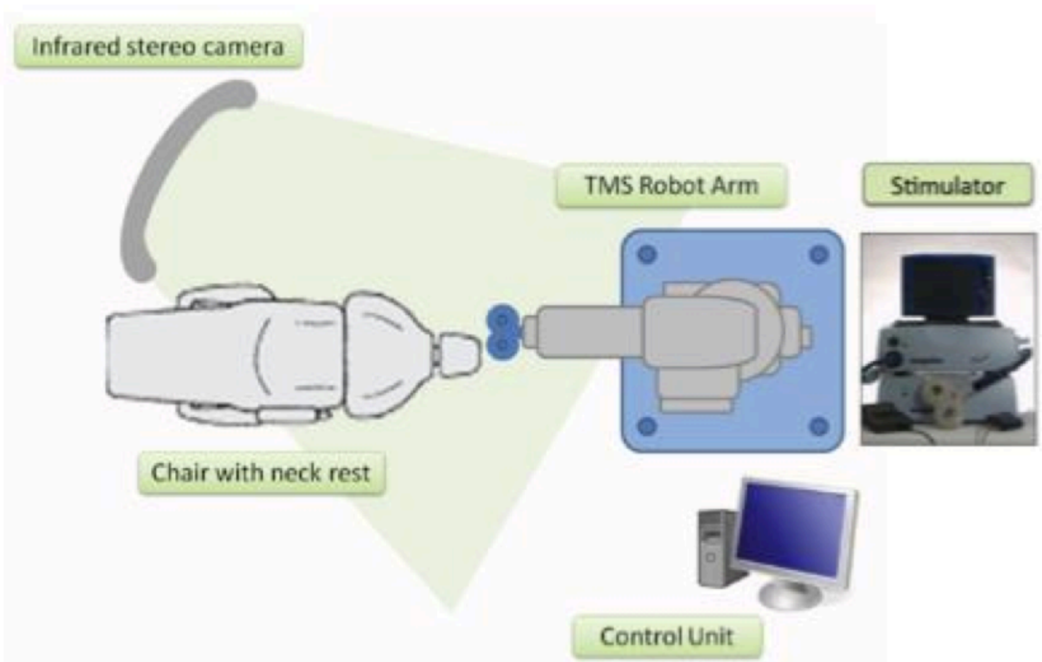


Deng et al Rev Pharm Tox, 2020

Neuronavigation with Frameless Stereotaxy



Robot-guided TMS targeting



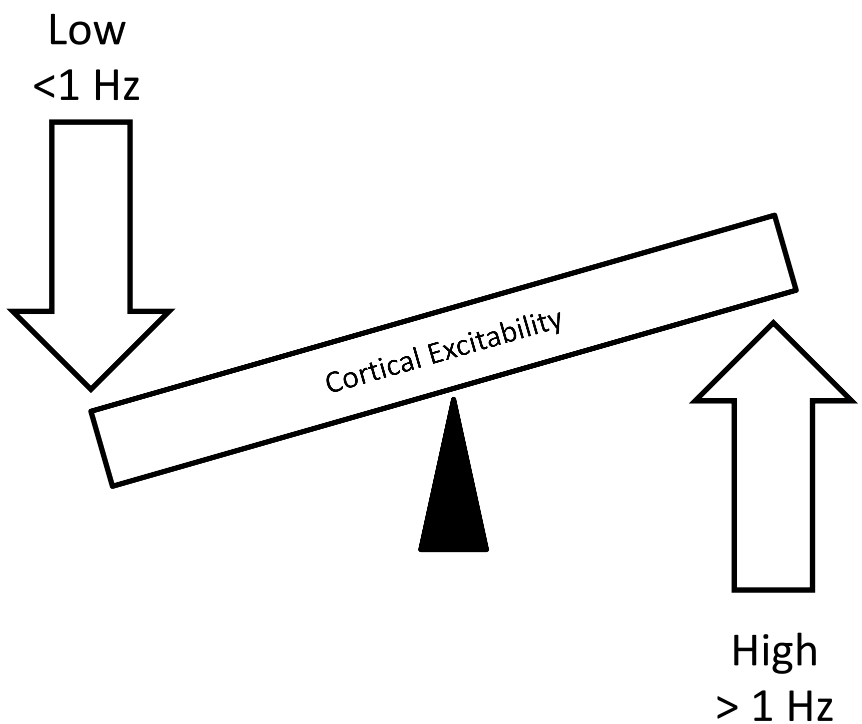
SmartMove™

System places the coil at the predefined target positions and keeps the coil in place even if the head of the patient/subject moves

Dosing, Intensity and the Motor Evoked Potential

- Direct effects are clear:
  - with greater intensity, have greater effective depth and spread
  - But also a greater risk of seizure
- Dosage:
  - Set relative to individual *motor threshold* for convenience - no other benchmark readily available

TMS Frequency

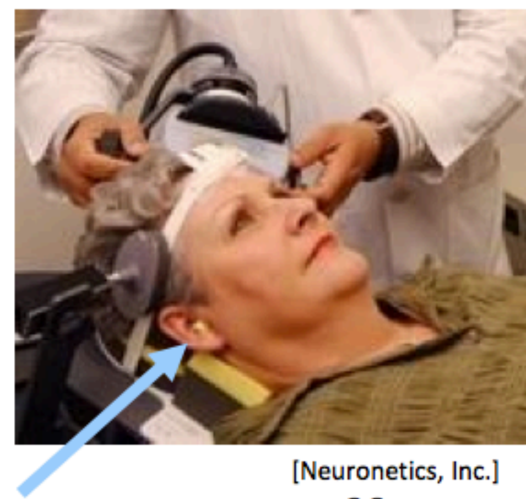


TMS modulates excitability in a frequency dependent manner

Online and Offline stimulation

TMS Coil Clicking & Tapping

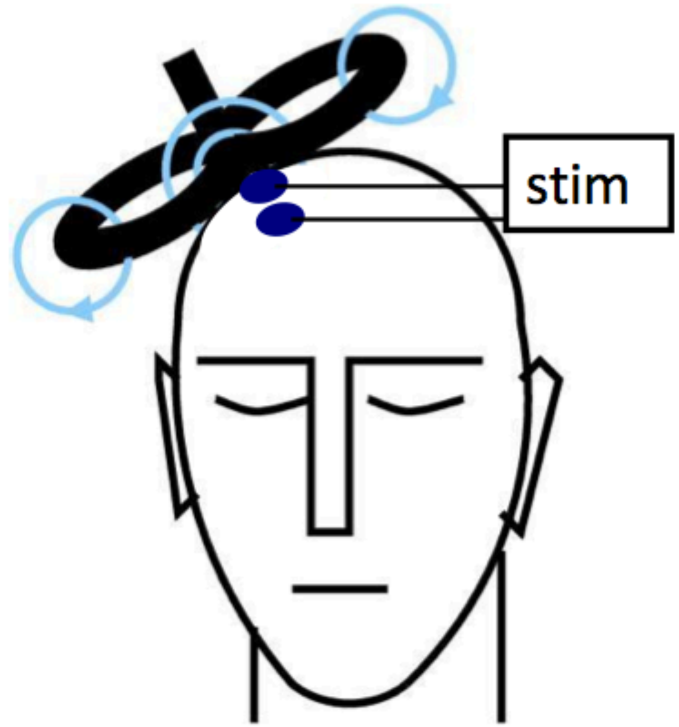
- TMS coil is subjected to brief, high internal electromagnetic forces during pulse (~ 2000 lb radial force)
- Internal forces result in vibration or "tapping"
- This vibration also emits loud clicking sounds
- Each click can be as loud as siren (~ 120 dB, 10 cm from coil), though it lasts for brief instant (~ 1 ms)
- To protect hearing, both subject and operator should wear ear protection (earplugs and/or headphones)



[Neuronetics, Inc.]

Experimental "Control" for TMS Studies i.e. "Sham"

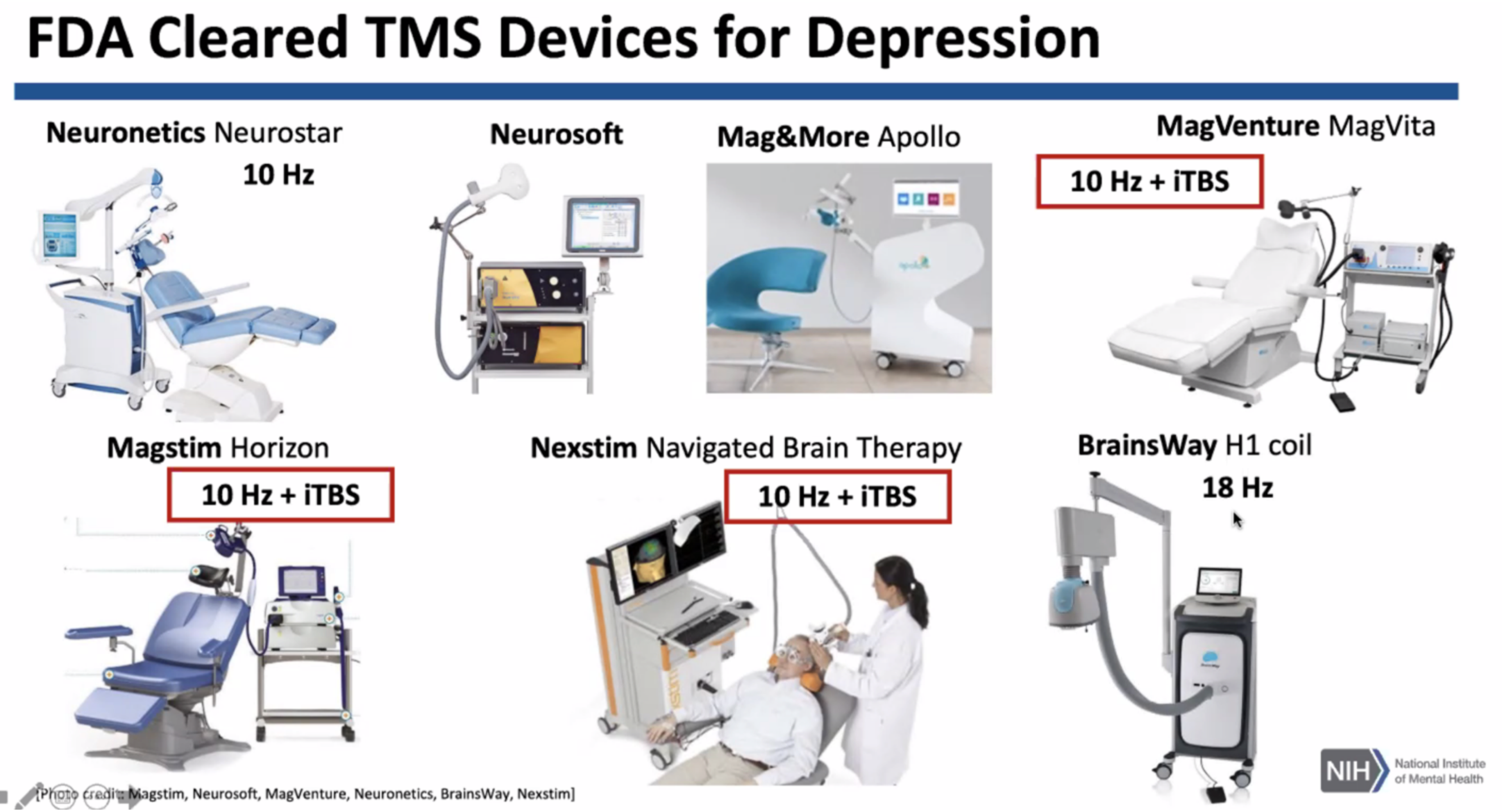
- Sham/placebo TMS condition is critical in many studies and clinical trials
- Ideal sham coil would (1) have identical appearance, produce same (2) sound and (3) tapping, (4) stimulate scalp as real coil, while NOT stimulating brain
- Various designs fulfill conditions (1), (2), and (3)
- Condition (4) can be met by using electrical stimulation with surface electrodes to emulate scalp sensation



TMS Applications – Clinical

- Depression (FDA approved since 2008)
- Schizophrenia
- PTSD
- Pre-surgical mapping (FDA approved)
- Addiction
- Tinnitus

- And more…



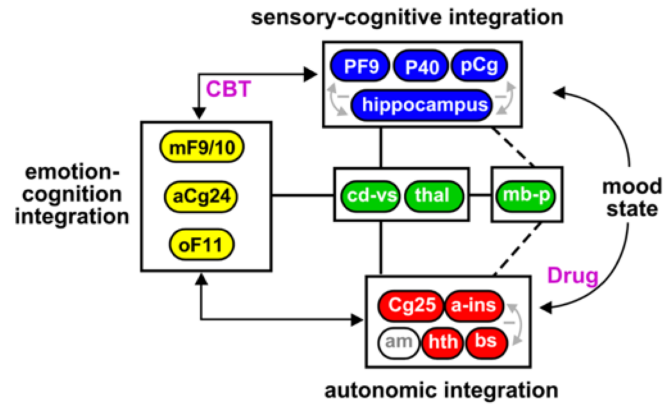
Updated slide from Holly Lisanby’s Grand Rounds talk, Nov 2020

Depression TMS

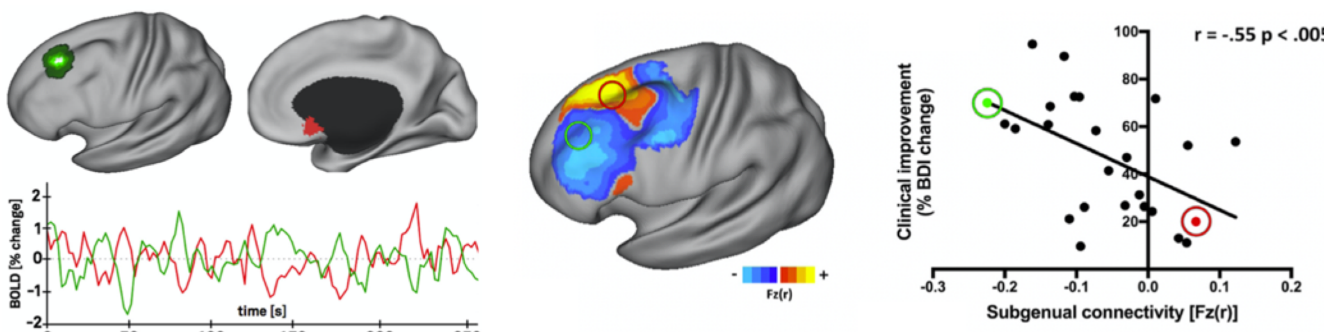
- Pathophysiology of many mental health problems stems from network dysregulation.

  e.g. in depression dorsal network is hypoactive / limbic areas are overactive

Seminowicz et al., 2004



- Functional connectivity between an individual's rTMS cortical target and subgenual cingulate predicts antidepressant response.



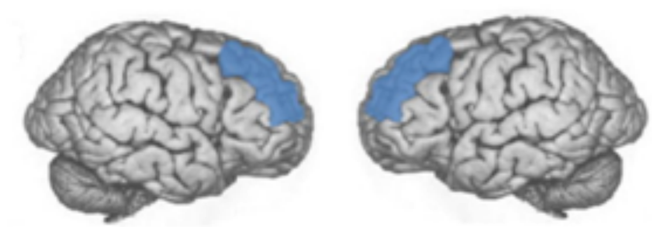
Weigand et al Biological Psych 2017

rTMS and clinical applications

rTMS and Depression

- <u>Reciprocal inhibitory interaction</u>:

  Hyper-metabolism of limbic system *Vs.* Hypo-metabolism of frontal areas



Koenings & Grafman (2009)

- <u>Frontal asymmetry hypothesis</u>:

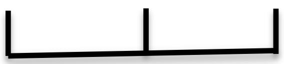
Imbalance between left and right DLPFC

Henriques & Davidson (1990)

rTMS and clinical applications

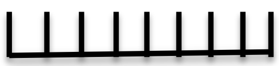
rTMS and Depression

- rTMS low frequency over the right DLPFC,



or

- rTMS high frequency over the left DLPFC,



or

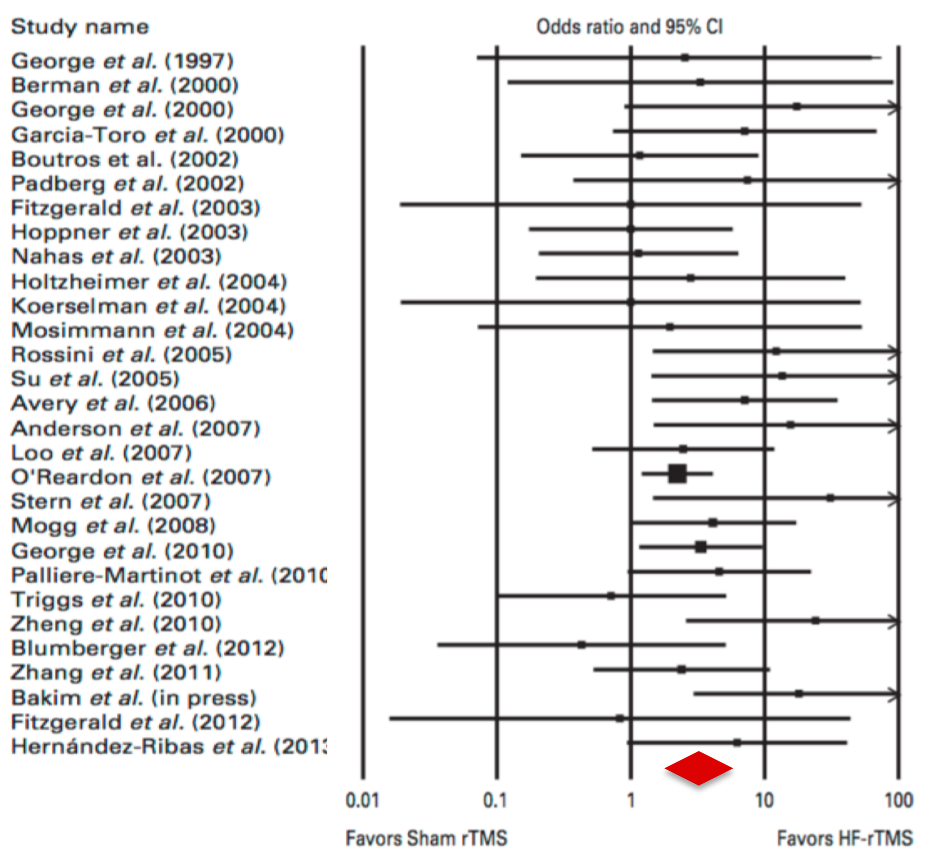
- Combination of both.

rTMS and clinical applications

rTMS and Depression

- HF rTMS:

Responder rate



OR = 3.3; $p < .0001$

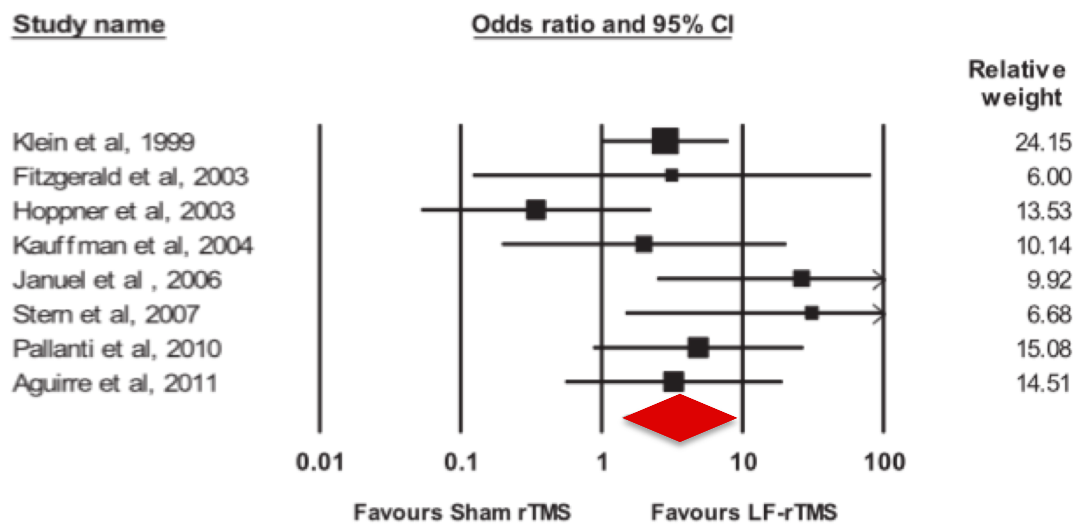
Berlim et al. (2014)

rTMS and clinical applications

rTMS and Depression

- LF rTMS:

Responder rate



OR = 3.35; p = .007

Berlim et al. (2013)

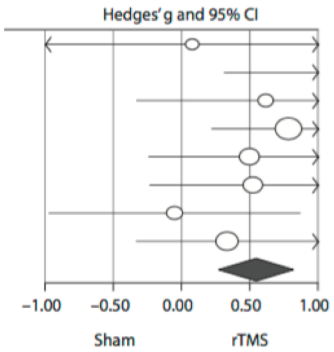
rTMS and clinical applications

rTMS and…

- **Schizophrenia:**

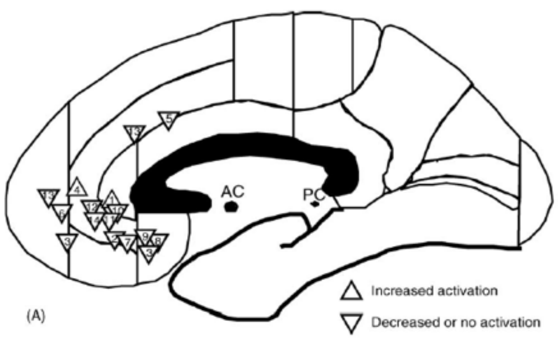
Auditory Hallucination rTMS over the lTPC .

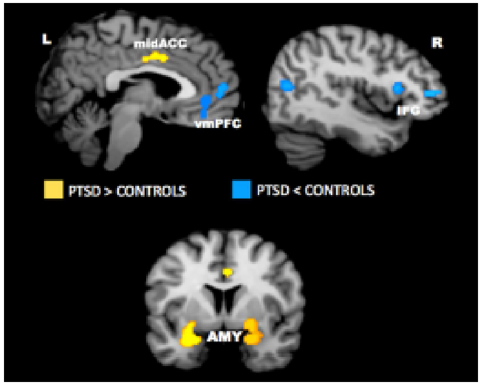
Negative Symptoms rTMS over the lDLPFC

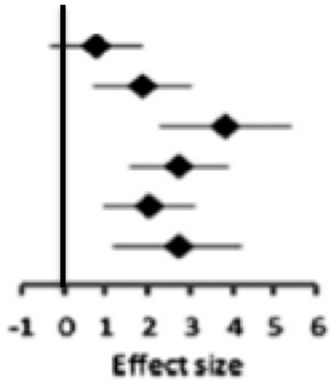


Slotema et al. (2010)

- **Post Traumatic Stress Disorder:**



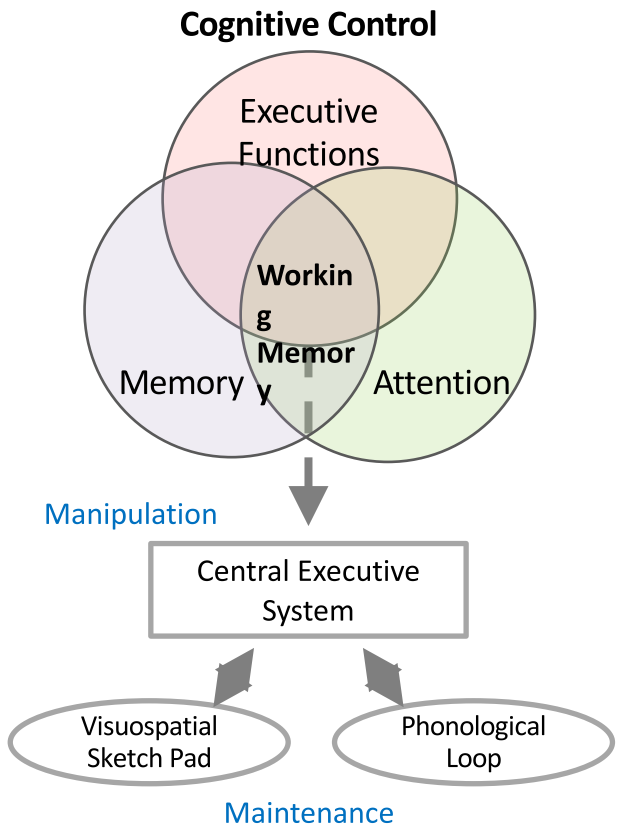


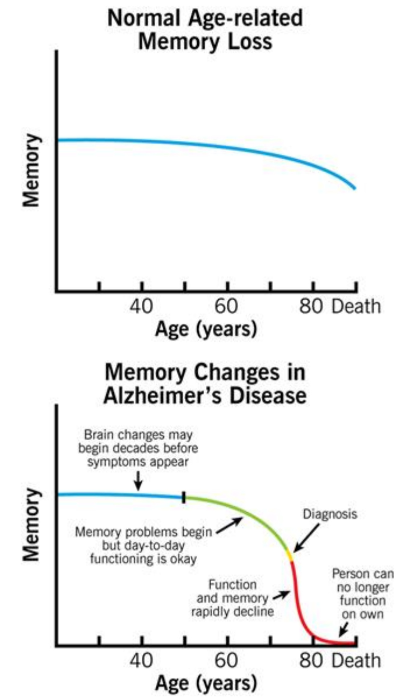


Milad et al., 2006

- **Others:** Autism spectrum disorders, Anxiety, ADHD, OCD…

Working Memory

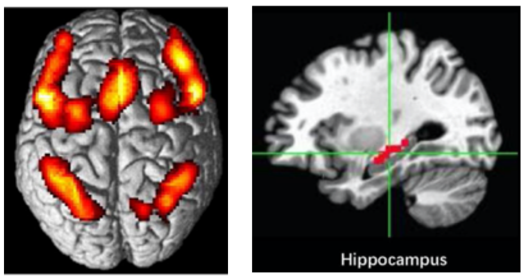




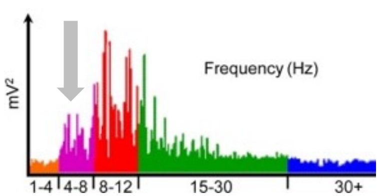
Cleveland Clinic, 2019

Working Memory + rTMS

Frontal-Parietal Network communication with hippocampus

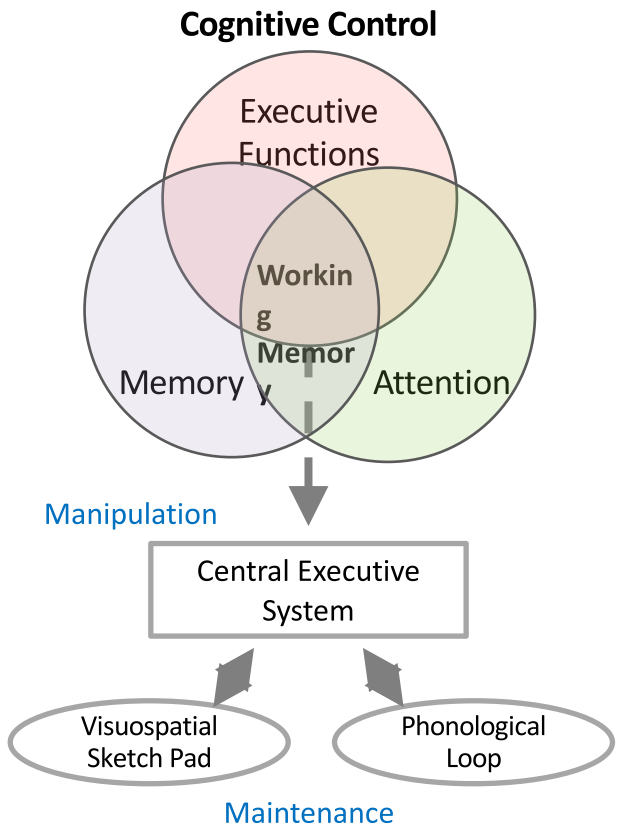


Meta analysis, 189 studies
Rottechy et al 2012



Theta oscillations (5Hz) play important role in hippocampal communication underlying WM

Roux & Uhlhaas 2014

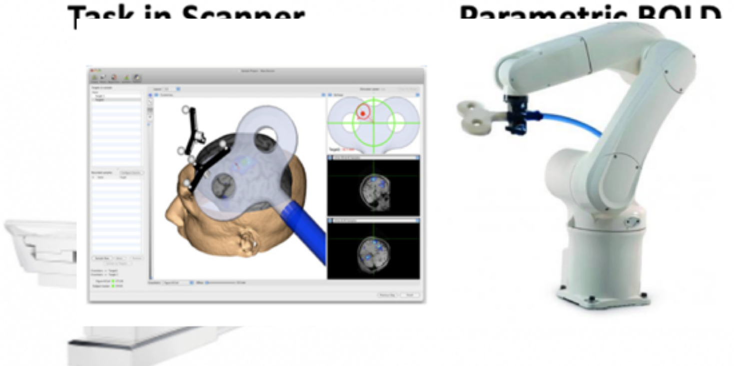


Hypothesis:

Online 5Hz rTMS during WM training will improve communication in FP-network leading to improved memory performance over sham stimulation.

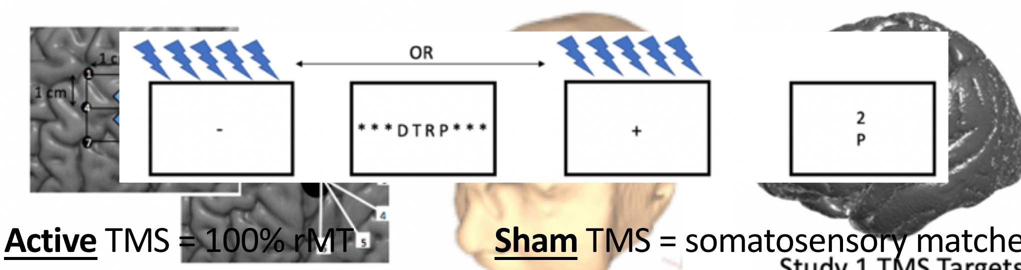
Multi-week individualized WM + TMS protocols

Task in Scanner **Parametric BOLD**



Electric Field Model for Target Optimization

<u>rTMS</u>: 25 pulses at 5Hz, before encoding or during delay



<u>Active</u> TMS = 100% rMT

<u>Sham</u> TMS = somatosensory matched

Study 1 TMS Targets

“2” Letter in array BUT does NOT match correct position (40%)

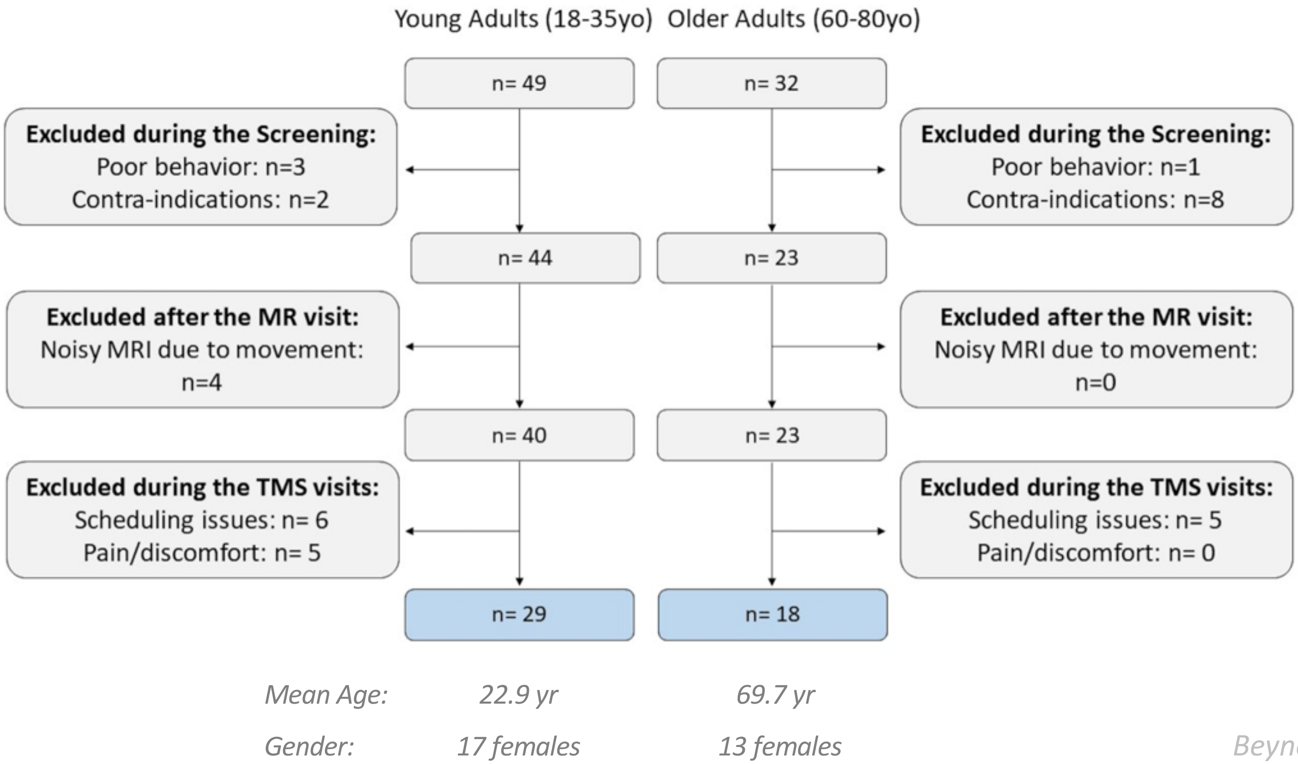
“3” Letter was not in the array (20%)

Within-Subject alternating each ½ session

Beynel et al, PLOS One 2020

Liu et al, PSE 2020

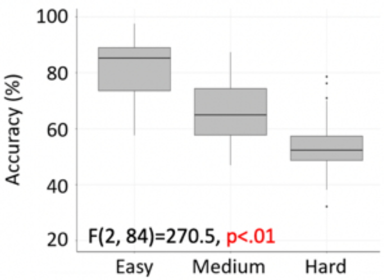
Consort flow diagram

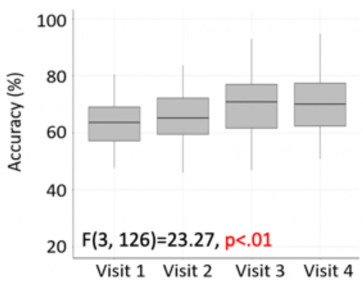


Beynel et al PLOS One, 2019

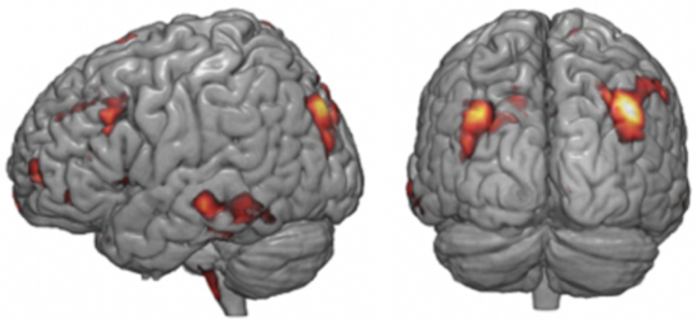
Study 1 Results

Good psychometric WM task





Activations during the delay associated with increased difficulty were strongest in the parietal cortex



→ **Some evidence that 5Hz rTMS might enhance enhance**

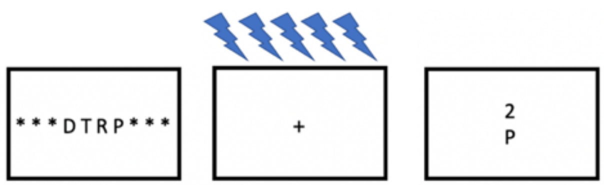
→ **But .. The effect size is small. Can we make it stronger?**

Beynel et al PLOS One, 2019

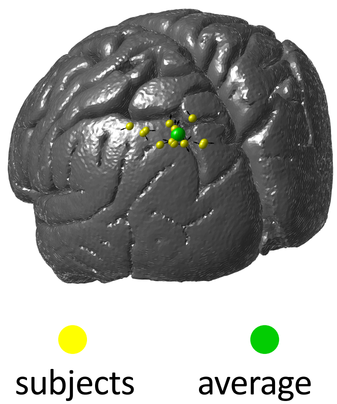
Study 2 – Parietal Stimulation

Design

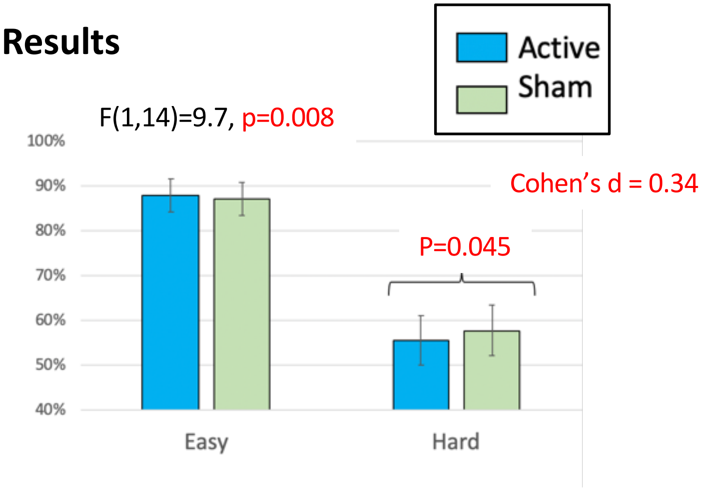
- Parietal target
- Two level of difficulty
- Stimulation only during delay
- Intensity individualized on e-field



Targeting



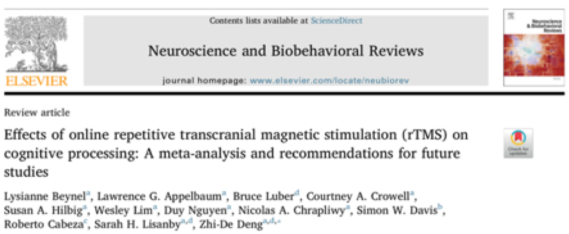
Results



- Significant interaction
- Medium effect size
- Difference in hard condition.
- rTMS disrupted performance!

Beynel et al Brain Sciences, 2020

Meta-Analysis of Online rTMS


Contents lists available at ScienceDirect

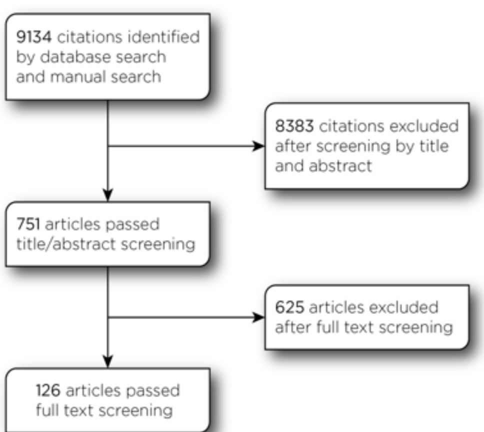
Neuroscience and Biobehavioral Reviews

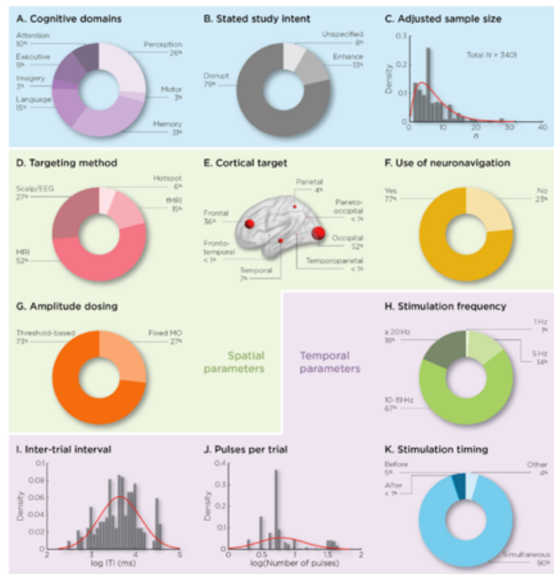
journal homepage: www.elsevier.com/locate/neubiorev

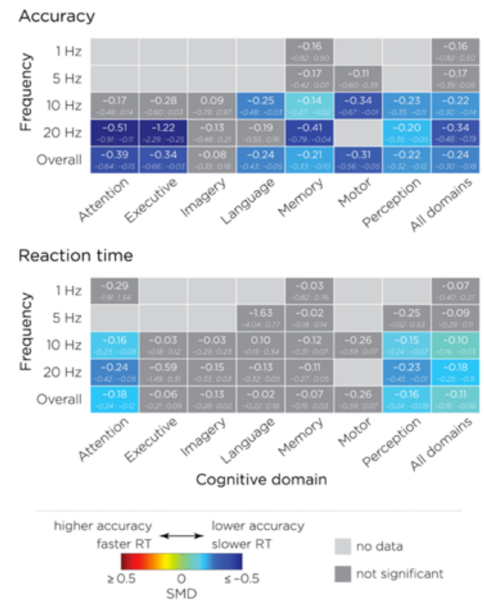
Review article

Effects of online repetitive transcranial magnetic stimulation (rTMS) on cognitive processing: A meta-analysis and recommendations for future studies

Lysianne Beynel[a], Lawrence G. Appelbaum[a], Bruce Luber[d], Courtney A. Crowell[a], Susan A. Hilbig[a], Wesley Lim[a], Duy Nguyen[a], Nicolas A. Chrapliwy[a], Simon W. Davis[b], Roberto Cabeza[c], Sarah H. Lisanby[a,d], Zhi-De Deng[a,d,*]







<u>Conclusions</u>

- Effects of online rTMS disrupt performance
- Little evidence of facilitation

Beynel et al Neurosci and Biobehavioral Rev 2020

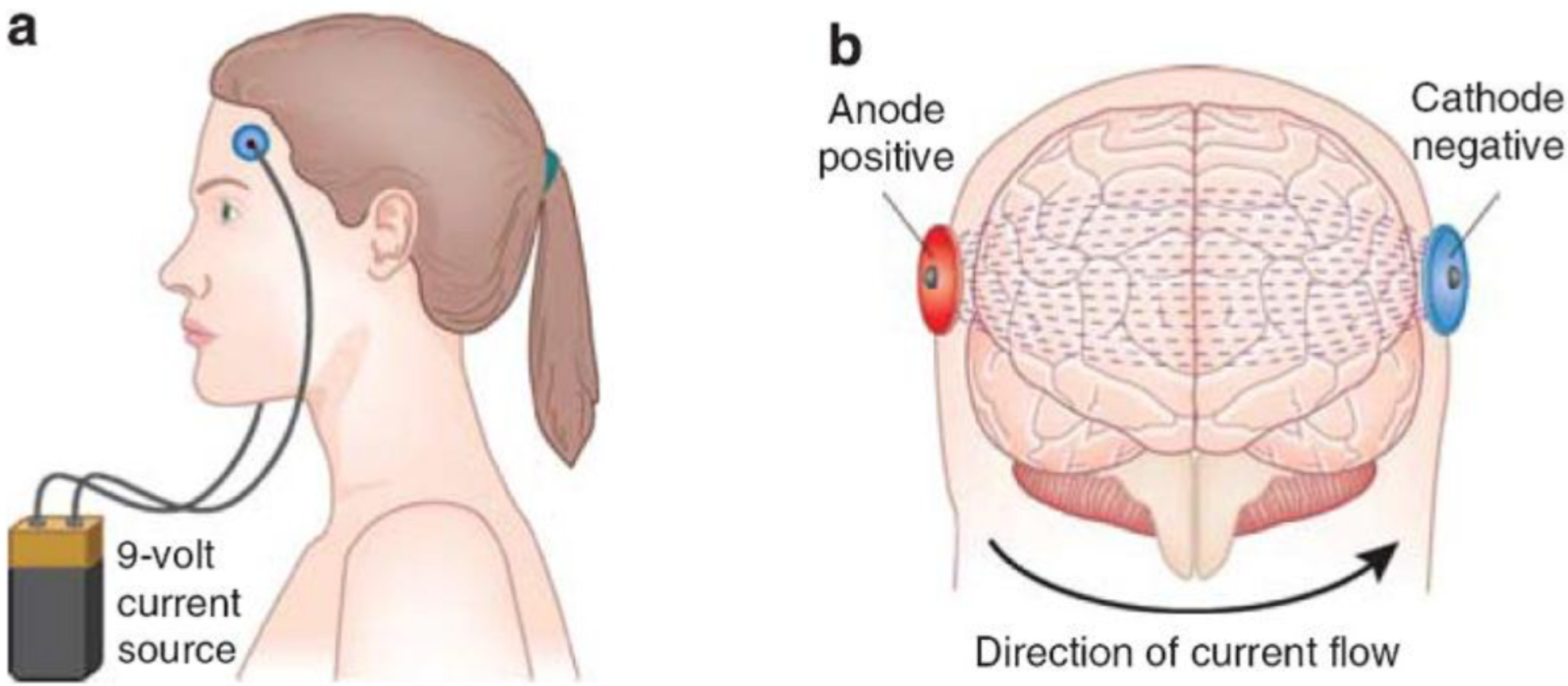
Transcranial Direct Current Stimulation

- What is it?
- tDCS to improve motor learning
- tDCS and clinical applications

- And many more…

What is Transcranial Direct Current Stimulation?

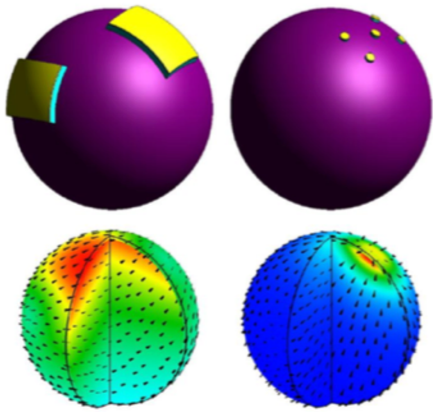
- Direct current applied via scalp electrodes
- Low currents (1-2 mA) applied for minutes
- Anode depolarizes, and facilitates cortical function
- Cathode hyperpolarizes, and inhibits cortical function



tDCS

- Mechanisms of Change
  - Anodal tDCS decreases GABA
  - Cathodal tDCS decreases Glutamate
  - Changes sustained over 20 min
- Pros
  - Safe
  - Painless
  - Low cost
  - Portable
  - Easy to blind
- Cons
  - Nonfocal (but can be improved with novel electrode configurations)
  - Several minor risks such as skin irritation or burns if not used correctly, headaches

Improved focality with multi-electrode configuration



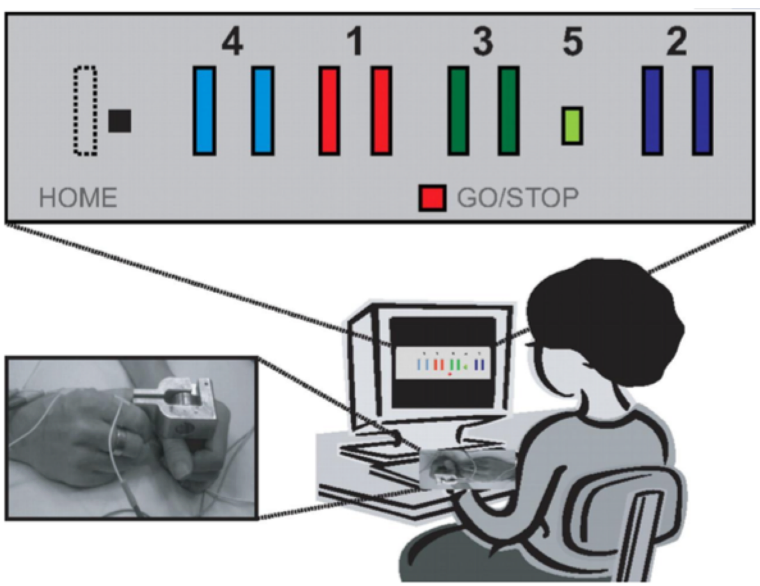
tDCS to facilitate motor learning

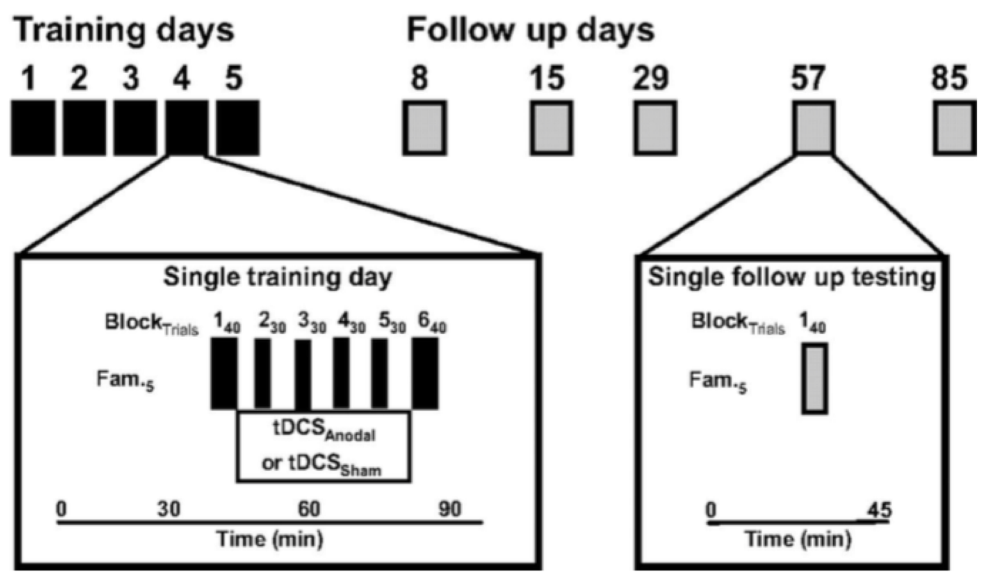
Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation

Janine Reis[a,b], Heidi M. Schambra[a], Leonardo G. Cohen[a,1], Ethan R. Buch[a], Brita Fritsch[a,b], Eric Zarahn[c], Pablo A. Celnik[d,1,2], and John W. Krakauer[c,2]

[a]Human Cortical Physiology Section and Stroke Neurorehabilitation Clinic, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892; [b]Department of Neurology, Albert-Ludwigs-University, Freiburg 79106, Germany; [c]Motor Performance Laboratory, Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY 10032; and [d]Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD 21287

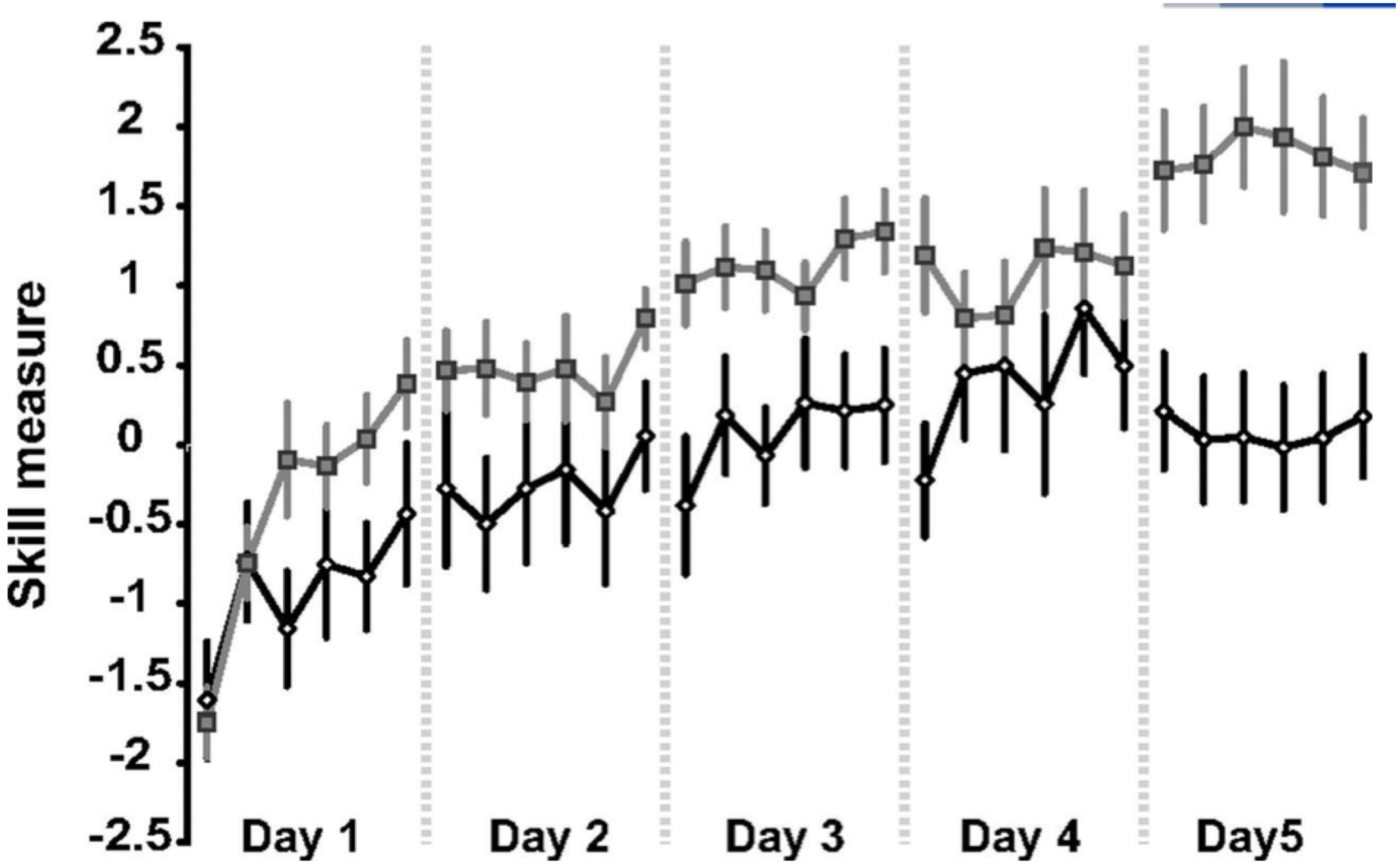
Sequential visual isometric pinch task





Reis J. et.al. PNAS 2009;106:1590-1595

Learning curve for the sham (white diamonds) and anodal (gray squares) tDCS groups for the 30 training blocks over 5 days



Reis J. et.al. PNAS 2009;106:1590-1595

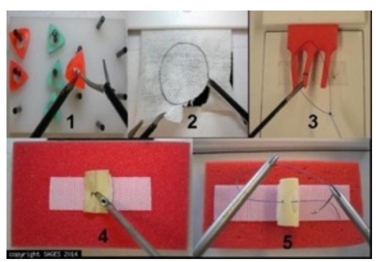
tDCS accelerated precision motor learning!

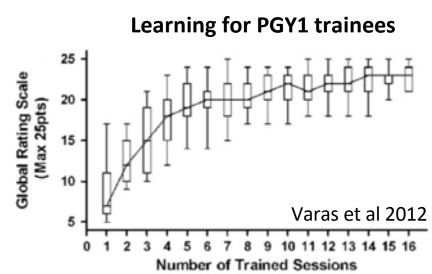
Surgical Skill Learning

Laparoscopic Surgery

Laparoscopic Surgery Training

FLS Curriculum, Learning and Board Certification

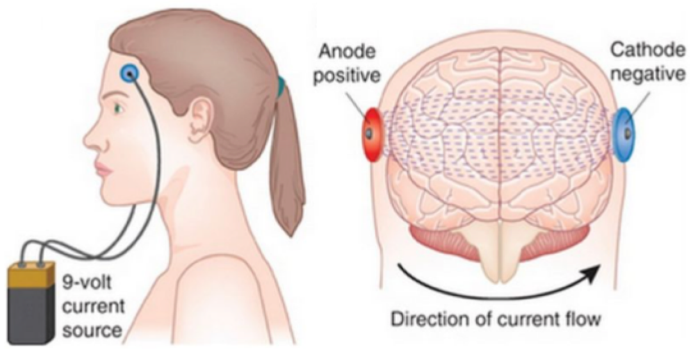


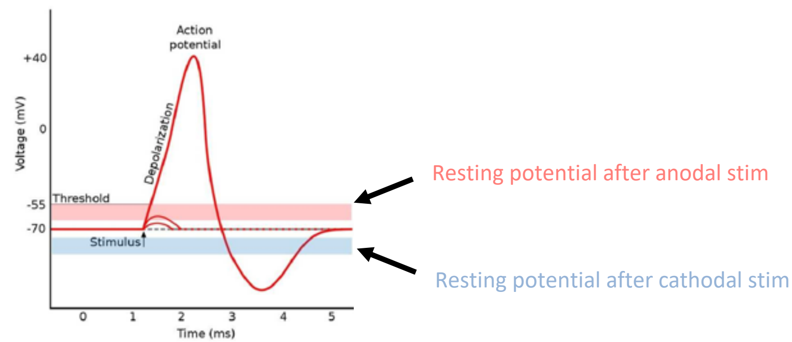


Can we accelerate FLS learning through application of electrical brain stimulation?

Cox et al, Brain Stimulation 2020

Transcranial Direct Current Stimulation





- Low voltage current via electrodes on the scalp creates changes in polarization altering long term potentiation
- When paired with practice, tDCS makes it easier for neurons to fire… so it makes it easier to "fire together / wire together" (i.e., Hebbian Learning)

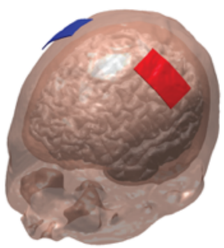
Cox et al, Brain Stimulation 2020

Design and Protocol

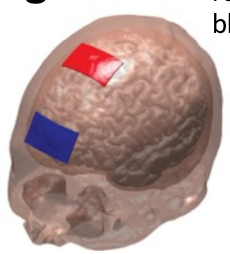
Pre-registered, randomized, double-blind, sham-controlled trial… *CT.gov #03083483*

Stimulation Montages

red = anode
blue = cathode



bM1



SMA

Peg Transfer Task

Intervention

bM1 = 20 subjects
SMA = 20 subjects
Sham = 20 subjects (10 each montage)

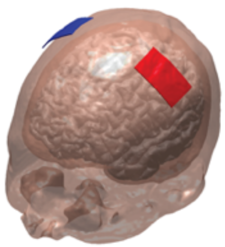
2 mAmp current intensity during FLS practice

	Visit 1	**Visit 2**	**Visit 3**
	20 min task	20 min task	20 min task
tDCS+Task	5 min break	5 min break	5 min break
	20 min task	20 min task	20 min task

Total pegs transferred, minus penalty -3 out-of-view drop, -1 in-view drop

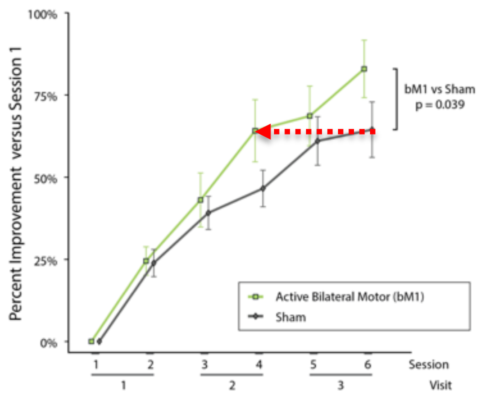
Cox et al, Brain Stimulation 2020

Results

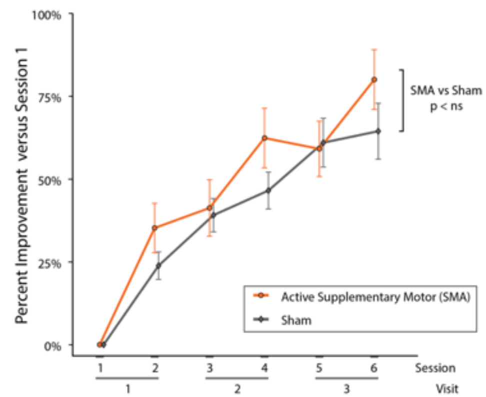


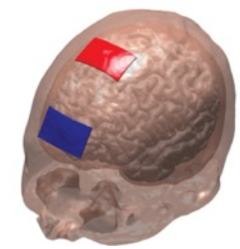
bM1

bM1 versus Sham



SMA versus Sham





SMA

- Significant main effect of sessions ($p<0.001$)
- Significant group x session interaction.
- Compared to Sham, bM1 had significantly greater improvement ($p=0.039$),
- No significant difference between SMA and Sham ($p=0.40$).
- Active bM1 stimulation leads to 14% more improvement!

Interim Conclusions

In this pre-registered, double-blind, randomized trial active stimulation produced significant and meaningful gains in learning over sham.

Effects of Transcranial Direct-Current Stimulation on Neurosurgical Skill Acquisition: A Randomized Controlled Trial

Patrick Ciechanski[1], Adam Cheng[2], Steven Lopushinsky[3], Kent Hecker[4,5], Liu Shi Gan[6], Stefan Lang[1,7], Kourosh Zareinia[7], Adam Kirton[2,6]

Effects of transcranial direct-current stimulation on laparoscopic surgical skill acquisition

P. Ciechanski[1], A. Cheng[2], O. Damji[7], S. Lopushinsky[3], K. Hecker[4,5], Z. Jadavji[1] and A. Kirton[2,6]

Departments of [1]Neuroscience, [2]Pediatrics, [3]Surgery, [4]Veterinary Medicine, [5]Community Health Sciences and [6]Clinical Neurosciences, and [7]Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
Correspondence to: Dr A. Kirton, Department of Pediatrics, University of Calgary, 2888 Shaganappi Trail NW, Calgary, Alberta, Canada, T3B 6A8
(e-mail: adam.kirton@albertahealthservices.ca)

PROGRAM CONTACT:

SUMMARY STATEMENT
(Privileged Communication)

Release Date: **10/23/2020**
Revised Date:

Application Number: **1 R01 NS121338-01**

Principal Investigator
APPELBAUM, LAWRENCE G.

Applicant Organization: DUKE UNIVERSITY

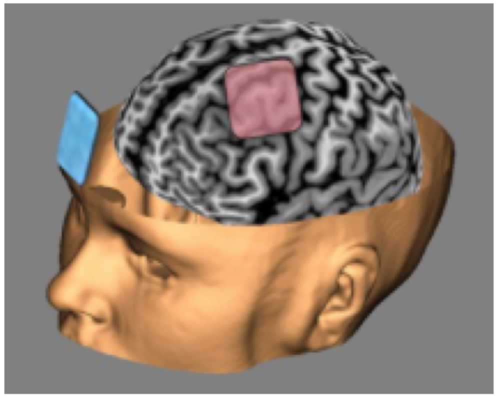
Review Group: **BTSS**
Bioengineering, Technology and Surgical Sciences Study Section

tDCS Clinical

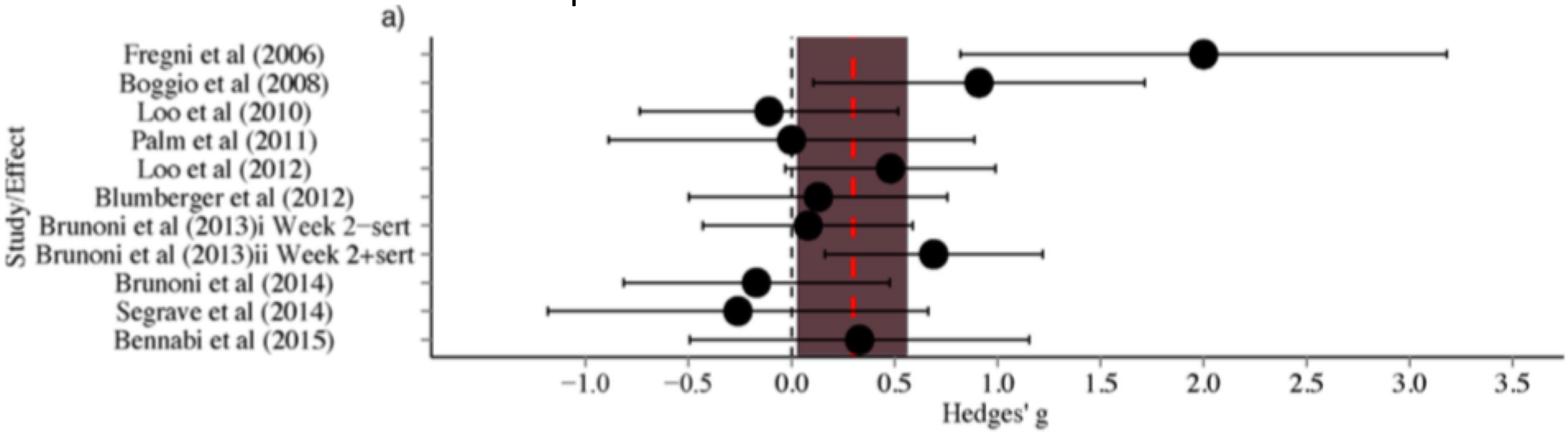
tDCS and depression:

Anode over the left DLPFC

Cathode over the right DLPFC or right supra-orbital area

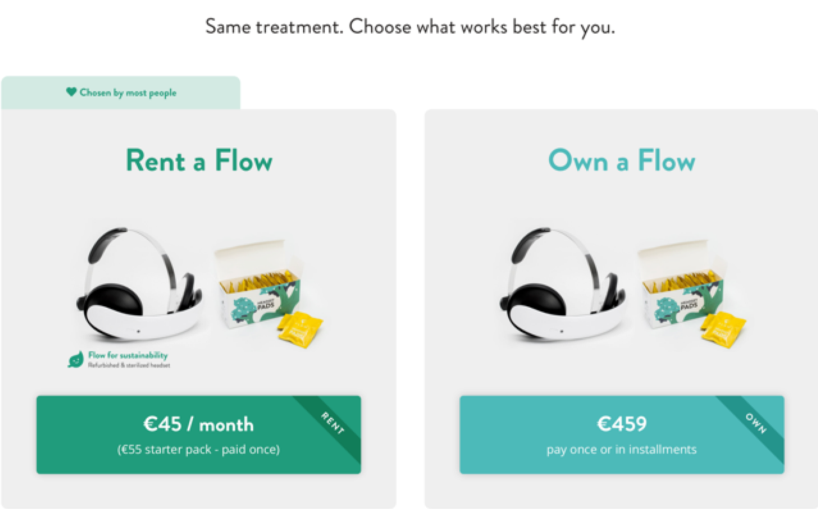


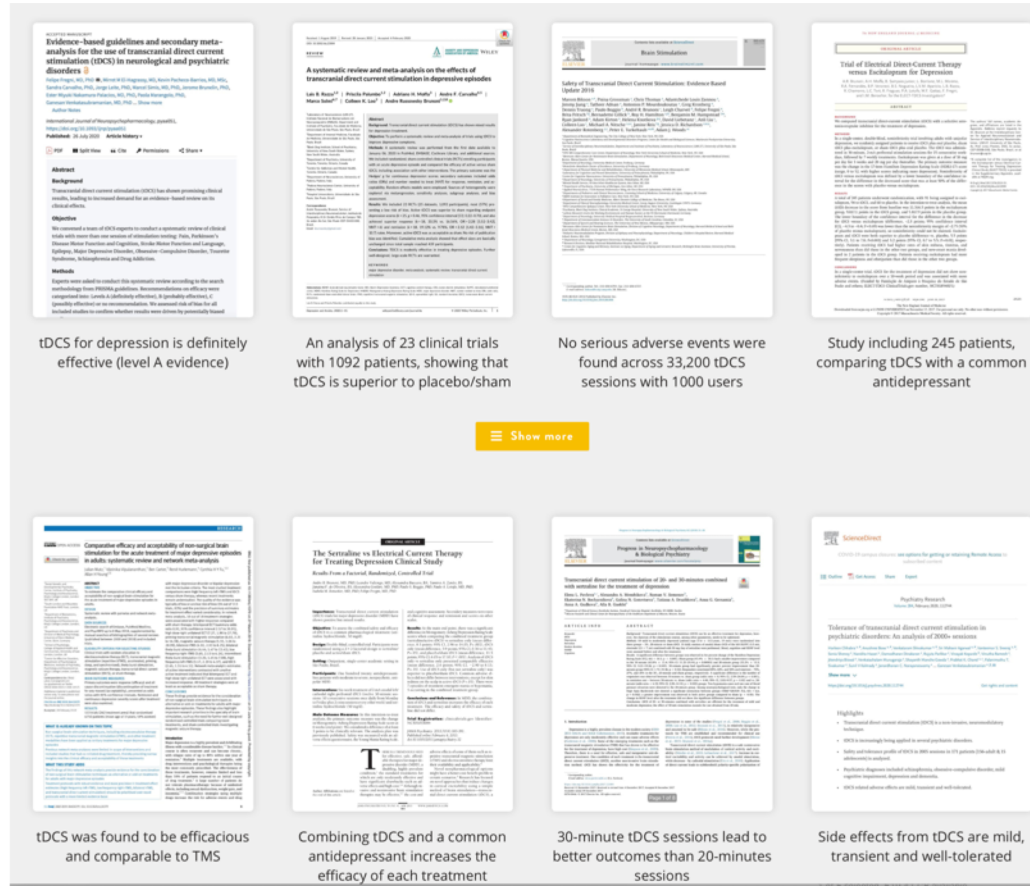
Forest plot of effect sizes for active versus sham treatment



Meron et al. (2015)

tDCS Clinical





Take Aways…

- Brain stimulation is a growing enterprise in neuroscience and clinical care.
- On balance there is evidence for the effectiveness of these techniques, but refinement is still needed to increase efficacy and to identify individuals most likely to respond.
- Brain stimulation provides a means to causally test brain-behavior relationships.

Neurodoping?

Sports Med (2013) 43:649–653
DOI 10.1007/s40279-013-0027-z

CURRENT OPINION

Neurodoping: Brain Stimulation as a Performance-Enhancing Measure

Nick J. Davis

Published online: 16 March 2013

Park, *Cogent Social Sciences* (2017), 3: 1360462
https://doi.org/10.1080/23311886.2017.1360462

cogent social sciences

CrossMark

Received: 14 April 2017
Accepted: 22 July 2017
First Published: 28 July 2017

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Reviewing editor:
Vassil Girginov, Brunel University, UK

Additional information is available at the end of the article

SPORT | RESEARCH ARTICLE

Neuro-doping: The rise of another loophole to get around anti-doping policies

Kwangho Park[1]*

Abstract: The purpose of this study is to provide an overview of the emerging neuro-doping technology and its ability to enhance athletic performance, and to examine the physical and ethical risks associated with the technology. This study also suggests that sports governing bodies charged with anti-doping regulation begin to consider prohibiting the application of electrical stimulus to the brain as a means of physical manipulation aimed at enhancing performance.

Subjects: Law; Sociology of Media; Politics & International Relations; Sports and Leisure; Social Sciences; Health Communication

Keywords: neuro doping; anti-doping policy; transcranial direct-current stimulation; world anti-doping agency

Thank you

Special thanks to
Lysianne Beynel
Angel Peterchev
Zhi Deng
Bruce Luber
Holly Lisanby
For use of slides from the TMS Fellowship Course

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