Neurostimulation & Neuromodulation
Introduction to Transcranial Magnetic Stimulation

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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.
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. 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, on pyramidal conduction velocity in multiple sclerosis, and on pelvic neuropathy related to faecal incontinence.
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
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
1. Calibrate TMS intensity
2. Measure cortical excitability

Active Motor I/O Curve

\[ \text{Slope} = \frac{\text{MEP}_{\text{max}} - \text{MEP}_{\text{min}}}{2 \times \text{Spread}} \]

Lim, Sundman & Chou, manuscript under revision
2. Measure cortical excitability

Single-Pulse TMS

Active Motor Response

EMG (mV)

-1
0
1

TMS
-50
0
CSP
250

Time (msec)

Lim, Sundman & Chou, manuscript under revision
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
Single-Pulse TMS

Repetitive TMS

Low-Frequency rTMS

High-Frequency rTMS

Decreasing Brain Activity

Increasing Brain Activity

< 1 Hz

> 5 Hz
TMS effect does not last beyond the duration of stimulation (100-300 ms)

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.
In 2013, FDA approved the first device using single-pulse TMS as a treatment for migraine with aura.
In 2018, FDA permitted marketing of the first device using Deep TMS as a treatment for obsessive-compulsive disorder.
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.
Effect of Repetitive Transcranial Magnetic Stimulation on fMRI Resting-State Connectivity in Multiple System Atrophy

Ying-hui Chou, Hui You, Han Wang, Yan-Ping Zhao, Bo Hou, Nan-kuei Chen, and Feng Feng
TMS

Single-Pulse TMS
TMS effect does not last beyond the duration of stimulation (70-300 ms)

Repetitive TMS

Low-Frequency TMS
Effect of 1 session of repetitive TMS lasts up to 60 minutes

High-Frequency TMS
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 propagating 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.

After

Transient enlargements 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>
<thead>
<tr>
<th>Strong potential hazard</th>
<th>Relative hazard</th>
<th>Strong potential hazard</th>
<th>Relative hazard</th>
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<tr>
<td>Alcohol</td>
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<td>Quetiapine</td>
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<tr>
<td>Amitriptyline</td>
<td>Anticholinergics</td>
<td>Reboxetine</td>
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<td>Amphetamines</td>
<td>Antihistamines</td>
<td>Risperidone</td>
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<td>BCNU</td>
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<td>Fluvoxamine</td>
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<td>Phencyclidine (PCP)</td>
<td>Haloperidol</td>
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<td>Imipenem</td>
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<td>Olanzapine</td>
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<td>Paroxetine</td>
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<td></td>
<td>Pimozide</td>
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Najib et al., 2014
## TMS Safety Guidelines

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

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<thead>
<tr>
<th>Freq (Hz)</th>
<th>90 % MT</th>
<th>100 % MT</th>
<th>110 % MT</th>
<th>120 % MT</th>
<th>130 % MT</th>
<th>140 % MT</th>
<th>150 % MT</th>
<th>160 % MT</th>
<th>170 % MT</th>
<th>180 % MT</th>
<th>190 % MT</th>
<th>200 % MT</th>
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<td>&gt;1,800</td>
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<td>&gt;5</td>
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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.

<table>
<thead>
<tr>
<th>Inter-train interval (ms)</th>
<th>Stimulus intensity (% of MT)</th>
<th>100%</th>
<th>105%</th>
<th>110%</th>
<th>120%</th>
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<td>Safe</td>
<td>Safe</td>
<td>Safe</td>
<td>Insufficient data</td>
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<td></td>
<td></td>
<td></td>
<td>Safe</td>
<td>Safe</td>
<td>Unsafe (EMG spread after 2 trains)</td>
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<td>Unsafe (EMG spread after 3 trains)</td>
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<td>Part A</td>
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<td>5000</td>
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<td>Frequency (Hz)</td>
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<td></td>
<td>Duration (s)/pulses</td>
<td>Duration (s)/pulses</td>
<td>Duration (s)/pulses</td>
<td>Duration (s)/pulses</td>
<td>Duration (s)/pulses</td>
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<td>Part B</td>
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*Rossi et al., 2009*

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*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.*
Thank you!

Ying-hui Chou
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Brain Imaging and TMS Laboratory
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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
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 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).
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)
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
Gamma Entrainment

- 40 Hz tACS increases the duration of perceived vertical motion.
Interference
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 Zeehle et al. (2013) 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)
Alpha Power Increase After Transcranial Alternating Current Stimulation at Alpha Frequency (α-tACS) Reflects Plastic Changes Rather Than Entrainment

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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.

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• $\alpha$-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) ± 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°.

Polenia et al., 2012
• Balloon analog risk task during dlPFC stimulation (Sela et al., 2012)
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 $\mu$A.

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

- 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

Motor Movement Induction

Induced selective whisker & paw movement
Human Somatosensory

Biomechanical mechanism

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
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

<table>
<thead>
<tr>
<th>Mood Scale (circle a number for each question)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How alert do you feel?</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Very little</td>
</tr>
<tr>
<td>How sad do you feel?</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Very little</td>
</tr>
<tr>
<td>How tense do you feel?</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Very little</td>
</tr>
<tr>
<td>How much of an effort is it to do anything?</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Very little</td>
</tr>
<tr>
<td>How happy do you feel?</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Very little</td>
</tr>
<tr>
<td>How calm do you feel?</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Very little</td>
</tr>
</tbody>
</table>
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
Global Affect

Baseline           After               Post

-15             Post
-30

-4
-2
0
2
4
6

Right side

TUS
Placebo

n = 56

Global Affect

Baseline       After       Post-15       Post-30

*
Resting State Functional Connectivity

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

Administering 2 minutes of TUS

PRE-POST CHANGES IN RSFMRI
Seed: DMN

Reduced functional connectivity post relative to pre for three seed regions

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

Pre TUS

Post TUS
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