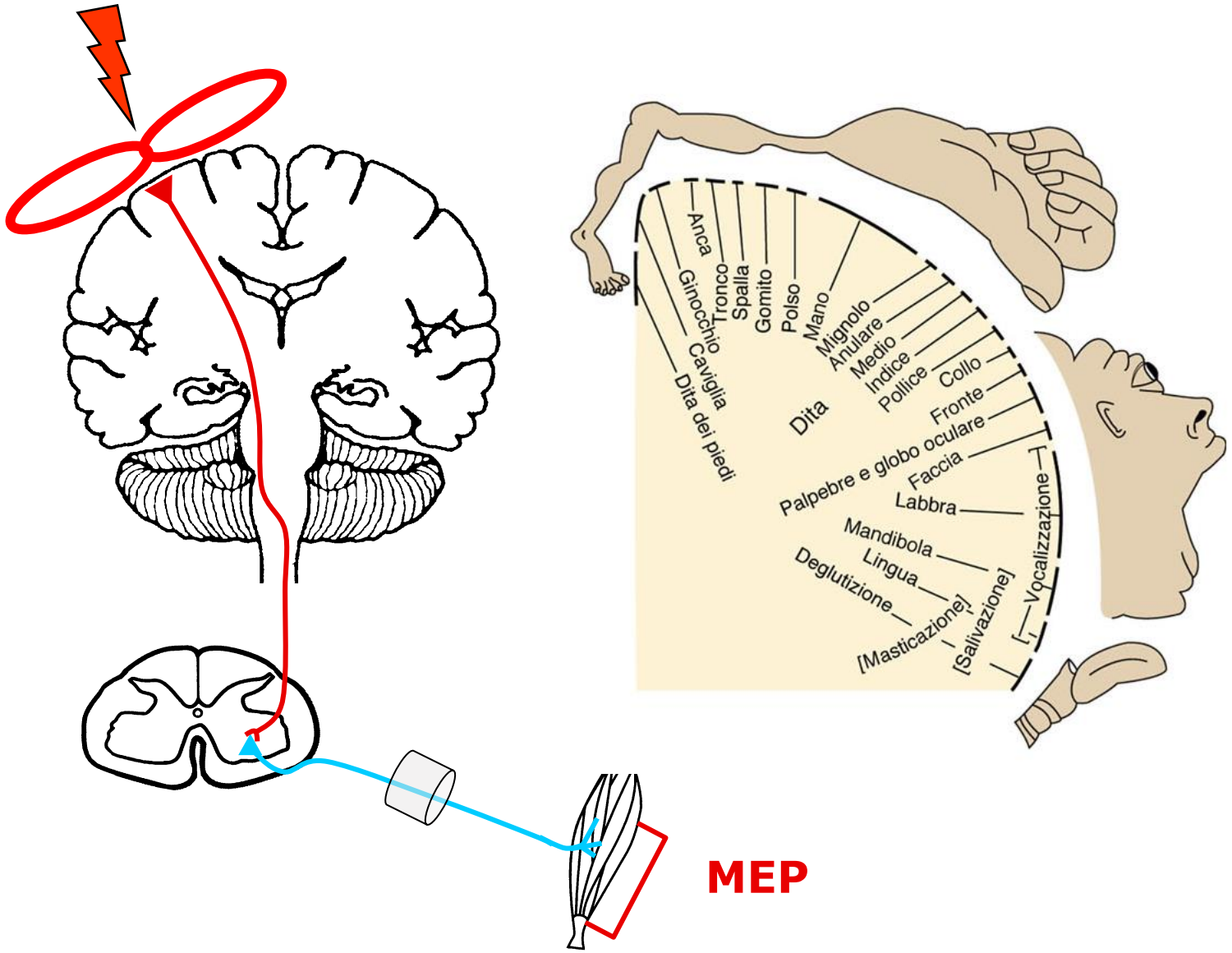
Therapeutic application of TMS: present and future

Angelo Quartarone

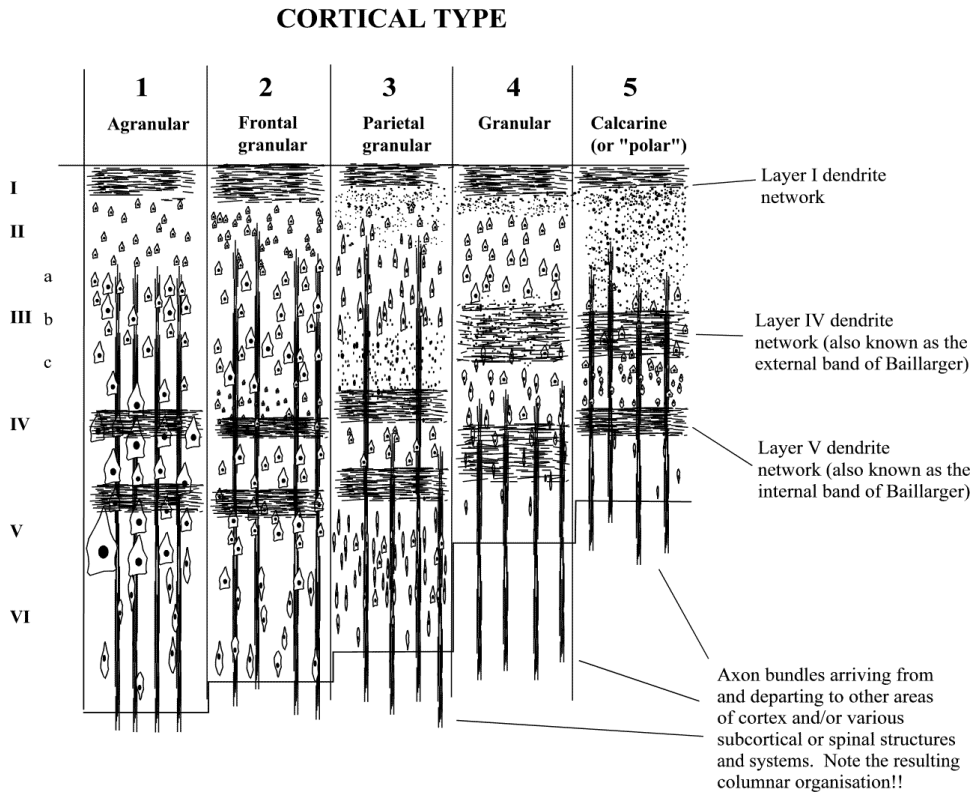
Catania, SIIN regionale 15 febbraio 2019

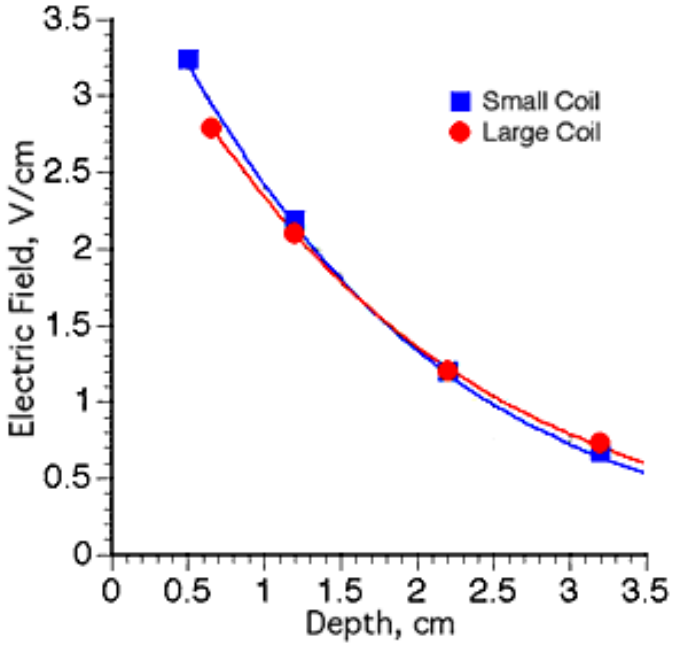
Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

Motor pathways evaluation



Which interneurons are targeted by TMS?



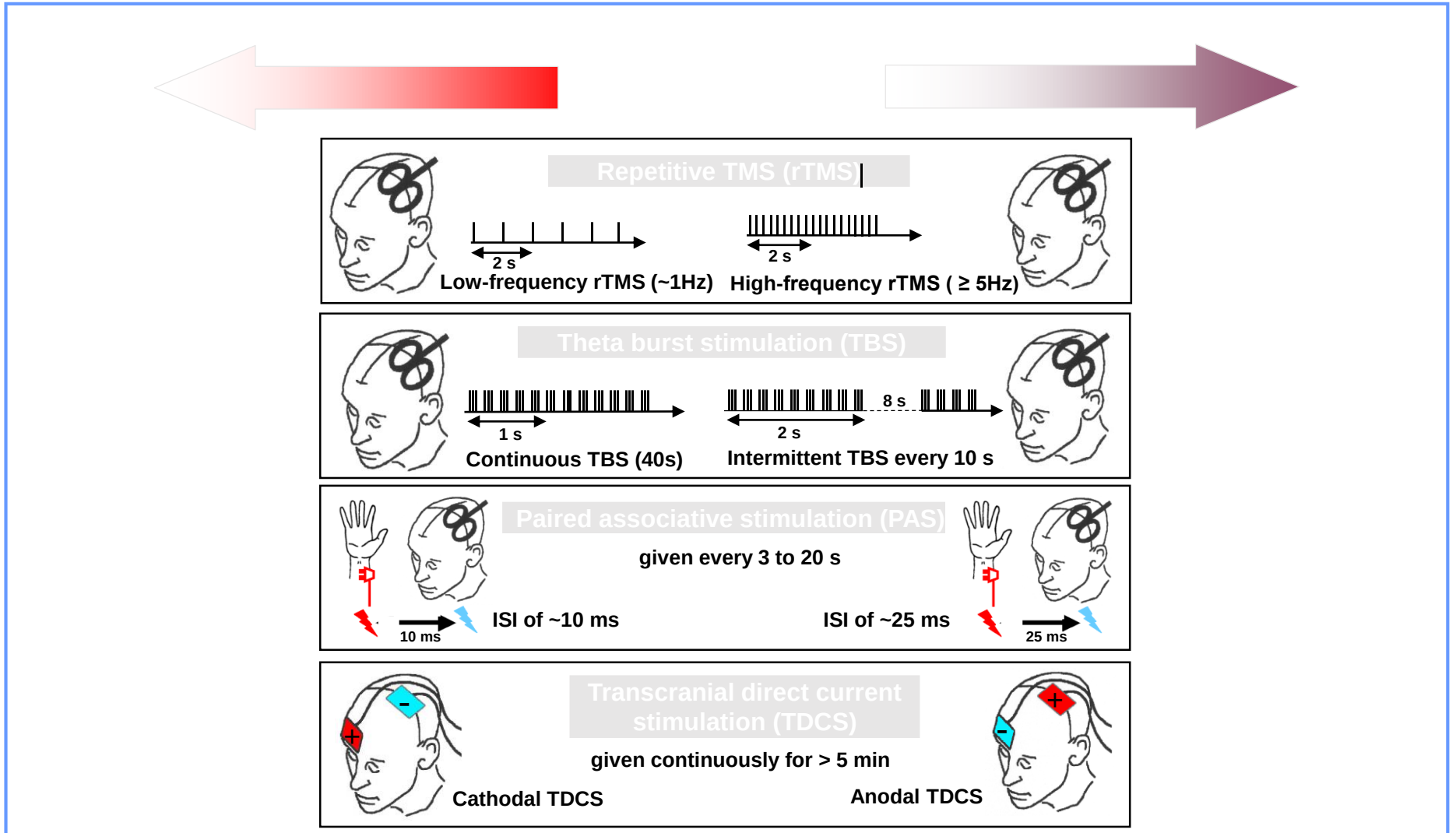


Front Neurol. 2019 Jan 24;9:1146. doi: 10.3389/fneur.2018.01146. eCollection 2018.

Is There a Future for Non-invasive Brain Stimulation as a Therapeutic Tool?

Terranova C[1], Rizzo V[1], Cacciola A[2], Chillemi G[3], Calamuneri A[3], Milardi D[3], Quartarone A[2,3].

Author information



Front Physiol. 2017 Jun 30;8:457. doi: 10.3389/fphys.2017.00457. eCollection 2017.

Mechanism of Action for rTMS: A Working Hypothesis Based on Animal Studies.

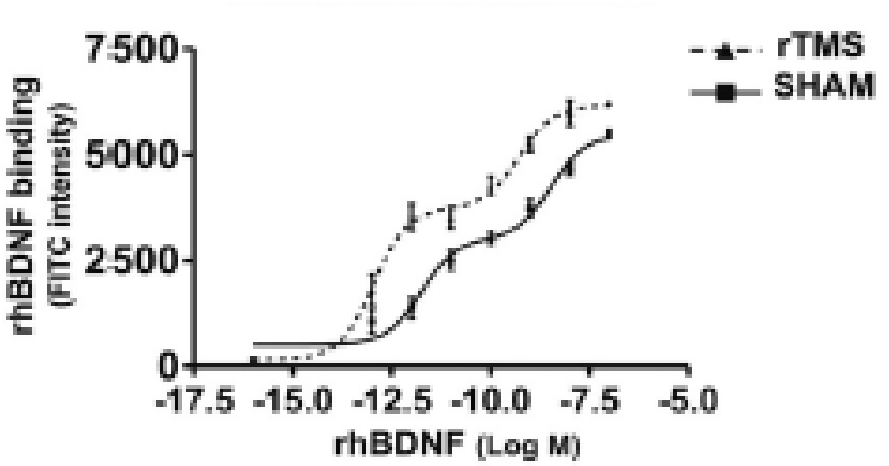
Soundara Rajan T[1], Ghilardi MFM[2,3], Wang HY[2], Mazzon E[1], Bramanti P[1], Restivo D[4], Quartarone A[1,5].

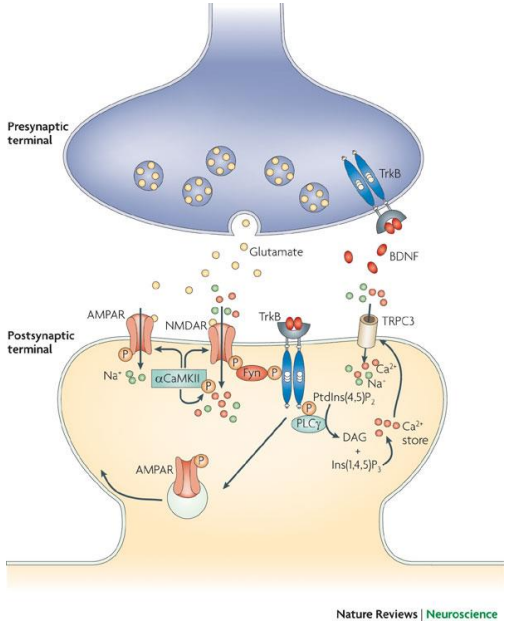
J Neurosci. 2011 Jul 27;31(30):11044-54. doi: 10.1523/JNEUROSCI.2125-11.2011.

Repetitive transcranial magnetic stimulation enhances BDNF-TrkB signaling in both brain and lymphocyte.

Wang HY[1], Crupi D, Liu J, Stucky A, Cruciata G, Di Rocco A, Friedman E, Quartarone A, Ghilardi MF.

•Chronic high-frequency rTMS increased the binding affinity between BDNF and its cognate receptor TrkB and augmented NMDA receptor-TrkB association in rat prefrontal cortex and in human and rat lymphocytes .





glutamatergic transmission

Clin Neurophysiol. 2014 Nov;125(11):2150-2206. doi: 10.1016/j.clinph.2014.05.021. Epub 2014 Jun 5.

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS).

Lefaucheur JP[1], André-Obadia N[2], Antal A[3], Ayache SS[4], Baeken C[5], Benninger DH[6], Cantello RM[7], Cincotta M[8], de Carvalho M[9], De Ridder D[10], Devanne H[11], Di Lazzaro V[12], Filipović SR[13], Hummel FC[14], Jääskeläinen SK[15], Kimiskidis VK[16], Koch G[17], Langguth B[18], Nyffeler T[19], Oliviero A[20], Padberg F[21], Poulet E[22], Rossi S[23], Rossini PM[24], Rothwell JC[25], Schönfeldt-Lecuona C[26], Siebner HR[27], Slotema CW[28], Stagg CJ[29], Valls-Sole J[30], Ziemann U[31], Paulus W[3], Garcia-Larrea L[32].

LEVEL A: definite efficacy → analgesic effect of **HF-rTMS over M1** in **pain**

→ **antidepressant effect** of **HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC)**

Clin Neurophysiol. 2014 Nov;125(11):2150-2206. doi: 10.1016/j.clinph.2014.05.021. Epub 2014 Jun 5.

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LEVEL B: probable efficacy

antidepressant effect of **low-frequency (LF) rTMS** of the **right DLPFC, HF-rTMS of the left DLPFC** for the **negative symptoms of schizophrenia**

LF-rTMS of contralesional M1 in **chronic motor stroke**

Clin Neurophysiol. 2014 Nov;125(11):2150-2206. doi: 10.1016/j.clinph.2014.05.021. Epub 2014 Jun 5.

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS).

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LEVEL C: possible efficacy

- LF rTMS of the left TPC on **tinnitus and auditory hallucinations**;
- HF rTMS (5–25 Hz) of bilateral (multiple) M1 areas on **motor symptoms of PD**;
- **CRPS type** I (HF rTMS of M1 contralateral to pain side;
- **hemispatial neglect** (cTBS of the contralesional left posterior parietal cortex);
- **epilepsy** (LF rTMS of the epileptic focus),
- **post-traumatic stress disorder** (PTSD) (HF rTMS of the right DLPFC);
- **cigarette consumption** (HF rTMS of the left DLPFC).

New applications of TMS

News From the Food and Drug Administration

September 18, 2018

Brain Stimulation Approved for Obsessive-Compulsive Disorder

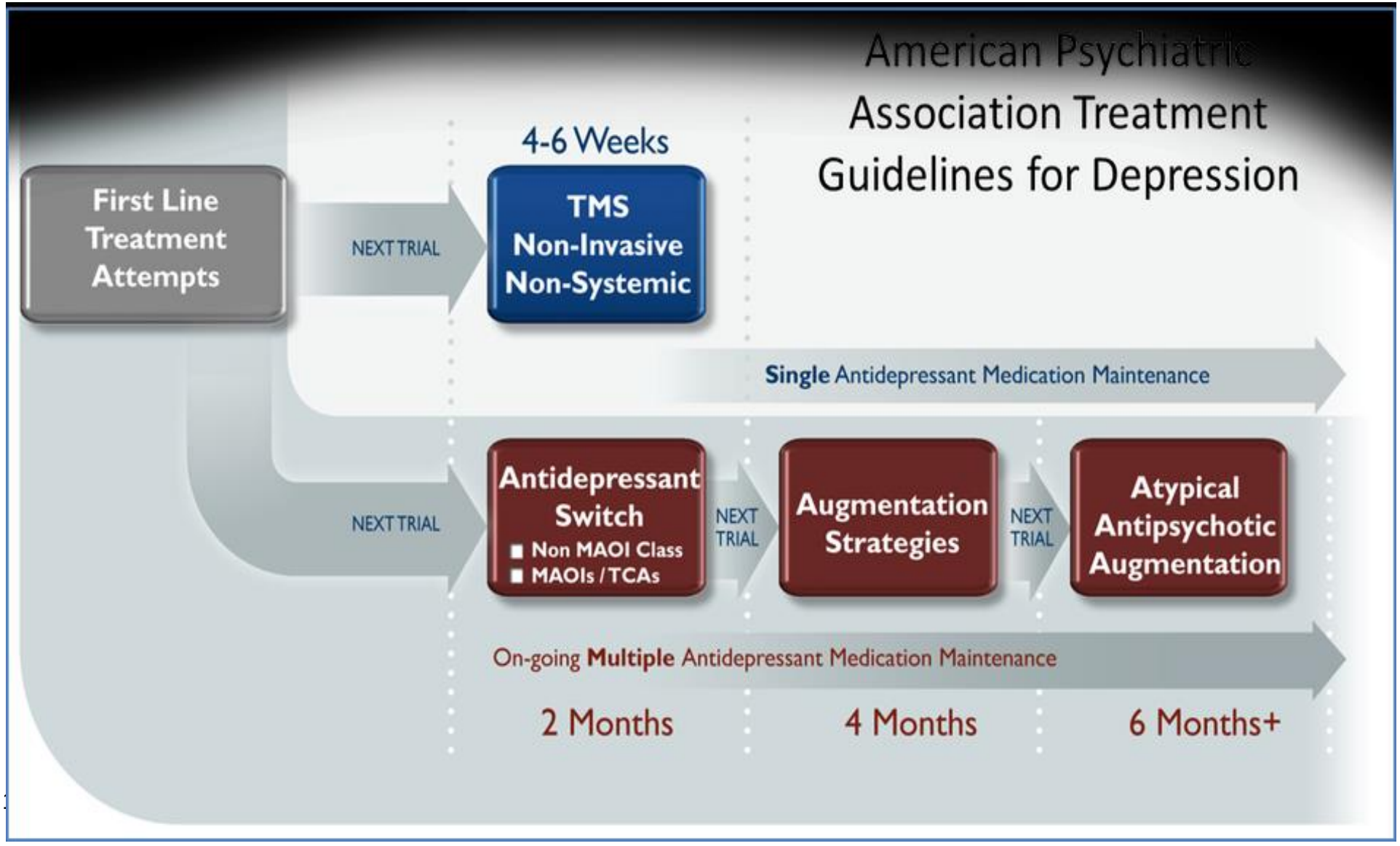
Rebecca Voelker, MSJ

JAMA. 2018;320(11):1098. doi:10.1001/jama.2018.13301

The FDA has expanded the approved indications for transcranial magnetic stimulation (TMS) to include obsessive-compulsive disorder (OCD). In 2008, TMS was approved to treat major depression and in 2013 got the nod for pain from certain migraine headaches.

Transcranial magnetic stimulation uses magnetic fields to stimulate neurons in the brain. In a randomized multicenter study involving 100 patients, about half were treated with TMS and half received treatment with a sham device. Patients who were taking medication for OCD continued their usual dosages.

APA Depression Treatment Guidelines

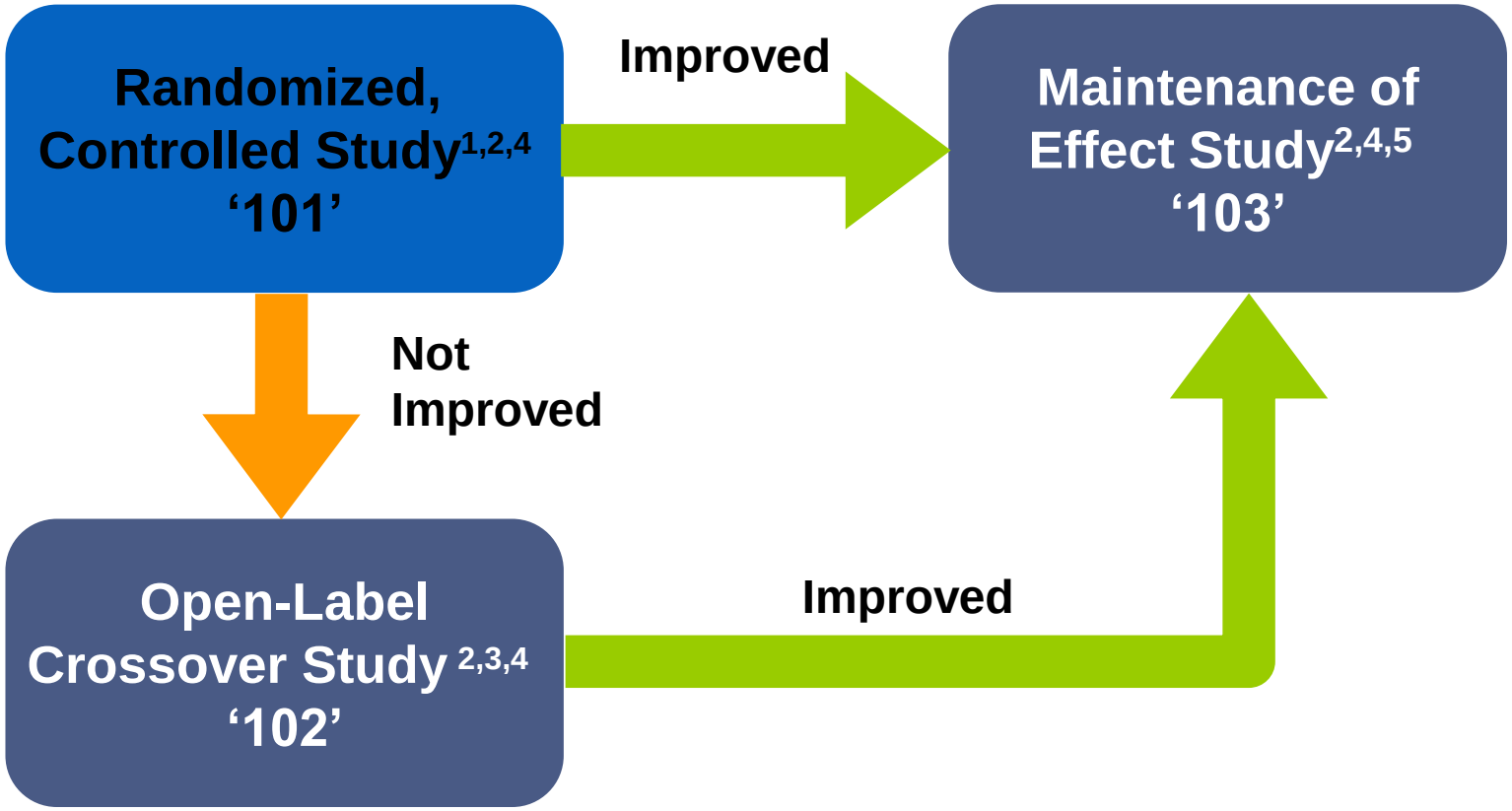


TMS Therapy Treatment Parameters in depression

- Treatment sessions
  - 37.5 minutes
- Treatment course
  - 5x/week for 4 to 6 weeks
  - Then taper over 3 weeks
- Treatment magnetic field strength = 120% of MT
- Treatment parameters
  - Stimulation time = 4 seconds
  - Pulses per second = 10
  - Interval = 26 seconds
  - Number of pulses = 3000

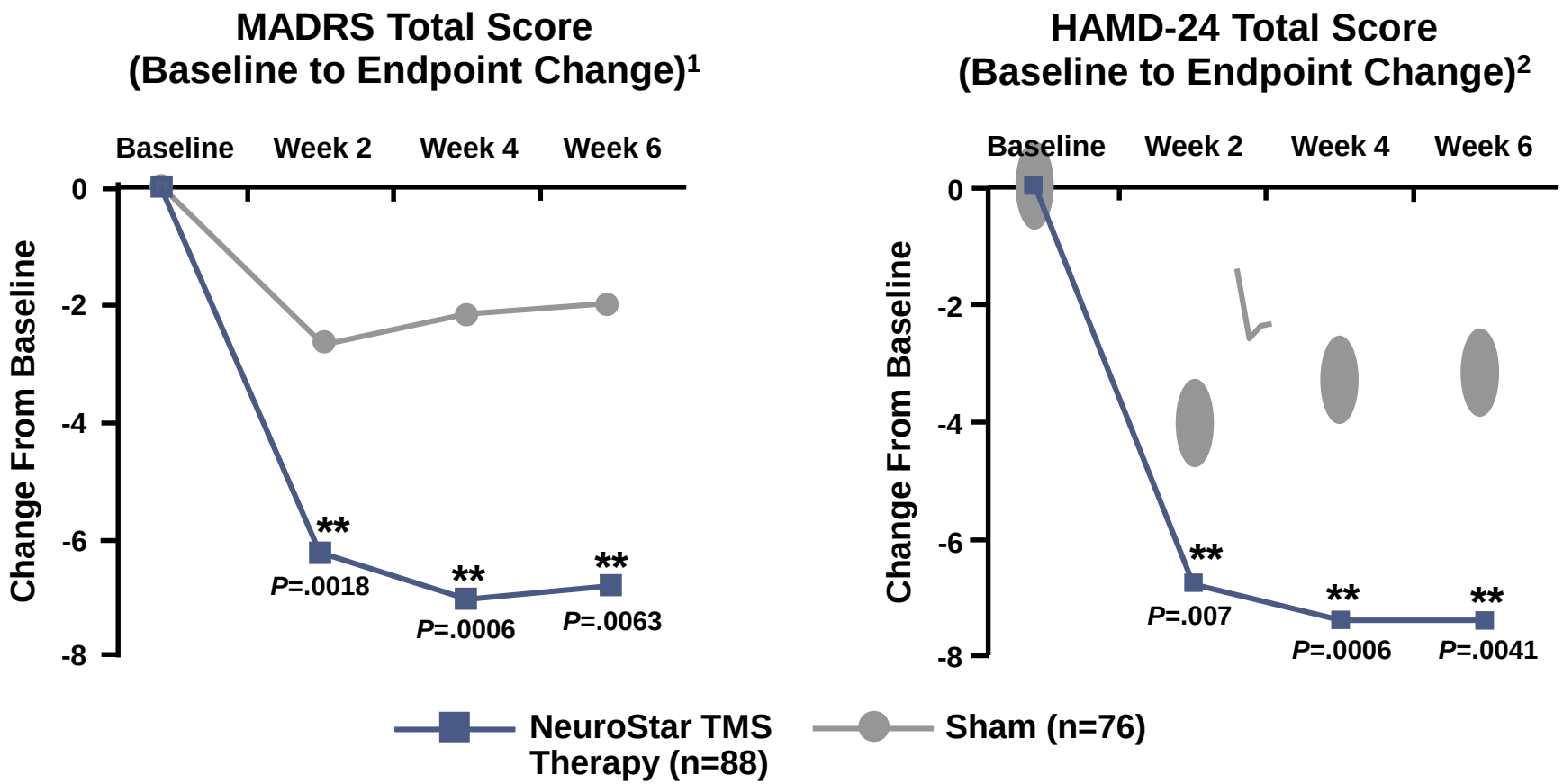
NeuroStar TMS Therapy System User Manual. Neuronetics, Inc: Malvern, PA; 2008.

NeuroStar TMS Therapy: Clinical Development Program



1. O'Reardon JP et al. *Biol Psychiatry*. 2007;62(11):1208-1216; 2. Janicak PG et al. *J Clin Psychiatry*. 2008;69(2):222-232; 3. Avery DH et al. *J Clin Psychiatry*. 2008;69(3):441-451; 4. Lisanby SH et al. *Neuropsychopharm*, 2009;34(1):522-534; 5. Data on file: Study 103. Neuronetics, Inc: Malvern, PA; 2008.

NeuroStar TMS Produced Significant Improvements in Depressive Symptoms

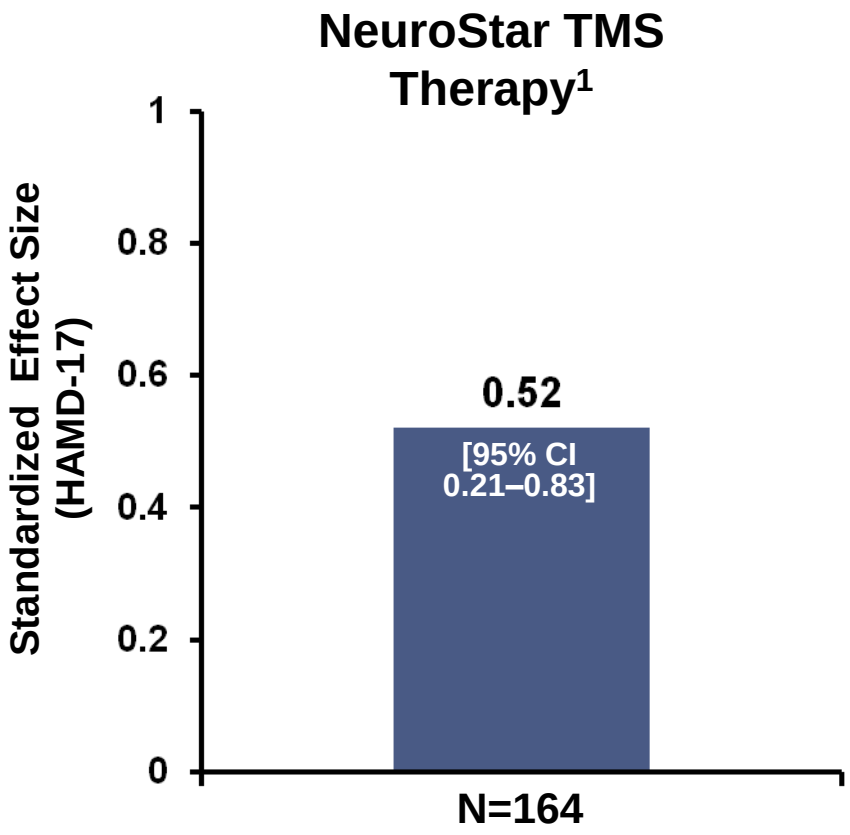


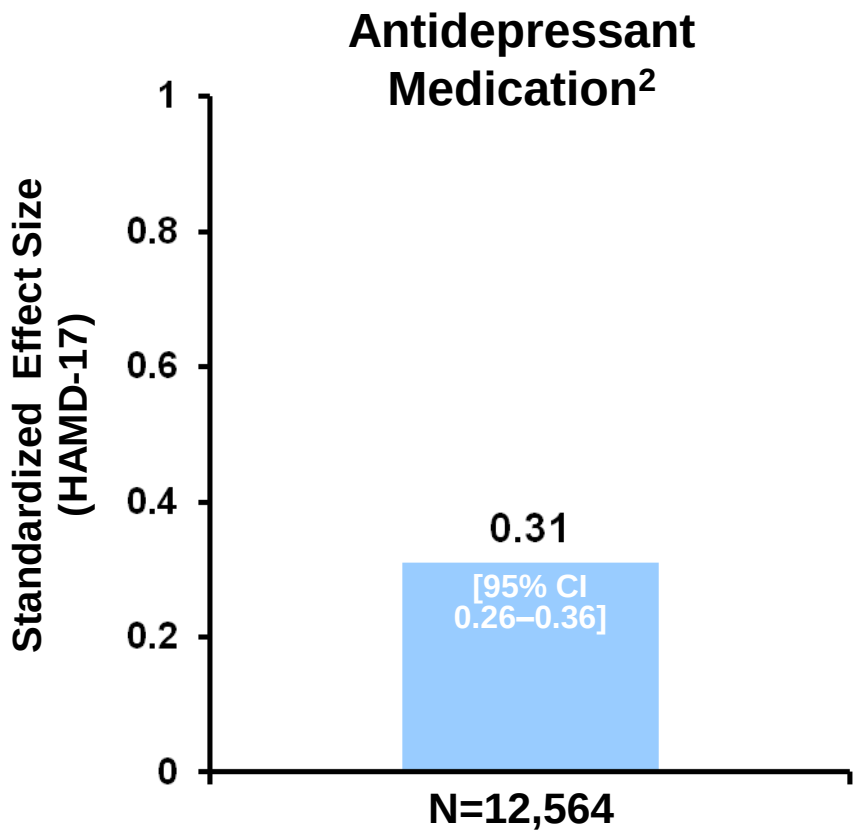
**** *P*<.01.**

LOCF analysis of evaluable study population.

1. Lisanby SH et al. *Neuropsychopharmacology*. 2009;34(2):522-534; 2. Data on file. Neuronetics, Inc: Malvern, PA; 2008.

Analysis of Effect Size:
TMS vs. Antidepressant Medications

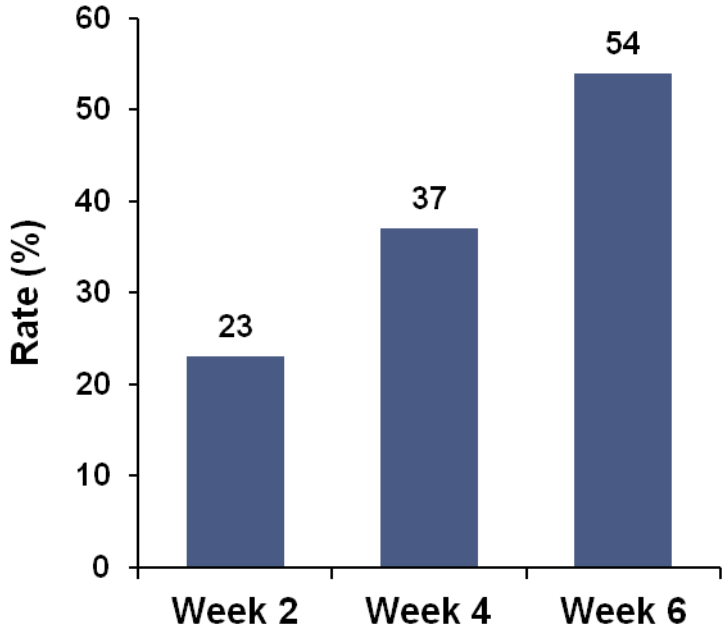




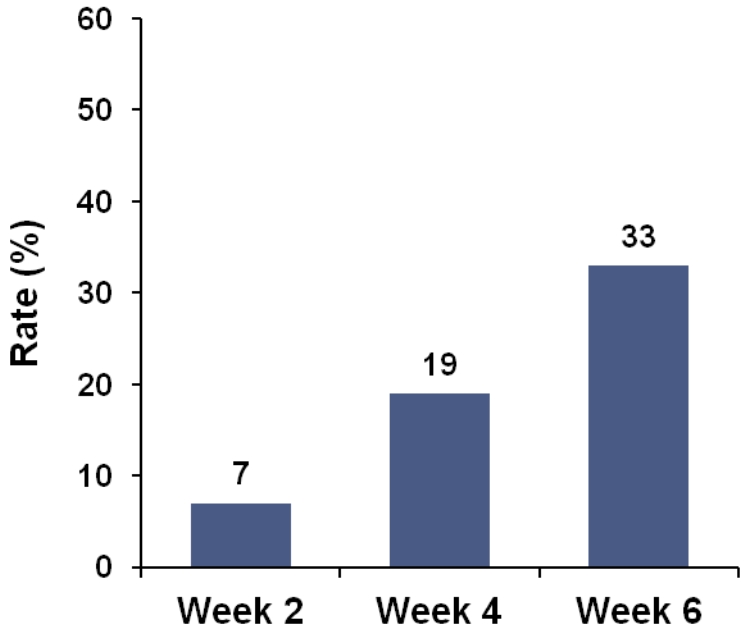
1. Data on file. Neuronetics, Inc: Malvern, PA; 2008.
2. Turner EH et al. *N Engl J Med*. 2008;358(3):252-260.

Clinically Meaningful Response and Remission Rates

HAMD-24 Response Rates
(>50% Improvement from Baseline)



HAMD-24 Remission Rates
(HAMD-24 Total Score <11)

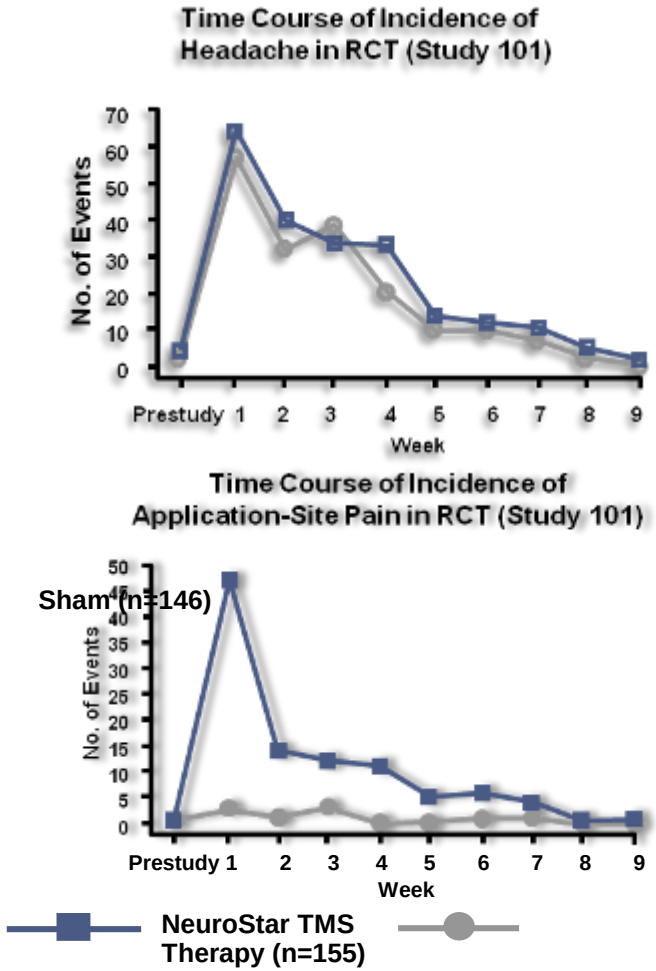


Data on file: Study 102. Neuronetics, Inc: Malvern, PA; 2008.

NeuroStar TMS Therapy: Safety Overview

More than 10,000 active treatments performed across all studies

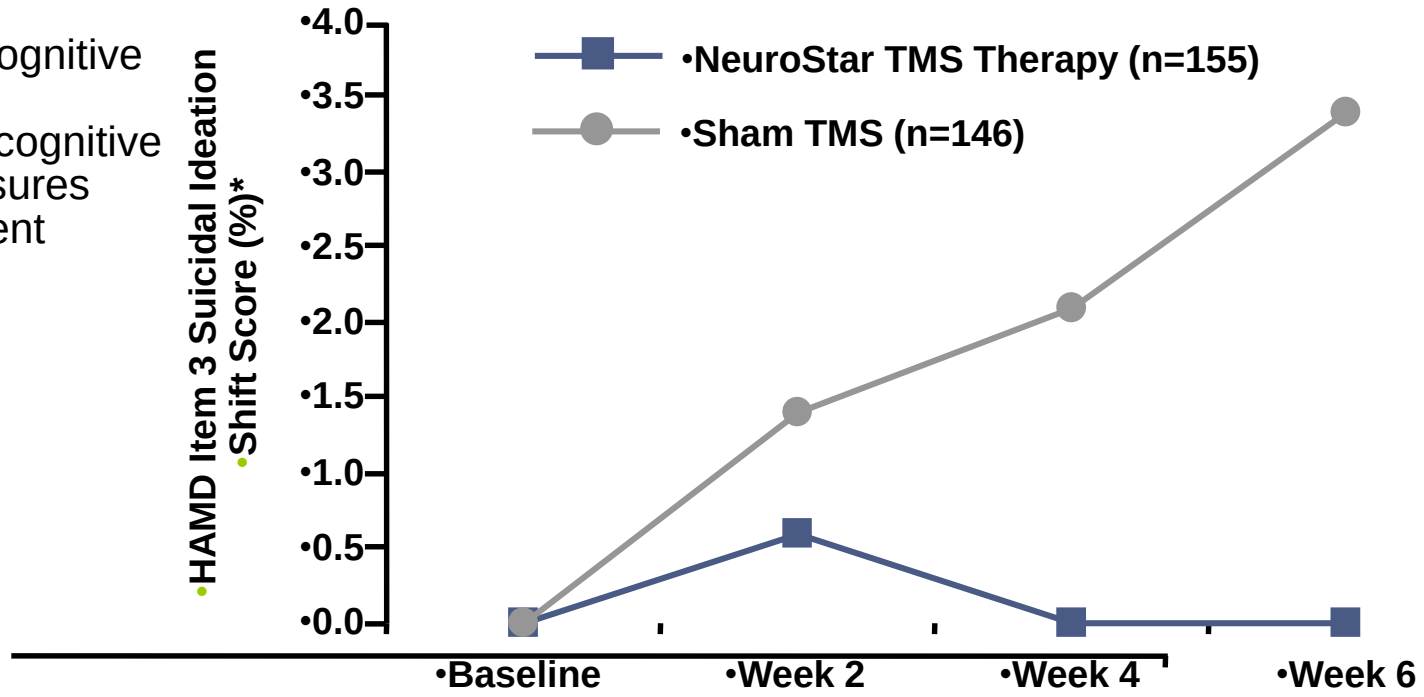
- No seizures
- No systemic side effects such as weight gain, sexual dysfunction, nausea, dry mouth, or sedation
- No adverse effect on cognition
- Most common adverse events were headache and scalp discomfort during active treatment
- <5% of patients discontinued due to adverse events



Janicak PG et al. *J Clin Psychiatry*. 2008;69(2):222-232.

No Evidence of Emergent Suicidal Ideation With TMS Therapy

- No adverse effect on cognitive function
- Tested across several cognitive function outcome measures
- No evidence of emergent suicidal ideation



*** Shift Score indicates the percent of subjects who experienced a change in HAMD Item 3 score from 0 or 1 at baseline to 3 or 4 at later point in time.**

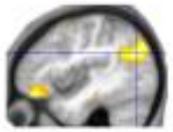
O'Reardon JP et al. *Biol Psychiatry*. 2007;62(11):1208-1216; Avery DH et al. *J Clin Psychiatry*. 2008;69(3):441-451; Janicak PG et al. *J Clinical Psychiatry*. 2008;69(2):222-232.

Toward a precision medicine

IMPROVING THE PRECISION AND EFFICACY OF TMS

Where to stimulate?

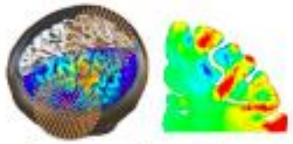
Determine **target site & device position/orientation** for stimulation based on...



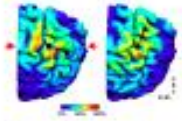
functional localizer

source localization

individual gyral anatomy



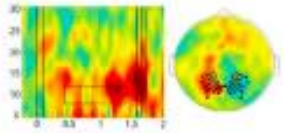
local strength of electric field



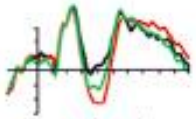
local direction of current flow

When to stimulate?

Determine **target onset/time window** relative to task or spontaneous event for stimulation based on...



induced power



latency of evoked responses

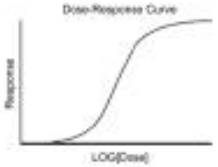
oscillatory phase

oscillatory power

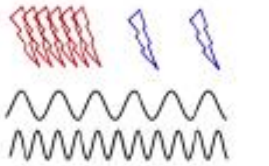
occurrence of specific events

How to stimulate?

Determine **specfic parameters** for stimulation such as...

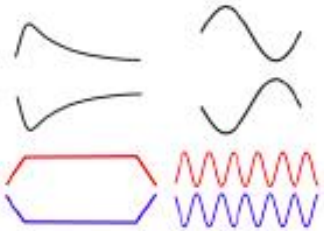


stimulation intensity



stimulation frequency

pulse/wave form



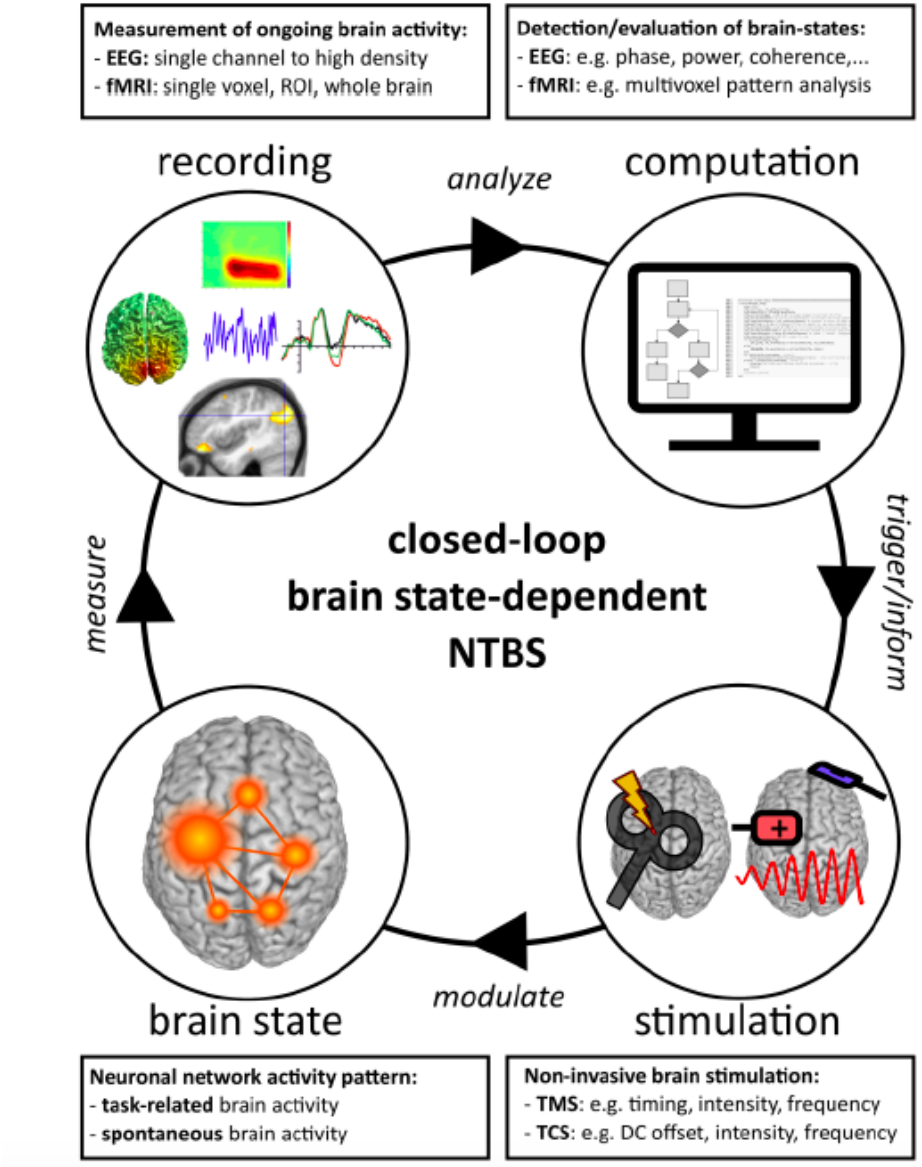
polarity

Brainsight® TMS

Axilum Robotics®

Robotic Coil Positioning TMS Experiment

CLOSED LOOP STIMULATION



The new frontiers of NIBS: FUS stimulation

5th International Symposium on Focused Ultrasound 2016
August 28 - September 1

FOCUSED ULTRASOUND FOUNDATION

Transcranial FUS stimulation of the primary visual cortex in humans

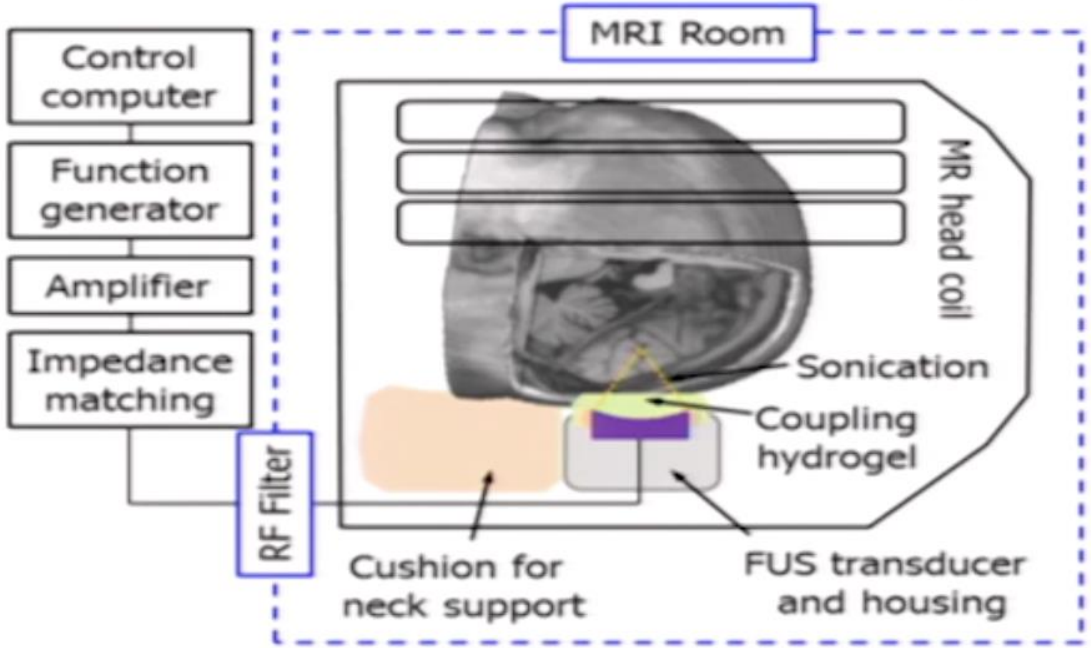
Wonhye Lee, Hyun-Chul Kim, Yujin Jung, Yong An Chung,
In-Uk Song, Jong-Hwan Lee, and Seung-Schik Yoo

Incheon St. Mary's Hospital, The Catholic University of Korea
Department of Brain and Cognitive Engineering, Korea University
Brigham and Women's Hospital and Harvard Medical School

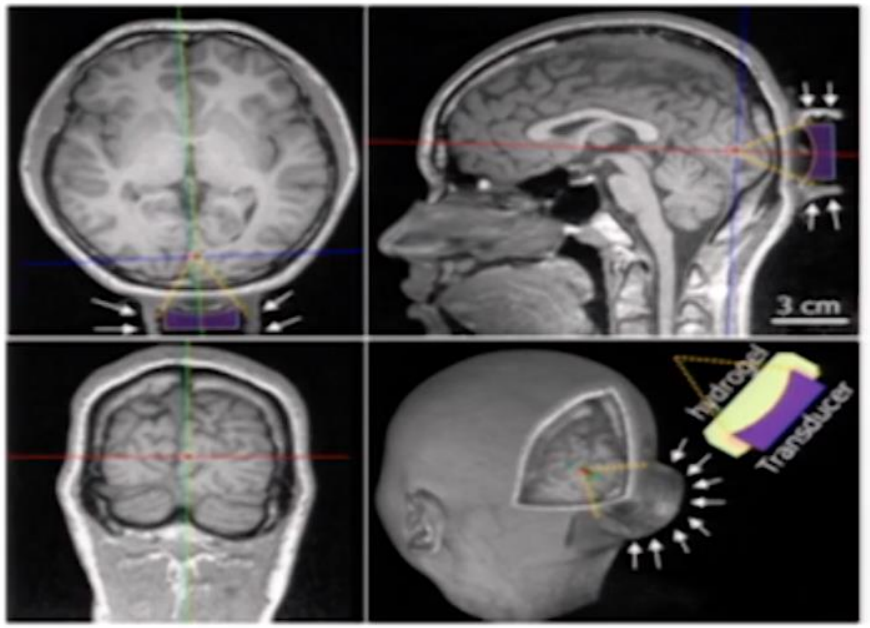
August 29, 2016
Bethesda North Marriott Hotel & Conference Center, Washington, DC

fMRI-FUS sonication sessions

fMRI-FUS setup



MR-guided FUS targeting

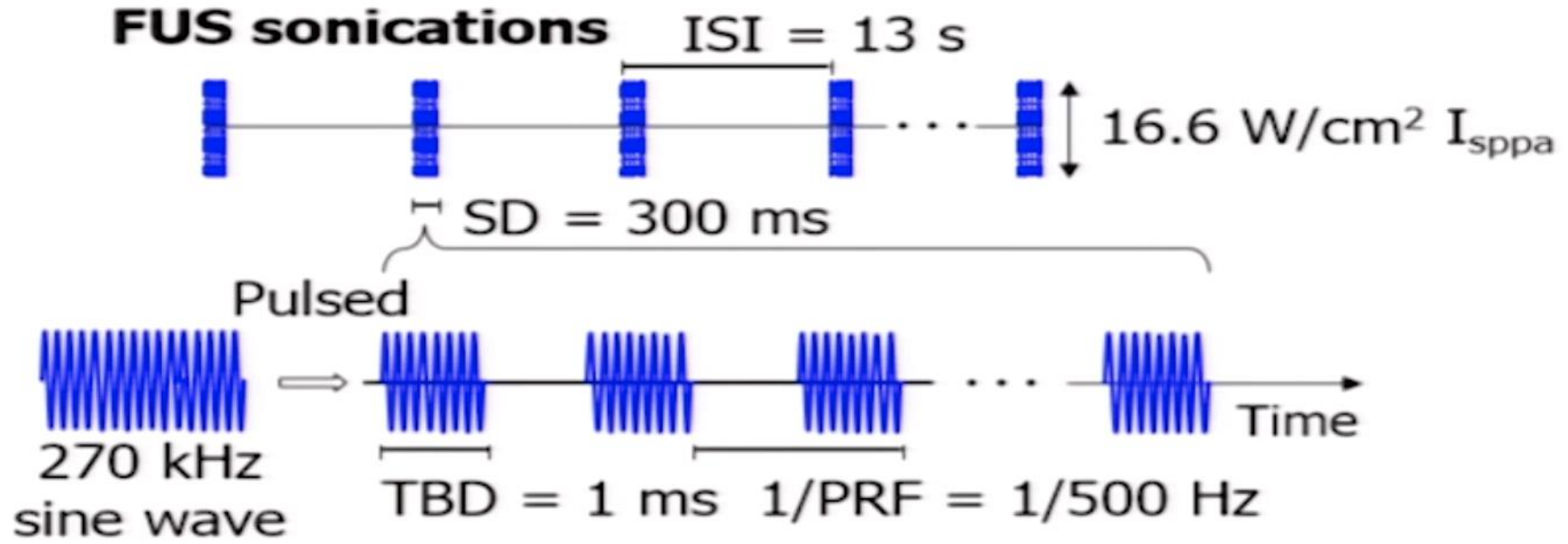


- Event-related fMRI was simultaneously conducted with (1) FUS, (2) sham FUS, and (3) photic stimulation without FUS.

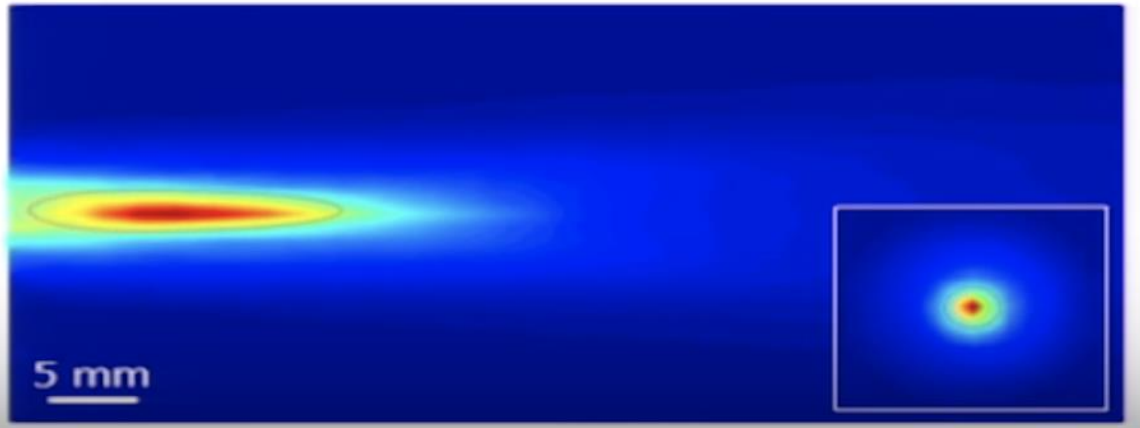
- 300 ms long stimulation was given 50 times every 13 s.

Sonication parameters

- Single-element FUS transducer (270 kHz) was used.



- Size of the focus at FWHM
  - 3 mm in diameter
  - 17 mm in length



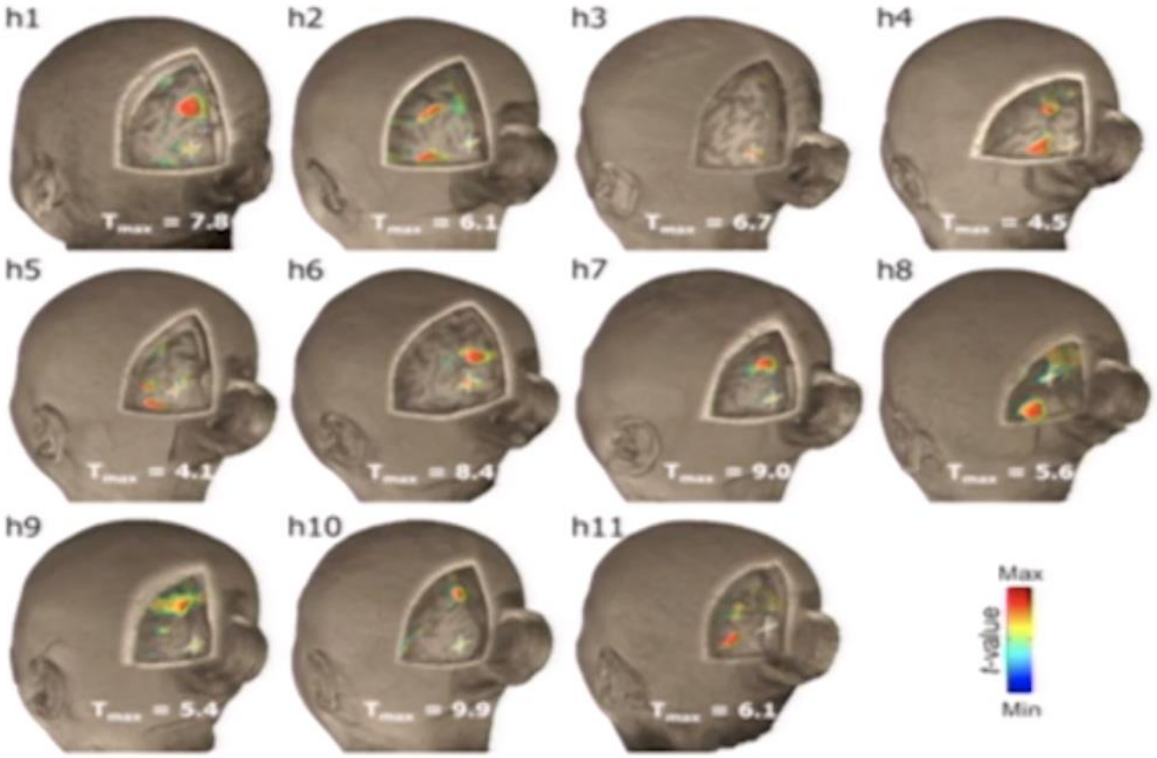
The presence of visual perception

- 11 subjects ('h1'–'h11') reported the perception of phosphene.
  - Most of the visual perceptions were described as a diffuse, amorphous, non-colored brightening of the entire visual fields that recurred intermittently.
    - without the presence of any retinotopical arrangement.
  - A few subjects reported patterned phosphene or colors in patterns.
- Other 8 subjects ('h12'–'h19') felt elicited phosphene events only a few times or did not report any sensations.

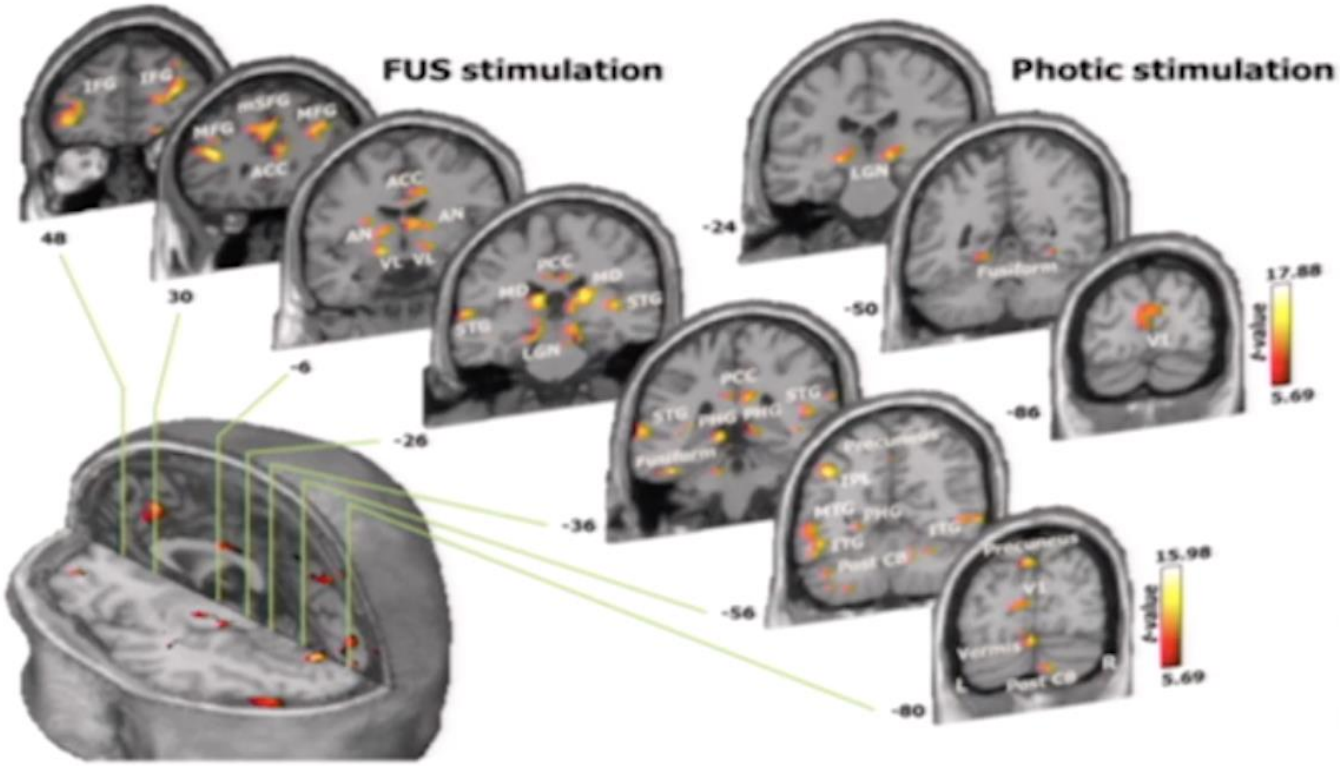
FUS stimulation shows fMRI responses.

- from the responsive subjects ($N = 11$) -

Individual fMRI responses



Group-level fMRI responses ($N = 11$)

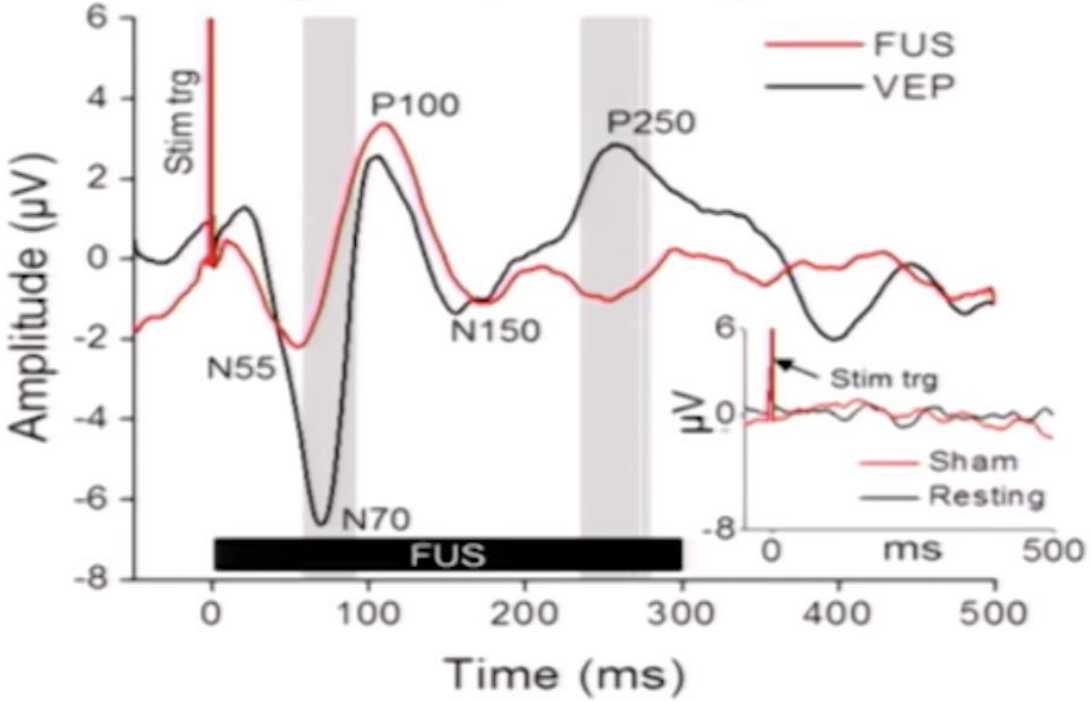


- The area showing activation in the V1 was spatially aligned with the sonication target.

- FUS activated not only the sonicated V1 but also other brain regions
  - Primary visual pathway, Visual association areas, and Attention-related network

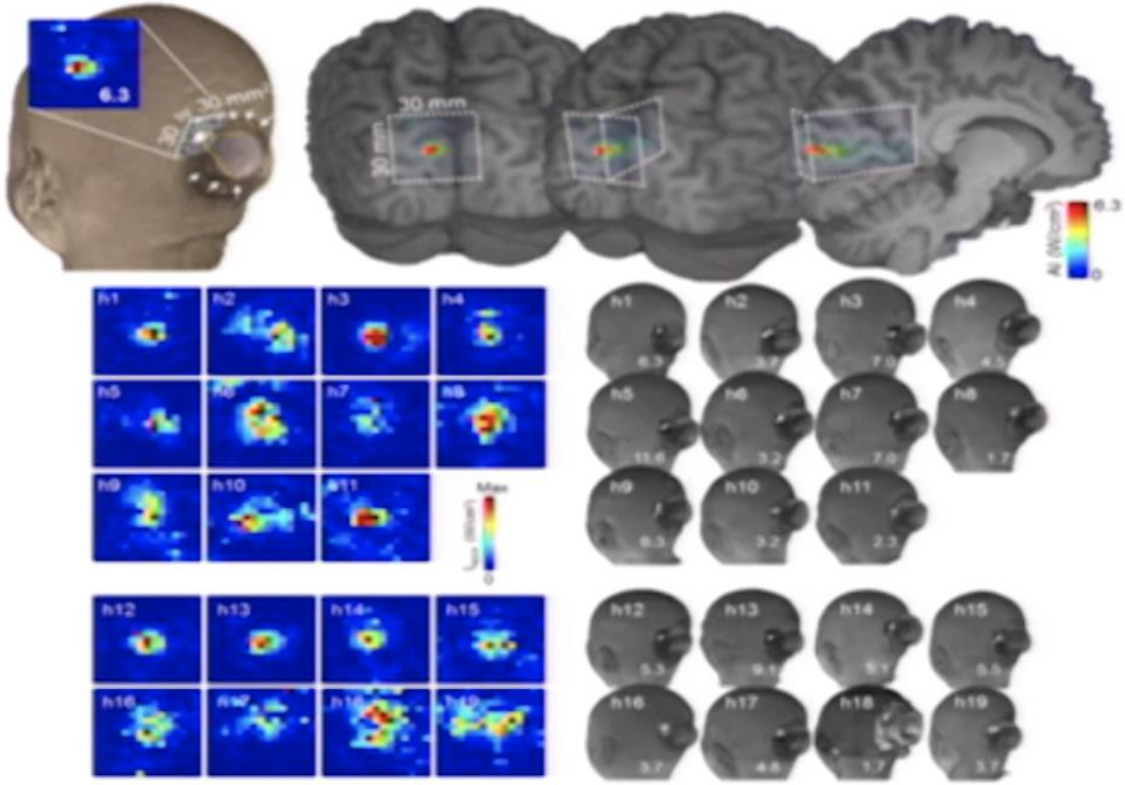
EEG responses & Acoustic simulation

The grand average EEG



- EEG-FUS session was conducted using an identical sonication setup as the FUS-MRI session.
- FUS generated stimulation-specific EEG responses having P100 component.

Simulated intensity profiles

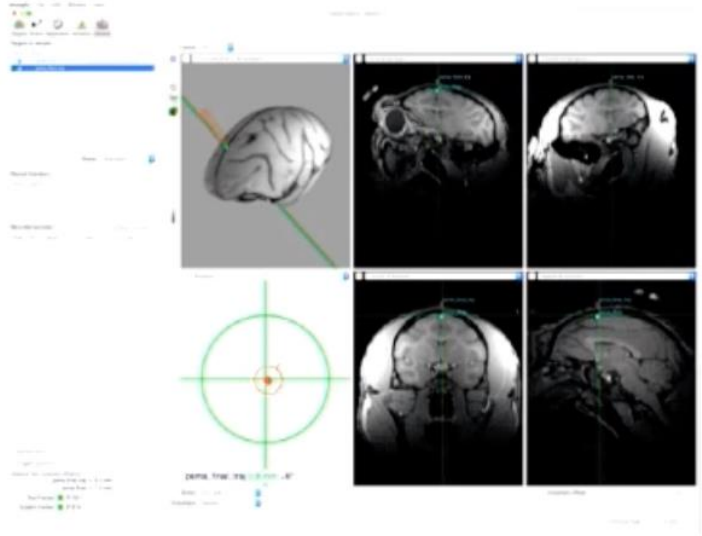


- Incident intensity was 16.6 W/cm^2 I_{sppa}
- I_{sppa} @ target = 3.0 ± 1.7 W/cm^2
- Spatial deviation of focus from the target = 3.3 ± 3.8 mm

IS FUS stimulation a safe procedure?

Cortical transcranial ultrasound stimulation : assessment of off-line activity change using functional MRI

MRI-guided stimulation



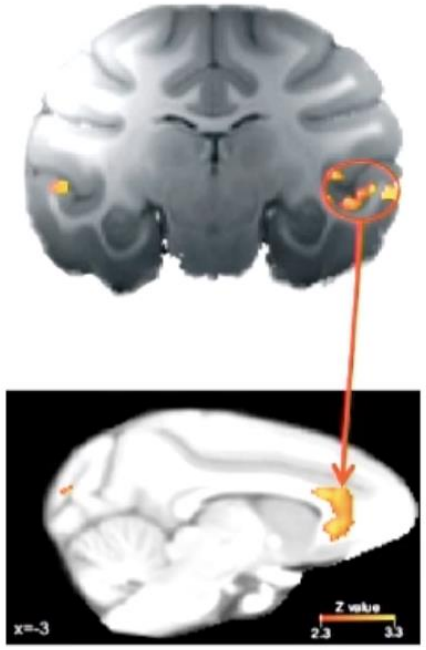
Stimulation protocol

- Single-element transducer H115-MR - Sonic Concept
- Stimulation frequency = 250 KHz
- Stimulation duration = 40s [30 ms bursts of ultrasound were generated every 100 ms]

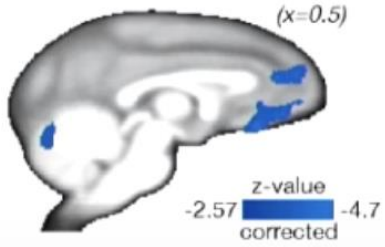
Scanning protocol

- 3T clinical scanner, horizontal bore
- rs-fMRI : 800vols per run (approx 26min) TR=2.28s, TE=31ms
- Anaesthesia maintained with isoflurane (expired iso <1%; spO2 > 95%)

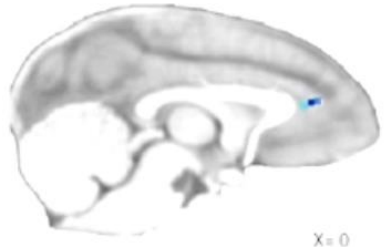
Disrupting the normal functioning of the perigenual ACC

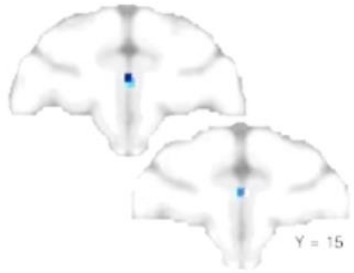


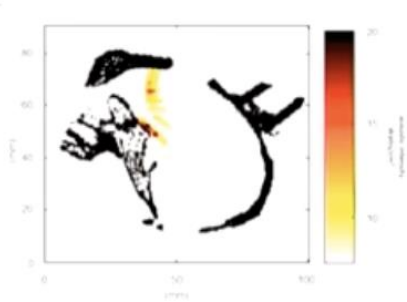
Sallet et al. 2011 Science



Fouragnan et al Submitted







Simulations based on Constans et al. 2017 IEEE Trans. Ultrason. Ferroelectr. Freq. Control

- I_{sppa} at stimulation target=17 W/cm²
- I_{spta}=5.1 W/cm²;
- max pressure=0.82 MPa

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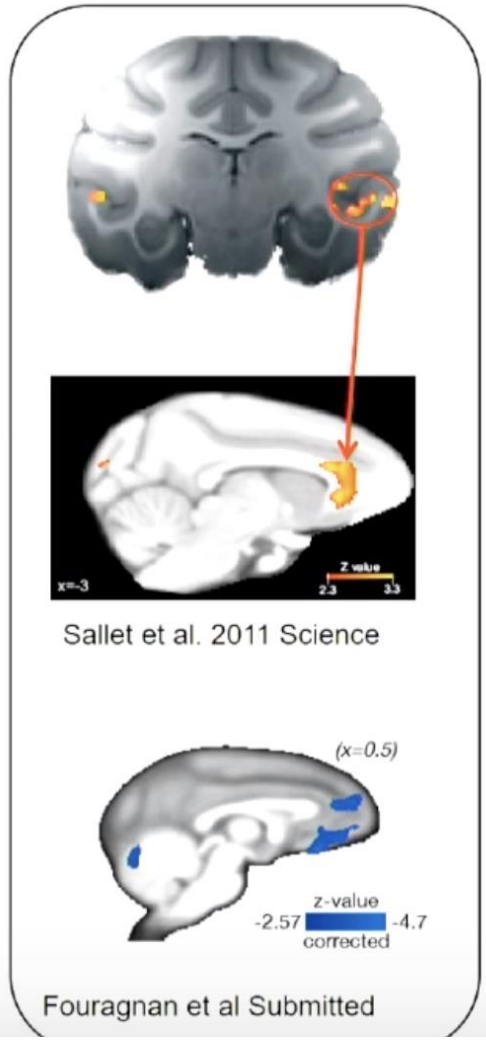
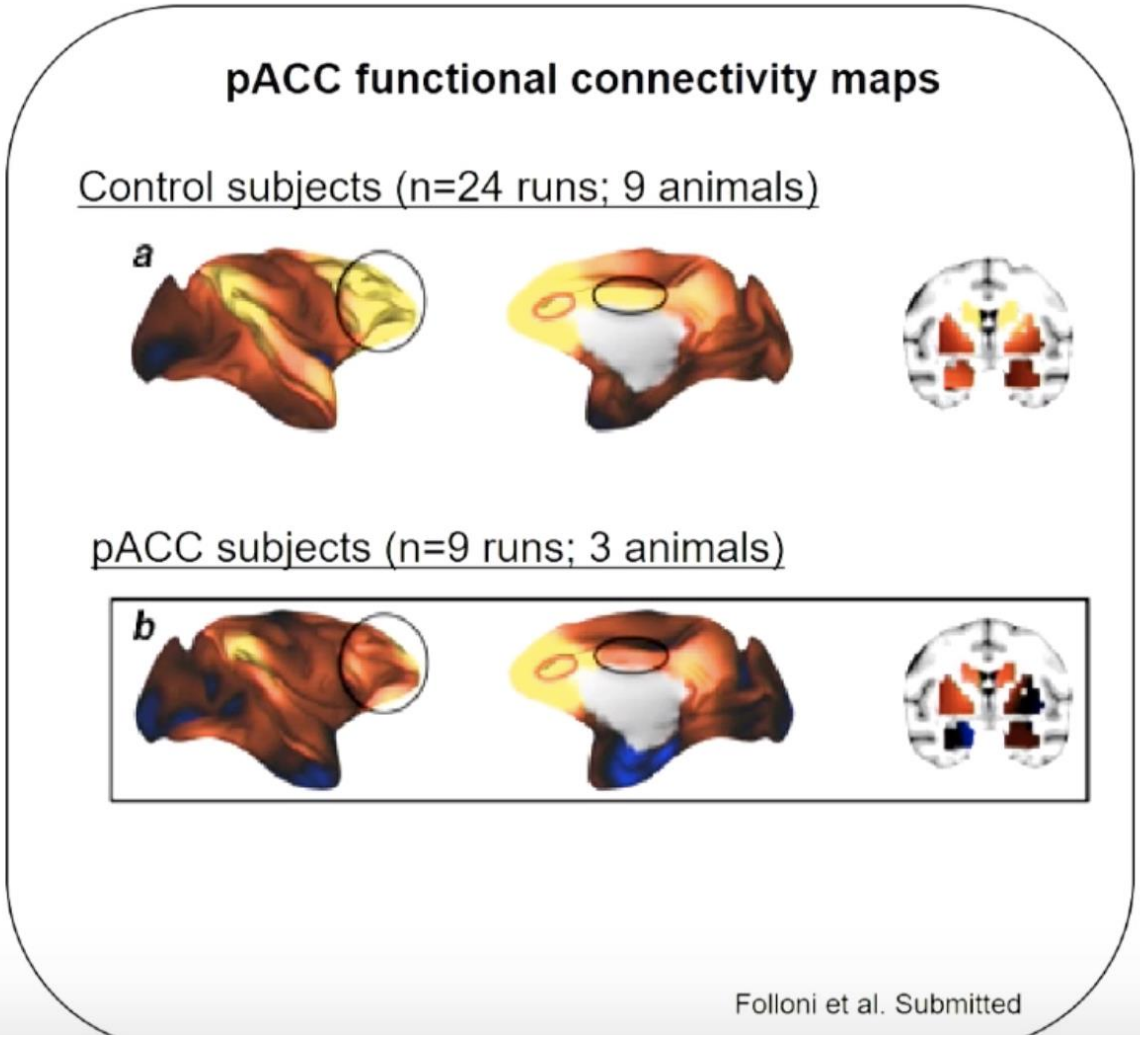
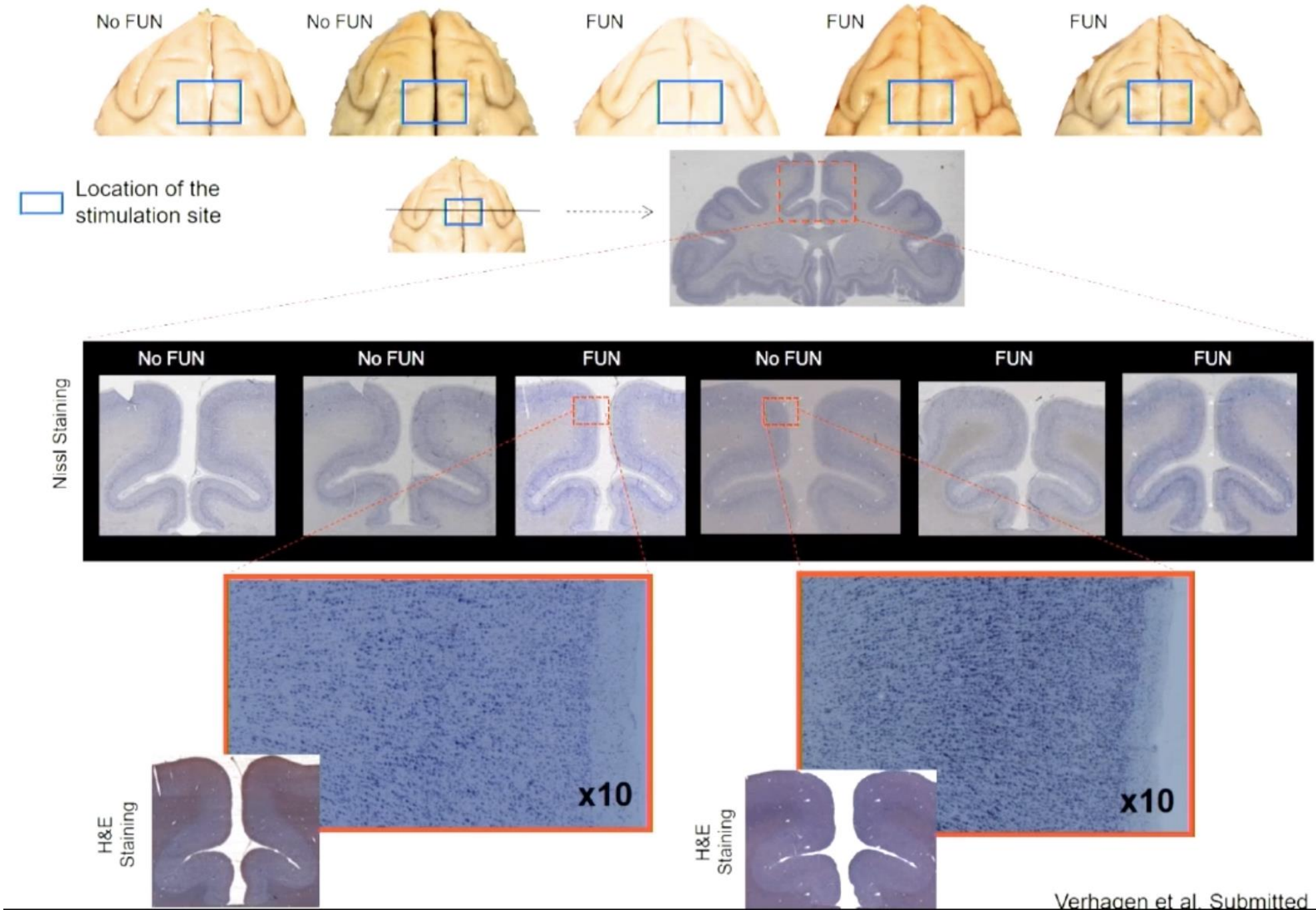
Disrupting the normal functioning of the perigenual ACC





The after effects on connectivity last for at least 2 hours!!!!!!

No tissue damage was observed following our stimulation protocol



Verhagen et al. Submitted

OPEN

Transcranial focused ultrasound neuromodulation of the human primary motor cortex

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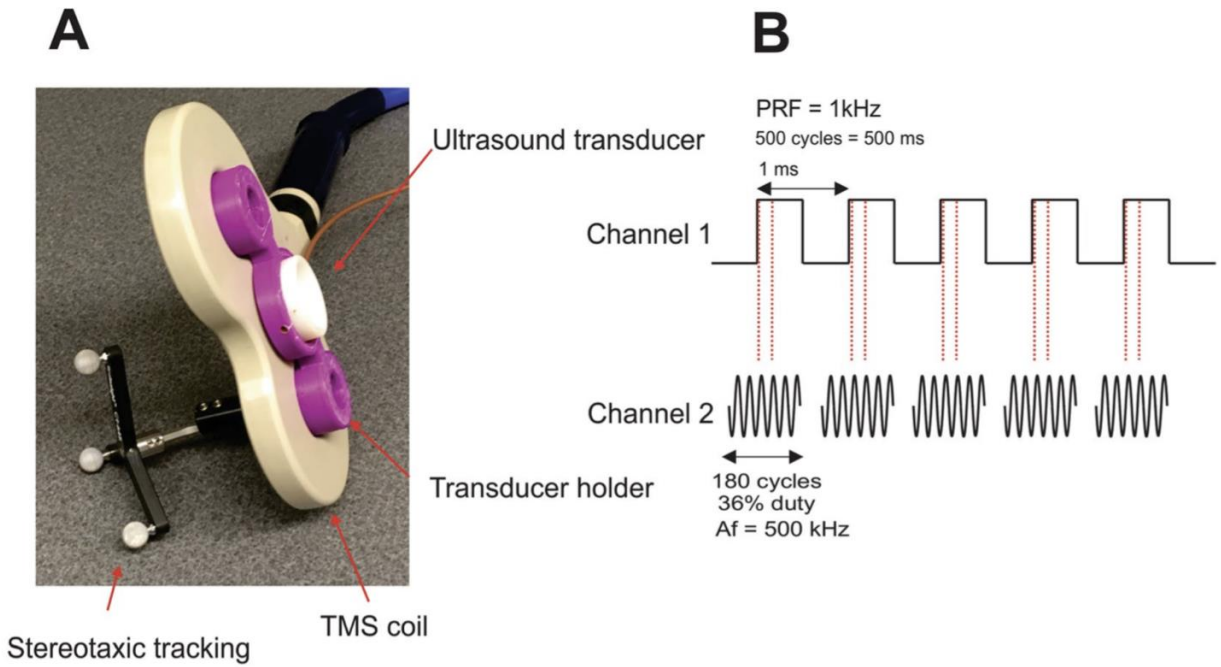
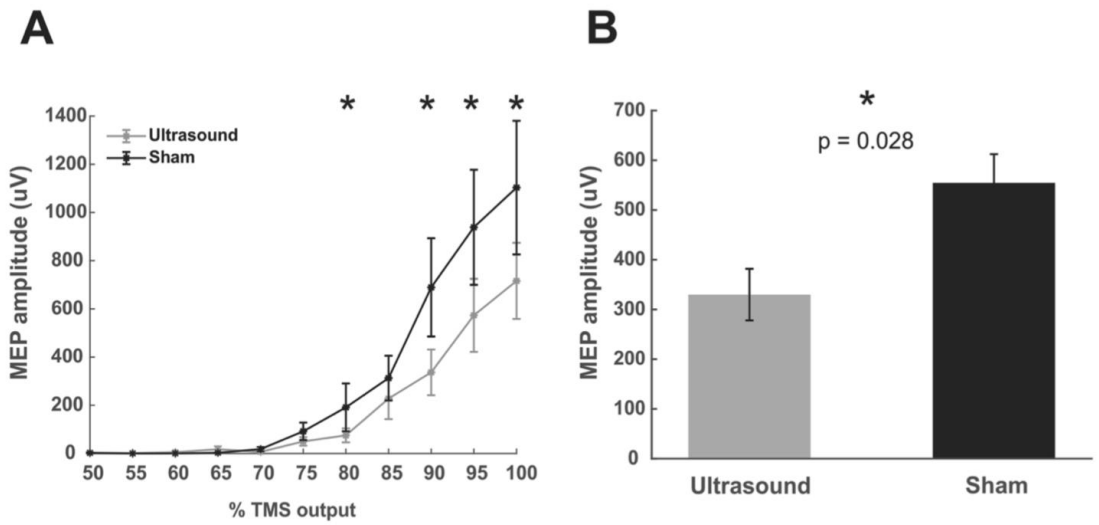
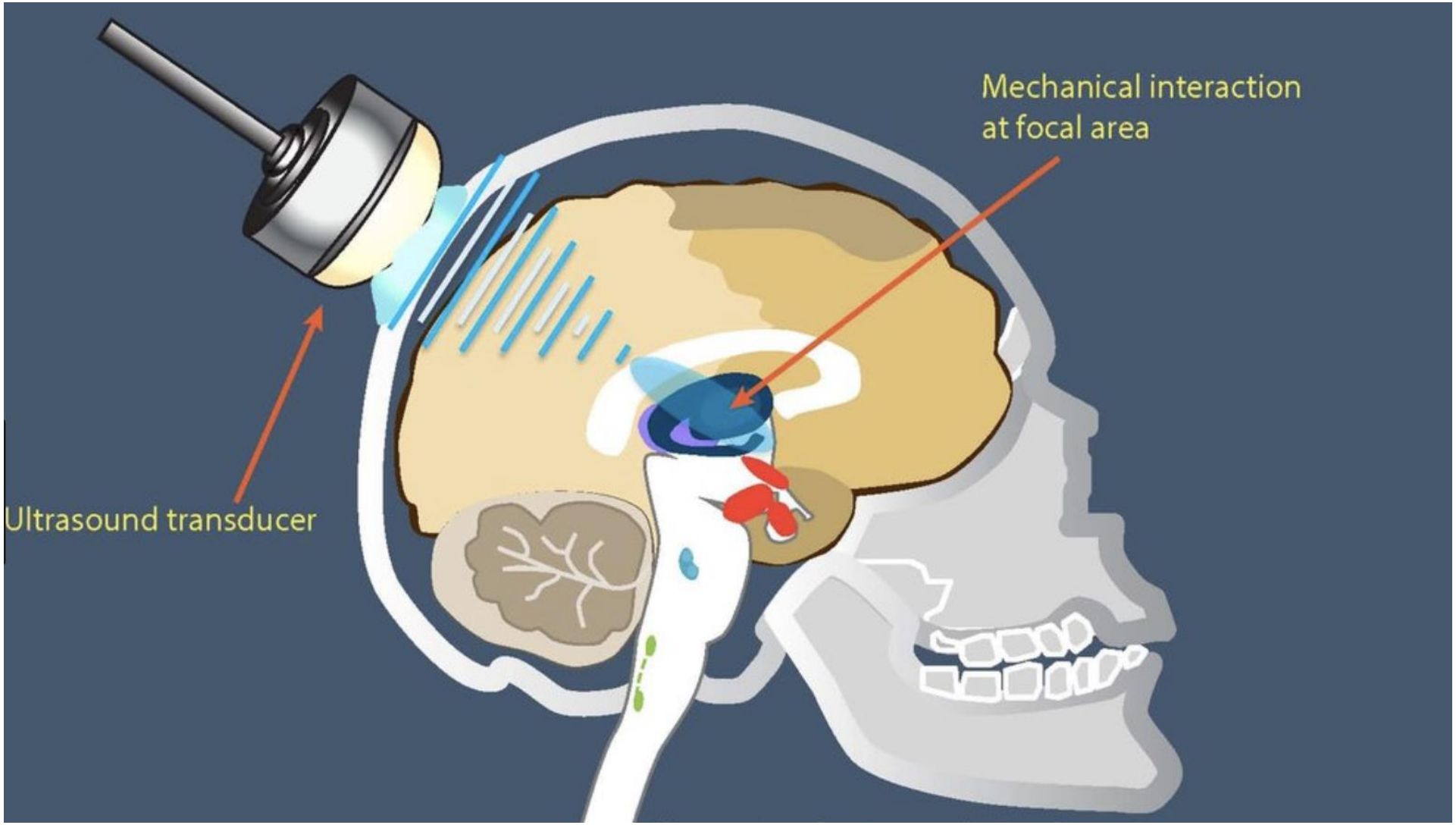




The future……..



FUS could be used in the future to target cortical and epsecially sub-cortical structures for therapeutic purposes