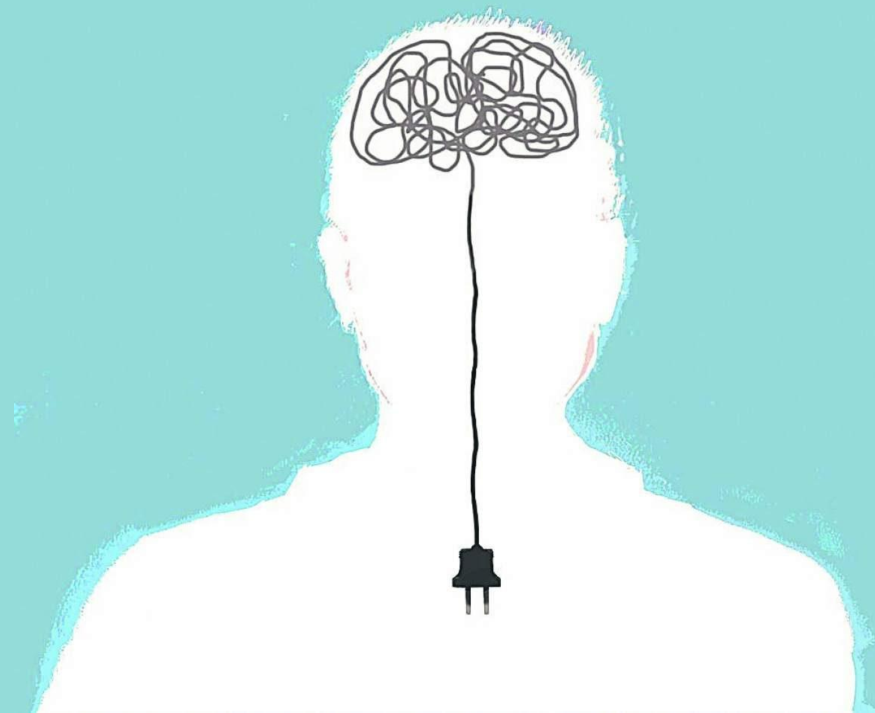
Neurostimulation and Neuromodulation

Jay Sanguinetti & Brian Lord

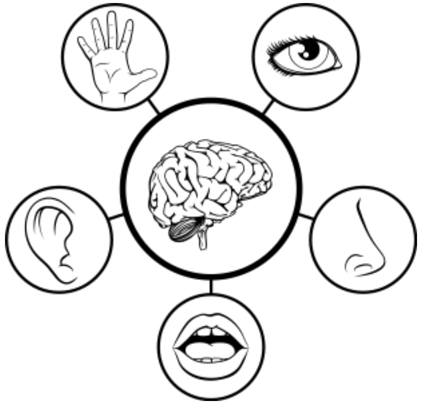


Outline

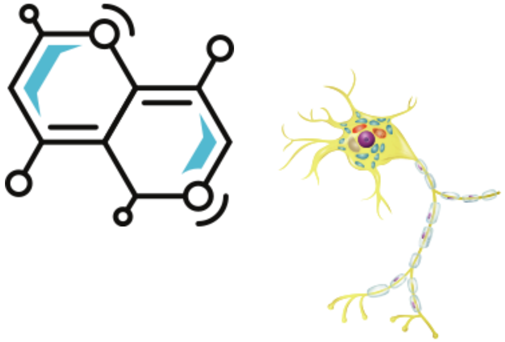
1. Why modulate the brain?
2. Historical context
   1. Invasive vs Noninvasive
   2. Causal Manipulation
3. Magnetic (TMS) – gold standard
4. Electric (tDCS/tACS) – needs work
5. Ultrasound (tFUS) – new kid on the block

Perturbing Neural Systems

SENSORY

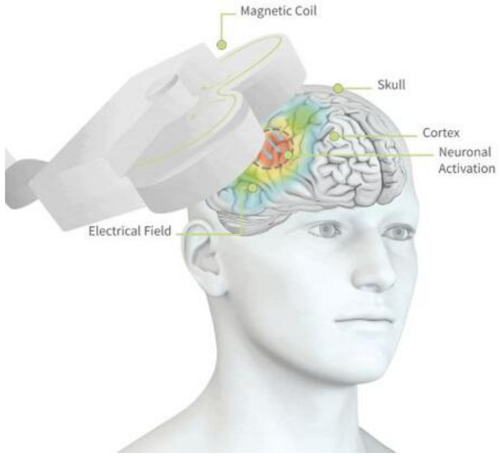


NEURAL & MOLECULAR



INVASIVE

NON-INVASIVE



UNDERSTAND

INTERVENE

Behavioral and imaging methods (EEG, fMRI, EKG) are correlational.

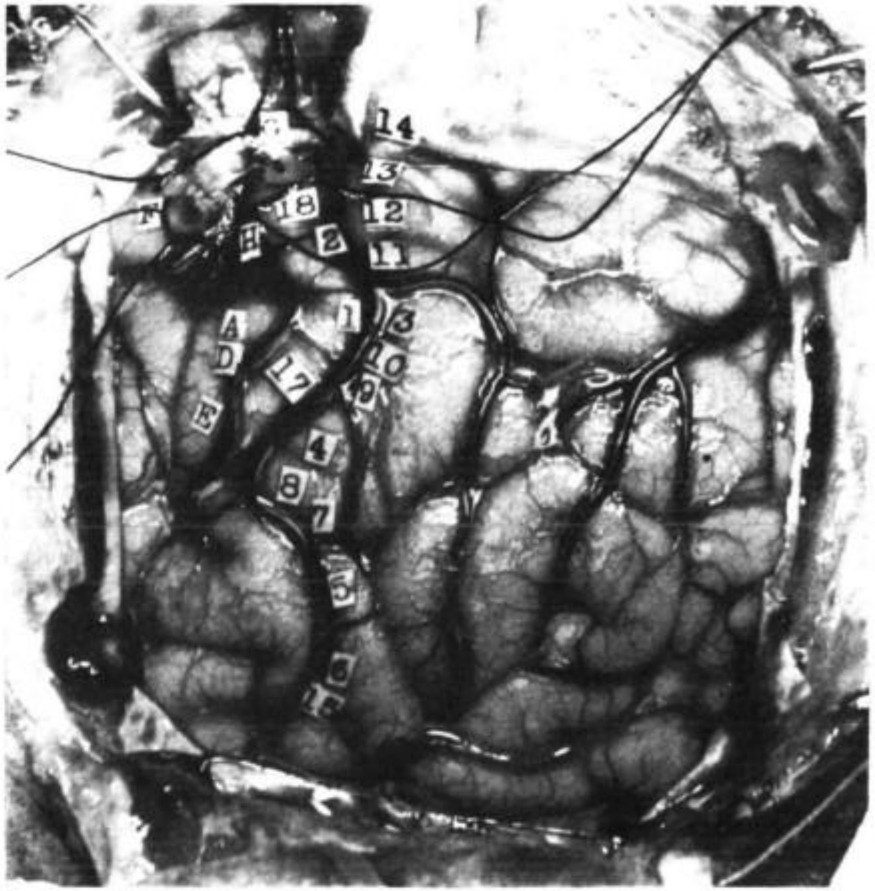
Brain stimulation directly manipulates neural activity.

- Causal links to behavior
- Maps brain to behavior
- Reduces likelihood of hidden variables

What is brain stimulation?

- Technological approach to **neuromodulation** – alteration of brain activity
- Can be **invasive** or **non-invasive**
- Effects are **temporary**, though they may have long-lasting impact
- Effects are **state-dependent** – strongly affected by what the brain is doing when the intervention is applied
- Can be used for clinical treatment or neuroenhancement, most techniques seem to enhance neuroplasticity
- Can be very precise, effective, and safe in certain scenarios
- But it is still an emerging space with lots of unknowns
  - Safety, dosage, reproducibility, large parameter space, individual differences, experimental methodological challenges (what is an appropriate control?)

[neurosurgery]



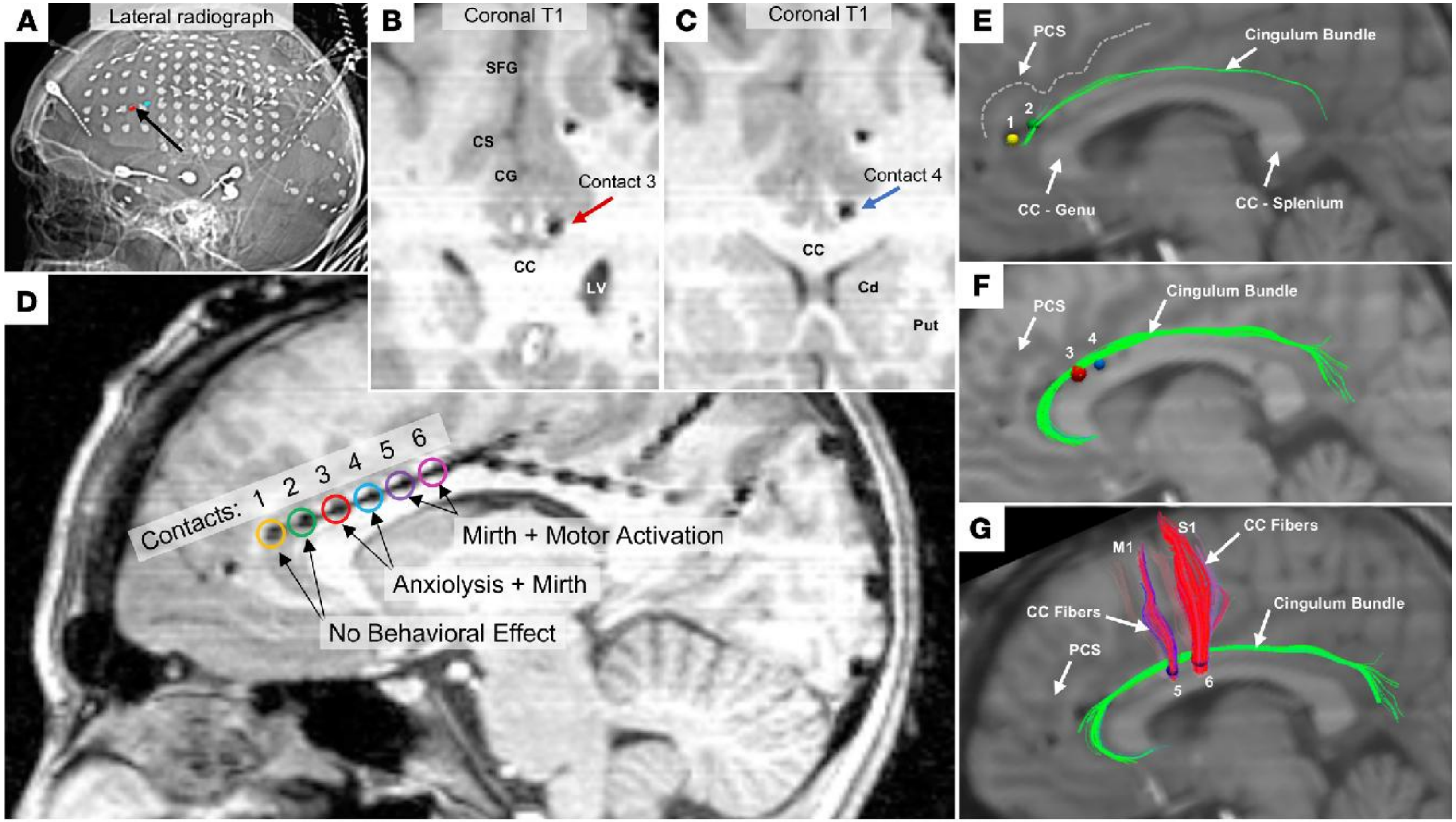
Wilder Penfield

https://www.youtube.com/watch?v=Rqxhdffo_0c

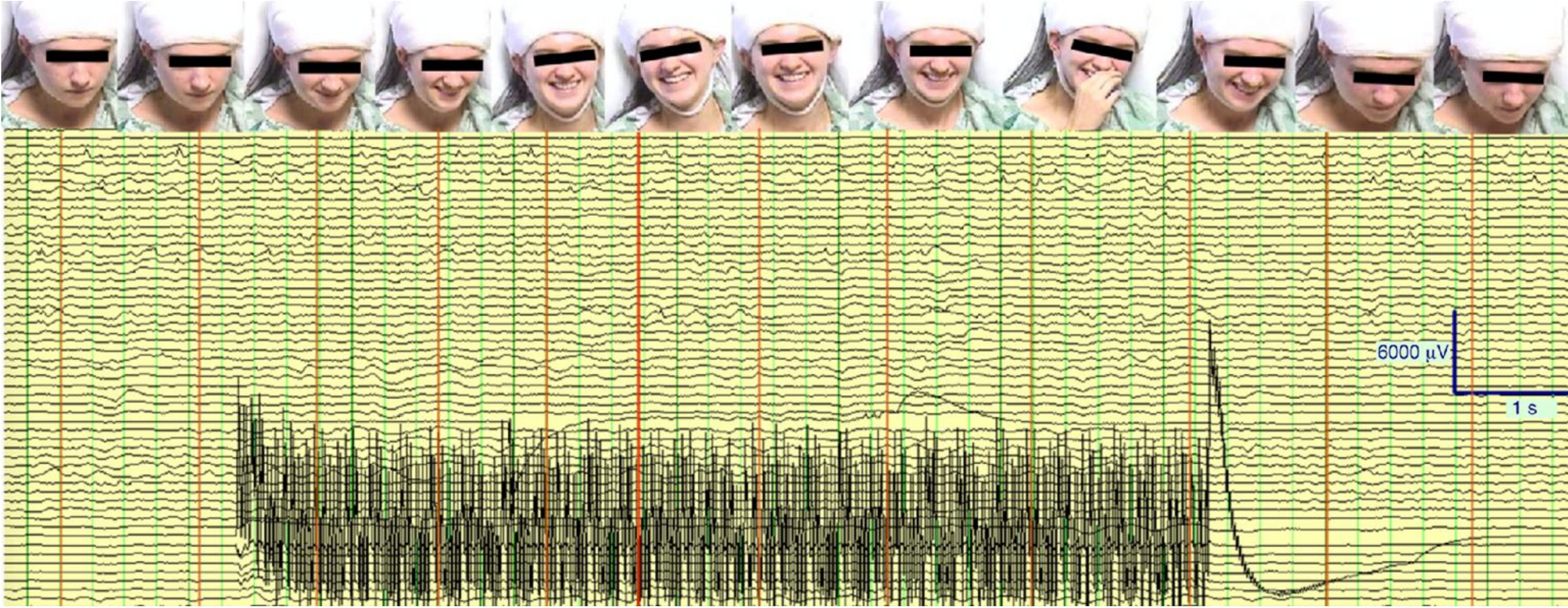
[intracranial stimulation]

Allows for causal testing

But very limited in scope and application



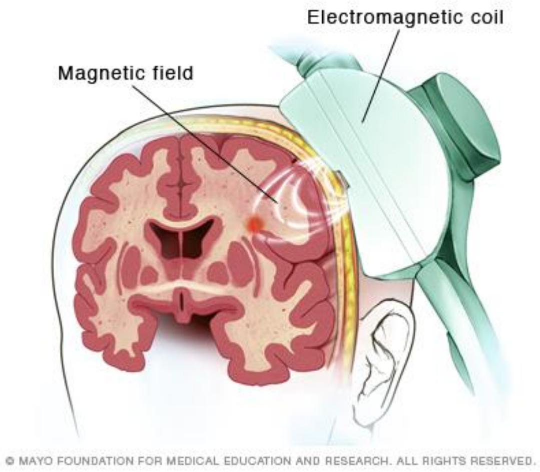
Bijanki, et al. 2019


6000 µV
1 s

Transcranial: passing or performed through the skull

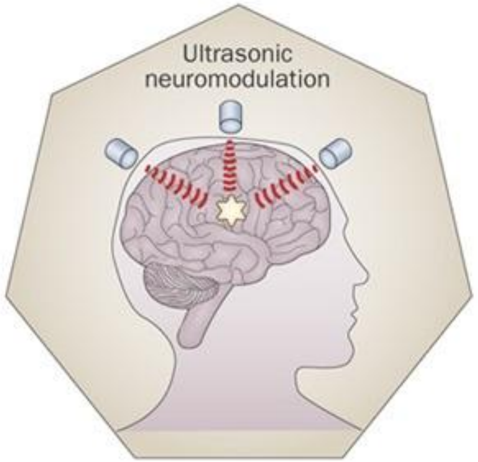
Noninvasive: not involved with incision or insertion of a medical instrument

Magnetic

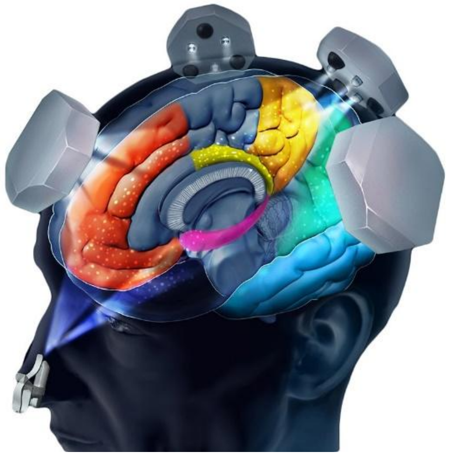


Electric

Sound



Light



Type	Invasiveness	Spatial Resolution	Depth	Mechanism
Deep brain stimulation (DBS)	Invasive	High	Deep, can be anywhere surgery will reach	Electrical impulses via implanted electrodes to modulate neural circuits
Transcranial Electrical Stimulation (TES)	Non-invasive	Low	Shallow, 1-2 cm	Weak electrical current to the scalp to alter neuronal excitability
Transcranial Magnetic Stimulation (TMS)	Non-invasive	Moderate	Loses accuracy as it goes deeper, 1-3 cm	Pulsed magnetic fields to induce electrical currents in target area
Transcranial Ultrasound (TUS)	Non-invasive	High	Deep, up to 6 cm or more	Focused ultrasound waves to modulate neural activity in target area
Photobiomodulation (PBM)	Non-invasive	Low	Shallow, 1-2 cm	Infrared light to stimulate cellular processes and enhance brain metabolism

Non-invasive brain stimulation (NIBS)

Magnetism (TMS)

Electricity (TES)

Sound (TUS)

Light (PBM)

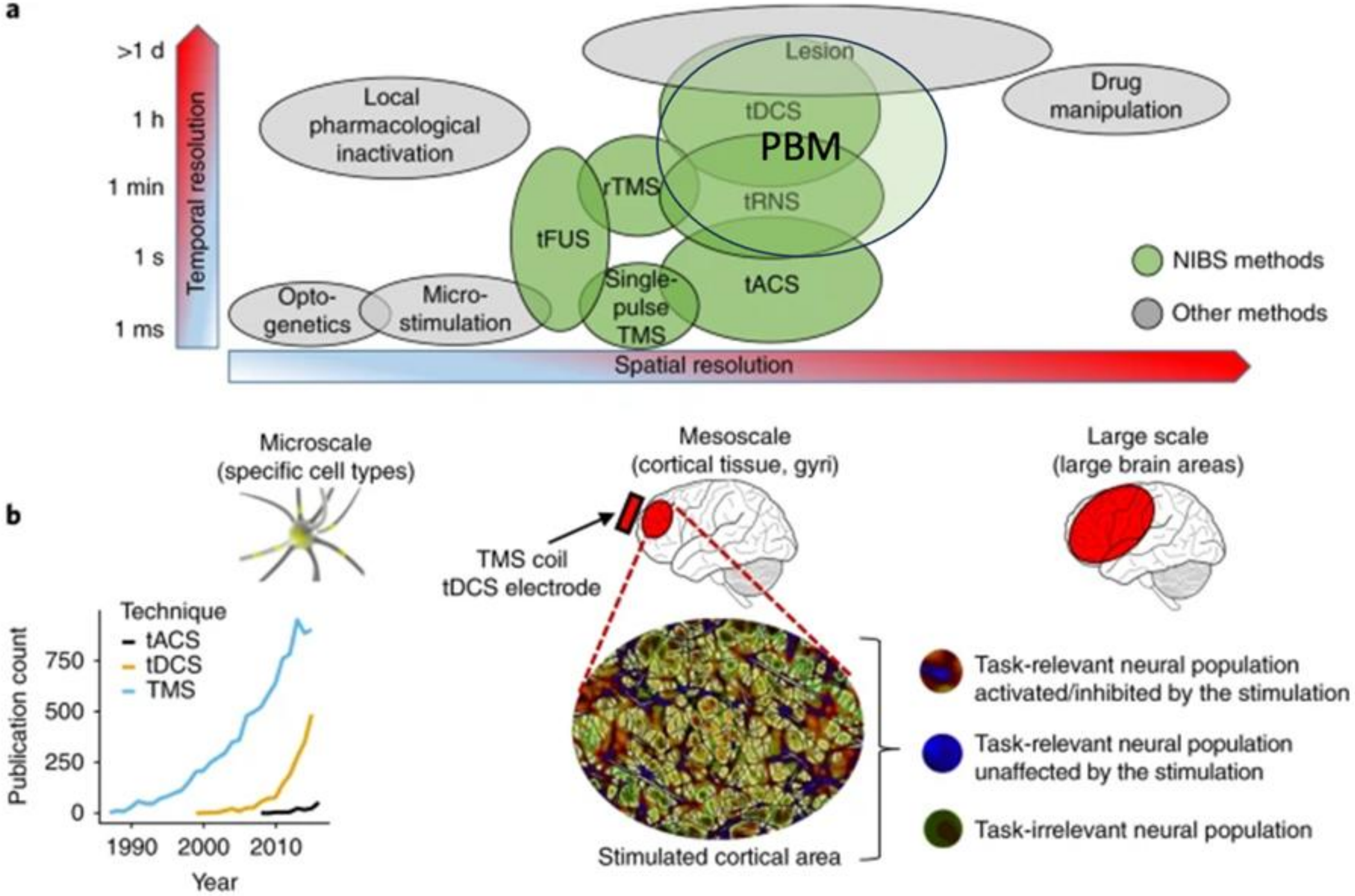
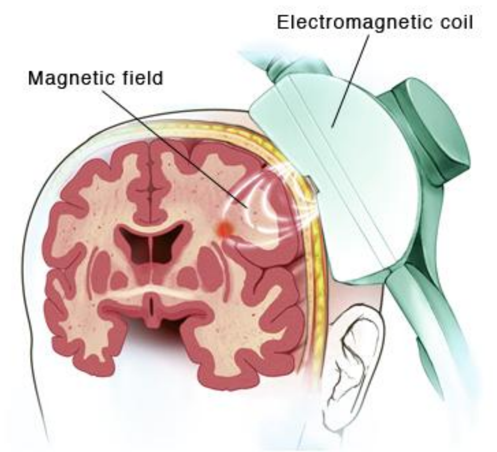


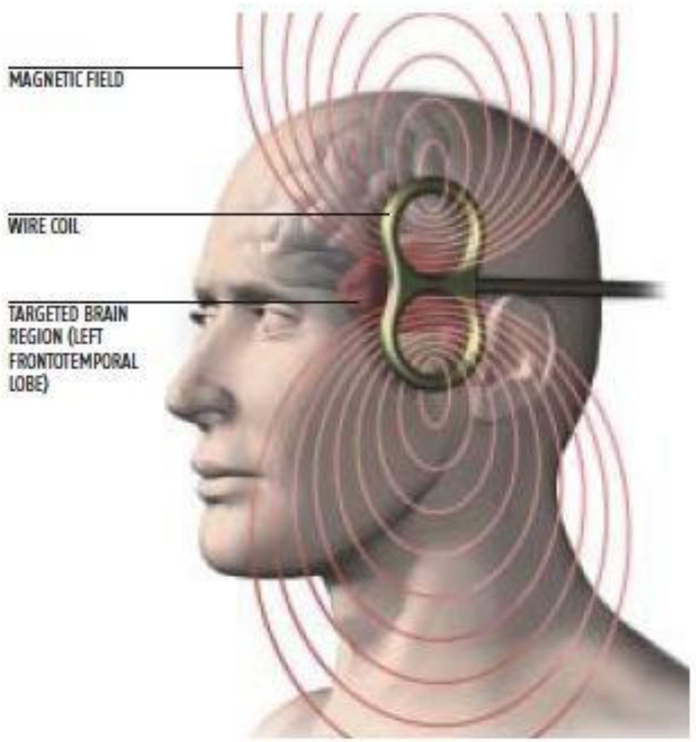
Figure from Polanía et al., 2018, with PBM added by me

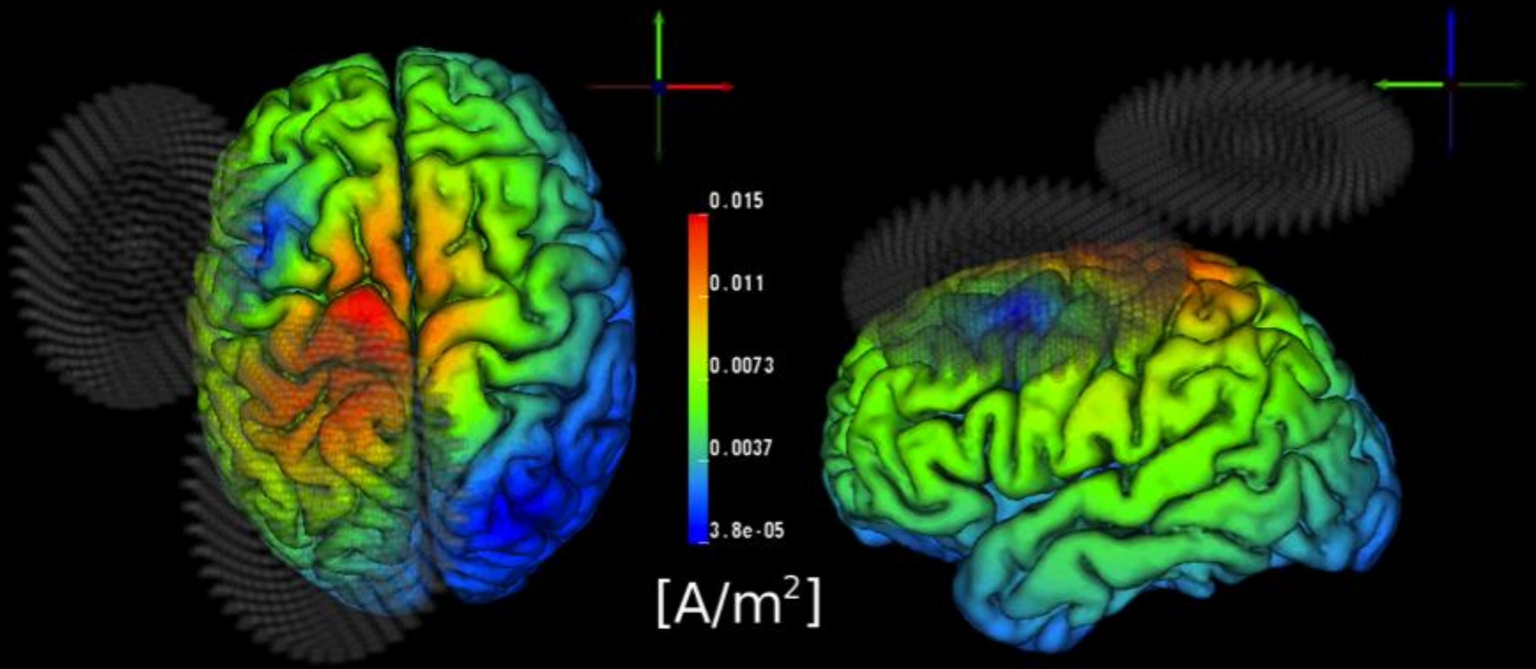
Magnetic



Transcranial Magnetic Stimulation (TMS)

- TMS device introduced by Anthony Barker and colleagues (1985; U of Sheffield, UK)

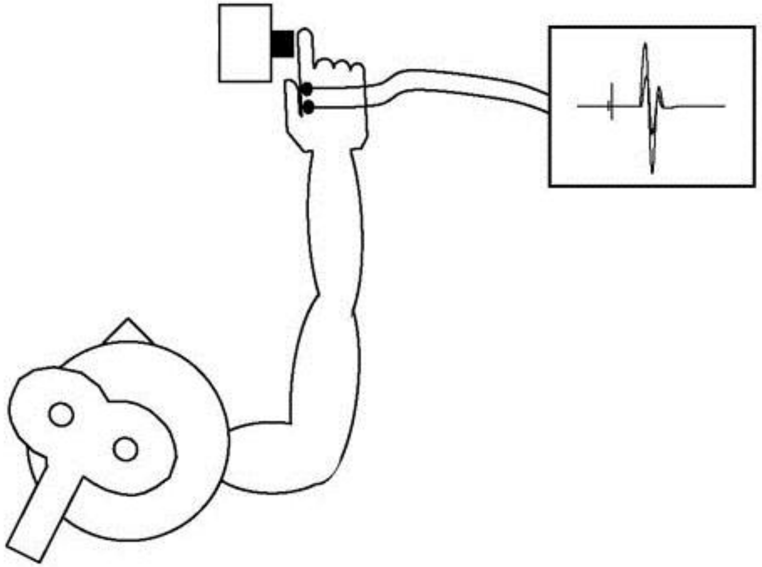




- Cell must be parallel to scalp to receive stimulation
- Geometry and orientation of the cell matters

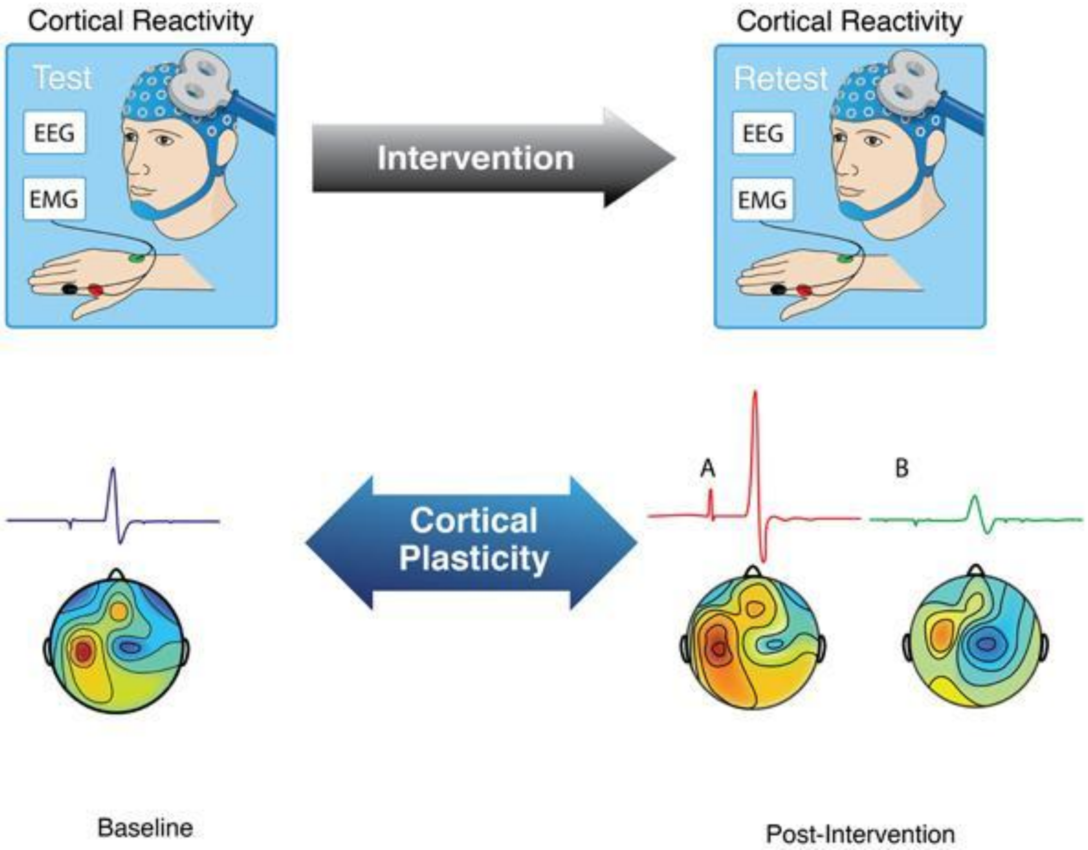
TMS Neurostimulation

Single or paired pulse TMS
(superthreshold)



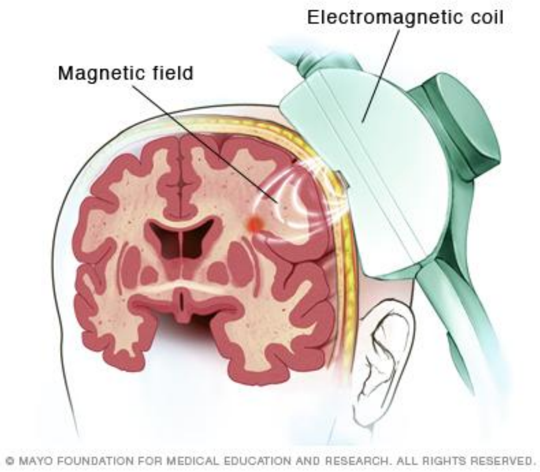
TMS Neuromodulation

Usually "repetitive TMS" (rTMS)
subthreshold – longer lasting effects



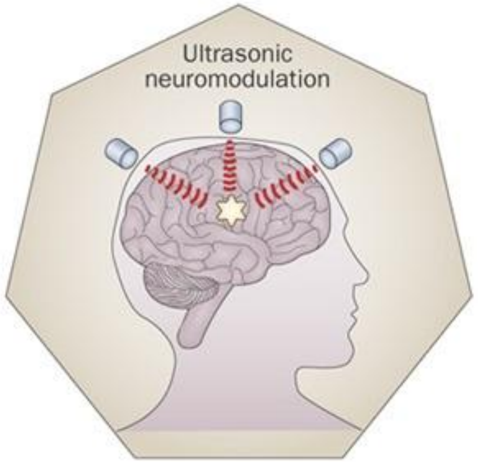
Freitas et al 2013

Magnetic

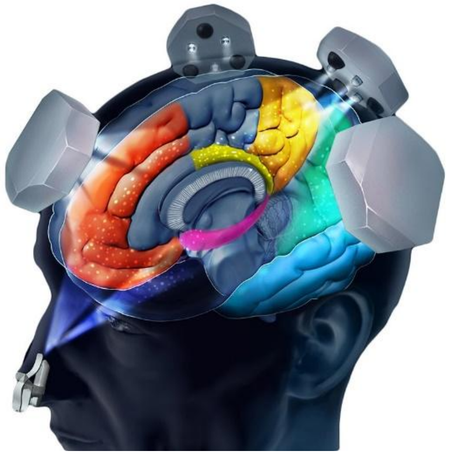


Electric

Sound



Light



Electric

tDCS is a neuromodulation method:

produces excitability changes in resting membrane potential

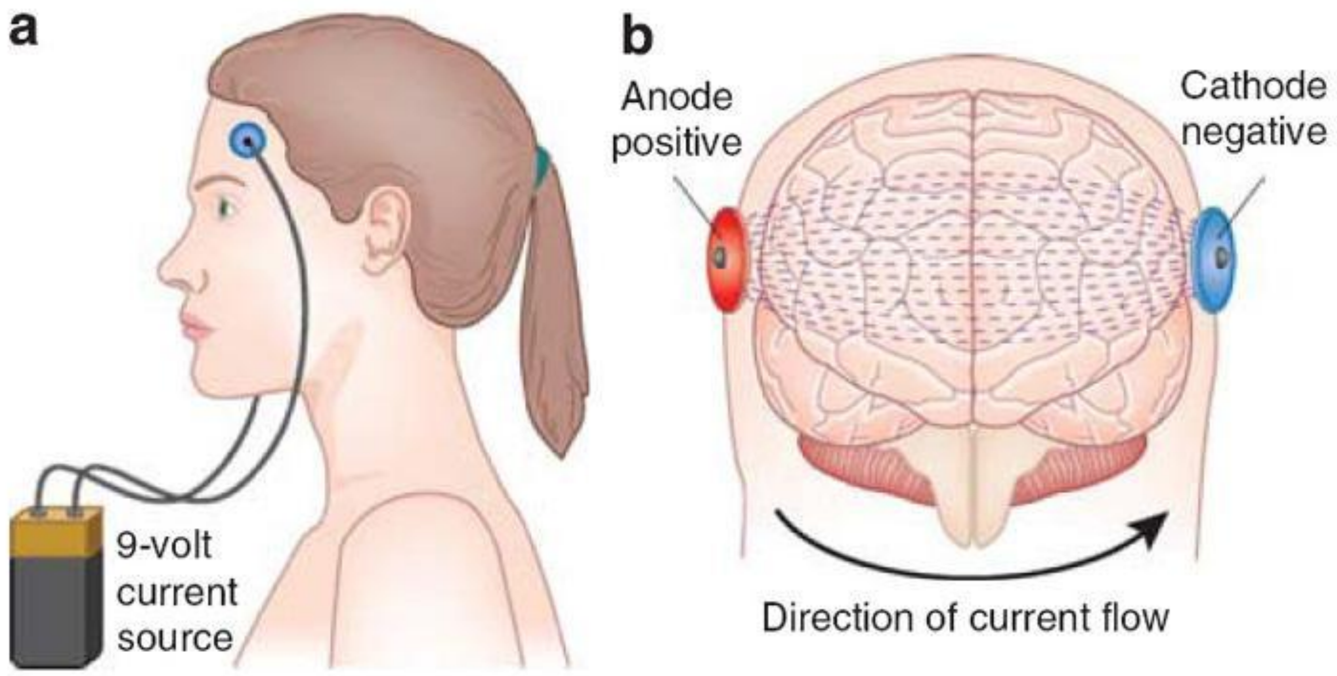
Types of electrodes

Anodal (causes subthreshold *depolarization*)

- more excitable

Cathodal (causes subthreshold *hyperpolarization*):

- less excitable

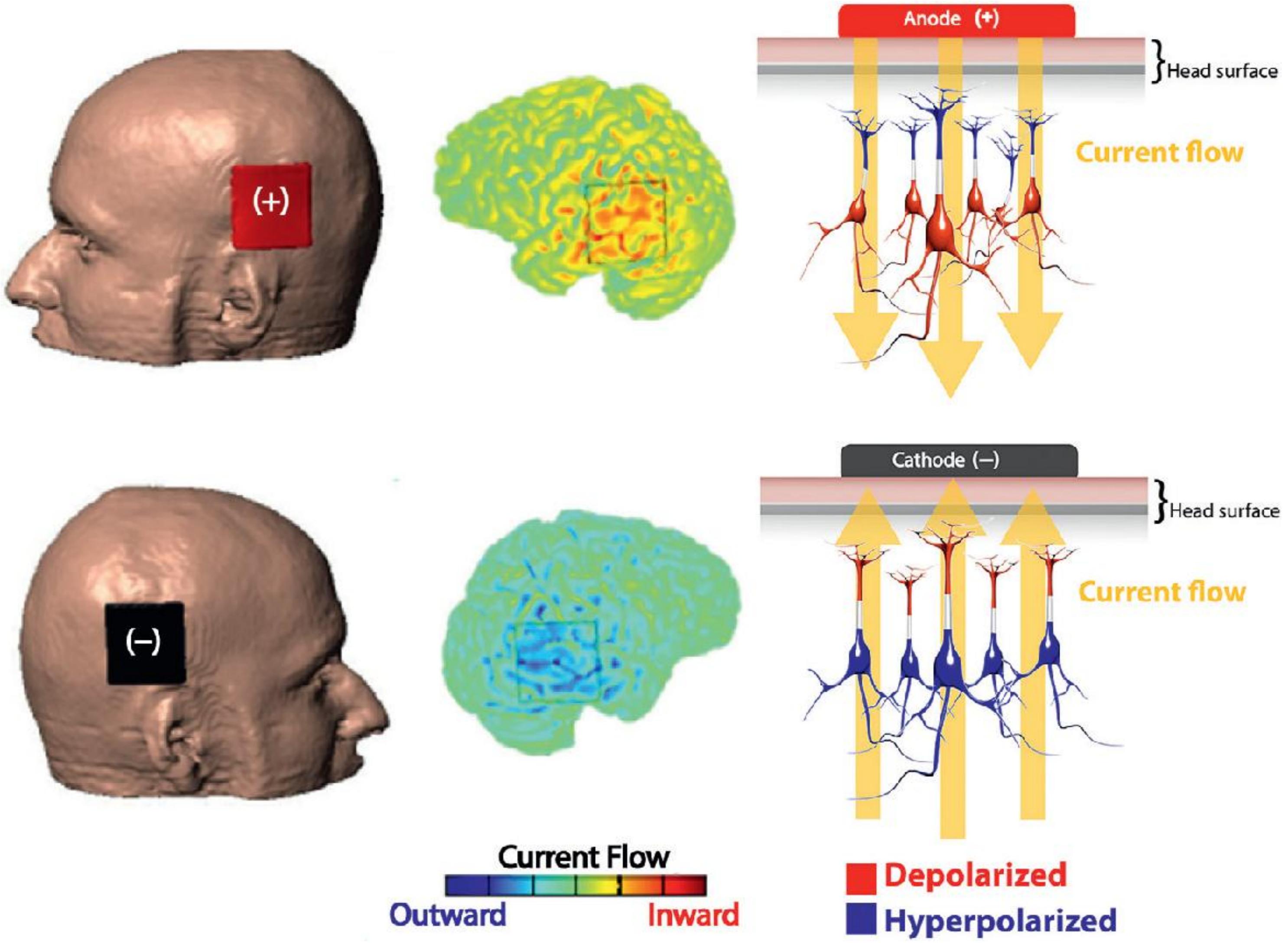


Anodal

Cathodal

Resting membrane potential (Terzuolo & Bullock, 1956; Malenka & Nicoll, 1999).

Effects last for up to several hours with 20 min+ stimulation (LTP and LTD? – cAMP, NMDA, and calcium levels altered; protein synthesis altered).



Transcranial Direct Current Stimulation (tDCS)

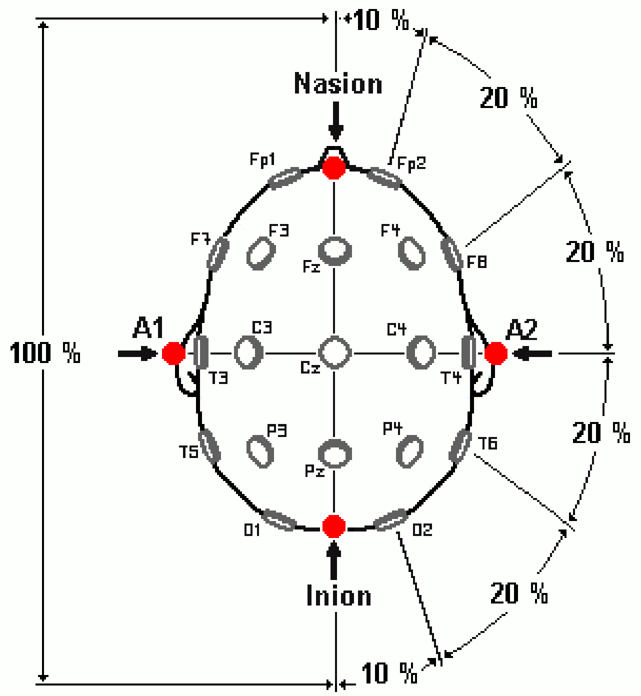
Electrodes applied using the international 10-20 EEG System

to target the intended area

Delivers **weak** direct currents to the scalp through electrodes (up to 2 mA typically)

Estimates are that
~10 to 50% of the direct current reaches the brain through the skull

- 0.3 mV/mm per 1mA applied

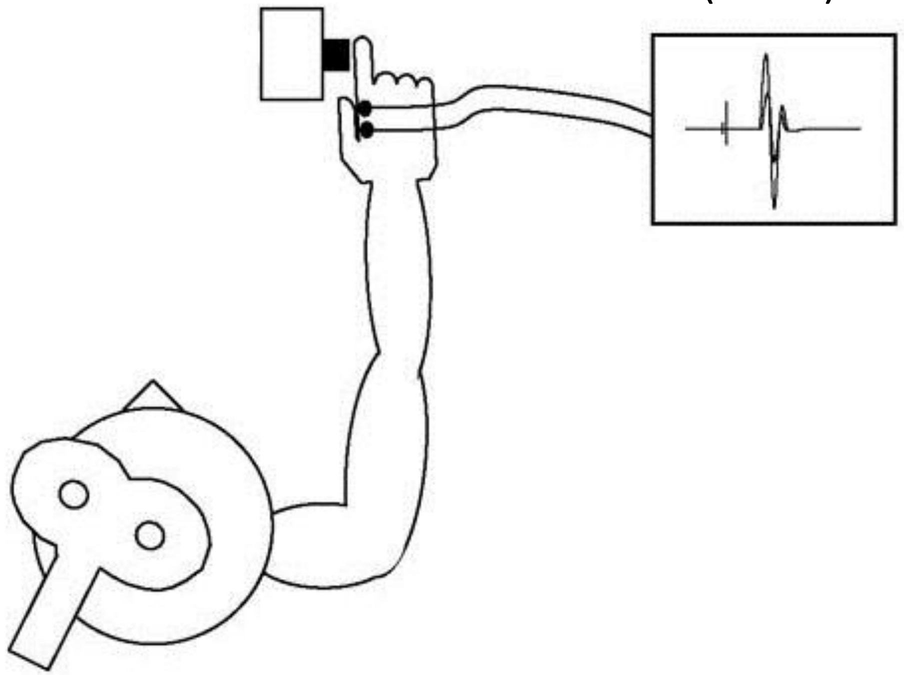


Using TMS to confirm that tDCS alters cortical excitability

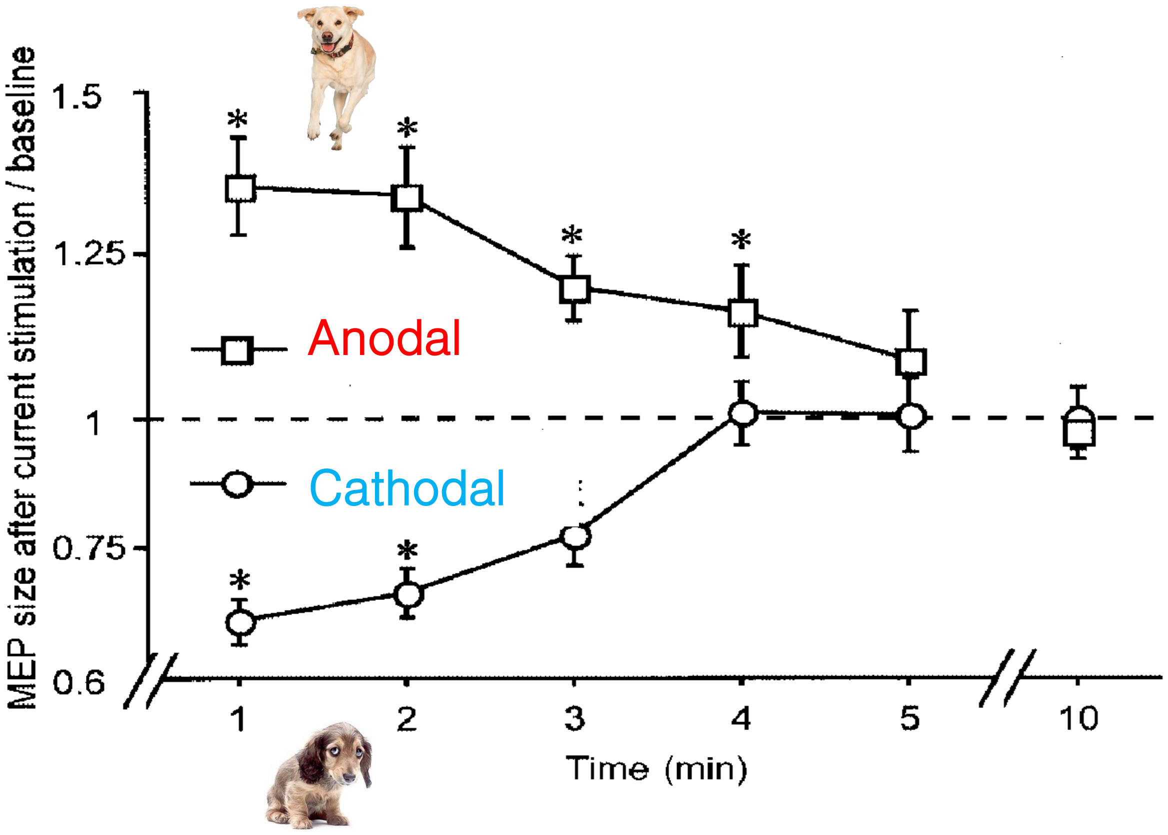
Nitsche and Paulus (2000)

- TMS
- measured motor evoked potentials (MEPs) induced by TMS in the ADM muscle of the hand

  MEP amplitude represents the excitability of the motor system



tDCS alters cortical excitability



- Anode over motor cortex: larger MEPs
- Cathode over motor cortex: smaller MEPs

Excitability changes ~ 40%.

Effects lasted for ~4 min

endurance due to LTP or LTD?

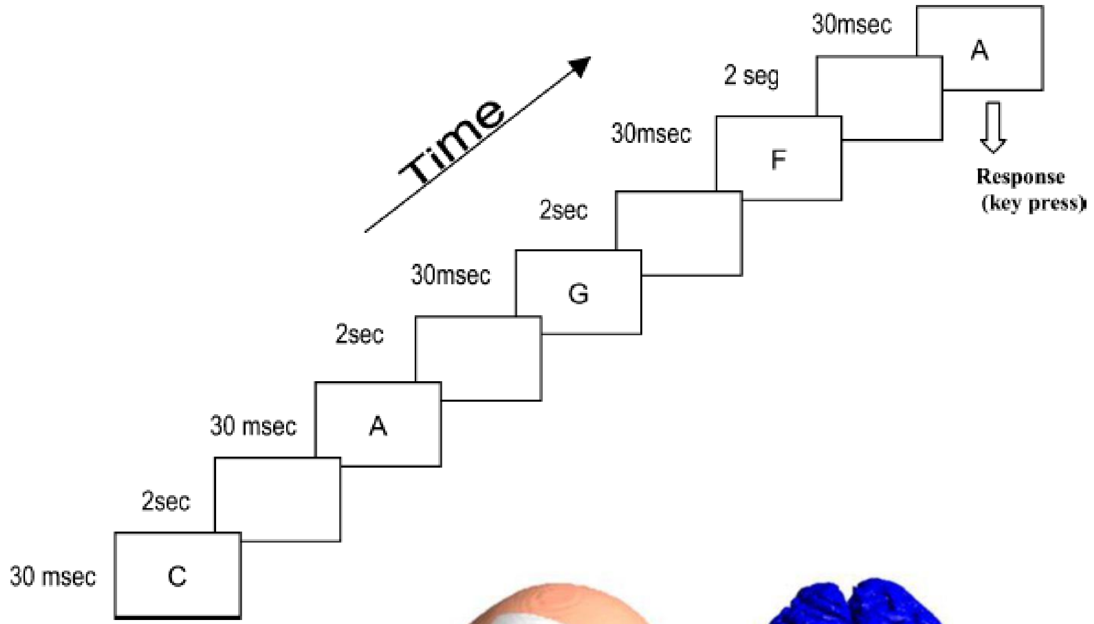
Nitsche & Paulus, 2000

Working memory (WM)

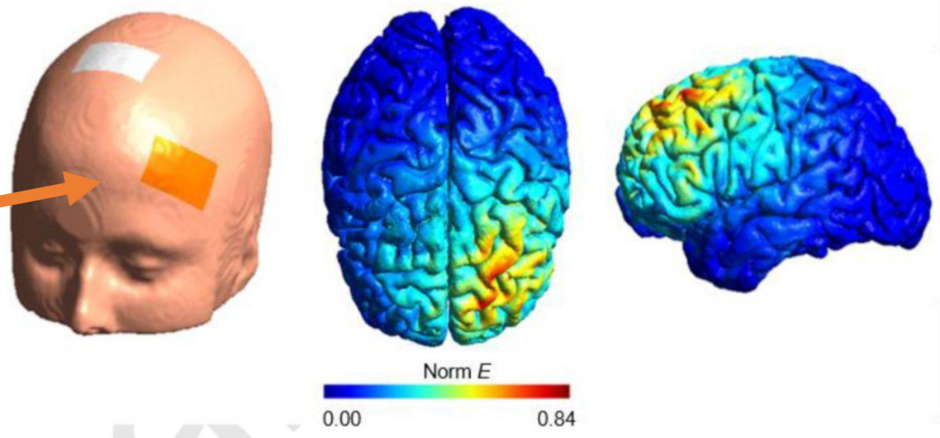
- Temporary storage and manipulation of the information necessary for complex tasks
- Common task to assesses WM: 3 back task

Task:
Respond when letter shown in the current frame (N) is the same as letter shown in frame N – 3.

(Targets separated by three to five letters)



Correlational evidence suggested the left Dorsolateral Prefrontal Cortex (DLPFC) plays a crucial role in WM



Fregni et al. (2005):
Does anodal stimulation of left DLPFC affect WM as indexed by 3-back task performance?

Procedure:

1. Subjects practiced the task for 20 min or until they reached an accuracy of ≥ 50%

2. Applied a constant current of 1 mA intensity for 10 min during task

   anode over DLPFC; cathode over right supraorbital area.

   (Subjects feel the current as an itching sensation at both electrodes at the beginning of the stimulation.)

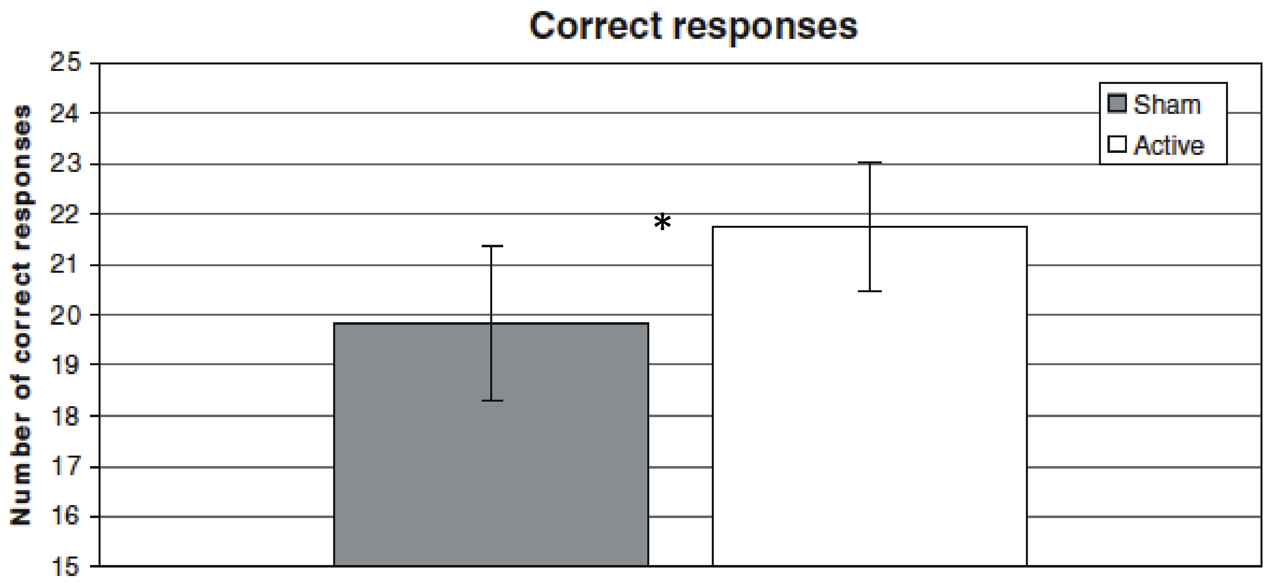
3. Or sham stimulation applied for 10 minutes during task

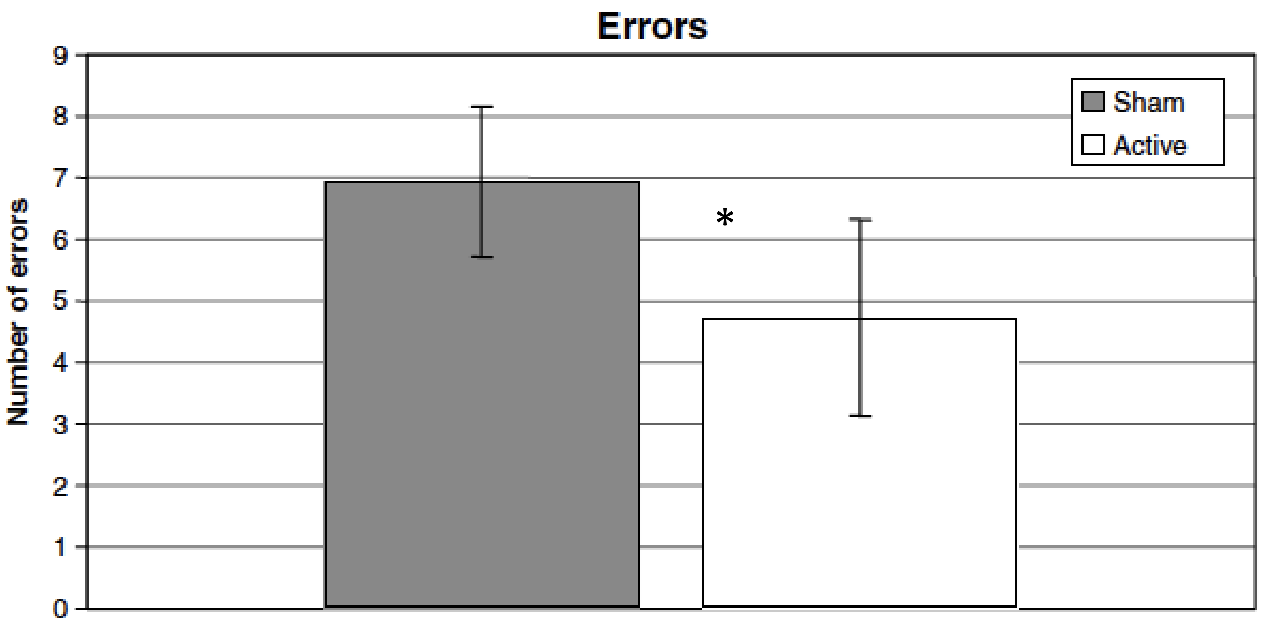
   Sham = electrodes placed in the same position but the stimulator was turned off after 5 s. Subjects feel initial itching sensation but received no current for the rest of the stimulation period. Subjects were blind to the respective stimulation condition

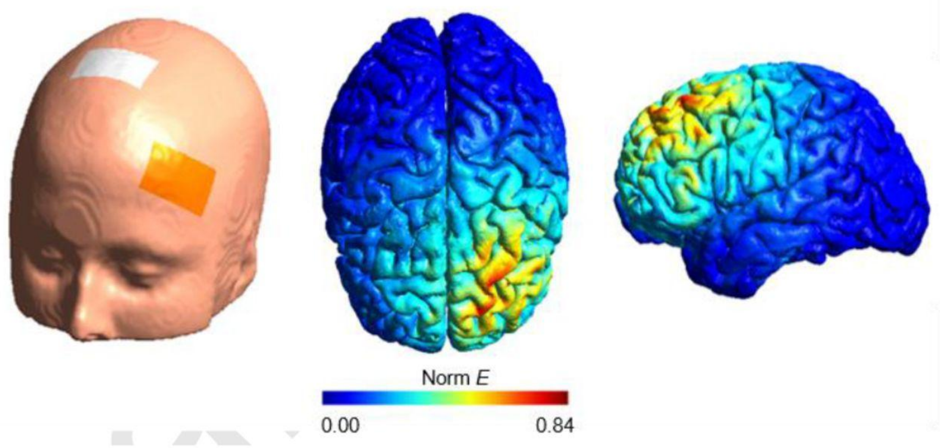
*** Order of active and sham stimulation was **counterbalanced** across subjects.

***Conditions were separated by at least 1 h so the effects of the previous run washed out

Results: (30 correct responses were possible)







(Hill et al. (2016): Meta-analysis supports these results

1. Electrodes are large & current flows between them – stimulation is not focal; large areas of brain are stimulated

Note: color coding of anode and cathode are reversed in figure below

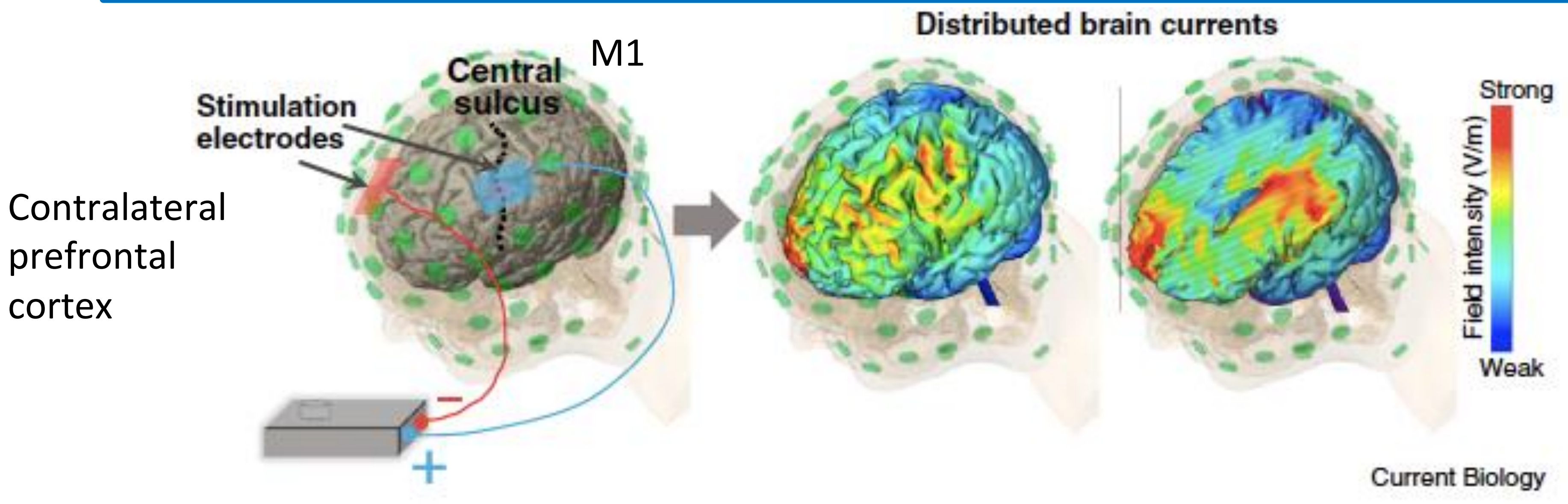
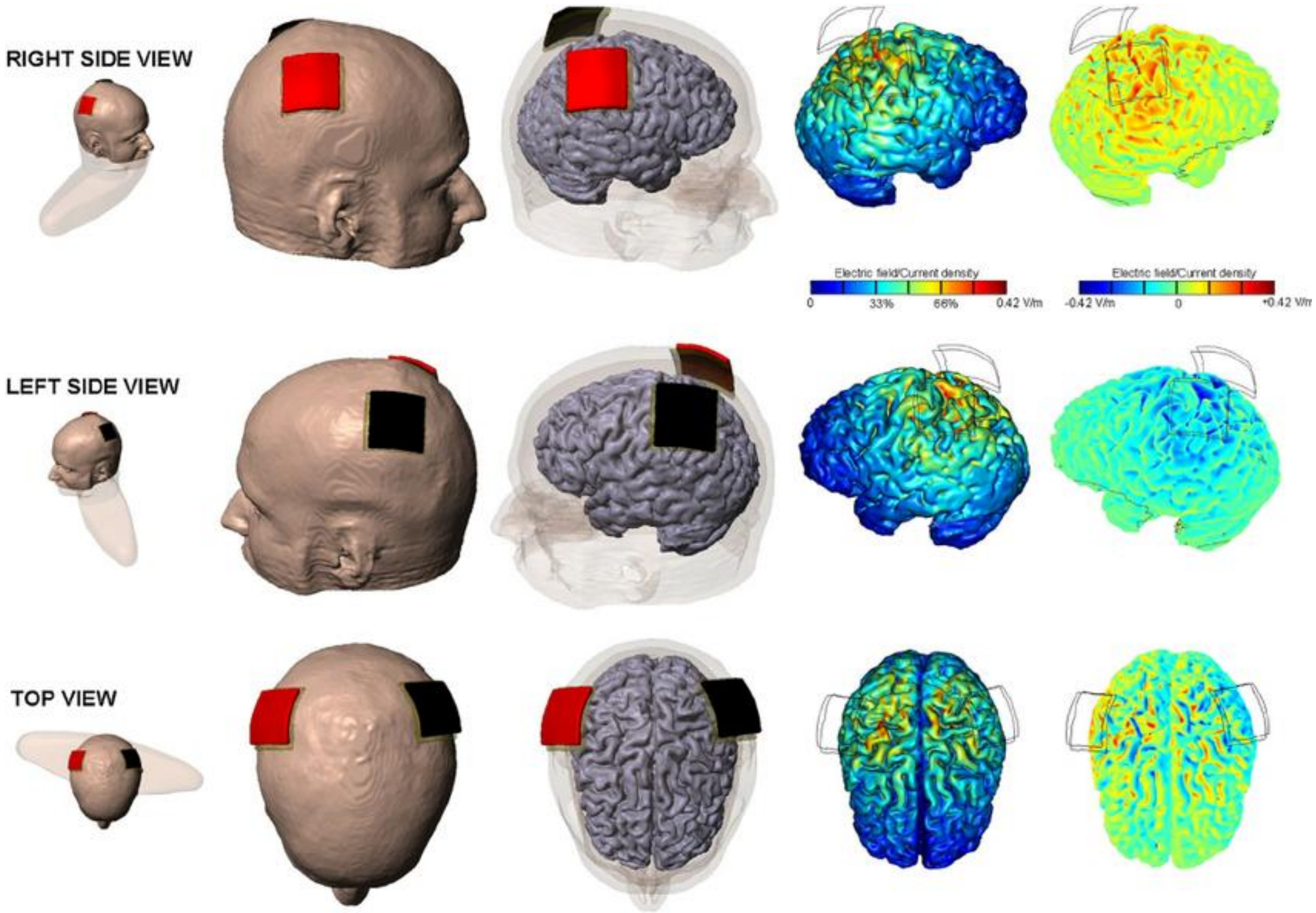


Figure 1. Example electrode montage most commonly used for stimulation of primary motor cortex.
One electrode (anode) is placed over central sulcus, and the other electrode (cathode) placed over contralateral prefrontal cortex. As shown on the right, the distribution of current inside the brain with this montage is not focal. Instead, peaks of current can not just occur under both electrodes, but also in brain regions in between and remote from the stimulation electrodes.



RIGHT SIDE VIEW
LEFT SIDE VIEW
TOP VIEW
Electric field/Current density
0
33%
66%
0.42 V/m
Electric field/Current density
-0.42 V/m
0
+0.42 V/m

2. Cathodal stimulation doesn’t always reverse anodal stimulation

3. Control conditions are not always straightforward reversals of experimental

4. Dose–response relationship can be non-linear, or even non-monotonic:

- e.g., high intensity stimulation (e.g., 2 mA) in M1 can null or even reverse effects seen with lower intensity stimulation.

5. Duration of stimulation matters:

anodal tDCS for 13 min in M1 enhanced motor cortical excitability
doubling this stimulation to 26 mins decreased motor cortical excitability.

Not clear why reversals exist, although scientists are working on this
(Answer is likely in pharmacological mechanisms and/or due to fact that effects are not focal; they occur at network levels)

Also not known whether same effects are found for all brain areas

As a consequence, unreliable research is a big problem in the literature

Many are working to correct this now, raising questions such as:

Are stimulation locations well-placed?

What is the best control condition?

- Supraorbital location is not non-cerebral!
- Is sham always indistinguishable from experimental?
- Have experiments been replicated?

A new technique with lots of promise, but also lots of junk papers

Working memory	
Fregni et al. (2005)	0.4 (+)
	0.1[a] (−)
Boggio et al. (2006)	0.5 (+)[1 mA]
	1.3 (+)[2 mA]
Zaehle et al. (2011)	Not available
Ferrucci et al. (2008)	−0.4 (+/−)[Cereb.]
	−0.5 (−)[F3] + [F4]
Berryhill et al. (2010)	−0.4[a] (+)
	−0.9[a] (−)
Andrews et al. (2011)	0.5 (+)[d]
Attention	
Nelson et al. (2013)	2.5[a] (+)
	2.5[a] (−)
Coffman et al. (2012b)	1.3 (+)
Stone and Tesche (2009)	−0.7[a] (+)
	−0.5[a] (−)
Sparing et al. (2009)	0.8[a] (+)
	−0.9[a] (−)
Kang et al. (2009)	0.9 (+)
Gladwin et al. (2012)	1.0 (+)
Moos et al. (2012)	−0.4 (+)[1mA]
	−0.9 (−)[1mA]
	−2.2 (−)[2mA]
Visual perception	
Korsakov and Matveeva (1982)	Not Available
Antal et al. (2001)	0.2[a] (+)[e]
	−0.6[a] (−)[e]
Antal et al. (2003a)	1.2[a] (+)[e]
	−1.1[a] (−)[e]
Antal et al. (2003b)	1.6[a] (+)[e]
	−2.0[a] (−)[e]
Antal et al. (2004a)	1.1[a] (+)
	−0.2[a] (−)
Antal et al. (2004b)	0.7[a] (+)[e]
	−1.1[a] (−)[e]

Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS).

Horvath JC[1], Forte JD[2], Carter O[2].

Author information

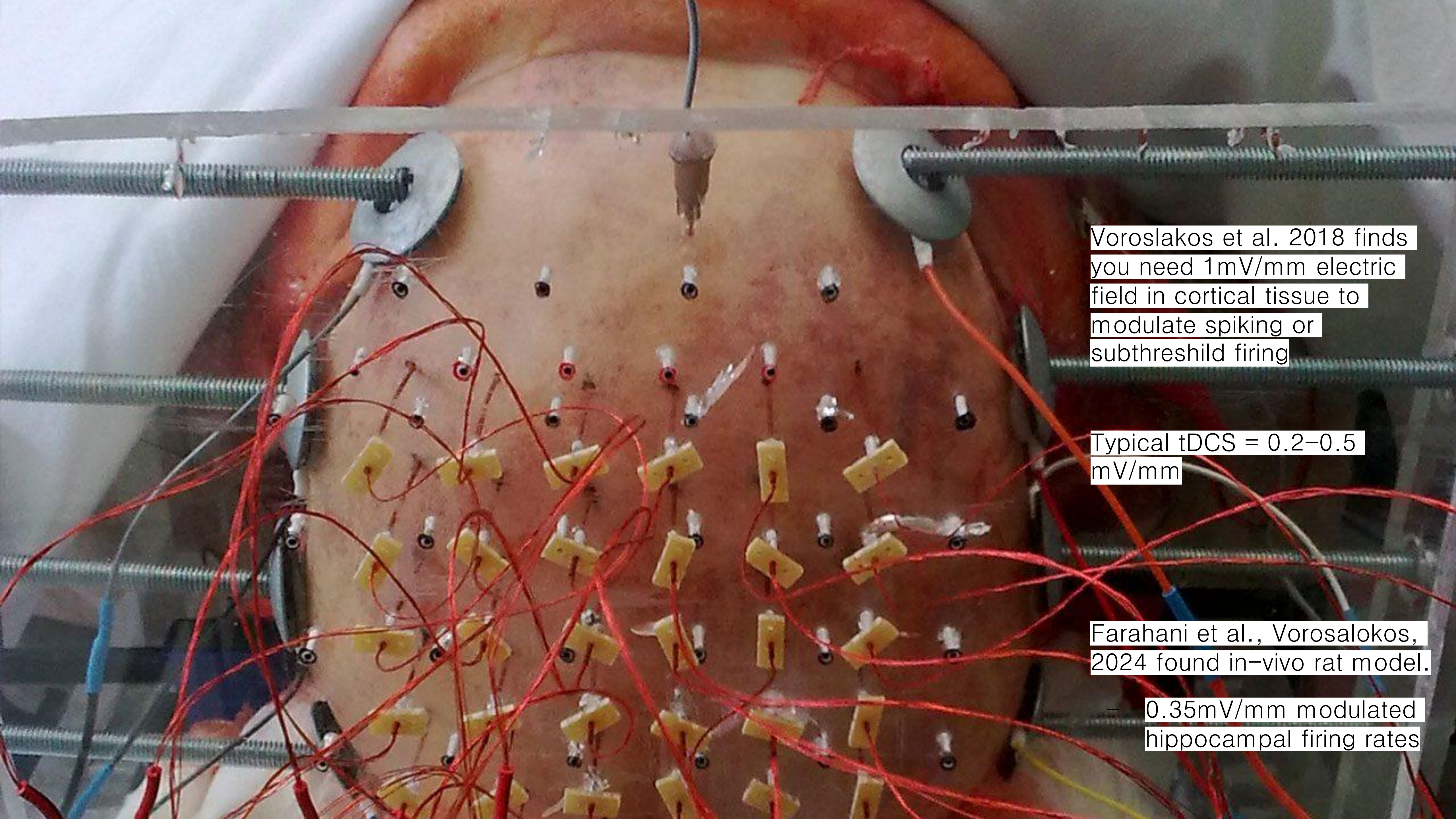
Abstract

BACKGROUND: Over the last 15-years, transcranial direct current stimulation (tDCS), a relatively novel form of neuromodulation, has seen a surge of popularity in both clinical and academic settings. Despite numerous claims suggesting that a single session of tDCS can modulate cognition in healthy adult populations (especially working memory and language production), the paradigms utilized and results reported in the literature are extremely variable. To address this, we conduct the largest quantitative review of the cognitive data to date.

METHODS: Single-session tDCS data in healthy adults (18-50) from every cognitive outcome measure reported by at least two different research groups in the literature was collected. Outcome measures were divided into 4 broad categories: executive function, language, memory, and miscellaneous. To account for the paradigmatic variability in the literature, we undertook a three-tier analysis system; each with less-stringent inclusion criteria than the prior. Standard mean difference values with 95% CIs were generated for included studies and pooled for each analysis.

RESULTS: Of the 59 analyses conducted, tDCS was found to not have a significant effect on any - regardless of inclusion laxity. This includes no effect on any working memory outcome or language production task.

CONCLUSION: Our quantitative review does not support the idea that tDCS generates a reliable effect on cognition in healthy adults. Reasons for and limitations of this finding are discussed. This work raises important questions regarding the efficacy of tDCS, state-dependency effects, and future directions for this tool in cognitive research.

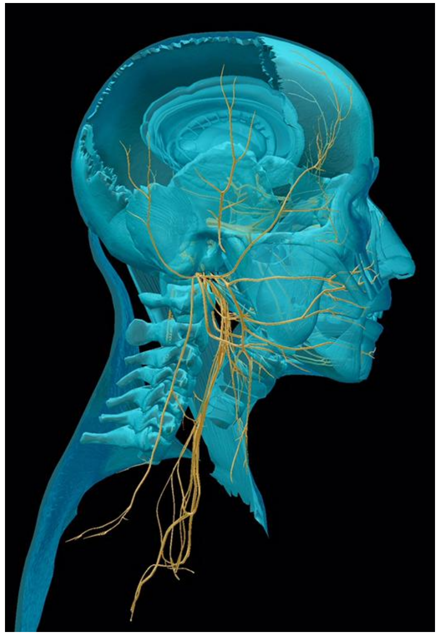


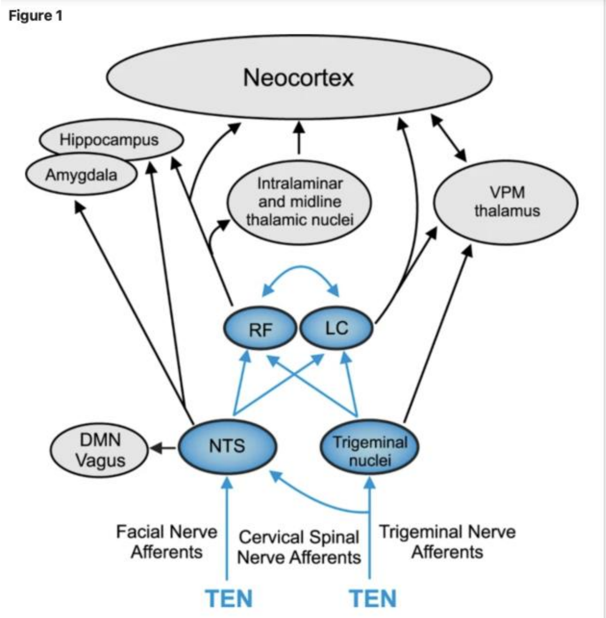
Voroslakos et al. 2018 finds you need 1mV/mm electric field in cortical tissue to modulate spiking or subthreshild firing

Typical tDCS = 0.2-0.5 mV/mm

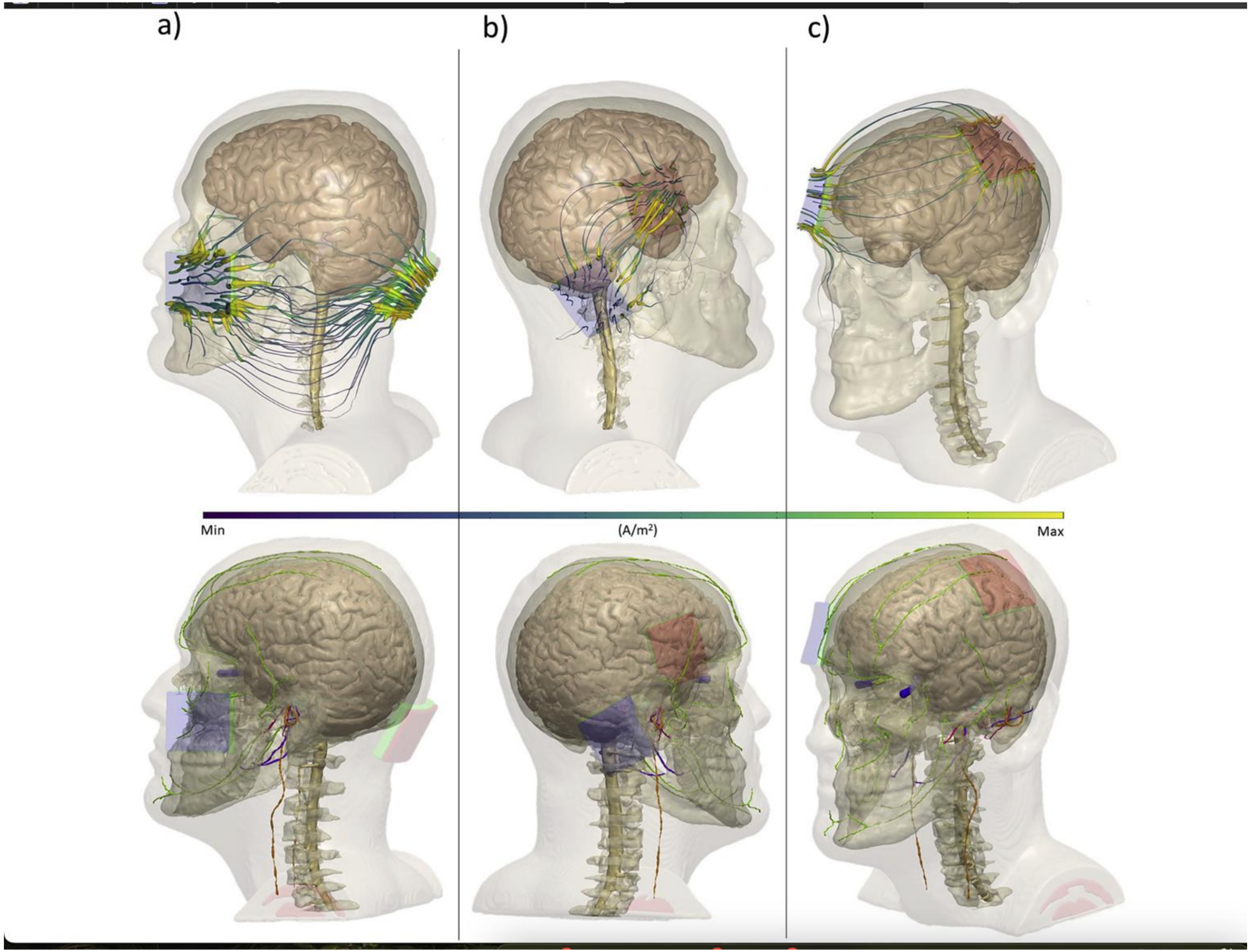
Farahani et al., Vorosalokos, 2024 found in-vivo rat model.

- 0.35mV/mm modulated hippocampal firing rates



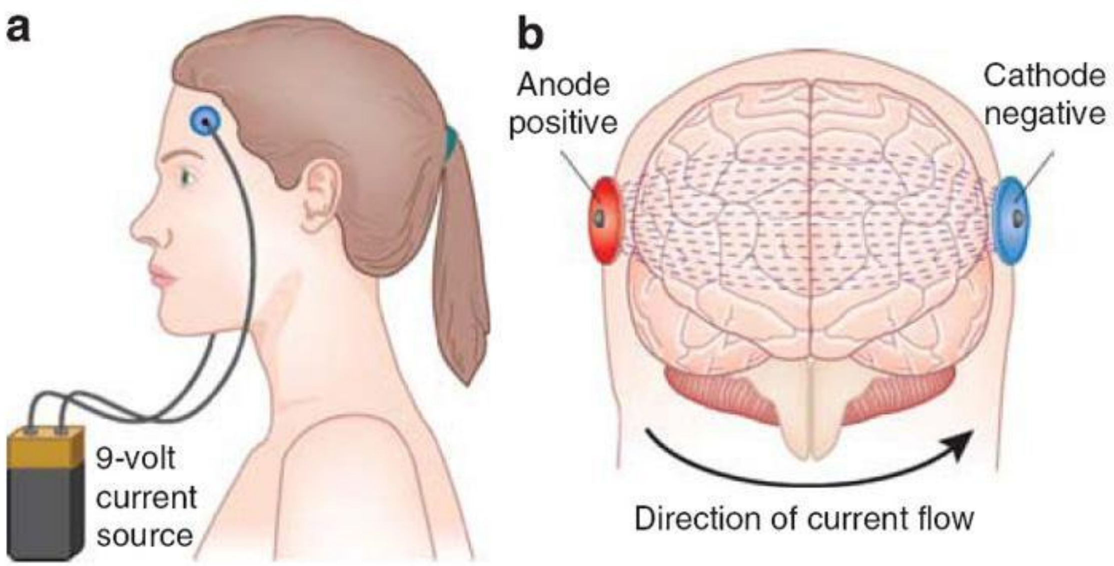


Tyler et al., 2015



Adair, et al., 2020

Evaluating tDCS (limitations)



Current covers large area of scalp!

- Electrode size
- Electrode position
- Electrode distance

<u>Be skeptical about:</u>

Conclusions about location (it's possible adjacent areas are affected)

Sham control

Crossover designs ("carry over" effects); effects might last for days

Small sample size

Replication of results (important here)

Claims that rely on mechanism

Placement of cathode!

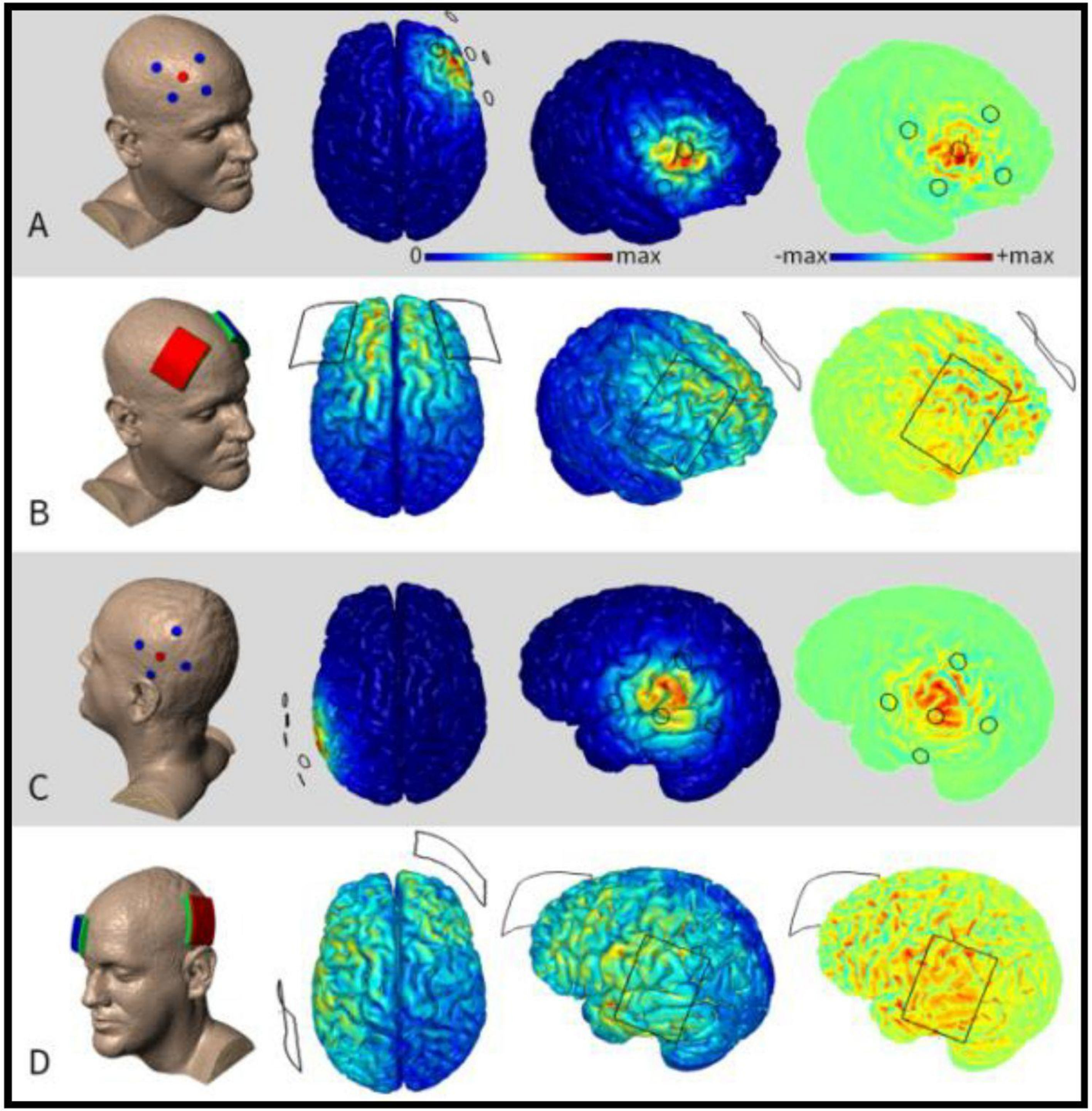
Cranial nerves?

HD-tDCS

tDCS

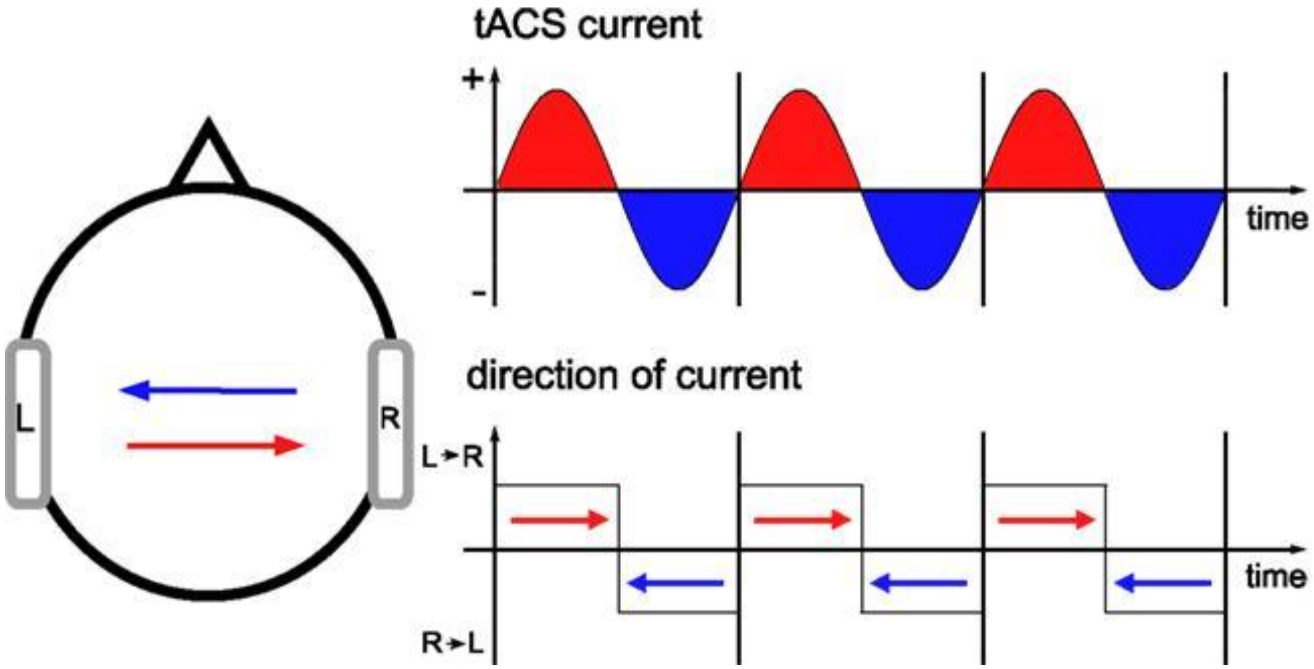
HD-tDCS

tDCS



Transcranial alternating current (tACS)

Different principles will apply

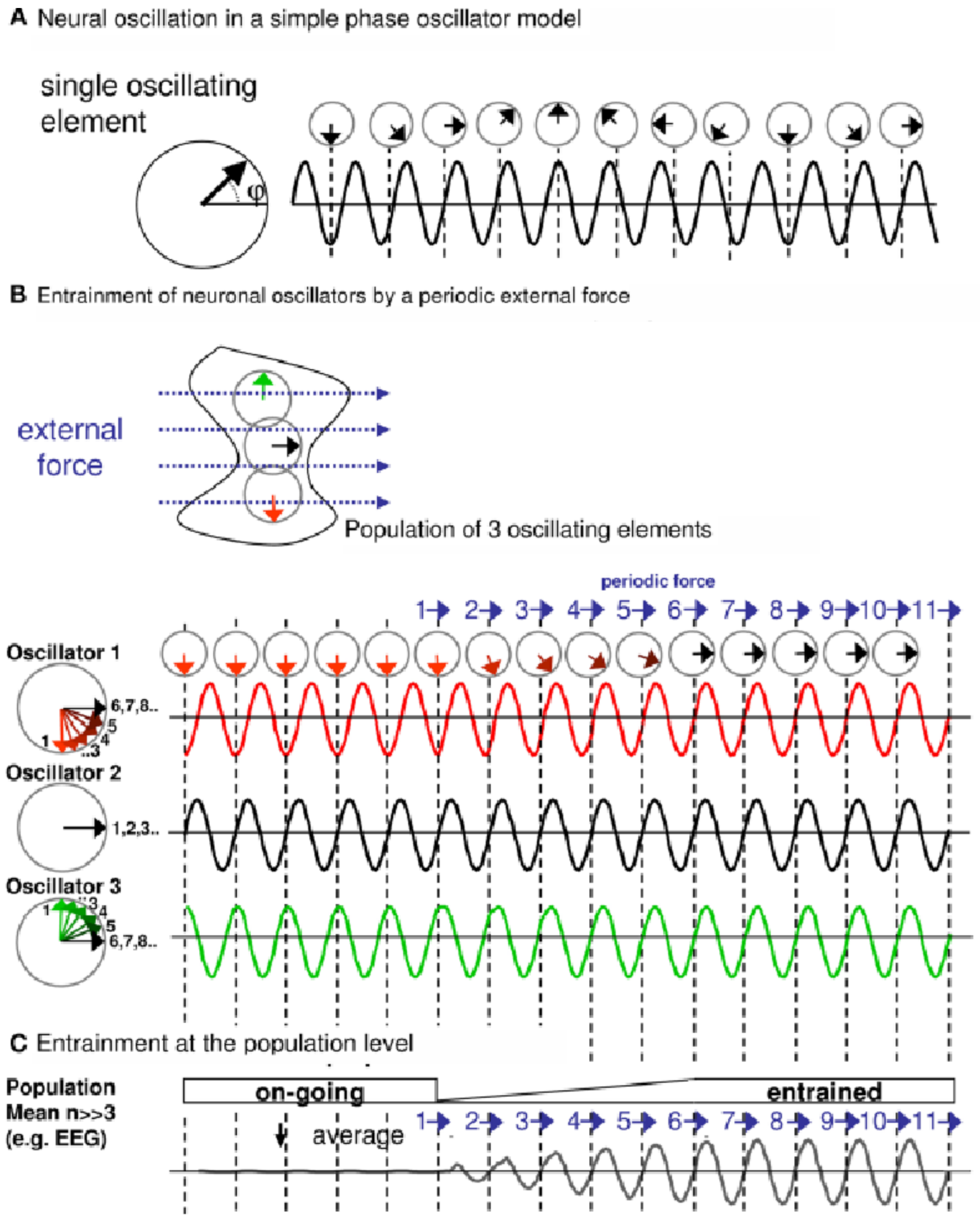


tACS for brain entrainment

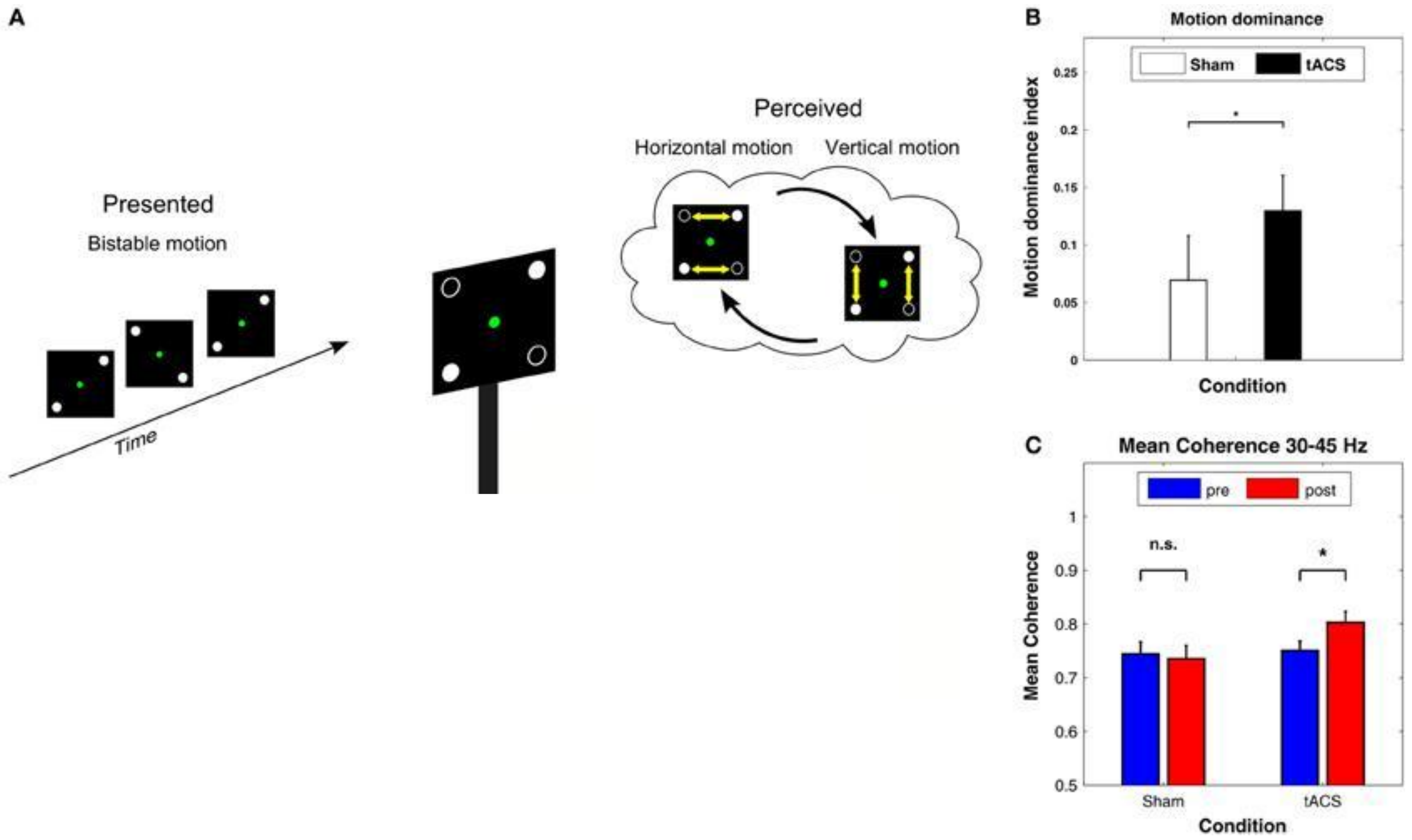
Control/induce oscillations!

Modulate cognition?

Causal testing



Thut, Schyns, Gross 2011



A
Presented
Bistable motion
Time
Perceived
Horizontal motion
Vertical motion
B
Motion dominance
Sham
tACS
Motion dominance index
0
0.05
0.1
0.15
0.2
0.25
*
Condition
C
Mean Coherence 30-45 Hz
pre
post
Mean Coherence
0.5
0.6
0.7
0.8
0.9
1
n.s.
*
Sham
tACS
Condition

Fun videos:

Great story about brain stimulation (5 min): https://www.youtube.com/watch?v=6nGAr2OkVqE

Podcast on tDCS (25 min; warning: n = 1!)

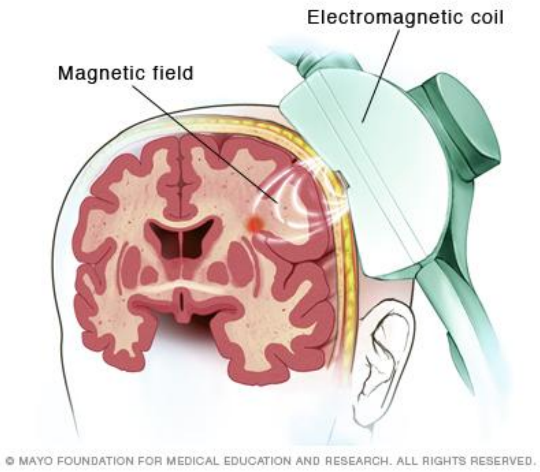
https://www.youtube.com/watch?v=8Ubb0Qvybdo

NY Times article

http://www.nytimes.com/2013/11/03/magazine/jumper-cables-for-the-mind.html?pagewanted=all&_r=0

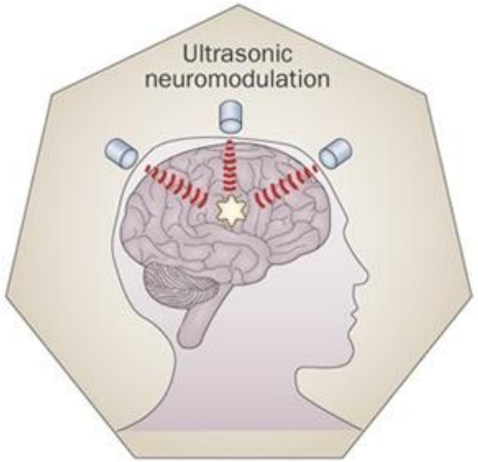

Questions?

Magnetic



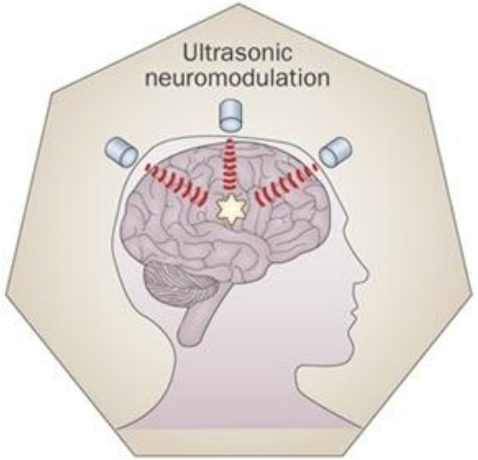
Electric

Sound



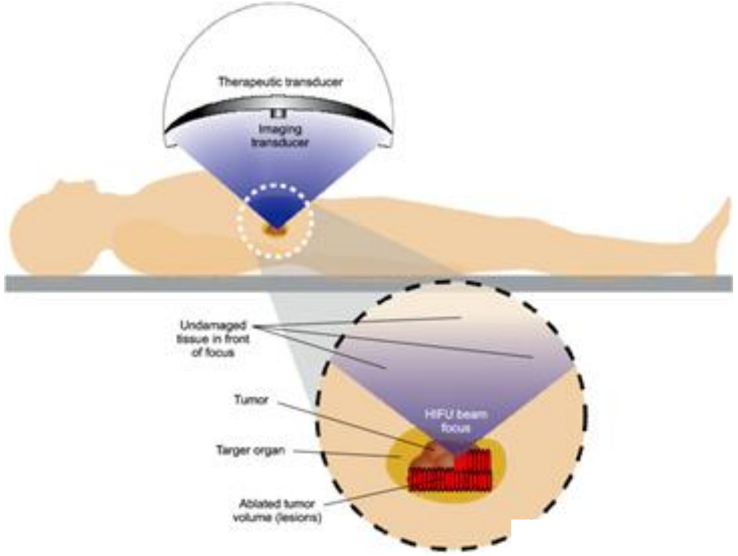
Light

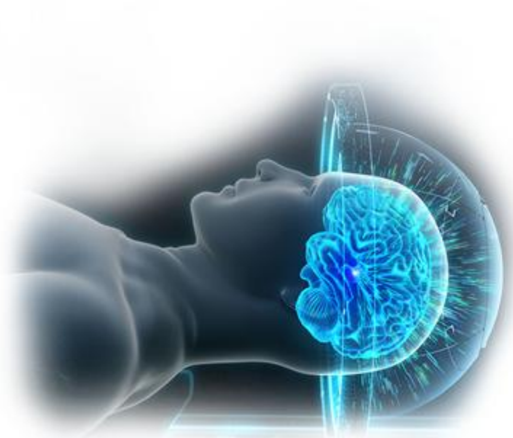
Sound



Low- Intensity

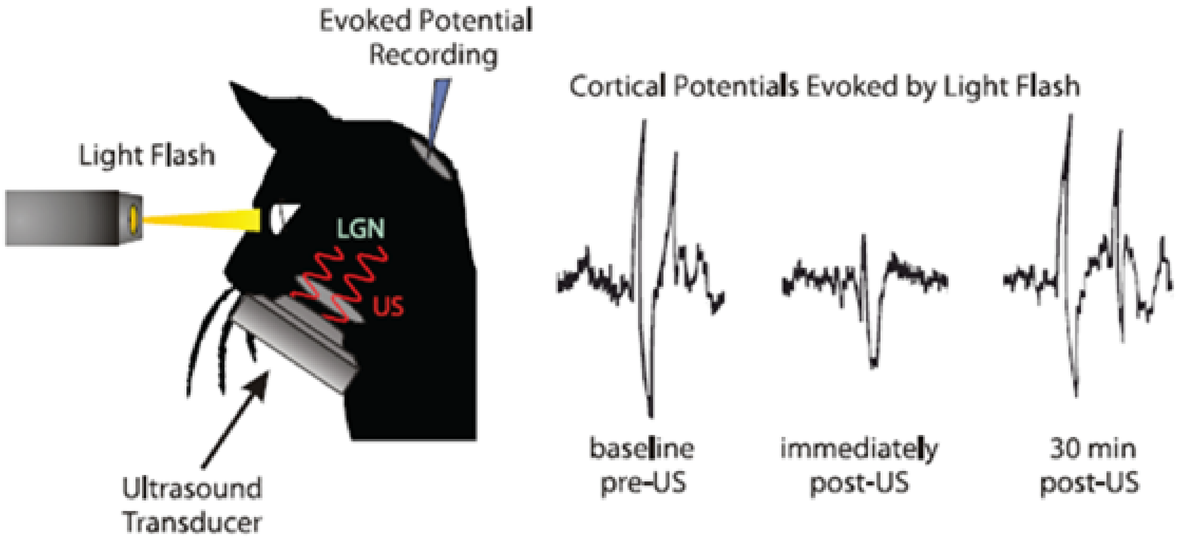
High-Intensity Ultrasound





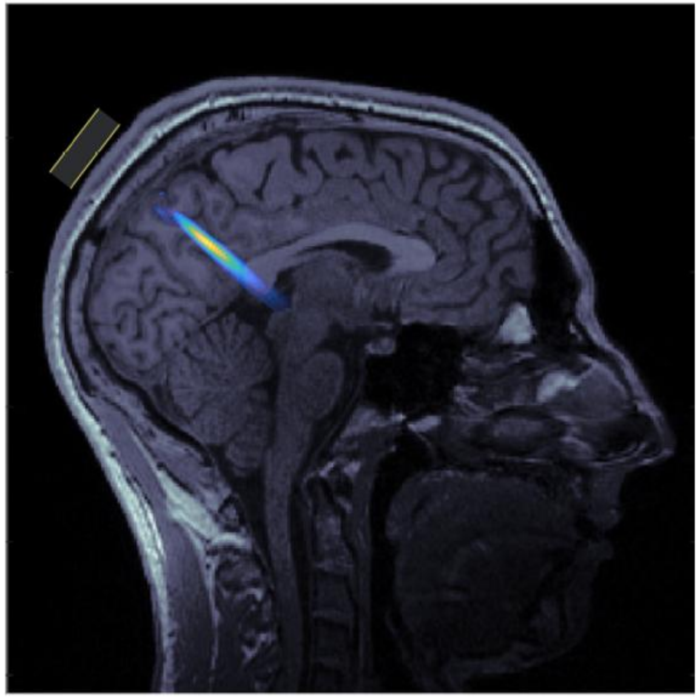
Modulation

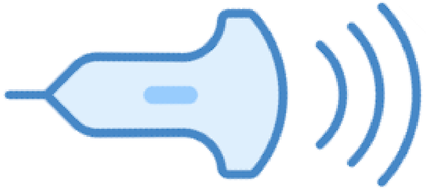
1920s-1990s

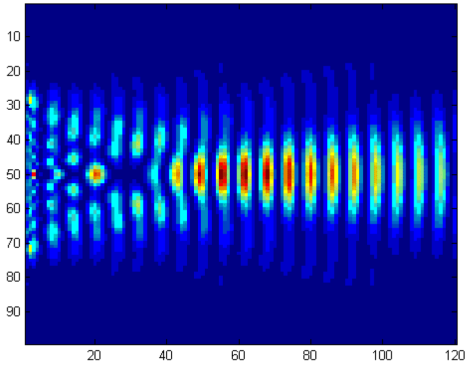


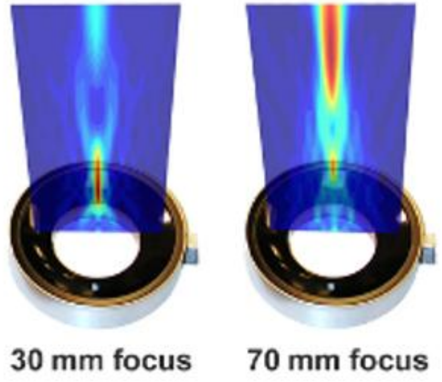
Fry, 1957, Figure: Tyler, 2013

Transcranial Focused Ultrasound – tFUS



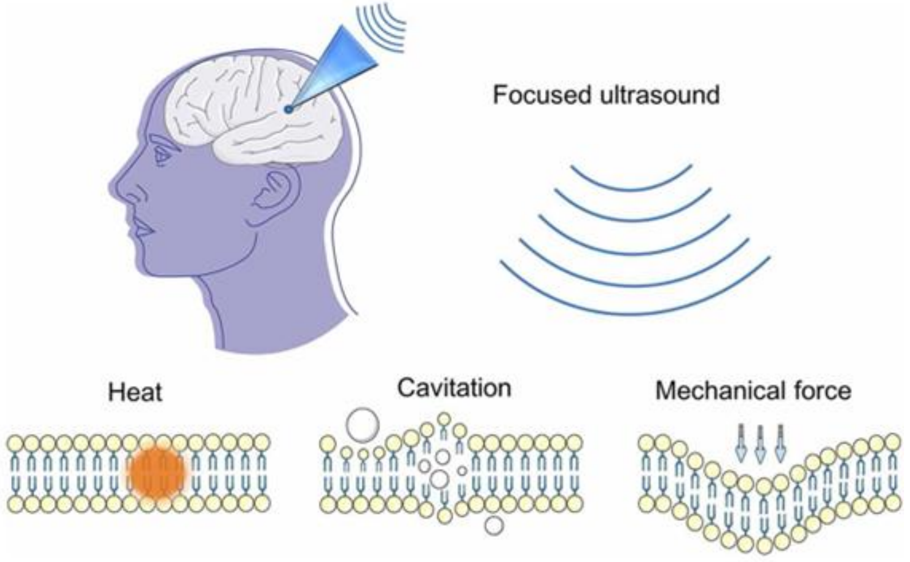


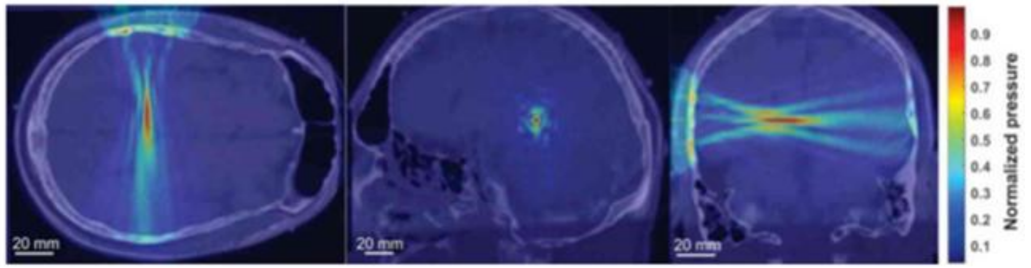


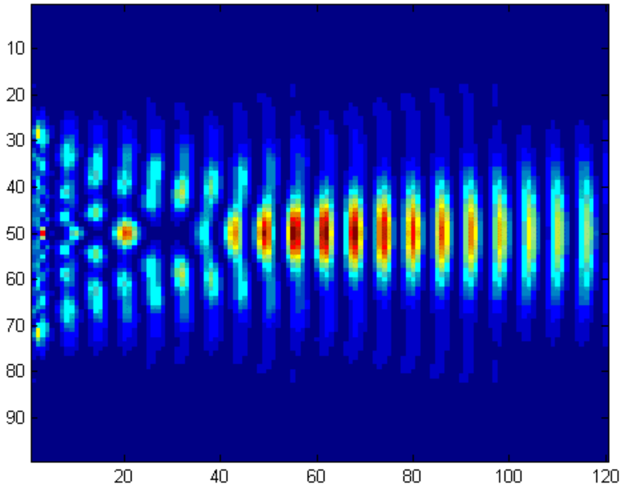


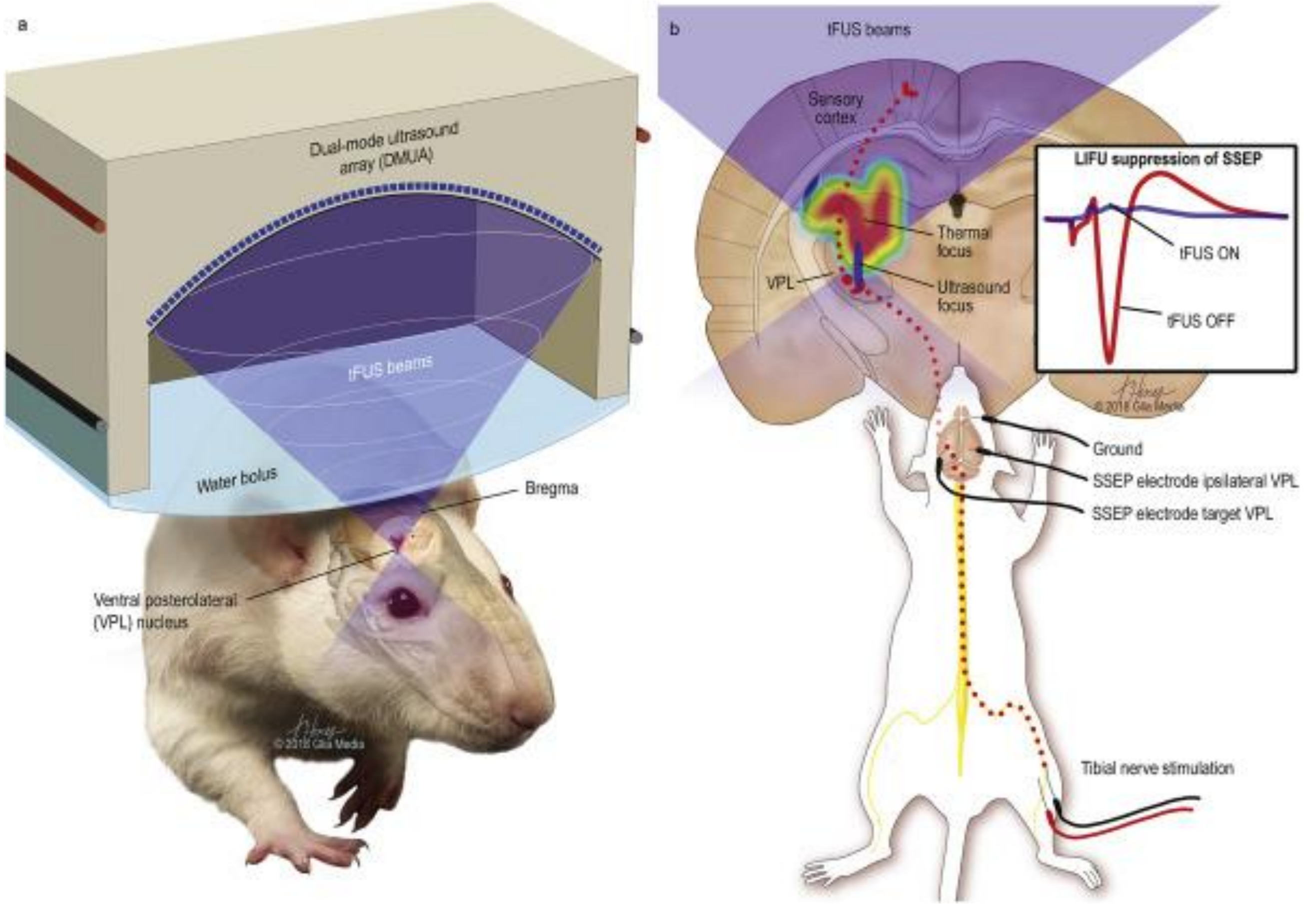
Transcranial Focused Ultrasound (tFUS)

- Uses focused ultrasound waves to modulate brain activity at precise targets
- Works through a variety of possible mechanisms – heat, mechanical, resonance effects
  - Field is still developing on what types of acoustic waves work best
- Only NIBS technique that can target **subcortically**, with high precision
- Induces heightened neuroplasticity
- Effects can last minutes to hours or more

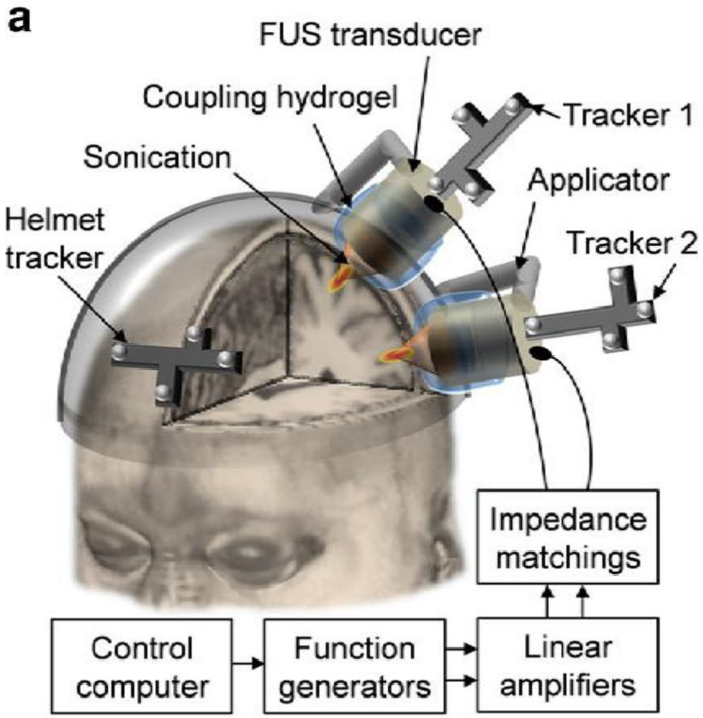


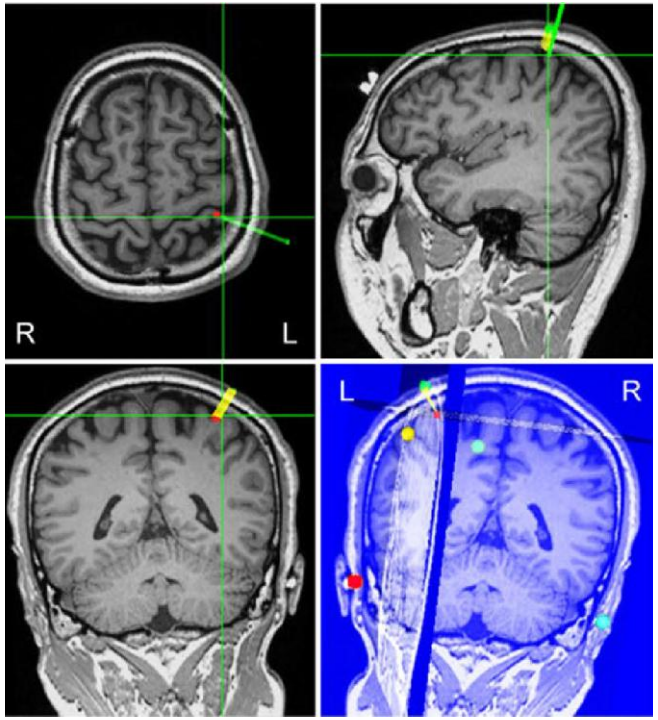


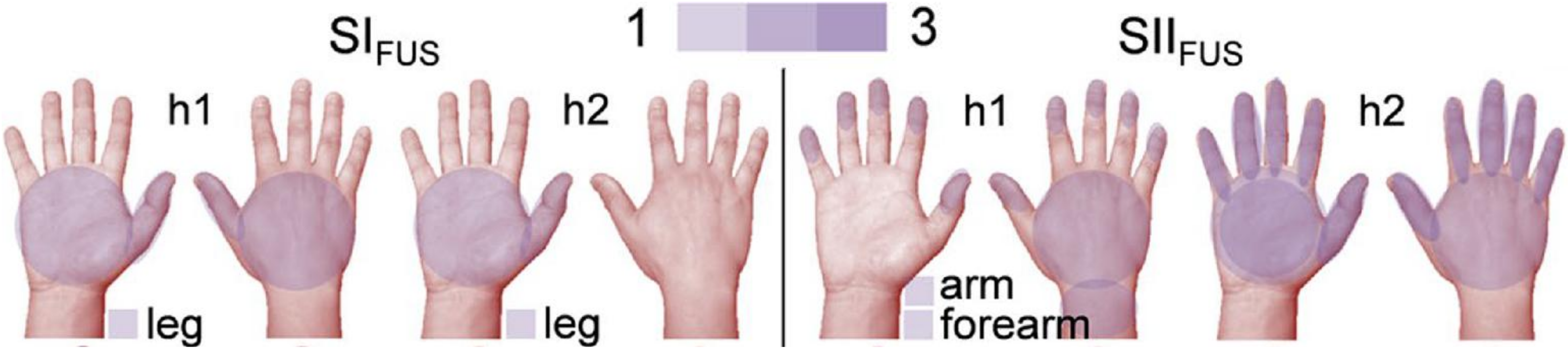




Darrow et al 2019

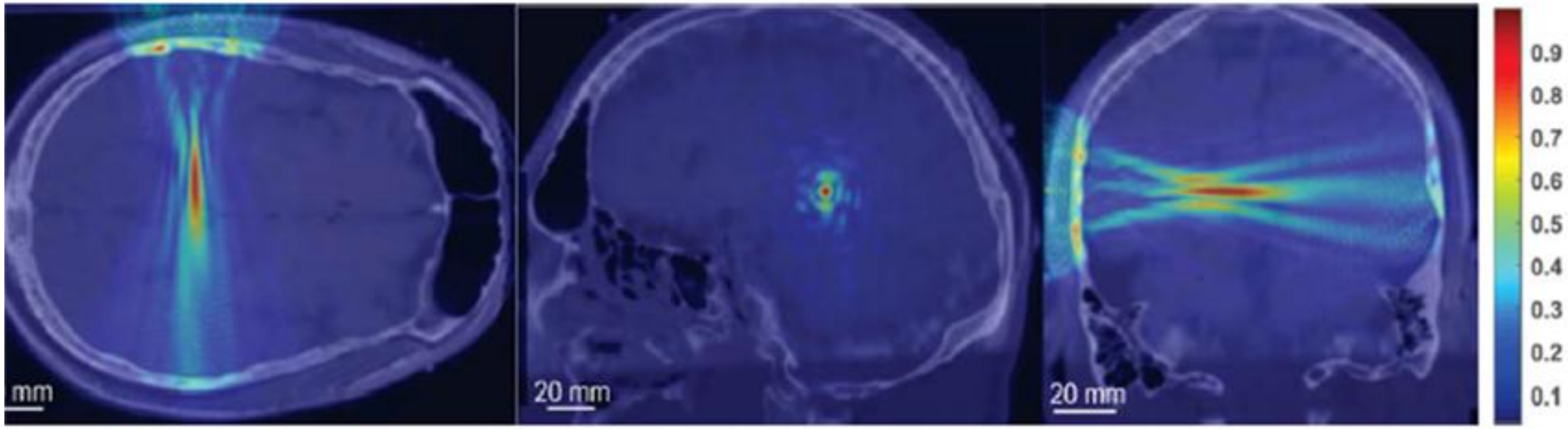


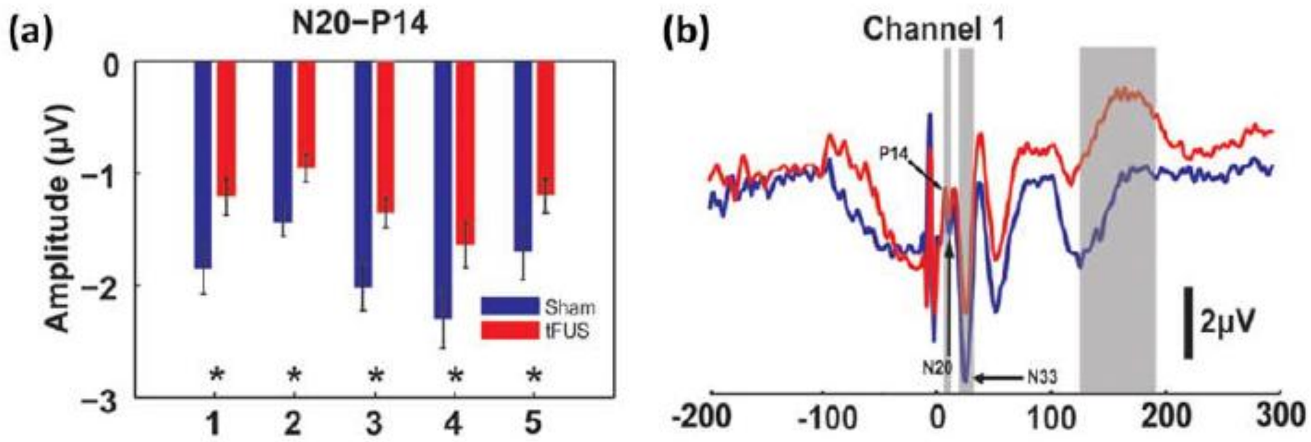




Lee, Chung Song, Yoo, 2016

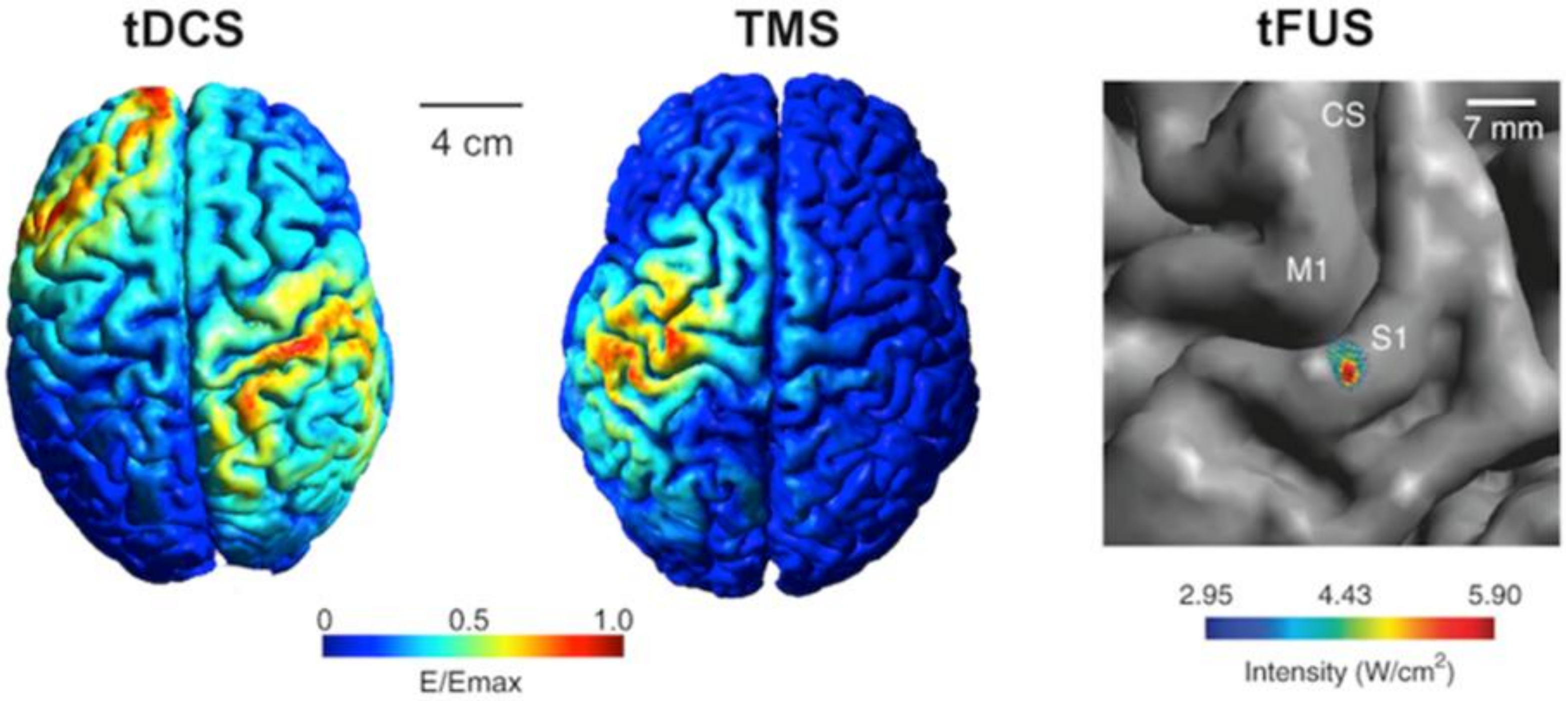
Transcranial Focused Ultrasound - tFUS





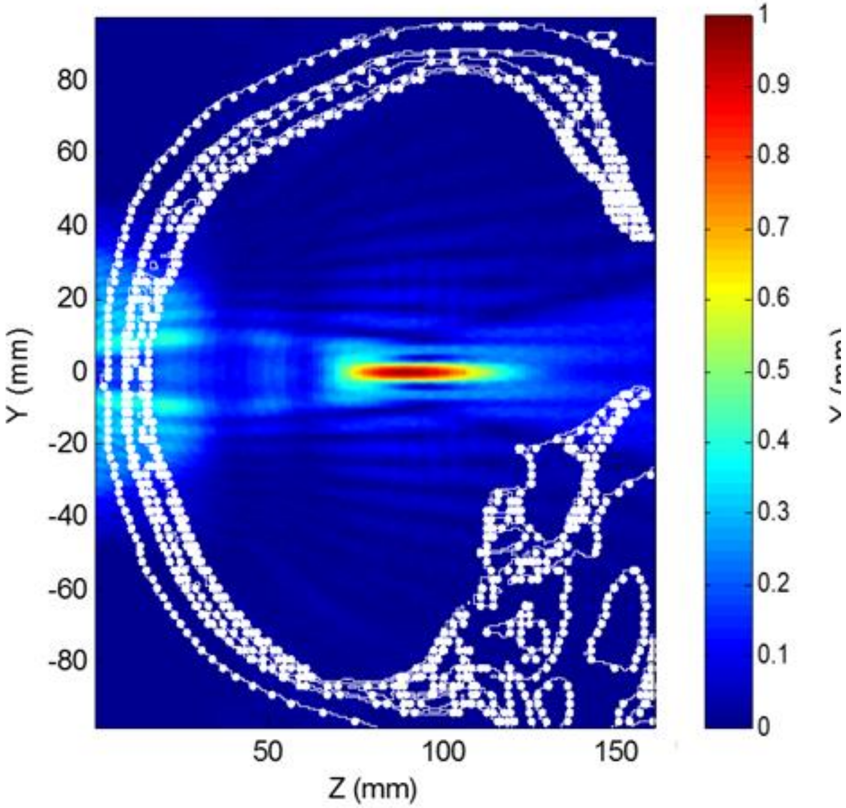
Legon et al., 2018

COMPARING METHODS



Tyler lab

HOMOGENEOUS BEAM



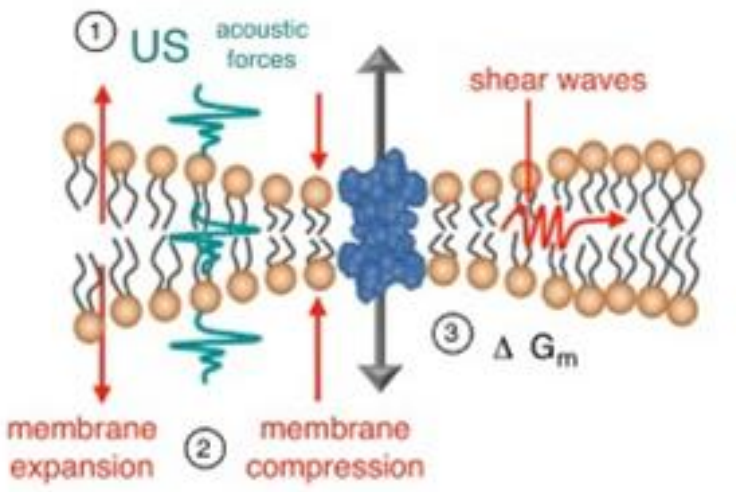
Vyas, Kaye, Pauly, 2012

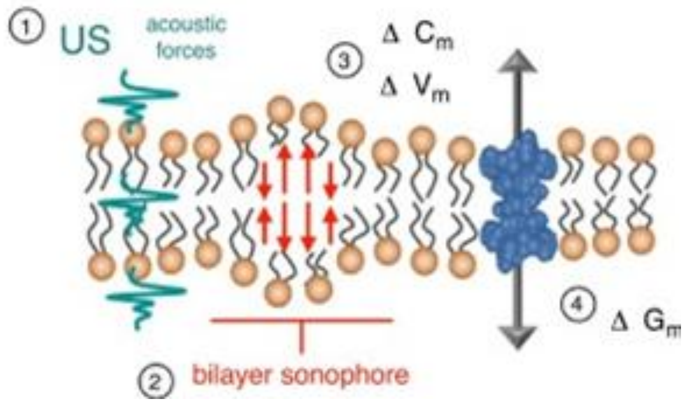
Potential mechanisms

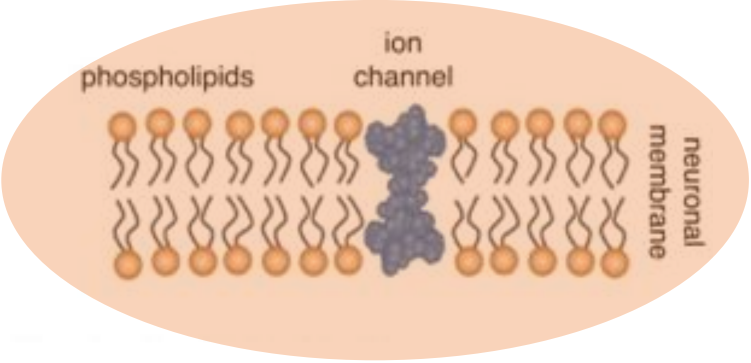
1. Radiation Force

2. Cavitation

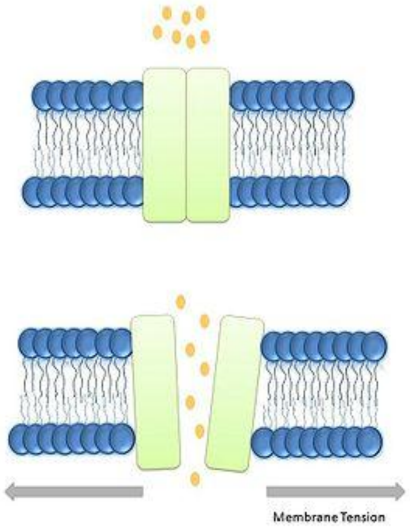
3. Heat







Biophysical mechanisms

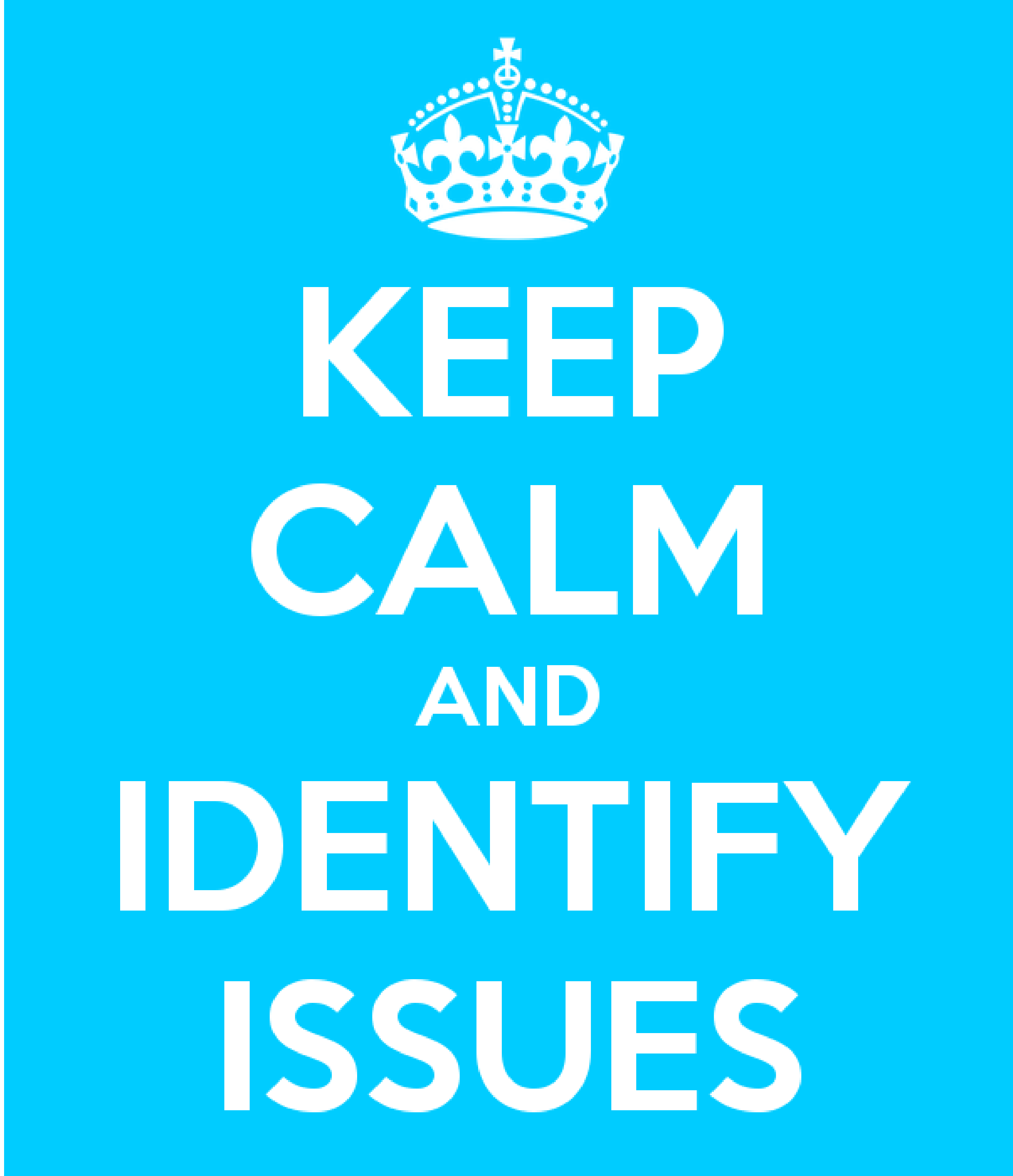


Stretch sensitive ion channels
(Mihran et al., 1990)

Tyler, Lani, Hwang, 2018

Caveats and Issues

- Ultrasound neuromodulation is new – lots to learn.
- Skull aberration is a big issue.
- Safety and reliability
- Need consensus and standards.
- Mechanisms and long-term effects are unknown.



Evaluating ultrasound neuromod (limitations)

Very new field

Parameters are not well understood

Excitation/inhibition not understood

Safety still being worked out

<u>Be skeptical about:</u>

Focality until aberration is solved

Sham control

Claims about mechanism


Thanks!
Questions?

Brain Photobiomodulation (PBM)

- Uses infrared light to stimulate brain activity and cellular processes
- Feeds energy to the cellular pathway that produces ATP, giving the cell more energy to do whatever it was already trying to do
- Can enhance cognitive functioning, healing from injury, slow neurodegeneration, reduce inflammation and oxidative stress
- Pulsing at different frequencies may induce different types of effects
- Infrared light therapy works in all areas of the body, not just the brain!