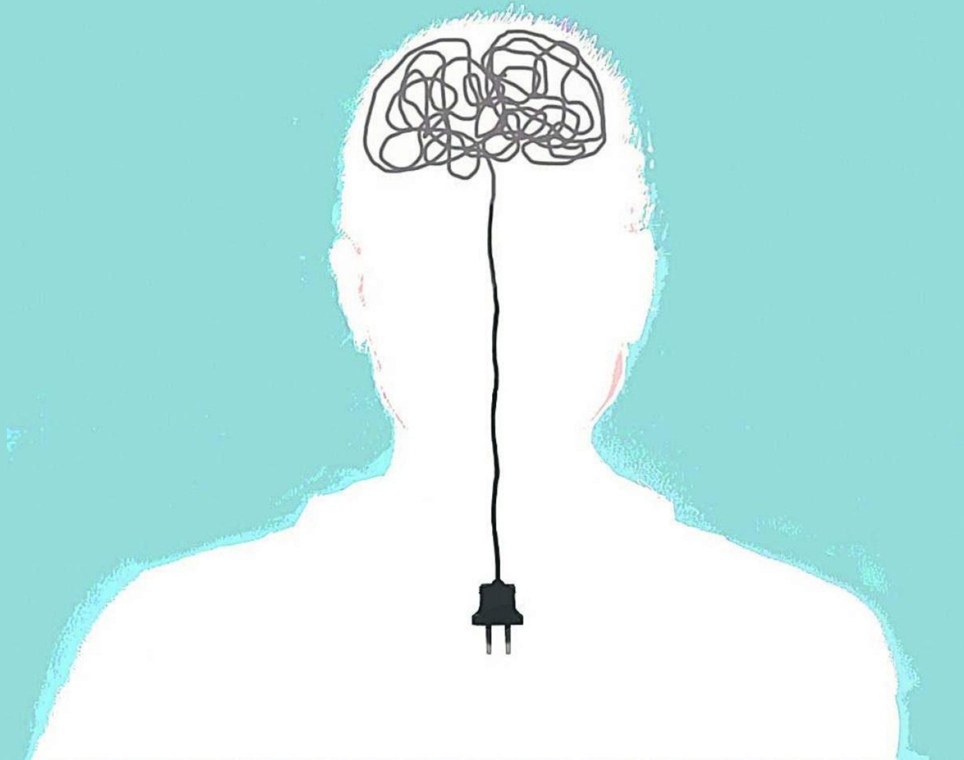
Neurostimulation and Neuromodulation

Jay Sanguinetti

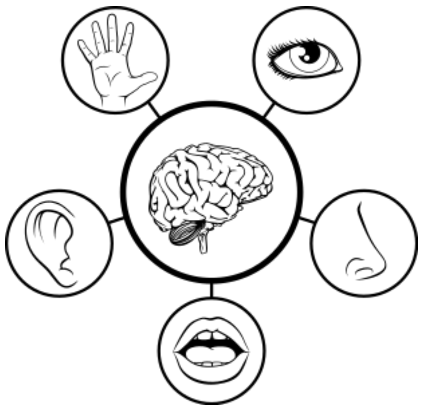


Outline

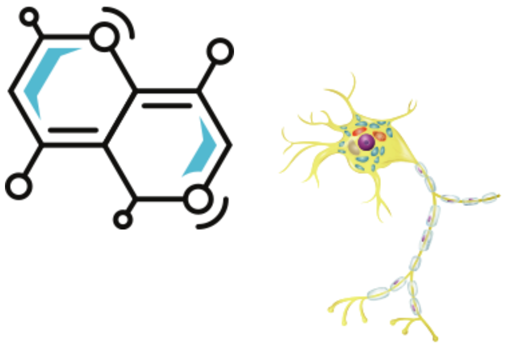
1. Why modulate the brain?
2. Historical context
    1. Invasive vs Noninvasive
    2. Causal Manipulation
3. Magnetic (TMS) – gold standard
4. Electric (tDCS/tACS) – needs work
5. Ultrasound (tFUS) – new kid on the block

Perturbing Neural Systems

SENSORY

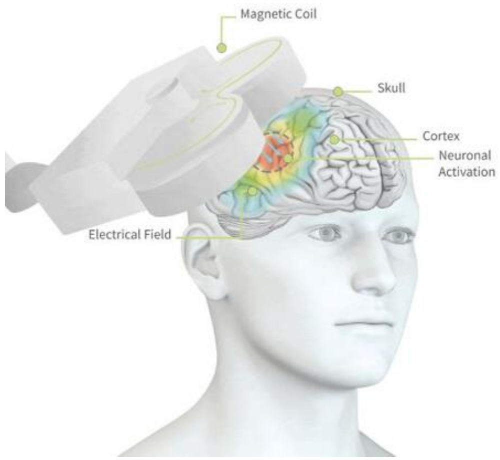


NEURAL & MOLECULAR



INVASIVE

NON-INVASIVE



UNDERSTAND

INTERVENTION

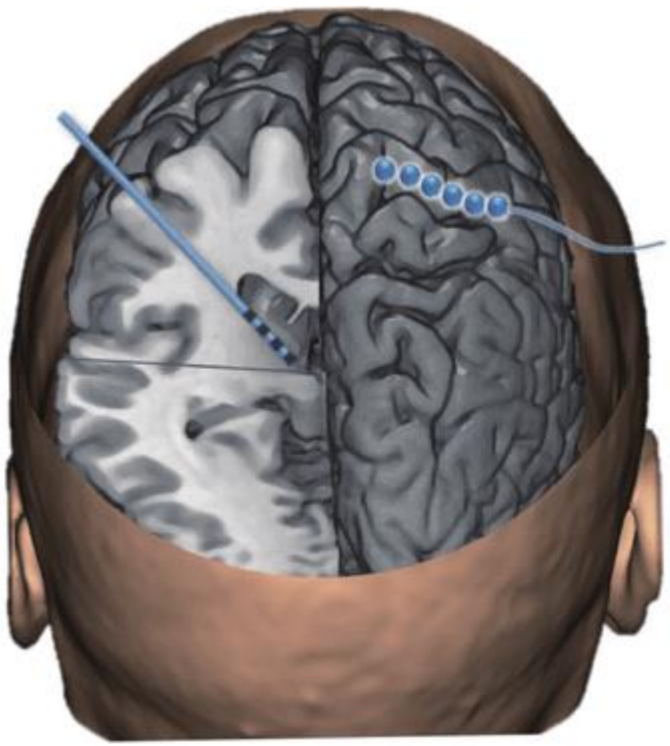
Behavioral and imaging methods (EEG, fMRI, EKG) are correlational.

Brain stimulation directly manipulates neural activity.

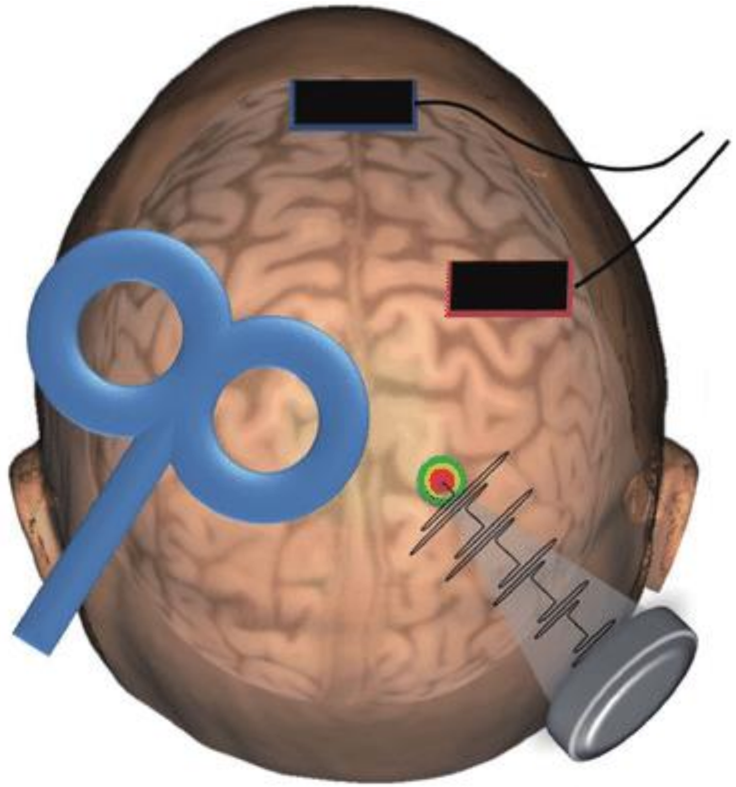
- Causal Manipulation
- Maps brain to behavior
- Reduces likelihood of hidden variables

Neurostimulation and Neuromodulation

Invasive



Noninvasive

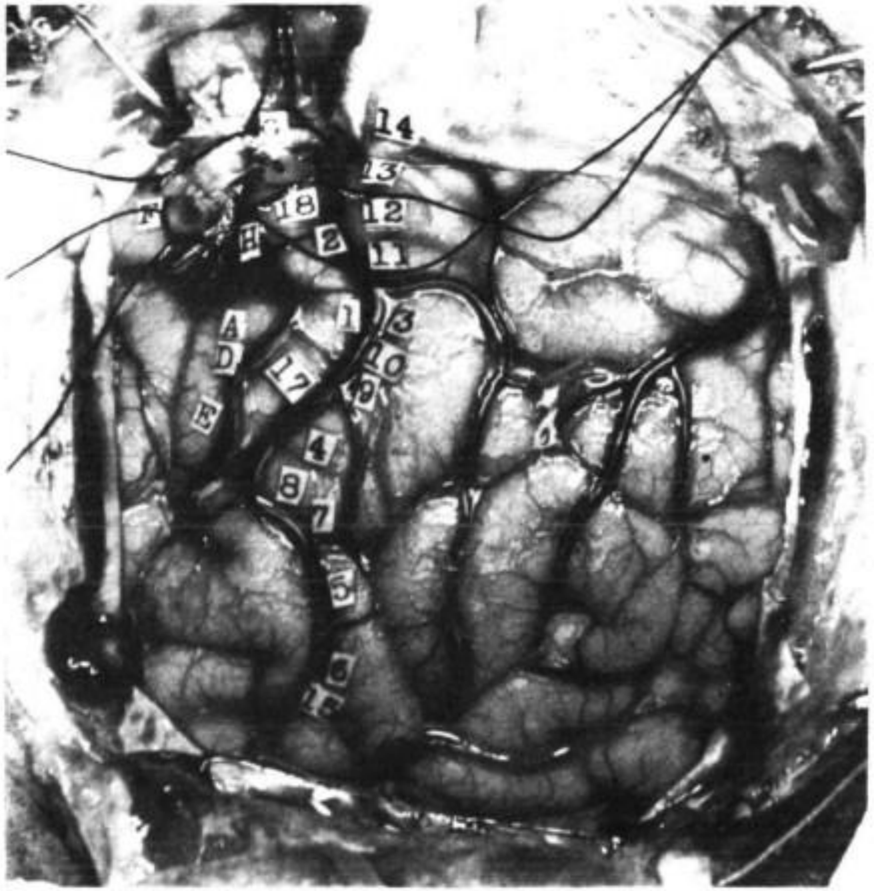


Neurosurgery

- Delivery of small electric current directly on cortical surface
- Causes temporary disruption or facilitation of function in cortex
- Used clinically to map function, to avoid critical regions

[neurosurgery]

Wilder Penfield



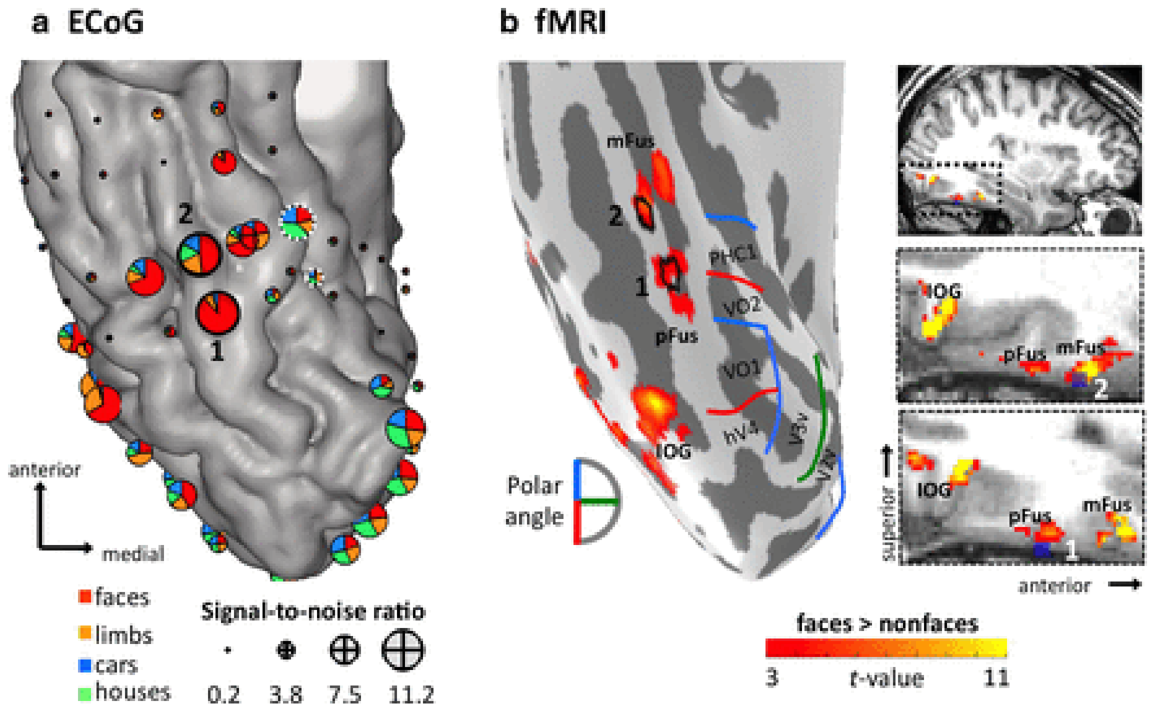
- Allows for causal testing

- But very limited in scope and application

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

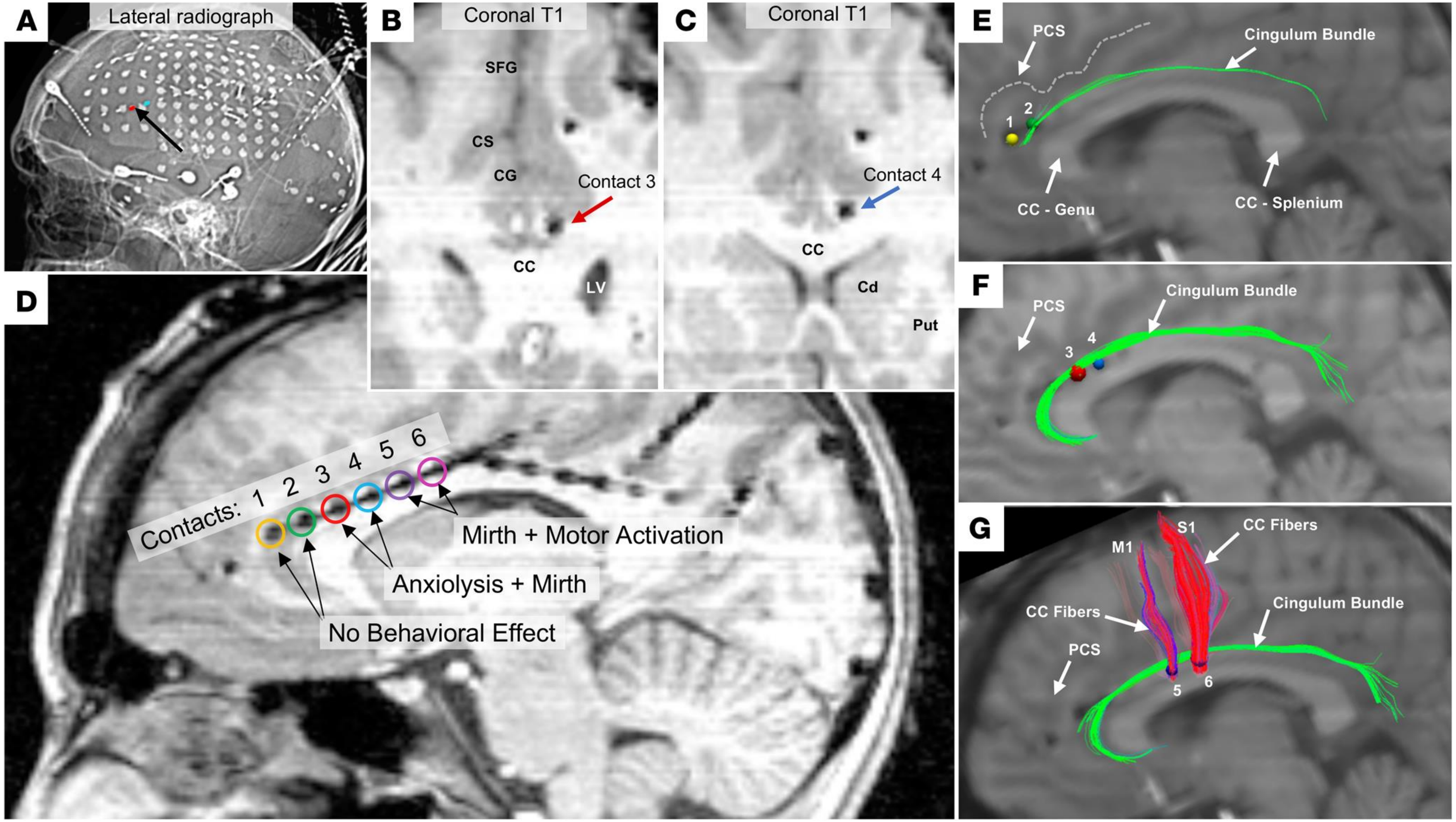
Fusiform face area

- mapping face processing with stimulation

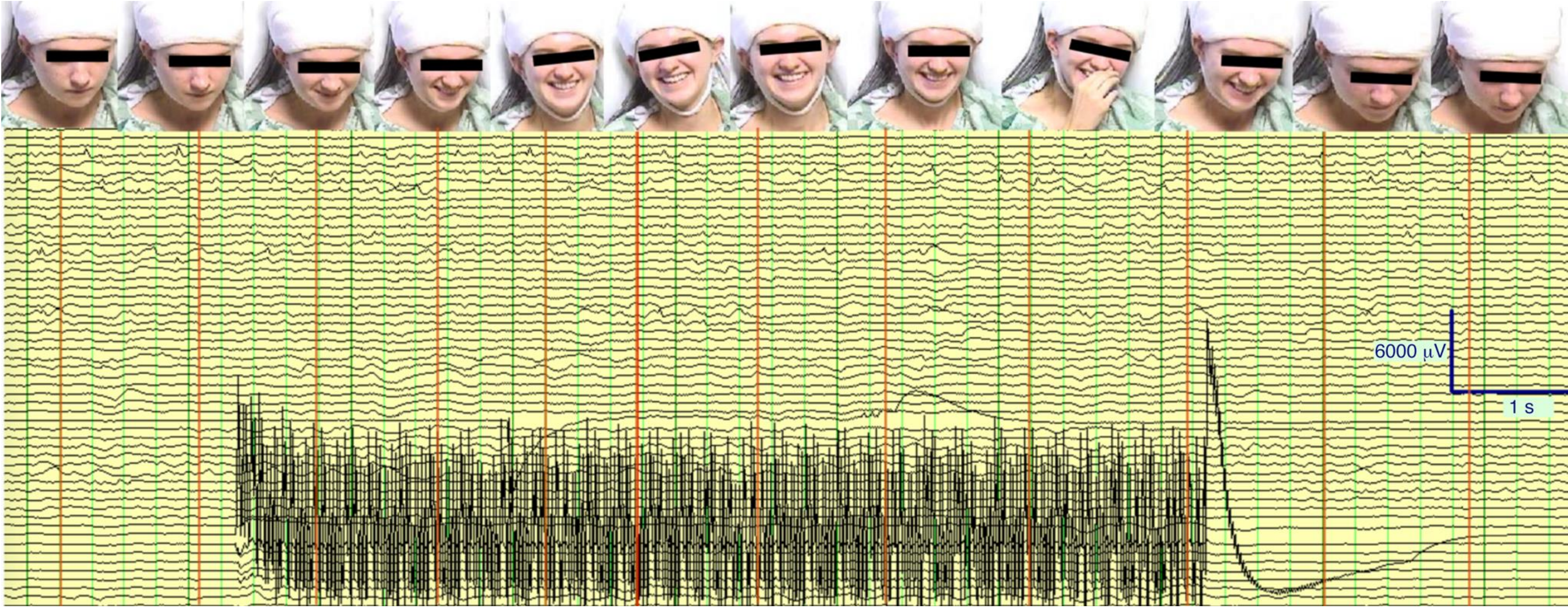


https://www.jneurosci.org/content/32/43/14915#media-1

[intracranial stimulation]

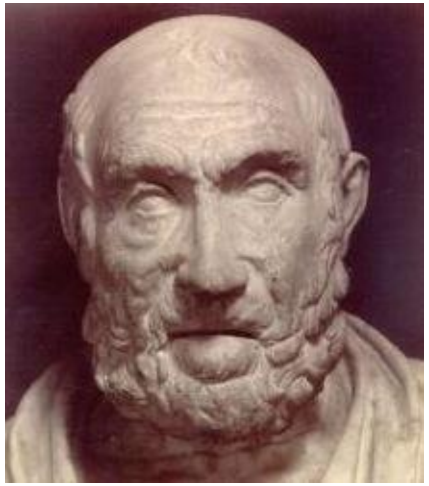


Bijanki, et al. 2019

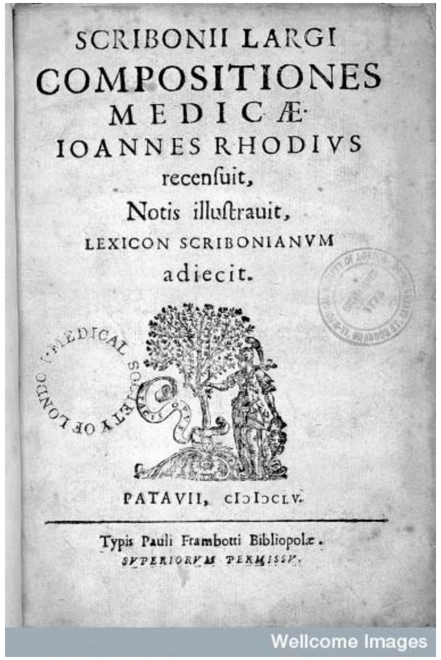

6000 µV
1 s

Transcranial: passing or performed through the skull

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



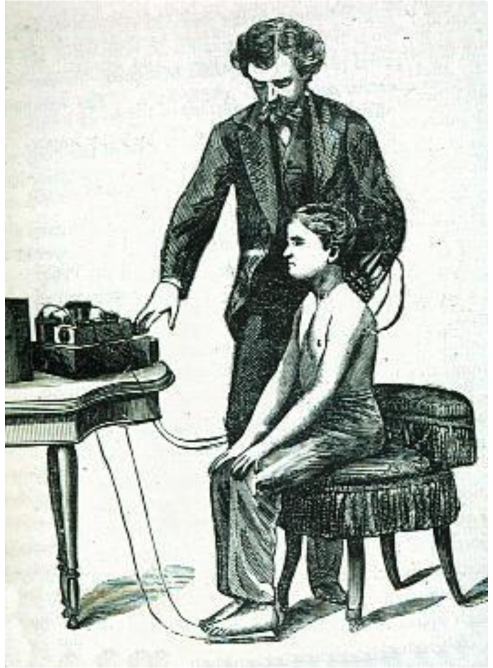
Scribonius Largus 57 AD

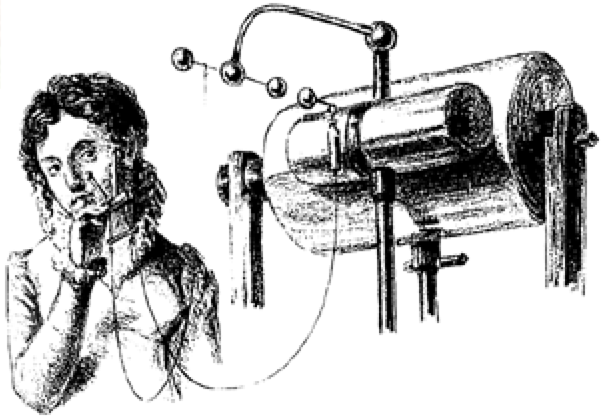


SCRIBONII LARGI
COMPOSITIONES
MEDICÆ
IOANNES RHODIVS
recenſuit,
Notis illuſtrauit,
LEXICON SCRIBONIANVM
adiecit.
MEDICAL SOCIETY OF LONDON
PATAVII, CIↃIↃCLV.
Typis Pauli Frambotti Bibliopolæ.
SVPERIORVM PERMISSV.

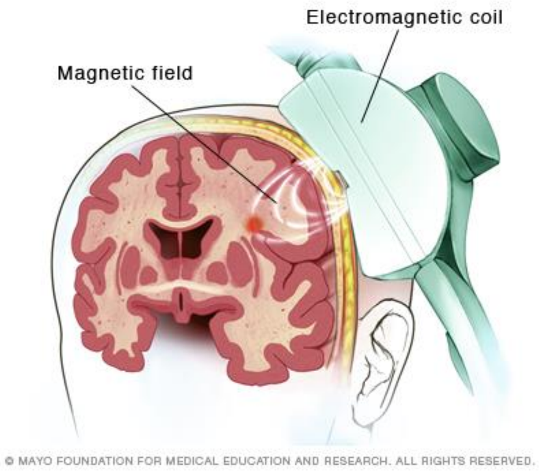
Novel idea: modulate mental states from outside the head with physical force, *but with some precision*

Electrical stimulation for everyone!



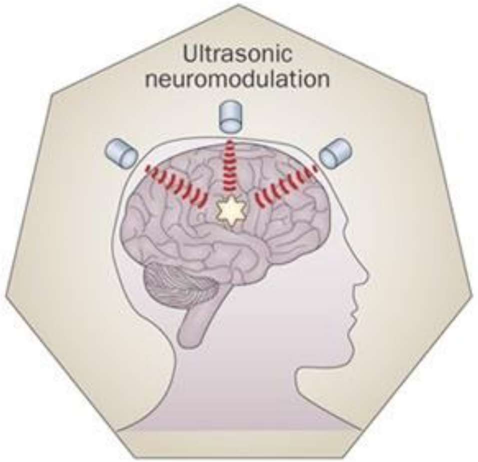


Magnetic



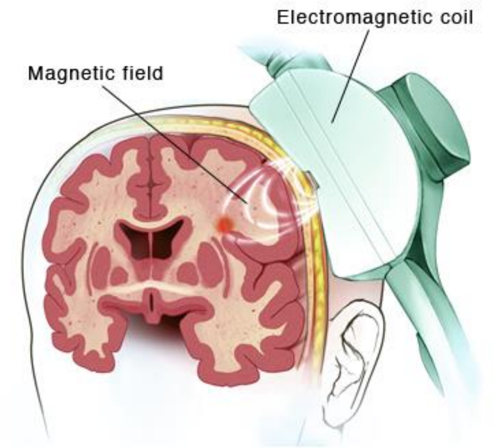
Electric

Sound



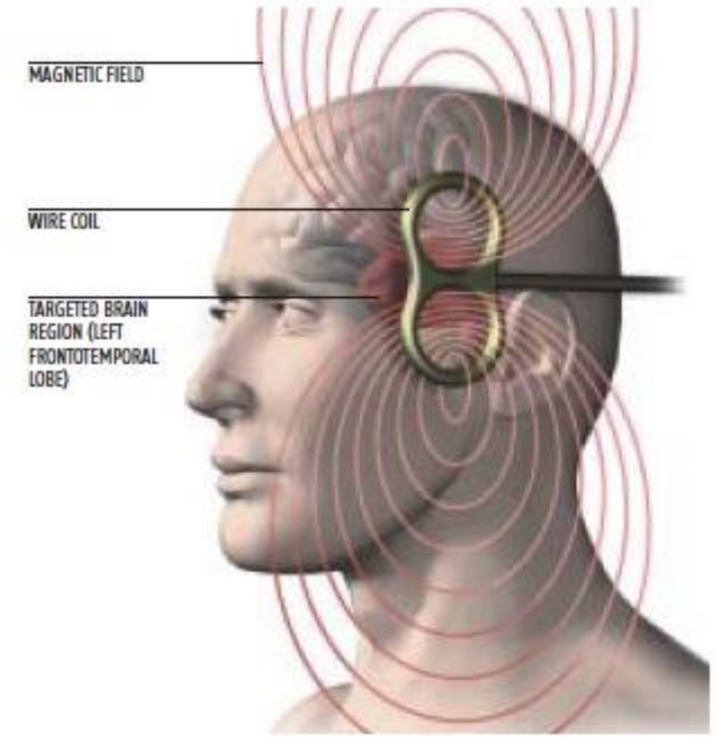
Light

Magnetic

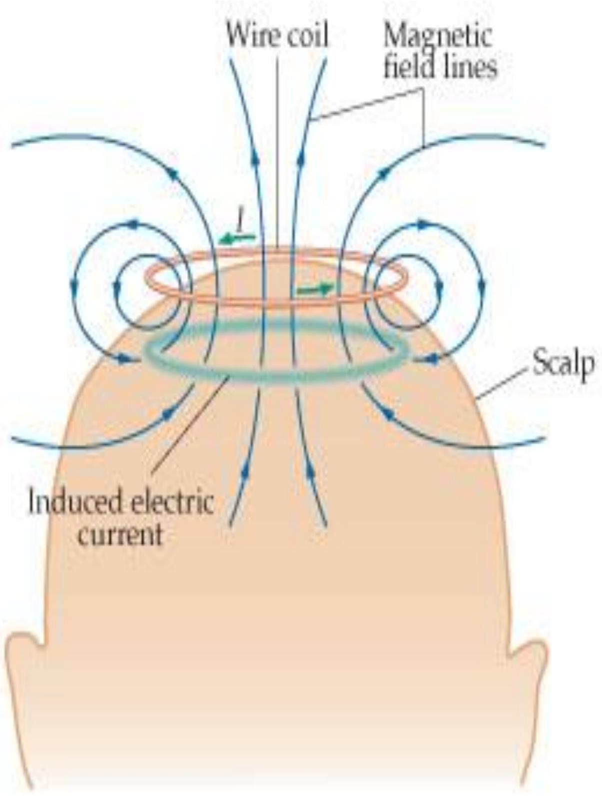


Transcranial Magnetic Stimulation (TMS)

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

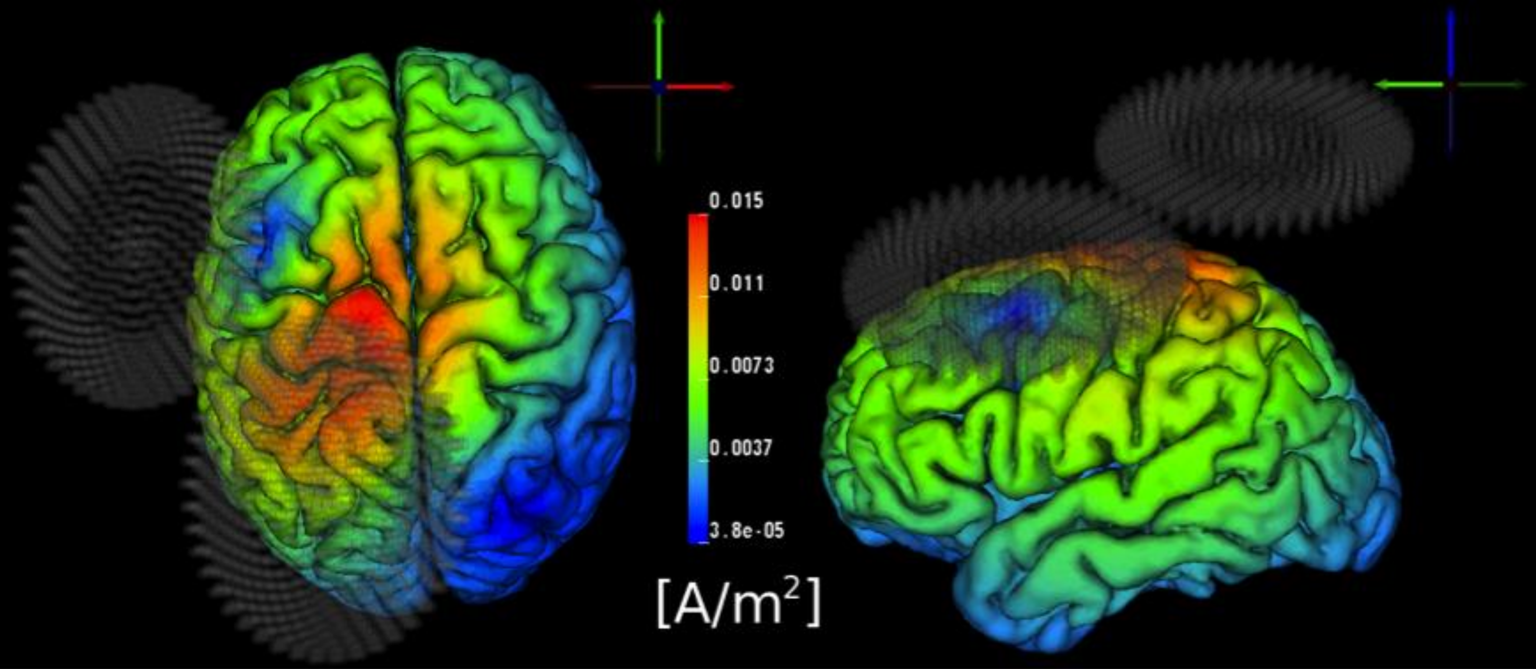


Transcranial Magnetic Stimulation (TMS)



Noninvasive neurostimulation via electro-magnetic induction

- Pulse of electric current sent through wire coil held tangential to scalp
- Generates a magnetic field
- Induces a secondary current in the brain (green) Currents induced in the brain primarily flow parallel to the plane of the coil
- Primarily activates neural elements oriented horizontally to the surface

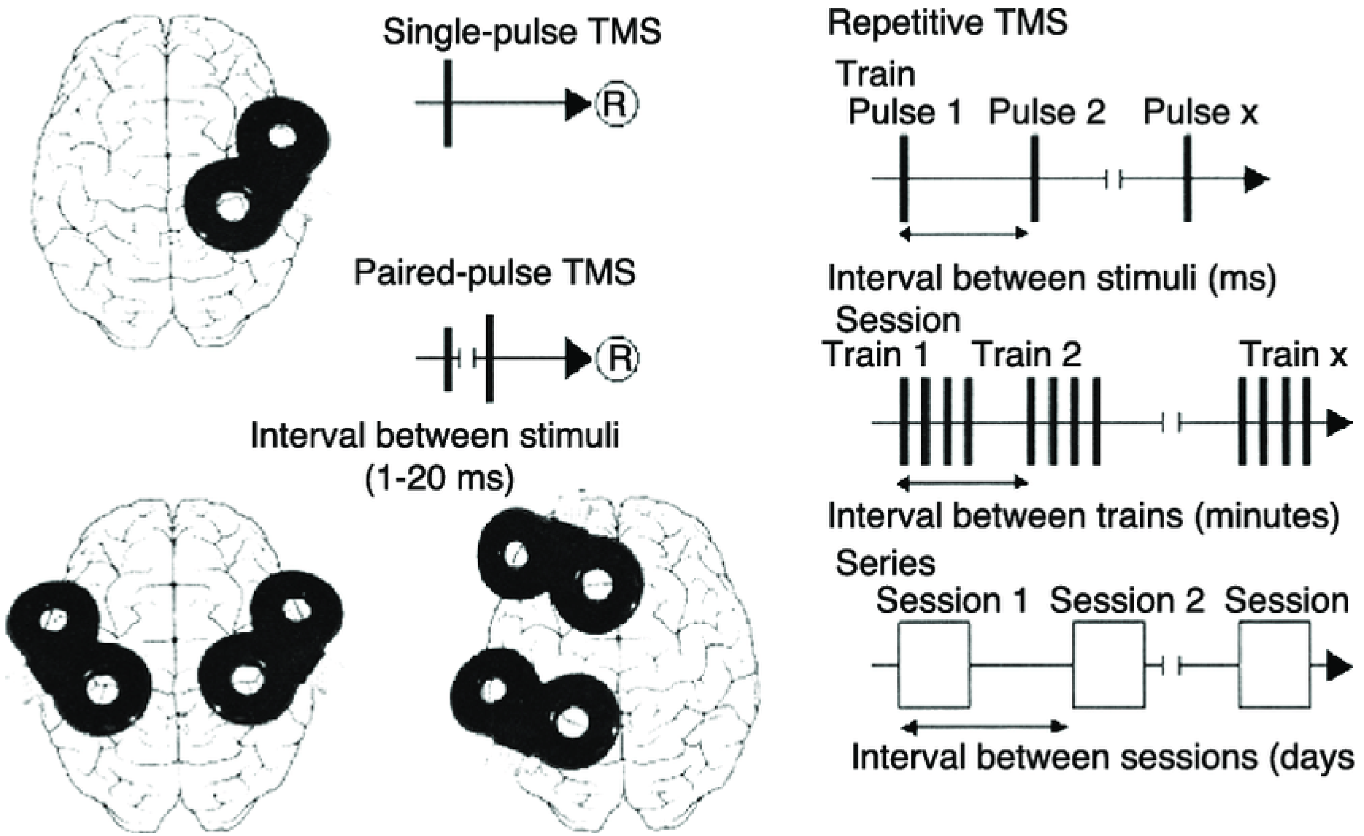


- Cell must be parallel to scalp to receive stimulation
- Geometry and orientation of the cell matters

- “Virtual lesions” – really just causing neurons to fire.
  Refractory period is “virtual lesion.”
  - Temporary / reversible

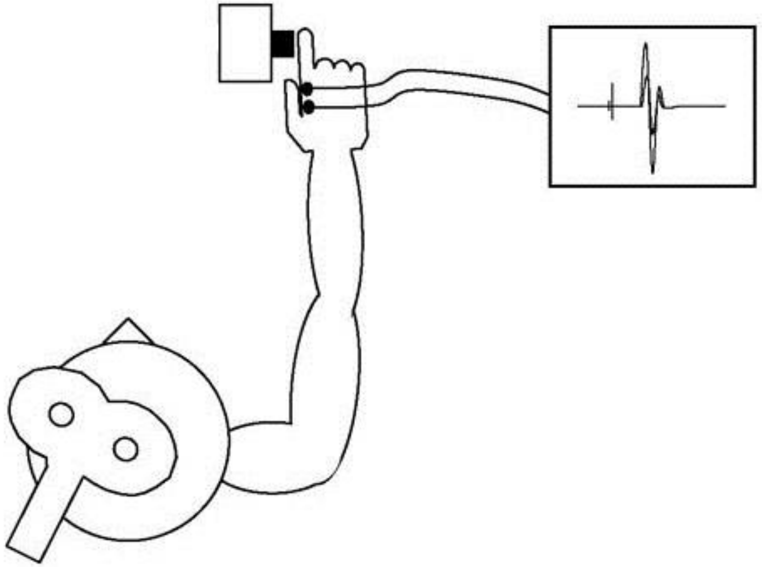
- Repeatable (within subjects designs possible)

- Effects last for milliseconds to minutes depending on the pulse parameters.



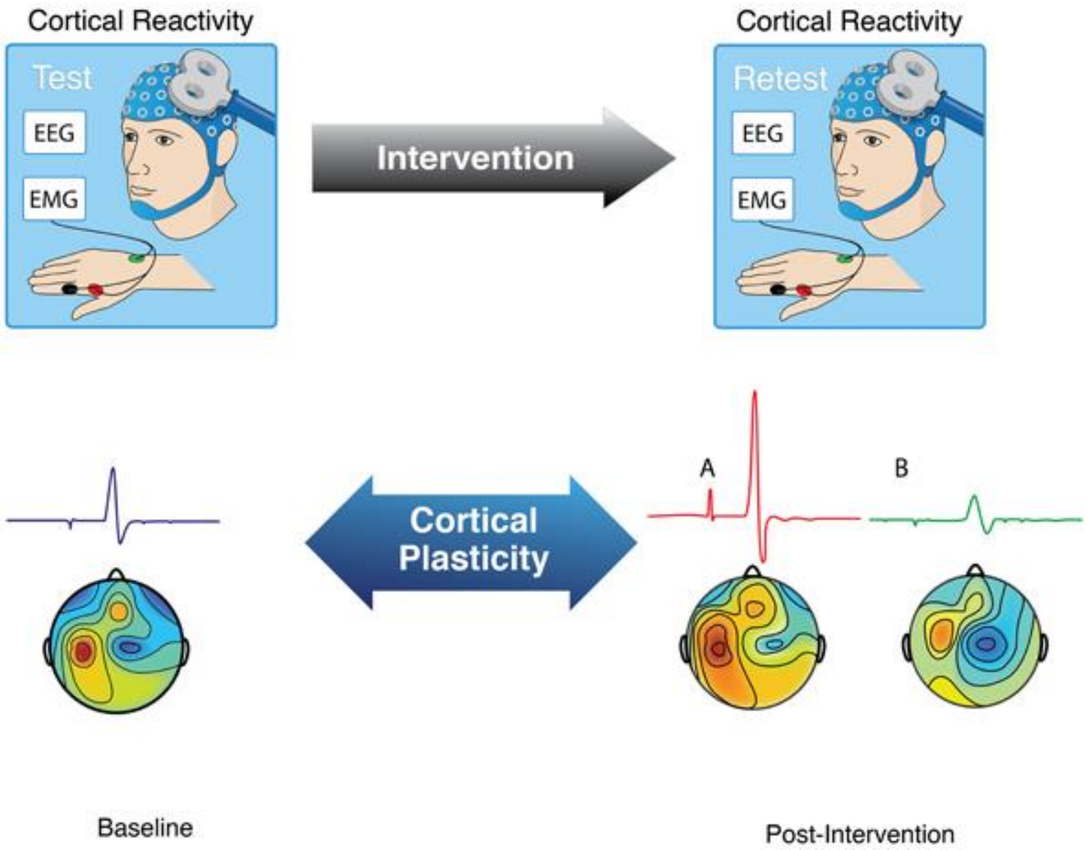
TMS Neurostimulation

Single or paired pulse TMS
(superthreshold)



TMS Neuromodulation

Usually “repetitive TMS” (rTMS)
subthreshold – longer lasting effects



Freitas et al 2013

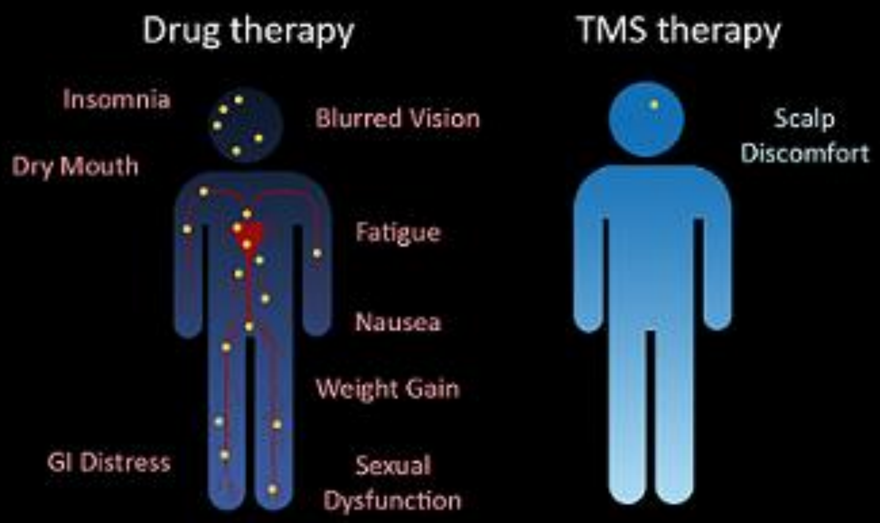
Repetitive transcranial magnetic stimulation (rTMS) developed early 1990s.

rTMS can increase or decrease excitability – depends on the pulse sequences.

- low freq (< 1 Hz) inhibits; higher freq (> 5 Hz) excites
- Theta burst stimulation

rTMS applied over many sessions can last for 3 months in patient populations (e.g., Parkinson's disease).

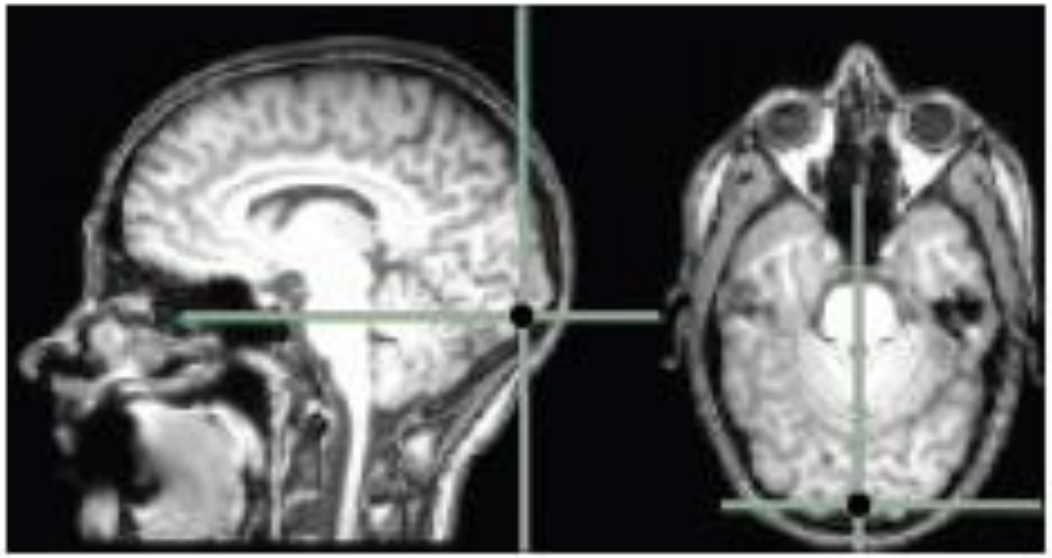
FDA Approved for Depression and Bipolar Disorder



- ~10 Open Label Trials, > 20 Control Trials
- Moderate to large effect sizes, 0.5 to 1.3
    - Clinical results not as impressive (23% improvement on HAMD)
    - Compare: ECT, 2.26; Antidepressants, 0.3-.5

A variety of ways to localize stimulation:

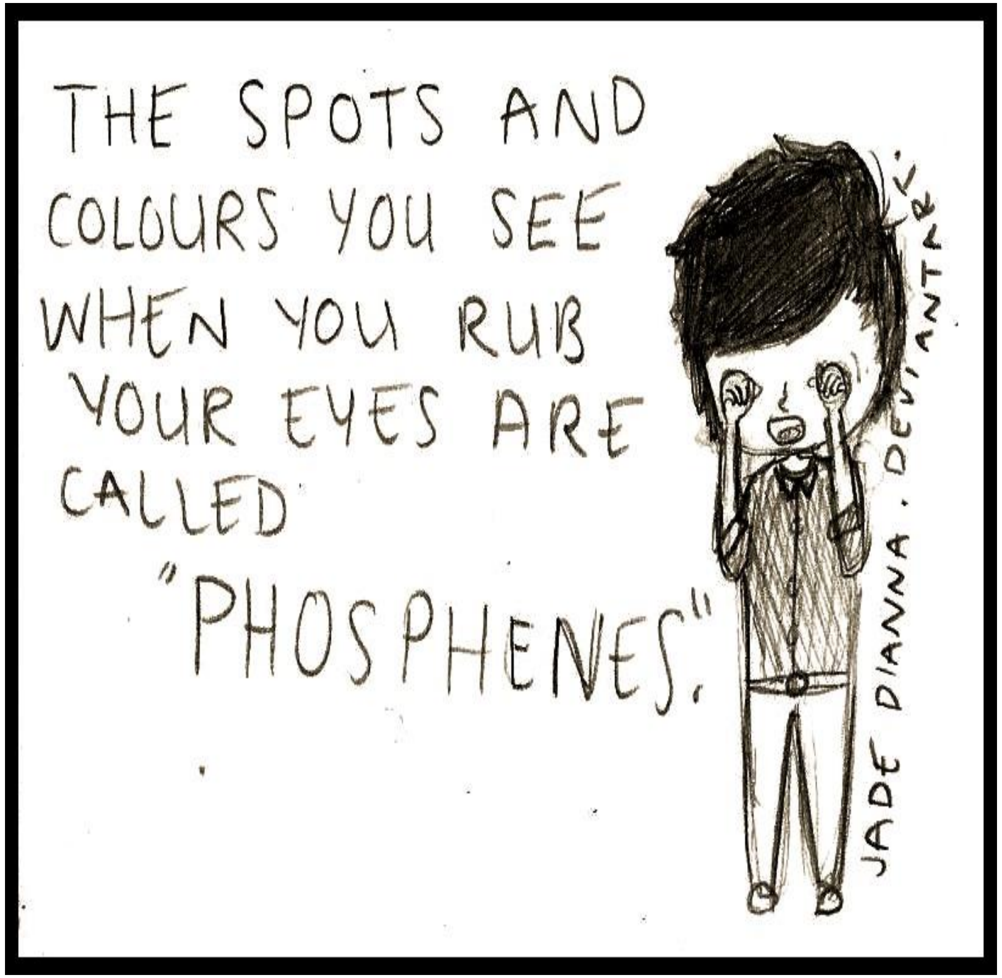
1. anatomy-based methods that target a single location across participants using landmarks
   (e.g., V1/V2 (primary visual cortex) is ~ 1.5 cm above the inion)



How to localize stimulation?

TMS can induce phosphenes

2. Phosphenes can be used to locate where to place stimuli in the visual field so they activate the stimulated brain area.



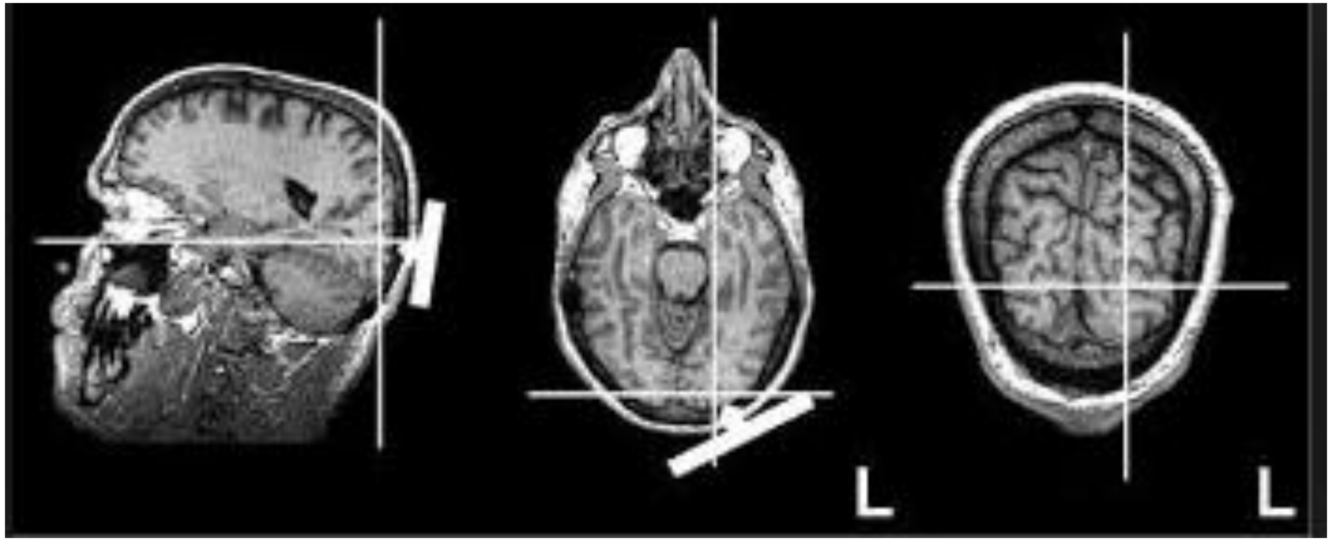
How to localize stimulation?

3. Customizing: Use T-1 weighted MRI to register TMS stimulation sites

Tracker on subject's head allows calibration of head with MRI image

Use pointer to touch reference points and save coordinates to computer.

Frameless stereotaxy – "neuronavigation"
provides a 3-D coordinate system
to locate brain regions during experiment



← Can view where in the brain stimulation is focused on-line (while conducting the experiment). Here, an occipital spot close to the midline in the L hemisphere (not linked to above photo)

Advantage of TMS over fMRI and EEG:

More than a simple correlation

Can disrupt activity in a certain site and then test behavior

Can reach conclusions about **causal brain-behavior relationships**

Can conduct a within-subjects experiment

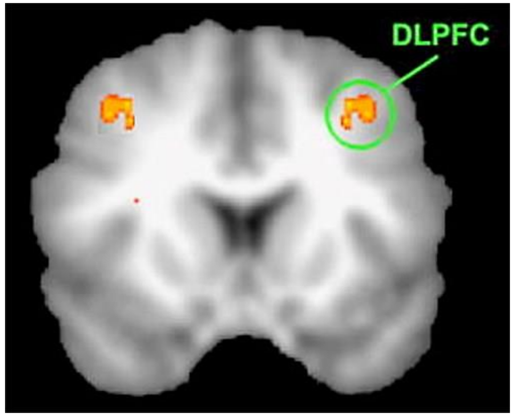
apply TMS on some trials and not on other trials

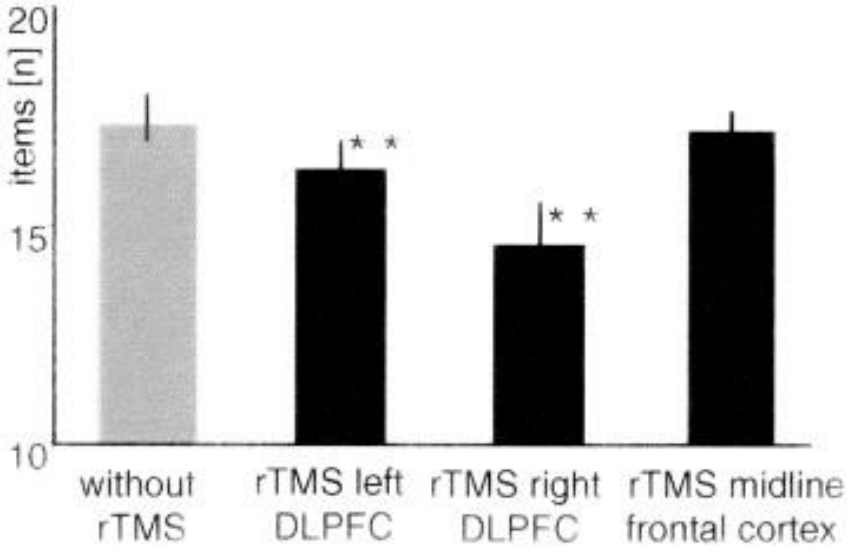
Can reveal the time course of normal processing:

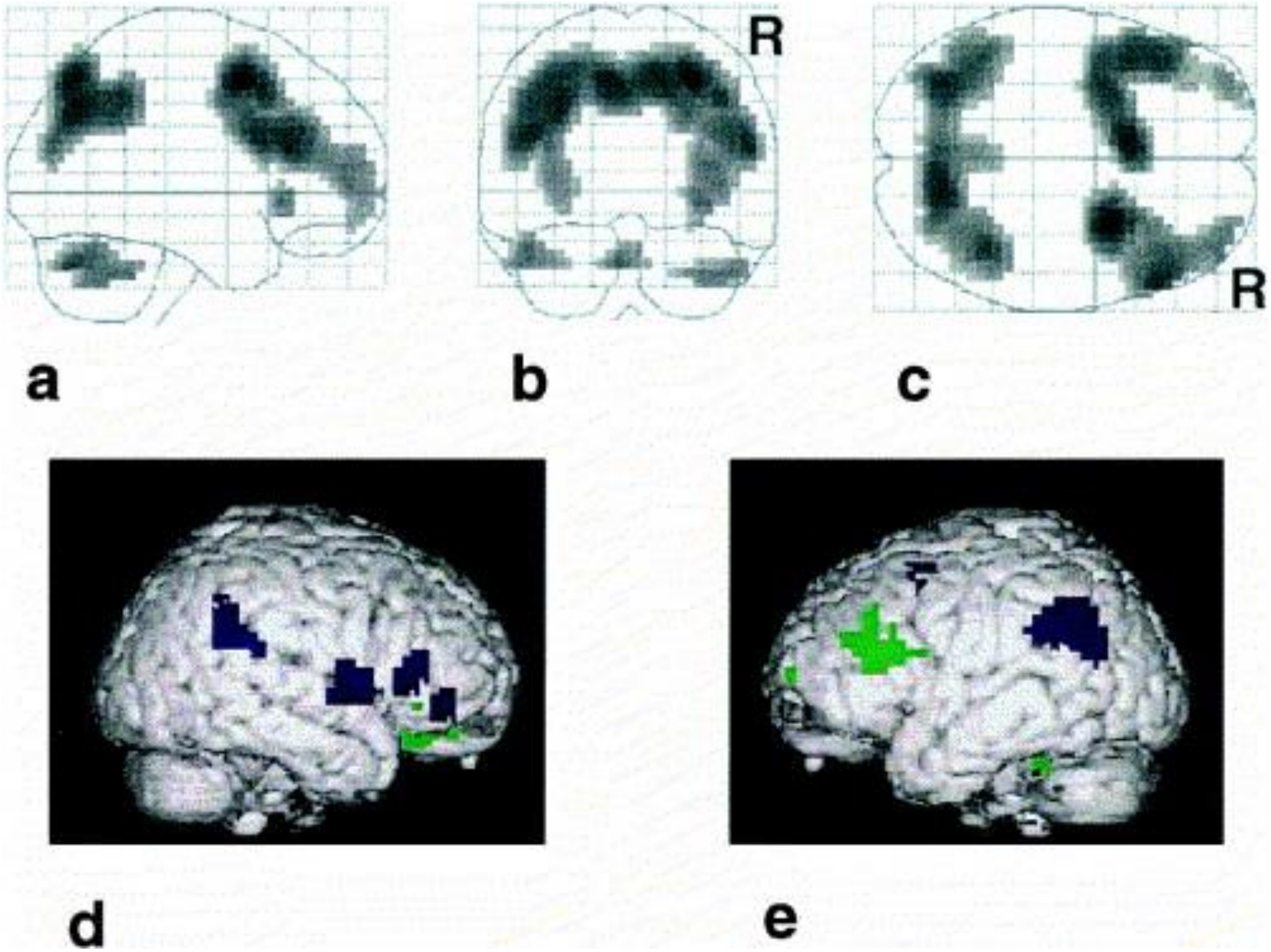
vary time between stimulus & pulse

"**Chronometric studies**"

Dorsolateral Prefrontal Cortex
Working Memory





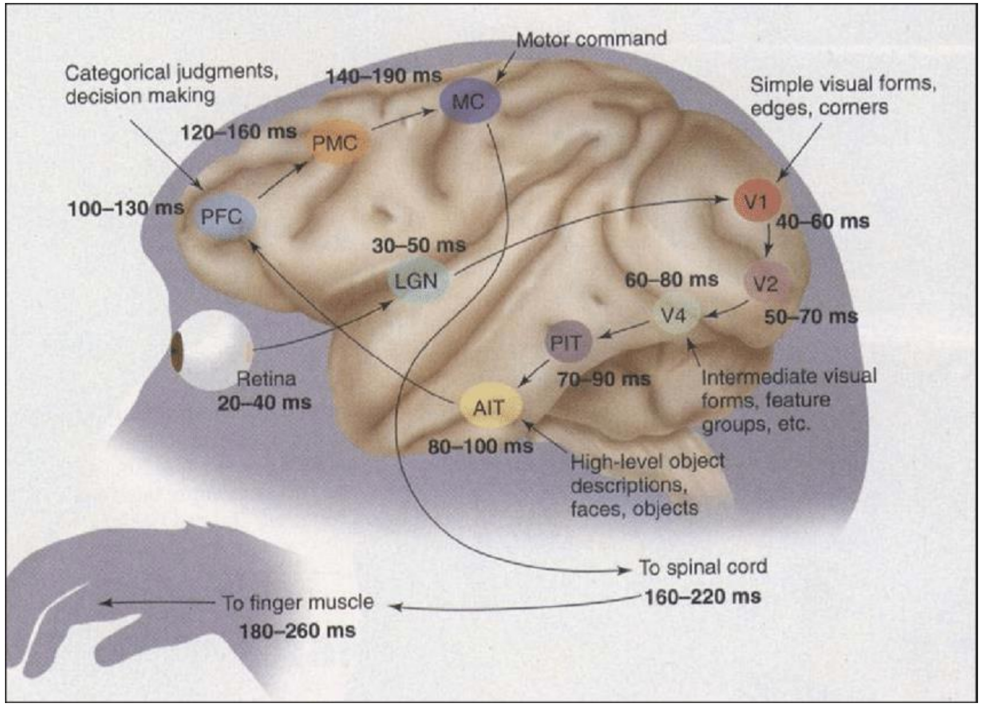


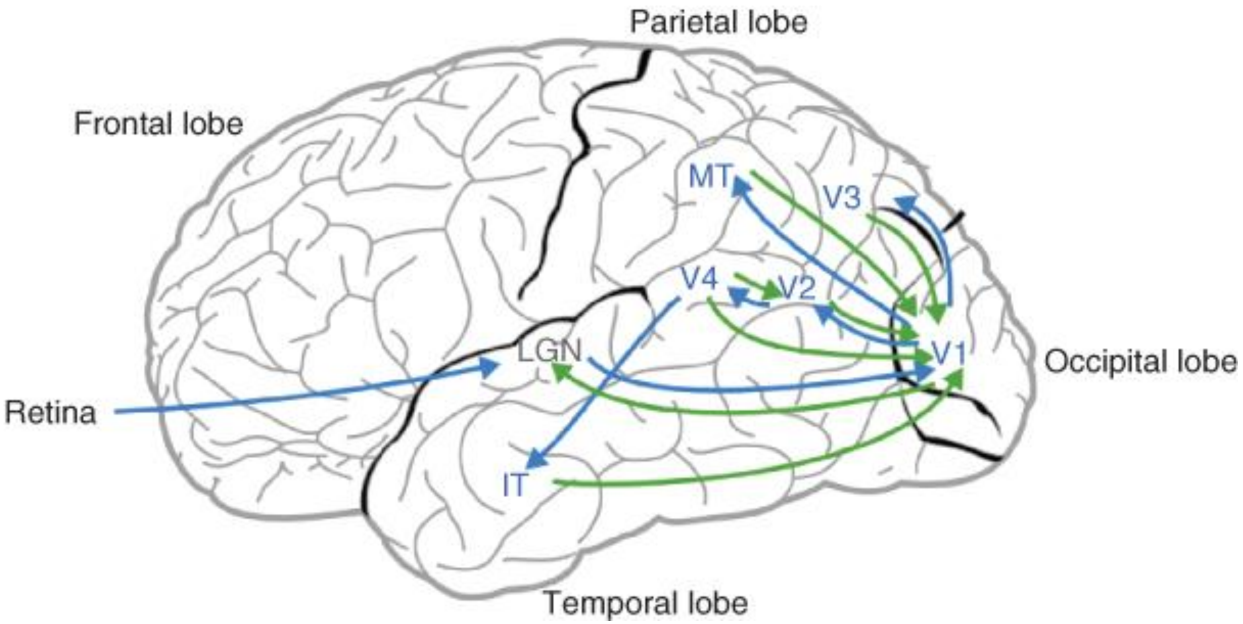
Mottaghn et al., 2000

Feedforward and Feedback Professing in the Visual System

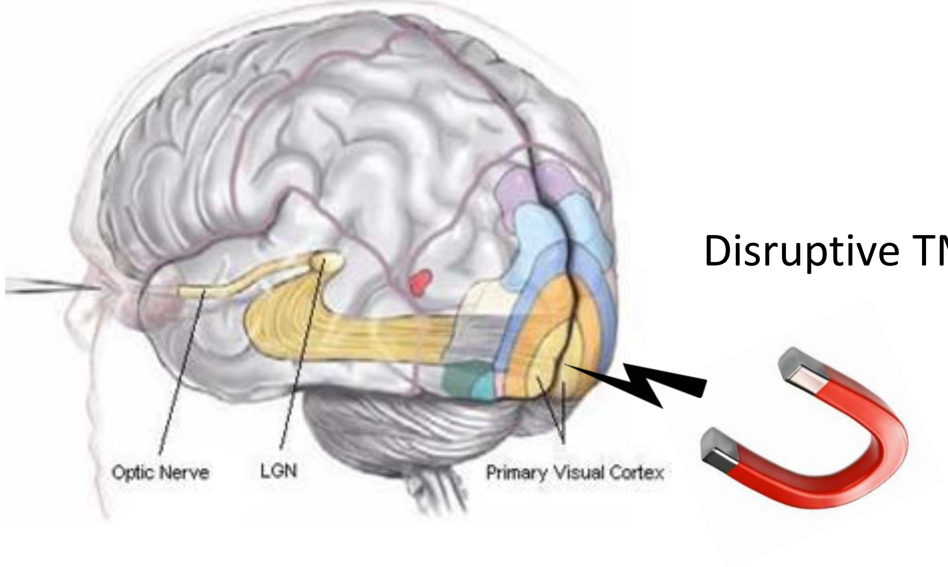
What is the timing of neural processing?

[Mental chronometry]()





Disruptive TMS



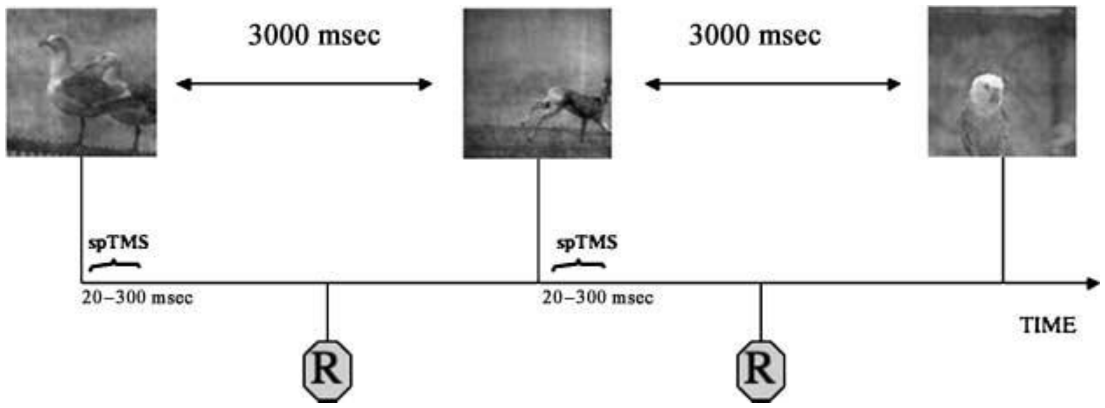
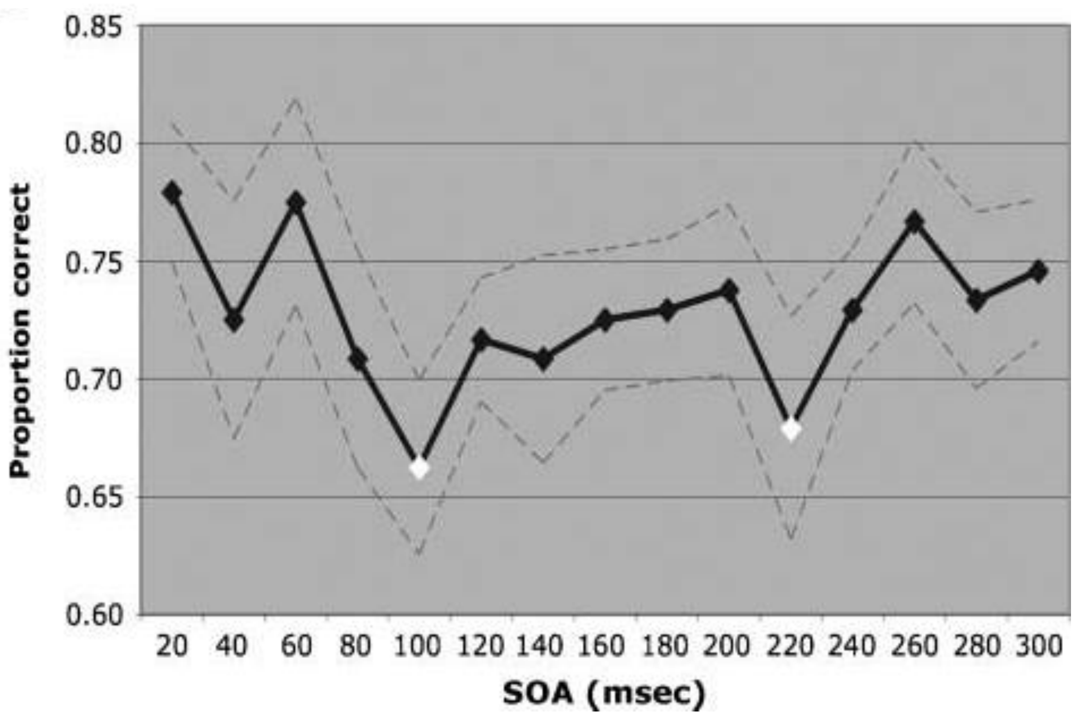


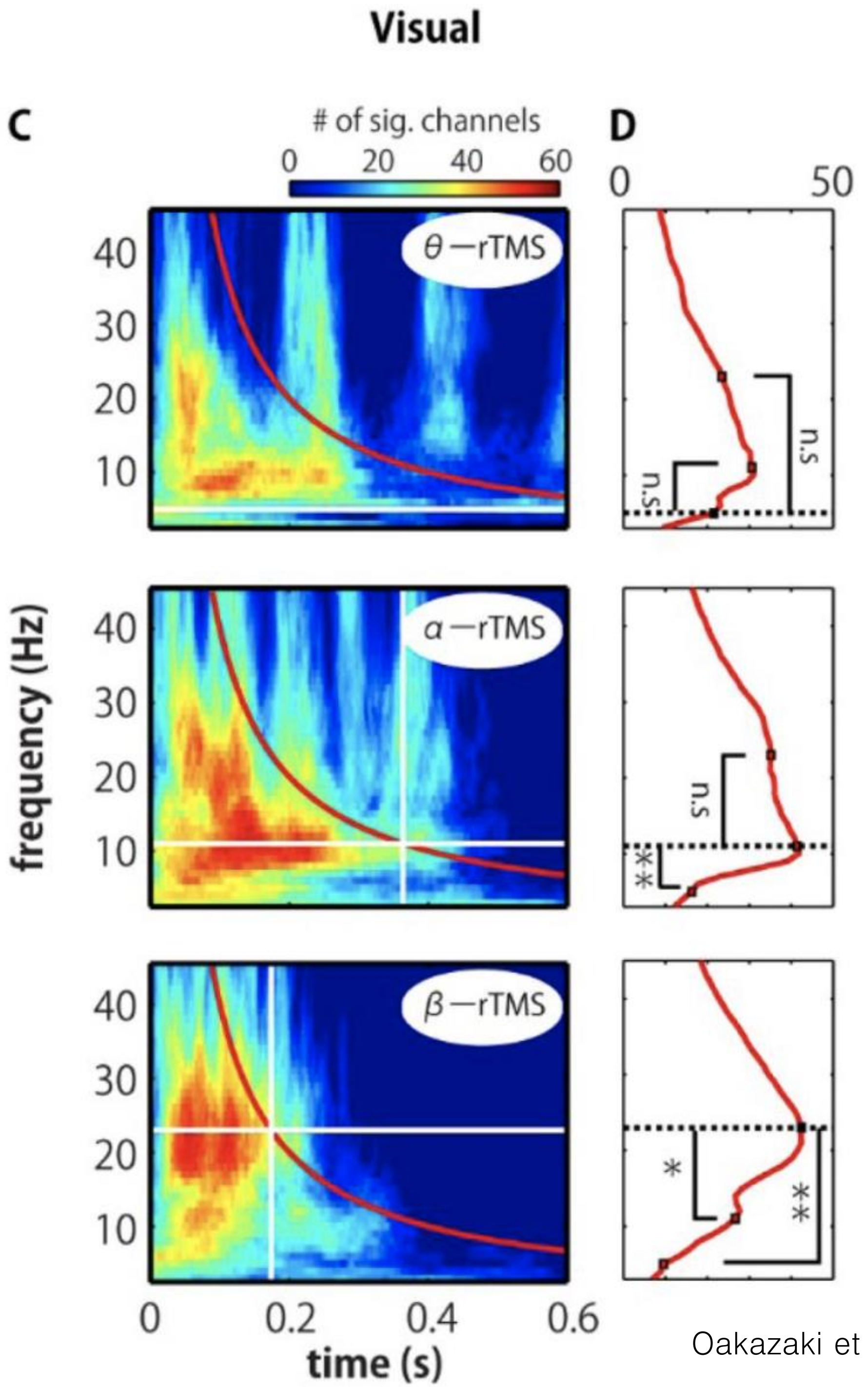
Figure 1. Experimental design. Images were flashed for one refreshment rate (14 msec) and subjects were asked to categorize the images with a button click. Following image presentation, a single pulse of TMS was applied at any one of 15 possible SOAs (from 20 to 300 msec). The next image appeared 3000 msec after the TMS pulse.



results of Experiment 2 in detail. The *SEM* is highlighted in dotted lines, and the significant SOAs are marked in orange. TMS was capable of significantly impairing recognition at two different time points: 100 and 220 msec.

Camprodon et al 2010

- rTMS can drive neural oscillations (Thut et al, 2011).
- Causal relationship between brain rhythms and behavior.
- For example, can you drive alpha oscillations to modulate perception?



Oakazaki et al 2020

Safety with TMS

- Very rare cases of inducing seizures
- Painful on some areas (placebo effects)
- Mild headaches
- Mechanism still not fully known – long term effects?

Evaluating TMS (limitations)

Only penetrates 1-4 cm (0.5 cm focality at best).

Only neurons horizontal to the coil are modulated.

Mechanisms are unknown

Be skeptical about:

Conclusions about location (its possible adjacent areas are affected)

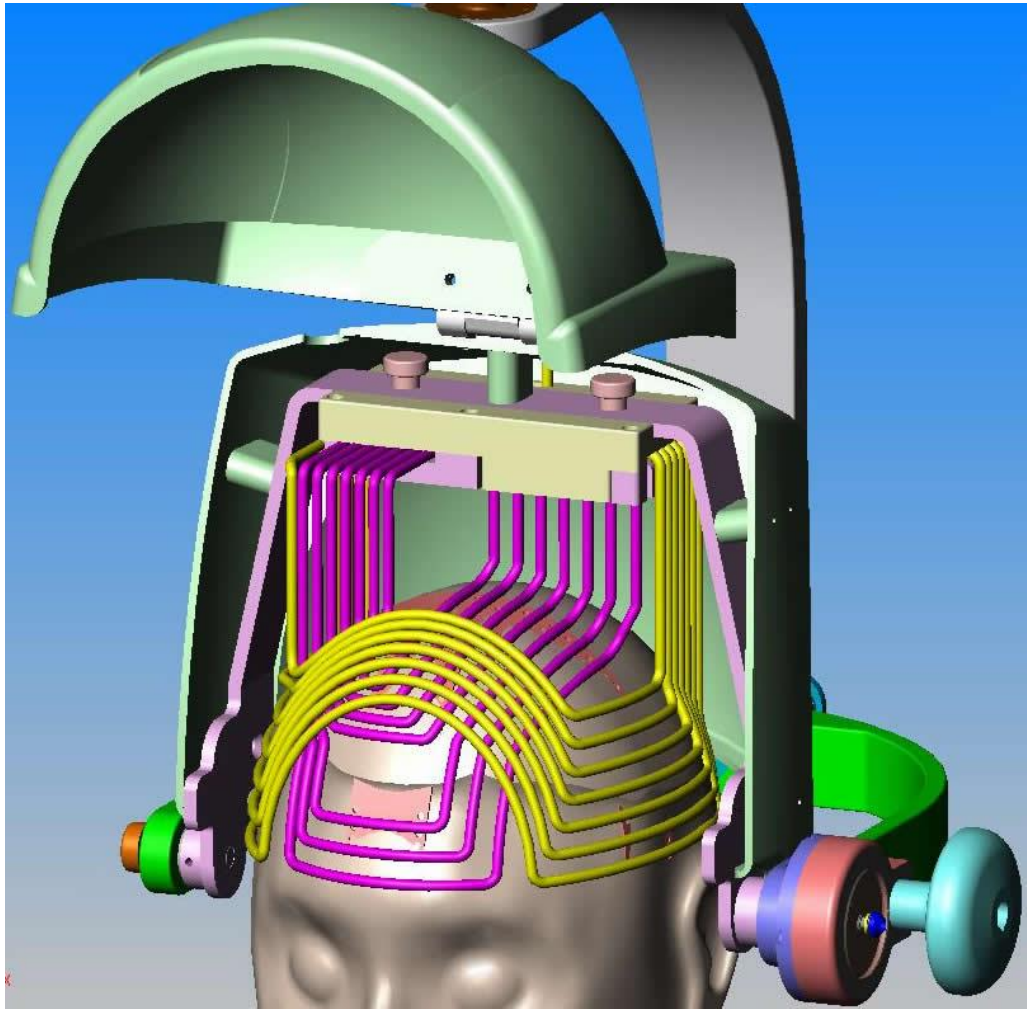
Sham control

Well-developed field

Standards of practice

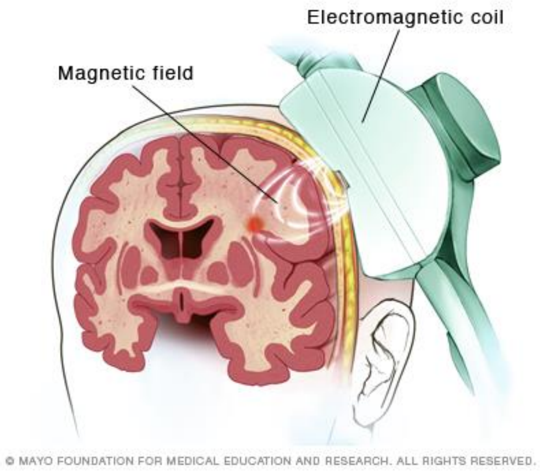
Effect sizes established


Brainsway
Brainsway



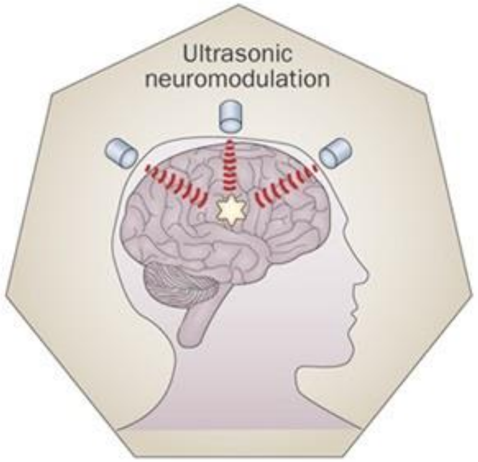
- The “Koren helmet” invented by Stanley Koren and Michael Persinger
- Subjects reported “sensed presence”
    - “mystical experiences and altered states”
- Used to study religious belief
- Been criticized – hard to replicate

Magnetic

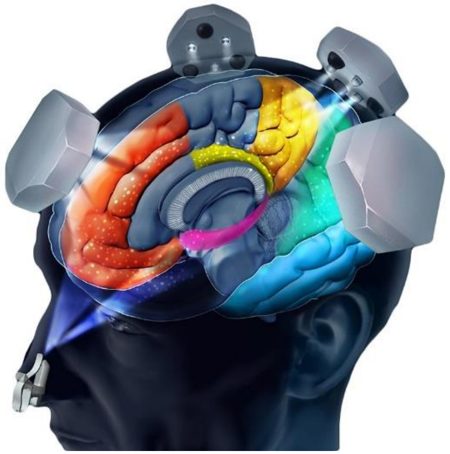


Electric

Sound



Light



Electric

tDCS is a neuromodulation method:

produces excitability changes in resting membrane potential

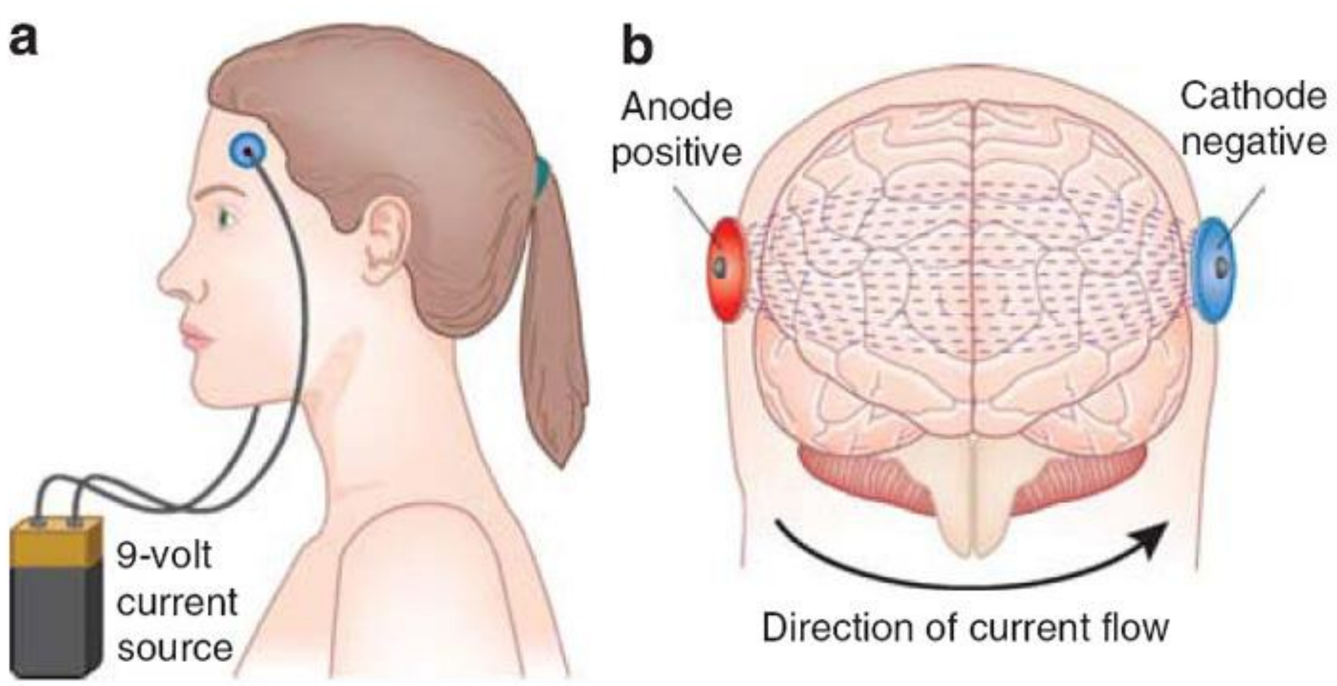
Types of electrodes

Anodal (causes subthreshold *depolarization*)

→ more excitable

Cathodal (causes subthreshold *hyperpolarization*):

→ less excitable

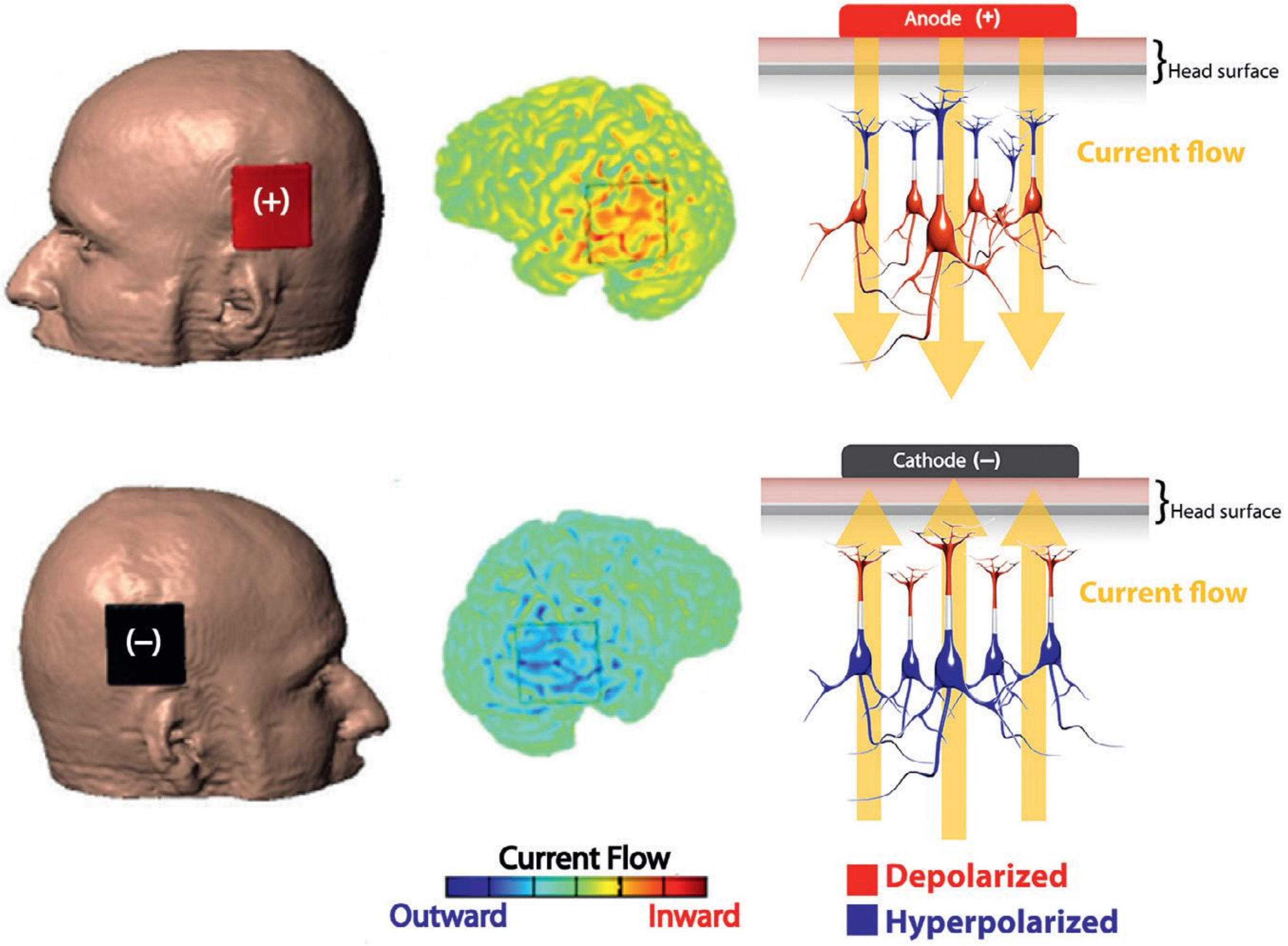


Anodal

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).



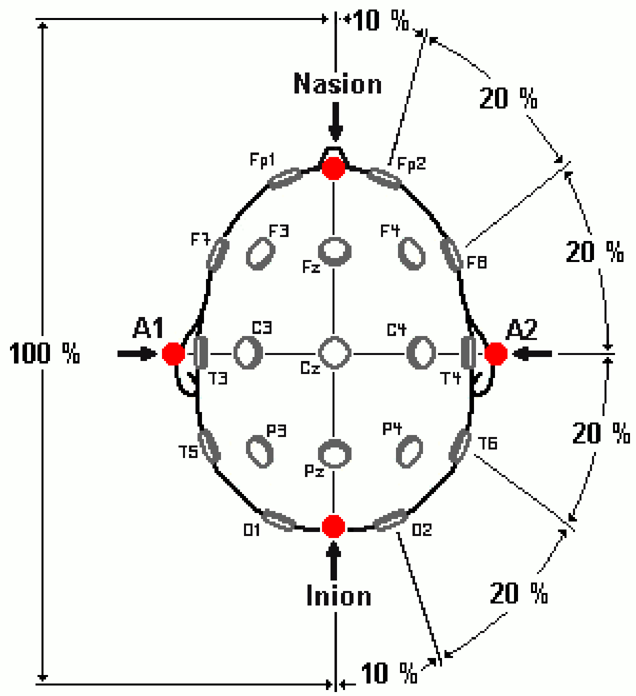
Transcranial Direct Current Stimulation (tDCS)

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 mV typically)

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

- 0.3 V/m per 1mA applied



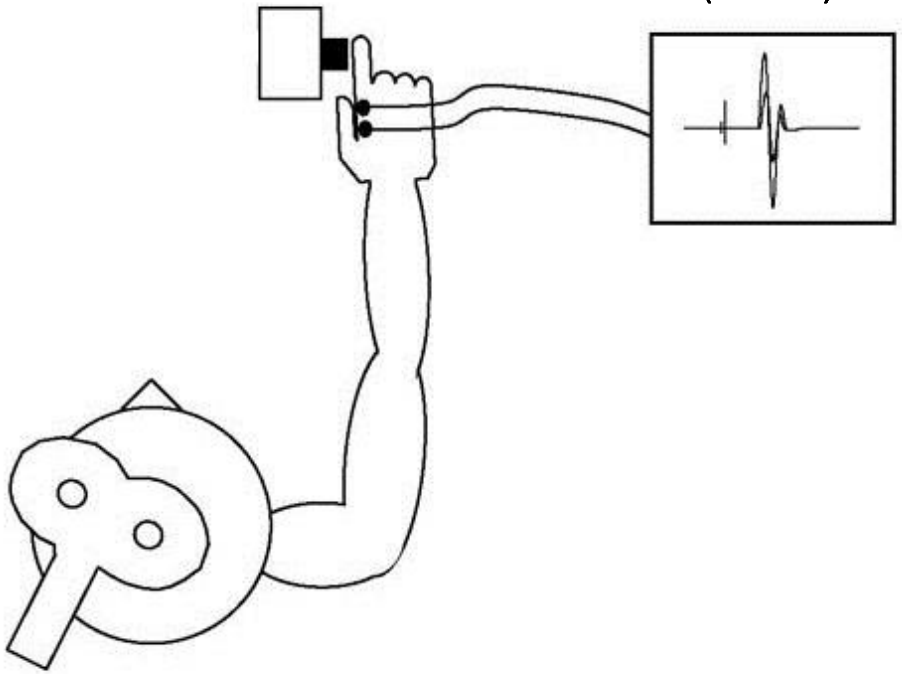
Using TMS to confirm that tDCS alters cortical excitability

Nitsche and Paulus (2000)

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

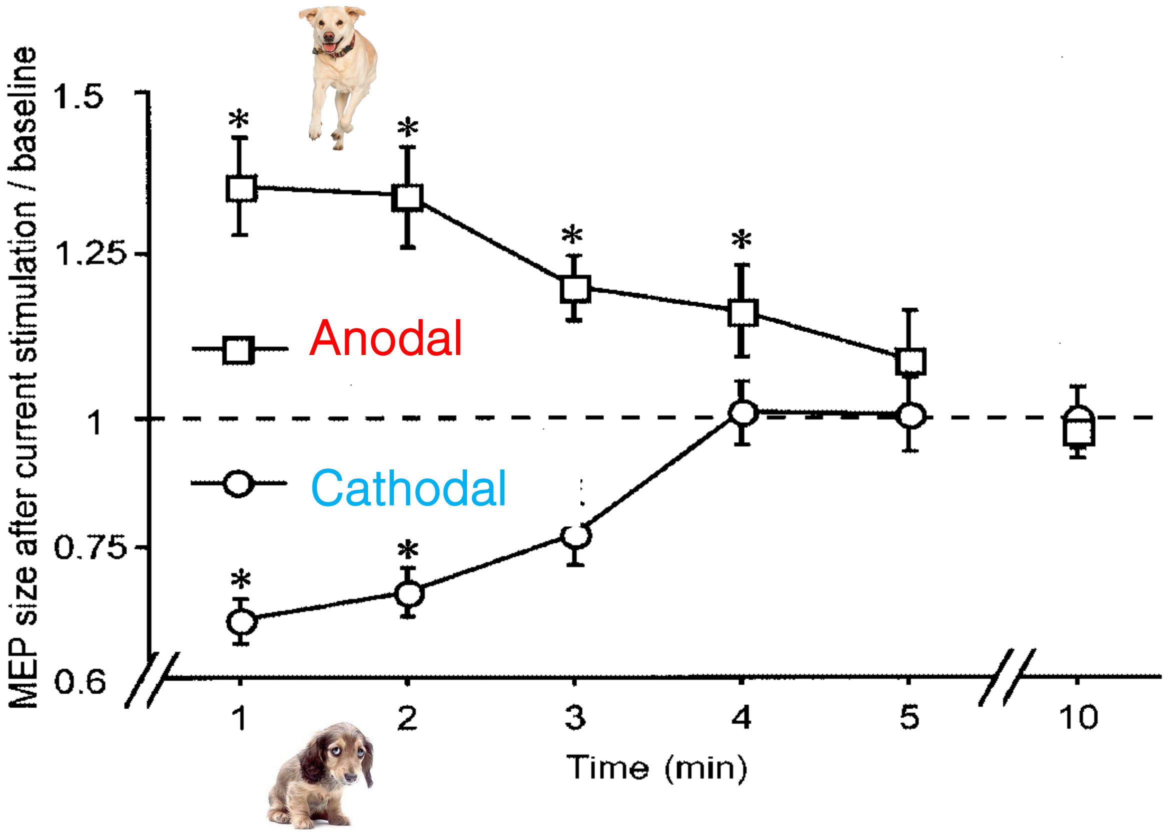
  MEP amplitude represents the excitability of the motor system

(MEPs)



(TMS over motor cortex)

tDCS alters cortical excitability



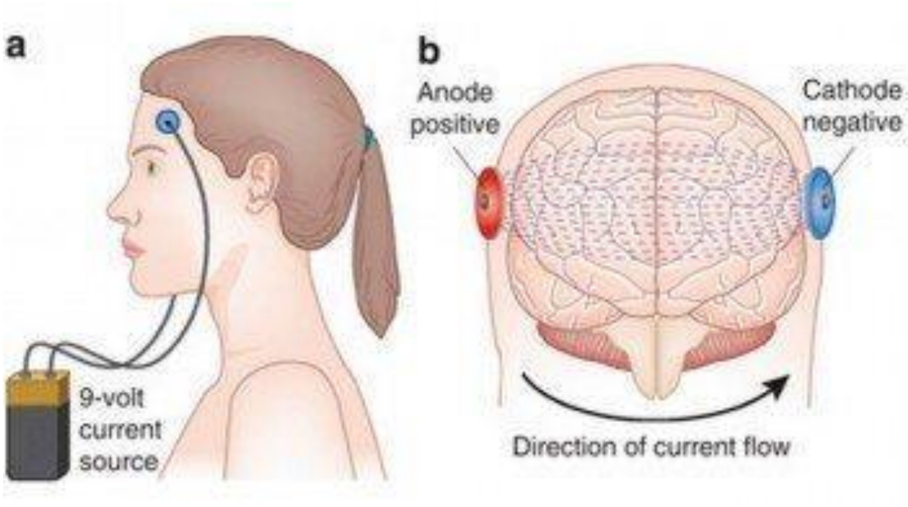
- Anode over motor cortex: larger MEPs
- Cathode over motor cortex: smaller MEPs

Excitability changes ~ 40%.

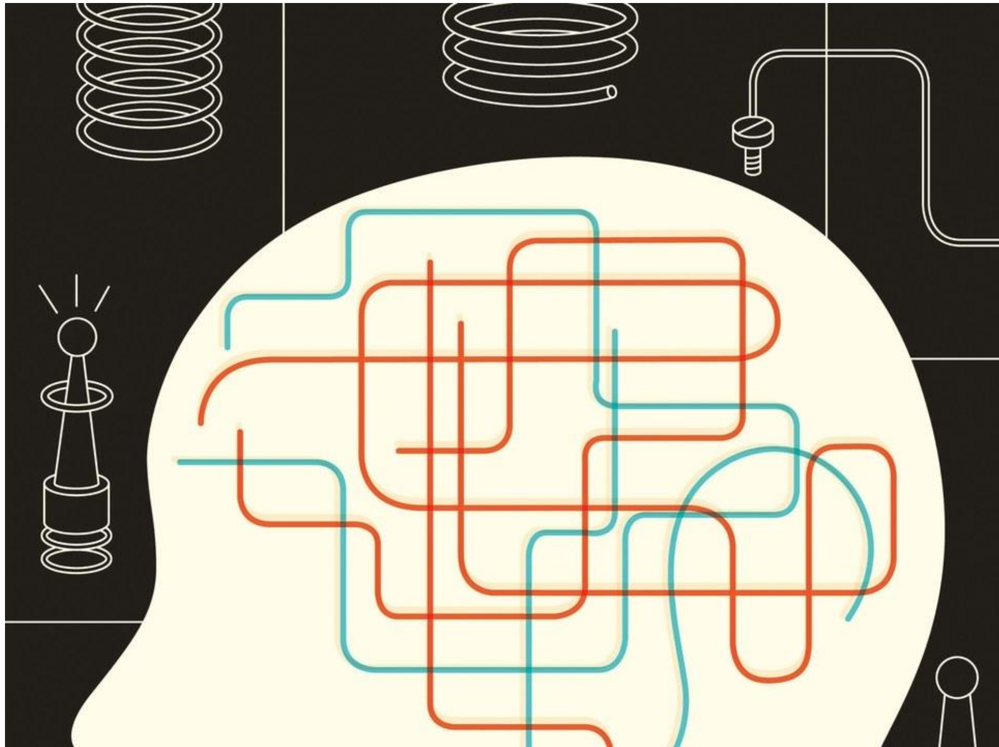
Effects lasted for ~4 min

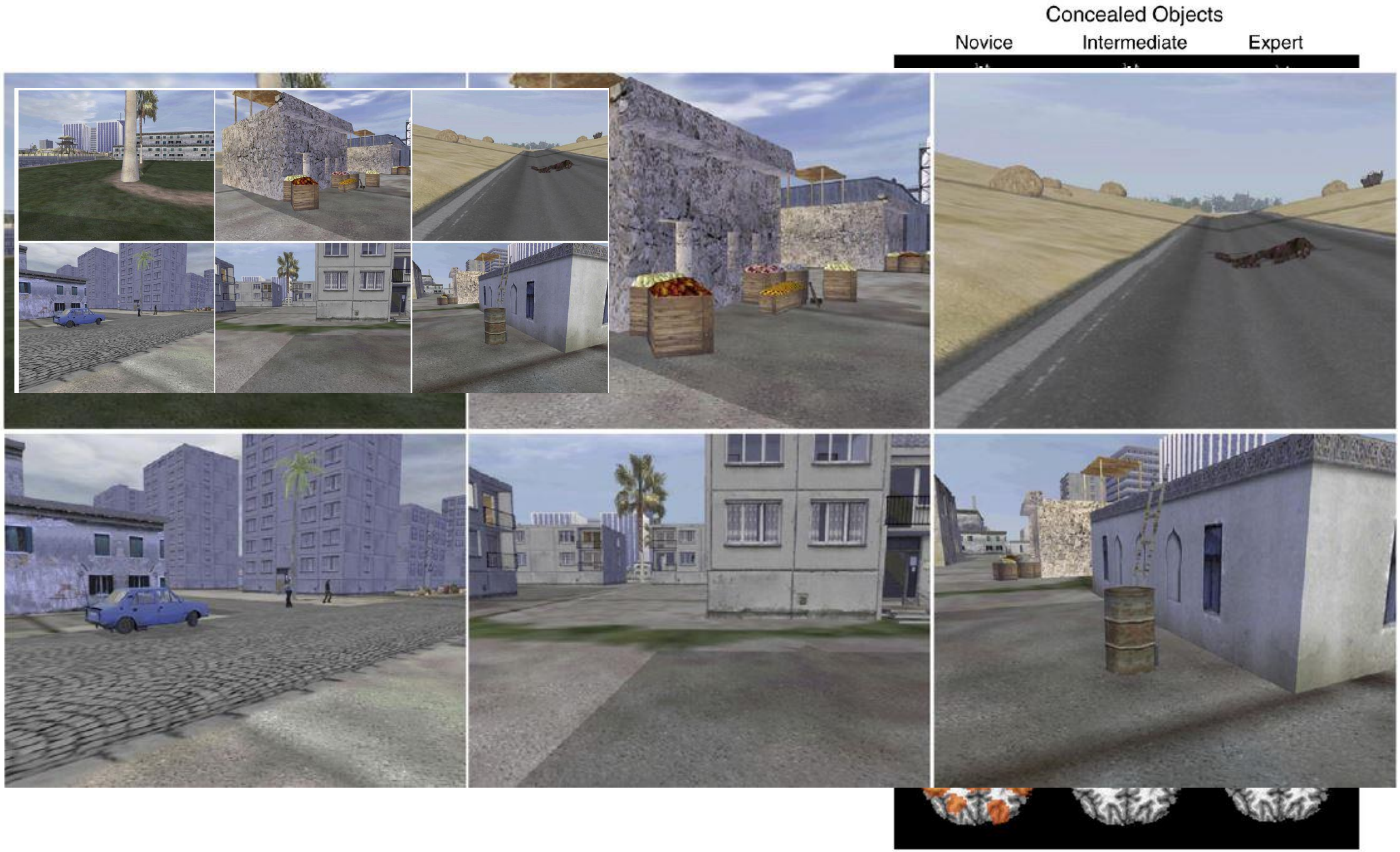
endurance due to LTP or LTD?

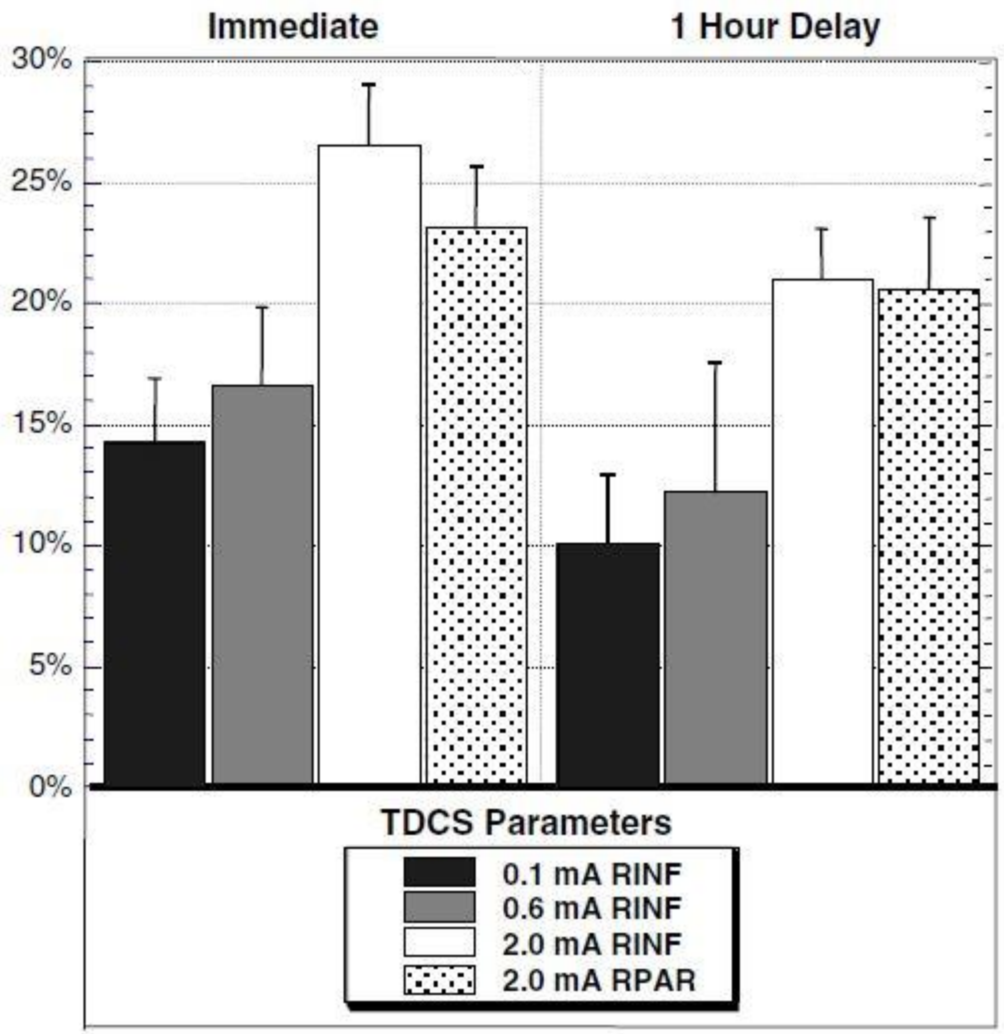
Nitsche & Paulus, 2000


a
9-volt
current
source
b
Anode
positive
Cathode
negative
Direction of current flow

Vince Clark




Concealed Objects
Novice
Intermediate
Expert



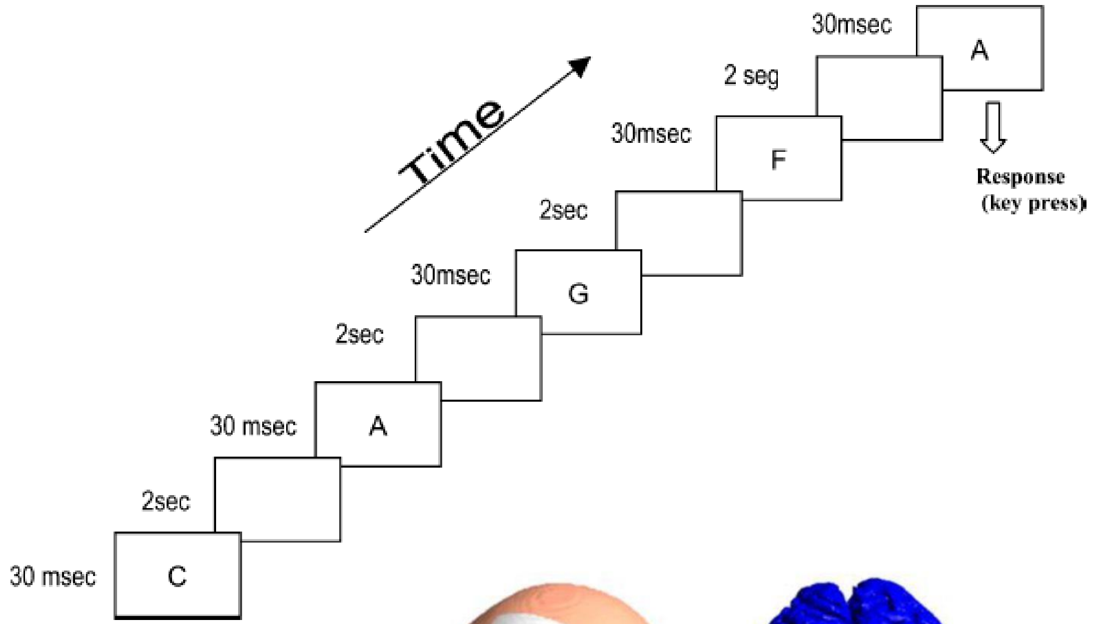
Immediate
1 Hour Delay
30%
25%
20%
15%
10%
5%
0%
TDCS Parameters
0.1 mA RINF
0.6 mA RINF
2.0 mA RINF
2.0 mA RPAR

Working memory (WM)

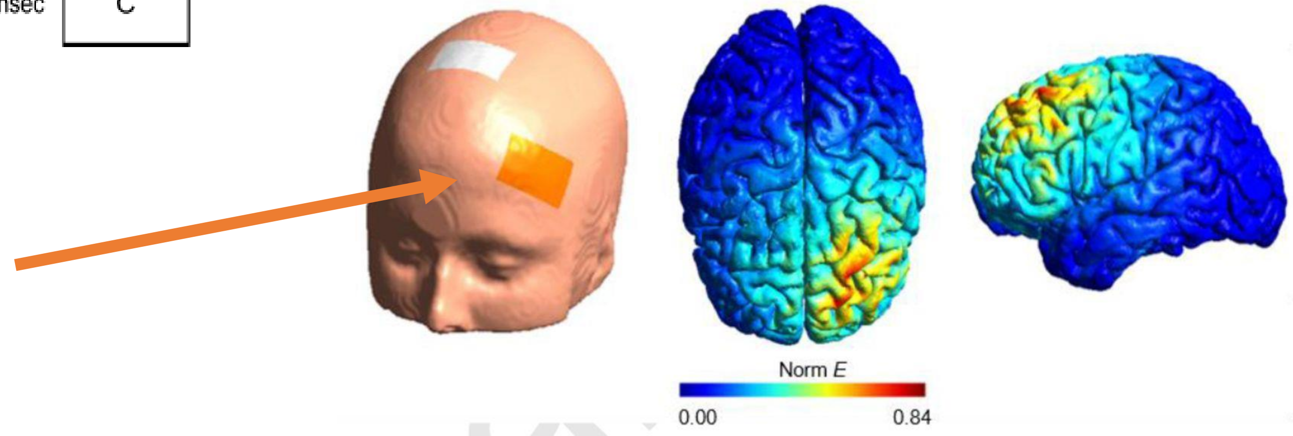
- Temporary storage and manipulation of the information necessary for complex tasks
- Common task to assesses WM: 3 back task

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 $\geq$ 50%

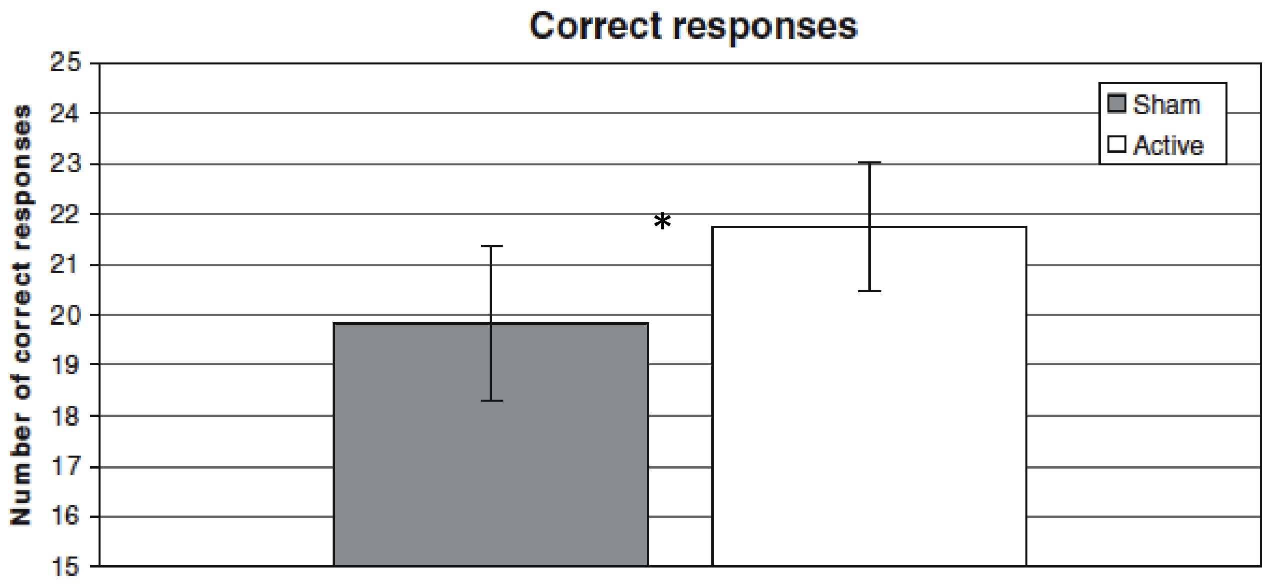
2. Applied a constant current of 1 mA intensity for 10 min during task
   anode over DLPFC; cathode over right supraorbital area.
   (Subjects feel the current as an itching sensation at both electrodes at the beginning of the stimulation.)

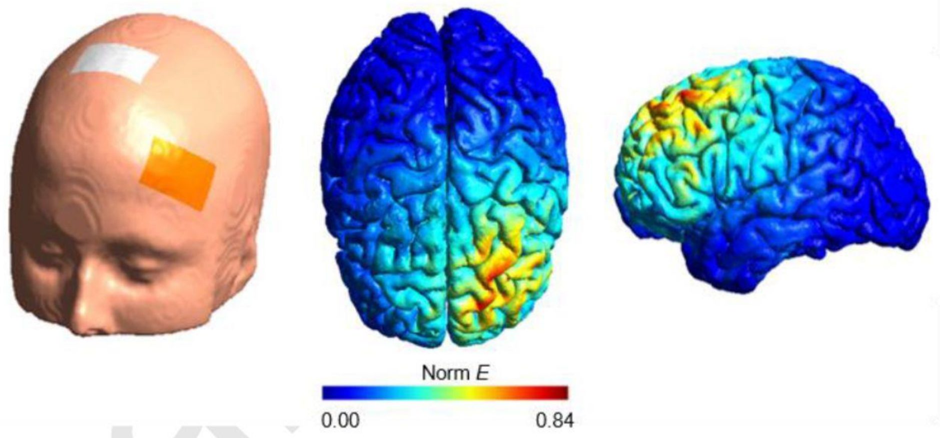
3. Or sham stimulation applied for 10 minutes during task
   Sham = electrodes placed in the same position but the stimulator was turned off after 5 s. Subjects feel initial itching sensation but received no current for the rest of the stimulation period. Subjects were blind to the respective stimulation condition

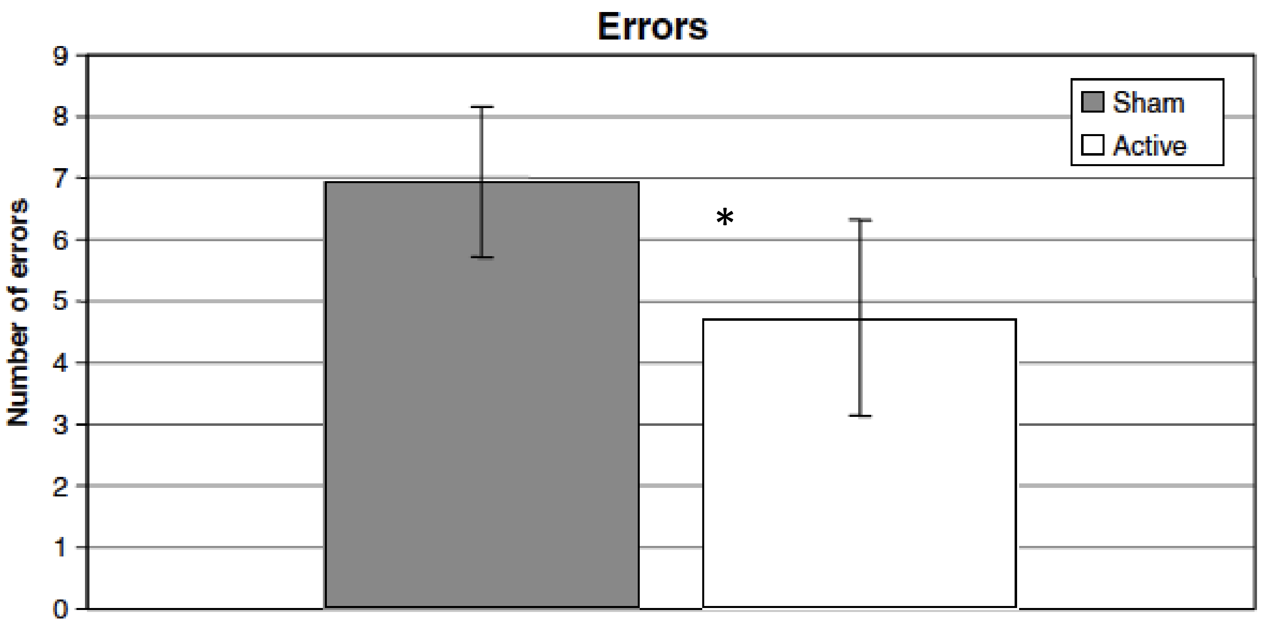
*** Order of active and sham stimulation was **counterbalanced** across subjects.

***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 tDCS is now widely employed in

basic and translational research, sports, military, and recreationally

At-home applications will not necessarily produce the desired enhancements and not all basic/translational results are interpretable because:
the concept of **anodal** **vs** **cathodal** stimulation is too simplistic

A number of reasons follow:

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

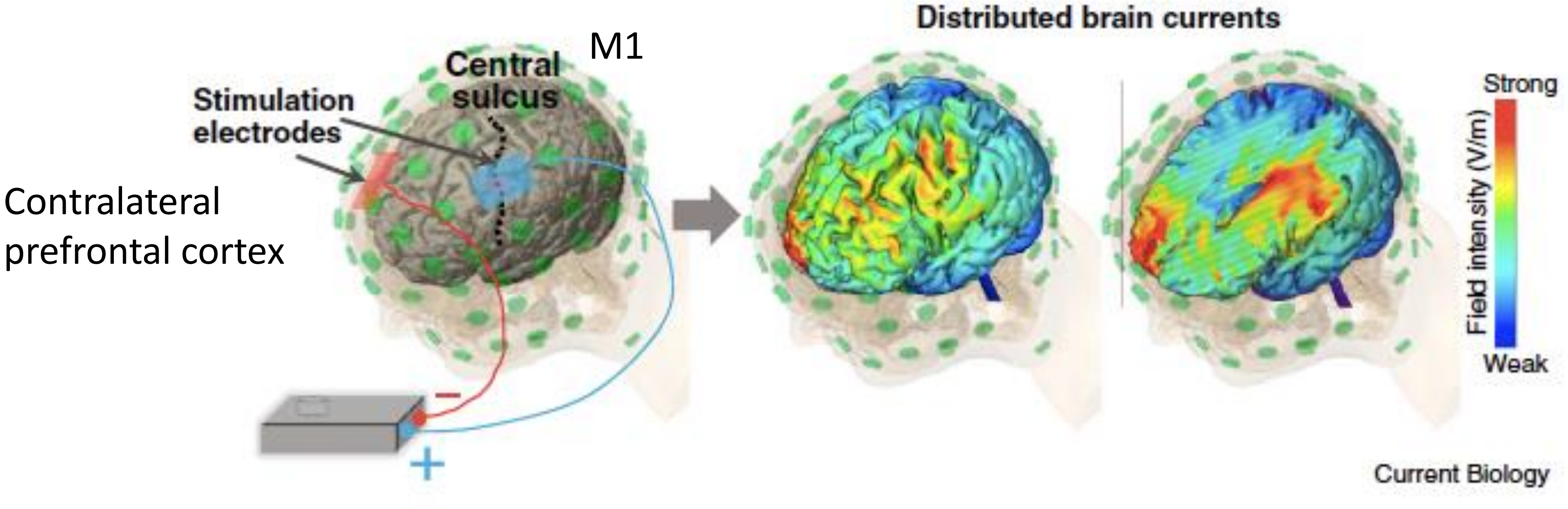
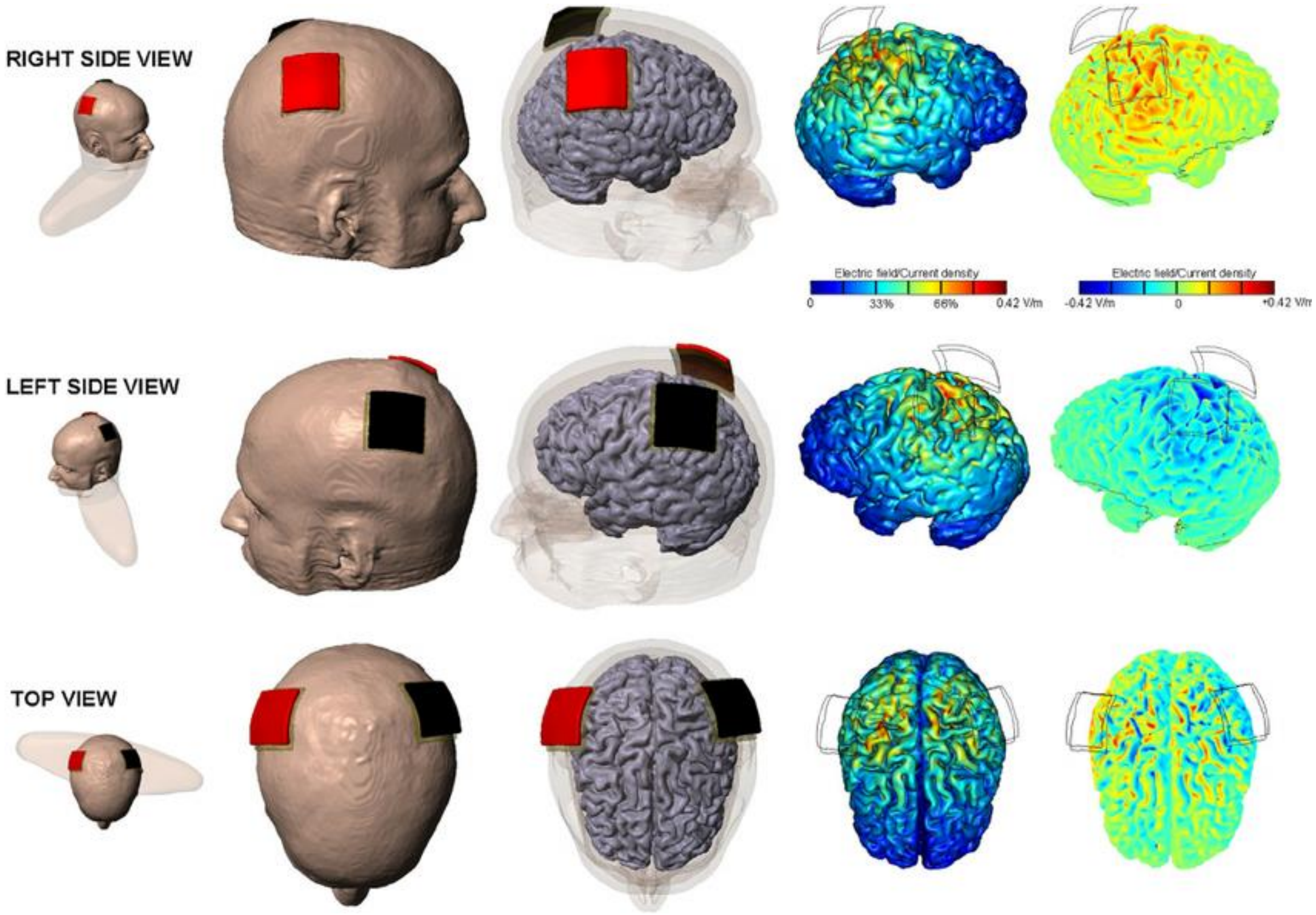


Figure 1. Example electrode montage most commonly used for stimulation of primary motor cortex.
One electrode (anode) is placed over central sulcus, and the other electrode (cathode) placed over contralateral prefrontal cortex. As shown on the right, the distribution of current inside the brain with 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 (+)$^{1\ \mathrm{mA}}$
	1.3 (+)$^{2\ \mathrm{mA}}$
Zaehle et al. (2011)	Not available
Ferrucci et al. (2008)	−0.4 (+/−)$^{\mathrm{Cereb.}}$
	−0.5 (−)$^{\mathrm{F3}}$ + $^{\mathrm{F4}}$
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 (+)$^{1\mathrm{mA}}$
	−0.9 (−)$^{1\mathrm{mA}}$
	−2.2 (−)$^{2\mathrm{mA}}$
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

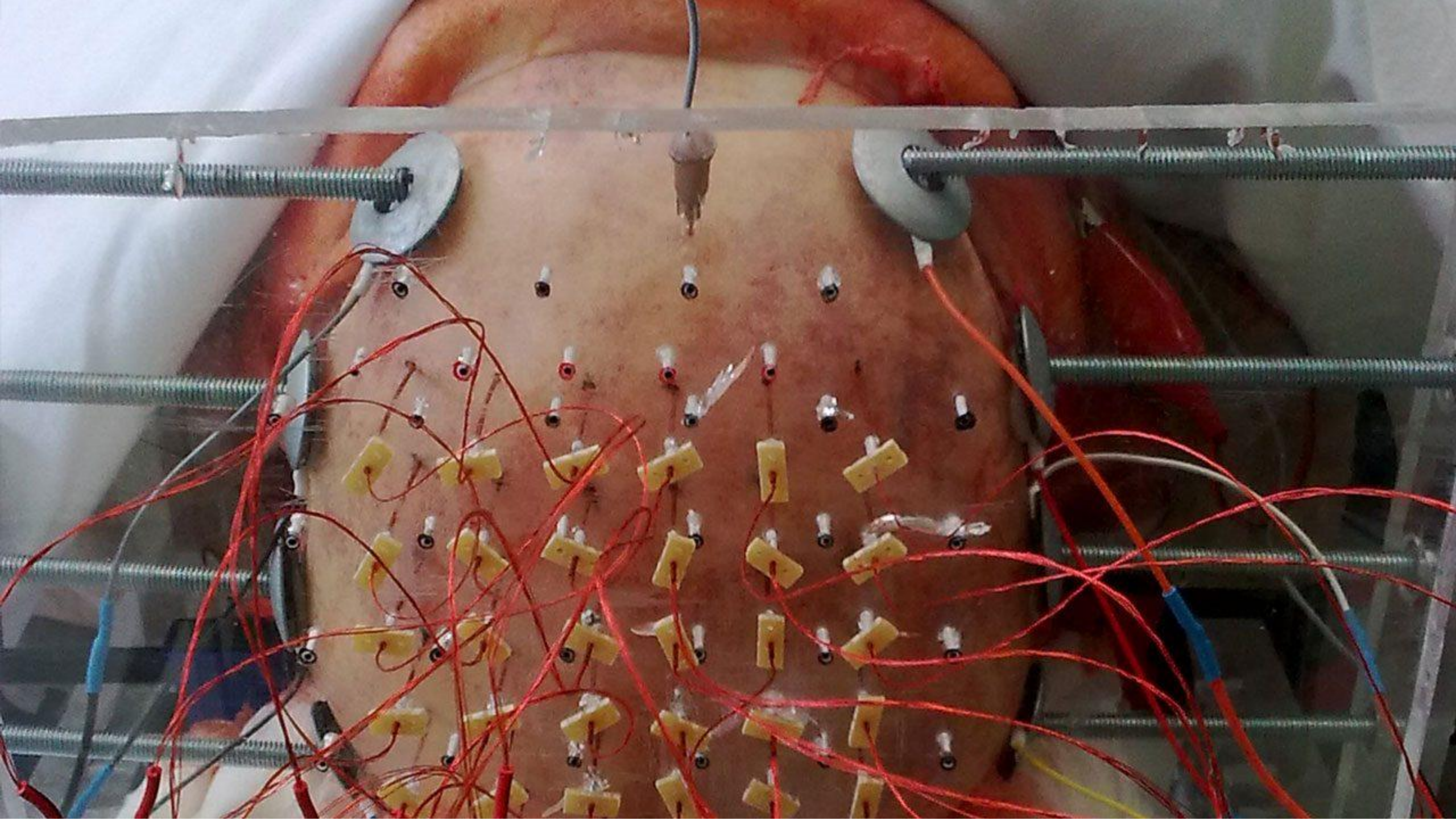
Abstract

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.

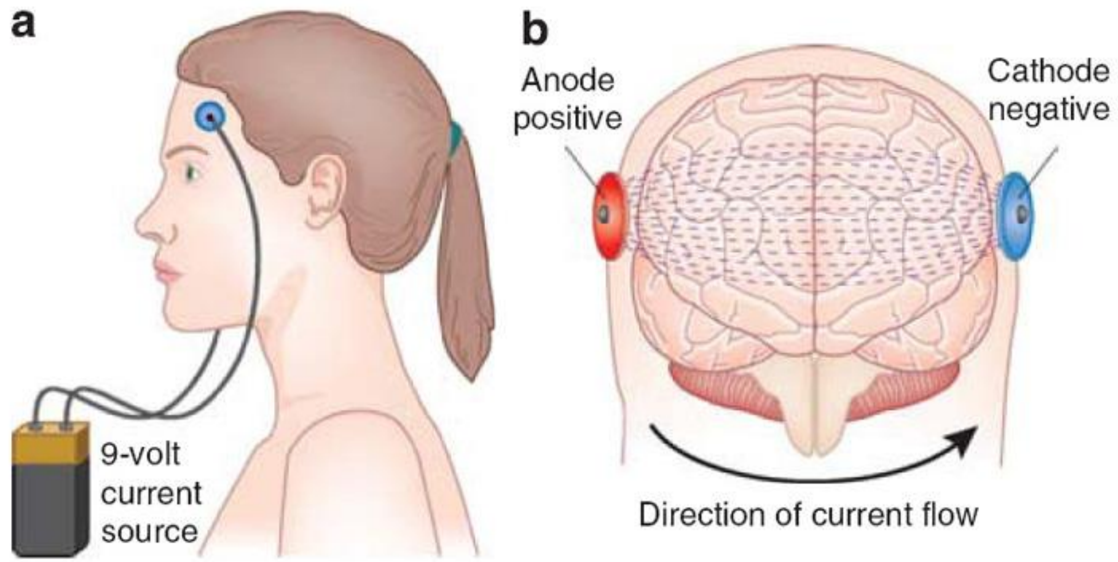
METHODS: Single-session tDCS data in healthy adults (18-50) from every cognitive outcome measure reported by at least two different research groups in the literature was collected. Outcome measures were divided into 4 broad categories: executive function, language, memory, and miscellaneous. To account 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.



Evaluating tDCS (limitations)



Current covers large area of scalp!

- Electrode size
- Electrode position
- Electrode distance

<u>Be skeptical about:</u>

Conclusions about location (its 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?

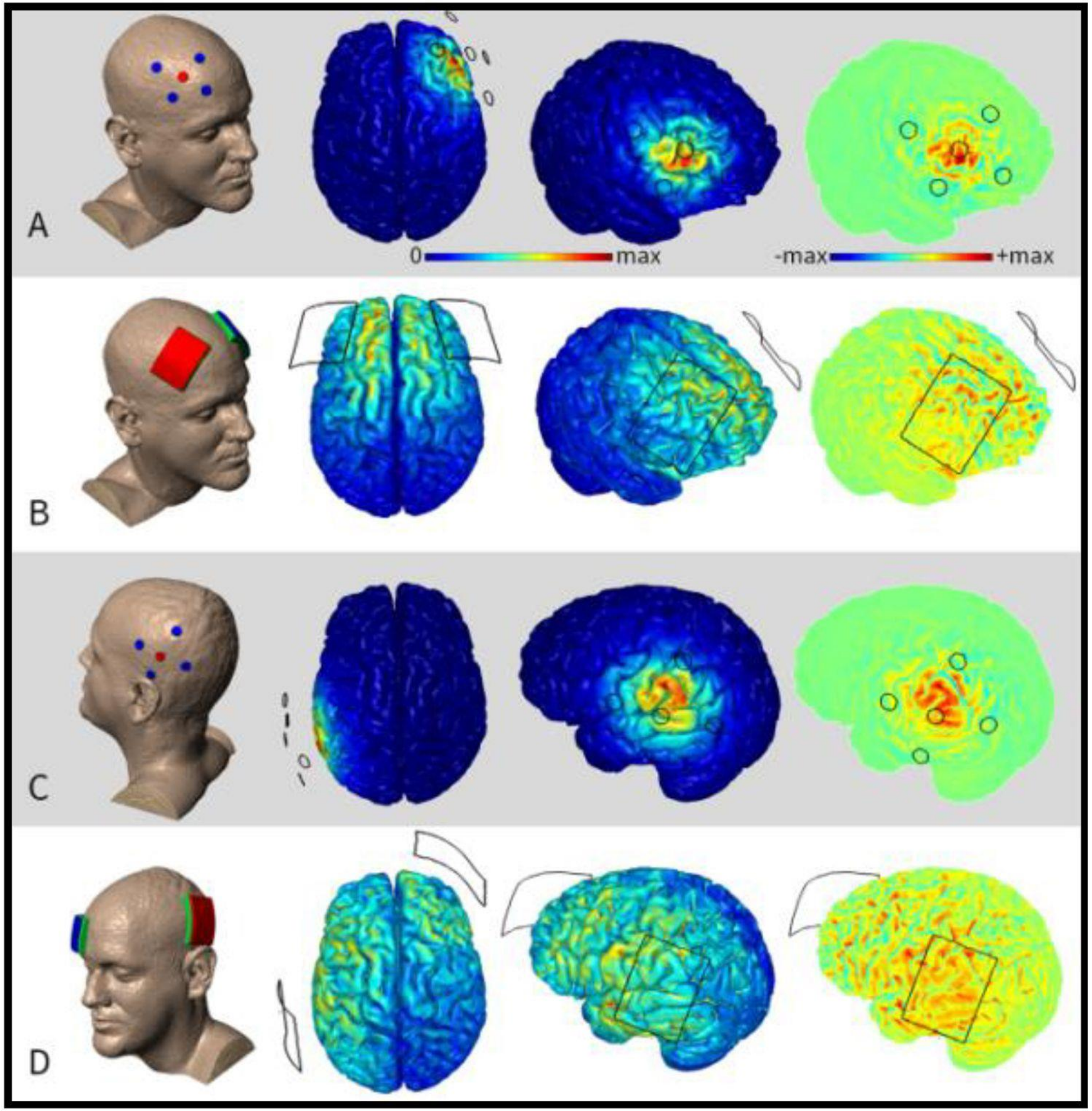
Foc.us

HD-tDCS

tDCS

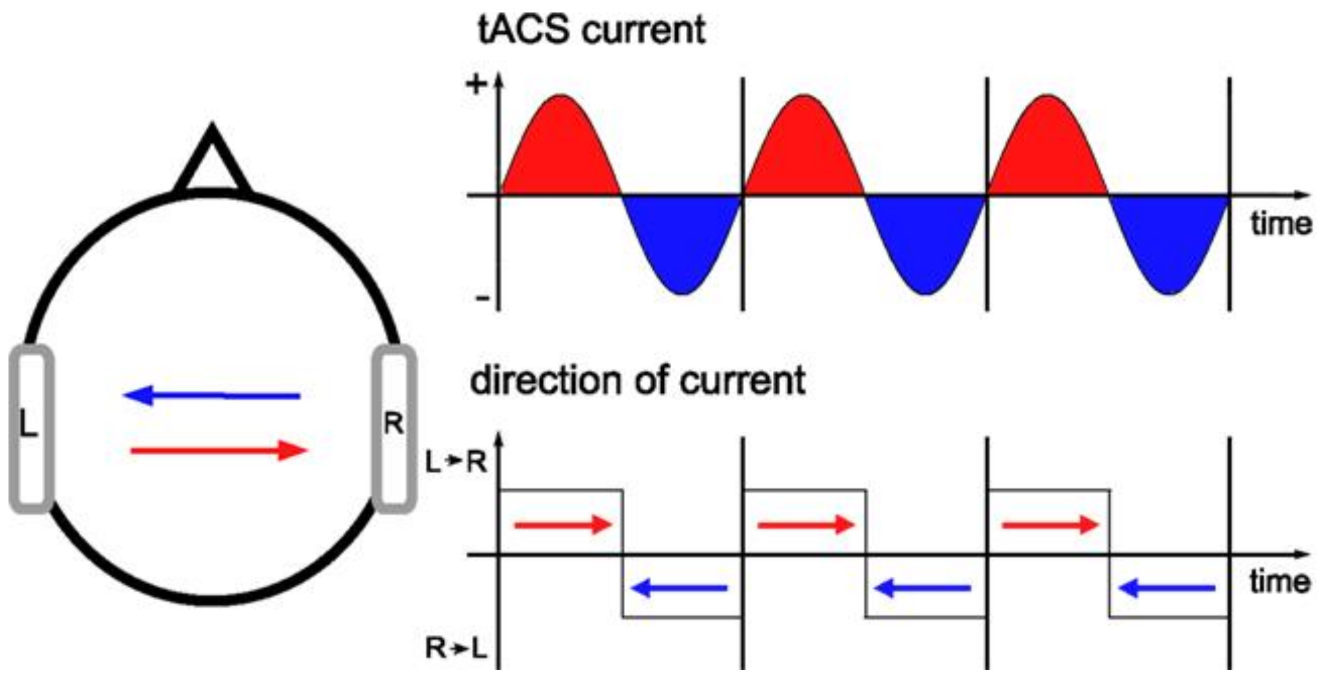
HD-tDCS

tDCS



Transcranial alternating current (tACS)

Different principles will apply

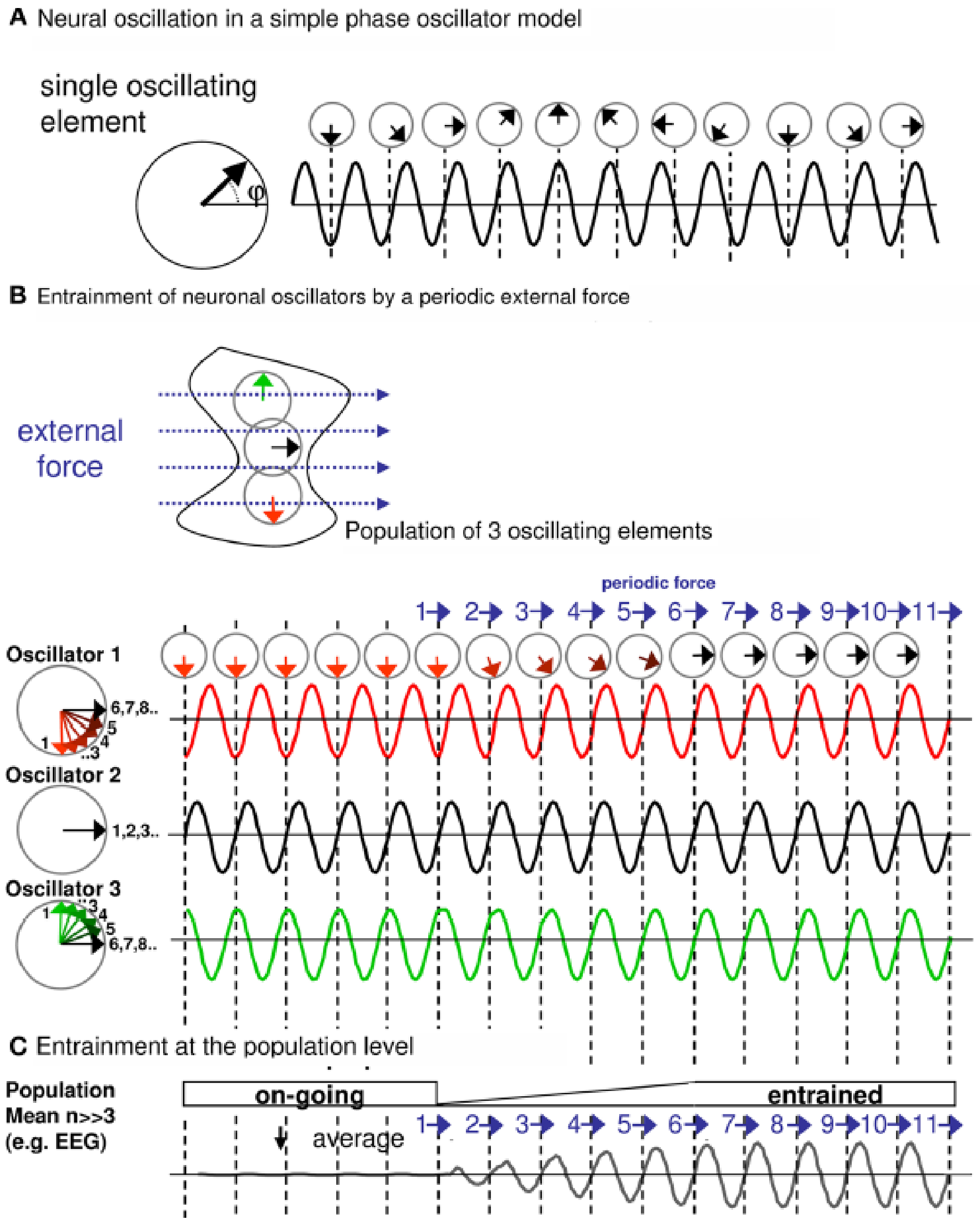


tACS for brain entrainment

Control/induce oscillations!

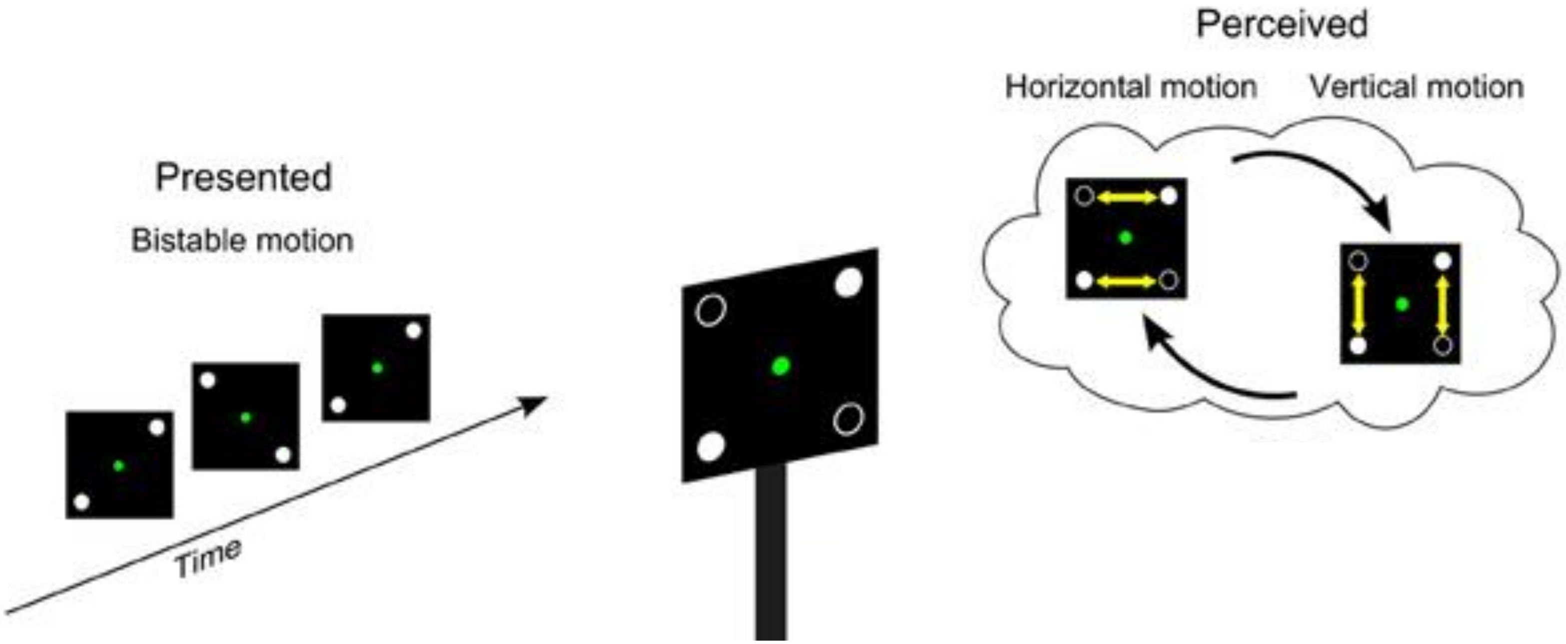
Modulate cognition?

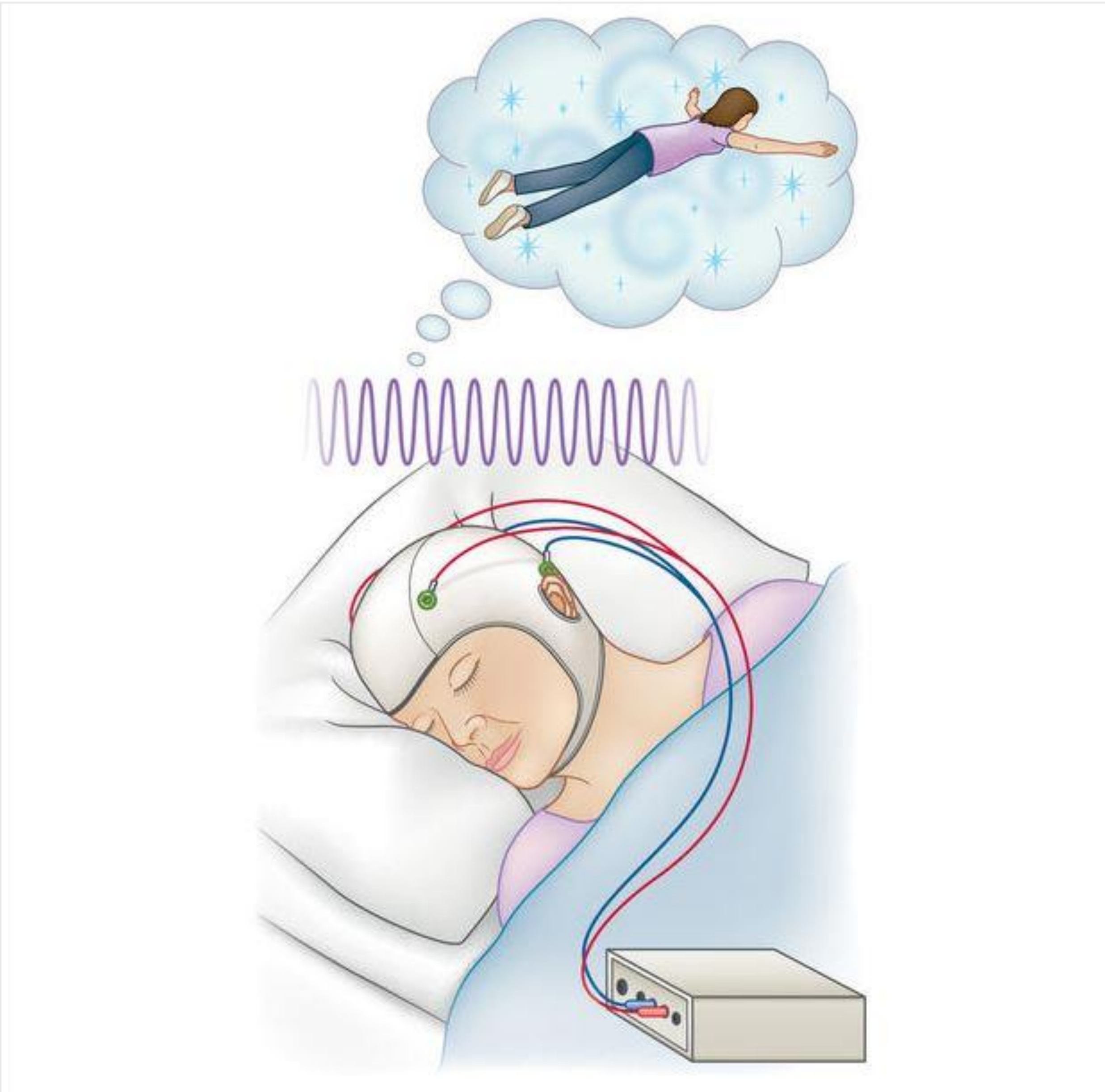
Causal testing



Thut, Schyns, Gross 2011

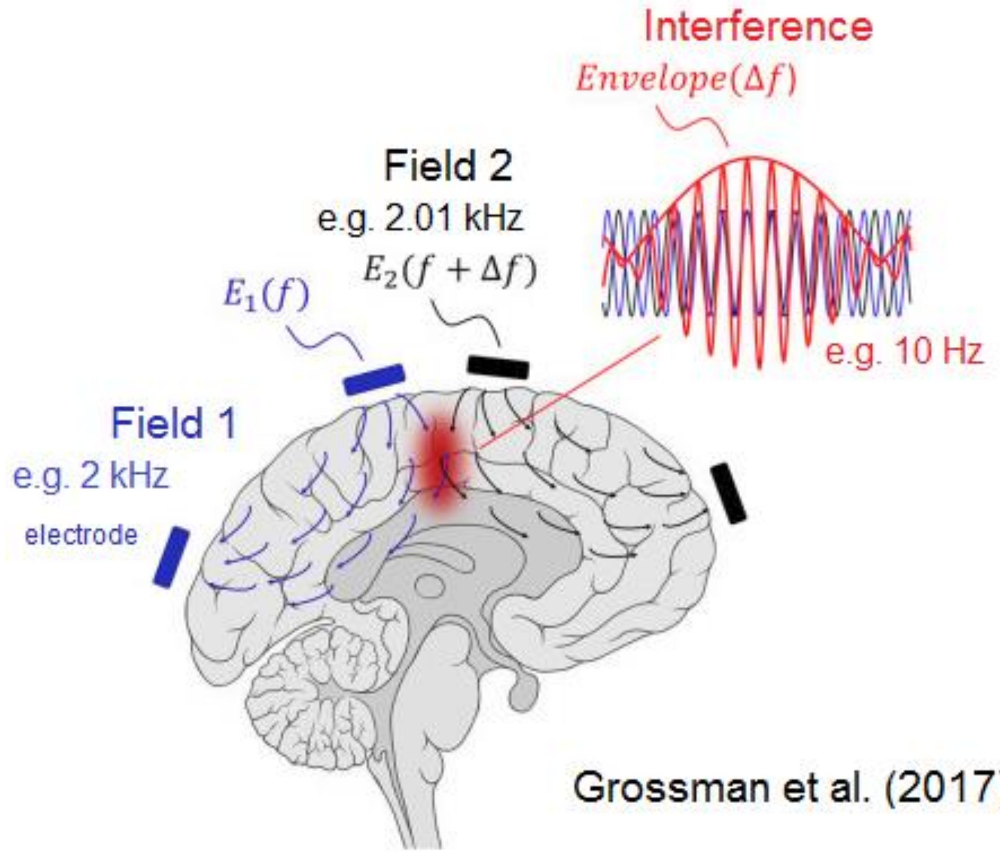
A


Presented
Bistable motion
Time
Perceived
Horizontal motion
Vertical motion

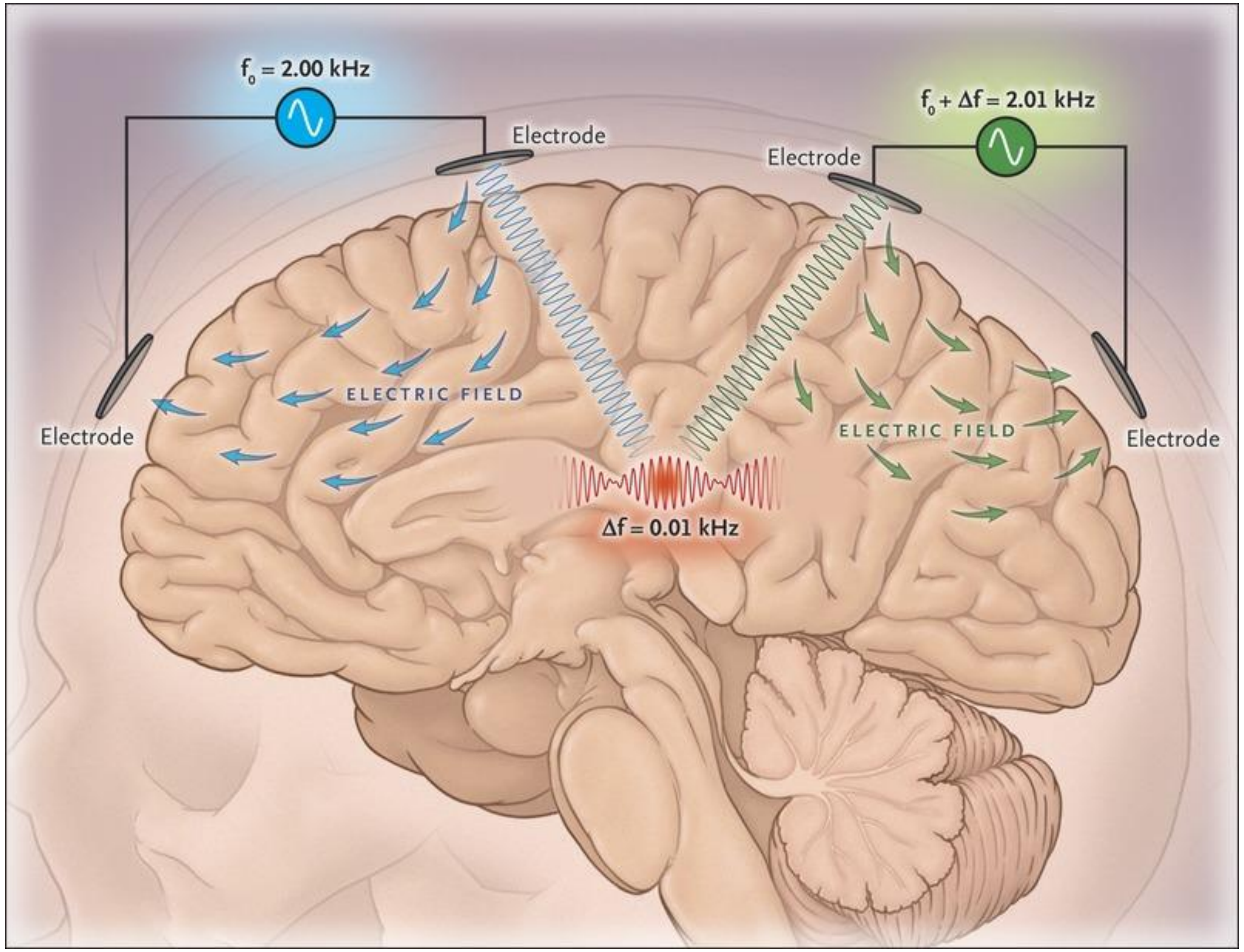


Payne at al, 2014

Temporal Interference (TI) stimulation



Grossman et al. (2017)



Fun videos:

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

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

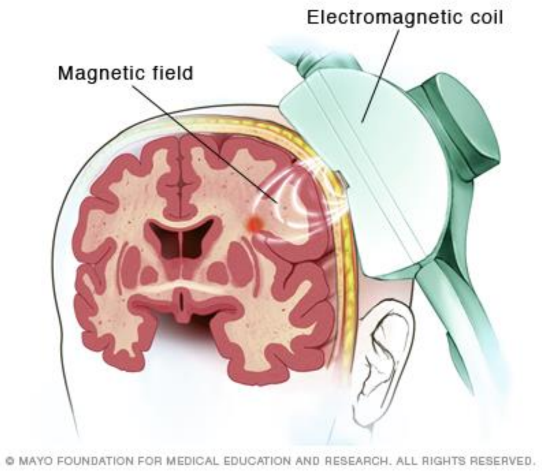
https://www.youtube.com/watch?v=8Ubb0Qvybdo

NY Times article

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

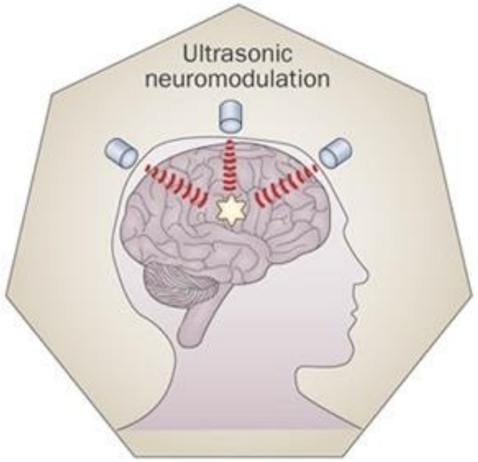

Questions?

Magnetic

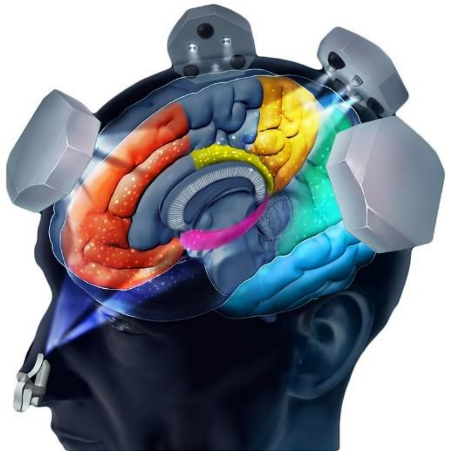


Electric

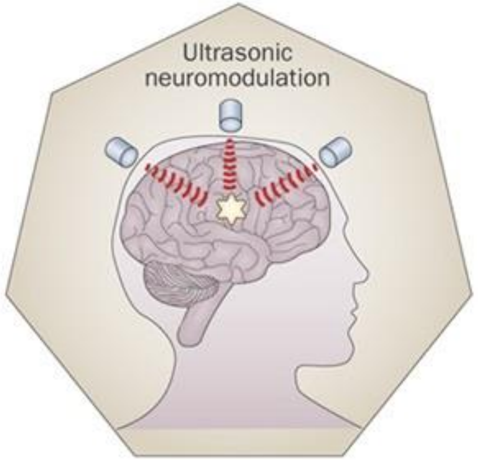
Sound



Light

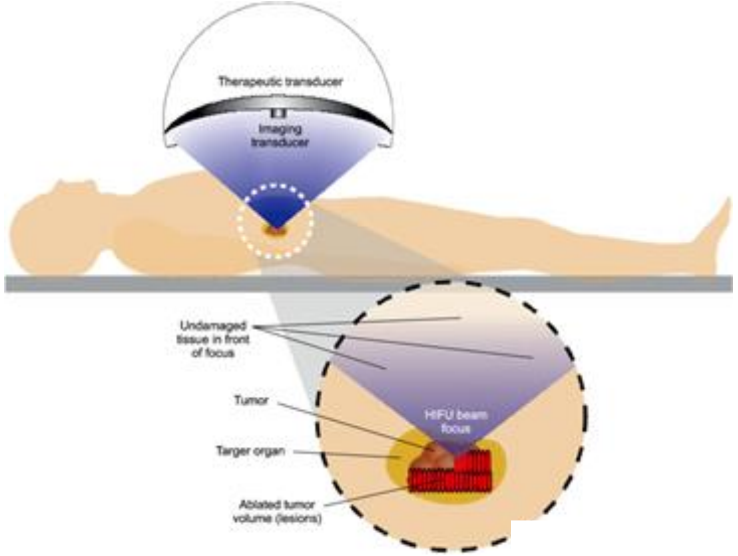


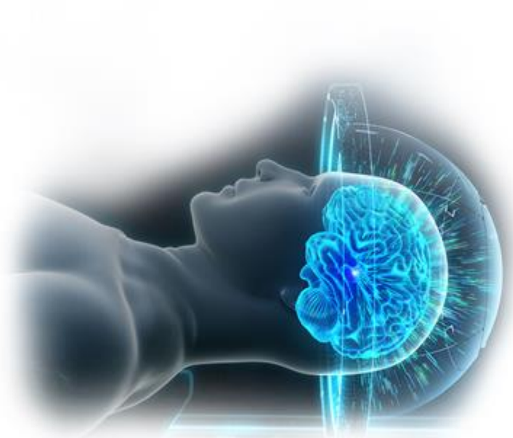
Sound



Low-Intensity Ultrasound

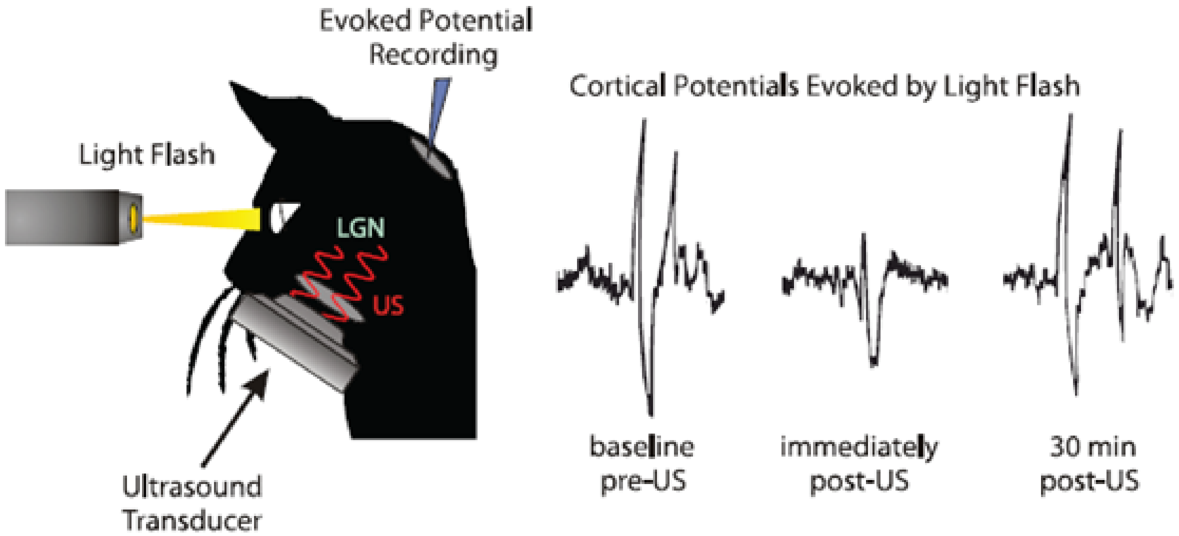
High-Intensity Ultrasound





Modulation

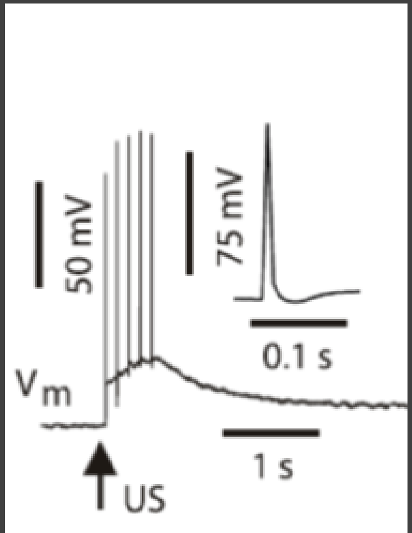
1920s-1990s

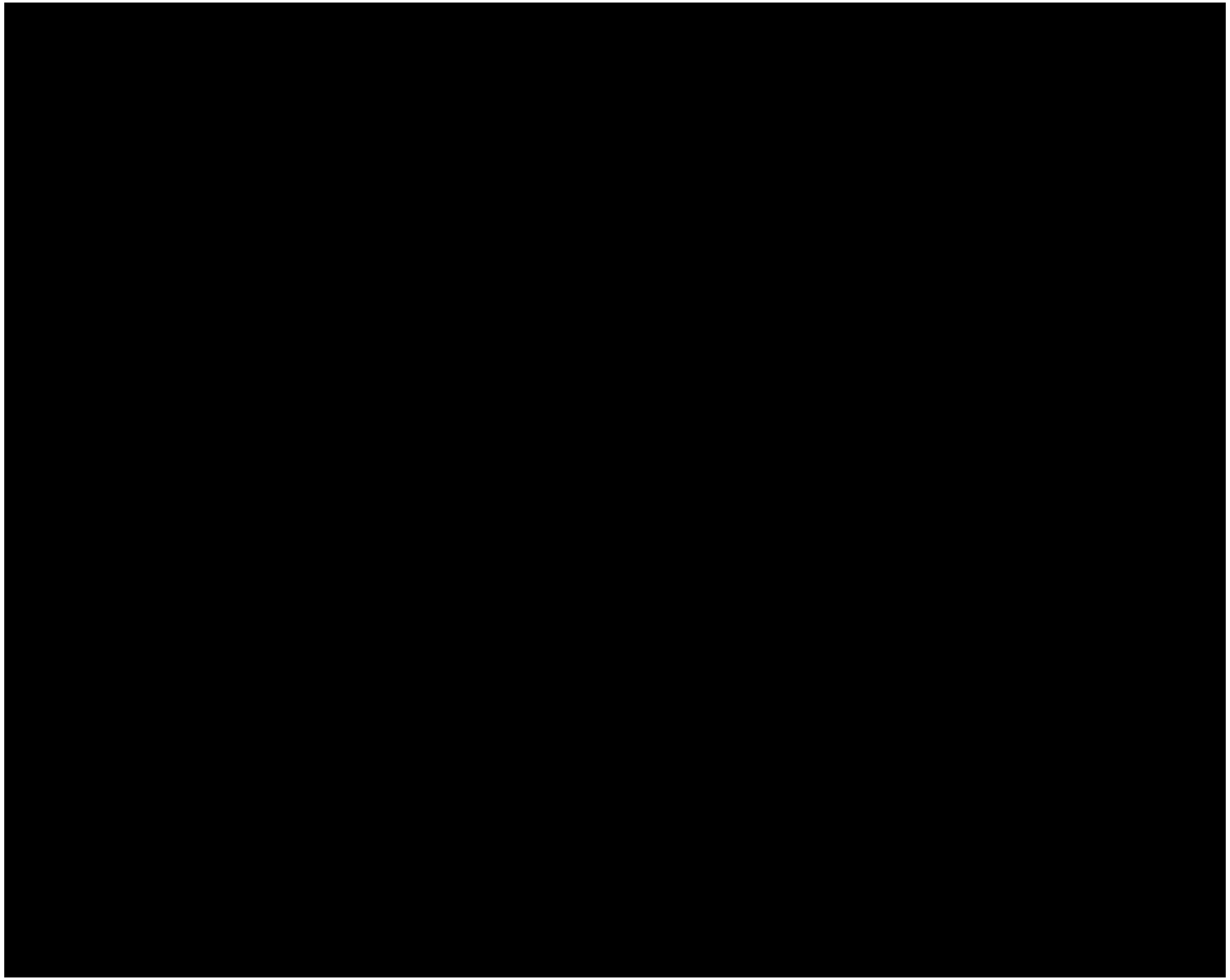


Fry, 1957, Figure: Tyler, 2013

EVOKE ACTIVITY

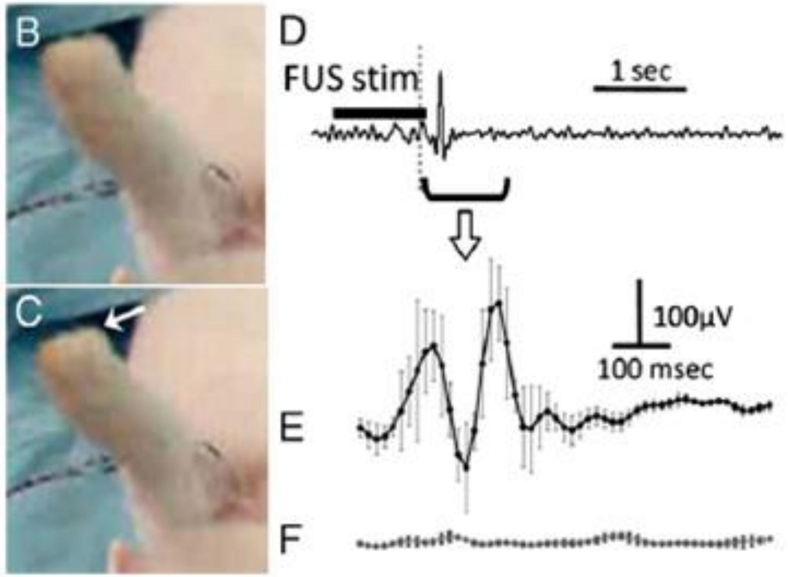
Activates neural activity/action potentials

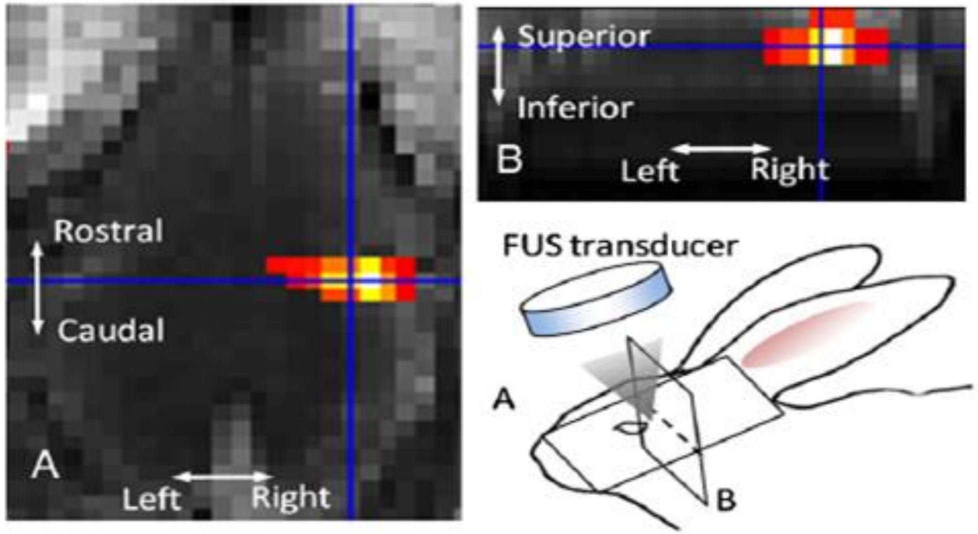


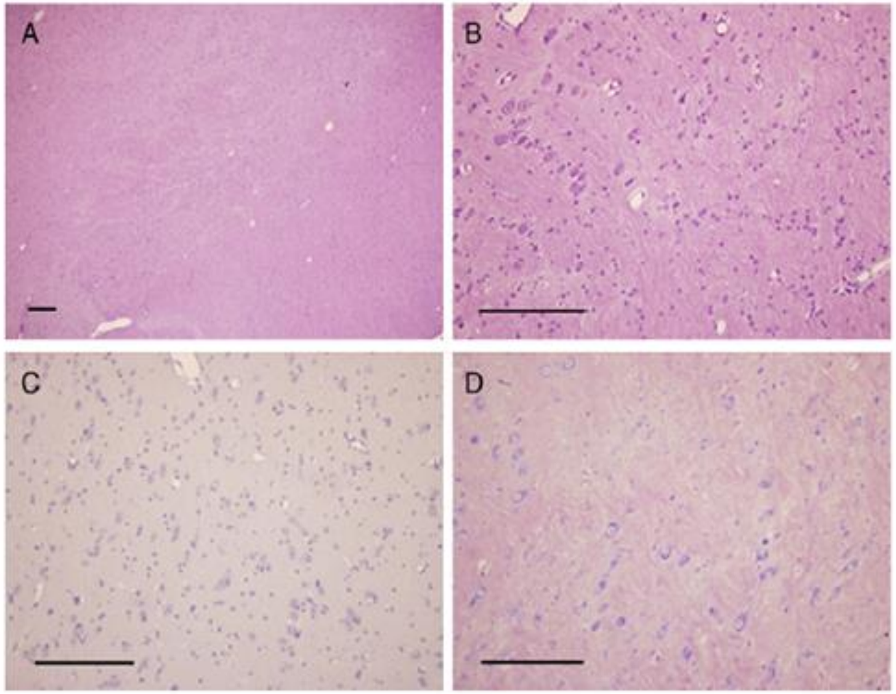


Tyler et al., 2008

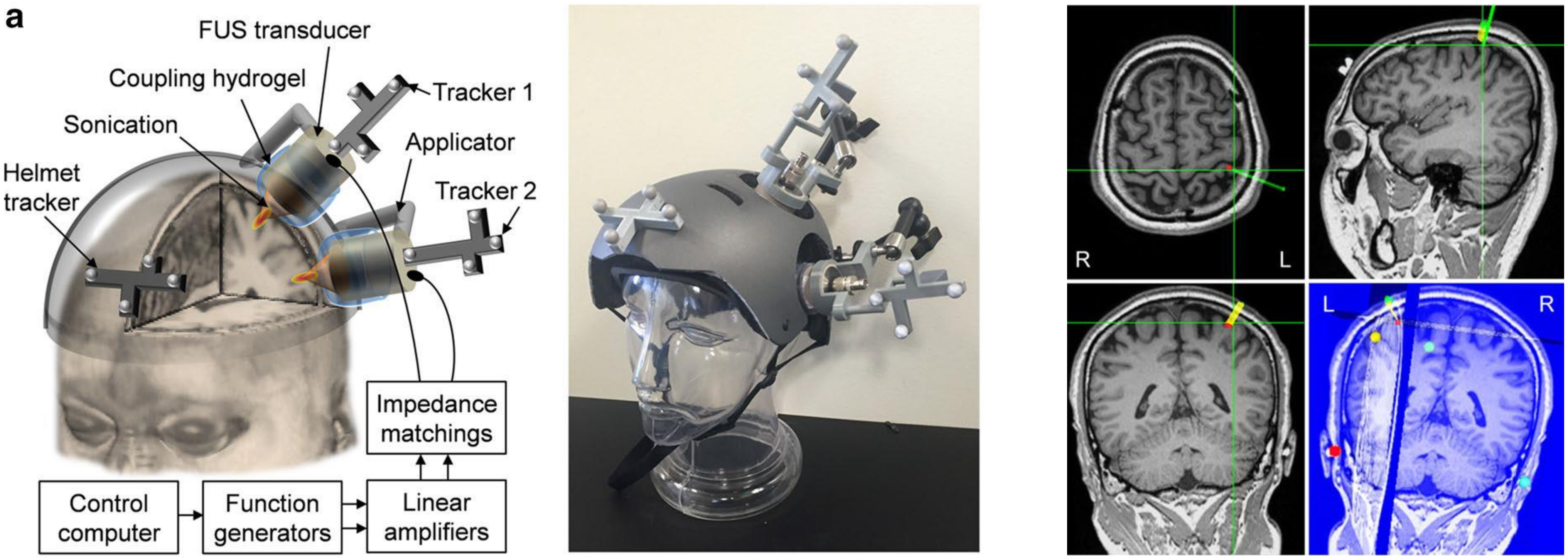
MR-GUIDED FOCUSED US

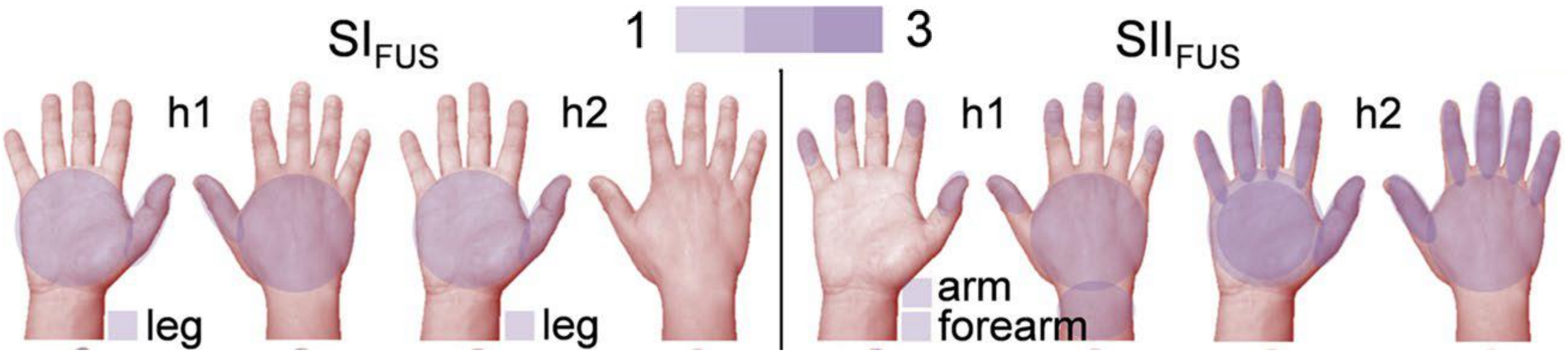






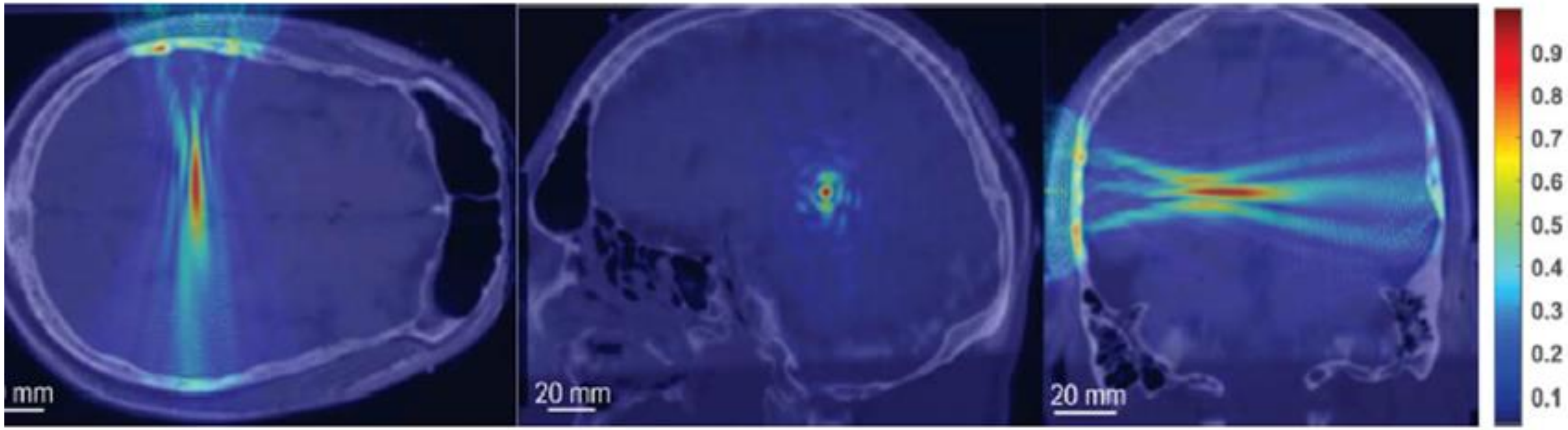
Yoo et al., 2012

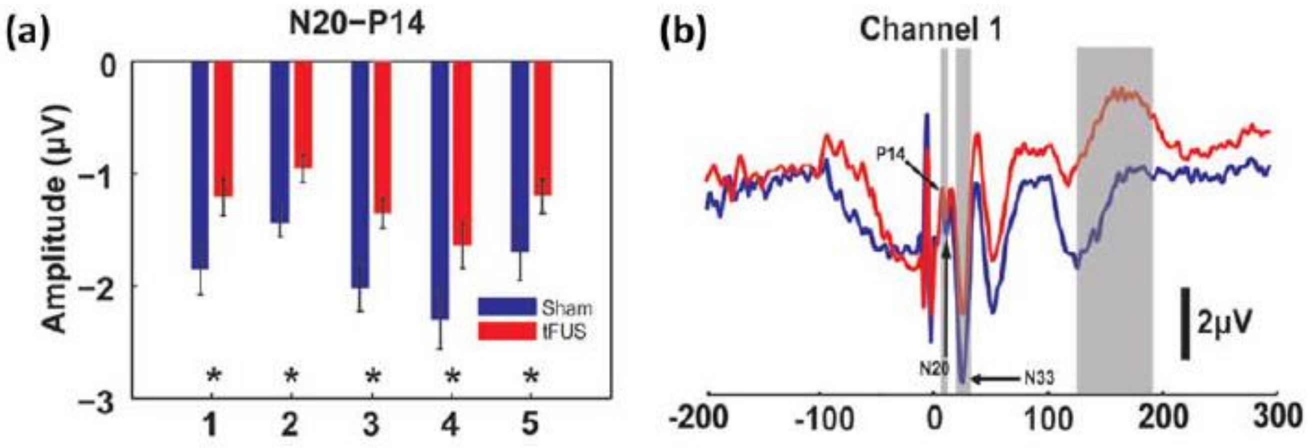




Lee, Chung Song, Yoo, 2016

Transcranial Focused Ultrasound - tFUS



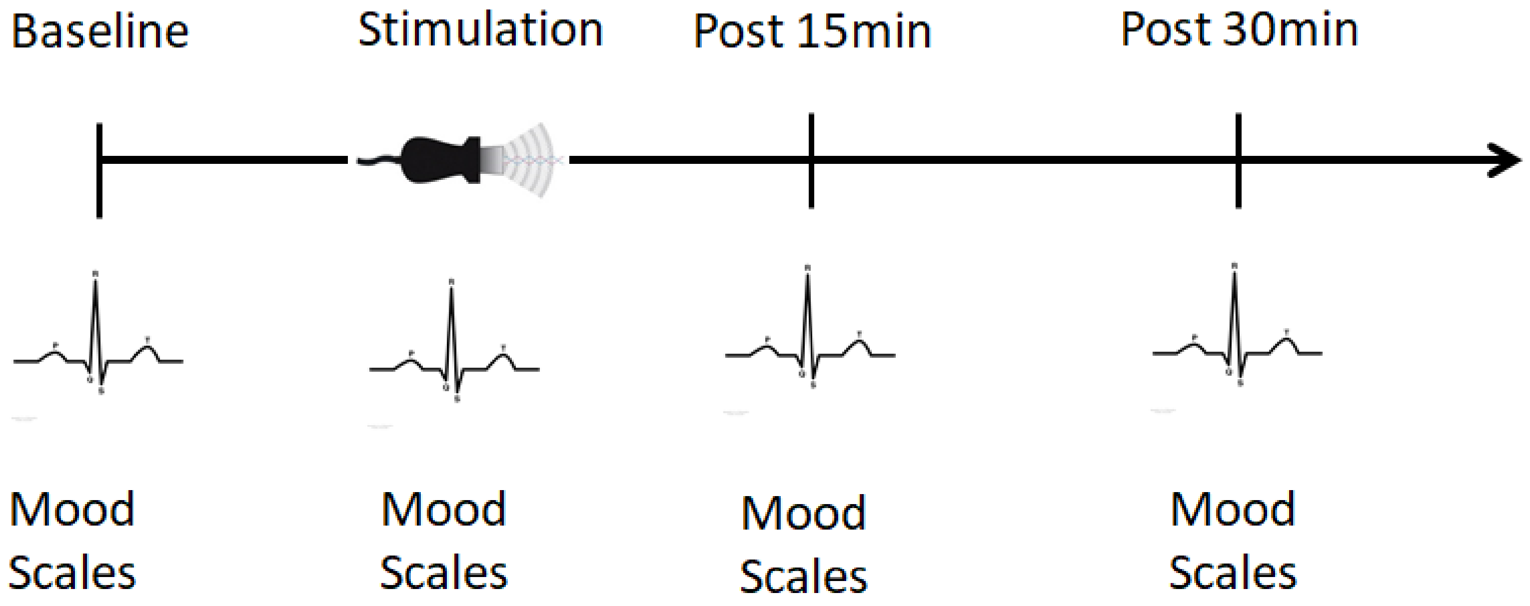


Legon et al., 2018

Experiment Outline

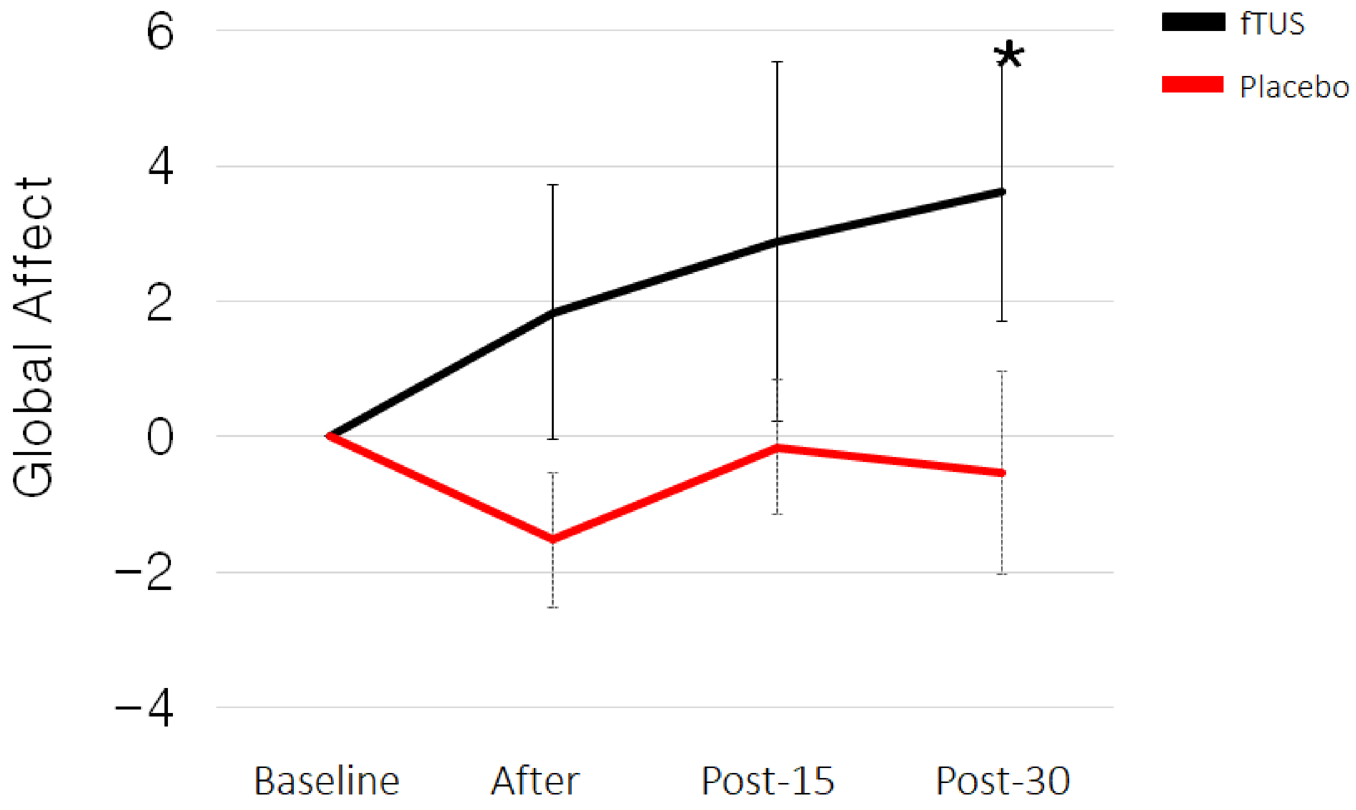
rIFG

- Response inhibition
- Regulation of negative emotions/mood



n = 56

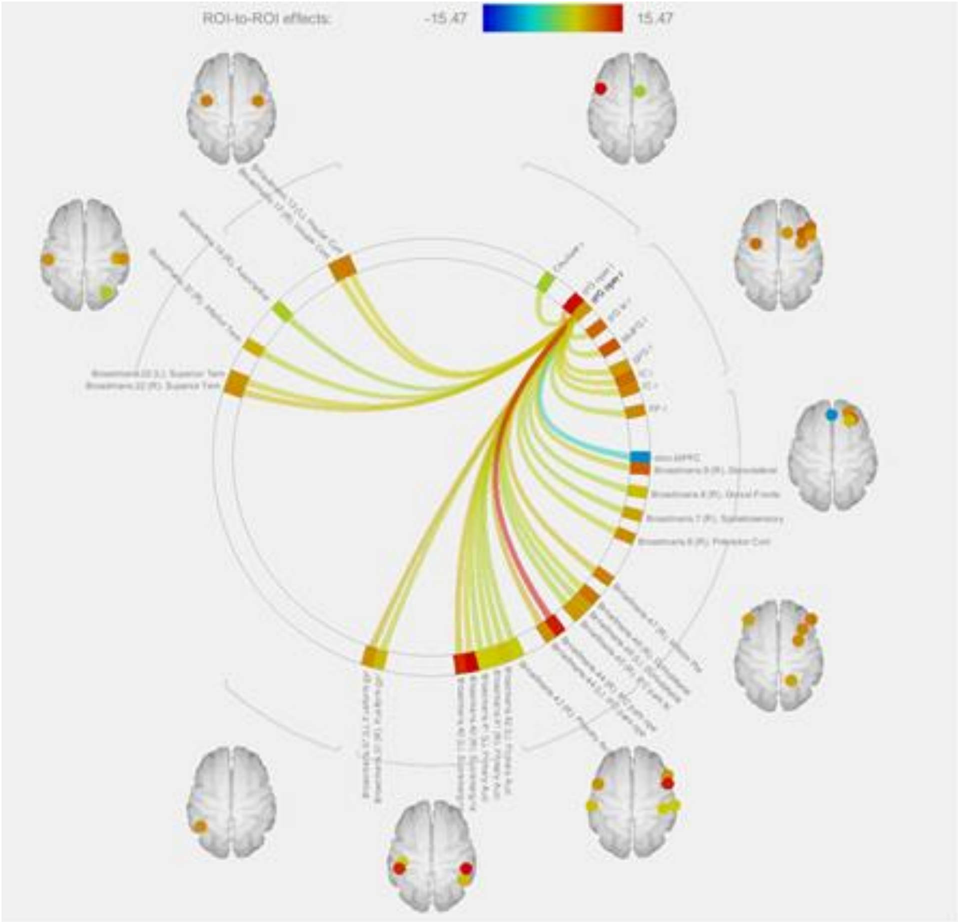
.5 kHz side vs Placebo rIFG



Sanguinett, et al., 2020

rIFG TUS enhanced mood

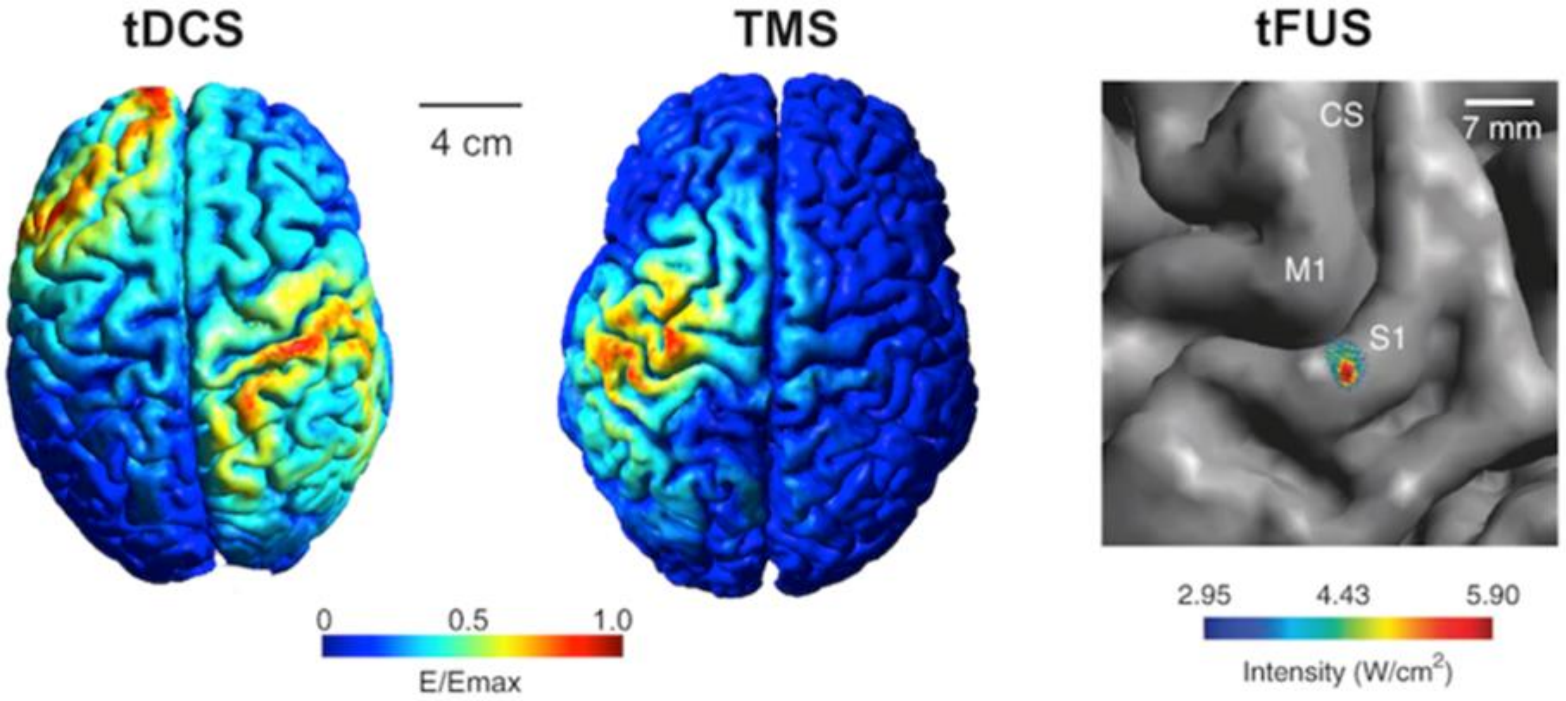
Suggests right prefrontal cortex is involved in mood regulation



Pre TUS

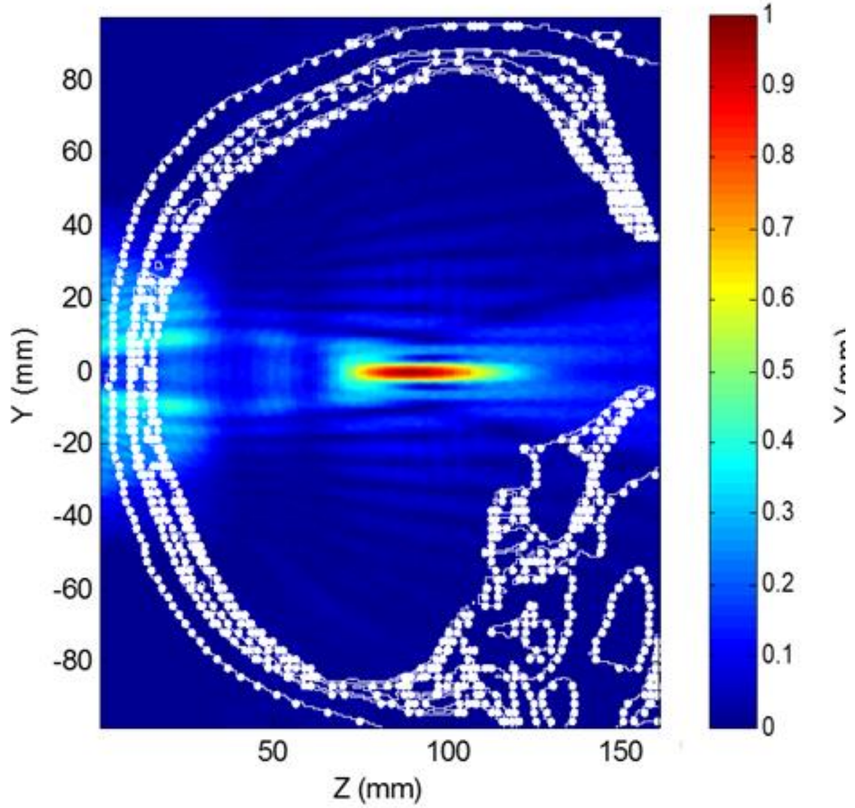
Sanguinetti, et al., 2020

COMPARING METHODS



Tyler lab

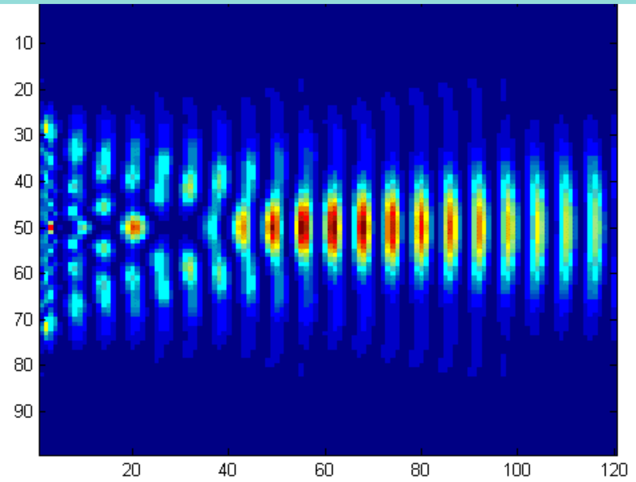
HOMOGENEOUS BEAM

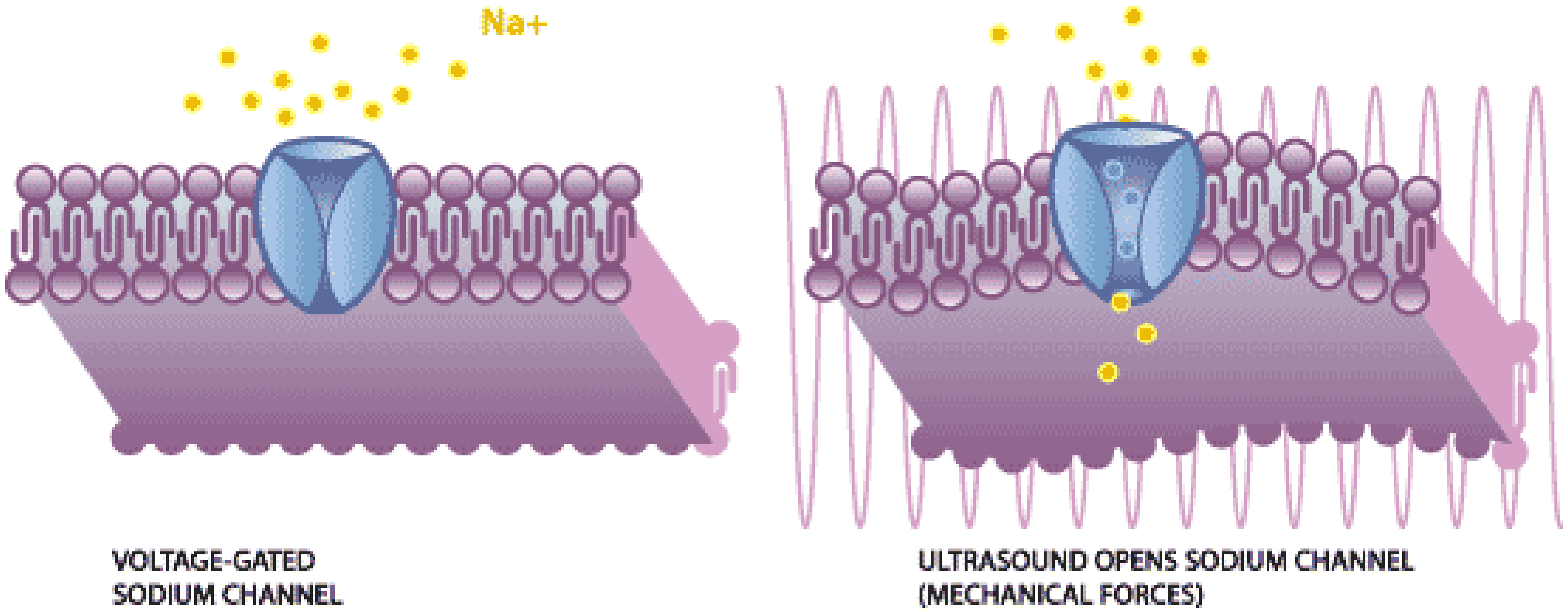


Vyas, Kaye, Pauly, 2012

US Waves propagate through bone and tissue

Mechanical perturbations → tiny disturbances of the mediums particles

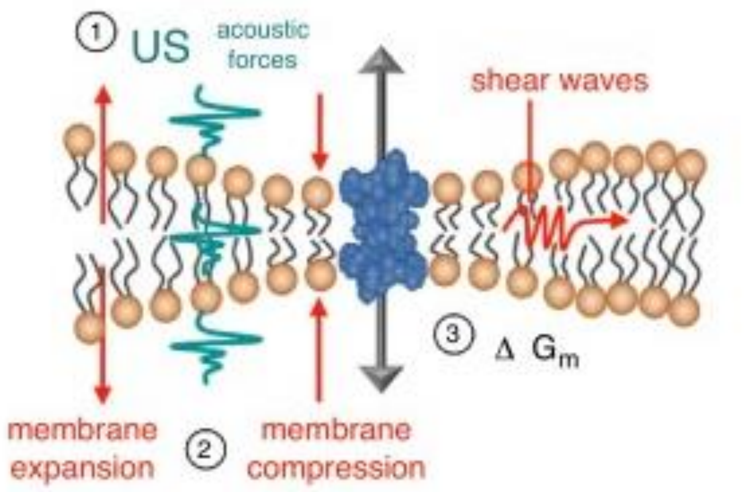




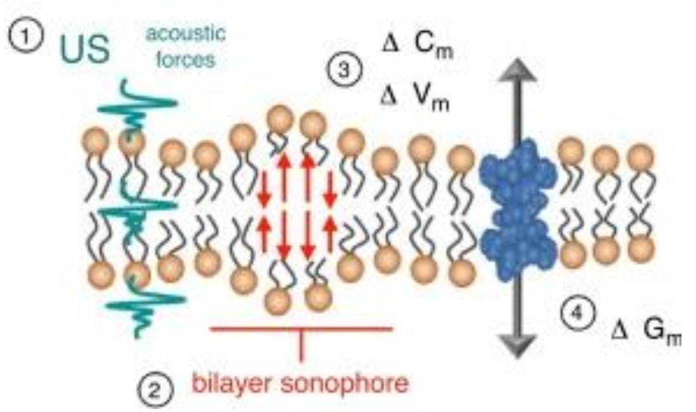
Tyler, 2011, *The Neuroscientist*

Potential mechanisms

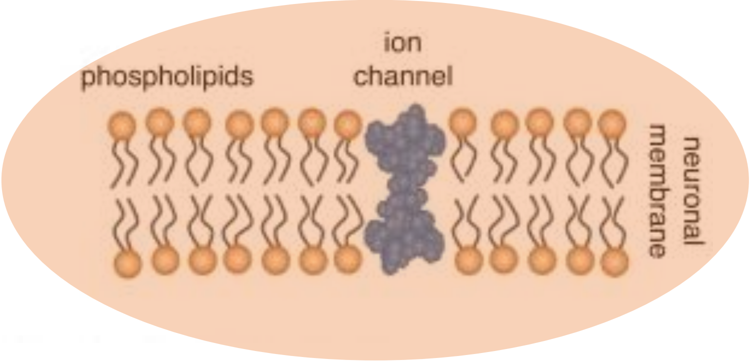
1. Radiation Force



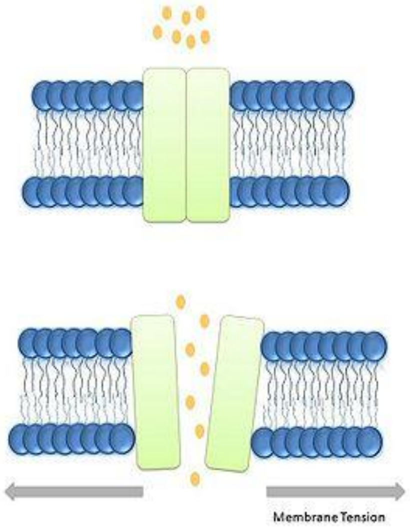
2. Cavitation



3. Heat



Biophysical mechanisms



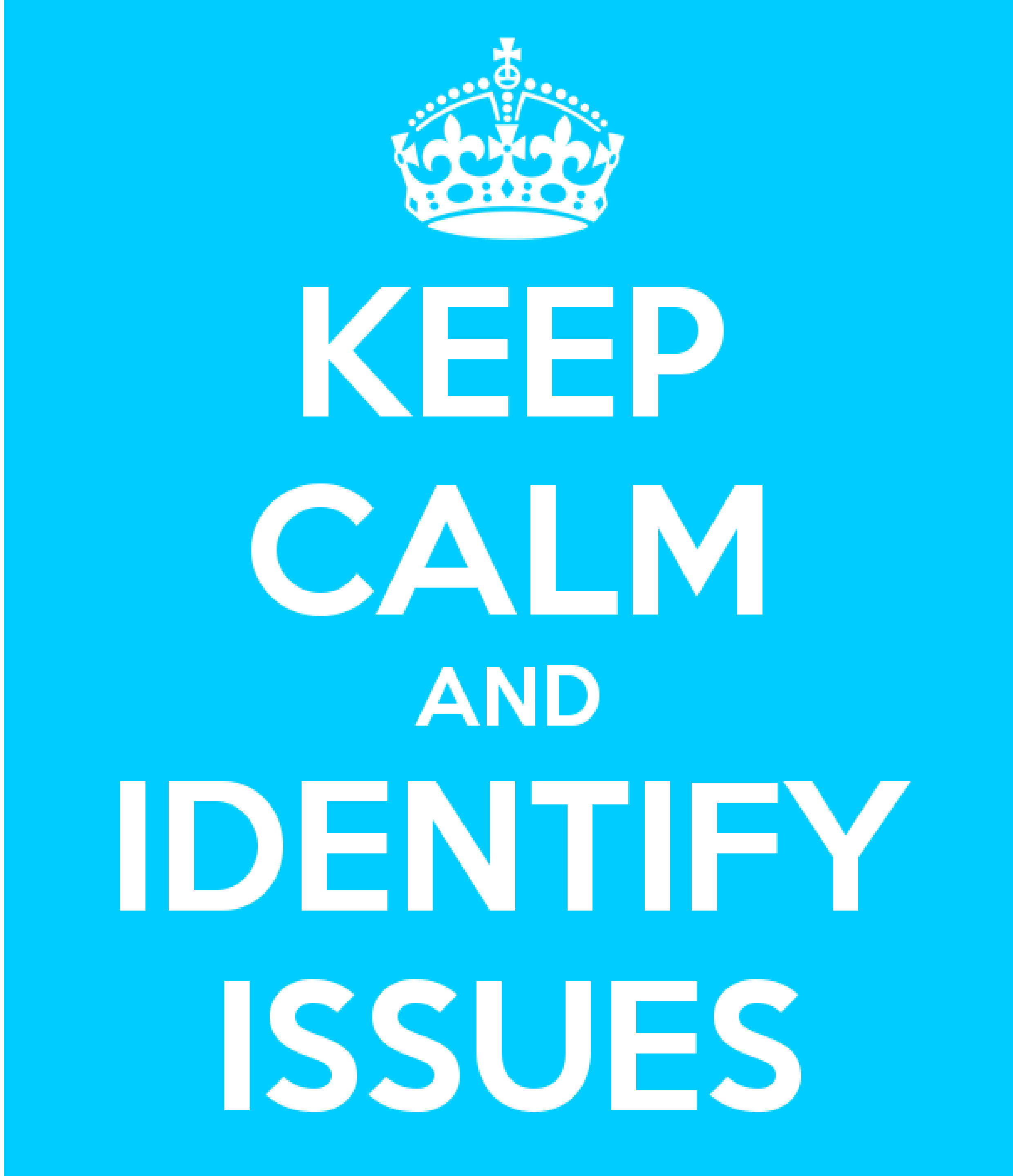
Stretch sensitive ion channels

(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

Be skeptical about:

Focality until aberration is solved

Sham control

Claims about mechanism


Thanks!
Questions?