Neurostimulation & Neuromodulation

Introduction to Transcranial Magnetic Stimulation

Ying-hui Chou

Director of Brain Imaging and TMS Laboratory

Psychology, BIO5 Institute, Center on Aging

University of Arizona, McKnight Brain Institute

1. How does TMS work?
2. What is single-pulse TMS? When do we use this paradigm?
3. What is repetitive TMS? How does frequency play a role in its effects?
4. How long do TMS effects last?
5. What are the clinical applications of TMS?
6. What is the potential mechanism of repetitive TMS effects?
7. Who can not be a subject of TMS studies?

What is Transcranial Magnetic Stimulation (TMS)?

A non-invasive brain stimulation technique

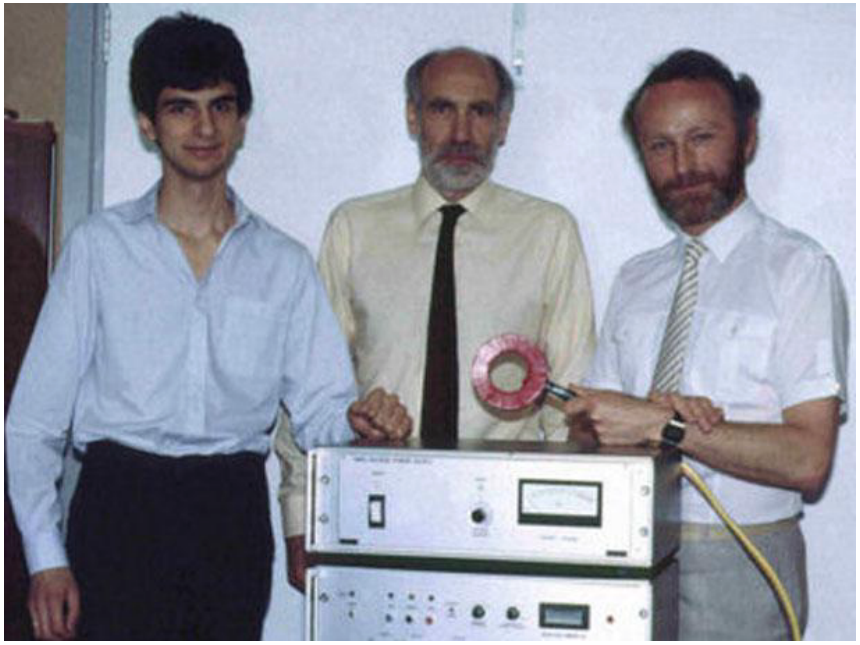
Does not require surgery, anesthesia, or sedation.

Photographer: J-M Mizell

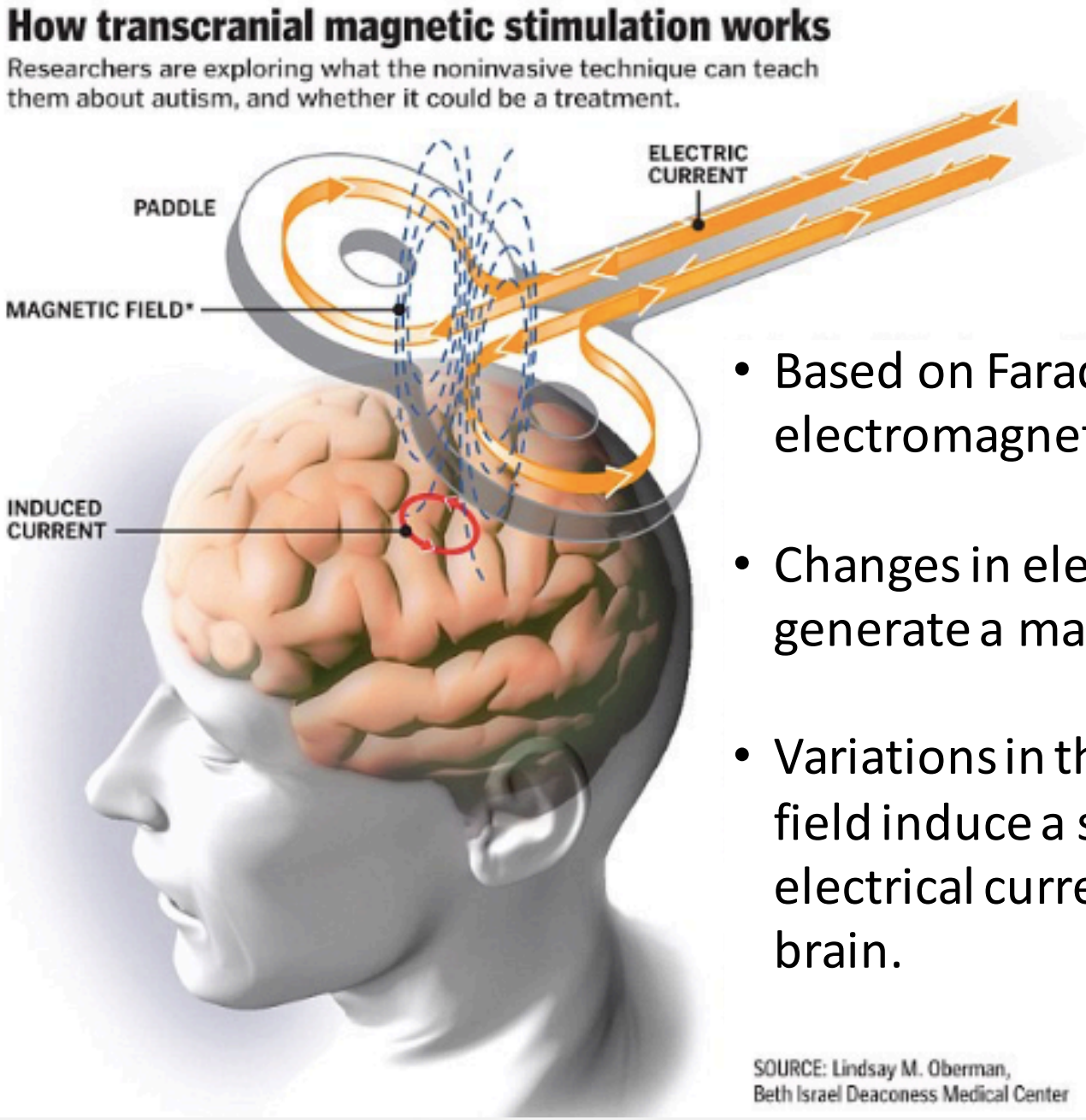
First TMS Machine (Barker et al., 1985)

NON-INVASIVE MAGNETIC STIMULATION OF HUMAN MOTOR CORTEX

SIR,—This note describes a novel method of directly stimulating the human motor cortex by a contactless and non-invasive technique using a pulsed magnetic field. Merton et al[1] have drawn attention to the electrical stimulation of human brain and spinal cord using external electrodes on the skin. Interesting results have been reported on the cortical threshold in Parkinson's disease,[2] on pyramidal conduction velocity in multiple sclerosis,[3] and on pelvic neuropathy related to faecal incontinence.[4]

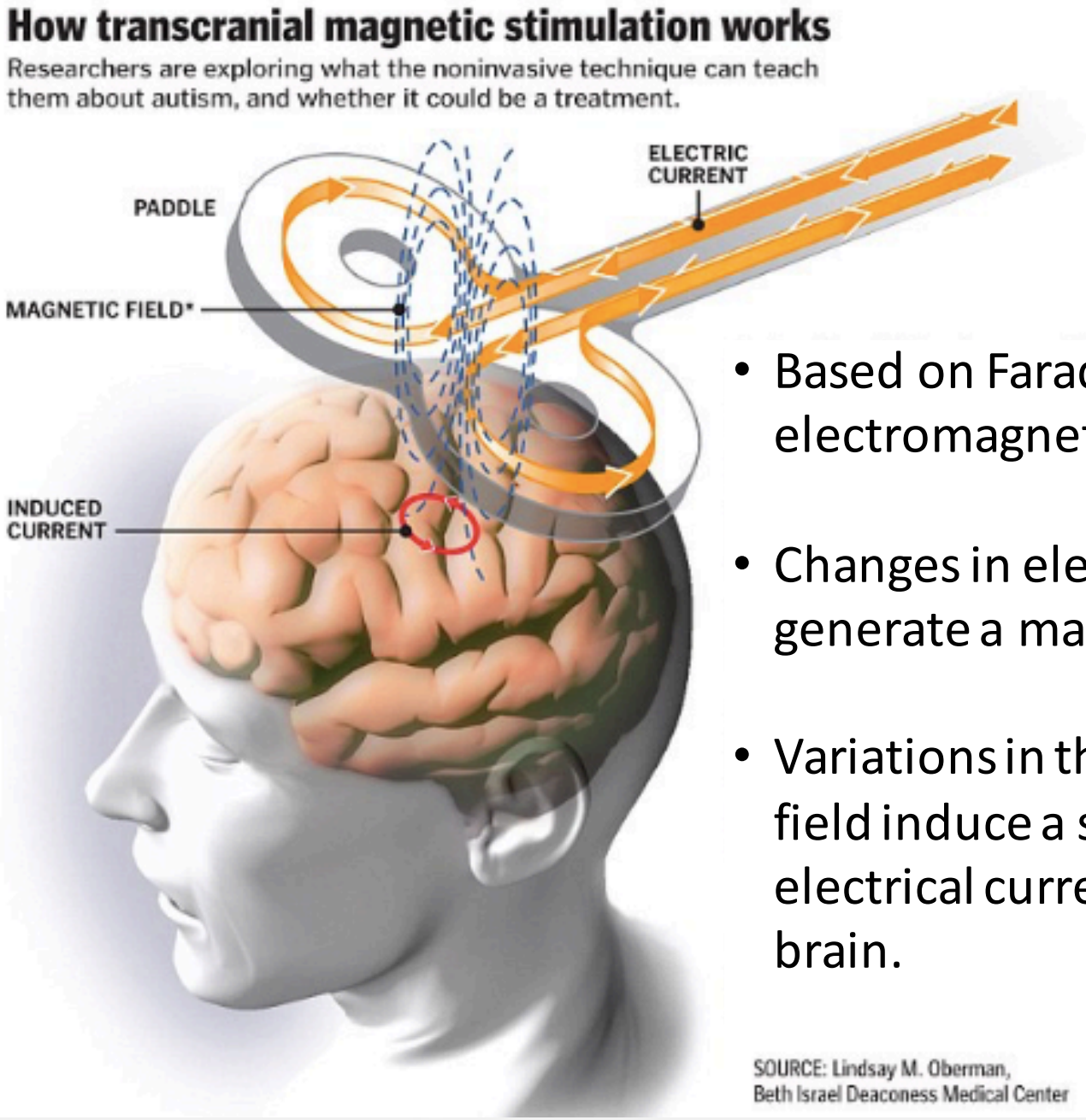


First Brain Stimulation Award (2017)



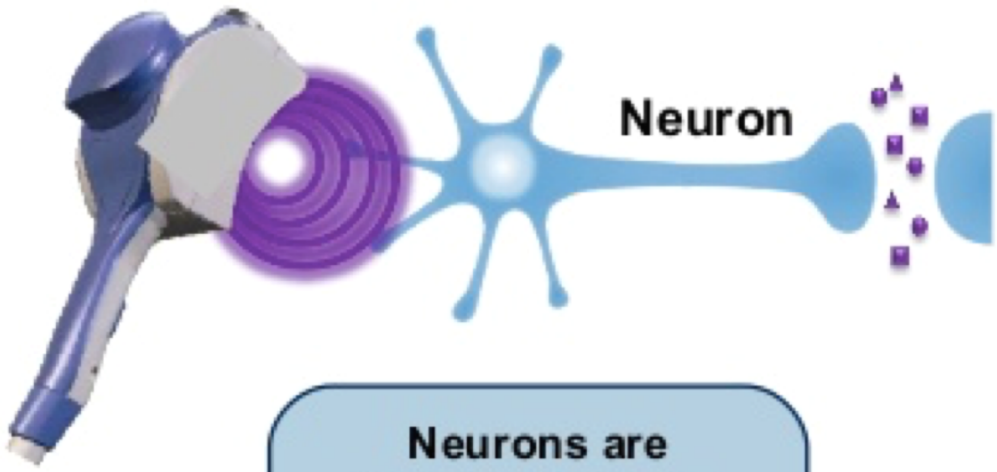
- Based on Faraday's electromagnetic induction
- Changes in electric current generate a magnetic field.
- Variations in the magnetic field induce a secondary electrical current in the brain.

Faraday's Electromagnetic Induction (1831)



- Based on Faraday's electromagnetic induction
- Changes in electric current generate a magnetic field.
- Variations in the magnetic field induce a secondary electrical current in the brain.

TMS Directly Depolarizes Cortical Neurons



Neurons are "electrochemical cells" and respond to either electrical or chemical stimulation

Pulsed magnetic fields from TMS:

- induce a local electric current in the cortex which depolarizes neurons
- eliciting action potentials
- causing the release of chemical neurotransmitters

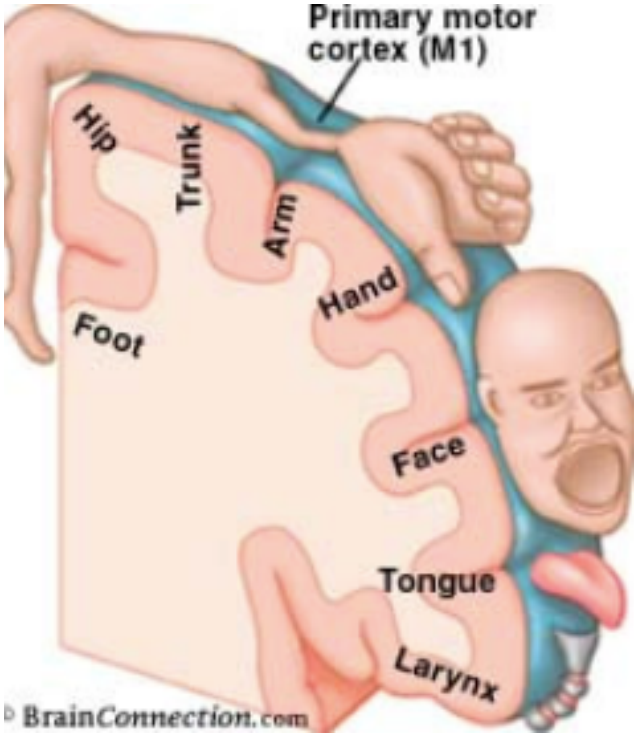
TMS Basics

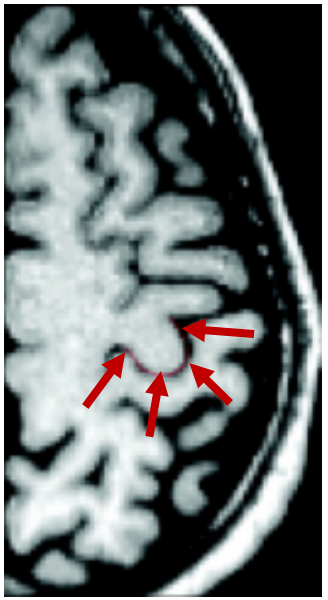
Time: 100-300 ms

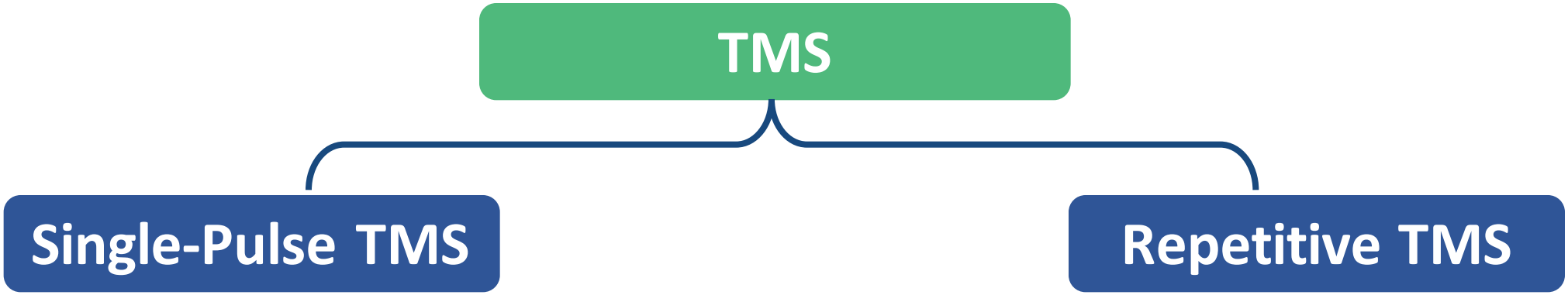
Depth: within 1 inch below surface

Temporal resolution: 100 Hz

Spatial resolution: < 0.5 x 0.5 inch^2





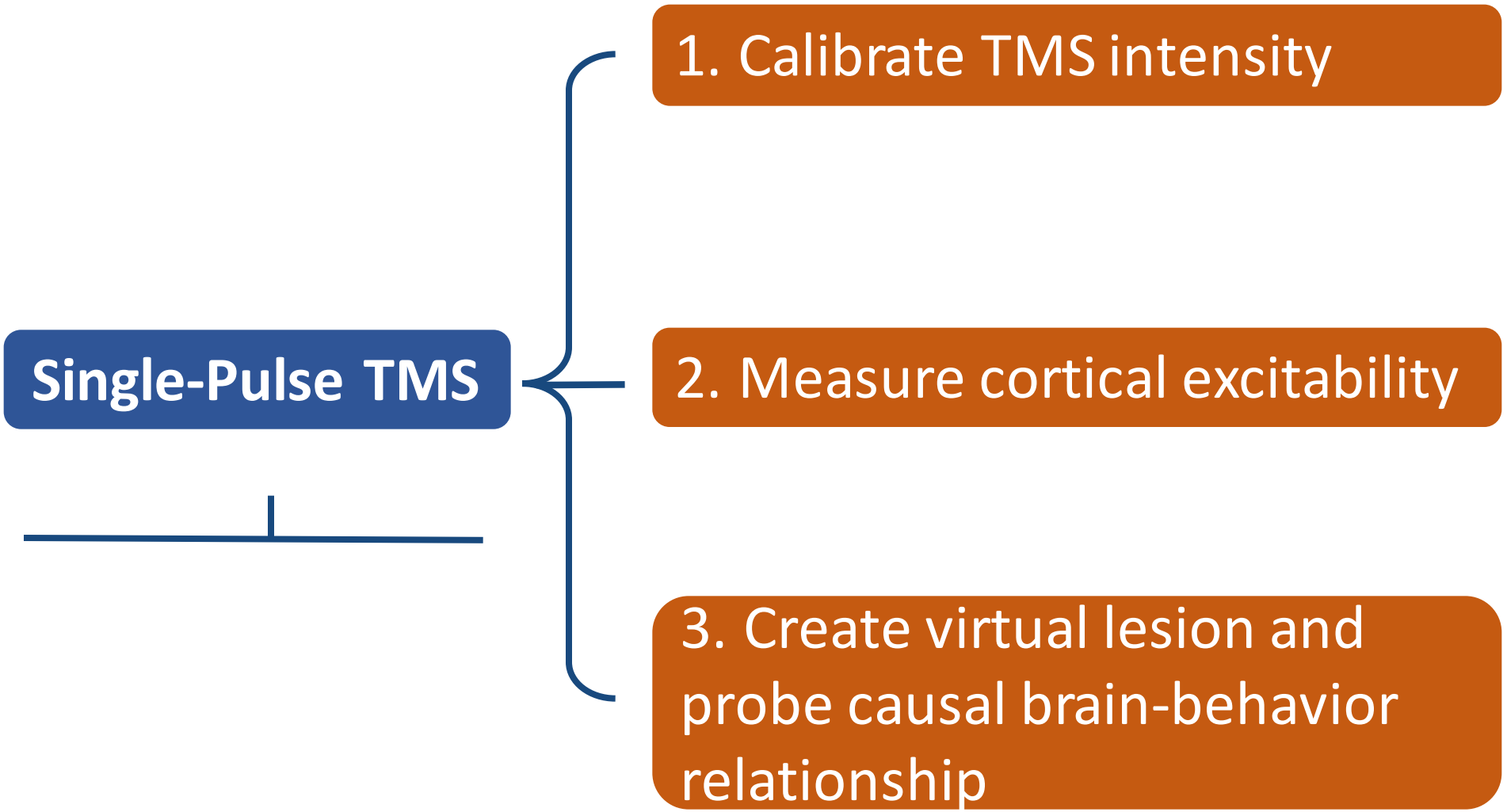

TMS
Single-Pulse TMS
Repetitive TMS

TMS

Single-Pulse TMS

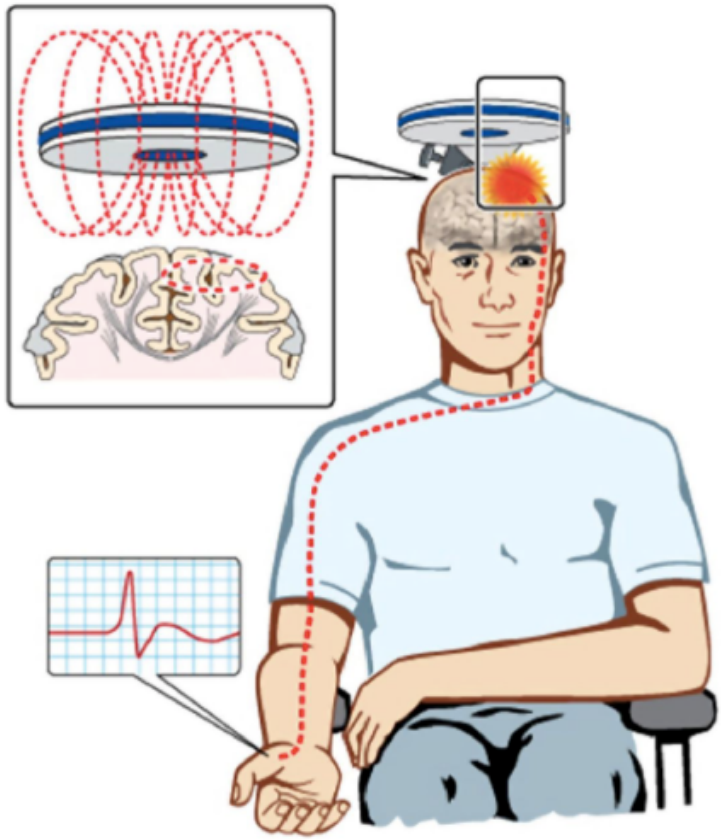
Repetitive TMS

- 0.1 Hz
- 1 Hz
- 5 Hz
- 10 Hz
- 20 Hz
- 50 Hz
- 100 Hz


Single-Pulse TMS
1. Calibrate TMS intensity
2. Measure cortical excitability
3. Create virtual lesion and probe causal brain-behavior relationship

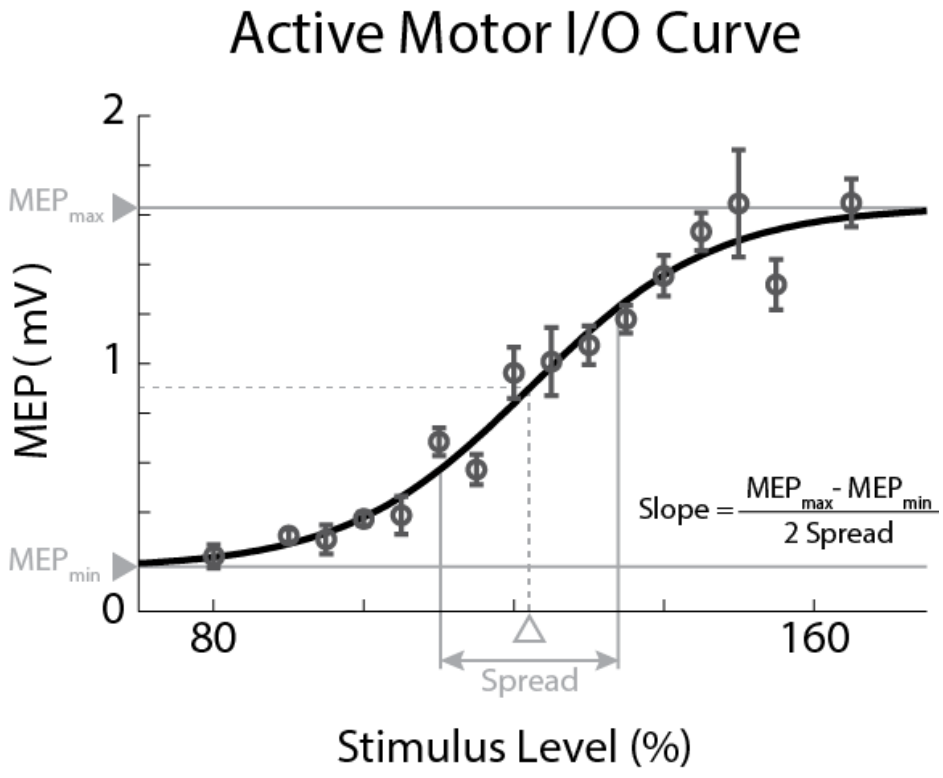
Single-Pulse TMS

1. Calibrate TMS intensity



Single-Pulse TMS

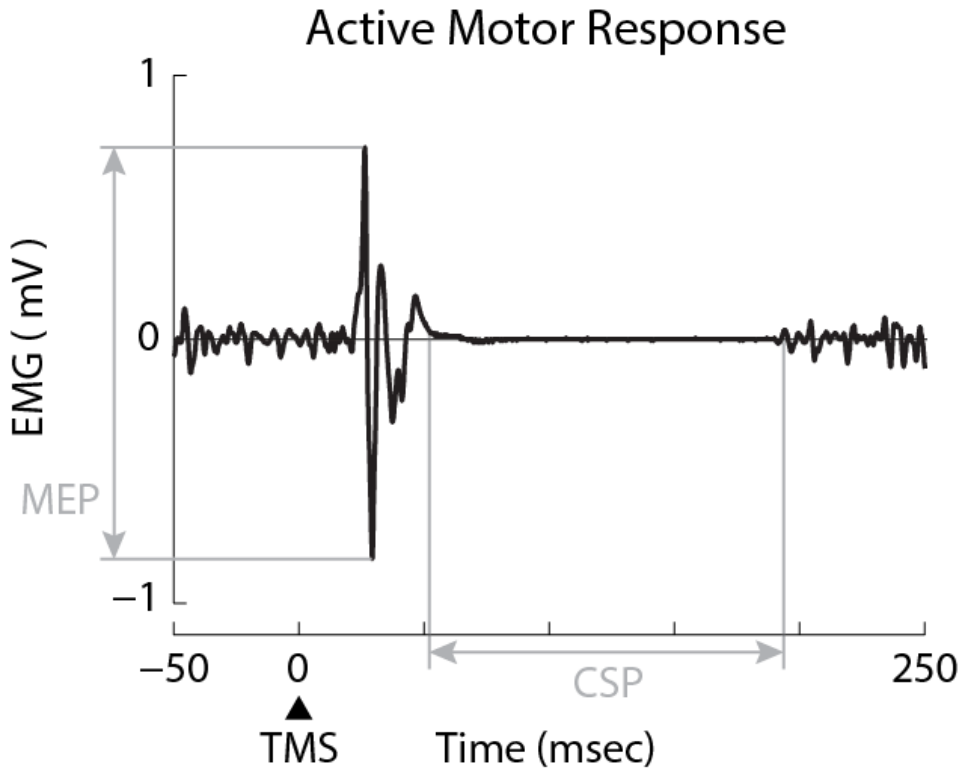
2. Measure cortical excitability



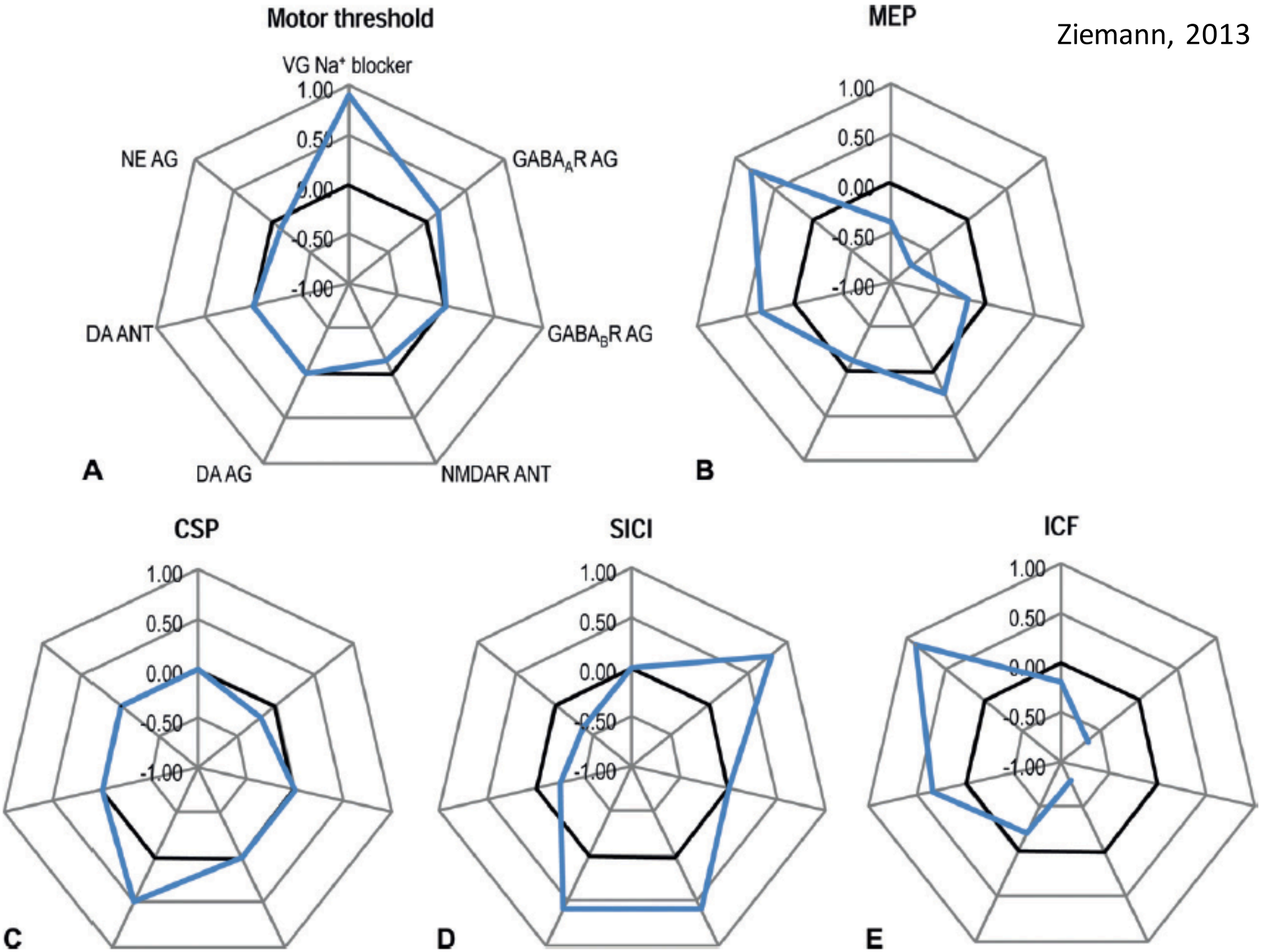
Lim, Sundman & Chou, manuscript under revision

Single-Pulse TMS

2. Measure cortical excitability



Lim, Sundman & Chou, manuscript under revision

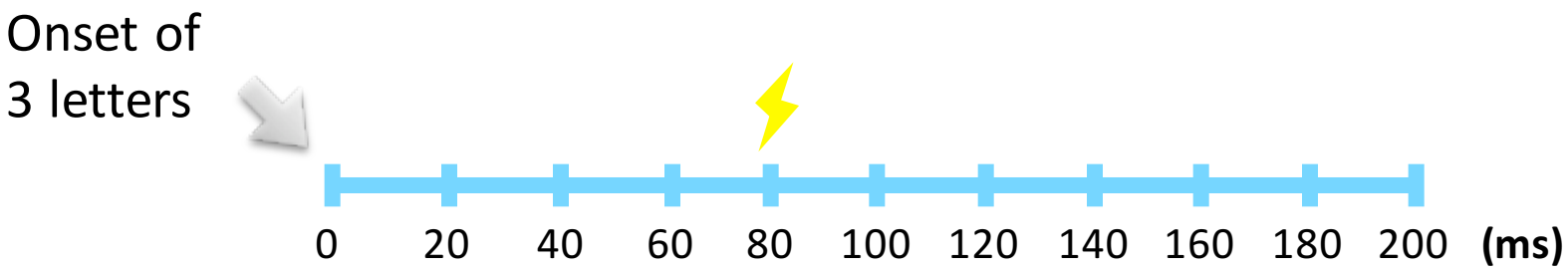


Ziemann, 2013

Single-Pulse TMS

3. Create virtual lesion and probe causal brain-behavior relationship

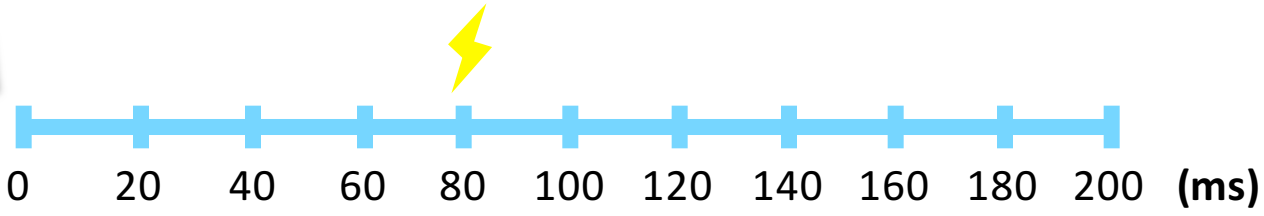
Virtual lesion – a transient disruption of the functioning of a given cortical region

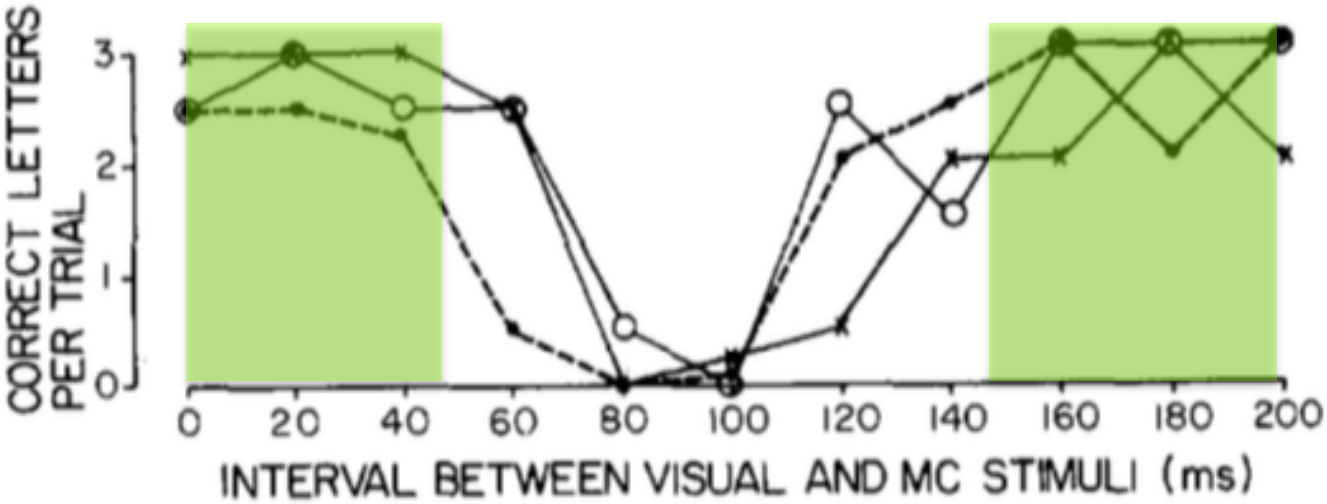


Participants were instructed to report 3 briefly presented, randomly generated letters (e.g., APD).

Amassian et al. 1989

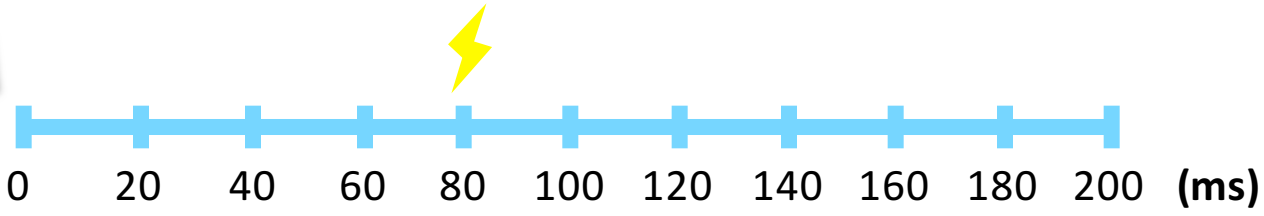
Onset of
3 letters

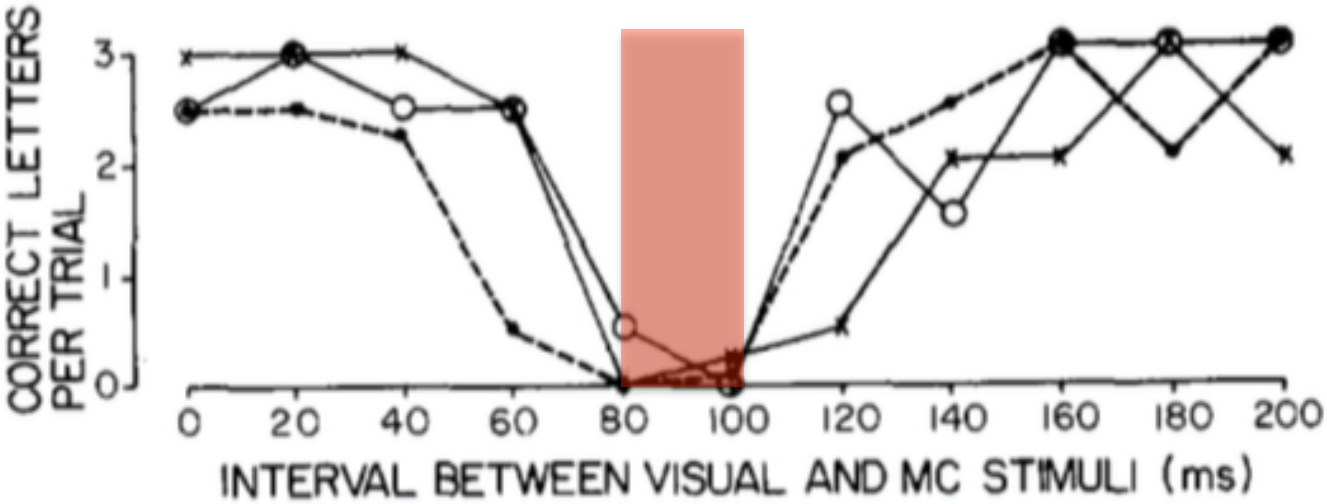




Amassian et al. 1989

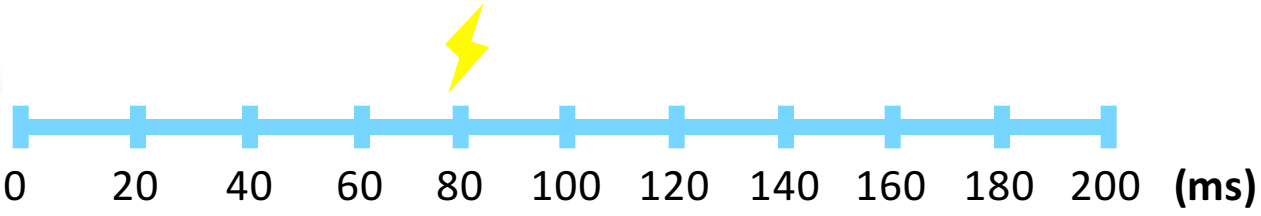
Onset of
3 letters

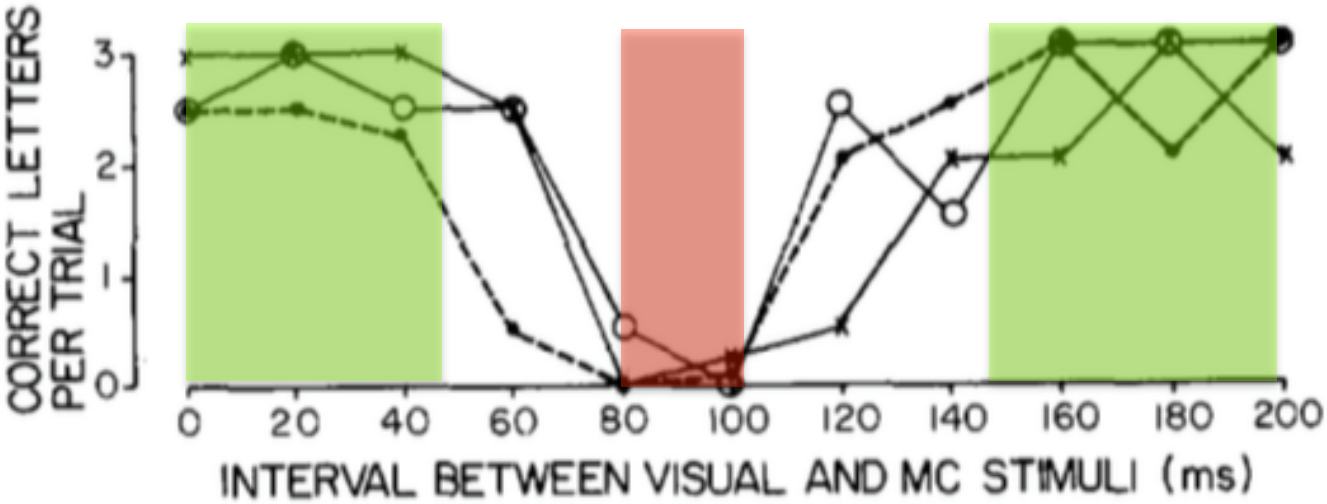




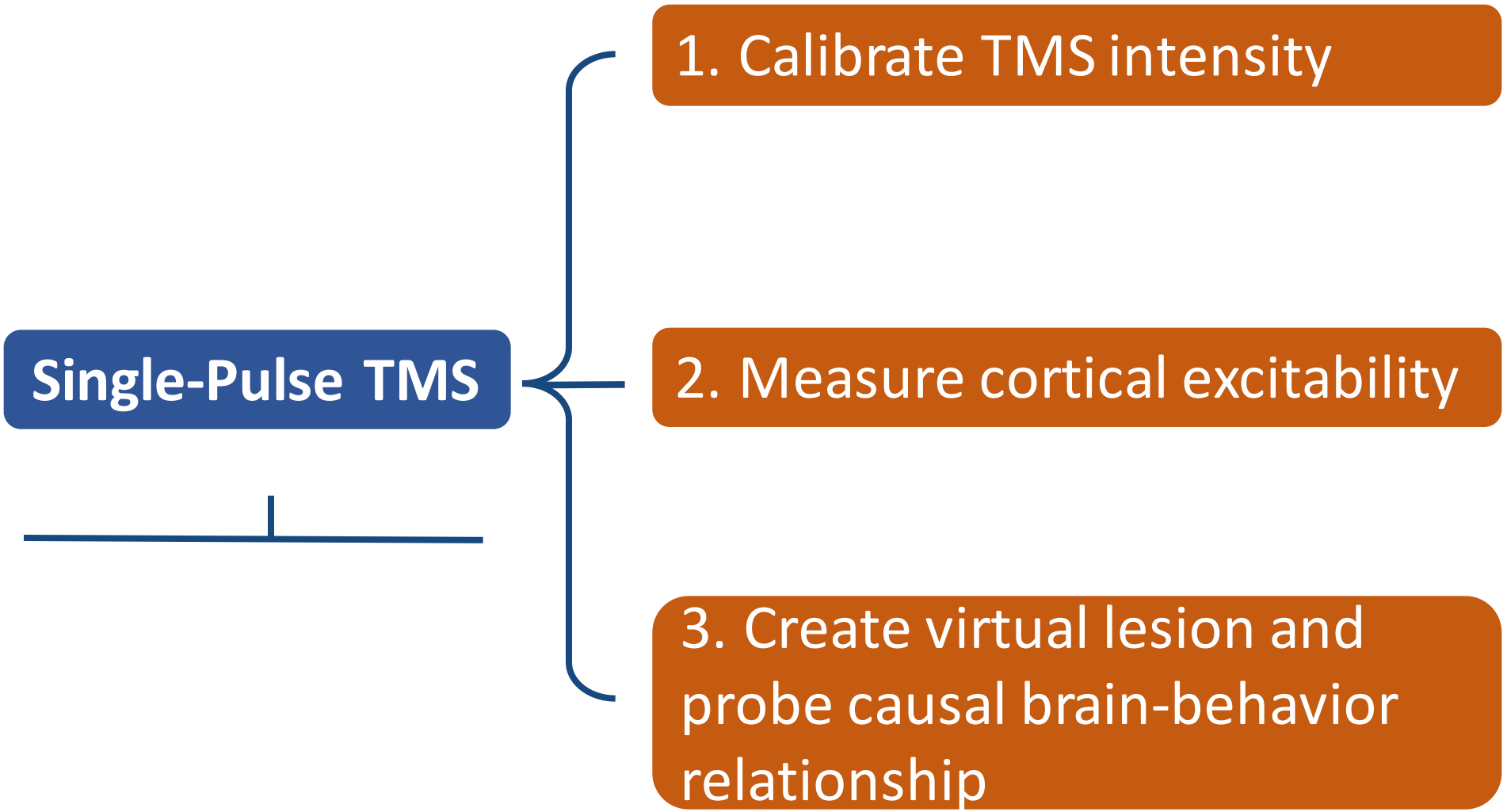
Amassian et al. 1989

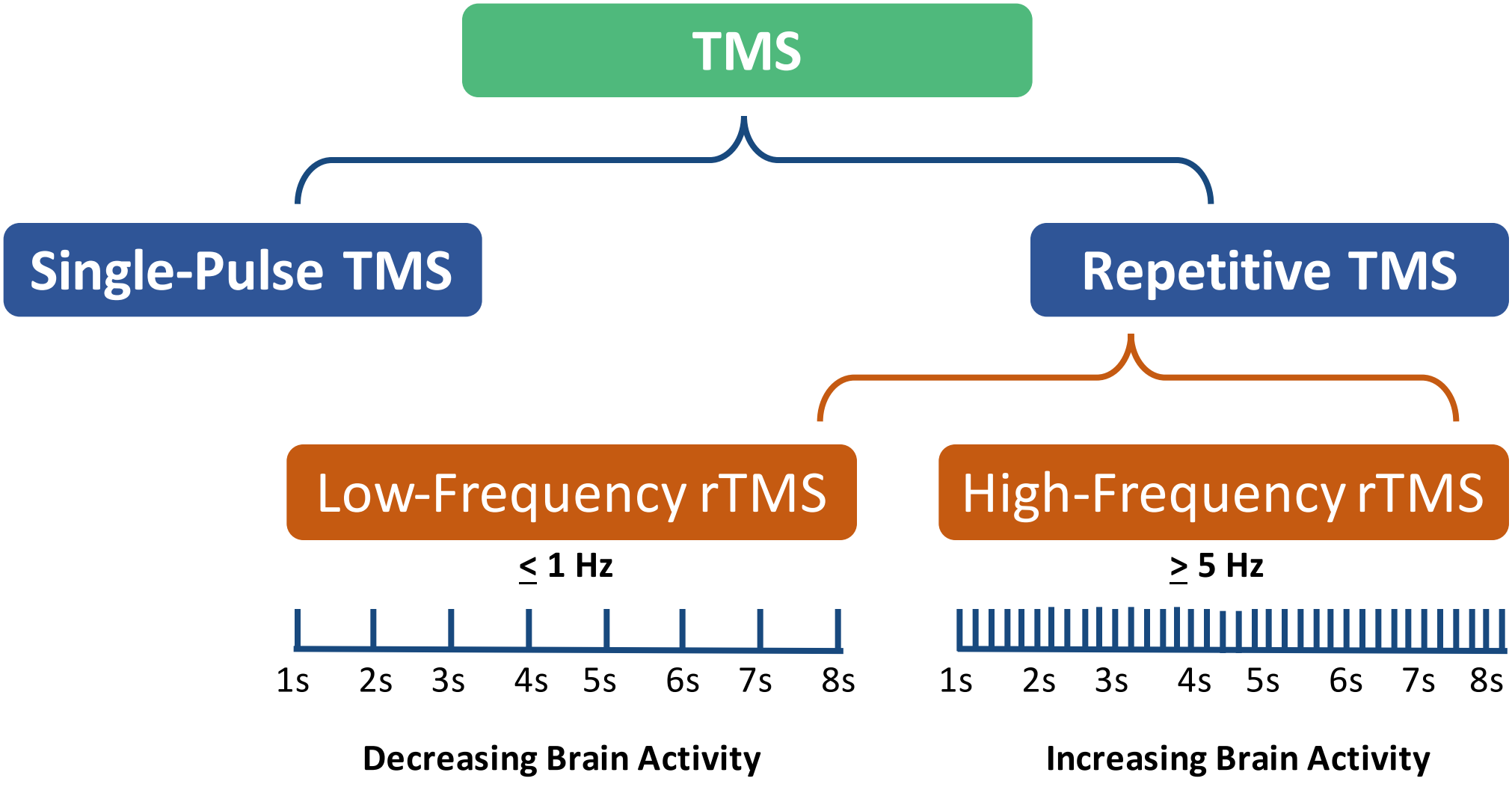
Onset of
3 letters

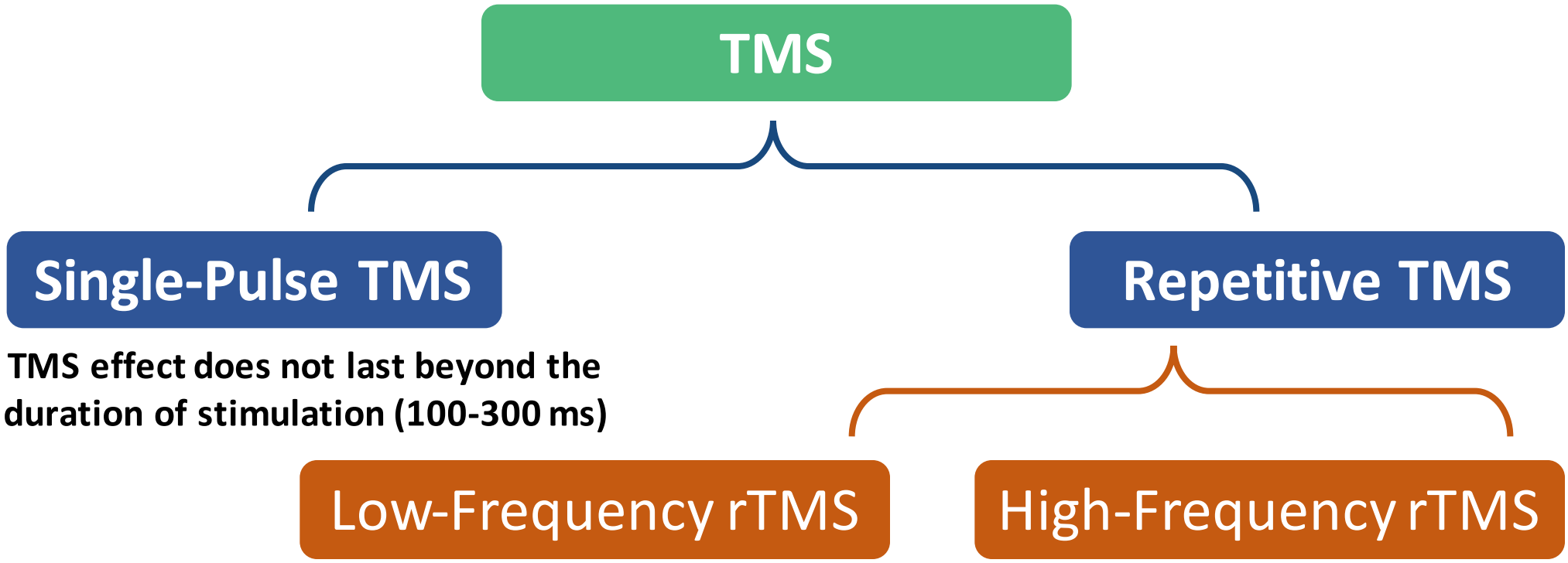




Amassian et al. 1989

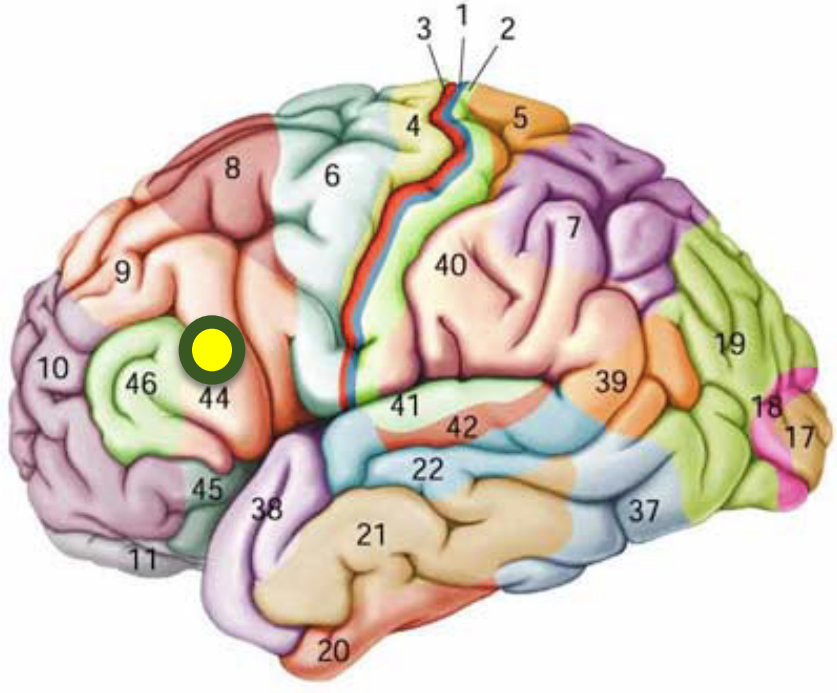

Single-Pulse TMS
1. Calibrate TMS intensity
2. Measure cortical excitability
3. Create virtual lesion and probe causal brain-behavior relationship


TMS
Single-Pulse TMS
Repetitive TMS
Low-Frequency rTMS
≤ 1 Hz
1s 2s 3s 4s 5s 6s 7s 8s
Decreasing Brain Activity
High-Frequency rTMS
≥ 5 Hz
1s 2s 3s 4s 5s 6s 7s 8s
Increasing Brain Activity


TMS
Single-Pulse TMS
Repetitive TMS
TMS effect does not last beyond the duration of stimulation (100-300 ms)
Low-Frequency rTMS
High-Frequency rTMS
Effect of 1 session of repetitive TMS lasts up to 60 minutes
Effect of multiple sessions of repetitive TMS lasts up to 3 months

Repetitive TMS for Depression

In 2008, FDA approved the first device using rTMS as a treatment for major depression for patients who do not respond to at least one antidepressant medication in the current episode.



Single-Pulse TMS for Migraine

In 2013, FDA approved the first device using single-pulse TMS as a treatment for migraine with aura.

Repetitive TMS for Obsessive-Compulsive Disorder

In 2018, FDA permitted marketing of the first device using Deep TMS as a treatment for obsessive-compulsive disorder.

Original Investigation

Effects of Repetitive Transcranial Magnetic Stimulation on Motor Symptoms in Parkinson Disease
A Systematic Review and Meta-analysis

Ying-hui Chou, ScD; Patrick T. Hickey, DO; Mark Sundman, BS; Allen W. Song, PhD; Nan-kuei Chen, PhD

IMPORTANCE Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique that has been closely examined as a possible treatment for Parkinson disease (PD). However, results evaluating the effectiveness of rTMS in PD are mixed, mostly owing to low statistical power or variety in individual rTMS protocols.

OBJECTIVES To determine the rTMS effects on motor dysfunction in patients with PD and to examine potential factors that modulate the rTMS effects.

DATA SOURCES Databases searched included PubMed, EMBASE, Web of Knowledge, Scopus, and the Cochrane Library from inception to June 30, 2014.

STUDY SELECTION Eligible studies included sham-controlled, randomized clinical trials of rTMS intervention for motor dysfunction in patients with PD.

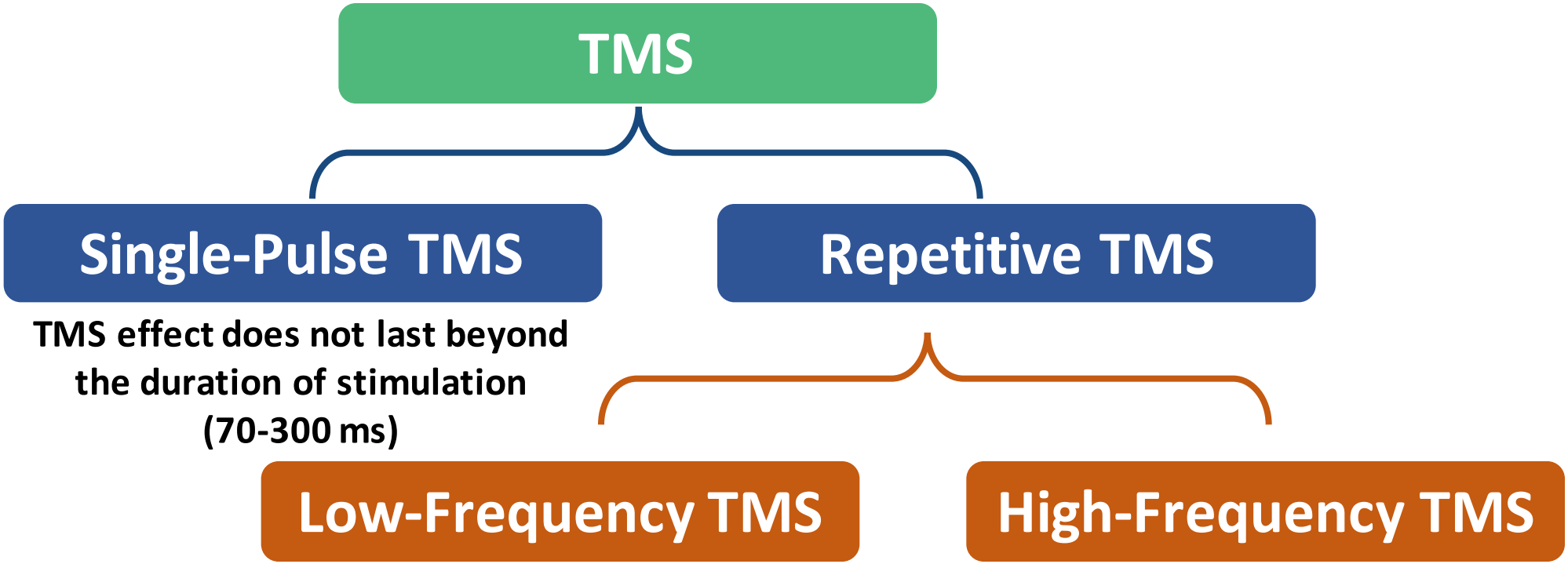
Supplemental content at jamaneurology.com

BRAIN CONNECTIVITY
Volume 5, Number 7, 2015

DOI: 10.1089/brain.2014.0325

Effect of Repetitive Transcranial Magnetic Stimulation on fMRI Resting-State Connectivity in Multiple System Atrophy

Ying-hui Chou,[1,2] Hui You,[3] Han Wang,[4] Yan-Ping Zhao,[3] Bo Hou,[3] Nan-kuei Chen,[1,5] and Feng Feng[3]



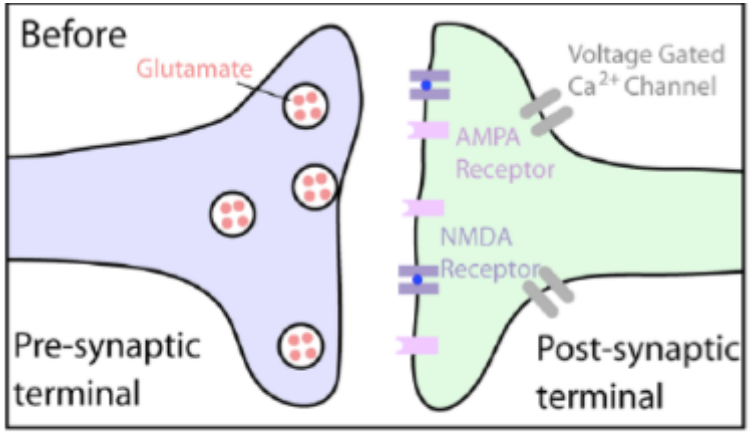
Effect of 1 session of repetitive TMS lasts up to 60 minutes

Effect of multiple sessions of repetitive TMS lasts up to 3 months

Mechanism Underlying the Plasticity Effects of rTMS

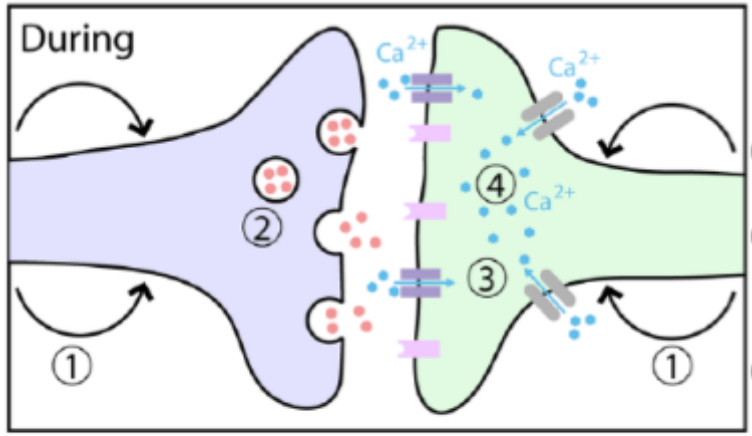
Changing effectiveness of synaptic interaction

(LTP-like and LTD-like plasticity)

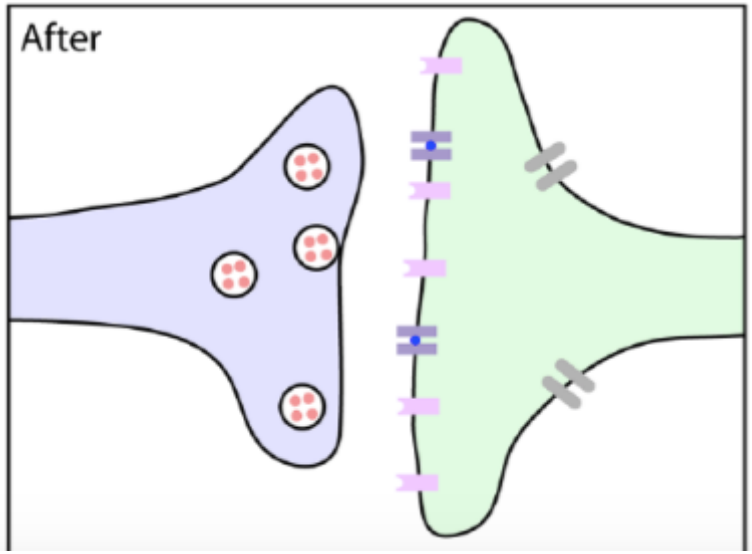


Pre-synaptic terminal: Glutamate neurotransmitter ready for release.

Post-synaptic terminal: Dendritic spine containing L-type voltage gated calcium channels, AMPA and NMDA receptors (glutamate receptors) are closed.



① rTMS induced membrane depolarisation induces simultaneous anterograde (pre-synaptic neuron) and backwards propogating action potentials (post-synaptic neuron).
② Glutamate neurotransmitter released from presynaptic terminal into synapse.
③ Removal of NMDA receptor magnesium block, activation of L-type voltage gated calcium channels.
④ Accumulation of post-synaptic calcium through opening of voltage gated calcium channels, AMPA and NMDA receptors.

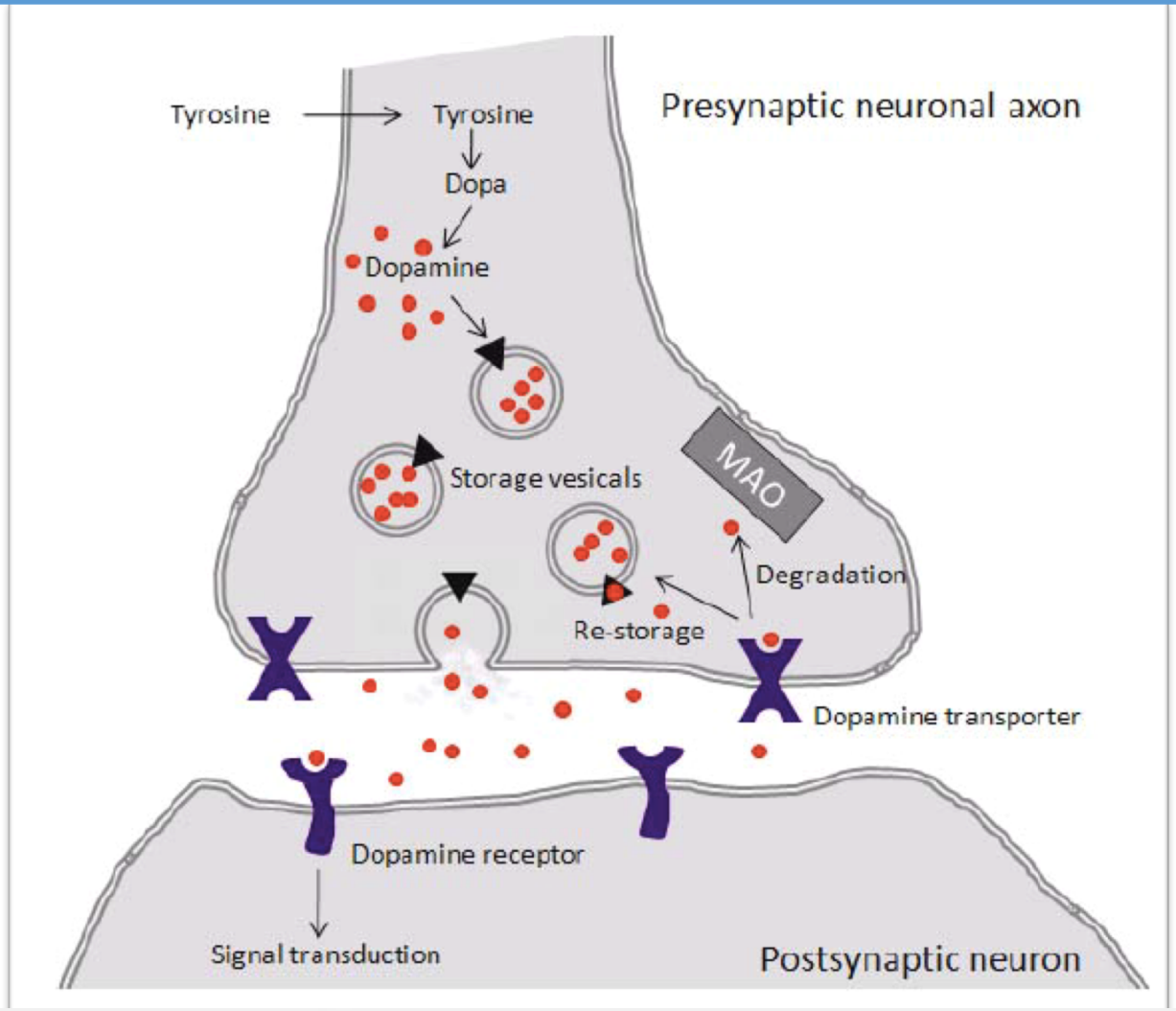


Transient enlagements of specific post-synaptic terminals ("small" spines) and the accumulation of AMPA receptors lead to LTP.

Tang et al., 2017

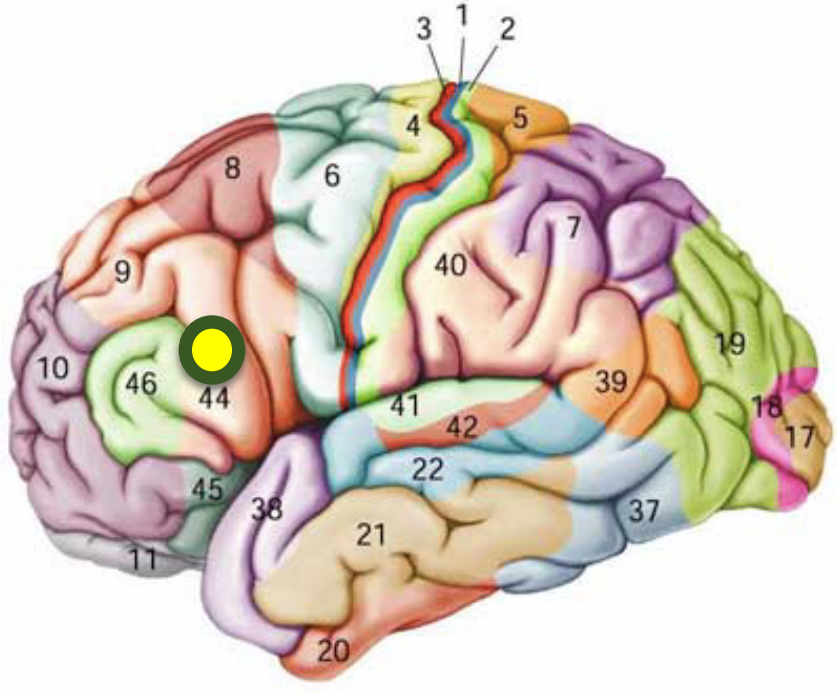
Single Photon Emission Computed Tomography (SPECT)

Striatal Dopamine Transporters (DaT) Scan – FDA Approval in 2011



2-Week Daily Sessions of 15 Hz rTMS at Left Dorsolateral Prefrontal Cortex

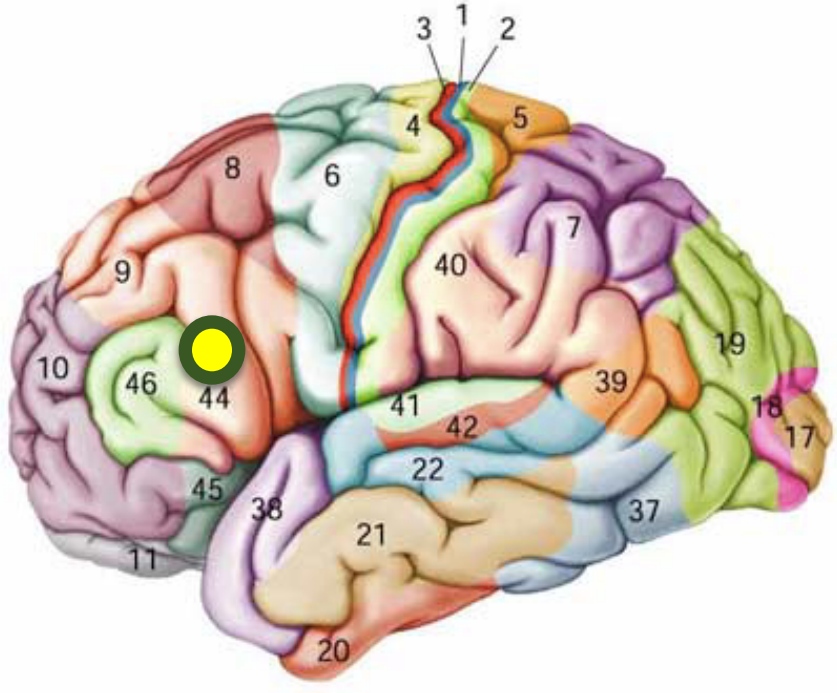
Striatal DaT Decreased in People with Gambling Addiction!



Pettorrusso et al., 2019

4-Week Daily Sessions of 10 Hz rTMS at Dorsolateral Prefrontal Cortex

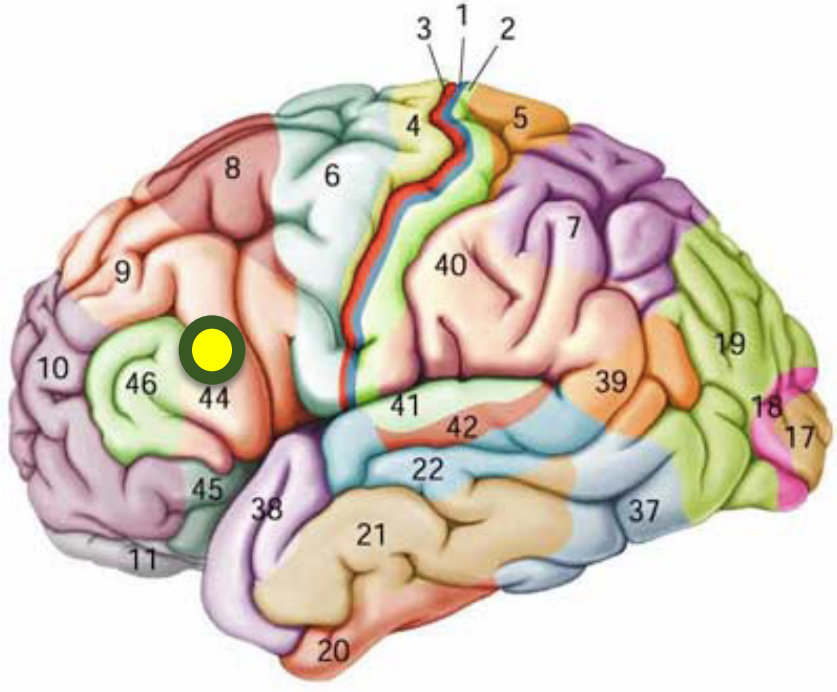
Striatal DaT Decreased in People with Alcohol Use Disorder!



Addolorato et al., 2017

3-Week Daily Sessions of 10 Hz rTMS at Left Dorsolateral Prefrontal Cortex

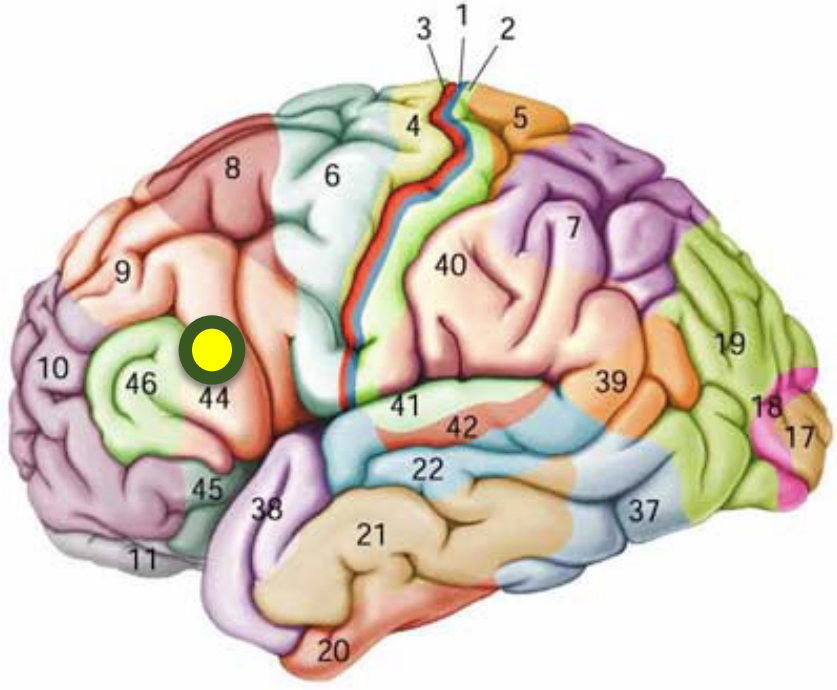
Striatal DaT Decreased in People with Depression!



Pogarell et al., 2006

1 Session of Inhibitory rTMS at Left Dorsolateral Prefrontal Cortex

Striatal Dopamine Increased in Healthy Adults!



Ko et al., 2008

TMS Safety Considerations

Possible side effects of TMS

- Transient headache or neck pain (<10% healthy people – 1% in our laboratory; 30% people with clinical disorders)
- Seizure (< 0.03%)

Contraindications to TMS

- Personal or family history of seizure
- Implanted cranial electrodes (heating)
- Cochlear implants (heating)
- Cerebral lesions (risk of seizure)
- Drug/Medication interactions
- Recent drug withdrawal
- Pregnancy
- Children
- Sleep deprivation

Table 2
Drugs with potential Hazards for rTMS

Strong potential hazard	Relative hazard
Alcohol	Ampicillin
Amitriptyline	Anticholinergics
Amphetamines	Antihistamines
Chlorpromazine	Aripiprazole
Clozapine	BCNU
Cocaine	Bupropion
Doxepine	Cephalosporins
Ecstasy	Chlorambucil
Foscarnet	Chloroquine
Gamma-hydroxybutyrate (GHB)	Citalopram
Ganciclovir	Cyclosporine
Imipramine	Cytosine arabinoside
Ketamine	Duloxetine
Maprotiline	Fluoxetine
MDMA	Fluphenazine
Nortriptyline	Fluvoxamine
Phencyclidine (PCP)	Haloperidol
Ritonavir	Imipenem
Theophylline	Isoniazid
	Levofloxacin
	Lithium
	Mefloquine
	Methotrexate
	Metronidazole
	Mianserin
	Mirtazapine
	Olanzapine
	Paroxetine
	Penicillin
	Pimozide
	Quetiapine
	Reboxetine
	Risperidone
	Sertraline
	Sympathomimetics
	Venlafaxine
	Vincristine
	Ziprasidone

Najib et al., 2014

TMS Safety Guidelines

Parameter safety issues: maximum recommended stimulation duration of single TMS trains (in seconds)

Freq (Hz)	90 % MT	100 % MT	110 % MT	120 % MT	130 % MT	140 % MT	150 % MT	160 % MT	170 % MT	180 % MT	190 % MT	200 % MT
1	>1,800	>1,800	>1,800	360	>50	>50	>50	>50	27	11	11	8
5	>10	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4
10	>5	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4
20	2.05	2.05	1.6	1.0	0.55	0.36	0.25	0.25	0.15	0.2	0.25	0.2
25	1.28	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12

Rossi et al., 2009

TMS Safety Guidelines

Adapted from Table 4 (Part A) and Table 3 (part B) of Chen et al., 1997, with permission from the authors. Safety recommendations for inter-train intervals for 10 trains at <20 Hz. The maximum duration of pulses for individual rTMS trains at each stimulus intensity should not exceed those listed in the Part B of the table. A consensus has been reached in adopting this table at this point. However, there is a need to extend these investigations and provide more detailed guidelines that may apply also to non-motor areas.

Inter-train interval (ms)	Stimulus intensity (% of MT)			
	100%	105%	110%	120%
Part A				
5000	Safe	Safe	Safe	Insufficient data
1000	Unsafe (EMG spread after 3 trains)	Unsafe[a]	Unsafe (EMG spread after 2 trains)	Unsafe (EMG spread after 2 trains)
250	Unsafe[a]	Unsafe[a]	Unsafe (EMG spread after 2 trains)	Unsafe (EMG spread after 3 trains)

Frequency (Hz)	100%		110%		120%		130%	
	Duration (s)/pulses		Duration (s)/pulses		Duration (s)/pulses		Duration (s)/pulses	
Part B								
1	>270	>270	>270	>270	>180	>180	50	50
5	10	50	10	50	10	50	10	50
10	5	50	5	50	3.2	32	2.2	22
20	1.5	30	1.2	24	0.8	16	0.4	8
25	1.0	25	0.7	17	0.3	7	0.2	5

[a] These stimulus parameters are considered unsafe because adverse events occurred with stimulation of lower intensity or longer inter-train interval, but no adverse effects were observed with these parameters.

Rossi et al., 2009

Thank you!

Ying-hui Chou
yinghuichou@email.arizona.edu
Brain Imaging and TMS Laboratory

1. How does TMS work?
2. What is single-pulse TMS? When do we use this paradigm?
3. What is repetitive TMS? How does frequency play a role in its effects?
4. How long do TMS effects last?
5. What are the clinical applications of TMS?
6. What is the potential mechanism of repetitive TMS effects?
7. Who can not be a subject of TMS studies?

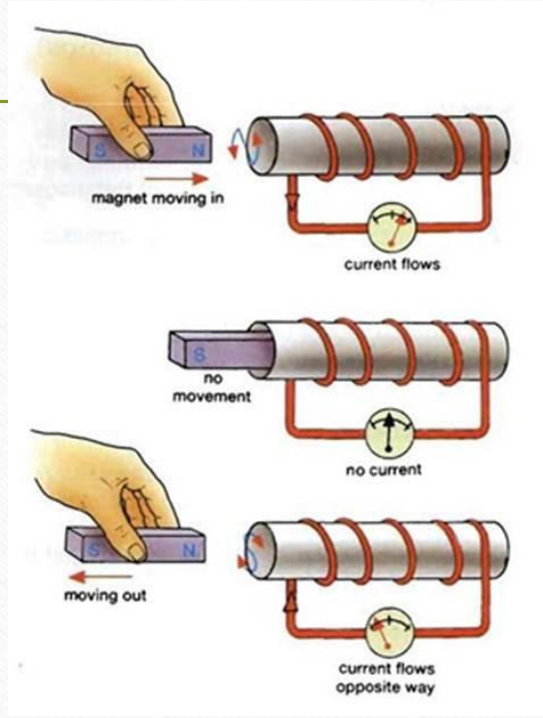
Transcranial Electrical Stimulation

501A

4-15-19

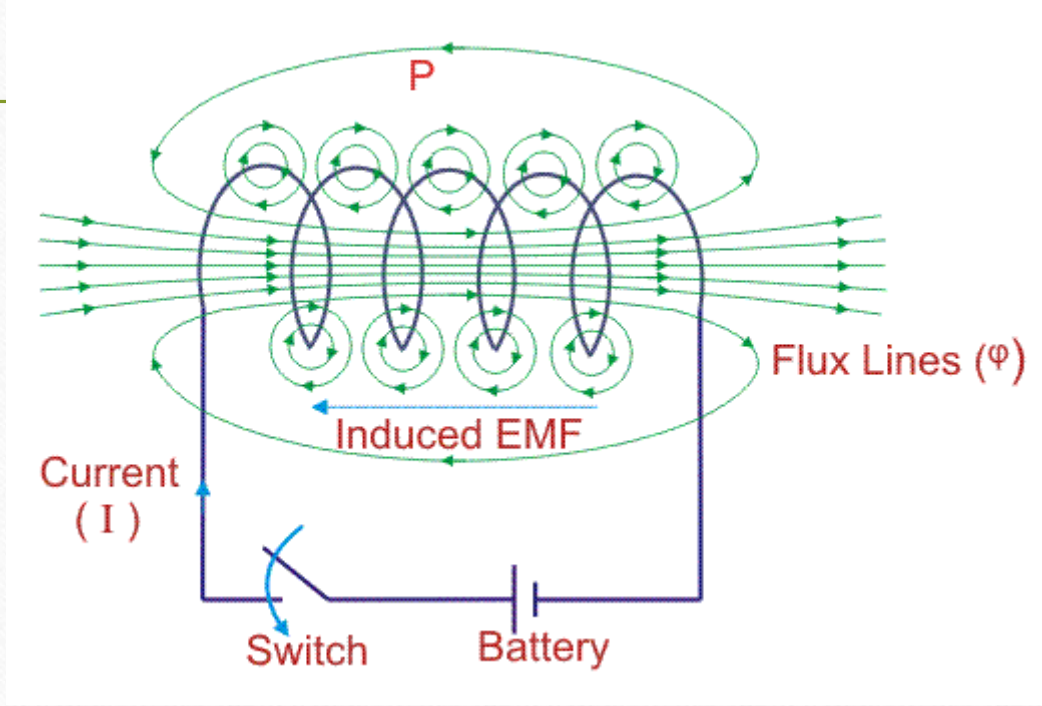
Background: basic electricity

Magnetic induction

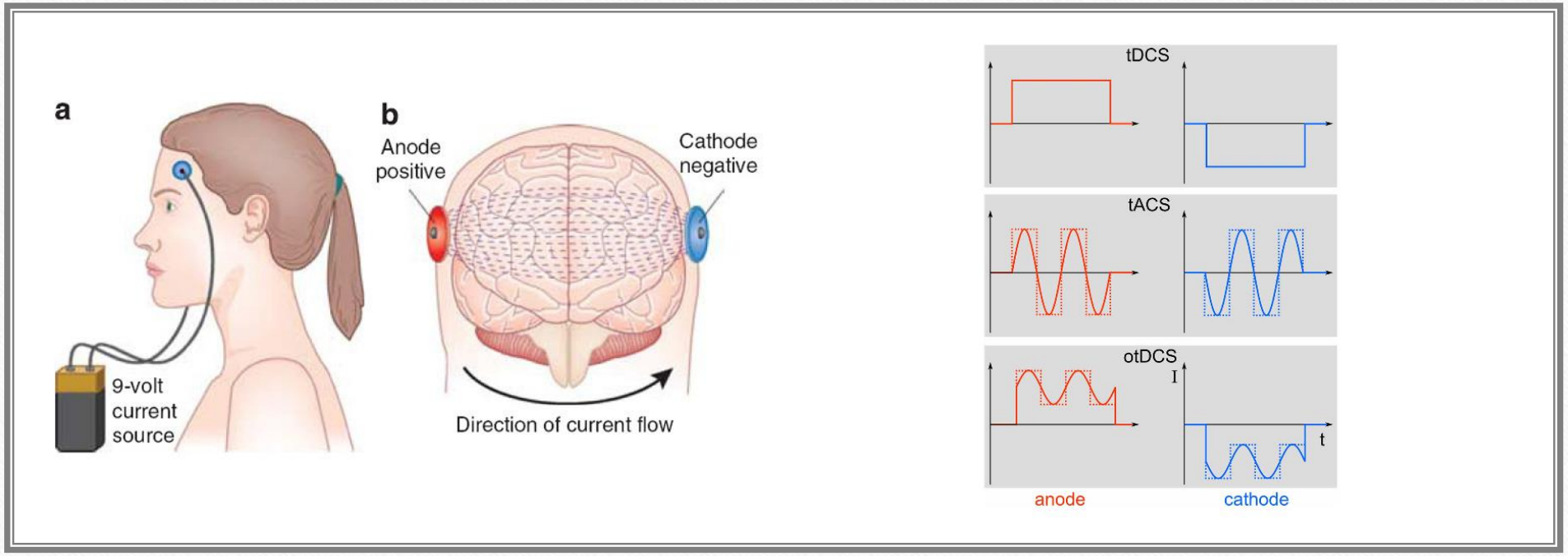


- Magnetic stimulation
  - pulsed magnetic field induces an electric current

Self induction



- Electrical stimulation
  - voltage-controlled current source induces an electric field



Transcranial Electrical Stimulation (TES)

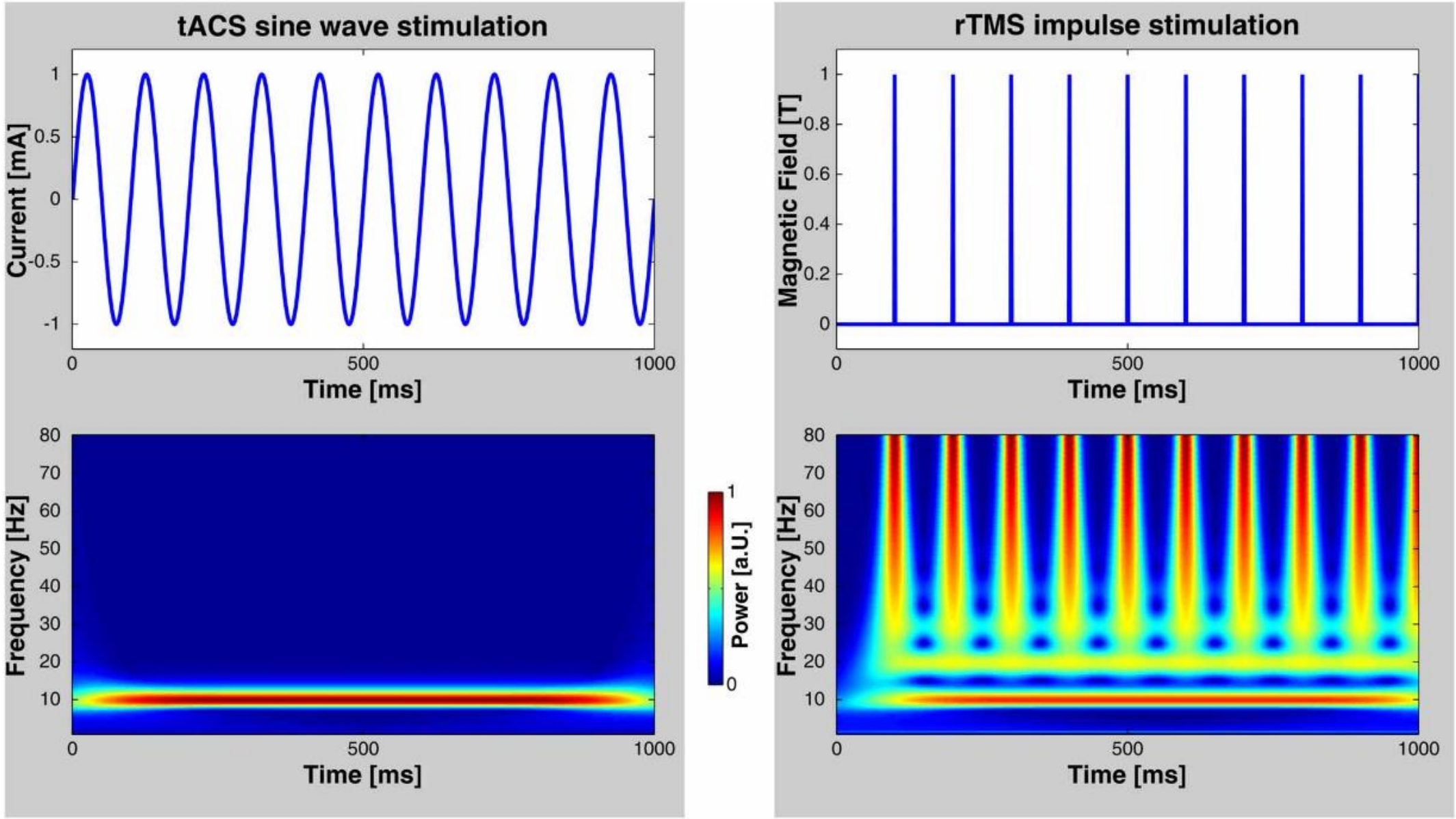
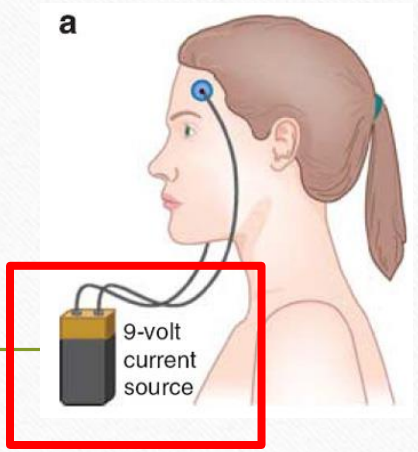
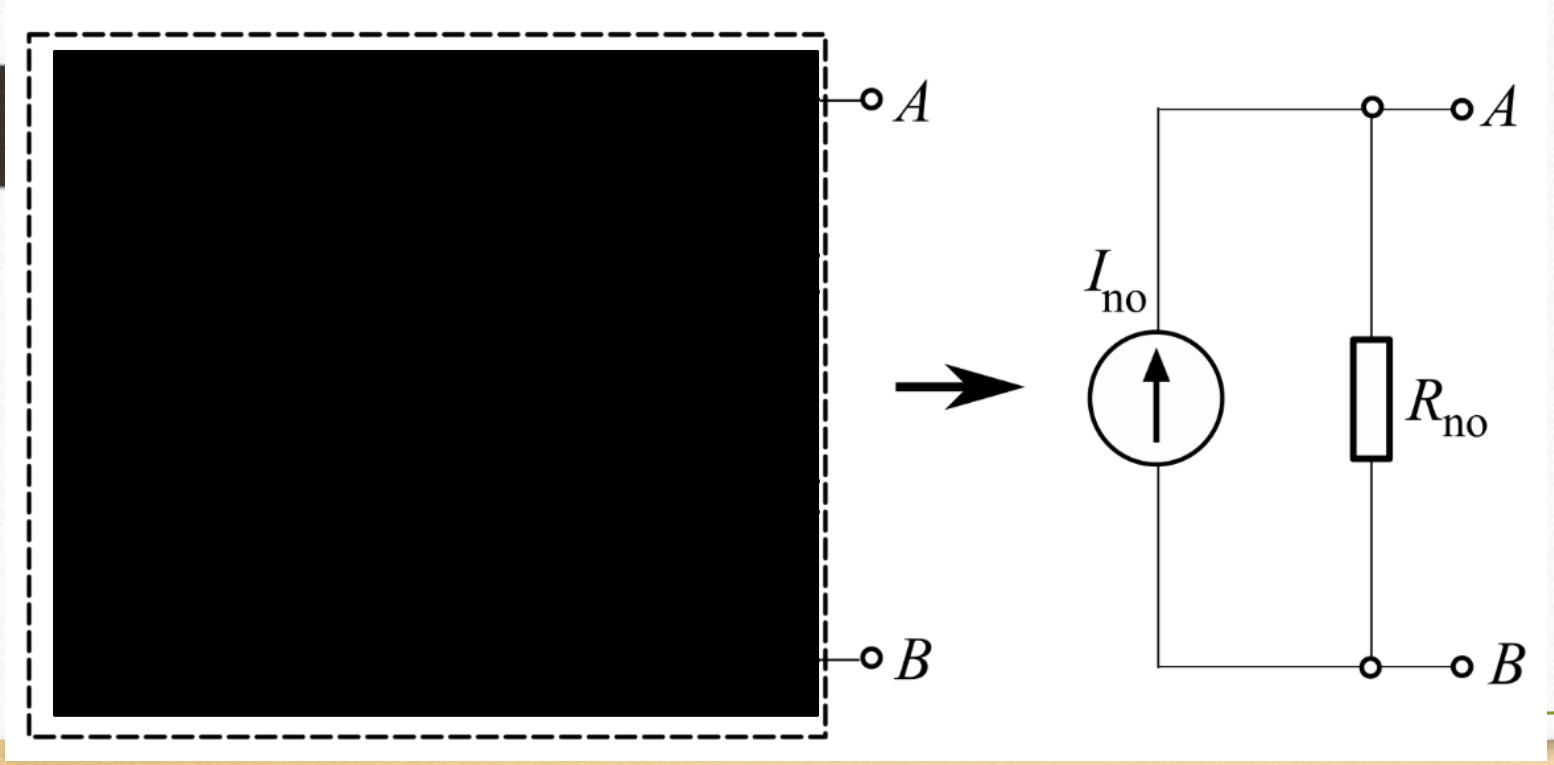


FIGURE 2 | Comparison of rTMS and tACS. Left: tACS uses sinusoidal currents which are restricted to one frequency as shown by a time-frequency wavelet transform. **Right:** rTMS, however, spans a wide range of frequencies in addition to the frequency of repetition. Note, that these diagrams depict only the stimulation currents/fields—not possible artifacts that may be elicited in the human brain.

Equivalent circuit diagram

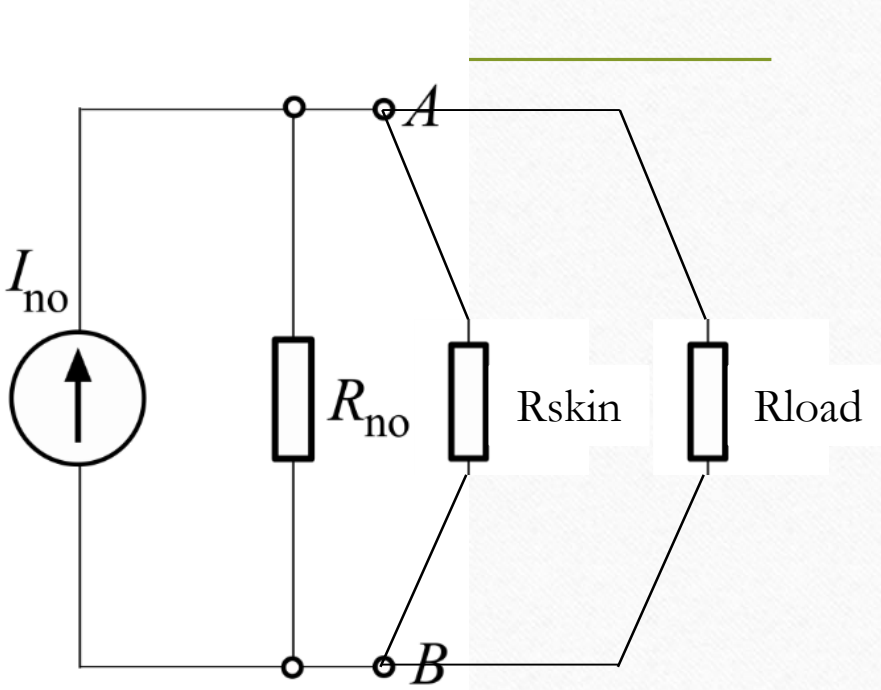
- Voltage-controlled current source
  - Independent of load resistance

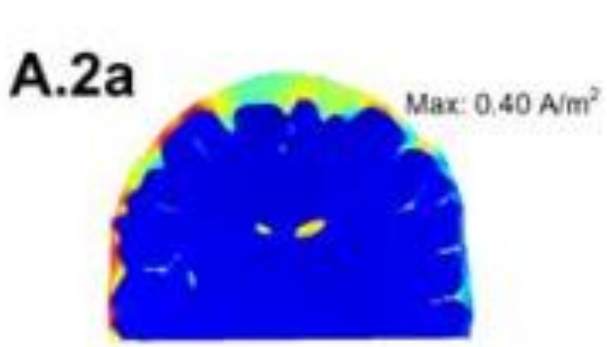


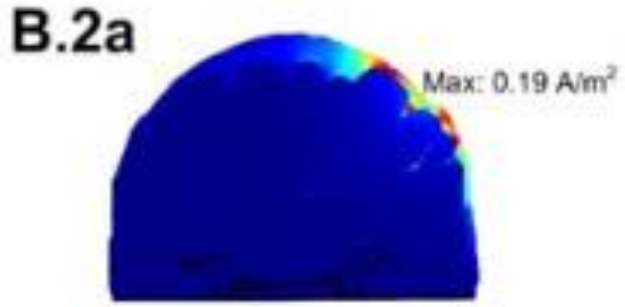


Only a small fraction of the extracranially applied current arrives intracranially

- Short-circuit paths
  - Current division due to finite output impedance of the current source.
  - Current division due to the low impedance scalp, compared to the high impedance skull.







How large is the induced electric field?

Opitz et al., 2016

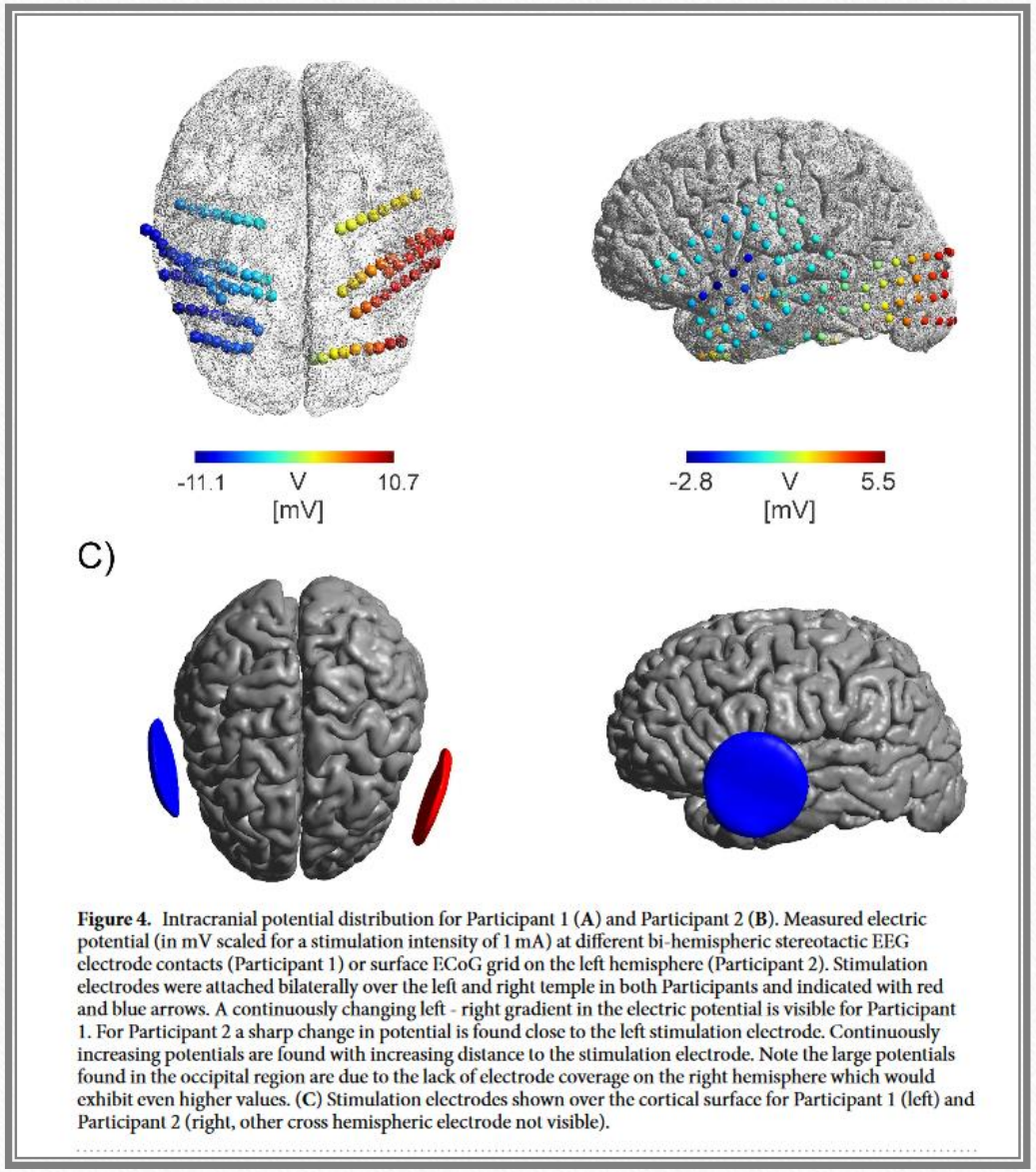


Figure 4. Intracranial potential distribution for Participant 1 (**A**) and Participant 2 (**B**). Measured electric potential (in mV scaled for a stimulation intensity of 1 mA) at different bi-hemispheric stereotactic EEG electrode contacts (Participant 1) or surface ECoG grid on the left hemisphere (Participant 2). Stimulation electrodes were attached bilaterally over the left and right temple in both Participants and indicated with red and blue arrows. A continuously changing left - right gradient in the electric potential is visible for Participant 1. For Participant 2 a sharp change in potential is found close to the left stimulation electrode. Continuously increasing potentials are found with increasing distance to the stimulation electrode. Note the large potentials found in the occipital region are due to the lack of electrode coverage on the right hemisphere which would exhibit even higher values. (**C**) Stimulation electrodes shown over the cortical surface for Participant 1 (left) and Participant 2 (right, other cross hemispheric electrode not visible).

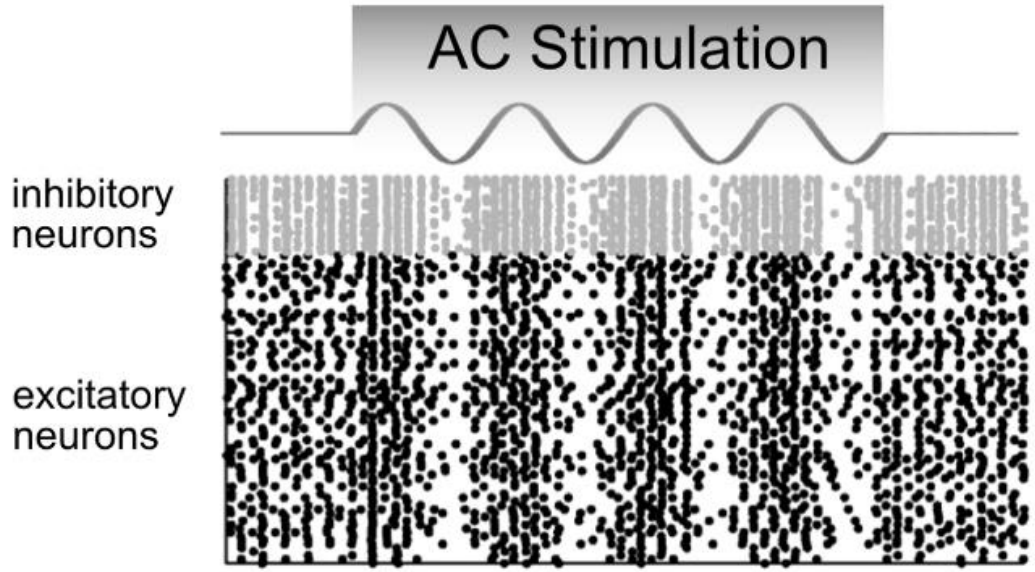


FIGURE 5 | Model predictions of how a network of neurons would behave in response to AC stimulation. The firing rates of inhibitory (gray) and excitatory (black) neurons are up- and down-regulated in phase with the AC current. In these raster plots, each dot represents a neural spike. Adapted from Reato et al. (2010).

Can we induce intracranial electric fields large enough to affect neural activity?

- AC stimulation up- and down-regulates the firing rate in an oscillatory manner without changing the average firing rate over a longer time interval.
  - 0.2 mV/mm result in enhanced coherence between spikes and the driving oscillation.

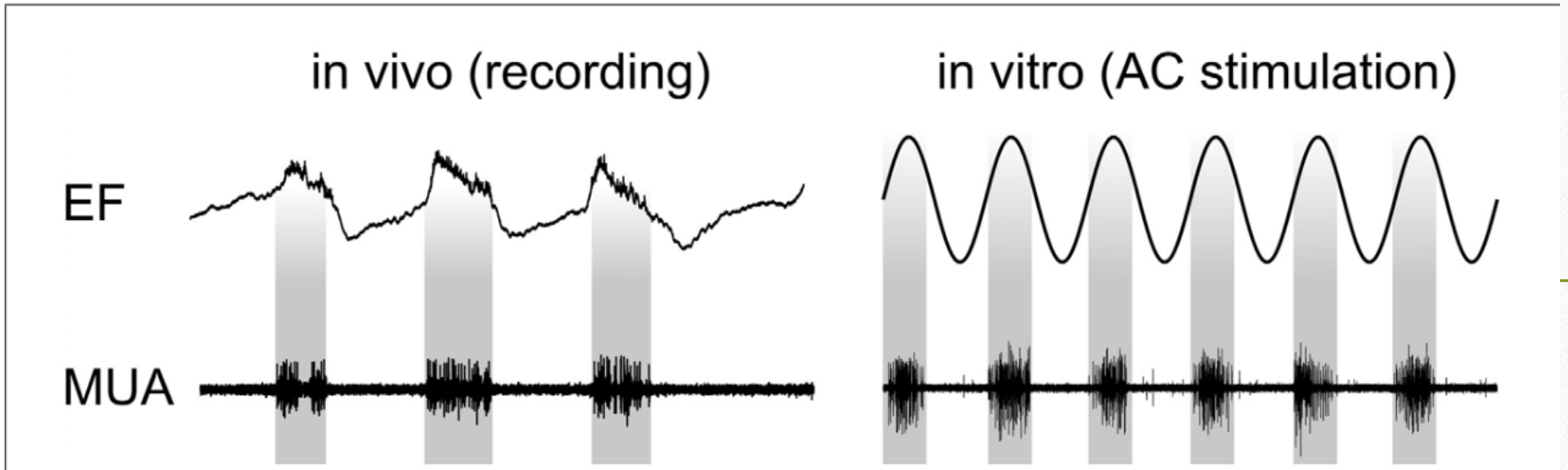
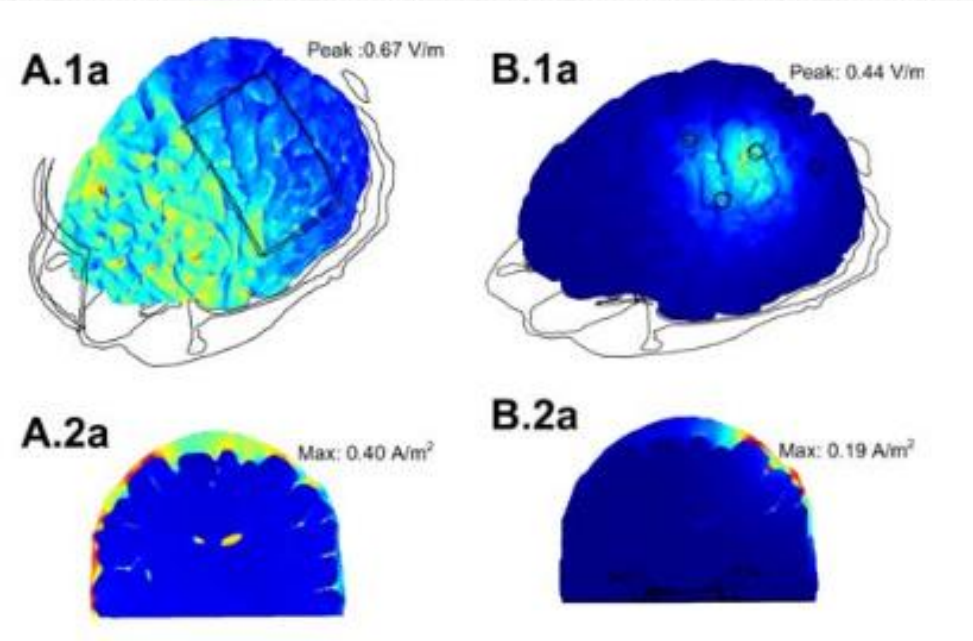


FIGURE 3 | Physiological mechanisms of tACS. Left: *In vivo* recordings in ferrets show that spontaneous neuronal activity seen in MUA synchronizes to certain phases of LFPs. **Right:** Stimulating slices of cortex electrically with sinusoidal currents results in a similar synchronization. Interestingly, the inter-burst frequency of the spontaneously occurring activity can be speeded up and slowed down resulting in neural entrainment [adapted from Fröhlich and McCormick (2010)].

Where does the current flow?



- 1 mA of tDCS/tACS results in an intracranial current density of 0.13 A/m2 amounting to a cortical electric field of 0.67 V/m when assuming a gray matter conductivity of 0.3 S/m (Datta et al., 2009)

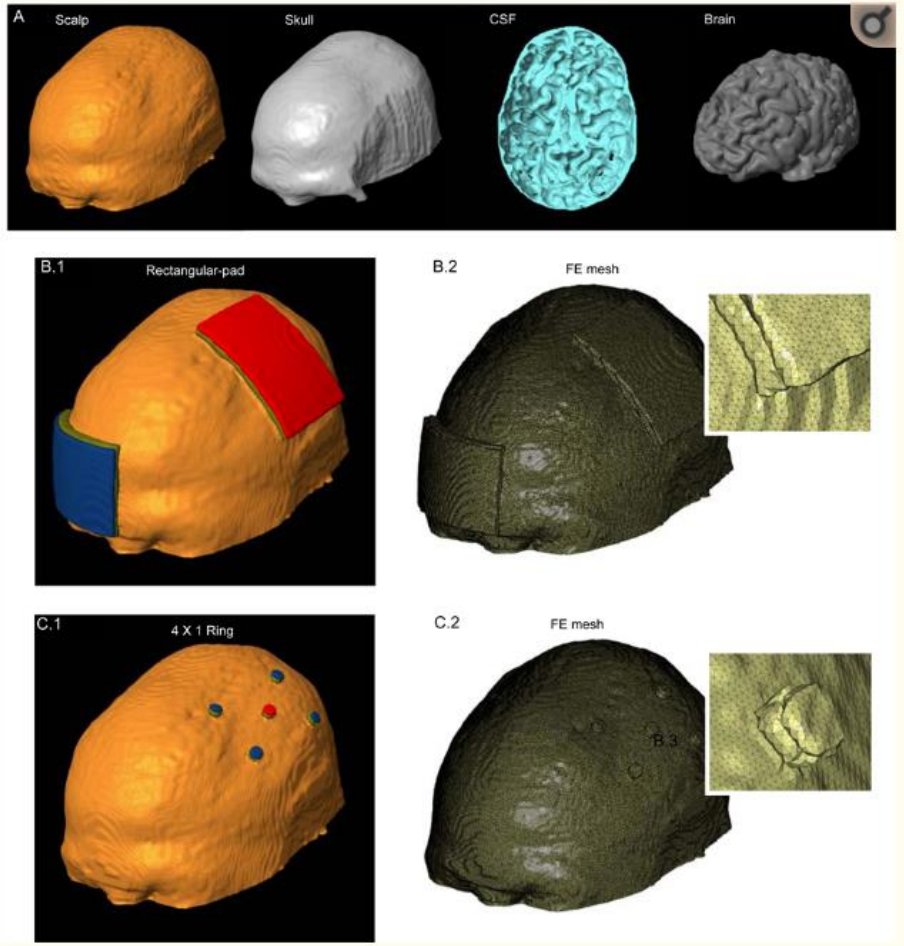


Figure 1

Finite element (FE) model of the conventional 7 × 5 cm^2 rectangular-pad and 4 × 1 ring configurations. (A) Segmented compartments in the following order: Scalp, Skull, CSF and Brain. (B.1) FE model of the conventional rectangular-pad configuration and corresponding FE mesh (B.2). (C.1) FE model of the 4 × 1 ring electrode configuration and corresponding FE mesh (C.2). The two insets show the zoomed mesh images, highlighting finer detail. 'Red': Anode electrode; 'Blue': Cathode electrode(s); 'Olive green': sponge/gel.

Physiological effects of TES

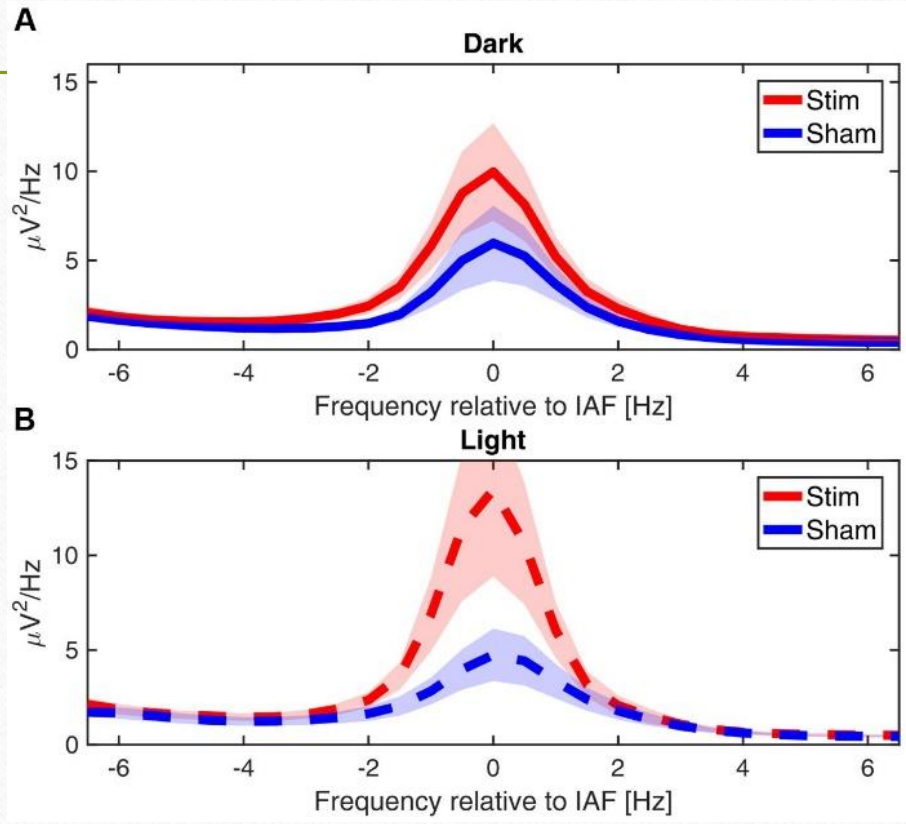
- Anodal stimulation:
  1. Transiently increases cortical excitability by (rhythmically) biasing the resting membrane potential.
  2. Increases intracellular calcium levels, resulting in neuroplasticity and learning.

- Entrainment of endogenous brain activity
- Constructive/destructive interference
- Plasticity via calcium channel dynamics

Entrainment

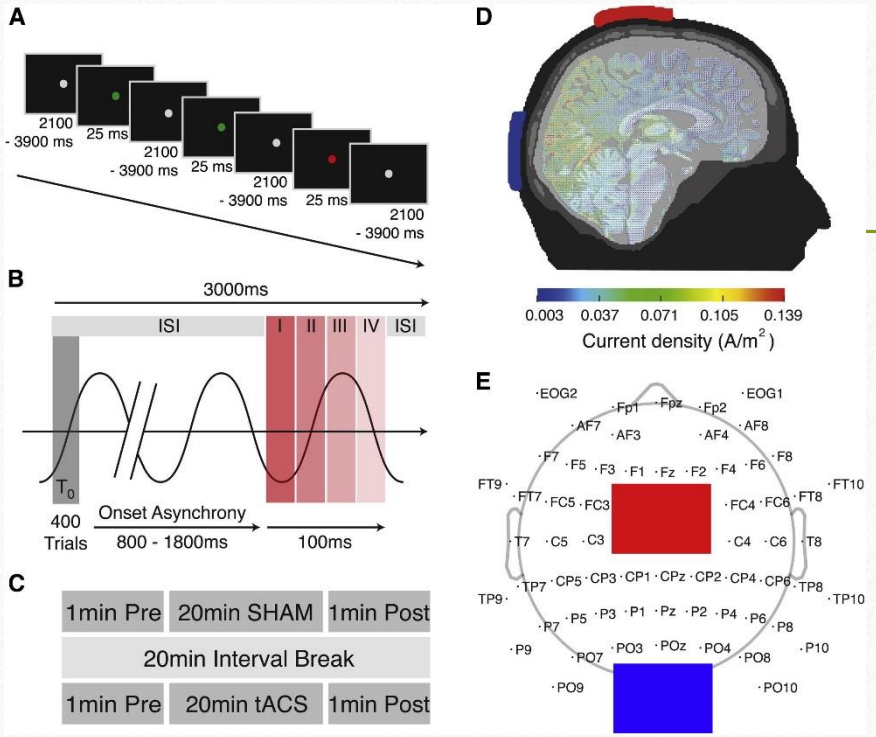
Alpha Entrainment

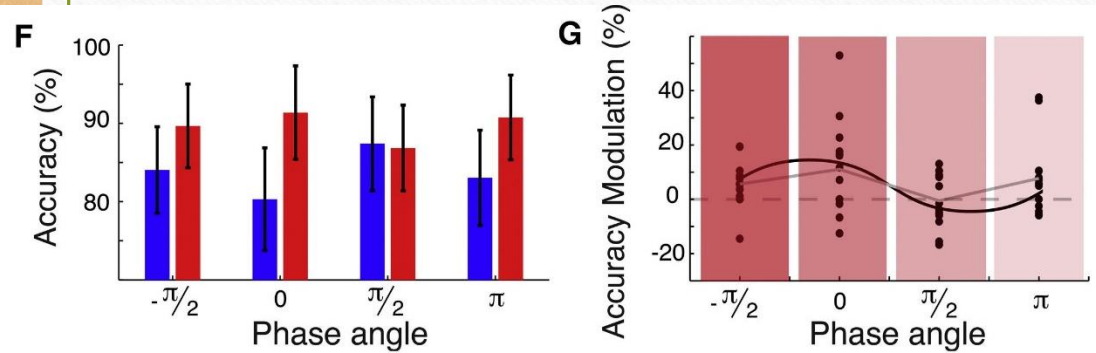
- tACS applied at participants' individual EEG alpha frequency resulted in an enhancement of the EEG alpha amplitude after 10 min of stimulation.
- EEG was recorded offline, i.e., three minutes before and after applying tACS.
- After tACS, spectral power was significantly increased specifically in the range of the individual alpha frequency (IAF~10±2 Hz) as compared to before tACS

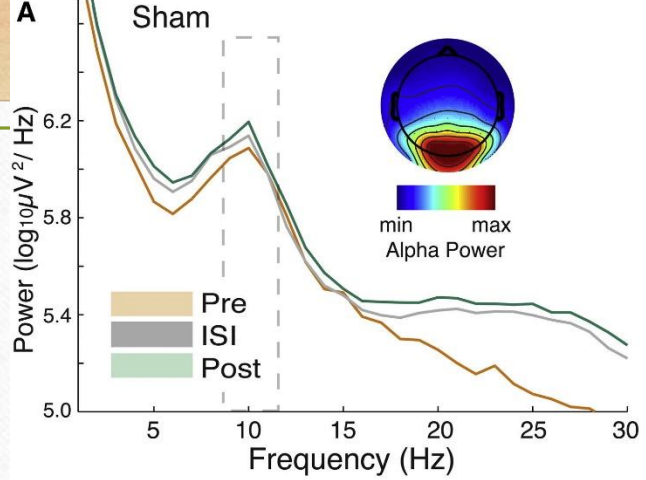


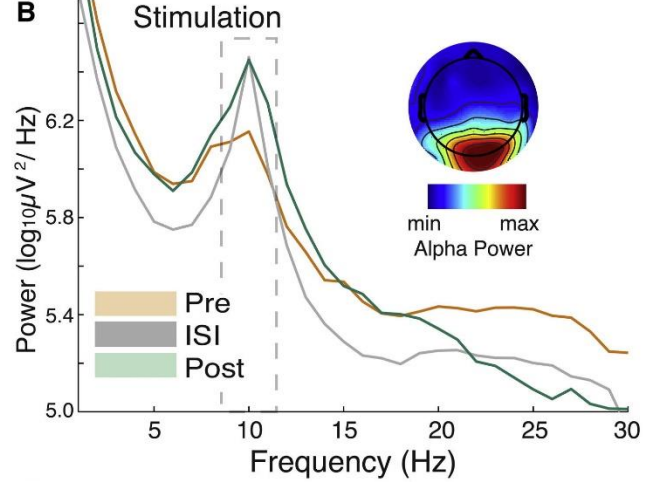
Stecher et al., 2018

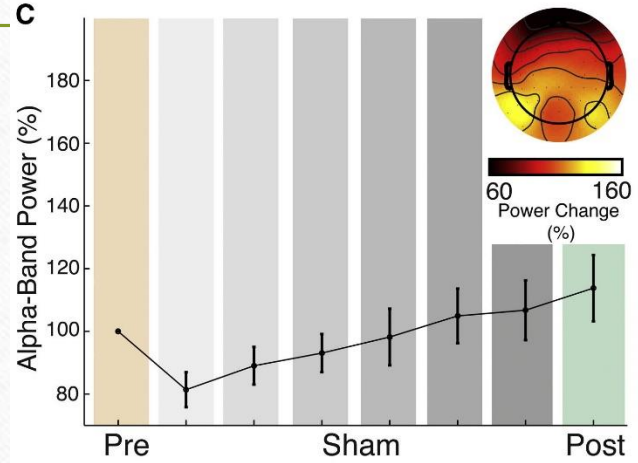
Helfrich et al., 2014

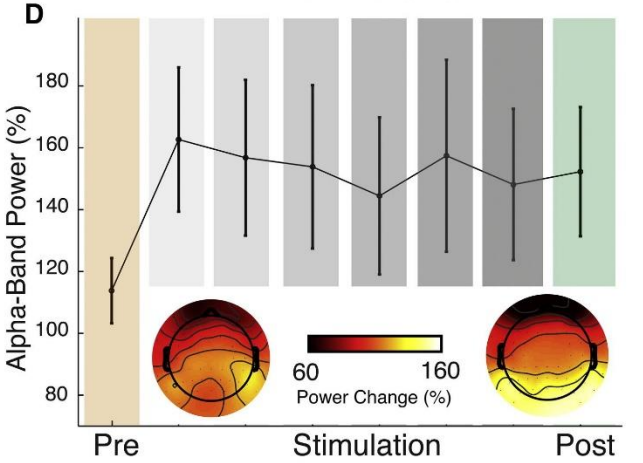


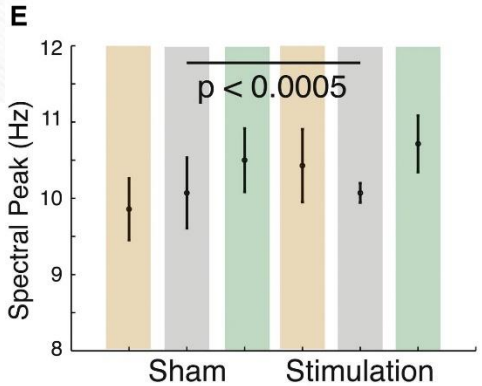


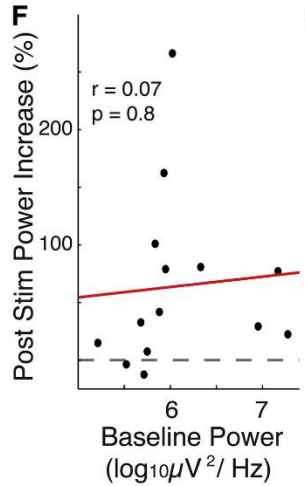


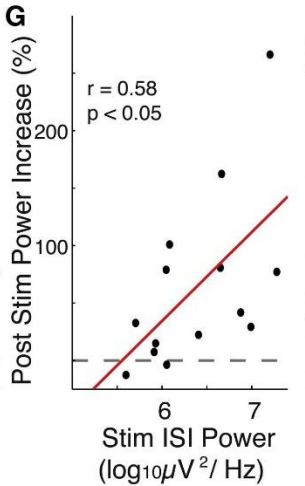


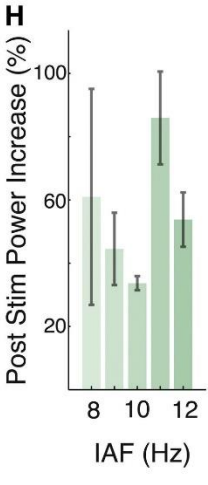












Gamma Entrainment

- 40 Hz tACS increases the duration of perceived vertical motion.

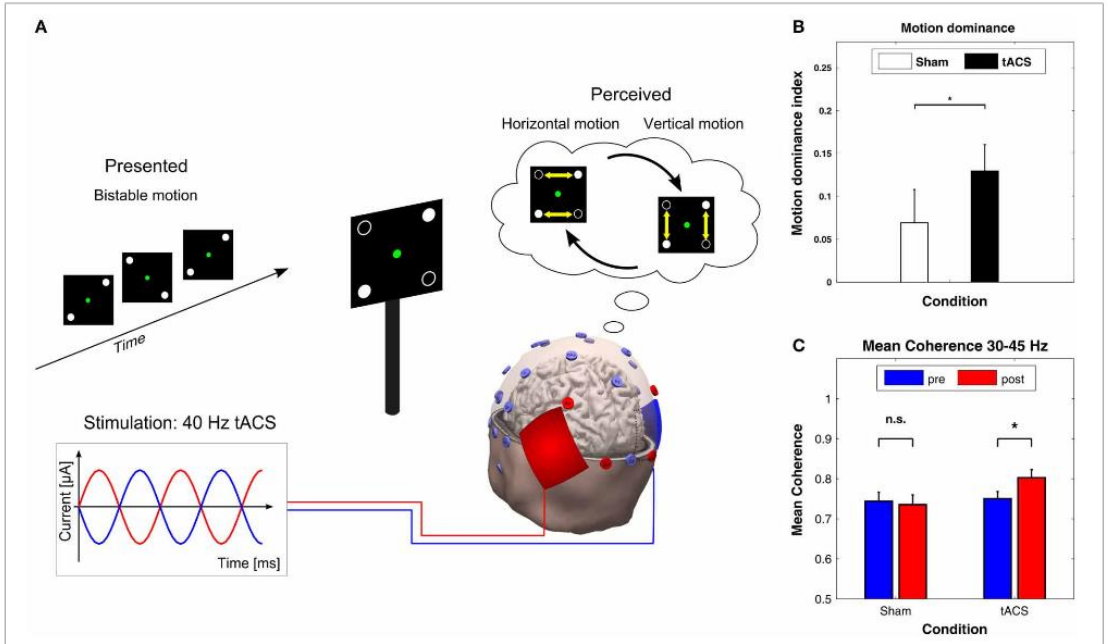
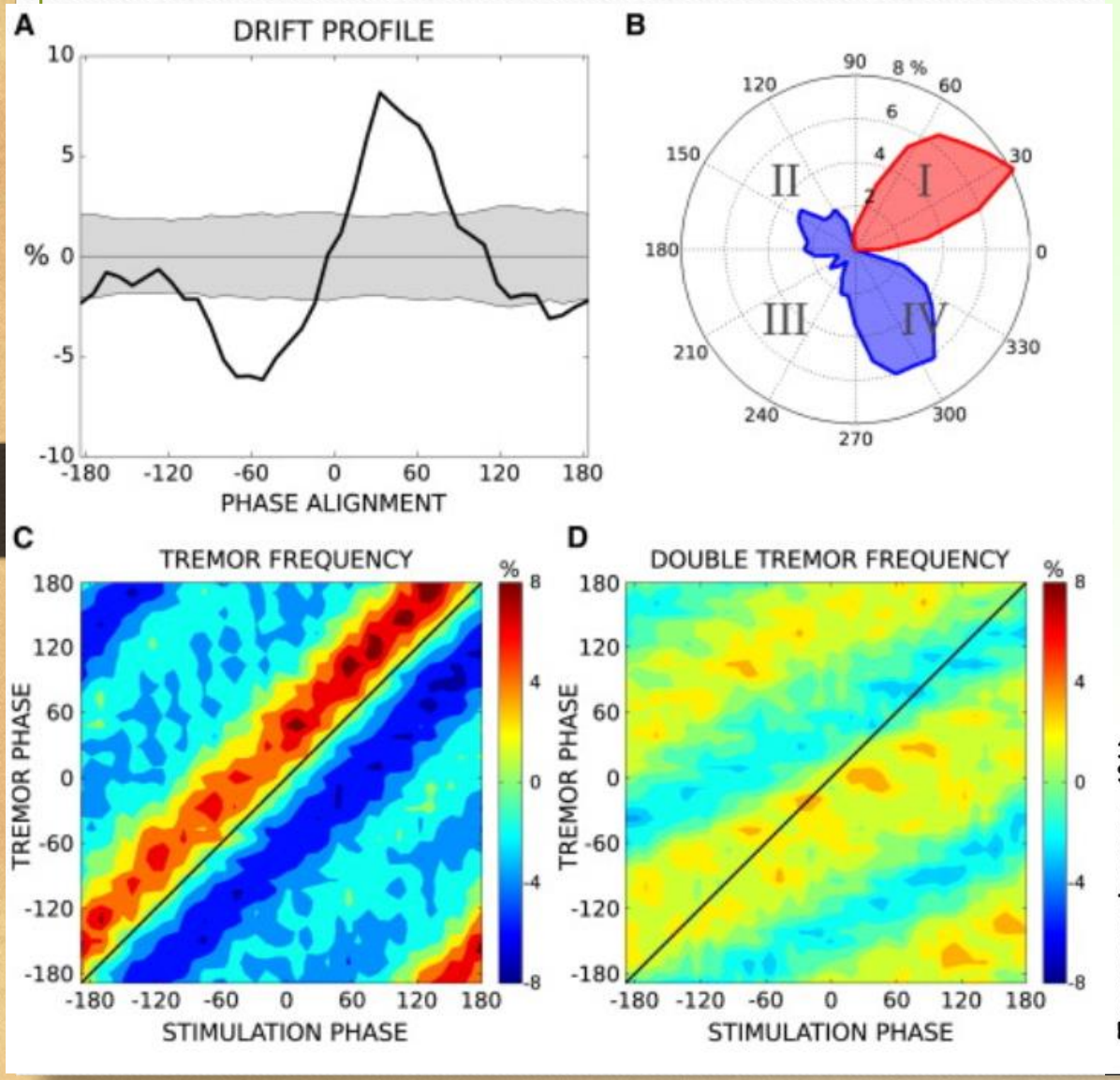
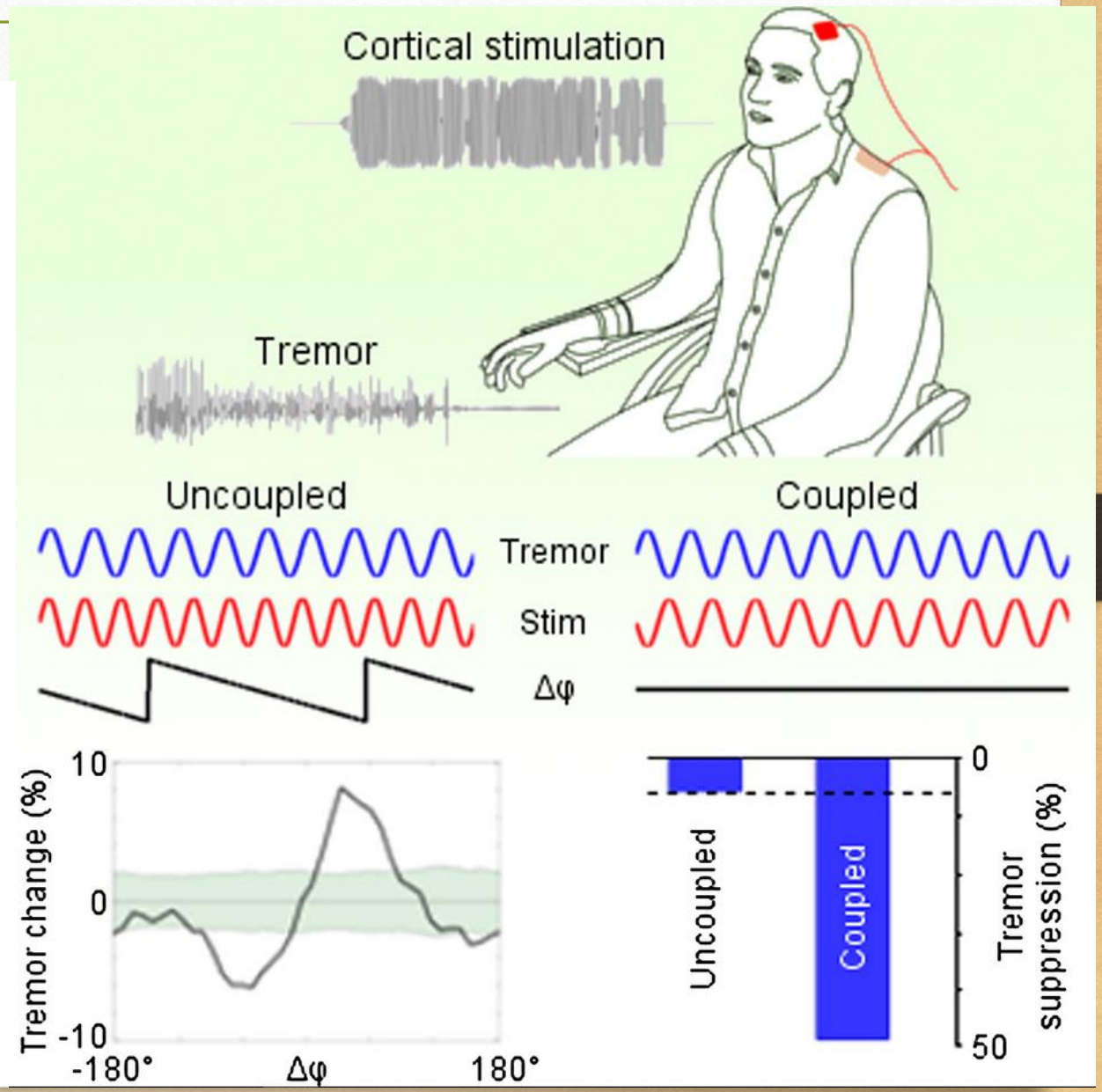


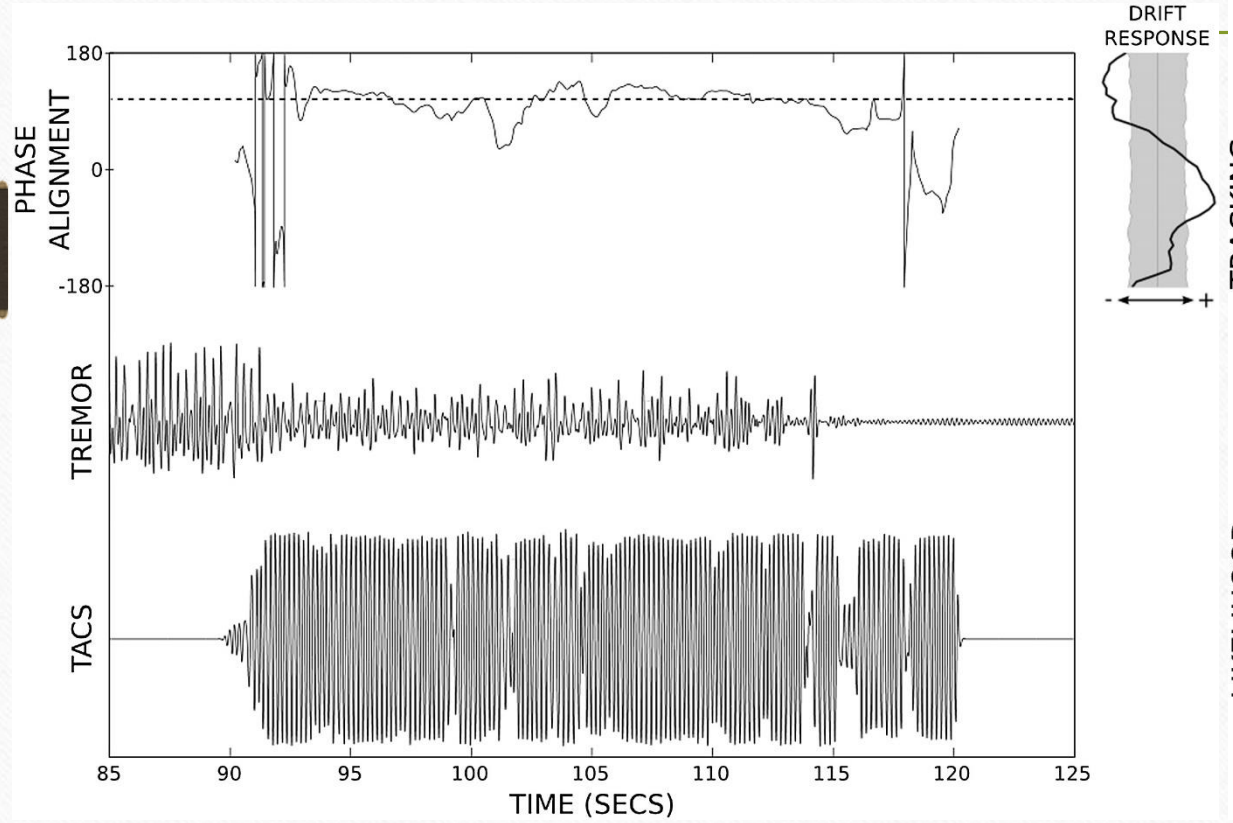
FIGURE 7 | Effects of 40 Hz tACS with 180° phase difference between hemispheres. (A) Configuration of the bistable apparent motion display together with the EEG and tACS electrode montage. EEG electrodes that were used for analyzing interhemispheric coherence are indicated in red. The tACS sponge electrodes were placed bilaterally over the parietal-occipital cortex. This montage leads to 40 Hz stimulation with 180° phase difference between hemispheres. **(B)** The motion dominance index is significantly enhanced during 40 Hz tACS (black bar) as compared to sham stimulation (white bar), indicating that 40 Hz tACS results in a longer total duration of perceived vertical motion (*$P < 0.05$). Error bars display the standard error of the mean. **(C)** Mean coherence within the 30–45 Hz frequency band shows a significant increase from pre-tACS to post-tACS (right), but not from pre-sham to post-sham (left). Error bars correspond to standard errors of the mean; *$P < 0.05$. Adapted from Strüber et al. (2013) with permission of the authors.

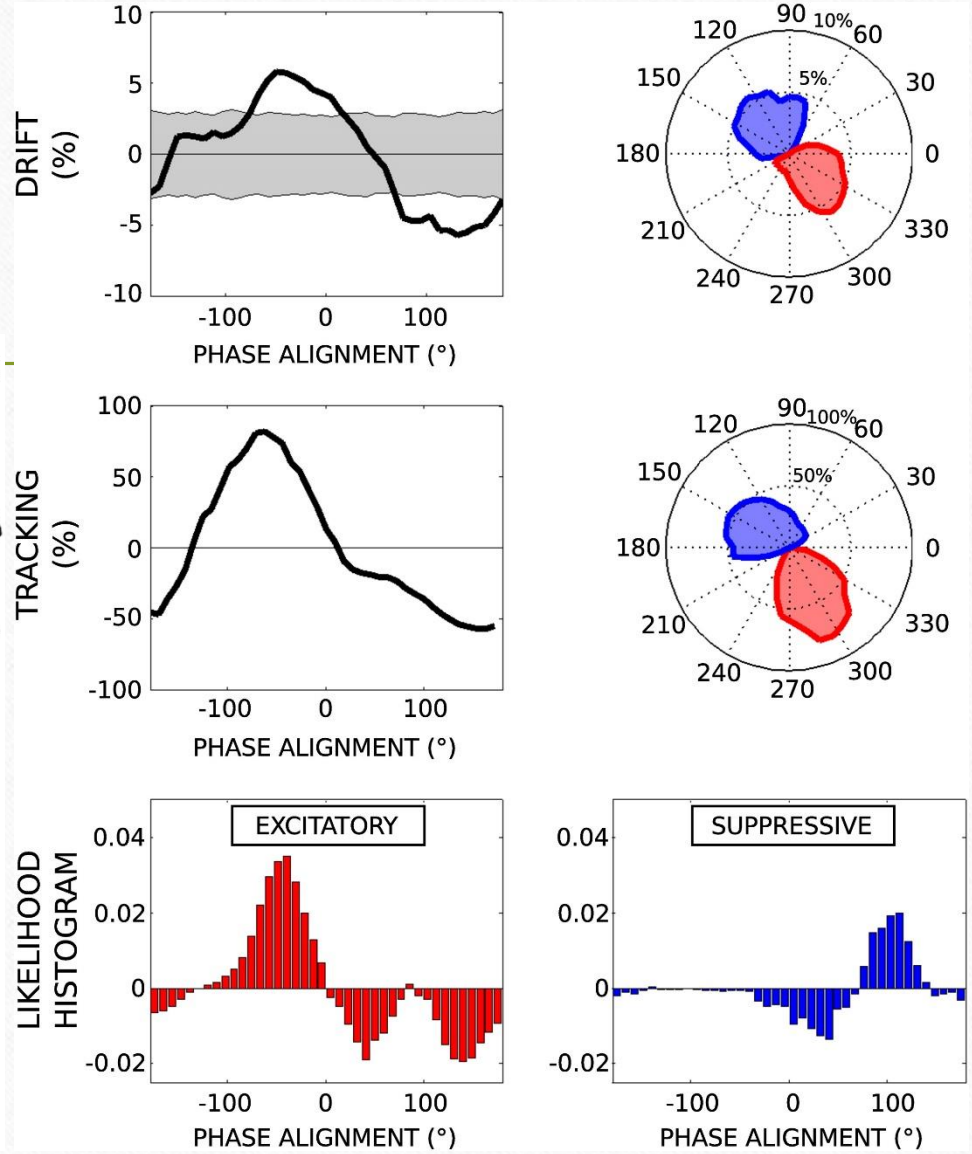
Interference

Britaain et al, 2013






PHASE ALIGNMENT
180
0
-180
TREMOR
TACS
85
90
95
100
105
110
115
120
125
TIME (SECS)
DRIFT RESPONSE
-
+


DRIFT (%)
10
5
0
-5
-10
-100
0
100
PHASE ALIGNMENT (°)
90
120
60
150
30
180
0
210
330
240
300
270
10%
5%
TRACKING (%)
100
50
0
-50
-100
-100
0
100
PHASE ALIGNMENT (°)
90
120
60
150
30
180
0
210
330
240
300
270
100%
50%
LIKELIHOOD HISTOGRAM
EXCITATORY
0.04
0.02
0
-0.02
-100
0
100
PHASE ALIGNMENT (°)
SUPPRESSIVE
0.04
0.02
0
-0.02
-100
0
100
PHASE ALIGNMENT (°)

Plasticity

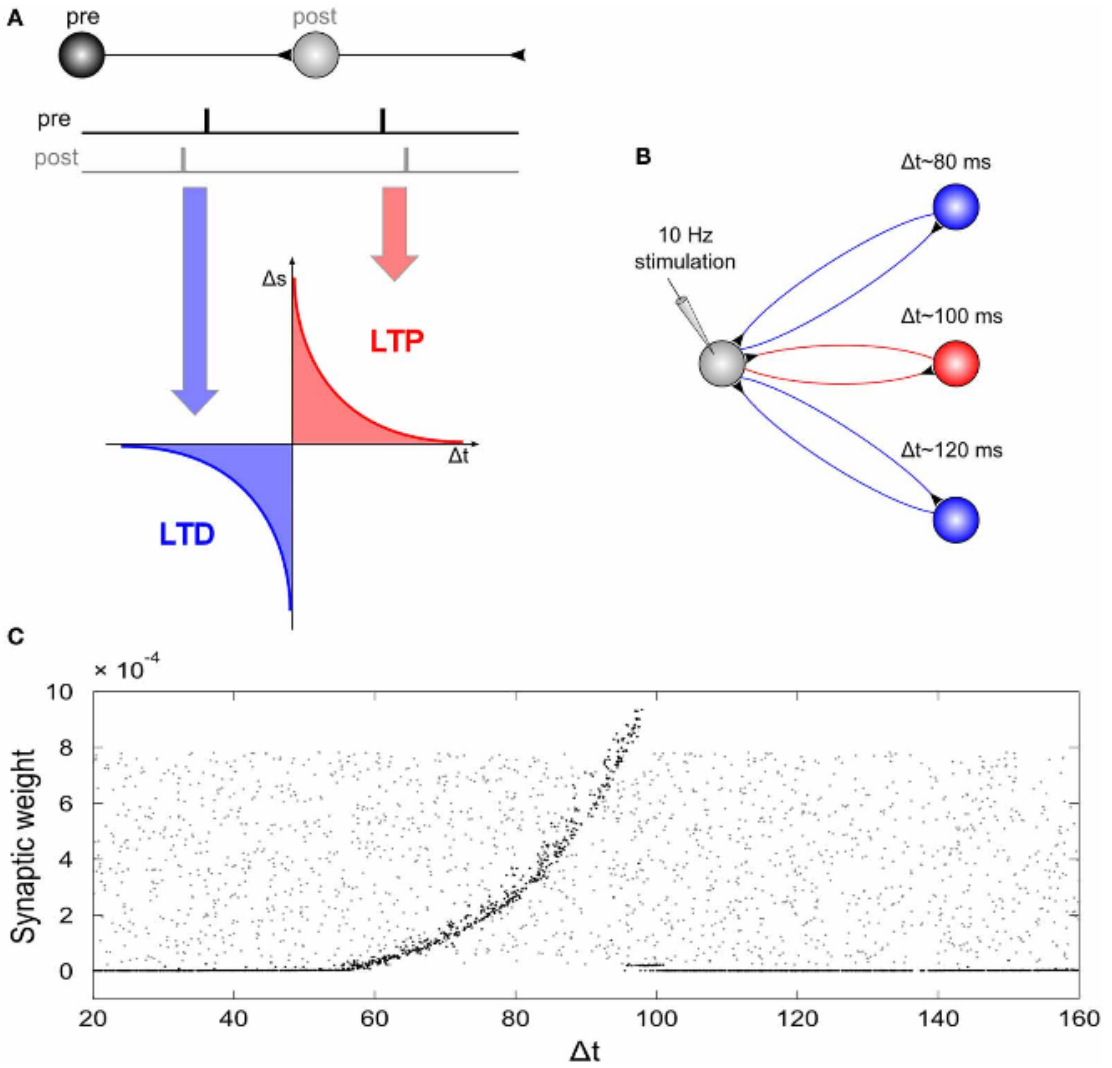
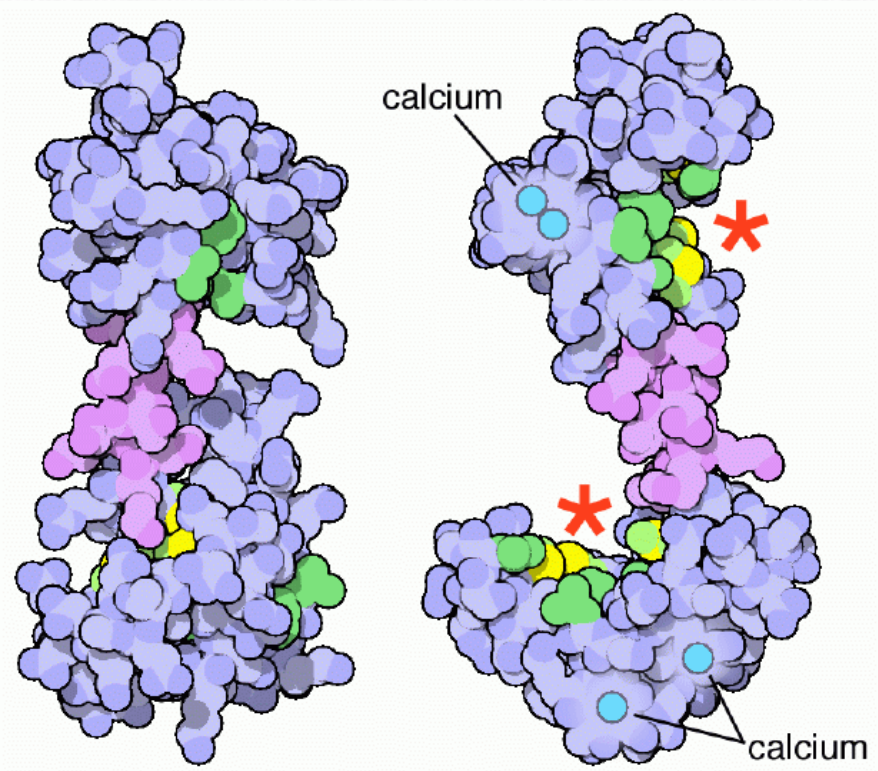
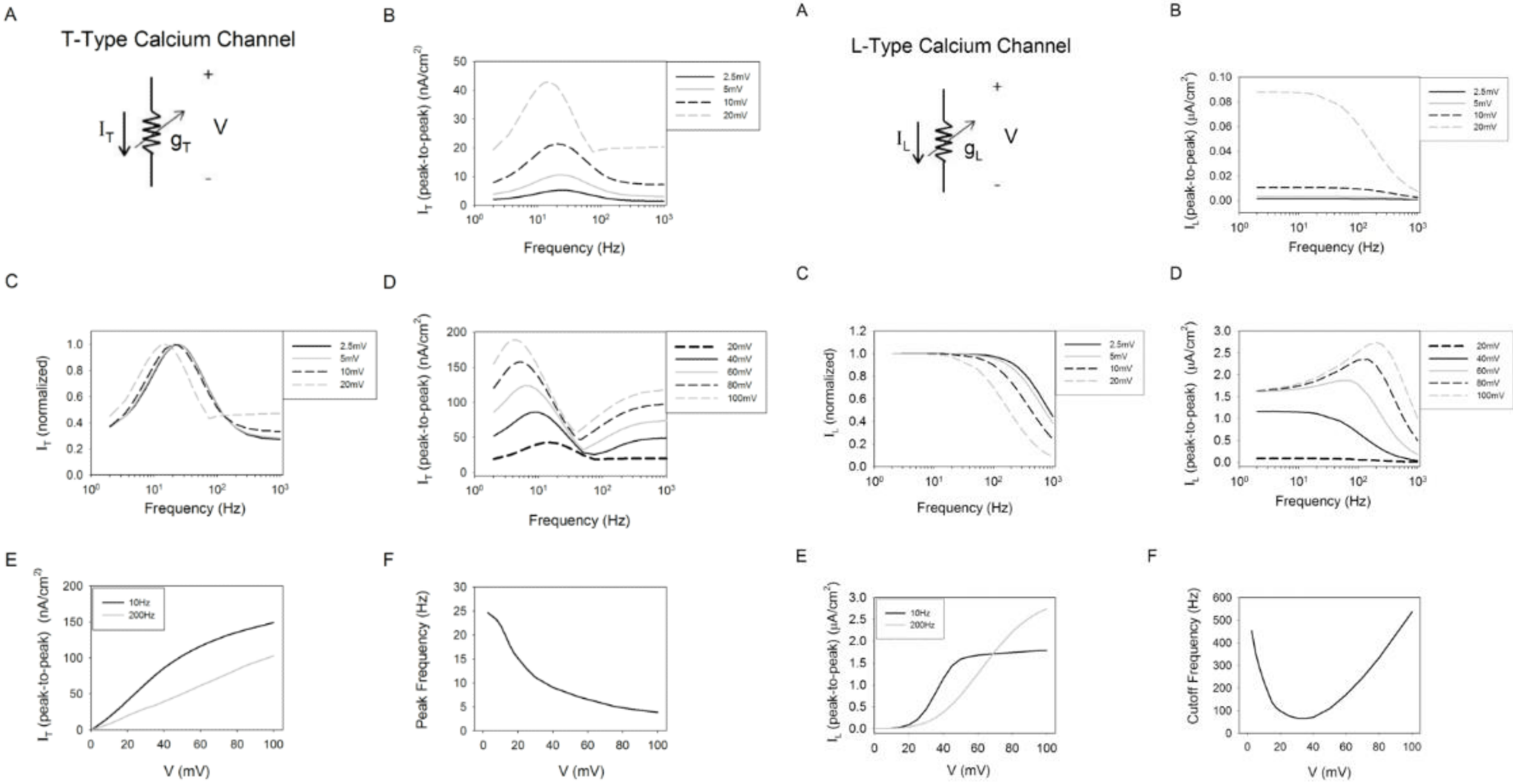


FIGURE 6 | Network simulation of tACS. (A) Spike timing dependent plasticity: synaptic weights are increased if a post-synaptic potential follows a pre-synaptic spike (long-term potentiation, LTP) and decreased if a post-synaptic potential occurs prior to a pre-synaptic spike (long-term depression, LTD). **(B)** Schematic illustration of the network: A driving neuron establishes a recurrent loop with each neuron of a hidden layer. The total synaptic delay, Δt, (i.e., the sum of both delays of the loop) varied between 20 and 160 ms. The driving neuron was stimulated with a spike train of 10 Hz repetition rate. **(C)** Synaptic weights of the back-projection as a function of the total synaptic delay of the recurrent loops: Gray dots display synaptic weights at the start of the simulation, black dots represent synaptic weights after the end of simulation. External stimulation of the driving neuron at 10 Hz resulted in increased weights for recurrent loops with a total delay between 60 and 100 ms, and dramatically reduced synaptic weights for loops with total delays outside this interval. Note, that the highest synaptic weights are observed at 100 ms, i.e., for loops with a resonance frequency near the stimulation frequency. Reprinted from Zaehle et al. (2010) with permission of the authors.

Plasticity depends on calcium channel dynamics

- The influx of calcium in granule and pyramidal cells combines with calmodulin to form a second messenger system, which produces metabolic changes:
  - CaMKII contributes to the phosphorylation of AMPA receptors, increasing their sensitivity.
    - Increased post-synaptic receptor density to the synaptic transmitter, glutamate.
    - Increased pre-synaptic neurotransmitter output.
- Calcium channel dynamics occur across a continuum of time scales from milliseconds to minutes and hours.
  - Very fast VGCC-mediated signaling (synaptic transmission), or very slow (long-term plasticity)





Freeman et al., 2011

Alpha Power Increase After Transcranial Alternating Current Stimulation at Alpha Frequency (α-tACS) Reflects Plastic Changes Rather Than Entrainment

Alexandra Vossen [a,*], Joachim Gross [b], Gregor Thut [b,**]

[a] School of Psychology, University of Glasgow, 58 Hillhead Street, Glasgow G12 8QB, United Kingdom
[b] Institute of Neuroscience and Psychology, University of Glasgow, 58 Hillhead Street, Glasgow G12 8QB, United Kingdom

ARTICLE INFO

Article history:
Received 4 September 2014
Received in revised form
3 December 2014
Accepted 14 December 2014
Available online 31 January 2015

Keywords:
Transcranial alternating current stimulation
Alpha oscillations
Entrainment
Spike-timing dependent plasticity
Electroencephalogram
Synchronization

ABSTRACT

Background: Periodic stimulation of occipital areas using transcranial alternating current stimulation (tACS) at alpha (α) frequency (8–12 Hz) enhances electroencephalographic (EEG) α-oscillation long after tACS-offset. Two mechanisms have been suggested to underlie these changes in oscillatory EEG activity: tACS-induced entrainment of brain oscillations and/or tACS-induced changes in oscillatory circuits by spike-timing dependent plasticity.

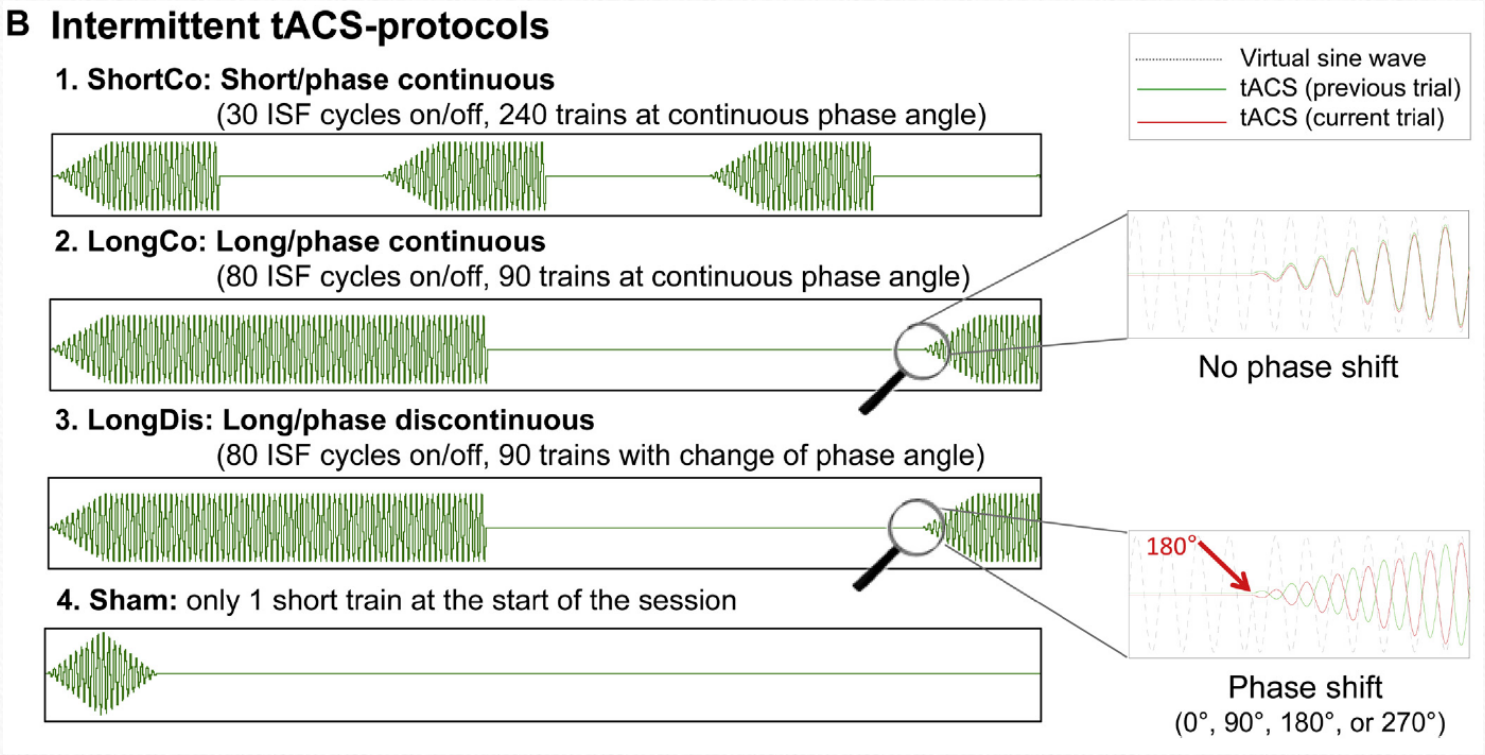
Objective: We tested to what extent plasticity can account for tACS-aftereffects when controlling for entrainment "echoes." To this end, we used a novel, intermittent tACS protocol and investigated the strength of the aftereffect as a function of phase continuity between successive tACS episodes, as well as the match between stimulation frequency and endogenous α-frequency.

Methods: 12 healthy participants were stimulated at around individual α-frequency for 11–15 min in four sessions using intermittent tACS or sham. Successive tACS events were either phase-continuous or phase-discontinuous, and either 3 or 8 s long. EEG α-phase and power changes were compared after and between episodes of α-tACS across conditions and against sham.

Results: α-aftereffects were successfully replicated after intermittent stimulation using 8-s but not 3-s trains. These aftereffects did not reveal any of the characteristics of entrainment echoes in that they were independent of tACS phase-continuity and showed neither prolonged phase alignment nor frequency synchronization to the exact stimulation frequency.

Conclusion: Our results indicate that plasticity mechanisms are sufficient to explain α-aftereffects in response to α-tACS, and inform models of tACS-induced plasticity in oscillatory circuits. Modifying brain oscillations with tACS holds promise for clinical applications in disorders involving abnormal neural synchrony.

- α-aftereffect does not differ between phase-continuous and phase discontinuous protocols



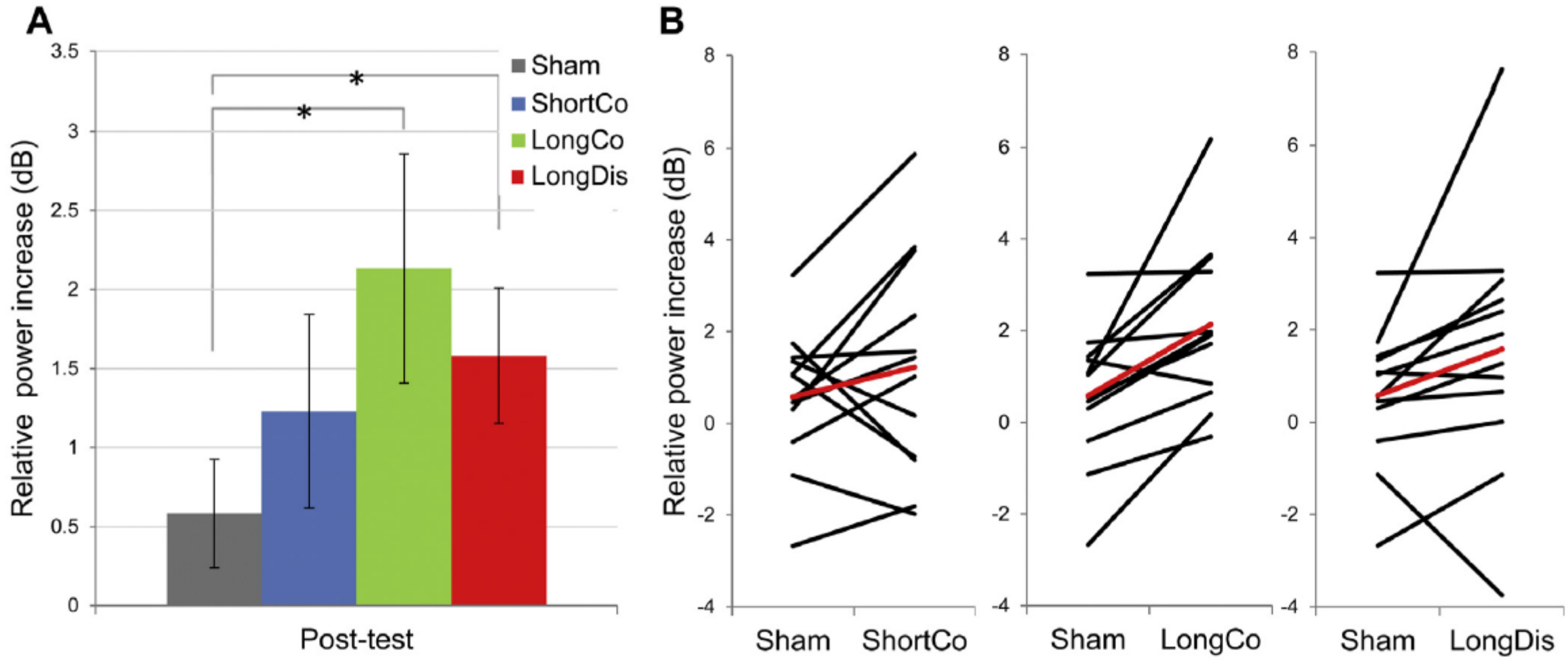
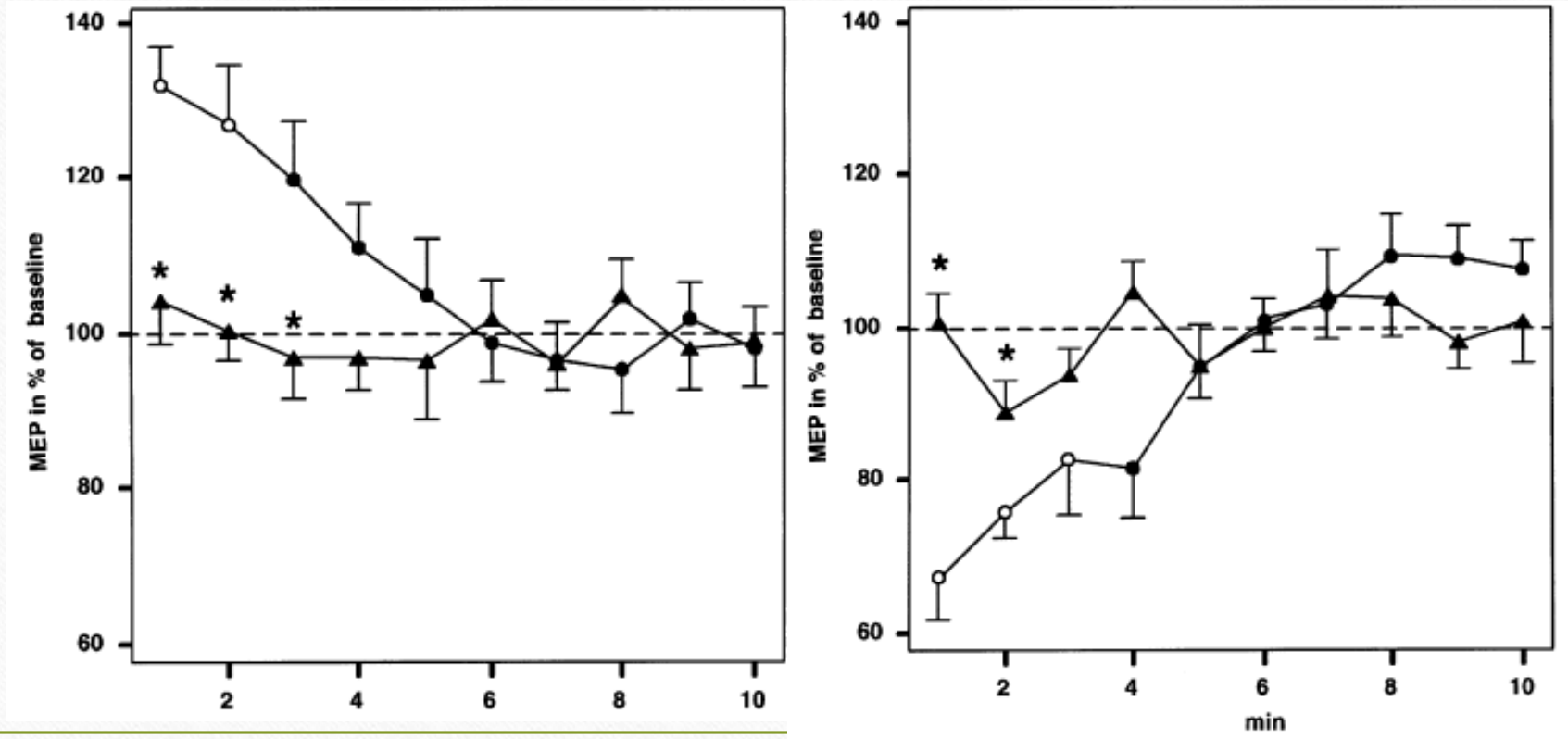


Figure 2. Alpha-aftereffects across protocols. A) Mean relative increase (dB) in individual alpha band power from pre-test to post-test. Both long protocols are followed by a significantly higher alpha-increase compared to sham. Asterisks reflect significant pairwise comparisons using Wilcoxon Signed Rank Tests ($\alpha = 0.05$). Only the respective comparisons between Sham and LongCo (lower brace), and Sham and LongDis (upper brace), were significant. B) Relative increase in mean power in the individual alpha band (individual stimulation frequency (ISF) $\pm$ 2 Hz) from pre-test to post-test per participant. Each active stimulation condition is compared to Sham. Black lines represent individual differences between sham and active conditions, red line represents the mean difference. Most volunteers show a greater increase after stimulation with long (80 cycles at ISF) trains compared to sham.

Pharmacological Intervention

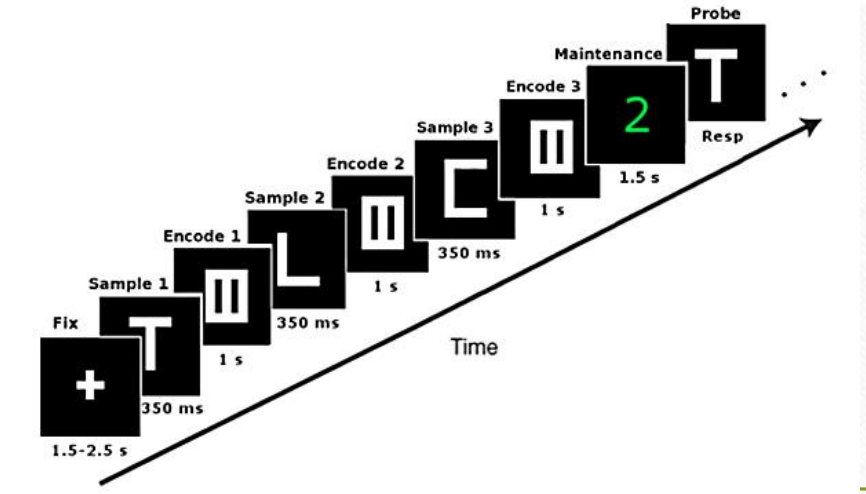
- DMO (NMDA receptor antagonist) 2 h before TES prevents post-stimulation changes in excitability (Nitsche & Paulus, 2002)

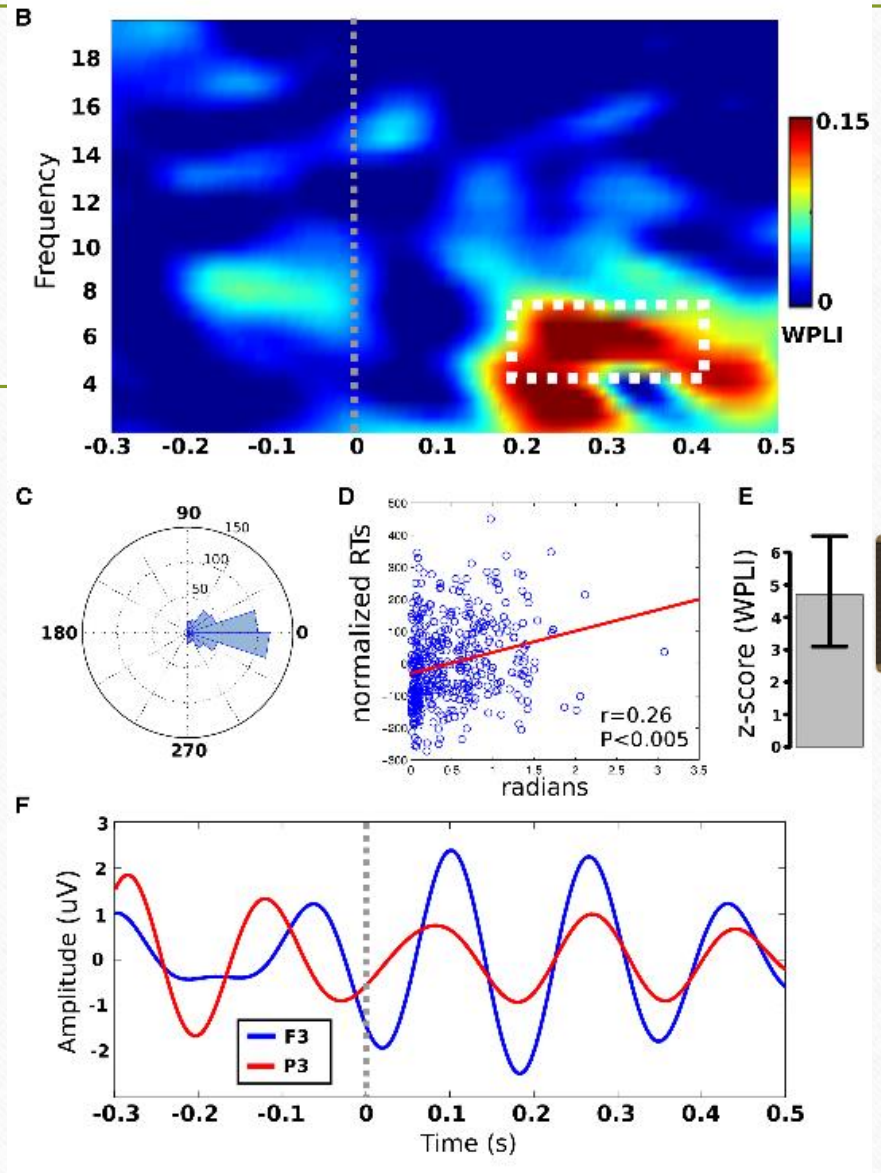


Higher Cognitive Processes

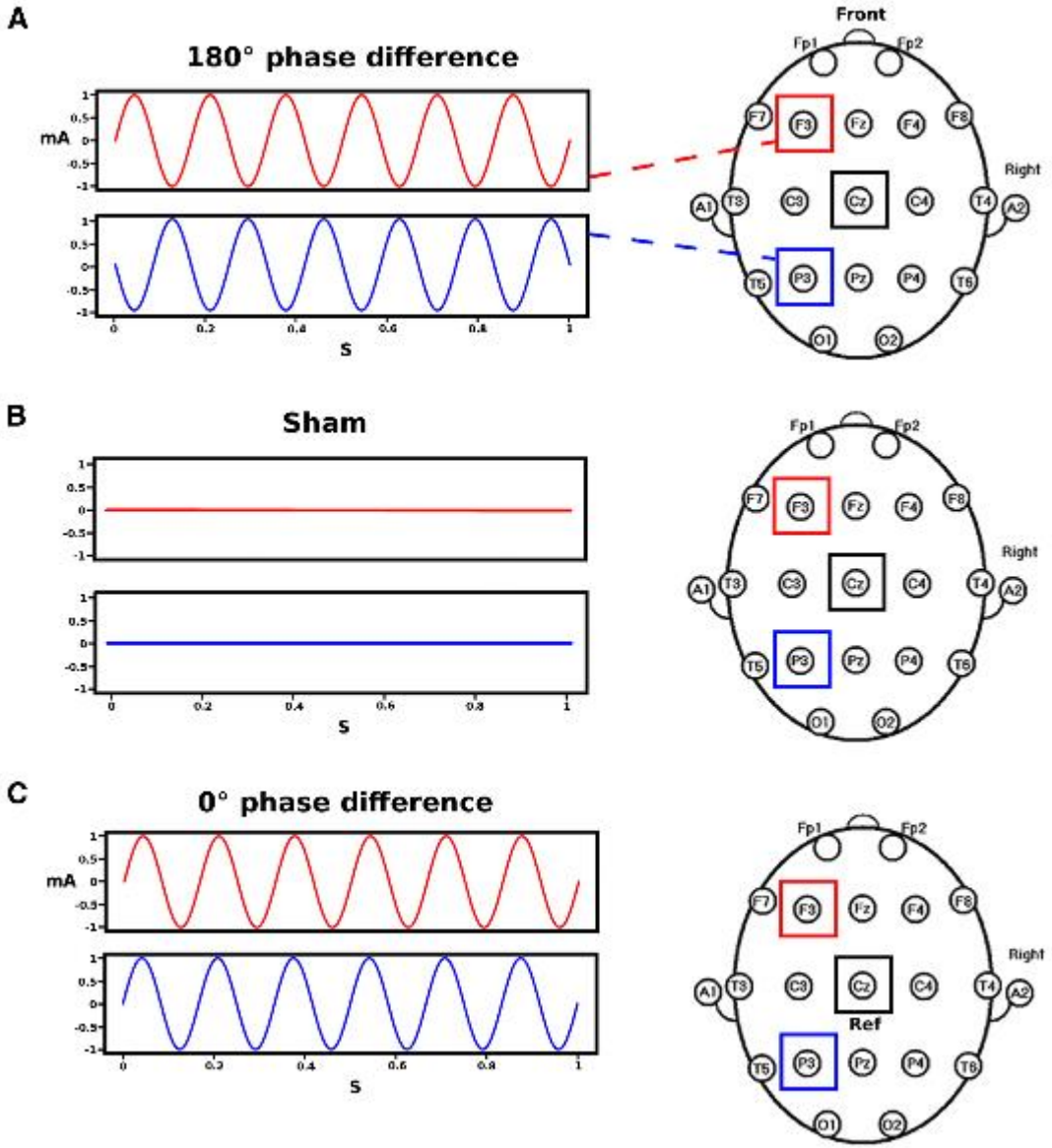
Working Memory

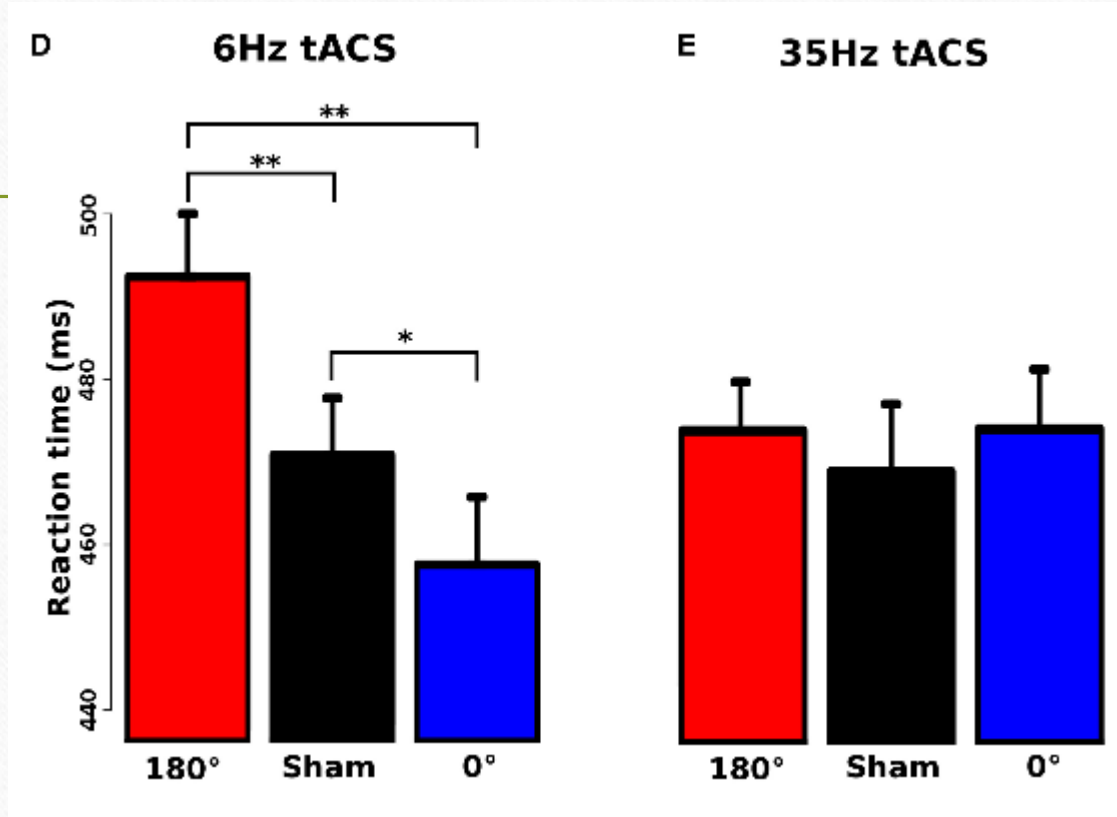
- Reaction times in the matching periods were faster when the phase lag between frontal and parietal oscillations was near to 0∘





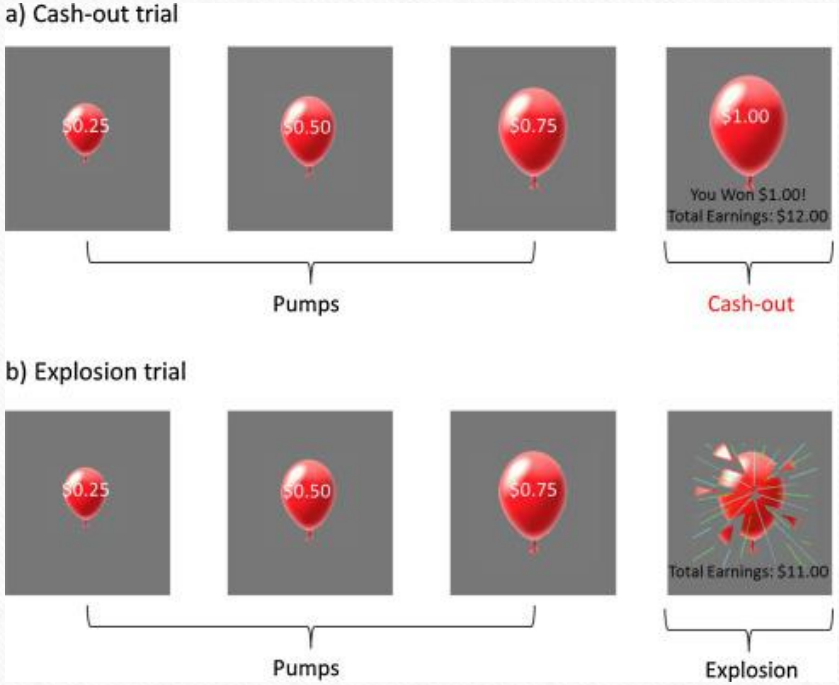
Polenía et al., 2012


A
180° phase difference
mA
s
Front
Right
B
Sham
C
0° phase difference
Ref


D
6Hz tACS
Reaction time (ms)
500
480
460
440
**
**
*
180°
Sham
0°
E
35Hz tACS
180°
Sham
0°

Decision-Making

- Balloon analog risk task during dlPFC stimulation (Sela et al., 2012)



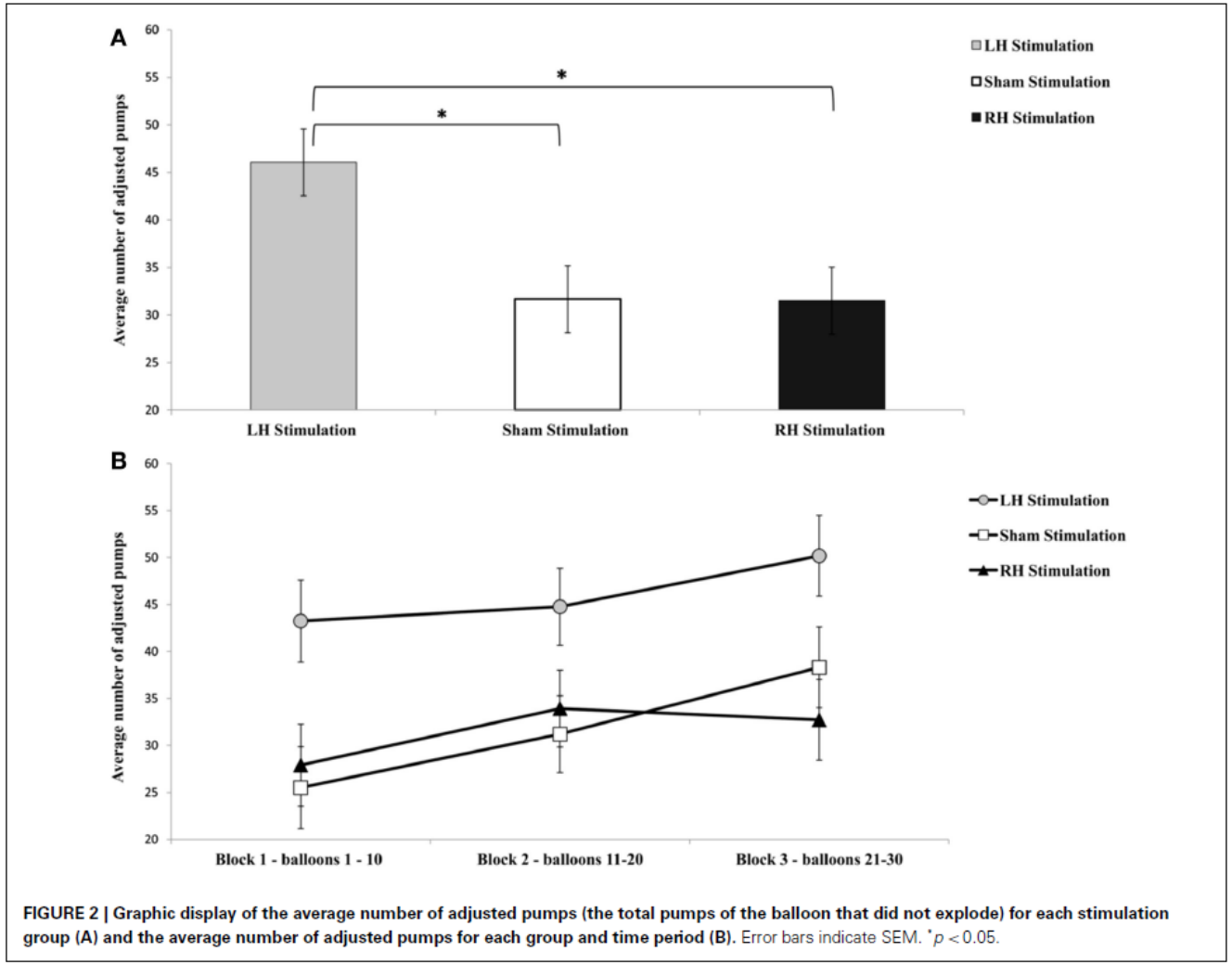
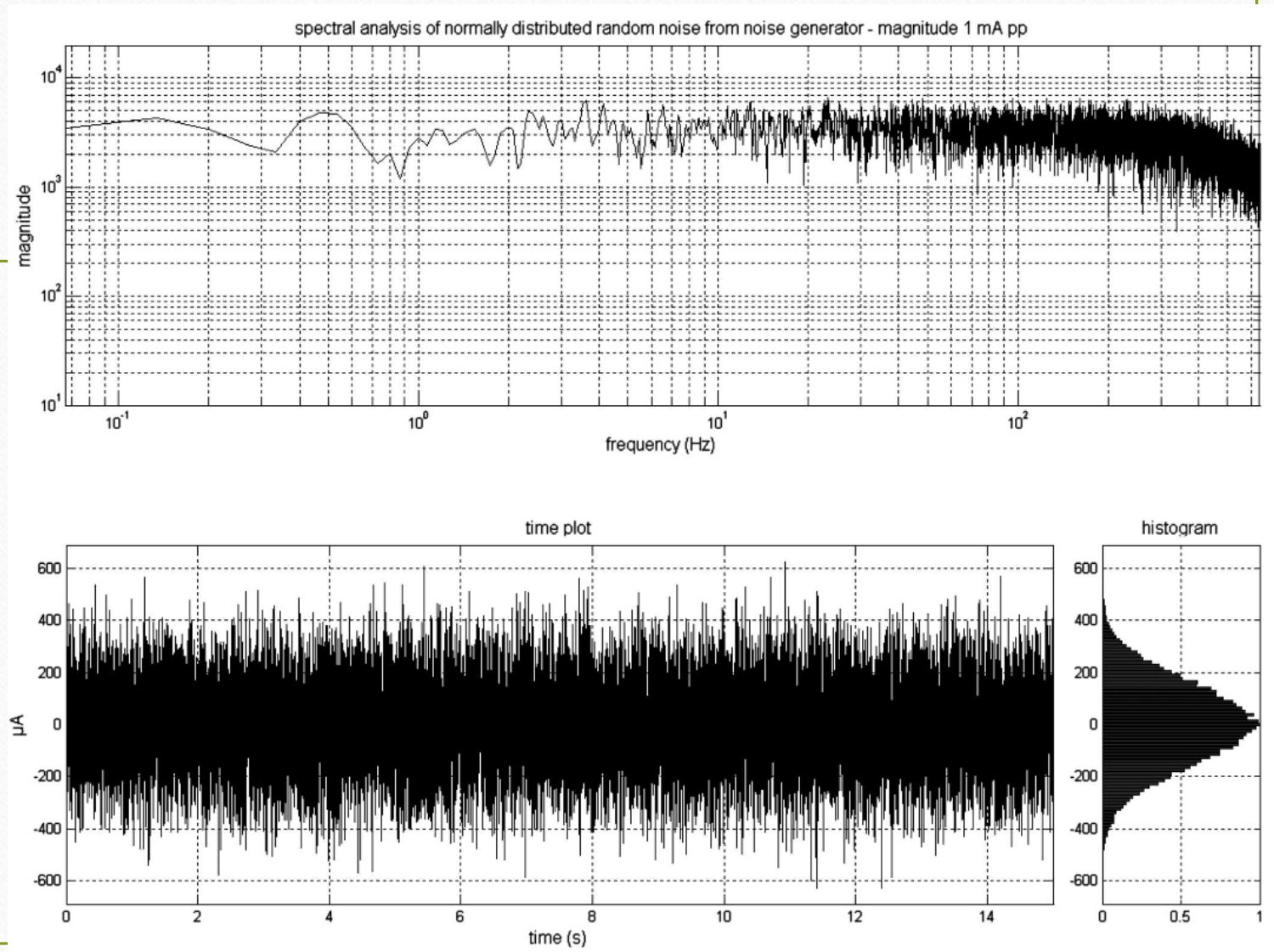


FIGURE 2 | Graphic display of the average number of adjusted pumps (the total pumps of the balloon that did not explode) for each stimulation group (A) and the average number of adjusted pumps for each group and time period (B). Error bars indicate SEM. $^{*}p < 0.05$.

Advanced TES methods

Random noise stimulation

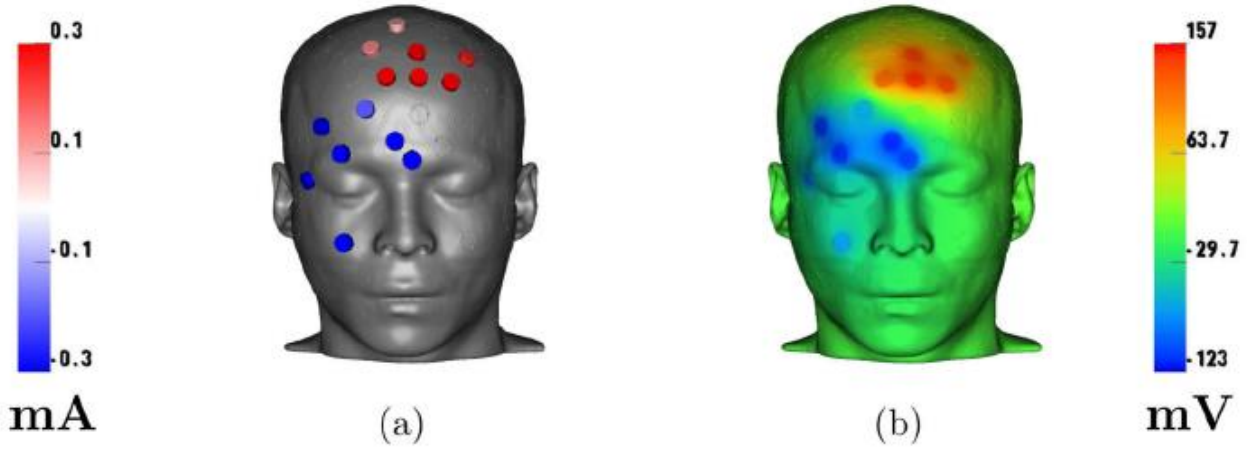
- Stimulate across all frequencies in a physiological range using a random noise frequency pattern (tRNS: transcranial random noise stimulation)
  - Normally distributed random level of current generated for every sample at a sampling rate of 1280 samples per second with no overall DC offset.
  - "white noise"

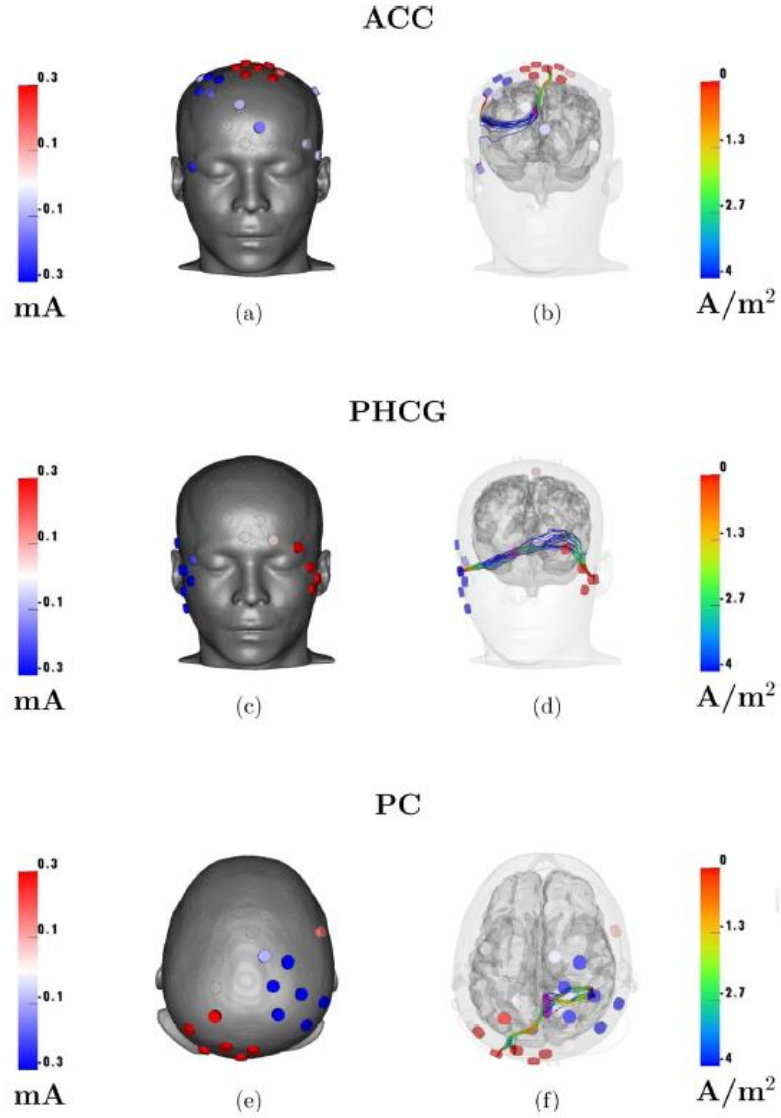


Terney et al., 2008

Dense-array TES

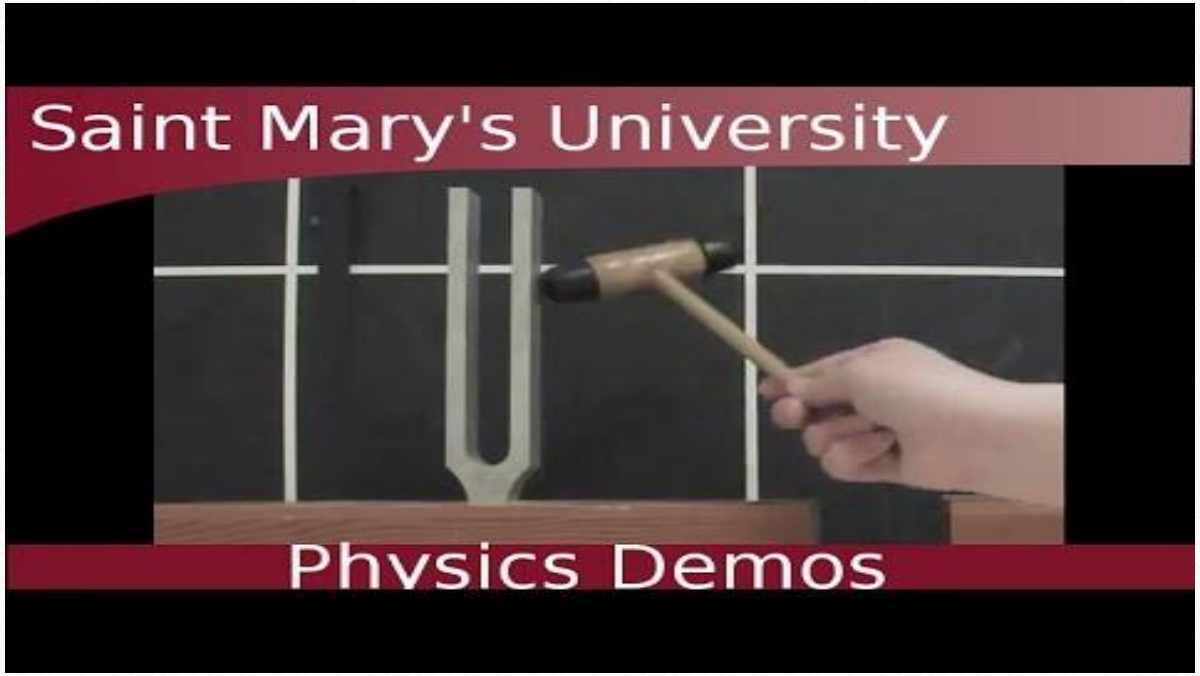
- Optimized TES to increase the spatial precision of the electric field in a focal ROI (Edwards et al., 2013; Guler et al., 2016, Ruffini et al., 2015).
  - simultaneously:
    - maximize current density inside the ROI;
    - minimize current density outside the ROI;
    - satisfy safety constraints on the total current and individual electrode currents.





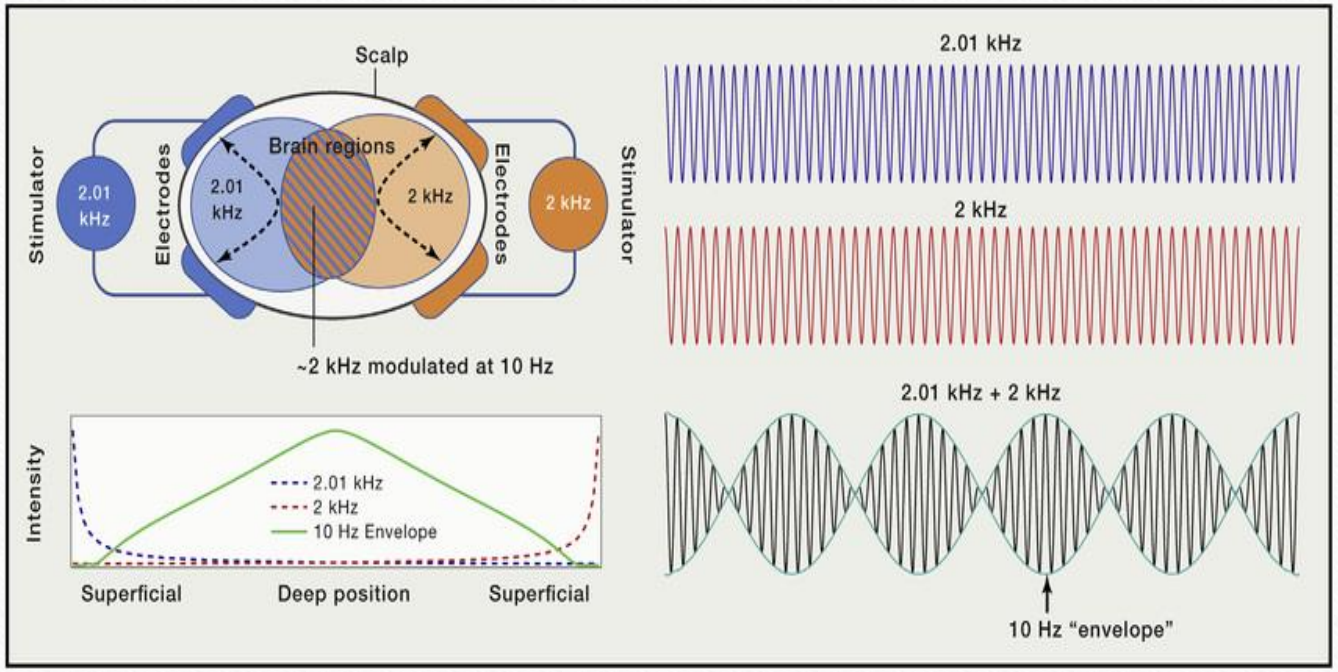
Temporal interference stimulation (TIS)

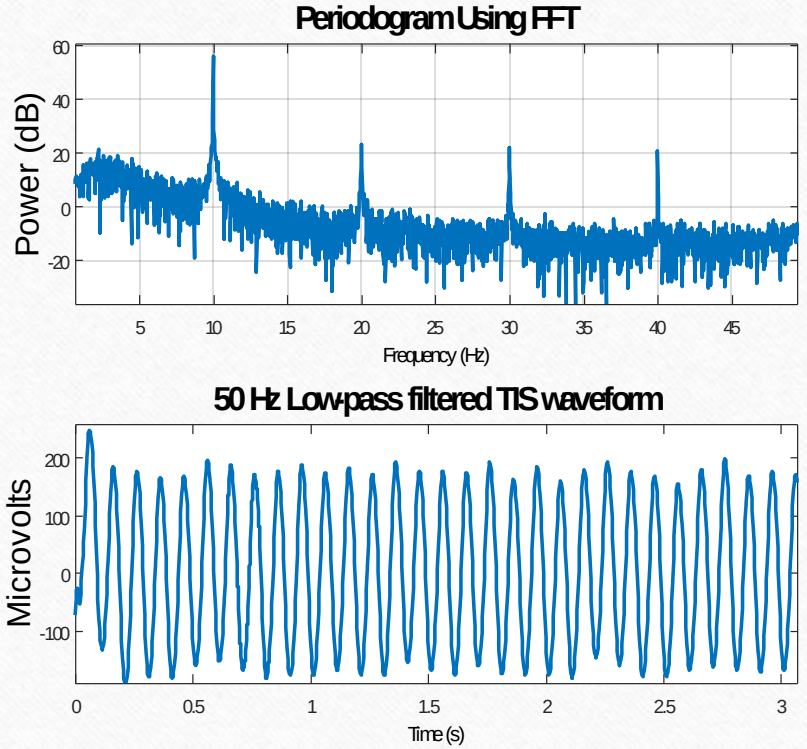
- The summation of multiple high frequency electric fields at slightly different frequencies (e.g. 2 kHz and 2.01 kHz)
  - Temporal interference pattern, or a "beat" frequency



Low frequency amplitude modulation via TIS

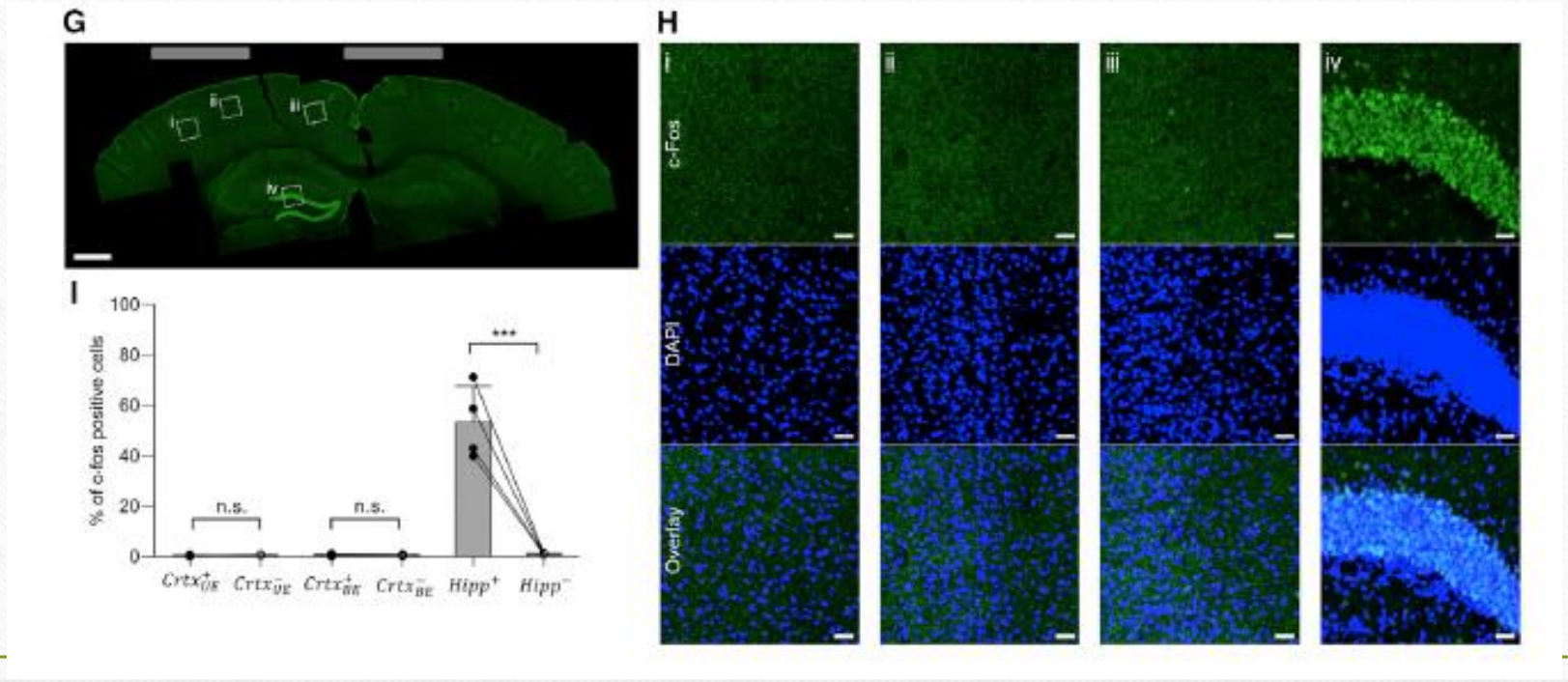
- The summation of multiple high frequency electric fields at slightly different frequencies (e.g. 2 kHz and 2.01 kHz)





Stimulate mouse hippocampus while only minimally exciting the overlaying cortex

- No tissue damage as a function of stimulation up to 125 μA.



Grossman et al. (2017)

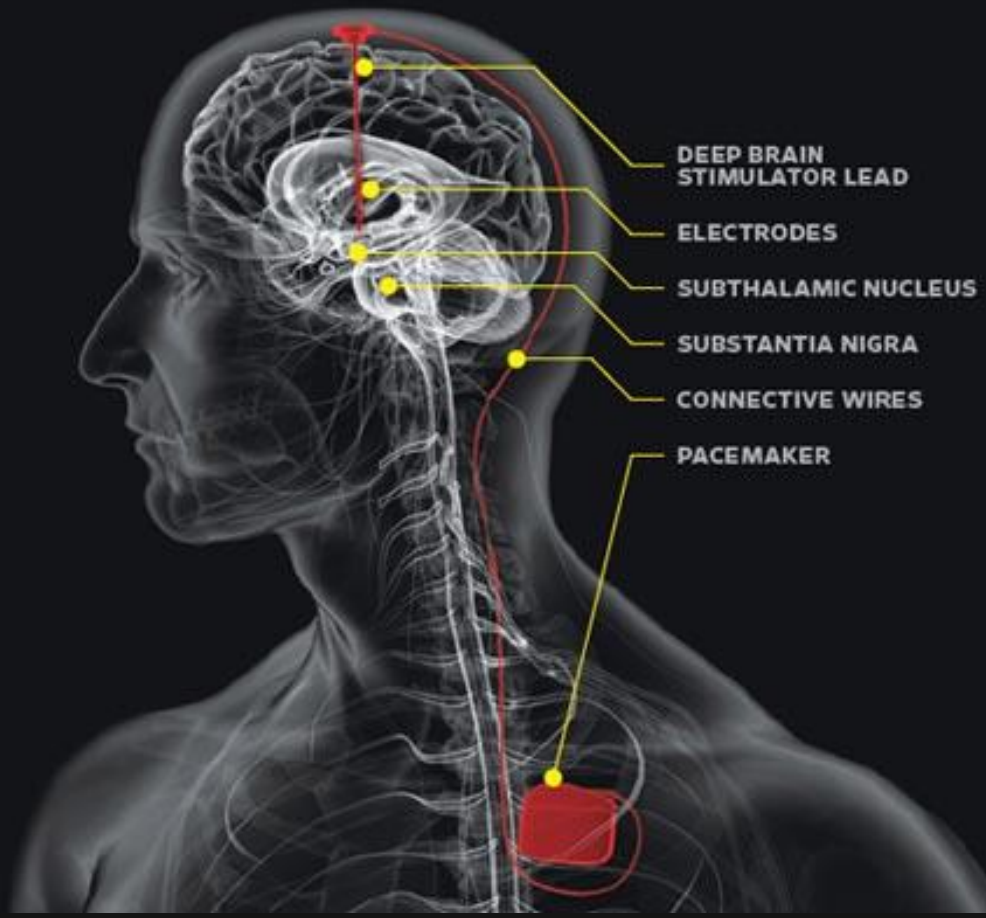
Transcranial Ultrasound, Mood, and Network Connectivity

With thanks to:

Jay Sanguinetti. Jamie Tyler, Stuart Hameroff,
Tomo Sato, Chris Daft, Lauritz Dieckman, & Ezra Smith

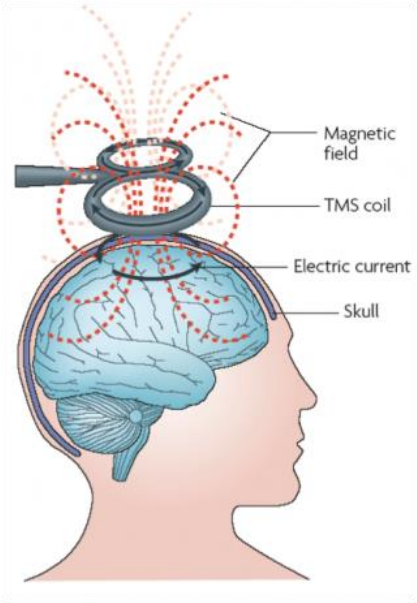
Neuromodulation

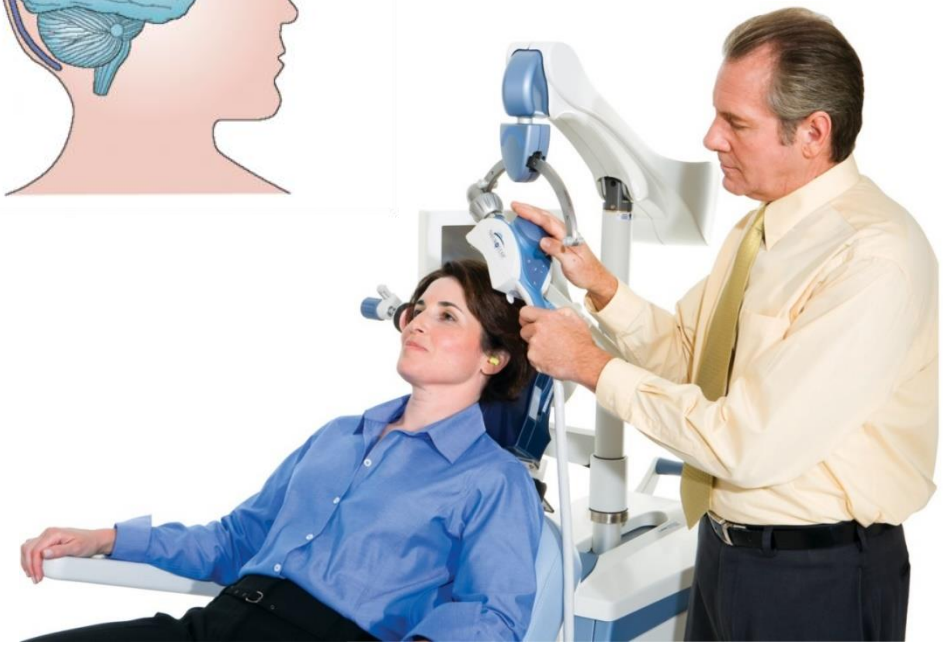
Invasive Neuromodulation: Deep Brain Stimulation (DBS)



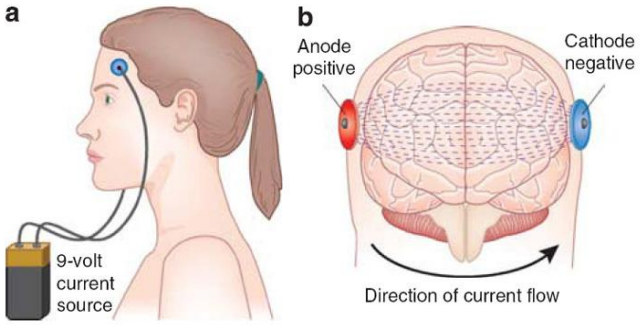
Noninvasive Neuromodulation

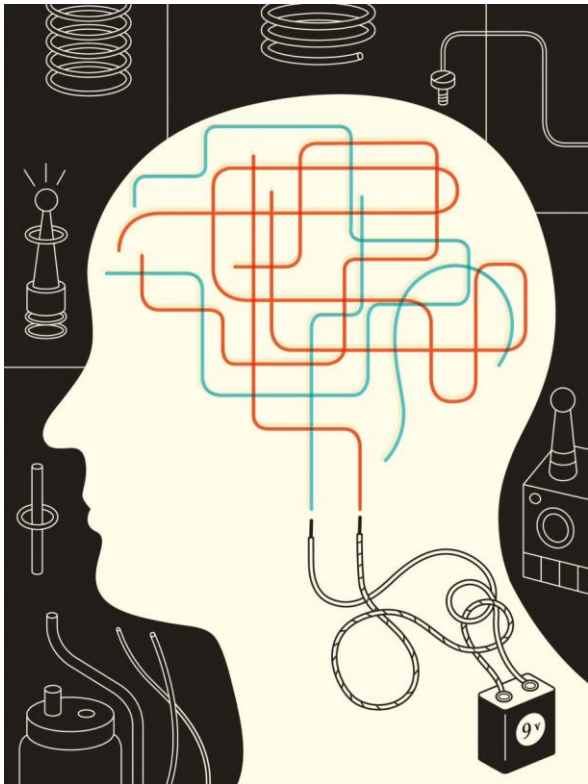
TMS



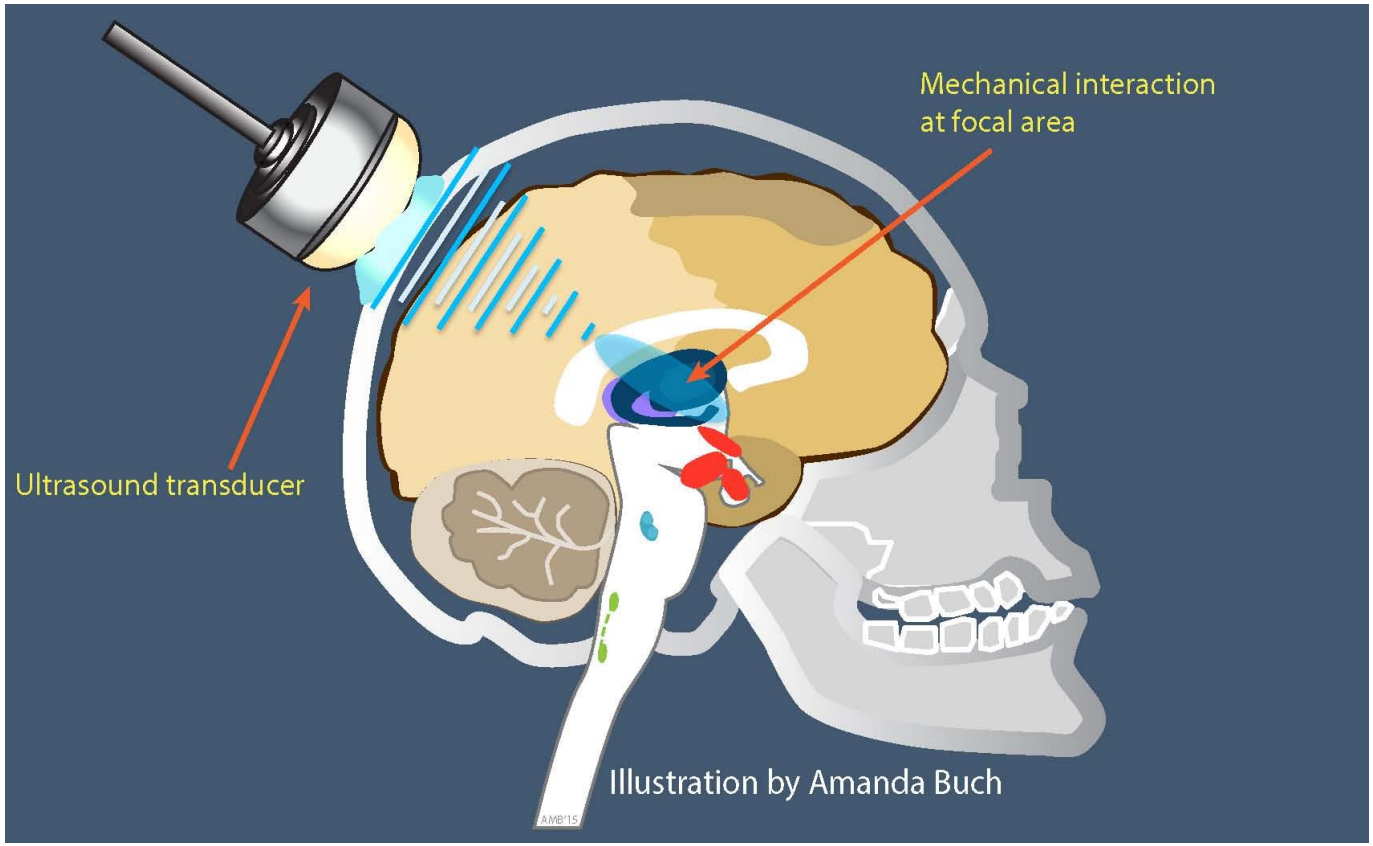


tDCS



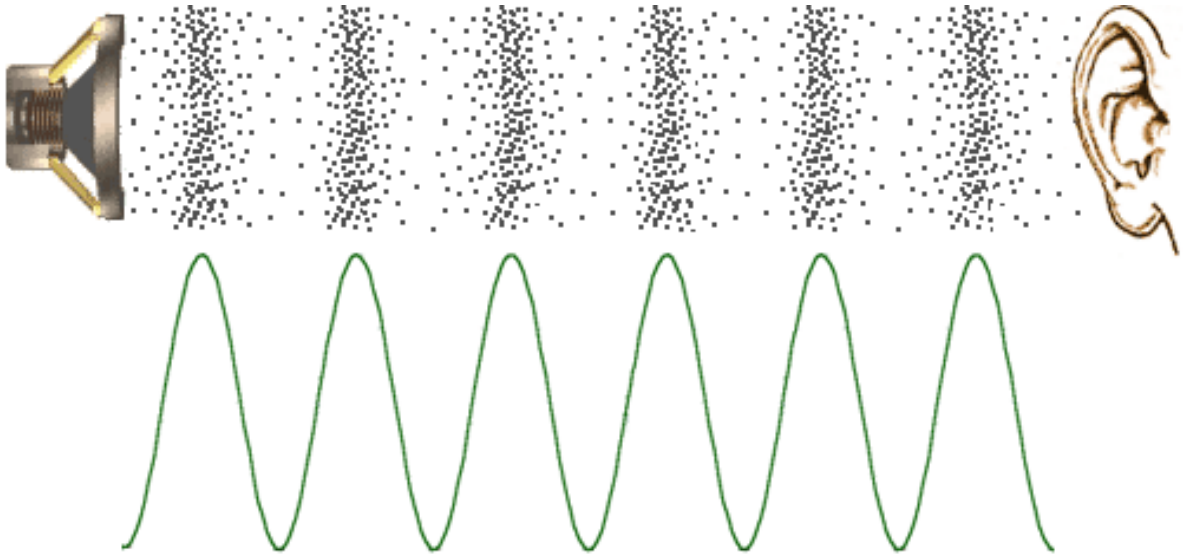


Transcranial Ultrasound (TUS)

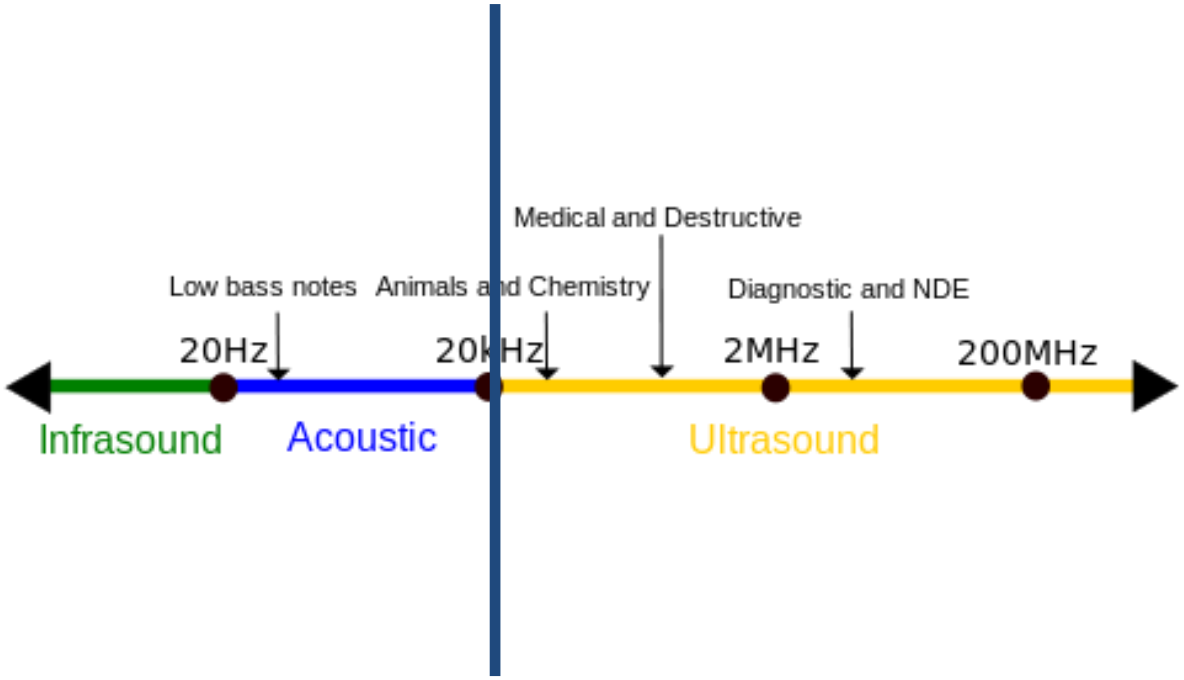


Sound Waves:

Pressure oscillations
at a given Frequency

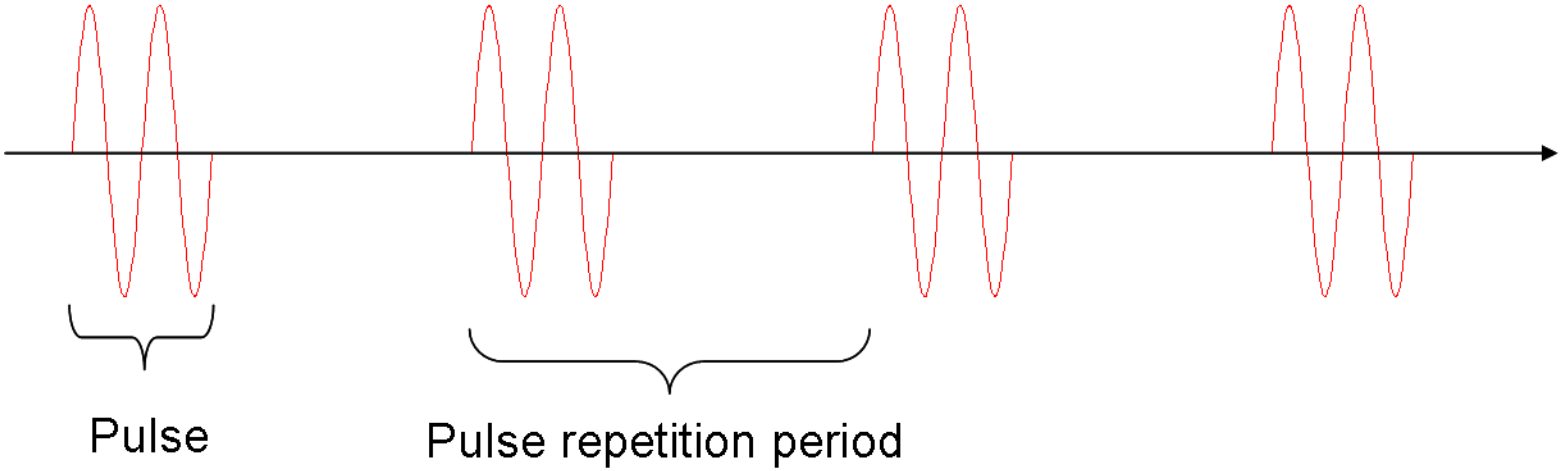


Ultrasound


Medical and Destructive
Low bass notes
Animals and Chemistry
Diagnostic and NDE
20Hz
20kHz
2MHz
200MHz
Infrasound
Acoustic
Ultrasound

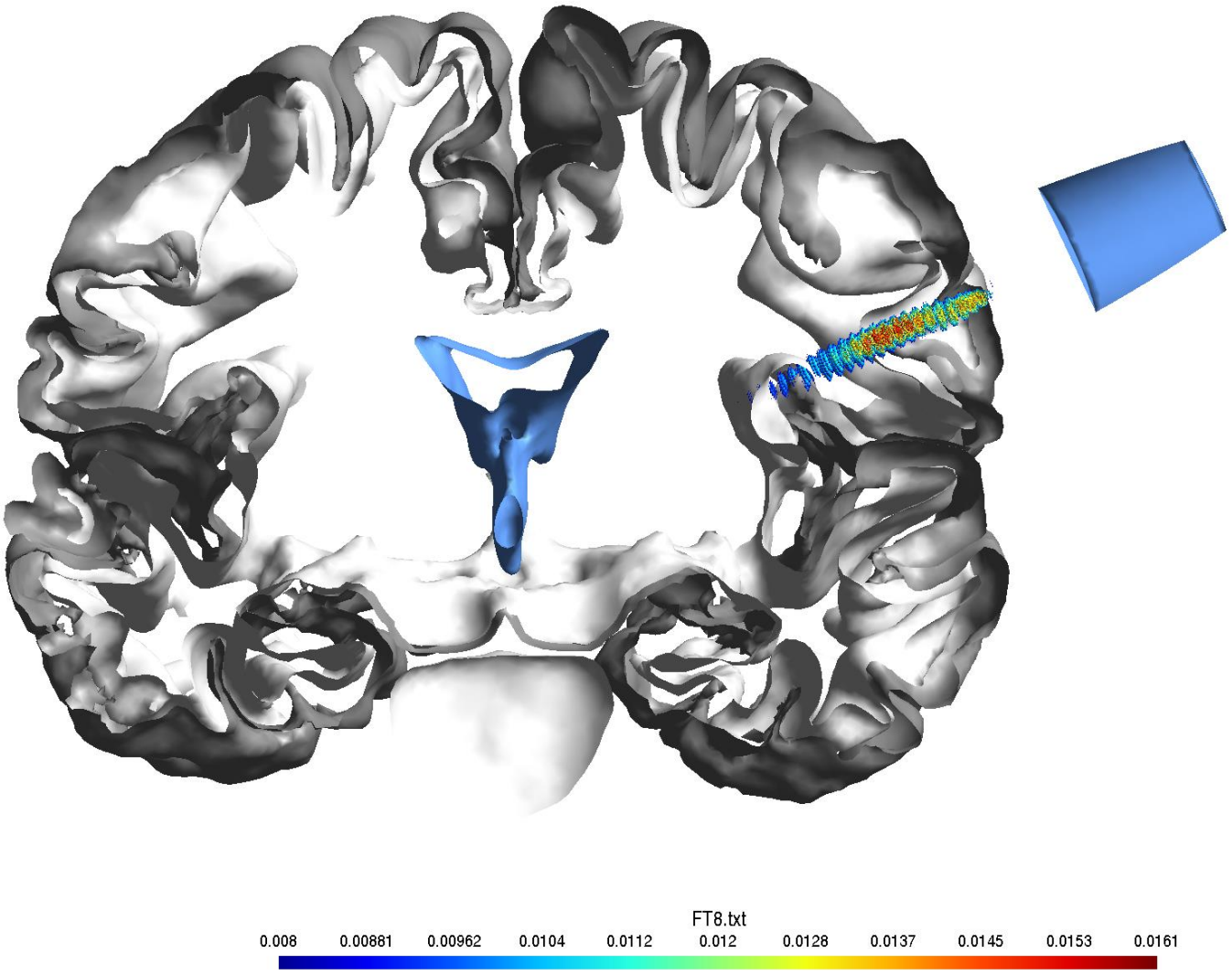
Pulsed FOCUSED ULTRASOUND

- Continuous Wave US
- Pulsed US
- Focused Ultrasound (FUS)

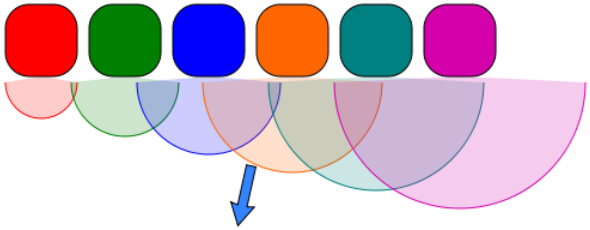


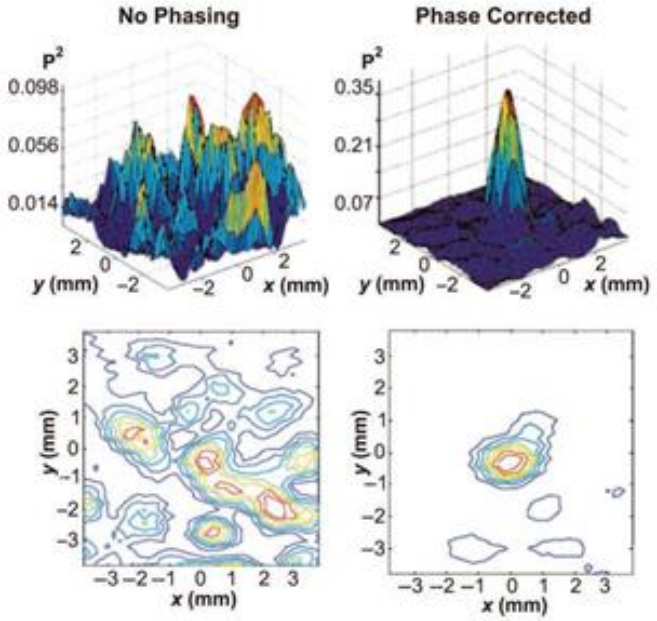
Ultrasound pressure measured in Mpa (Mega Pascals)

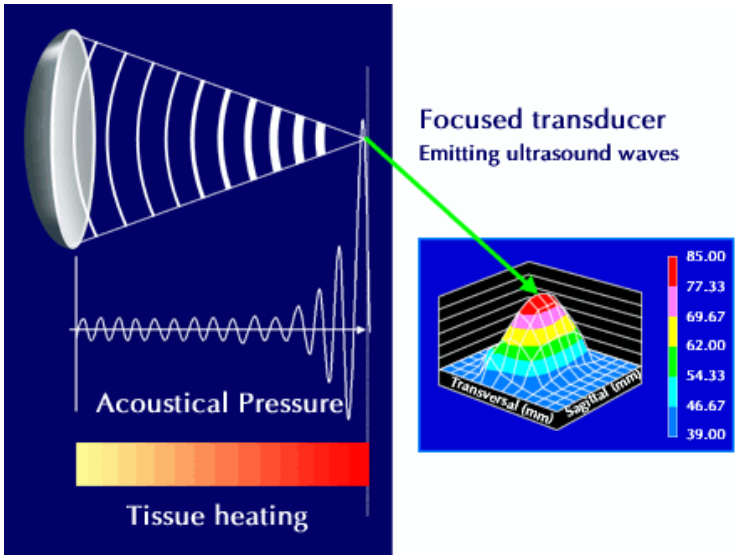
PULSED FOCUSED ULTRASOUND



Focused Ultrasound

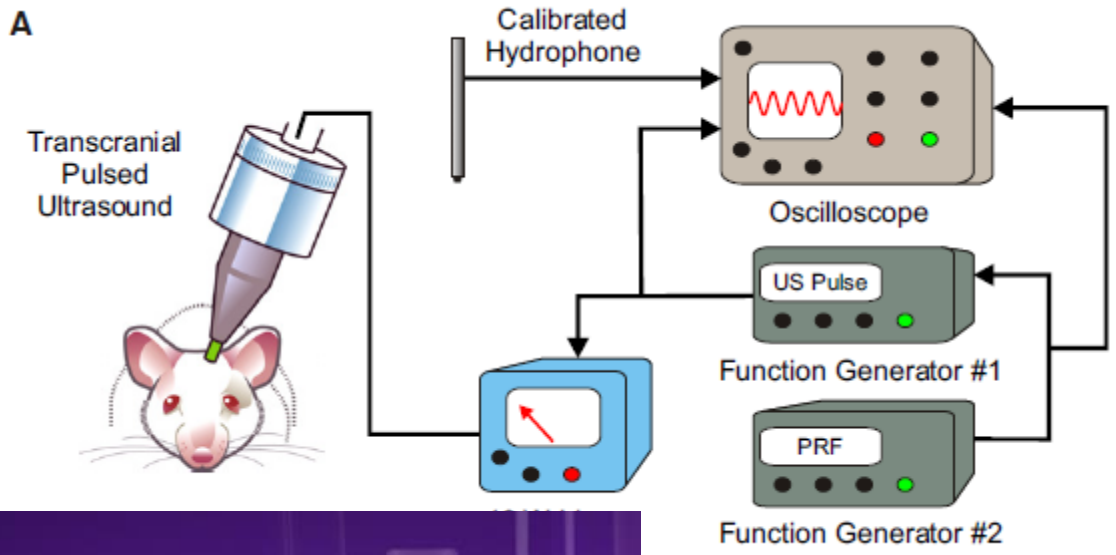






Hynynen, et al., *Phys. Med. Biol.*, 2004

Motor Movement Induction



Tufail et al, *Neuron*, 2010

nature protocols
Home | Current issue | Archive ▾ | Authors & referees ▾ | About the journal ▾

NATURE PROTOCOLS | PROTOCOL

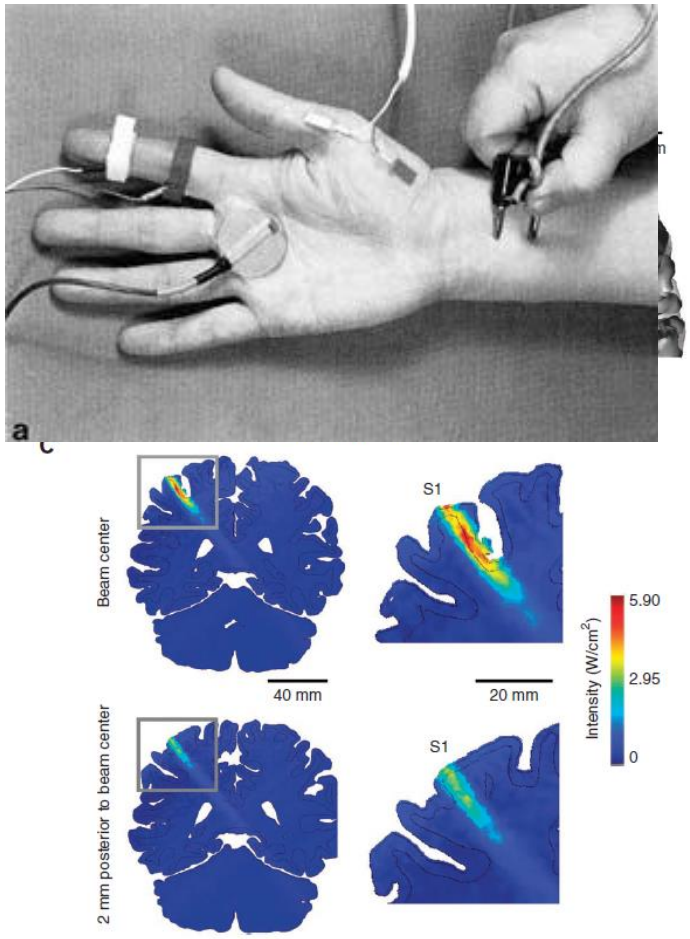
Ultrasonic neuromodulation by brain stimulation with transcranial ultrasound

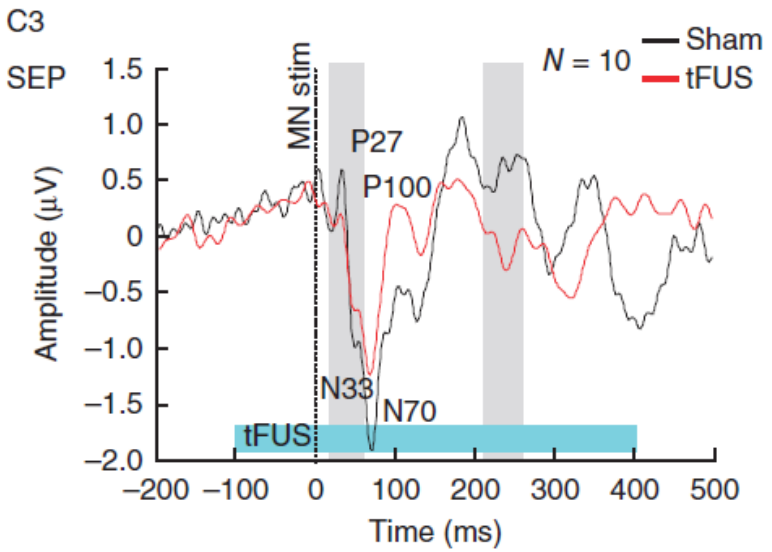
Yusuf Tufail, Anna Yoshihiro, Sandipan Pati, Monica M Li & William J Tyler

Nature Protocols **6**, 1453–1470 (2011) | doi:10.1038/nprot.2011.371
Published online 01 September 2011

Induced selective whisker & paw movement

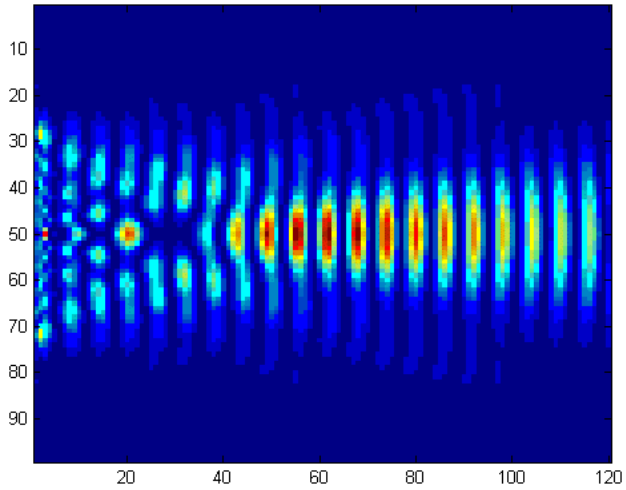
Human Somatosensory

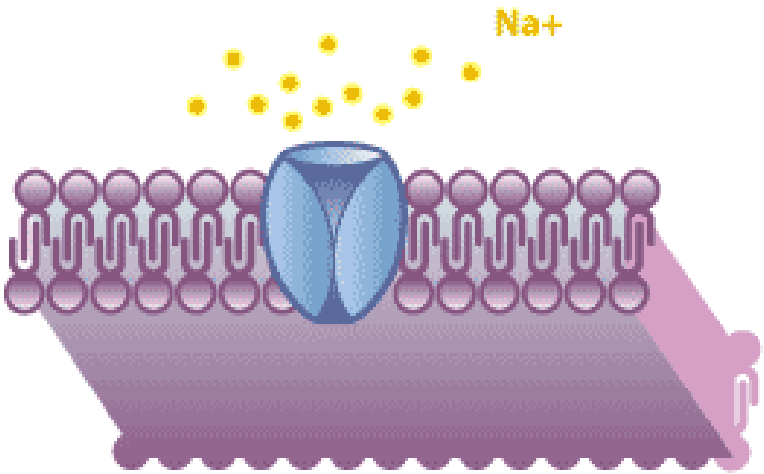




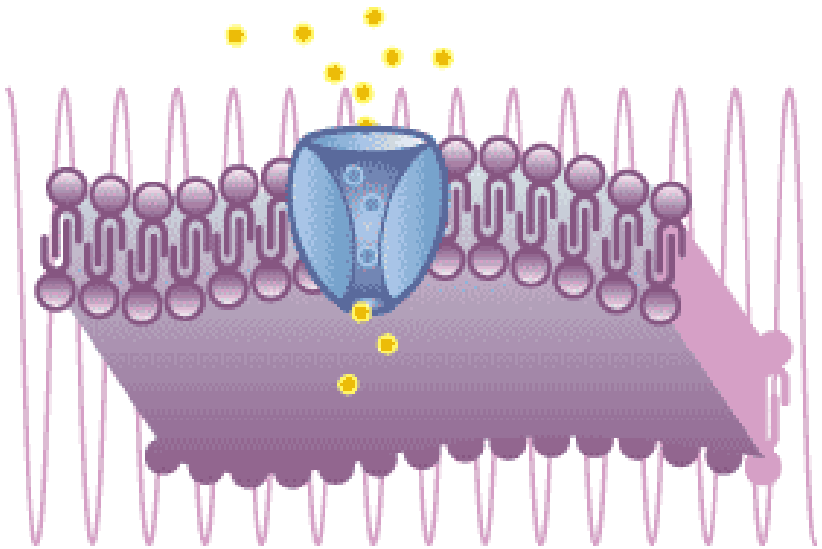
Legon, *Nature Neuro*, 2014

Biomechanical mechanism





VOLTAGE-GATED
SODIUM CHANNEL



ULTRASOUND OPENS SODIUM CHANNEL
(MECHANICAL FORCES)

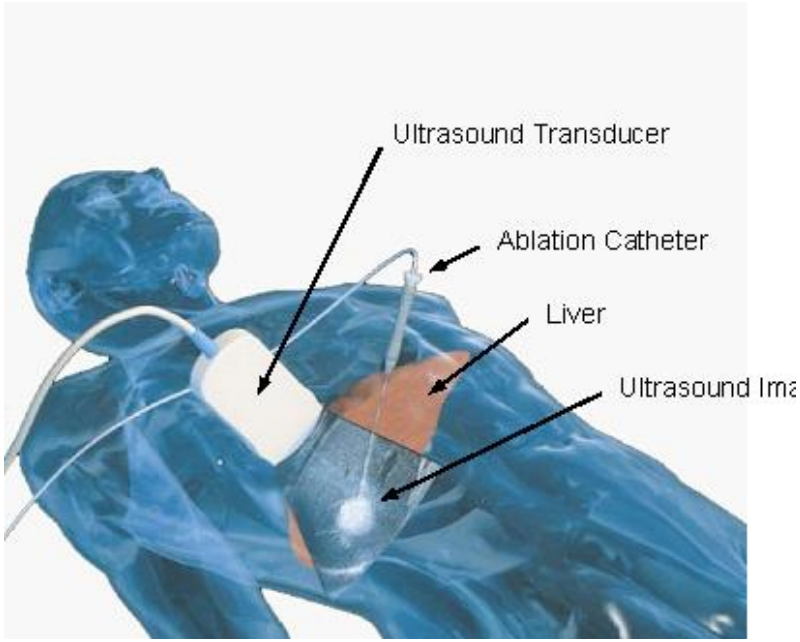
Tyler, *The Neuroscientist, 2011*

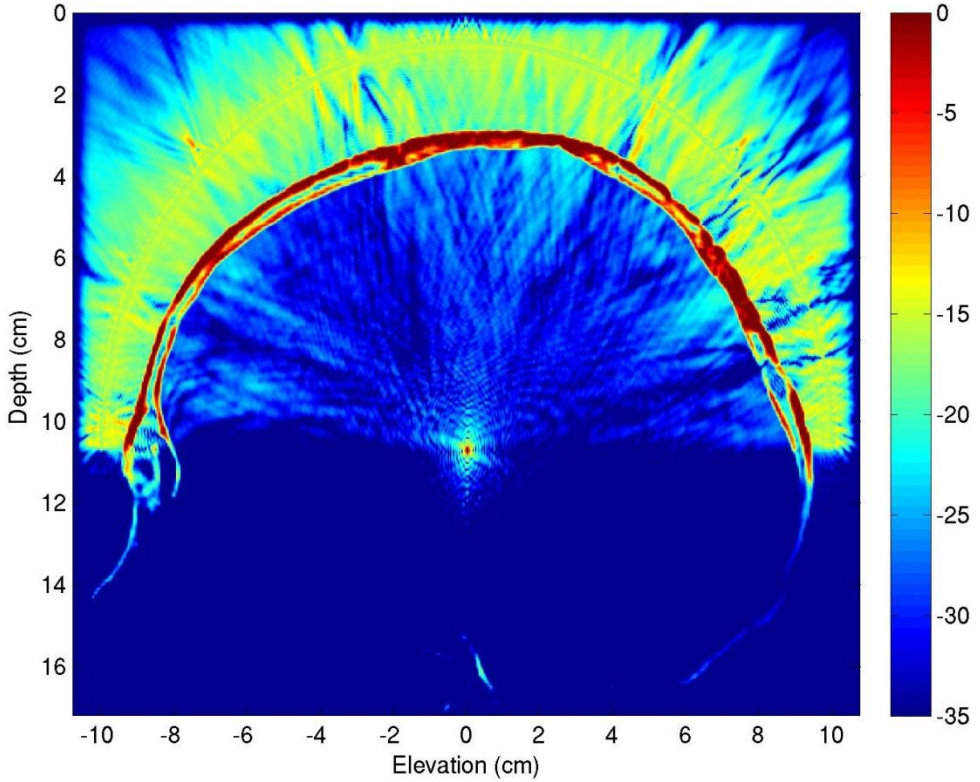
Is that safe?

Non-thermal, Low-Intensity

- Over 80 years medical use (Holscher et al., 2008)
- FDA guidelines:
  - 96 mW/cm² fetus
  - 720 mW/cm² adult, every part of body, including brain

Thermal US

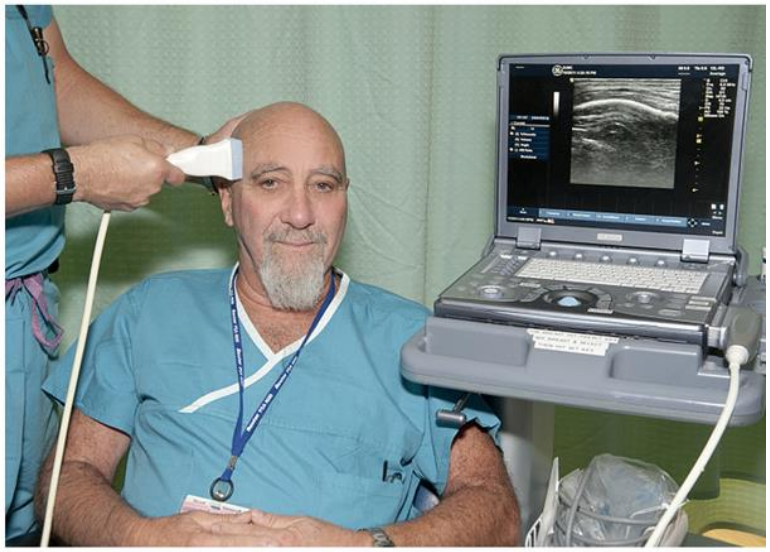




High Intensity, MR-Guided Focused Ultrasound

Nonthermal use in human neurmodulation

FIRST HUMAN BRAIN TUS STUDY



Hameroff et al., *Brain Stimulation,* 2012

No decrease in pain ($p = .07$)

Increase in mood ($p < .05$)

Where to focus the focused TUS?

- Clues from EEG Asymmetry research
  - Putative biomarker of risk for Depression
  - But … Poor spatial resolution
- Link to resting-state networks with fMRI
  - Within subjects, relates to IFG connectivity to sgACC seeded network
  - There exists a functional asymmetry in IFG in terms of cognitive control of emotion

Two TUS Experiments (GE Clinical Device)

- Experiment 1 (n=29, between Ss)
  - Aim: Determine optimal parameters
  - 2 MHz vs 8 MHz; 15 seconds stimulation
  - Non-blinded experimenters
- Experiment 2 (n=33, between Ss)
  - Aim: Rule out expectation (placebo)
  - 2 MHz vs Sham, 30 seconds stimulation
  - Double-blind
- Site in both studies is right temporal window (over right IFG)

Visual Analogue Mood Scale

- Global Affect
- Global Vigor

Mood Scale (circle a number for each question)

How alert do you feel?

0 1 2 3 4 5 6 7 8 9 10

Very little very much

How sad do you feel?

0 1 2 3 4 5 6 7 8 9 10

Very little very much

How tense do you feel?

0 1 2 3 4 5 6 7 8 9 10

Very little very much

How much of an effort is it to do anything?

0 1 2 3 4 5 6 7 8 9 10

Very little very much

How happy do you feel?

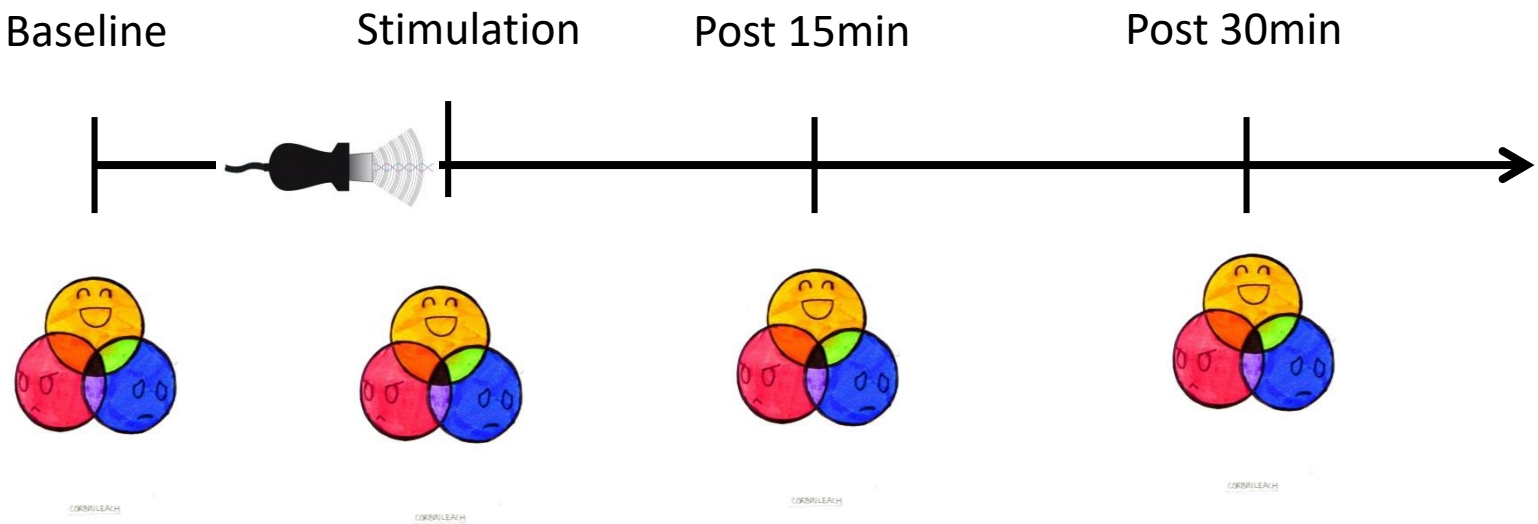
0 1 2 3 4 5 6 7 8 9 10

Very little very much

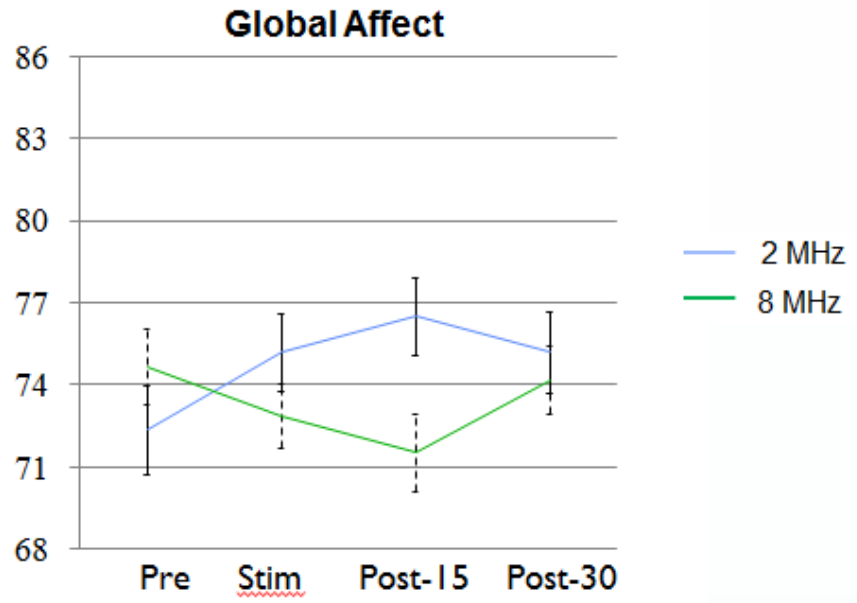
How calm do you feel?

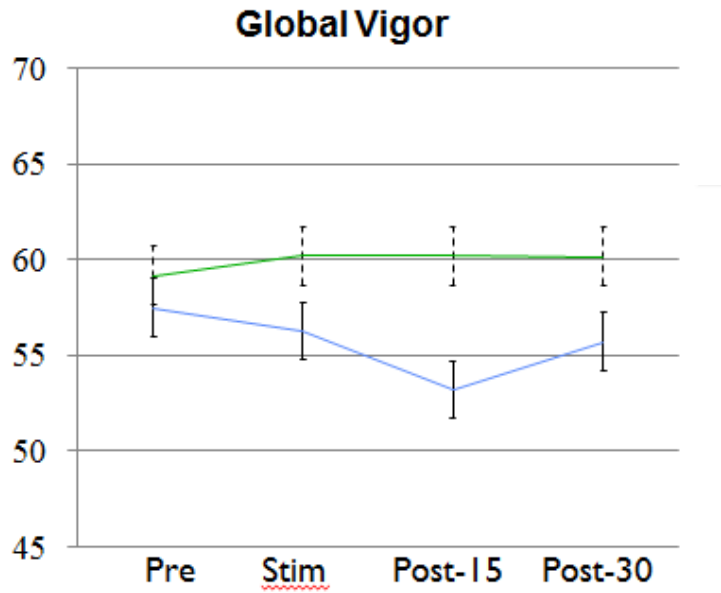
0 1 2 3 4 5 6 7 8 9 10

Very little very much

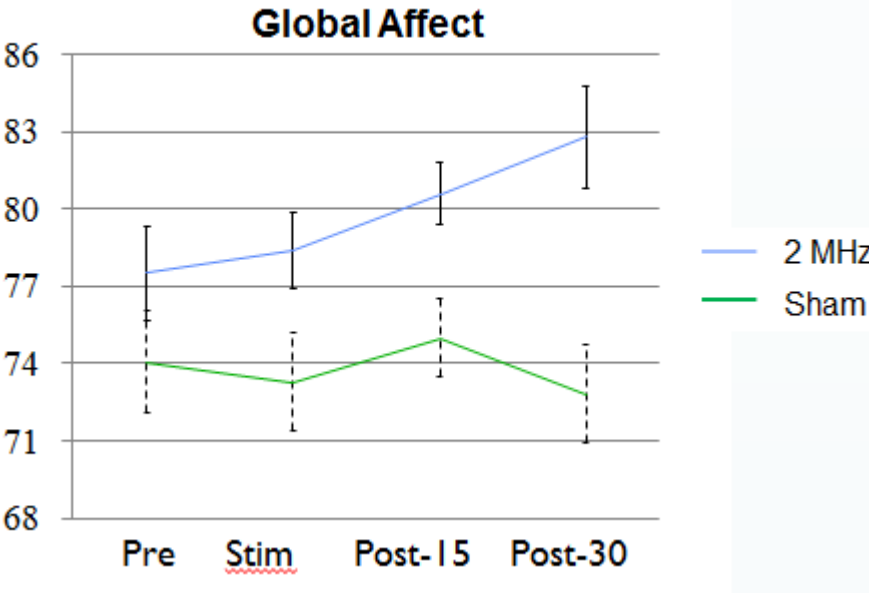

Baseline
Stimulation
Post 15min
Post 30min

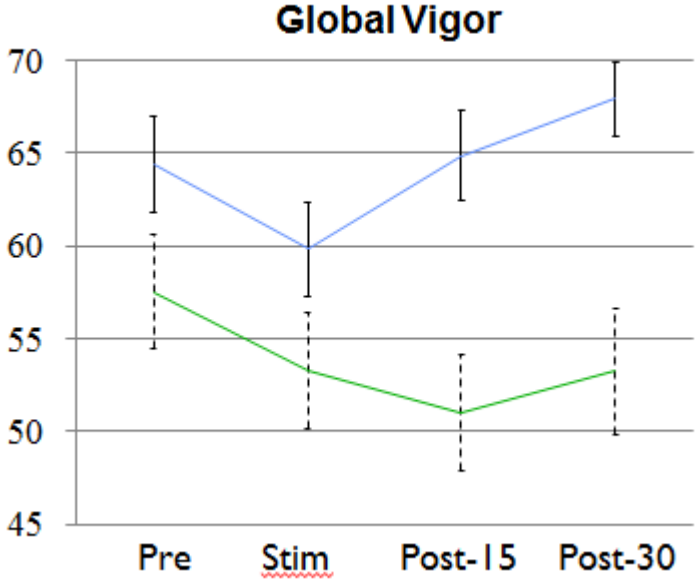
Experiment 1: 2 MHz vs 8 Mhz – 15 seconds





Experiment 2: 2Mhz vs Sham – 30 Seconds

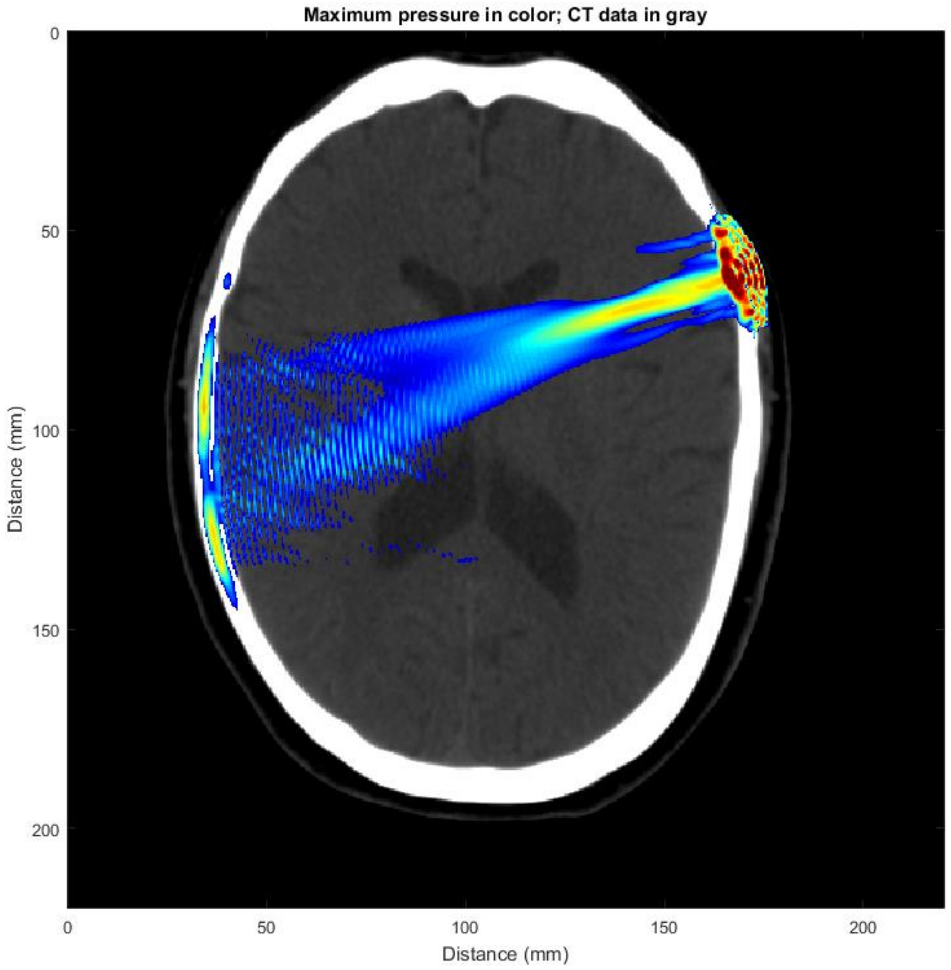


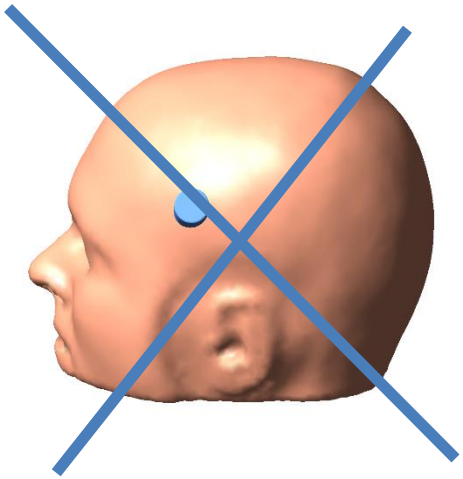


Human Focused TUS Device

Issy Goldwasser William Tyler

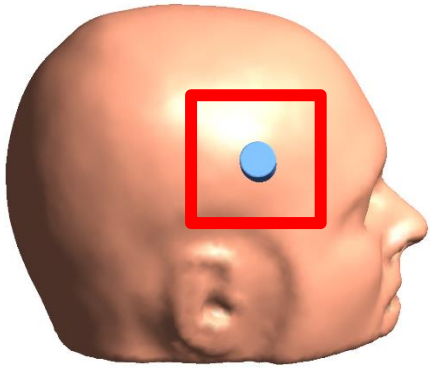
Focused TUS Modeling





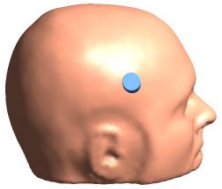
TUS

Placebo



TUS

Placebo



n = 56

Right side

TUS

Placebo

Global Affect

6

4

2

0

-2

-4

*

Baseline

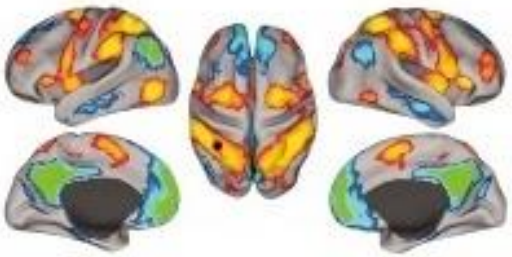
After

Post-15

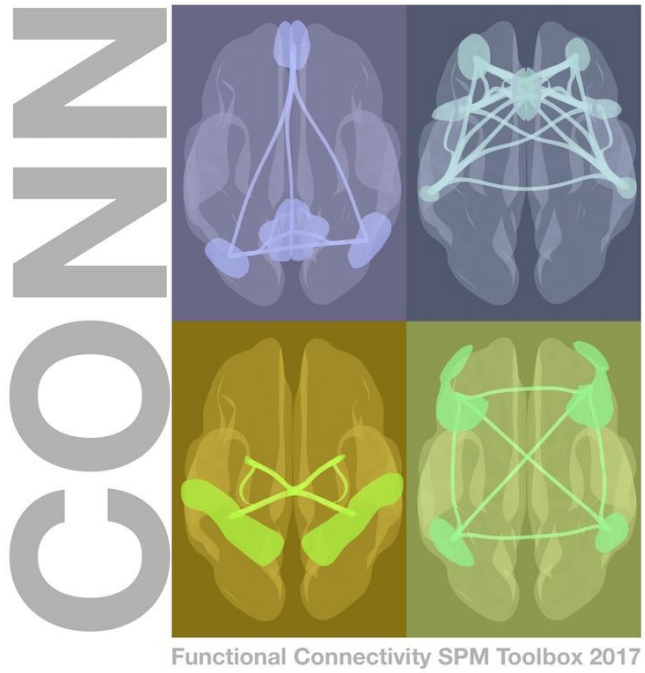
Post-30

Resting State Functional Connectivity

Seed-ROI based connectivity analysis



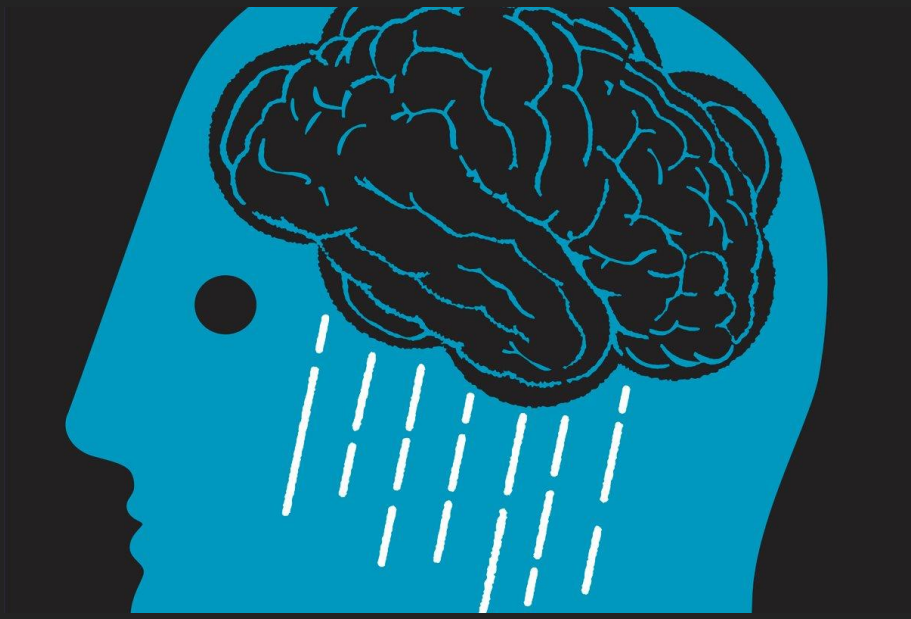
Michael D. Fox (2005) PNAS



Whitfield-Gabrieli, S., and Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity*. doi:10.1089/brain.2012.0073

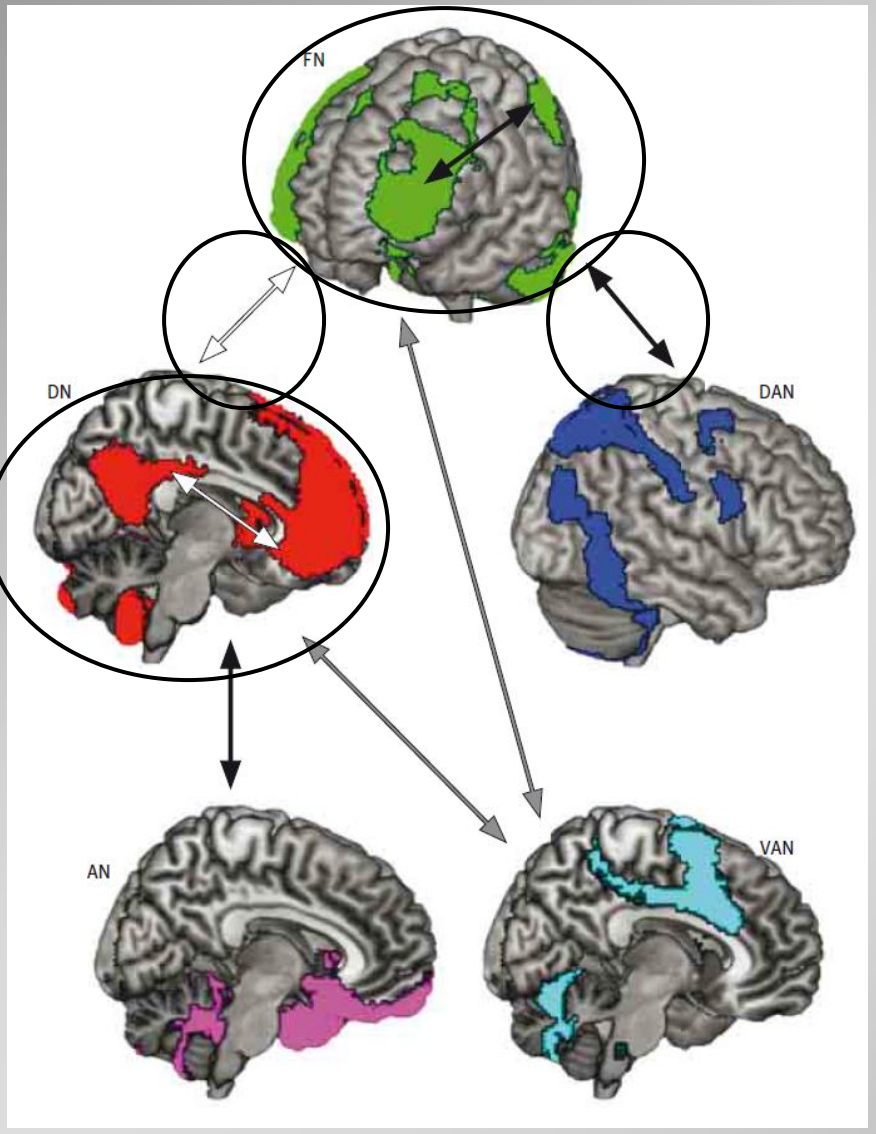
Connectivity in Mood Disorders

- Reduced coordination in cognitive control systems
- Altered communication between control systems
  - Internal thought (default mode)
  - Emotional regulation



Kaiser Andrews-Hanna Wager & Pizzagalli (2015), *JAMA Psychiatry*

Aberrant connectivity in MDD



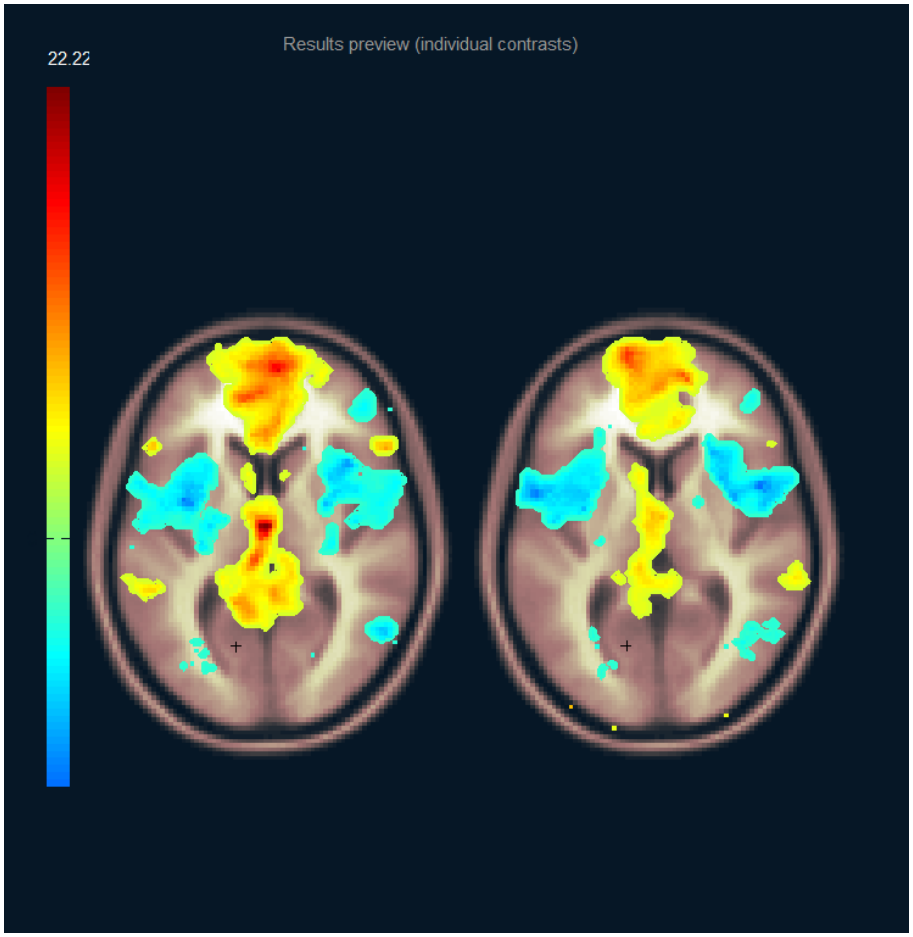
- ↑ Default Mode (DN): Propensity for self-focused mentation
- ↓ Frontoparietal (FN) connectivity: Deficits in Cognitive Control
- ↑ FN-DN Connectivity, along with ↓ FN-DAN Connectivity: biases toward ruminative thoughts at the cost of attending to the external world

Kaiser, Andrews-Hanna, Wager, & Pizzagalli (2015) *JAMA Psychiatry*

Administering 2 minutes of TUS

PRE-POST CHANGES IN RSFMRI

Seed: DMN



Pre TUS Post TUS

Reduced functional connectivity post relative to pre for three seed regions							
Seed Region	Cluster Coordinates	Cluster Size	Cluster Regions	BA	Voxels in Regions	Coverage	Cluster p value (p< .05 FDR)
Inferior Frontal Gyrus	-06 +28 -24	548	(L) Subgenual cortex	25	101	17%	0.001
			(R) Orbitofrontal cortex	11	83	3%	
			(L) Inferior prefrontal gyrus	47	41	2%	
			(L) Orbitofrontal cortex	11	32	1%	
			(L) Dorsal anterior cingulate	32	17	1%	
			(L) Posterior entorhinal cortex	28	12	2%	
			(L) Anterior entorhinal cortex	34	12	2%	
			(R) Subgenual cortex	25	4	1%	
			Not assigned or < 1% coverage		246		
Medial Prefrontal	-12 +08 +48	232	(L) Premotor cortex	6	96	1%	0.008
			(L) Ventral anterior cingulate	24	66	4%	
			(R) Premotor cortex	6	45	1%	
			Not assigned or < 1% coverage	-	25	-	
Posterior Cingulate	+20 -40 -10	263	(R) Parahippocampal cortex	36	97	13%	0.002
			(R) Fusiform gyrus	37	47	3%	
			(R) Associative visual cortex	19	26	1%	
			(R) Perirhinal Cortex	35	18	5%	
			(R) Posterior entorhinal cortex	28	7	1%	
			Not assigned or < 1% coverage	-	68	-	
	-34 -88 +28	145	(L) Associative visual cortex	19	105	2%	0.033
			Not assigned or < 1% coverage	-	40	-	

TUS Synopsis

- TUS to rIFG: positive mood effects
- Site specific changes in mood
- fMRI connectivity: regulation of mood and cognitive-control networks
- Low-intensity TUS as a safe, non-invasive brain stimulation method alongside TMS and tDCS.
- TUS offers advantages over established methods.
  - Can be focused for high spatial resolution
  - Can reach deep brain structures
  - Does not cause sensations on the skin
  - Brain mapping