



From Physics to Practice

Electric field modeling in TMS

Zhi-De **Deng**, PhD

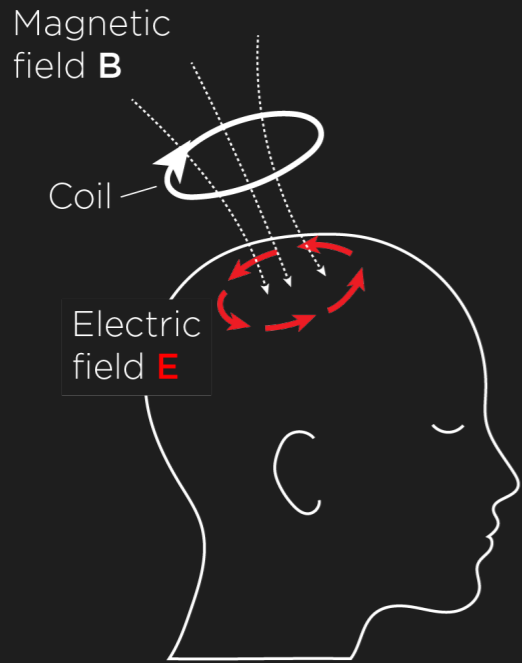
Senior Associate Scientist

Director, Computational Neurostimulation Research Program

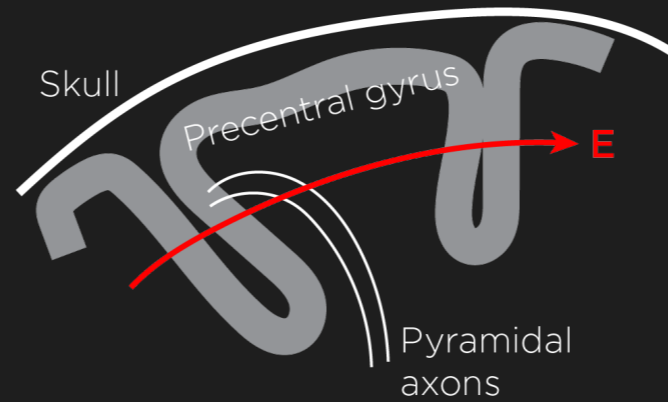
Noninvasive Neuromodulation Unit

Experimental Therapeutics & Pathophysiology Branch

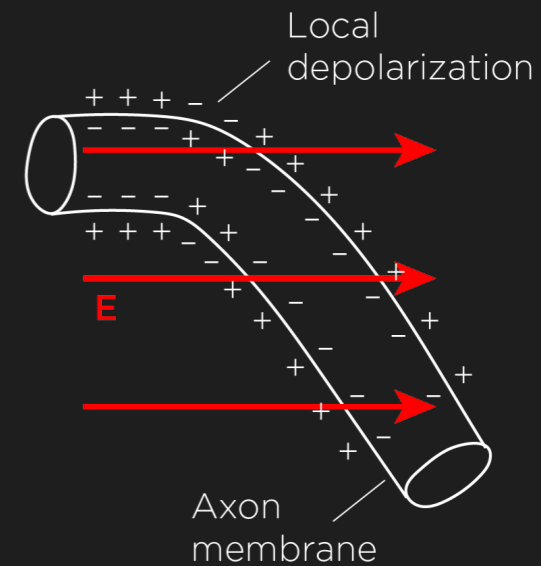
National Institute of Mental Health, NIH



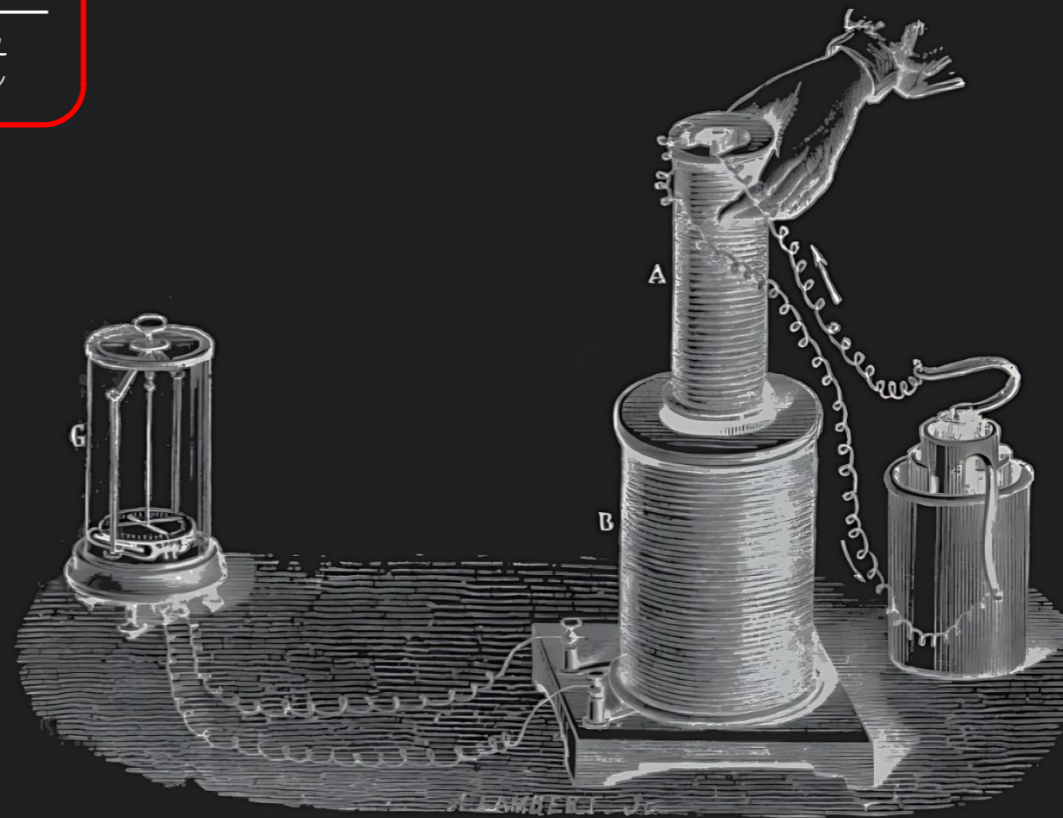
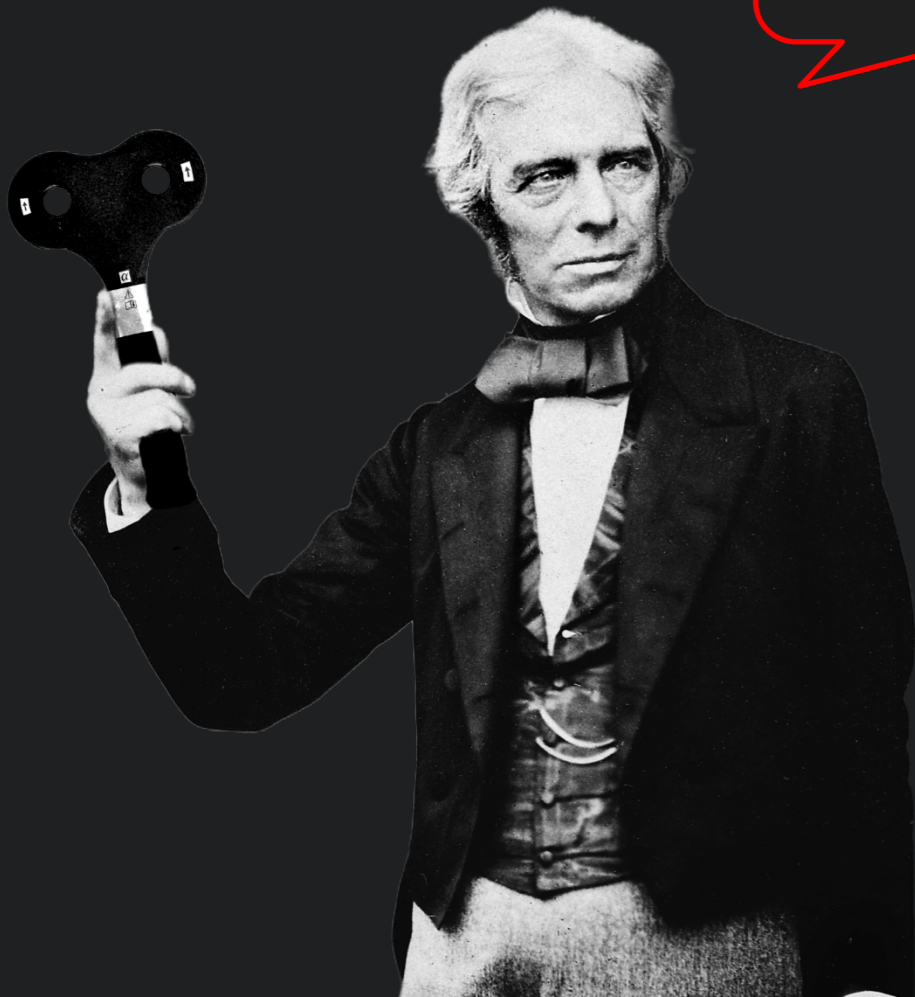
Intracranial **electric field**

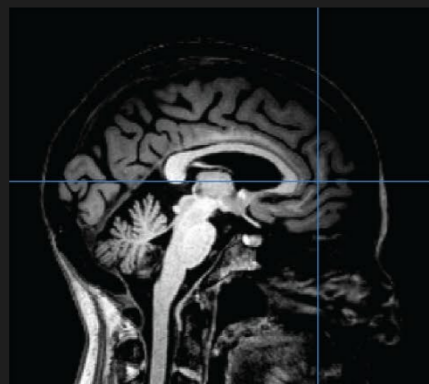


Microscopic response



$$\mathcal{E} = -N \frac{d\Phi_B}{dt}$$

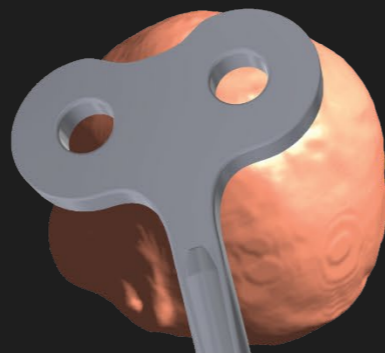




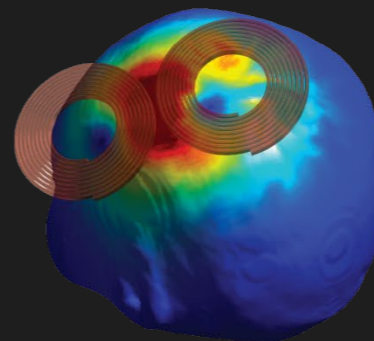
individual MRI



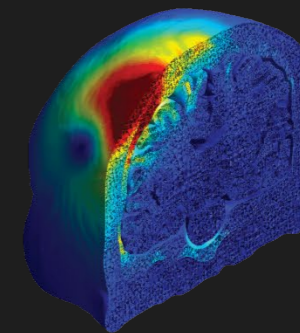
tissue segmentation



3D head model &
coil model



finite element solver



electric field analysis



Device-Facing



Preclinical & Mechanistic



Human & Clinical

1

Evaluate Devices

Compare focality, depth of penetration, and field strength across coil designs on realistic head models

3

Quantify Preclinical Dose

Translate animal/in vitro parameters into human-equivalent field strengths, enabling cross-species inference

5

Benchmark Technique

Verify control conditions deliver negligible cortical field, ruling out unintended active stimulation in blinded trials

2

Inform New Devices

Optimize coil geometry, winding patterns, and pulse waveforms in silico before committing to hardware prototypes

4

Study Mechanism

Couple macroscopic field models to neuronal ultrastructures to predict activation site and threshold

6

Individualize Dosing

Adjust intensity and targeting per subject based on head anatomy, skull thickness, and target location, moving beyond % machine output



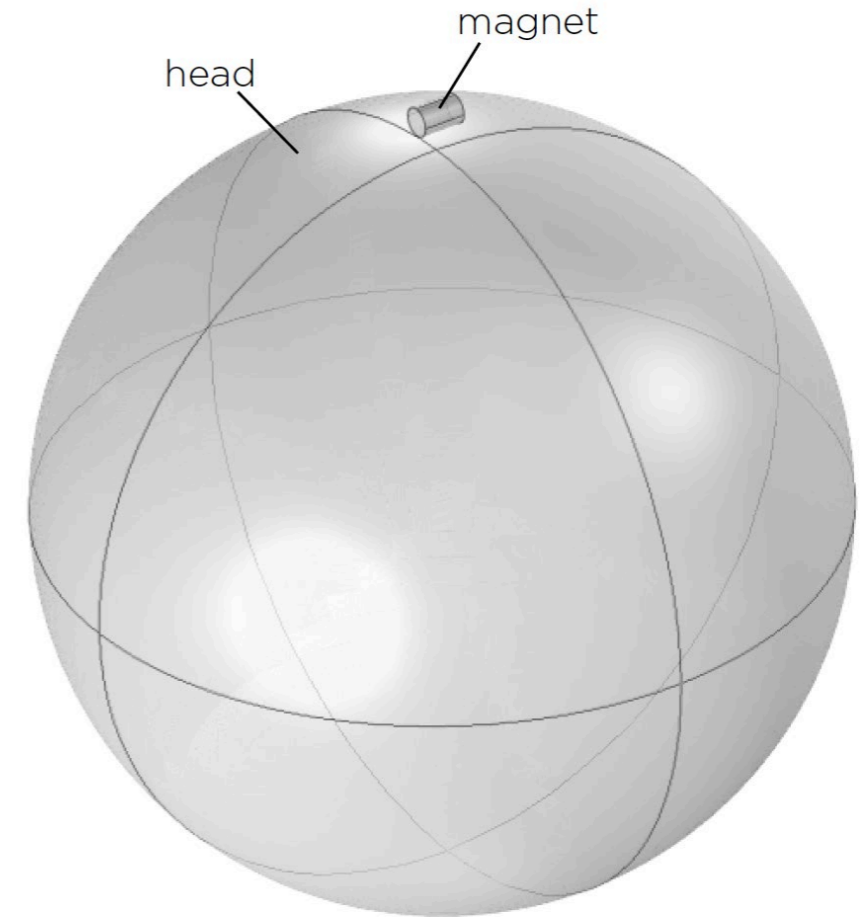
Helekar et al., *J Neurosci Methods*, 309:153-160, 2018



Leuchter et al., *Brain Stimul*, 8:787-794, 2015

- ❖ Axially magnetized cylindrical neodymium magnets (N52 grade)
- ❖ 3/8" long and 1/4" in diameter
- ❖ 7179 Gauss surface field strength at each pole, i.e. $B_{r_{max}} = 1.48 \text{ T}$
- ❖ manufacturer: K & J Magnetics

- ❖ Magnet is rotated perpendicular to the scalp
- ❖ Distance between the closest pole of the magnet and the scalp is 5 mm
- ❖ Speed of rotation is up to 24,000 rpm

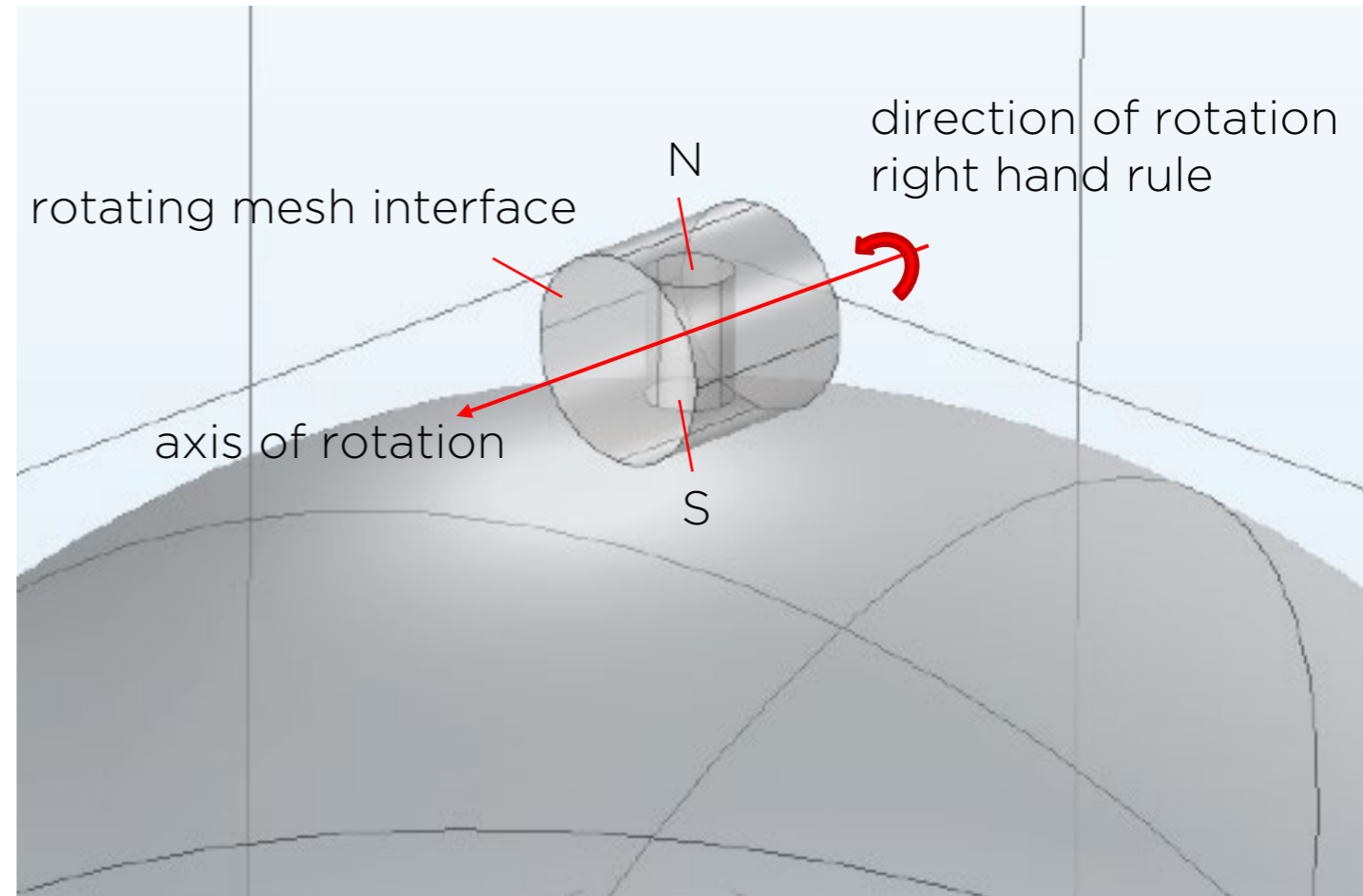


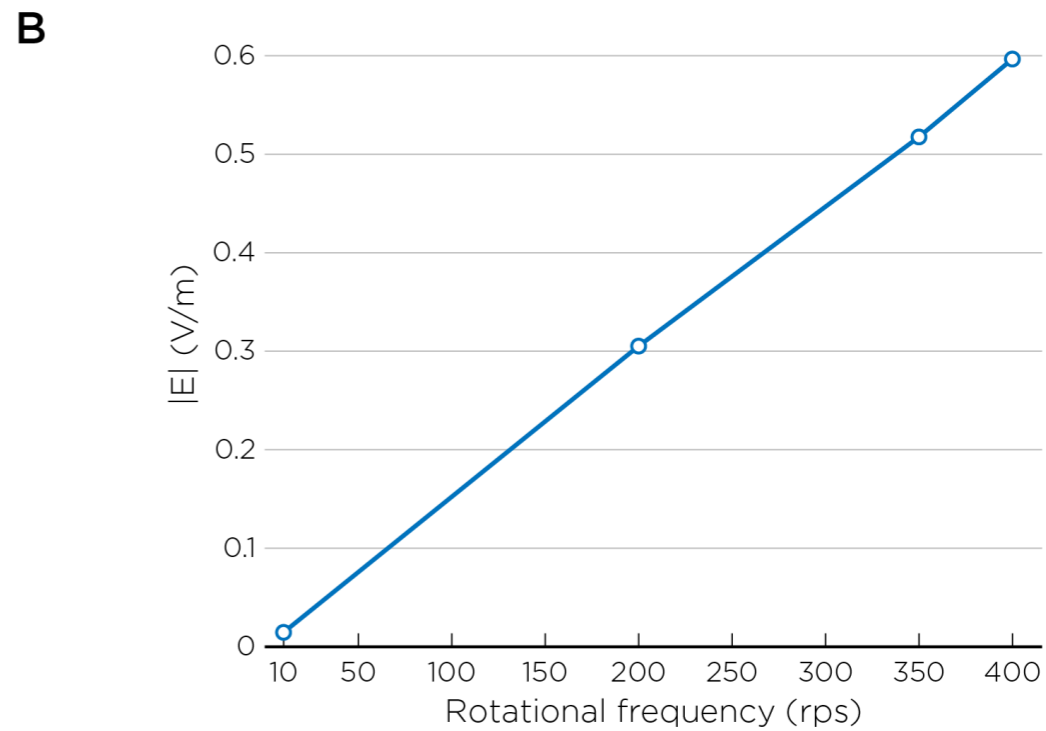
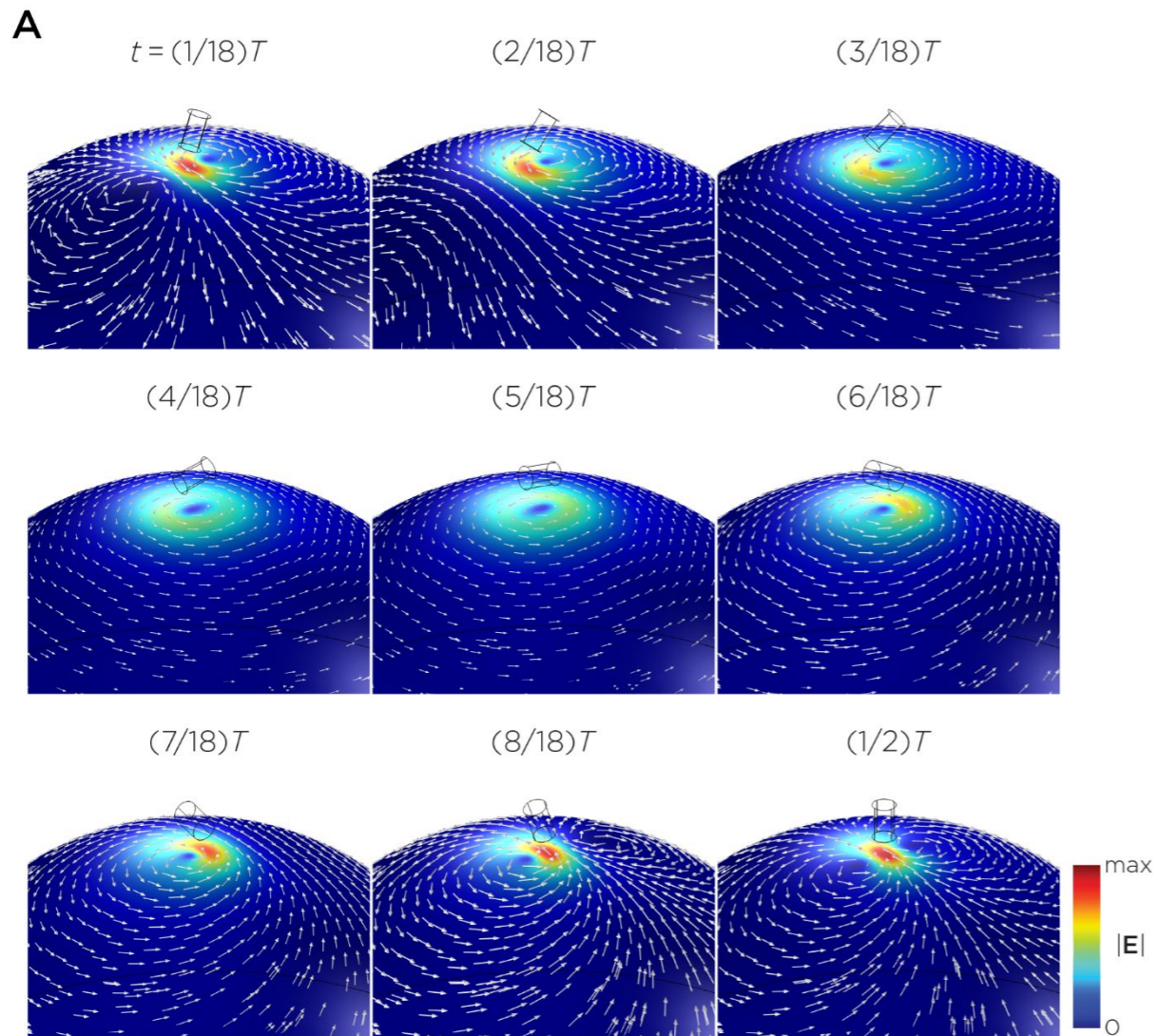
Conductive part of the rotor is modeled using

$$\sigma \frac{\partial \mathbf{A}}{\partial t} + \nabla \times \left(\frac{1}{\mu} \nabla \times \mathbf{A} \right) = 0$$

Nonconductive part of both rotor and stator are modeled using

$$-\nabla \cdot (\mu \nabla V_m - \mathbf{B}_r) = 0$$

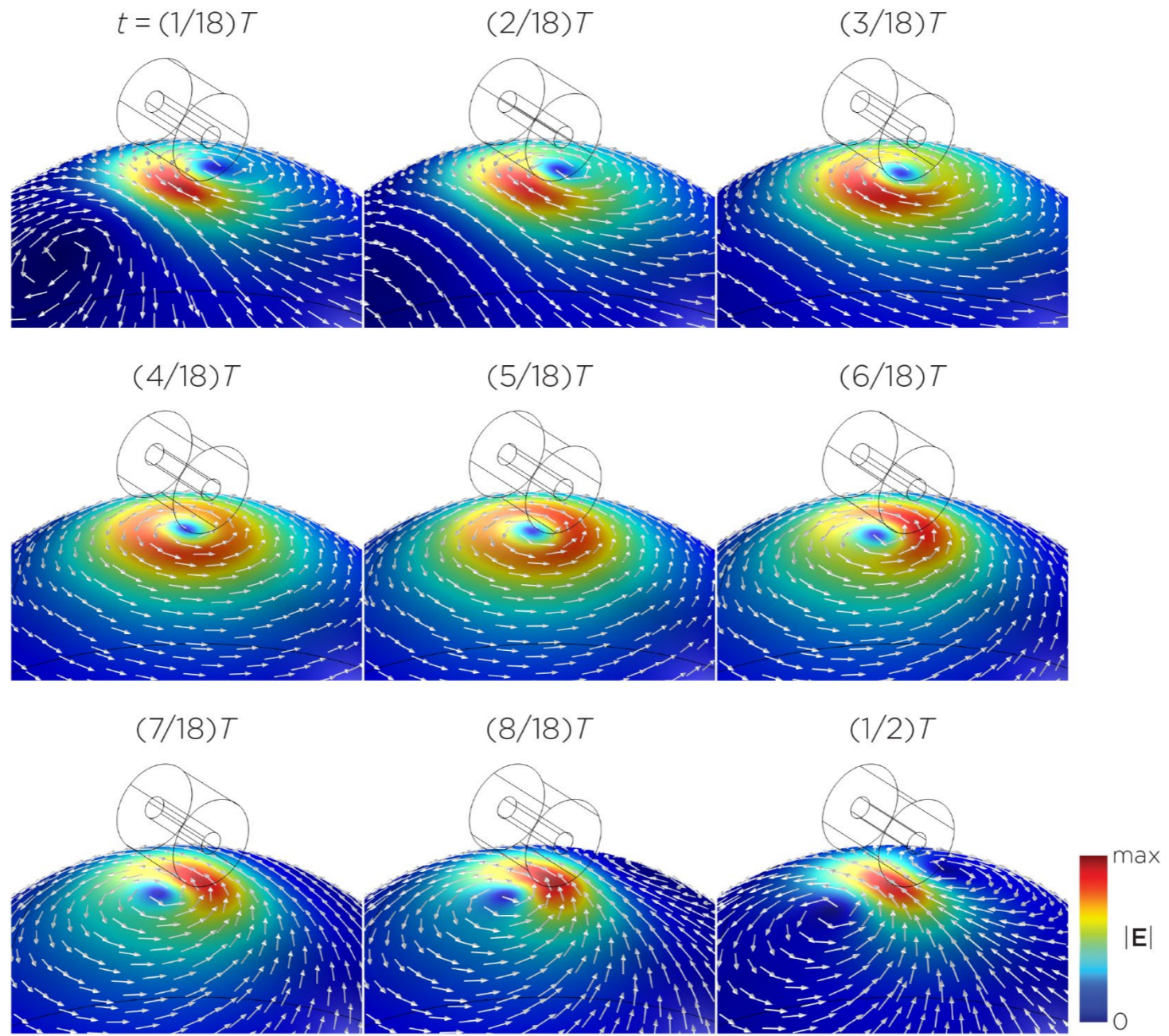


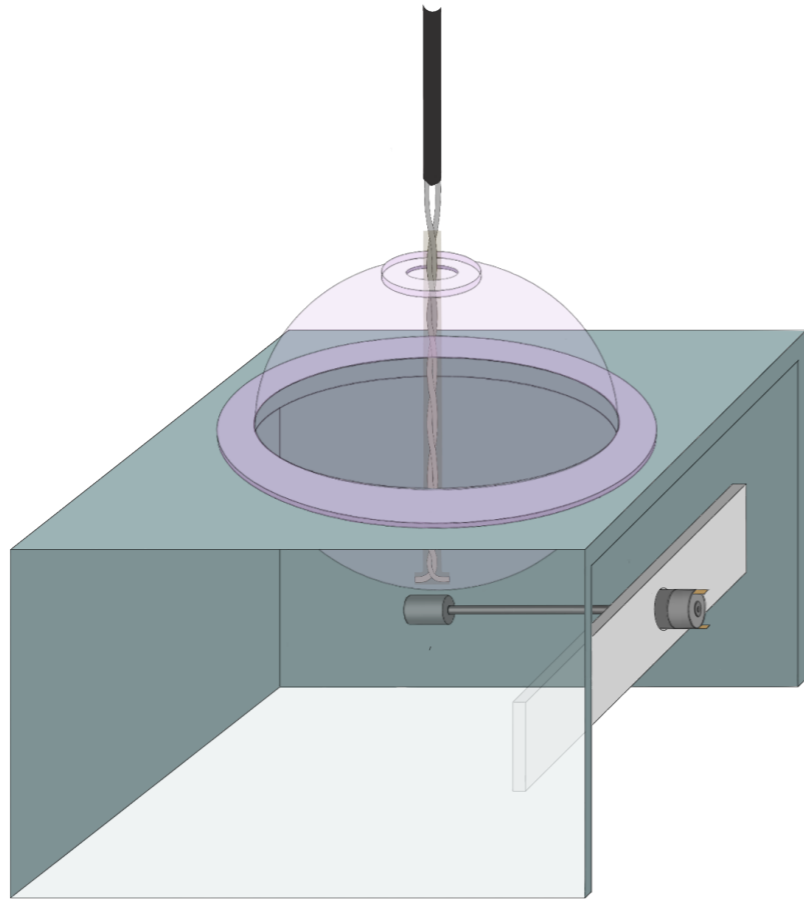


Synchronized TMS

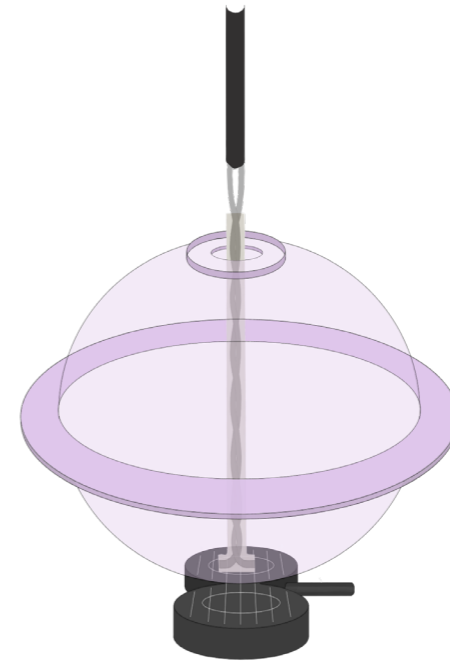
Diametrically magnetized magnets
Rotating parallel to the scalp
1 inch in diameter and height
Surface field 0.64 T
~10 Hz (IAF) rotation



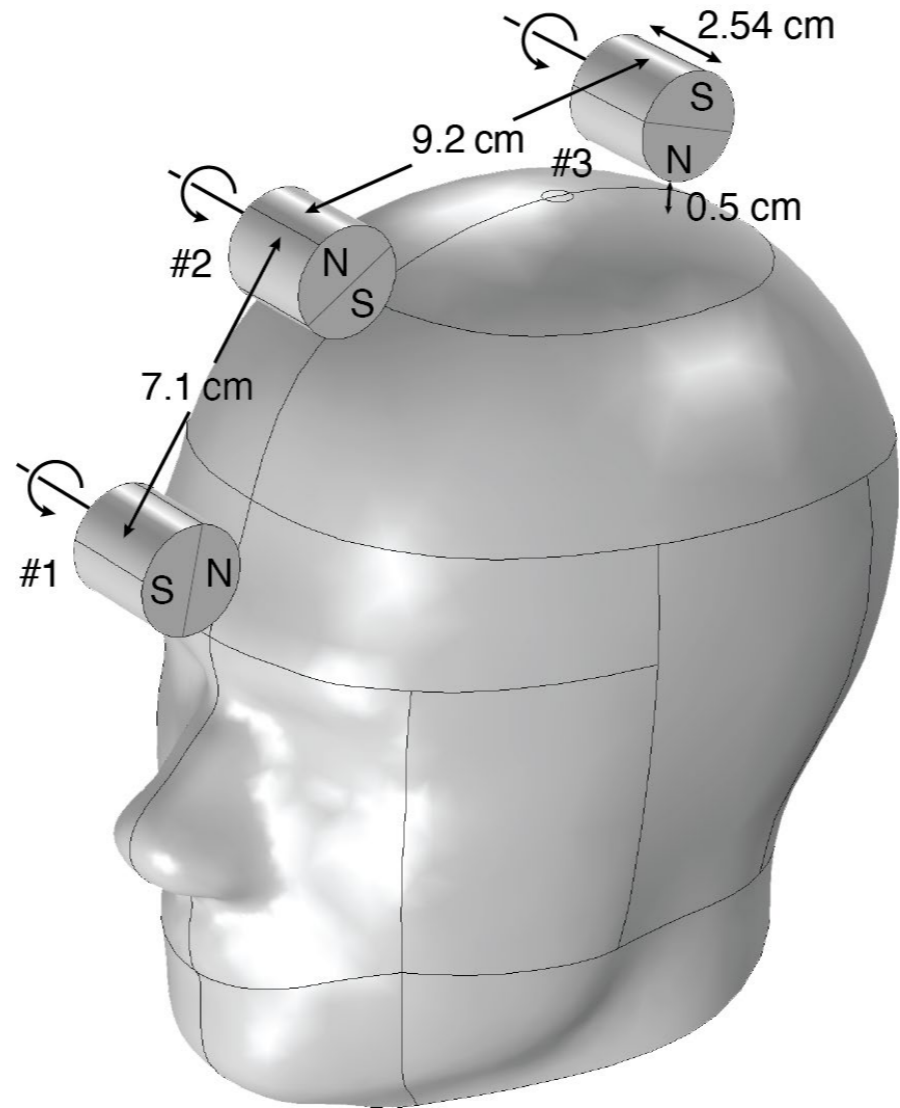


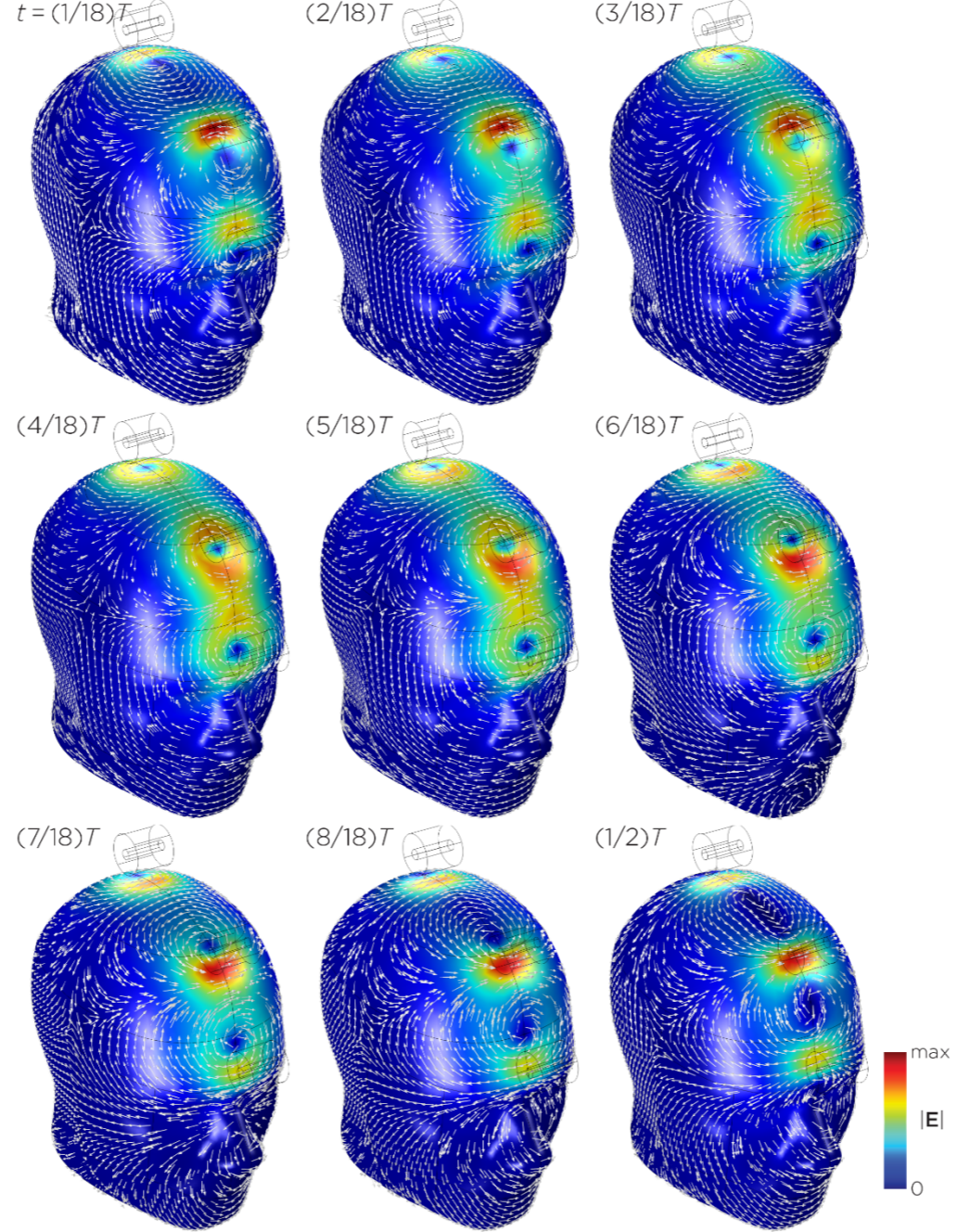


Rotational frequency 10.05 Hz
Max $|E|$: 0.082 V/m



Pulse frequency: 3448 Hz
Max $|E|$: 401.5 V/m





Predictors of response to synchronized transcranial magnetic stimulation for major depressive disorder

Noah S. Philip MD^{1,2} | Andrew F. Leuchter MD³ | Ian A. Cook MD^{3,4,5} |
Joe Massaro PhD⁶ | John W. Goette MD⁷ | Linda L. Carpenter MD²

“lower IAF predicted poorer response in participants who received 10 weeks of active sTMS (p = 0.001)”

¹Center for Neurorestoration and Neurotechnology, Providence (Alpert) Center, Providence, RI 02908, USA

²Butler Hospital Mood Disorders Research Program and Neuromodulation Research Facility, Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI 02906, USA

³Neuromodulation Division, Semel Institute for Neuroscience and Human Behavior, and Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA

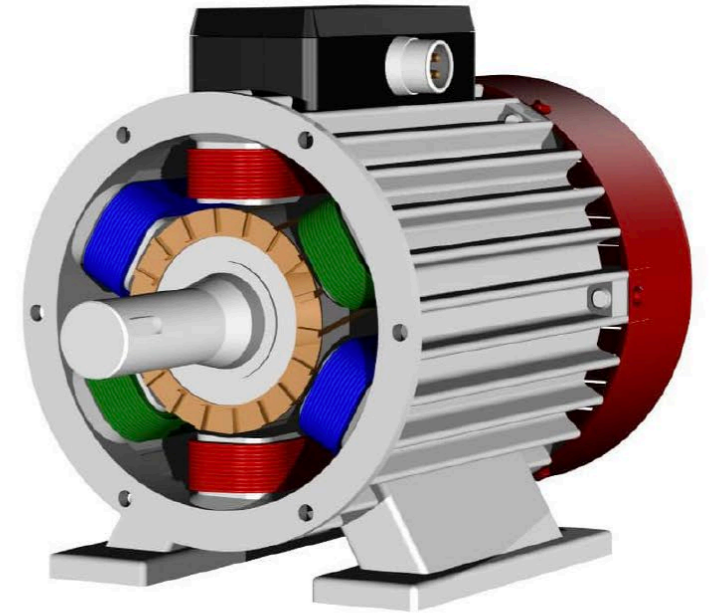
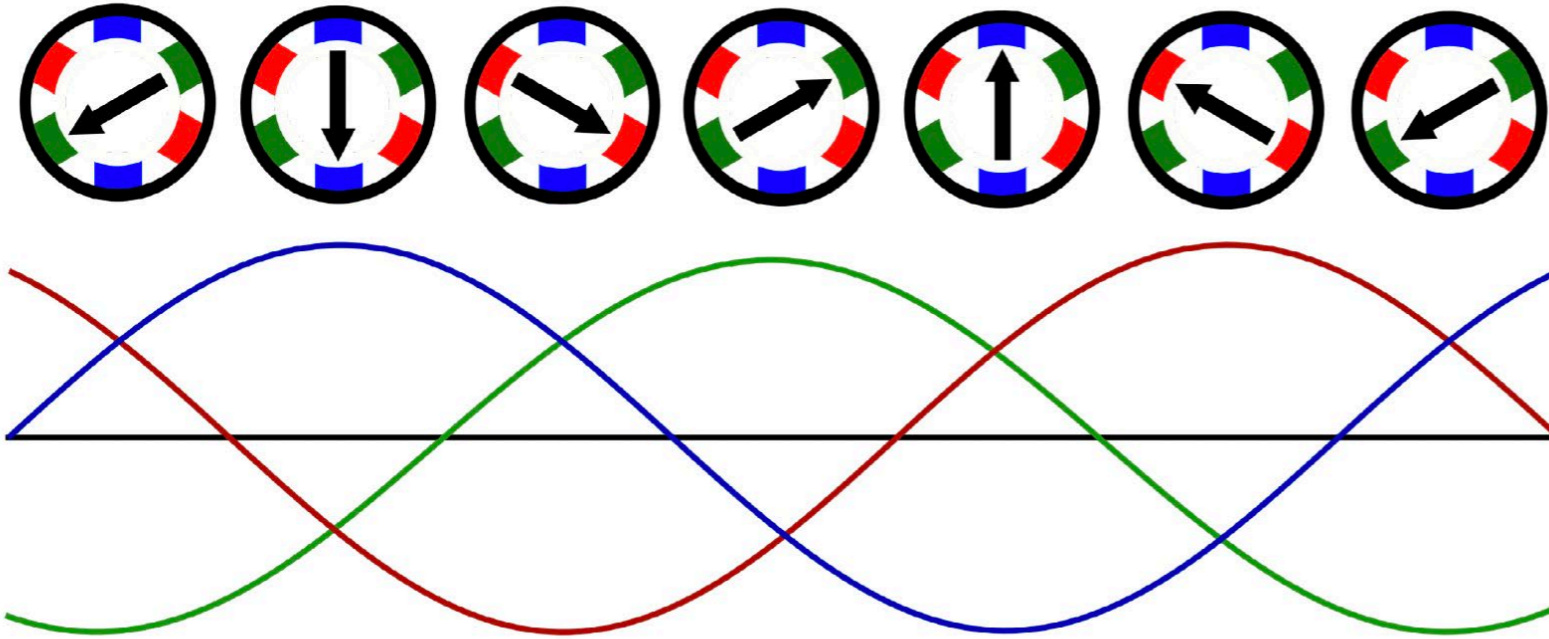
⁴Department of Bioengineering, Henry Samueli School of Engineering and Applied Science at UCLA, Los Angeles, CA 90095, USA

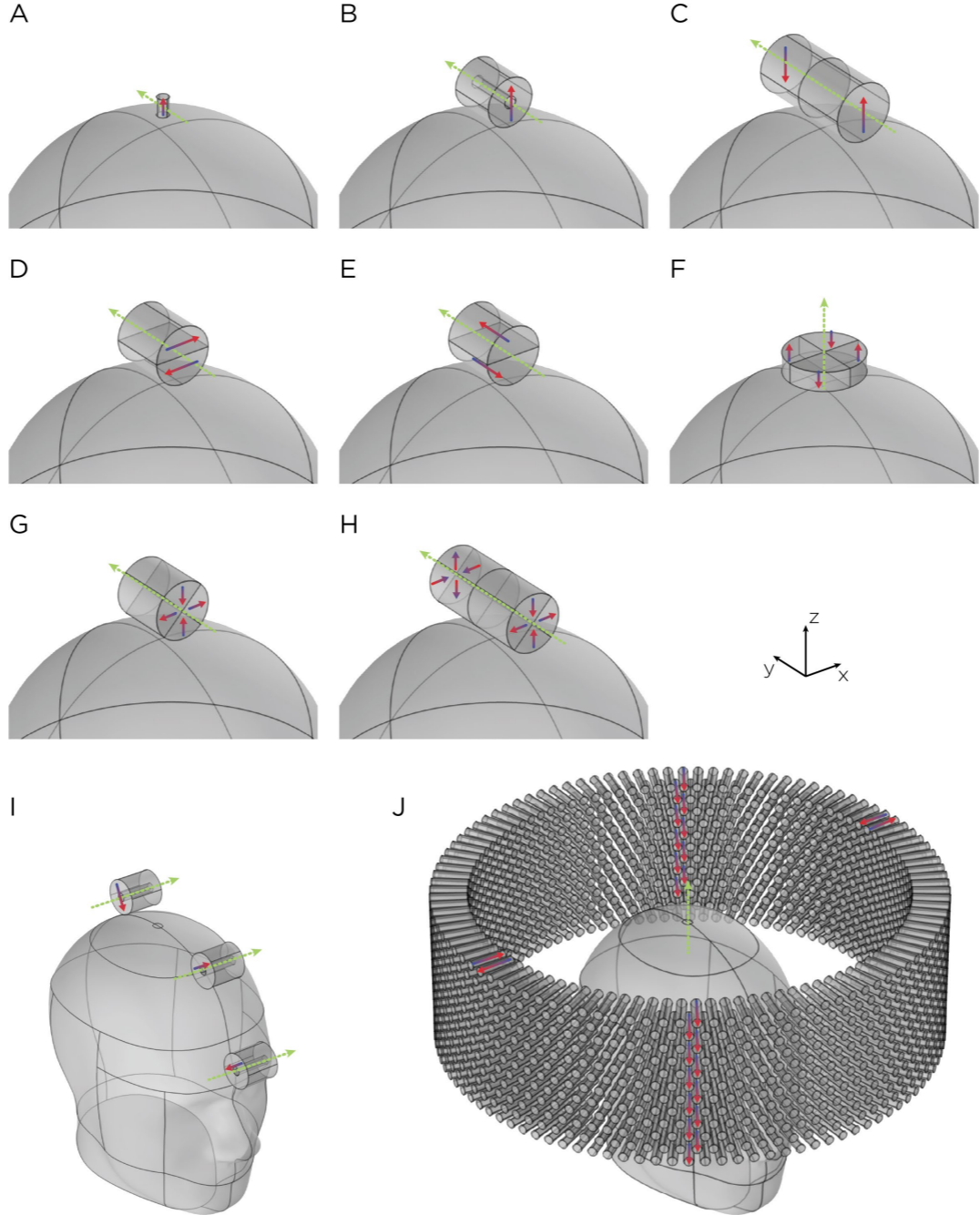
⁵Mood and TMS Services, Greater Los Angeles

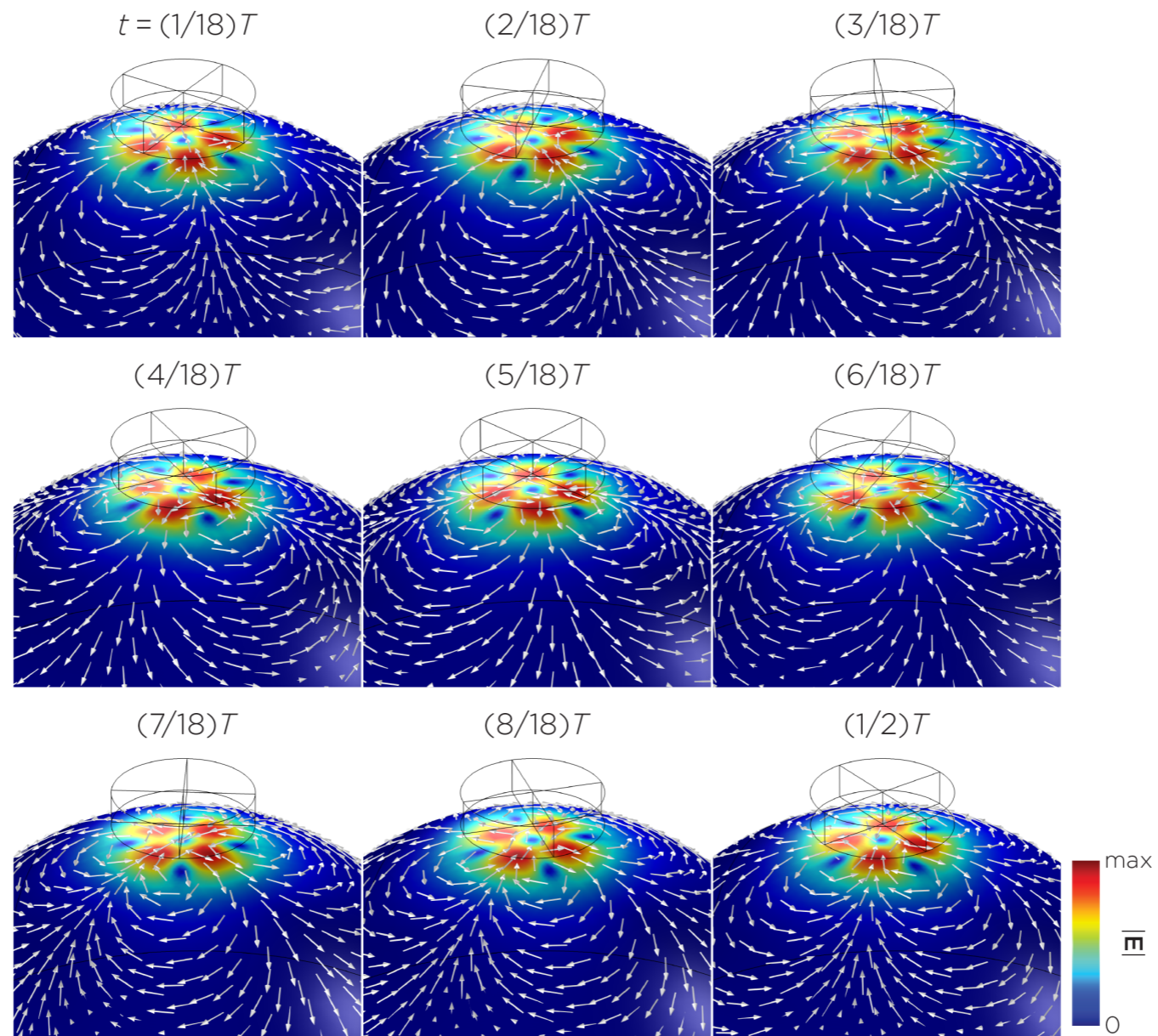
Transcranial magnetic stimulation (TMS) is a new modality to reduce symptoms of major depressive disorder (MDD). sTMS uses rotating neodymium magnets to deliver low-level stimulation targeted to the individual's theta frequency (IAF). A previous multi-site study showed that sTMS significantly reduced MDD symptoms in the per-protocol sample. To this end, we evaluated clinical features associated with optimal sTMS outcomes.

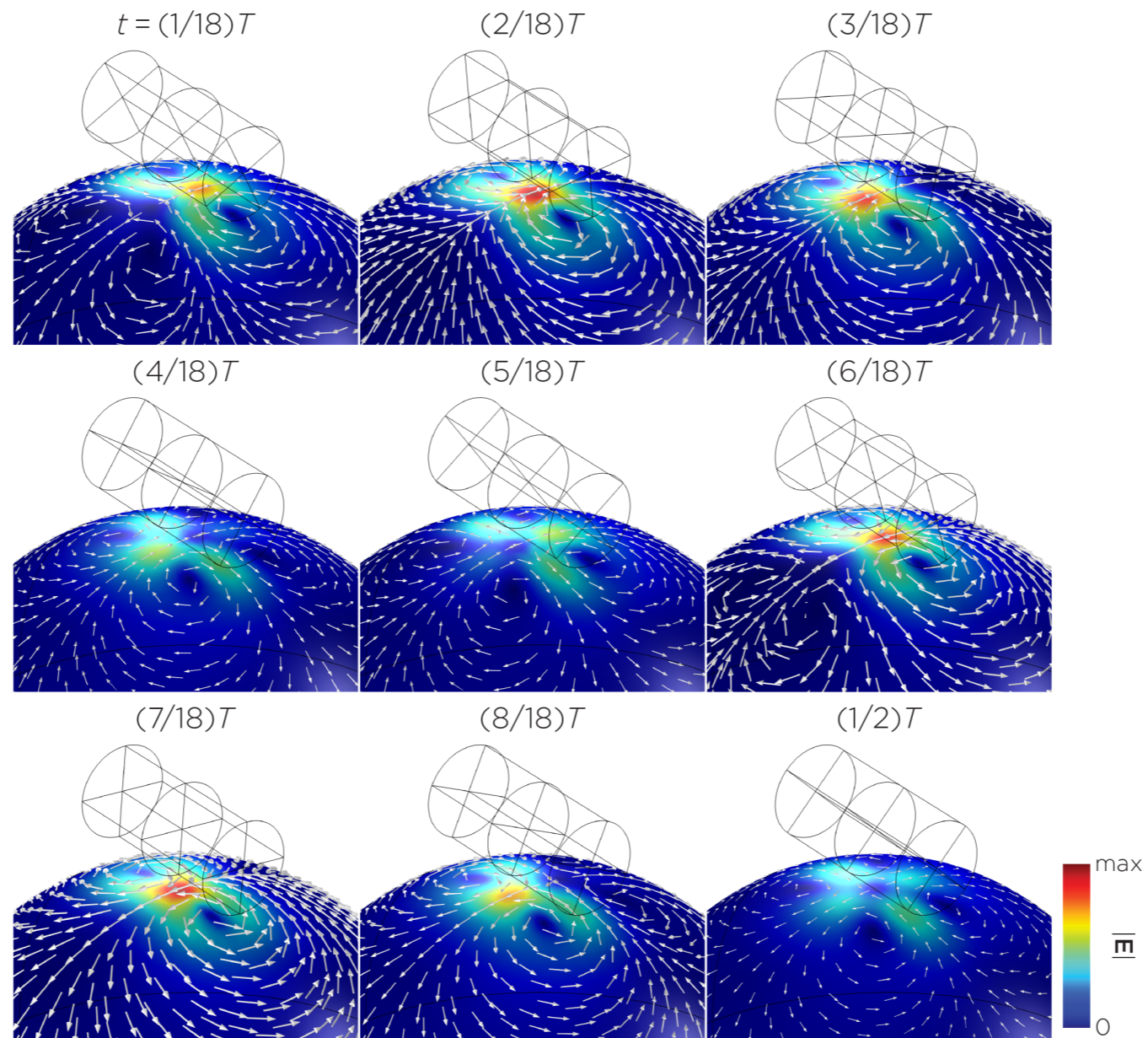
Methods: Using the per-protocol sample ($n = 120$) from the parent sham-controlled trial, we performed univariate and stepwise linear regression to identify predictors of response after 6 weeks of sTMS. A subsample ($n = 83$) that entered a 4-week open/active continuation phase also was examined. Candidate variables included age, sex, comorbid anxiety, number of failed antidepressants in the current depressive episode, MDD severity (17-item Hamilton Depression Rating Scale; HAMD17), anxiety symptom severity (HAMD17 anxiety/somatization factor), and IAF.

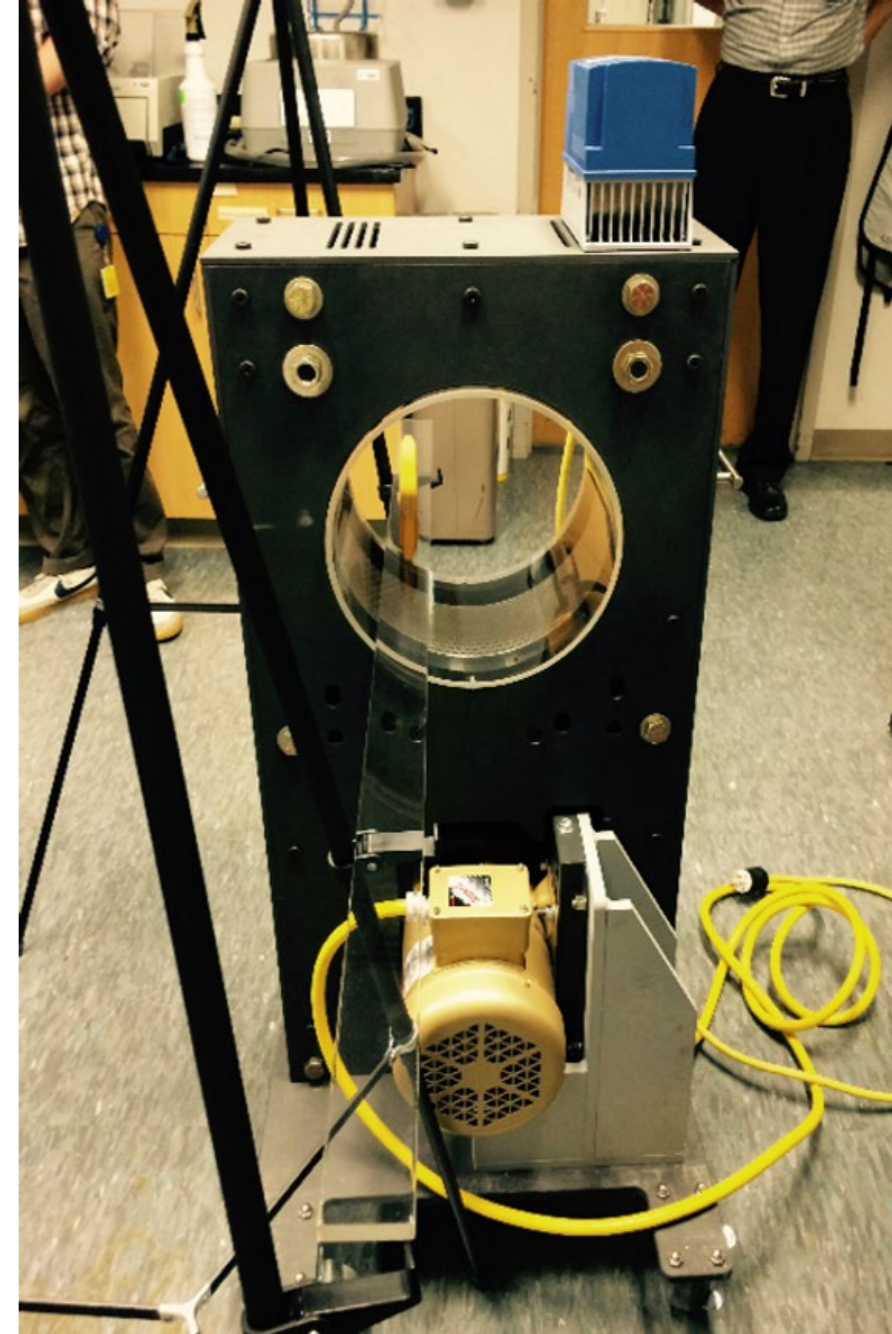
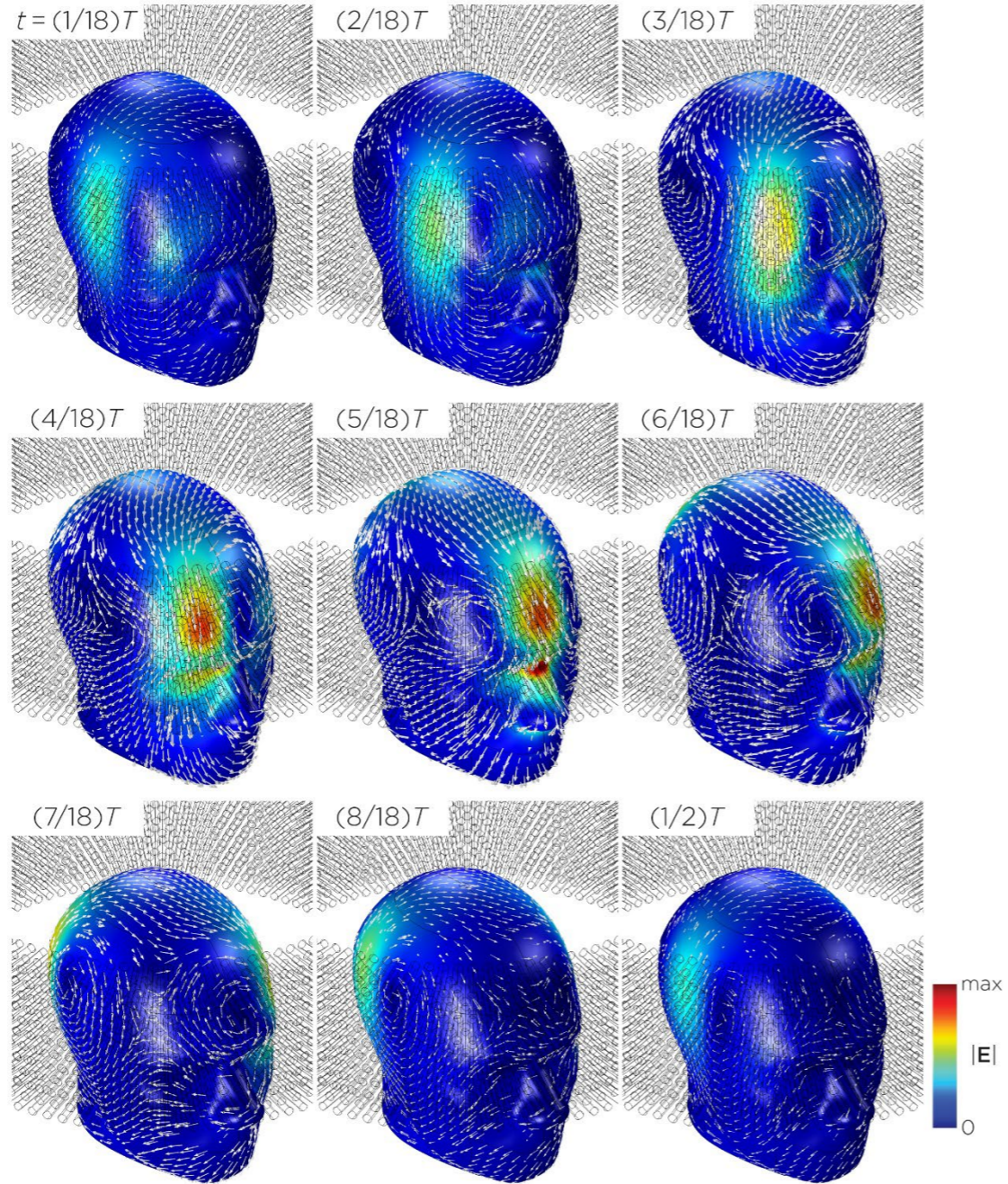
Results: We found that greater baseline depressive ($p < 0.001$) and anxiety ($p < 0.001$) symptom severity were associated with better response to active sTMS, whereas fewer failed antidepres-



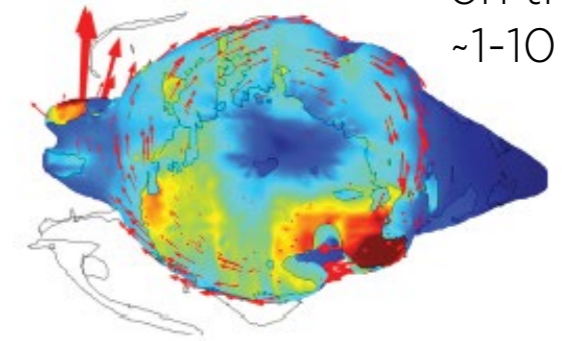
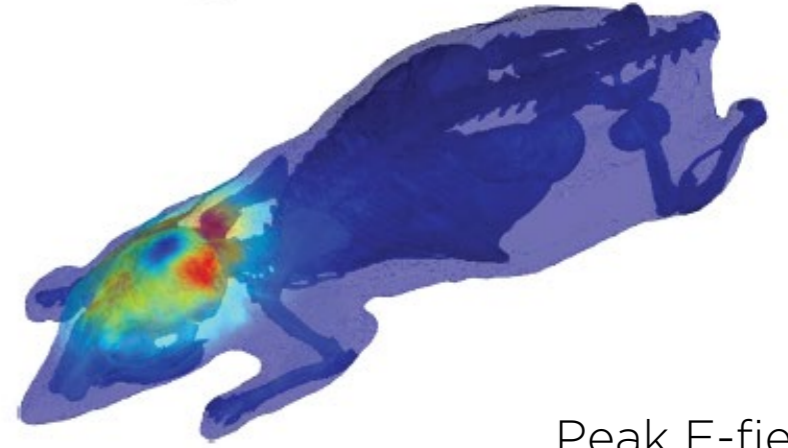
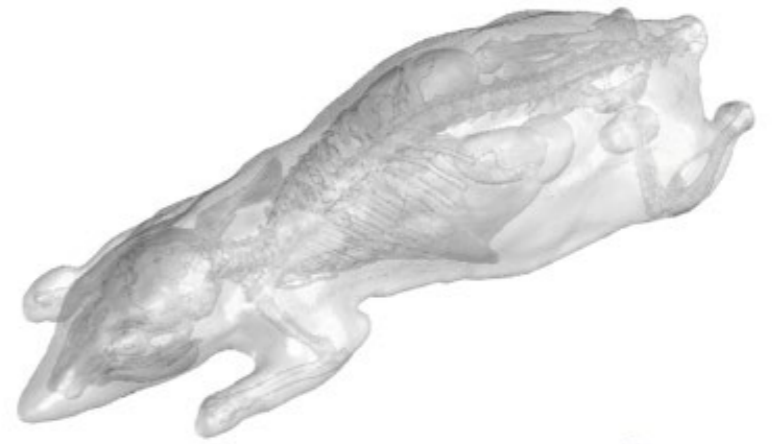




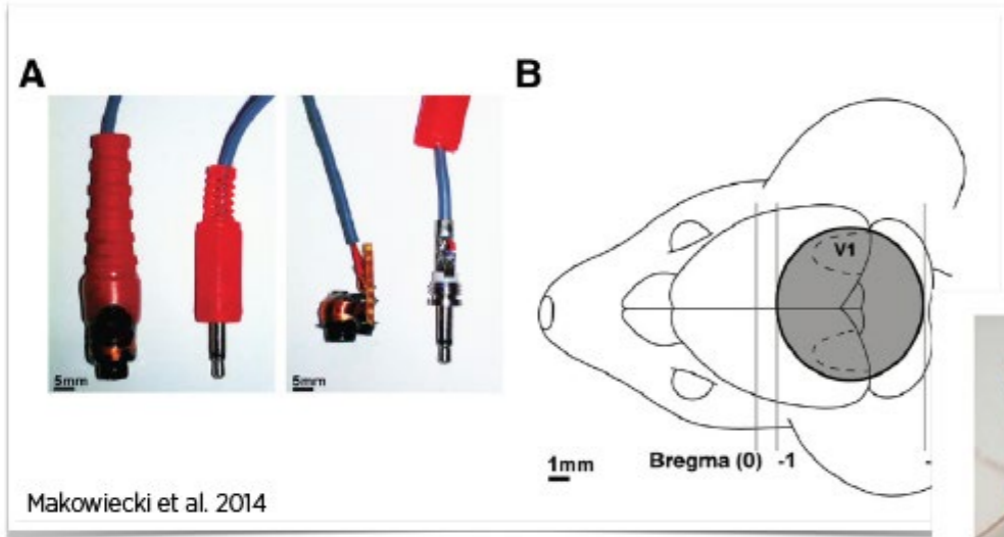




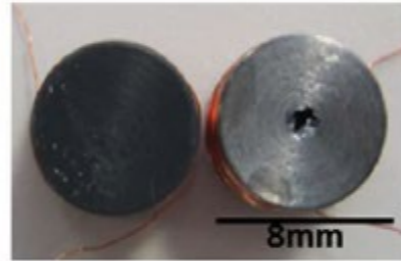
LFMS: Rodent model



Peak E-field
on the order of
 $\sim 1-10$ V/m



Makowiecki et al. 2014



Tang et al. 2016

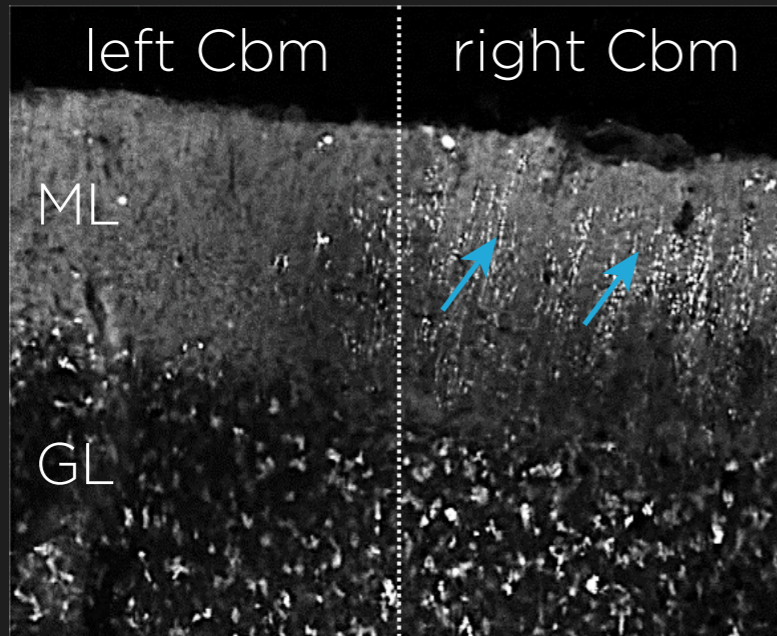
Rachel Sherrard, MD/PhD
Sorbonne



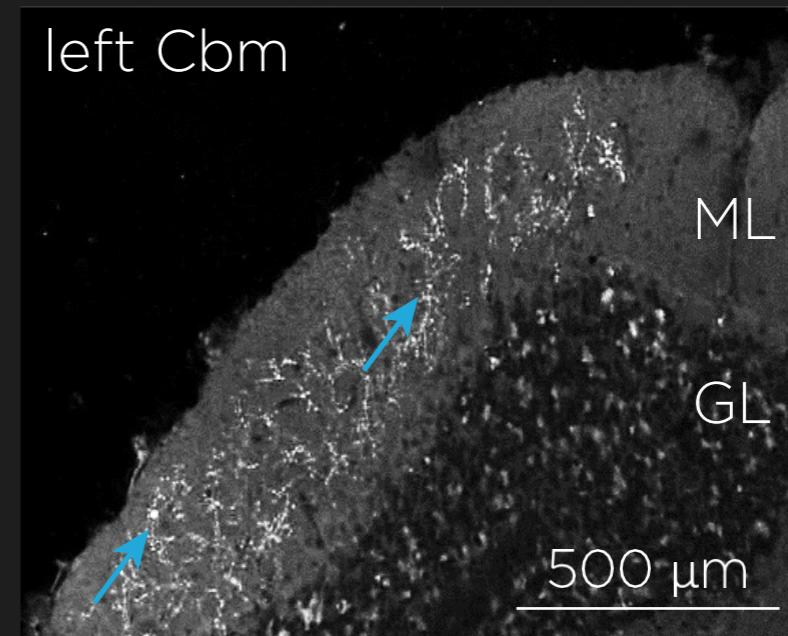
Jenny Rodger, PhD
UWA

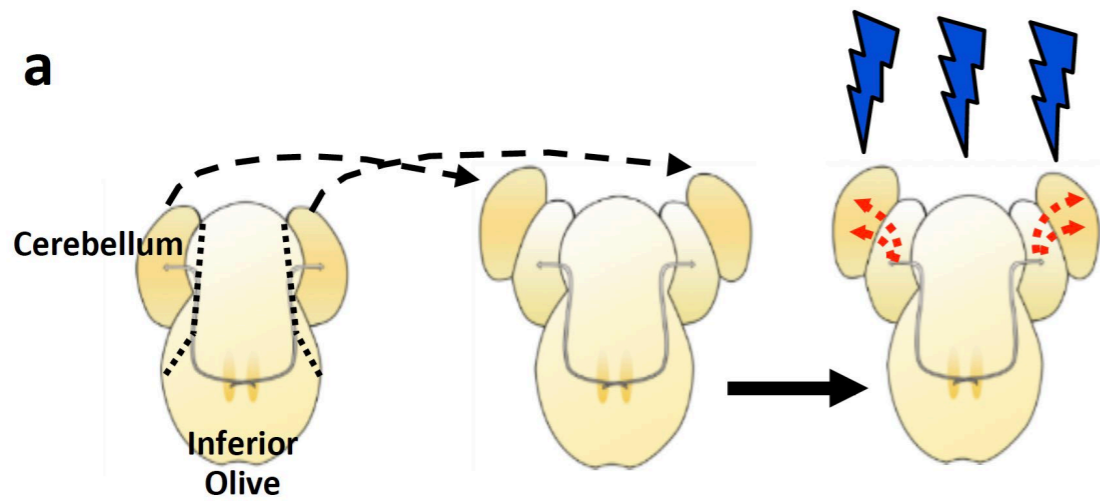
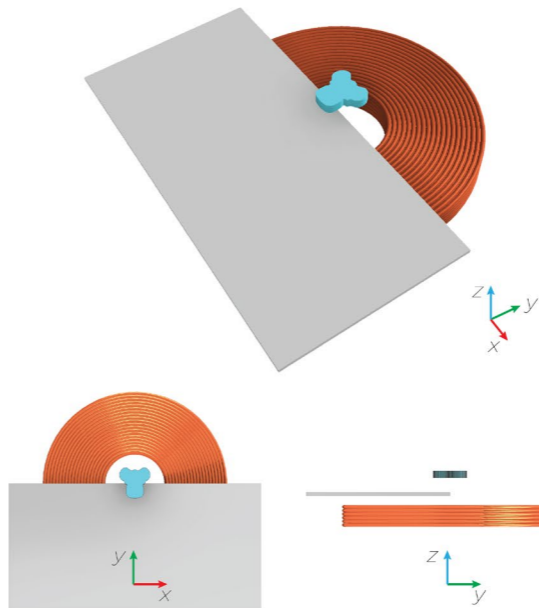
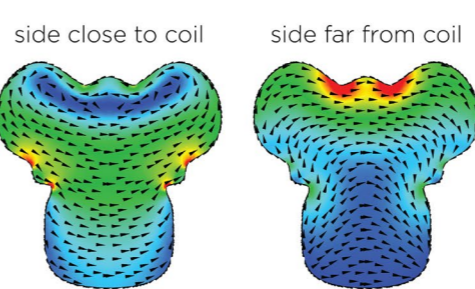
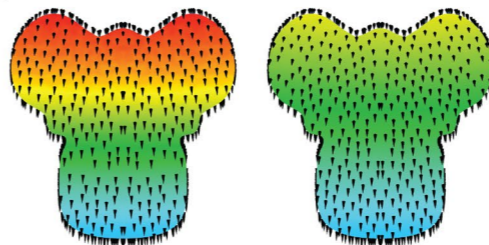
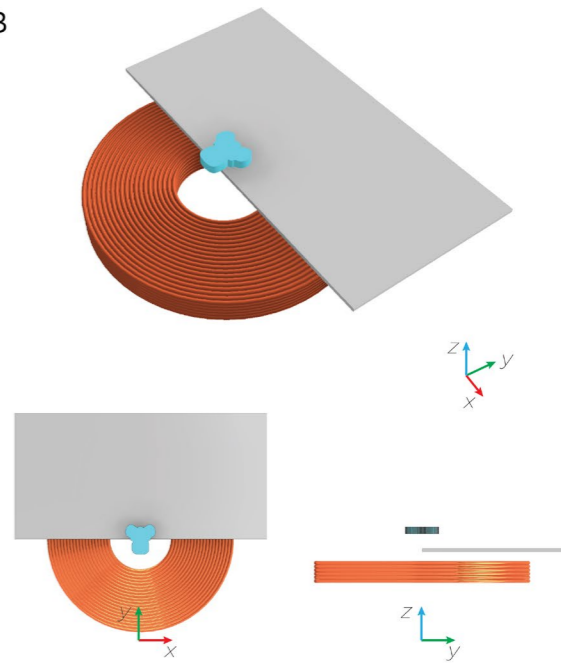
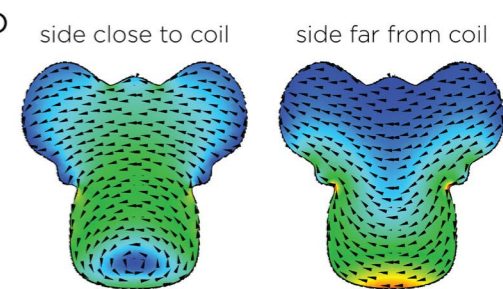
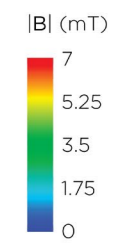
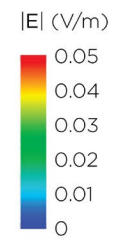
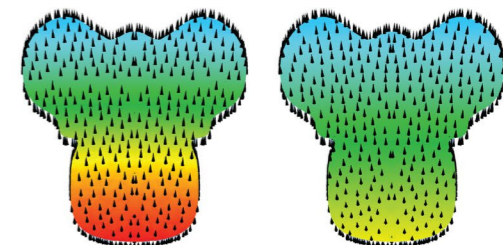
In vivo experiment

Left pedunculotomy
+ sham stimulation



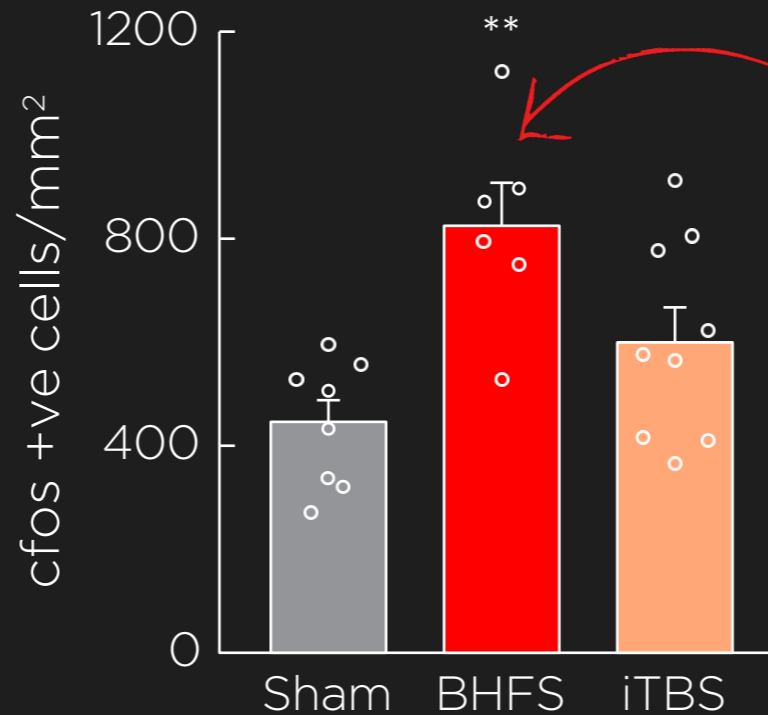
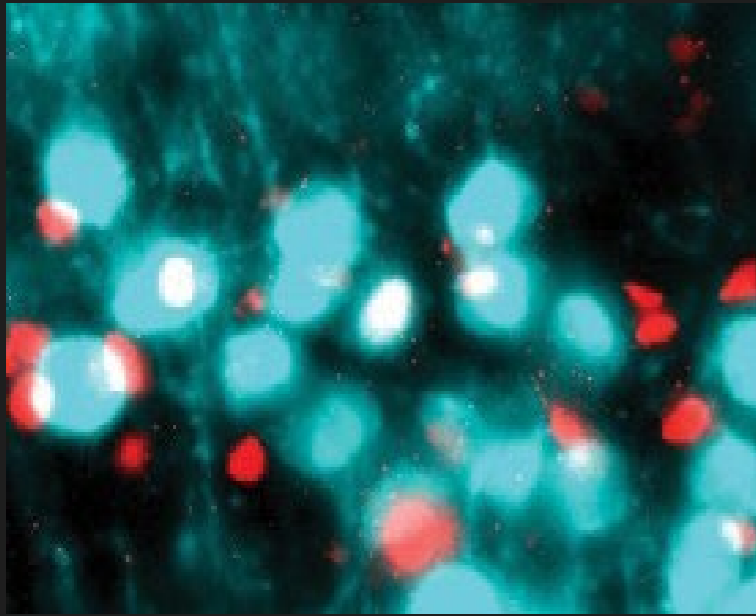
Biomimetic high frequency
stimulation (BHFS)



a**A****C****E****B****D****F**

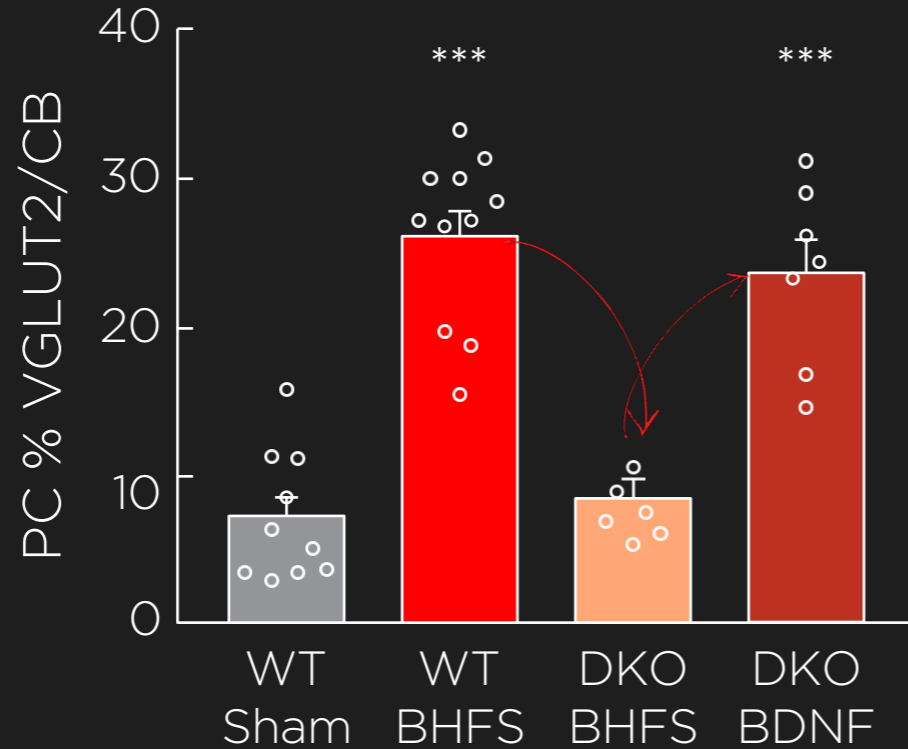
LFMS: Cellular activation

CB/cfos



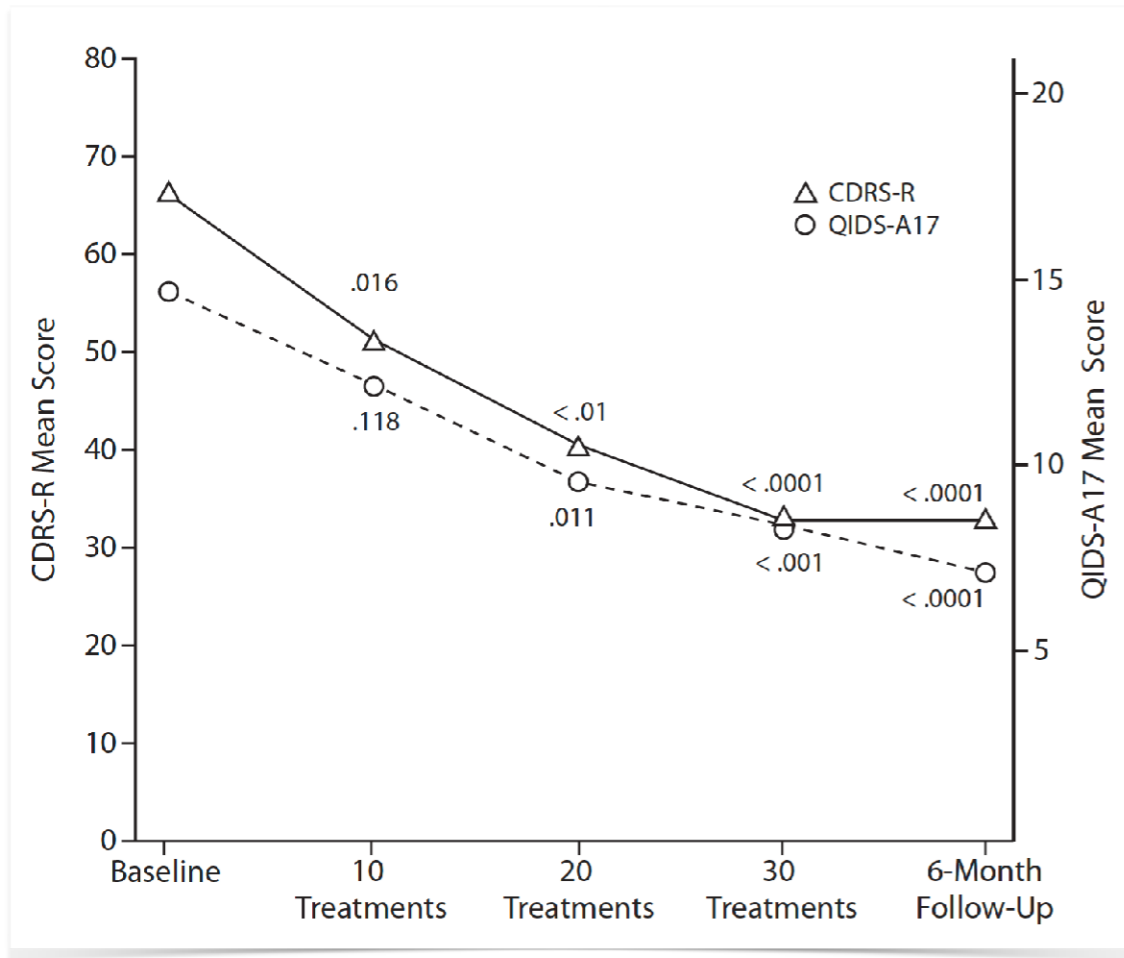
BHFS nearly doubled the number of cfos-positive cells compared to sham

LFMS: KO experiment



In explant cultures from $Cry1^{-/-}Cry2^{-/-}$ DKO mice, BHFS no longer induces reinnervation





- § Prospective, open labeled trial of active adjunctive rTMS
- § 8 adolescents with MDD that had not responded to 2 antidepressant trials
- § On stable dose of SSRI
- § 10-Hz rTMS, 5 days per week, over 6–8 weeks, up to 30 sessions



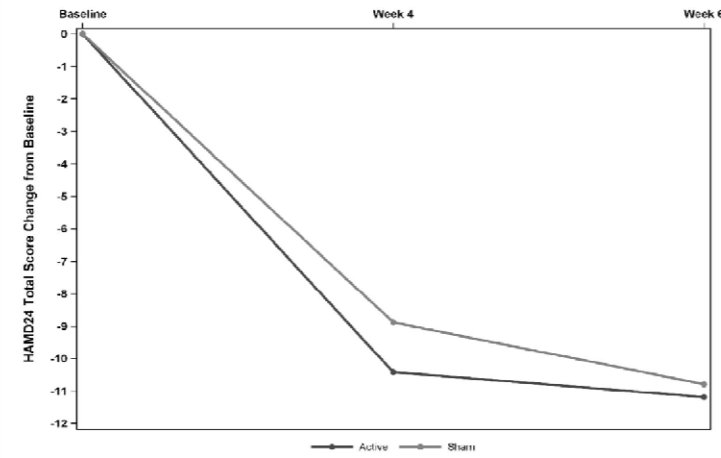
ARTICLE

Left prefrontal transcranial magnetic stimulation for treatment-resistant depression in adolescents: a double-blind, randomized, sham-controlled trial

Paul E. Croarkin¹, Ahmed Z. Elmaadawi², Scott T. Aaronson³, G. Randolph Schrodt Jr⁴, Richard C. Holbert⁵, Sarah Verdoliva⁶, Karen L. Heart⁷, Mark A. Demitrack⁸ and Jeffrey R. Strawn⁹

Treatment-resistant depression (TRD) is prevalent and associated with a substantial psychosocial burden and mortality. There are few prior studies of interventions for TRD in adolescents. This was the largest study to date examining the feasibility, safety, and efficacy of 10-Hz transcranial magnetic stimulation (TMS) for adolescents with TRD. Adolescents with TRD (aged 12–21 years) were enrolled in a randomized, sham-controlled trial of TMS across 13 sites. Treatment resistance was defined as an antidepressant treatment record level of 1 to 4 in a current episode of depression. Intention-to-treat patients ($n = 103$) included those randomly assigned to active NeuroStar TMS monotherapy ($n = 48$) or sham TMS ($n = 55$) for 30 daily treatments over 6 weeks. The primary outcome measure was change in the Hamilton Depression Rating Scale (HAM-D-24) score. After 6 weeks of blinded treatment, improvement in the least-squares mean (SE) HAM-D-24 scores were similar between the active (-11.1 [2.03]) and sham groups (-10.6 [2.00]; $P = 0.8$; difference [95% CI], -0.5 [-4.2 to 3.3]). Response rates were 41.7% in the active group and 36.4% in the sham group ($P = 0.6$). Remission rates were 29.2% in the active group and 29.0% in the sham group ($P = 0.95$). There were no new tolerability or safety signals in adolescents. symptom severity, this did not differ from response and examine the optimal dosing.

Neuropsychopharmacology (2021) 46:462–466

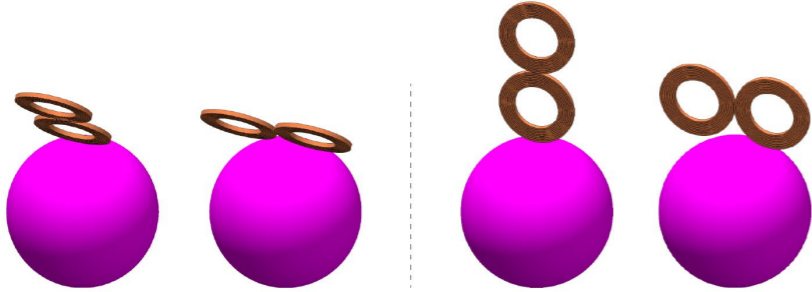


“ Although TMS treatment produced a clinically meaningful change in depressive symptom severity, this did not differ from sham treatment.

“Future studies should focus on strategies to reduce the placebo response and examine the optimal dosing of TMS for adolescents with TRD.

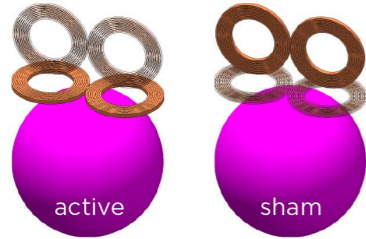
Coil tilt

A) 45°, 1-wing B) 45°, 2-wings C) 90°, 1-wing D) 90°, 2-wings

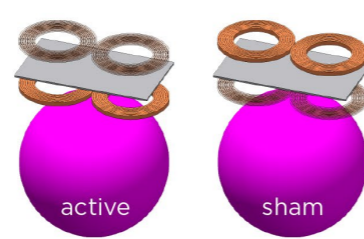


Two-coil configurations

E) Orthogonal coils



F) Sandwich coils

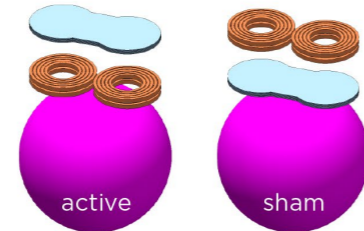


Dedicated sham systems

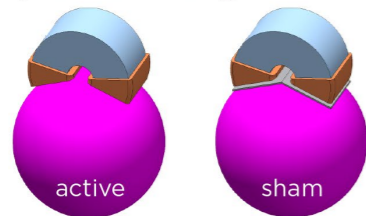
G) Reverse current



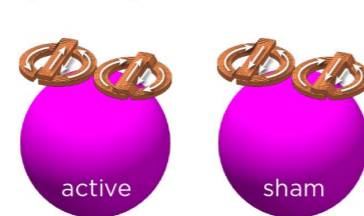
H) Spacer + passive shielding



I) Passive shielding



J) Quadrupole coil

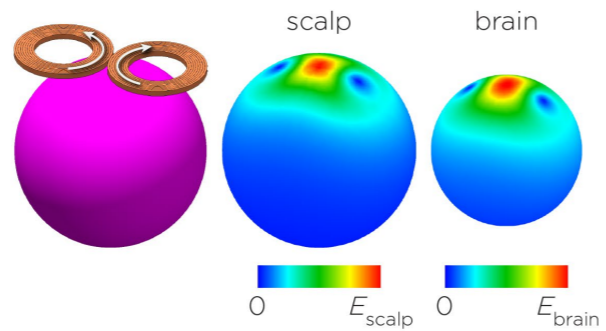


Elements of valid sham TMS

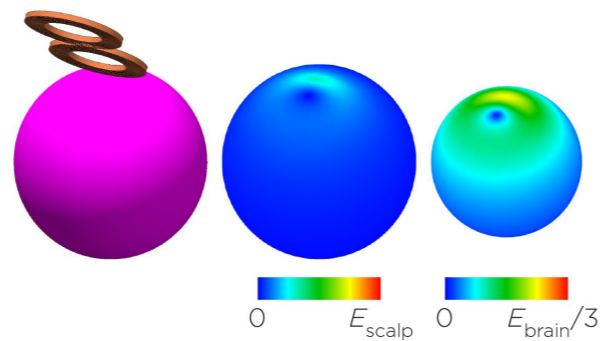
- Should look and sound like active
- Should reproduce the same somatic sensation (coil vibration, scalp nerve and muscle activation)
- No active brain stimulation, i.e., minimum E-field

Coil tilt

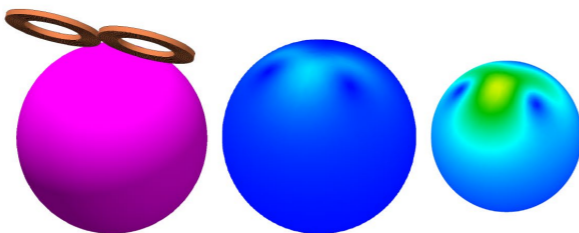
A) Active 70-mm figure-8



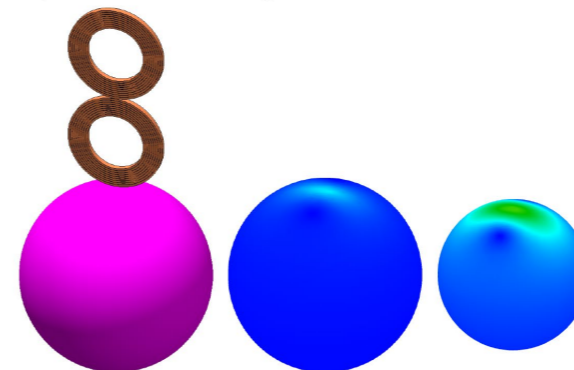
B) 45° tilt, 1-wing



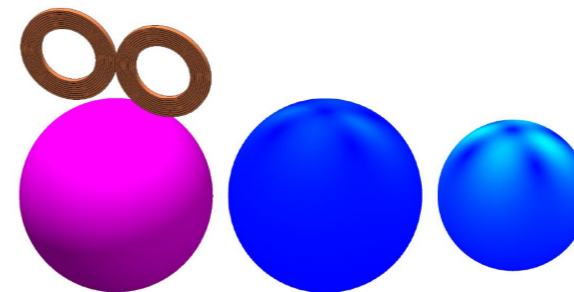
D) 45° tilt, 2-wings



C) 90° tilt, 1-wing



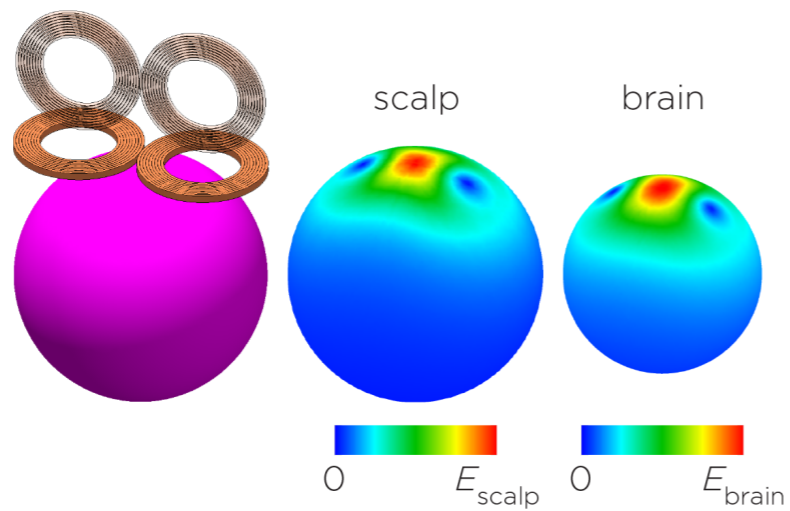
E) 90° tilt, 2-wings



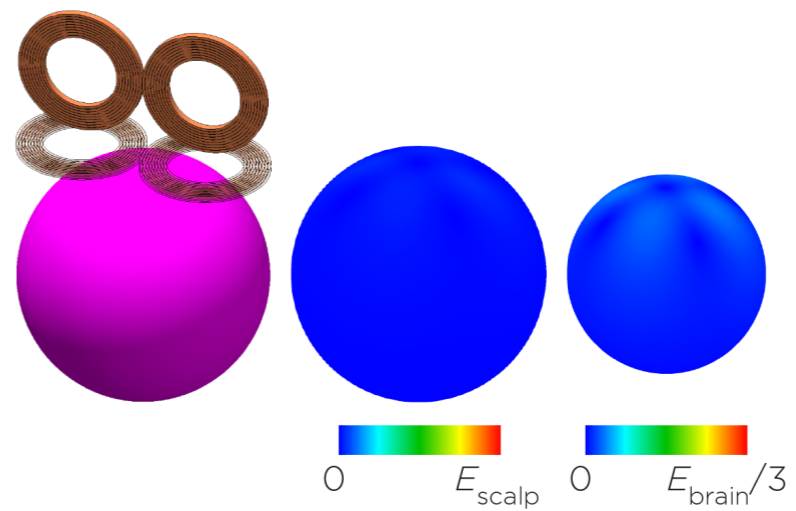
Two-coil configurations

A) Perpendicular coils

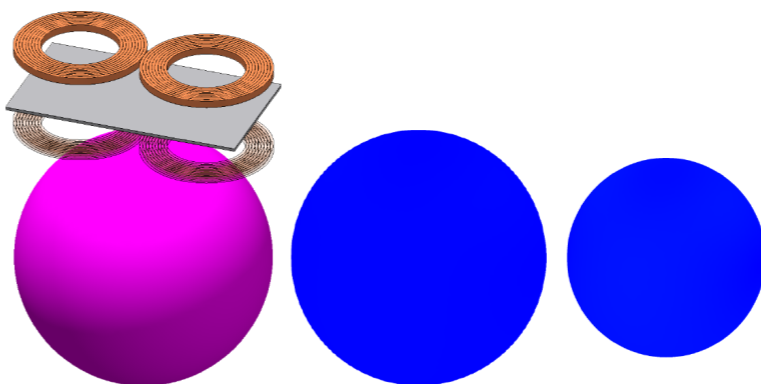
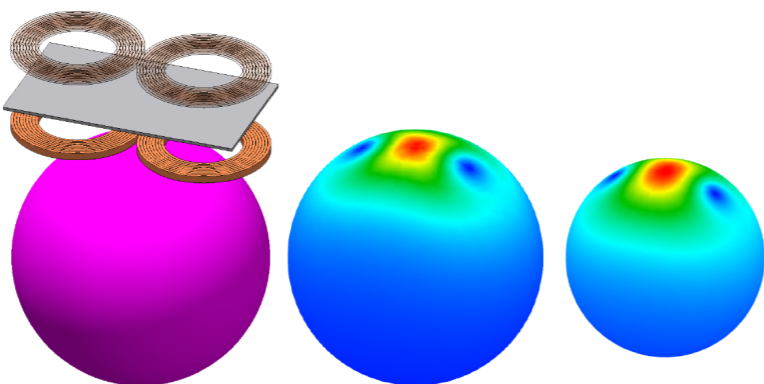
active



sham

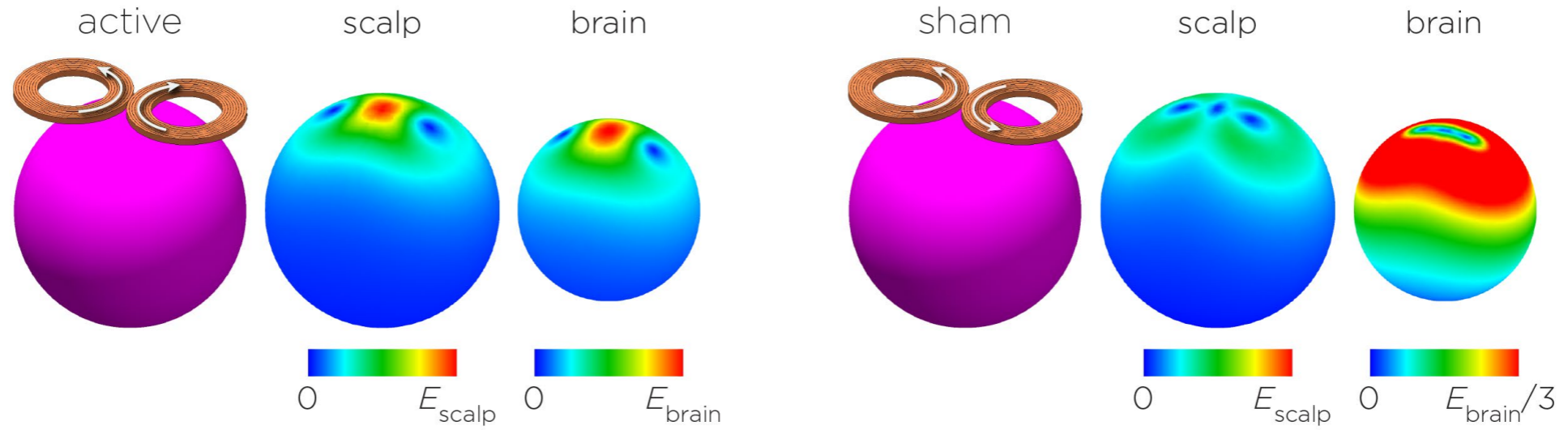


B) Sandwich coils

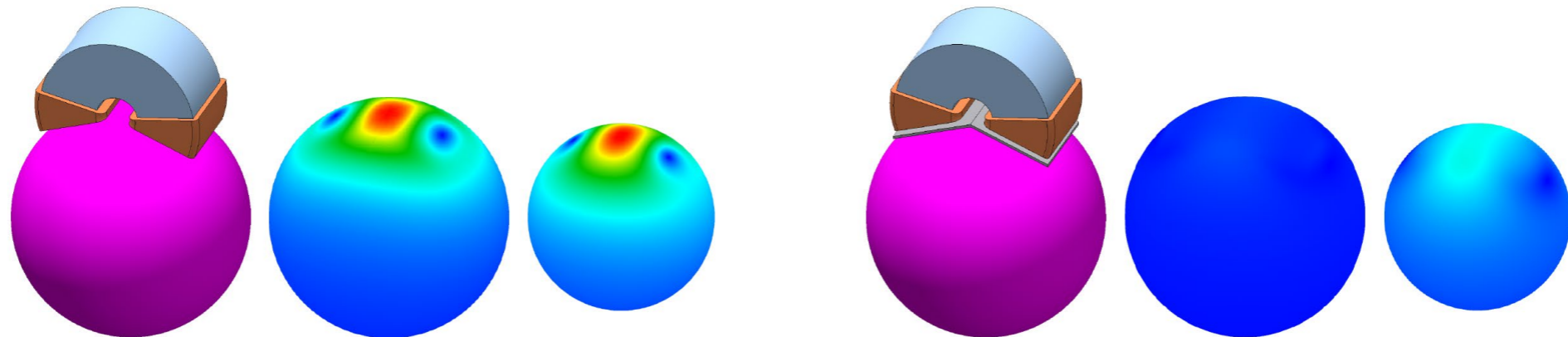


Dedicated sham systems

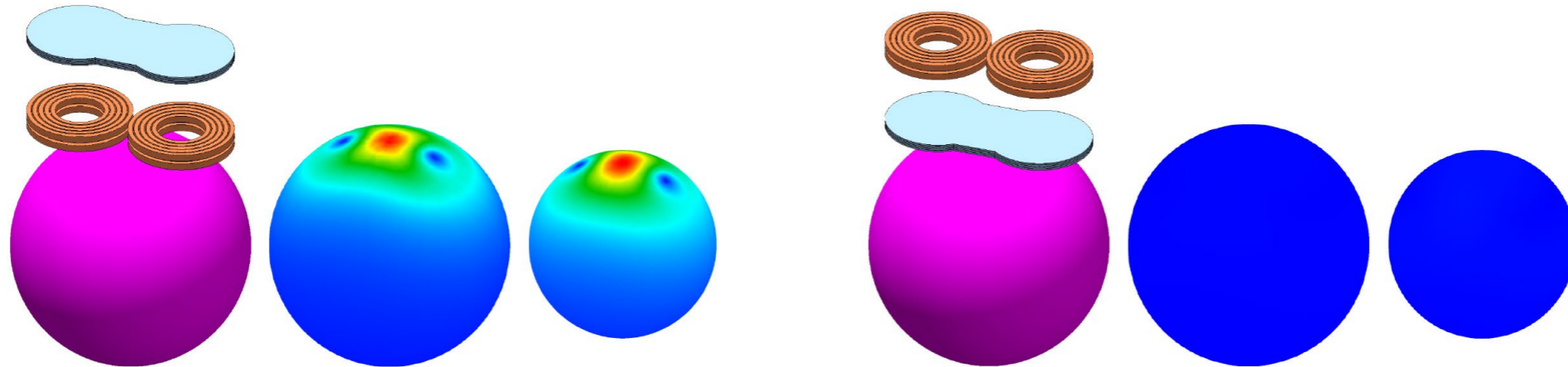
A) Reverse current



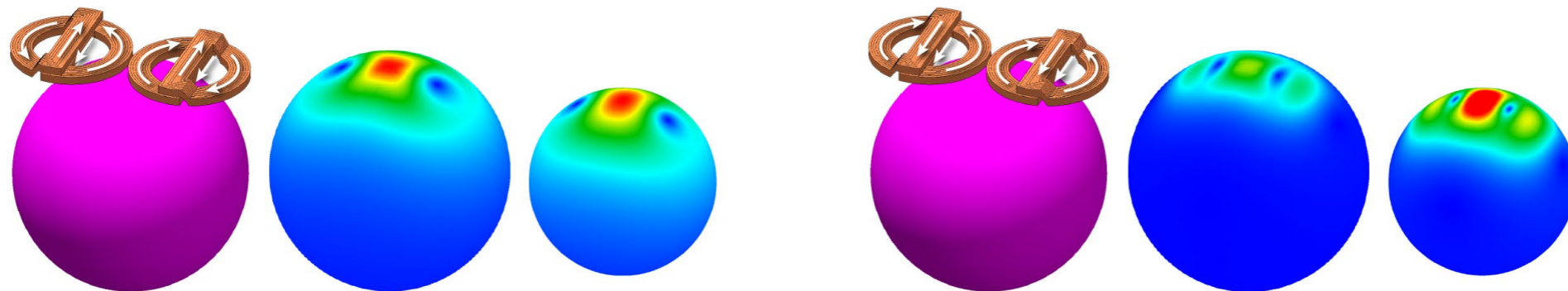
B) Passive shielding



C) Spacer + passive shielding

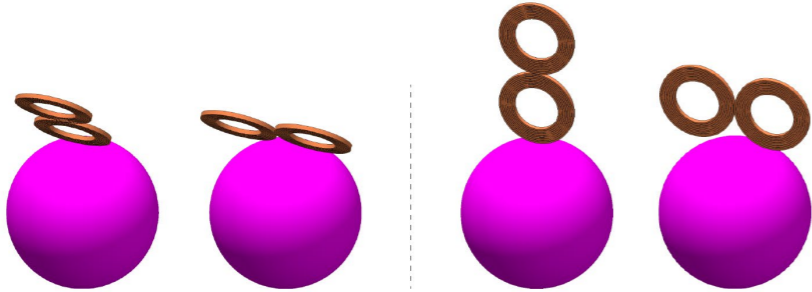


D) Quadrapole coil



Coil tilt

A) 45°, 1-wing B) 45°, 2-wings C) 90°, 1-wing D) 90°, 2-wings

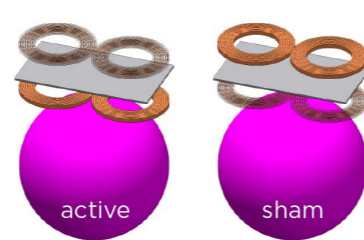


Two-coil configurations

E) Orthogonal coils



F) Sandwich coils

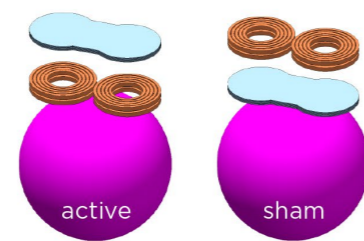


Dedicated sham systems

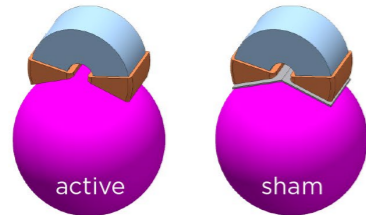
G) Reverse current



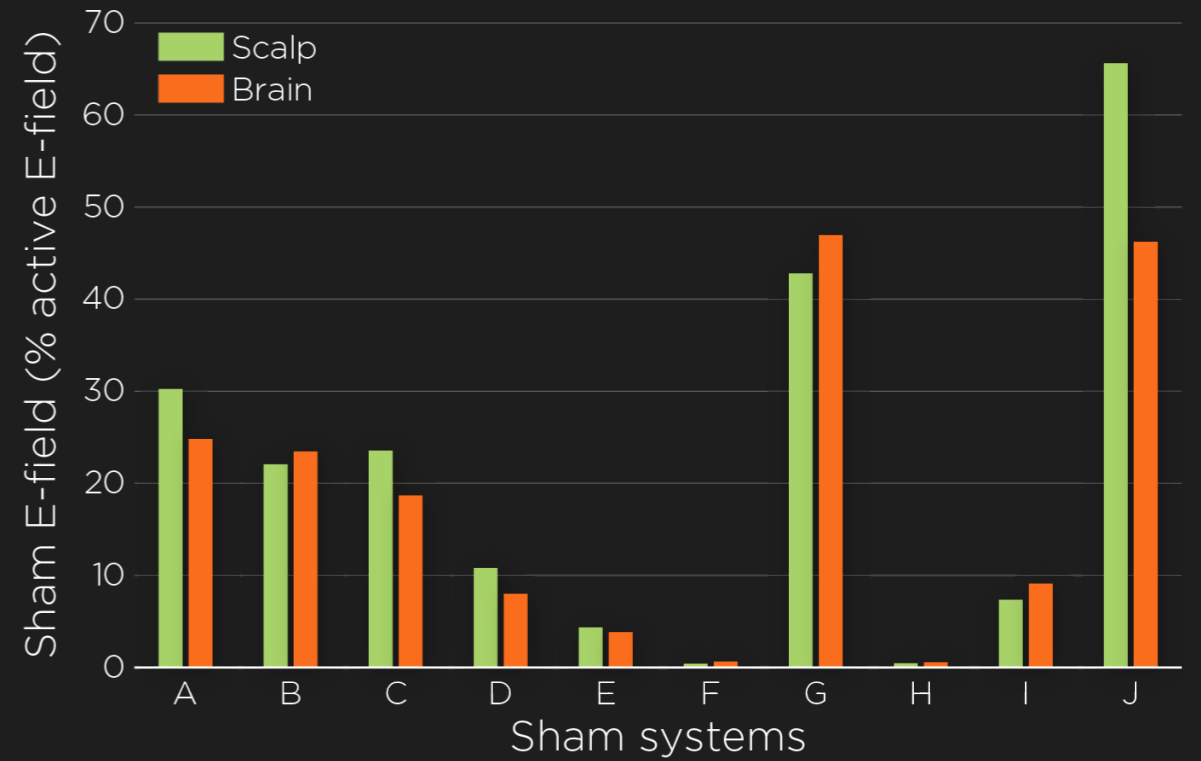
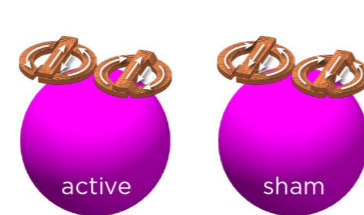
H) Spacer + passive shielding



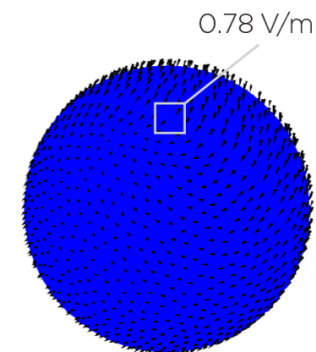
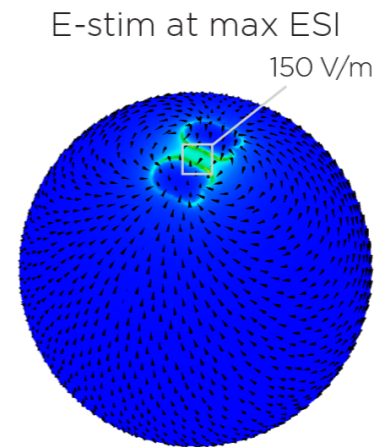
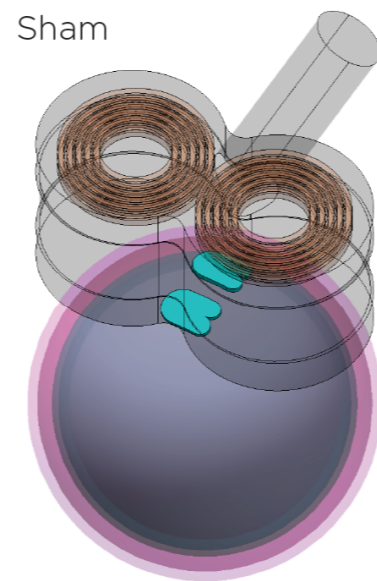
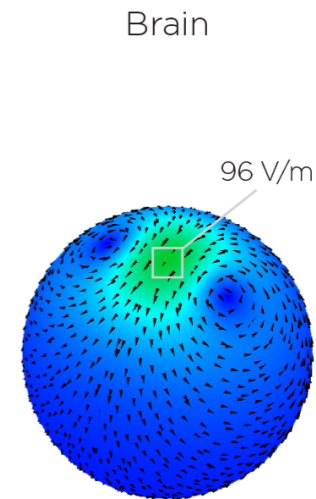
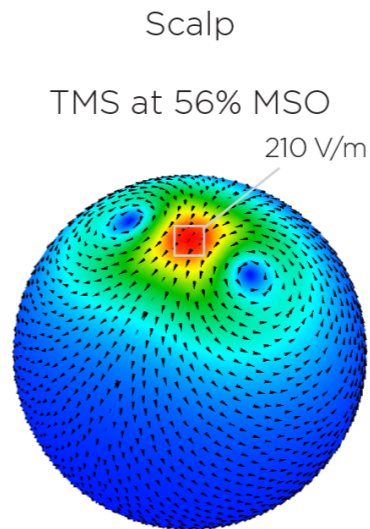
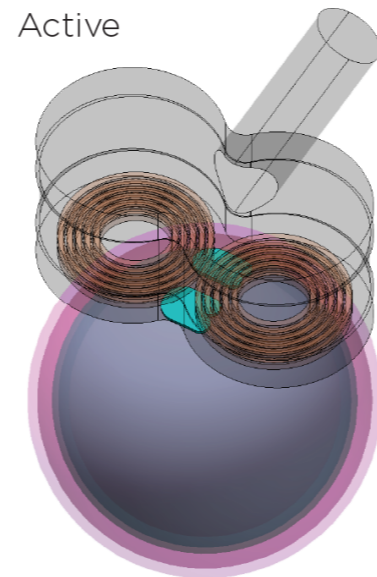
I) Passive shielding

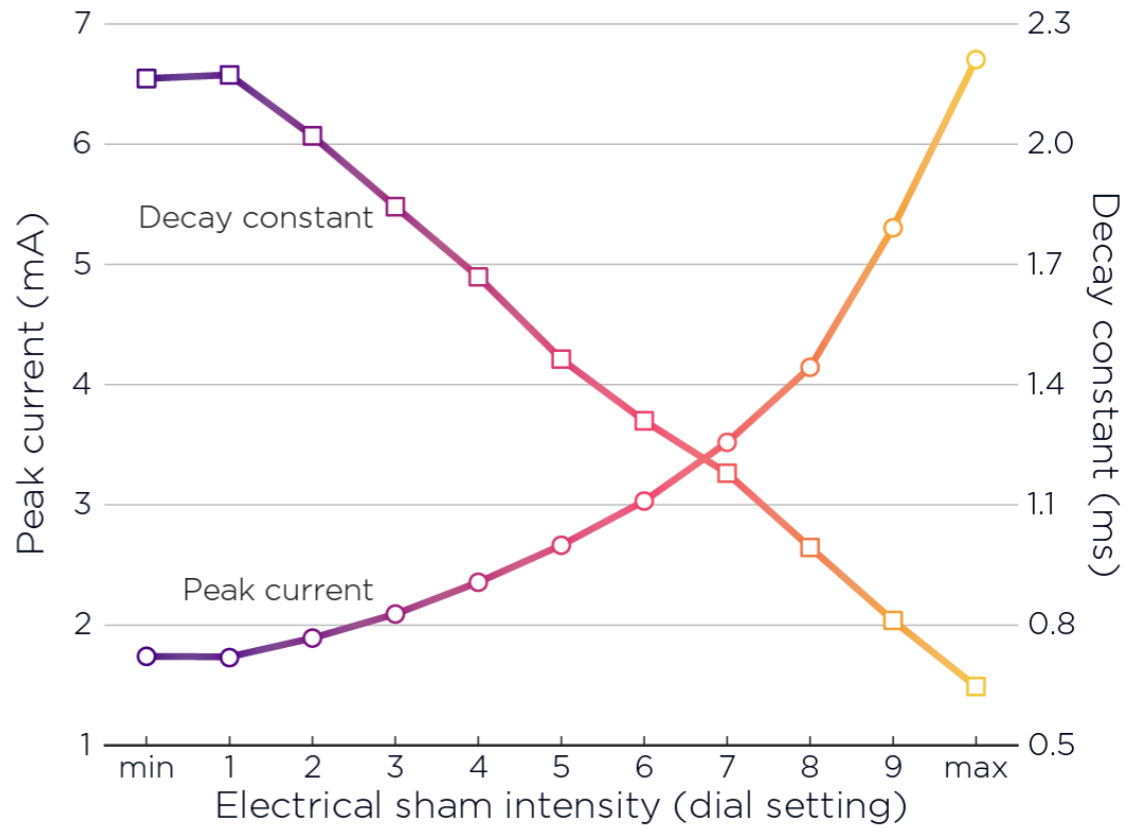
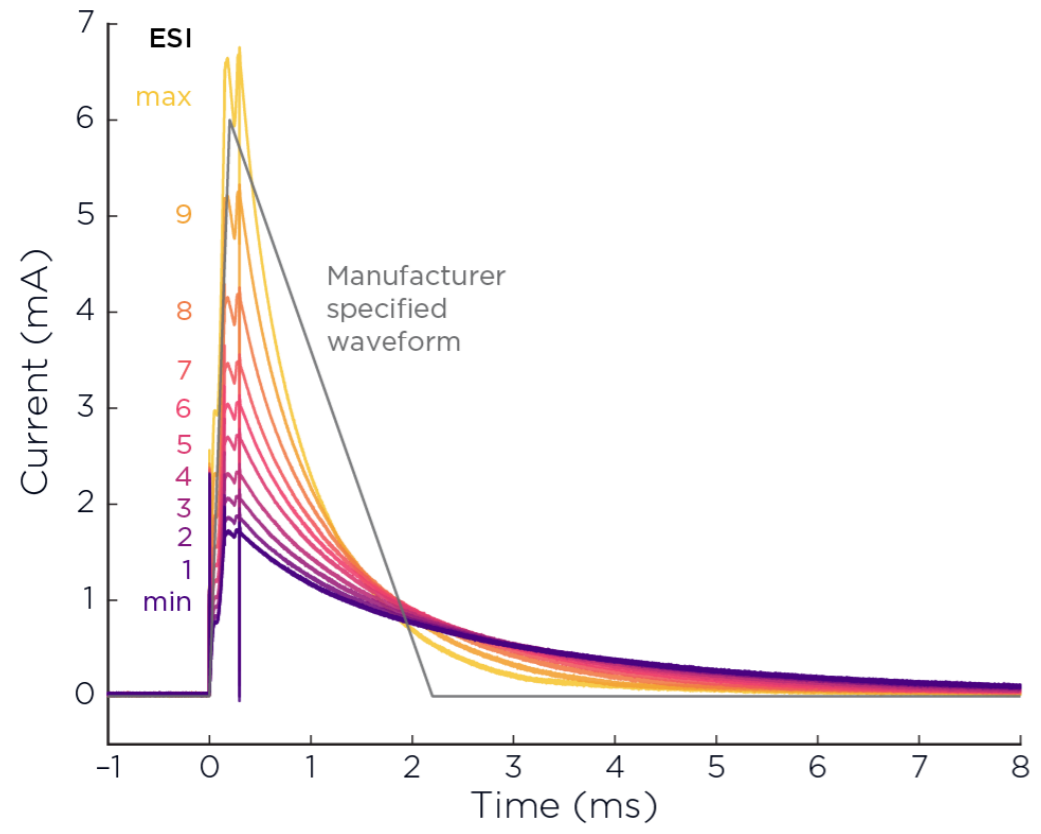


J) Quadrupole coil

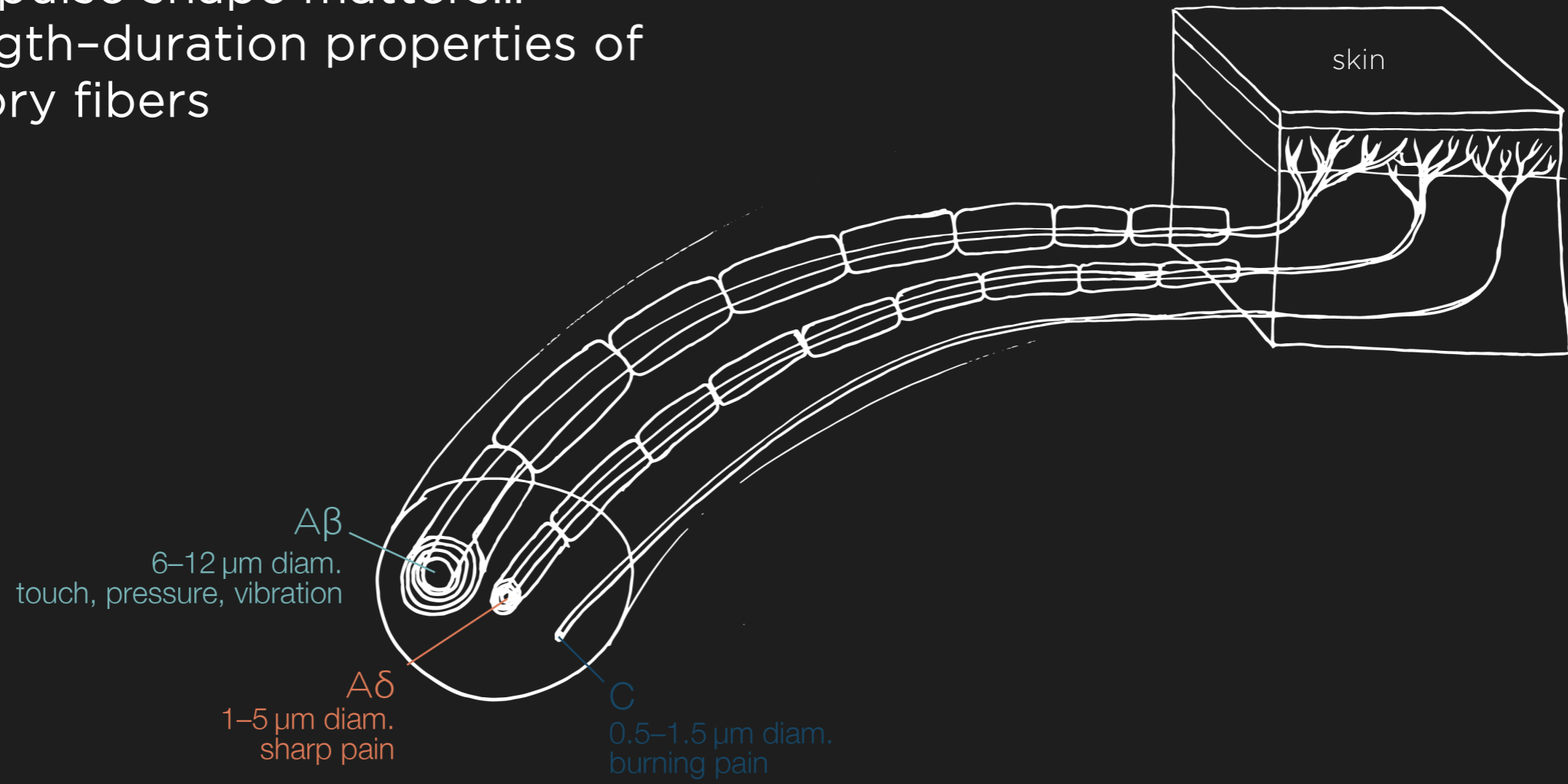


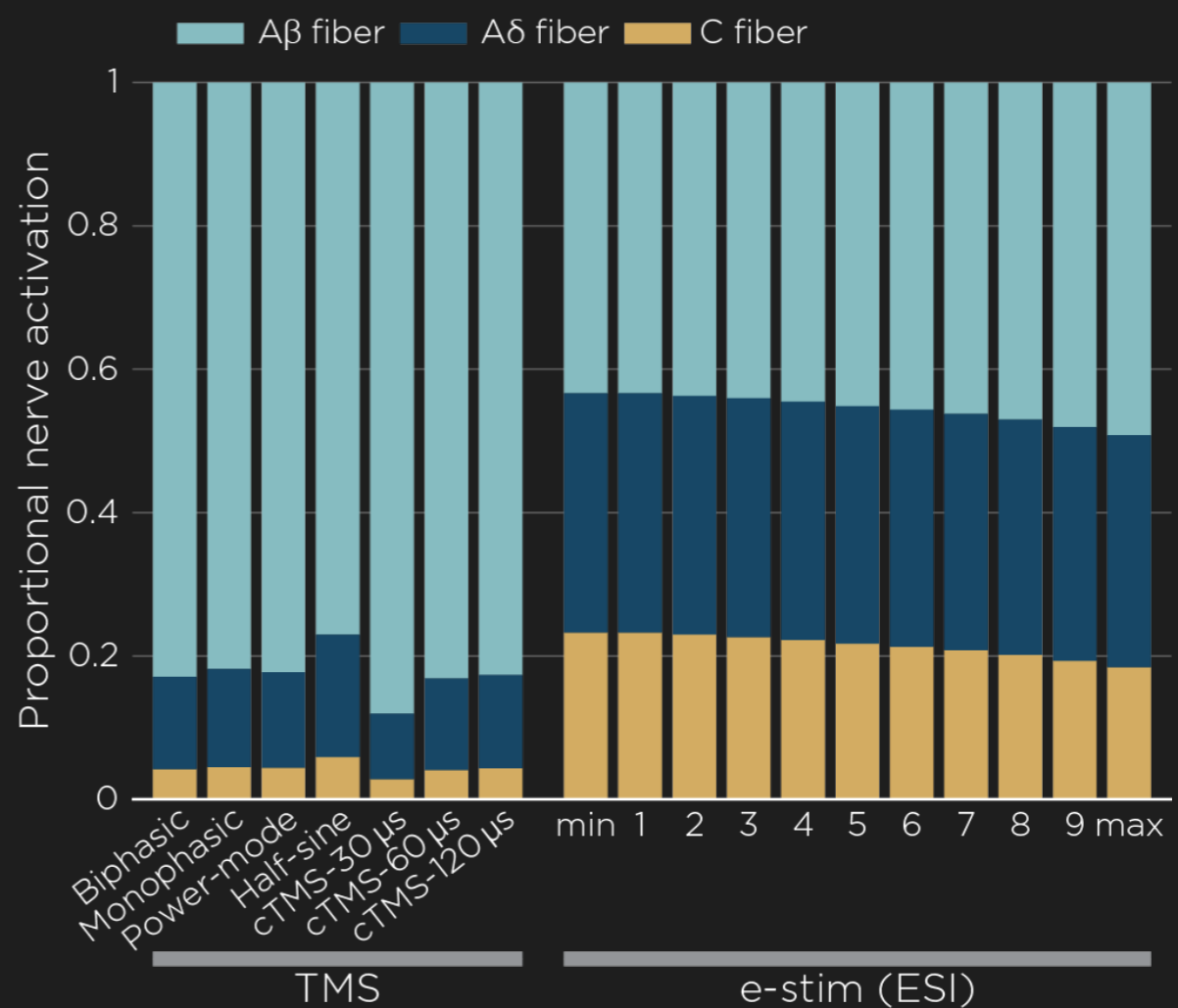
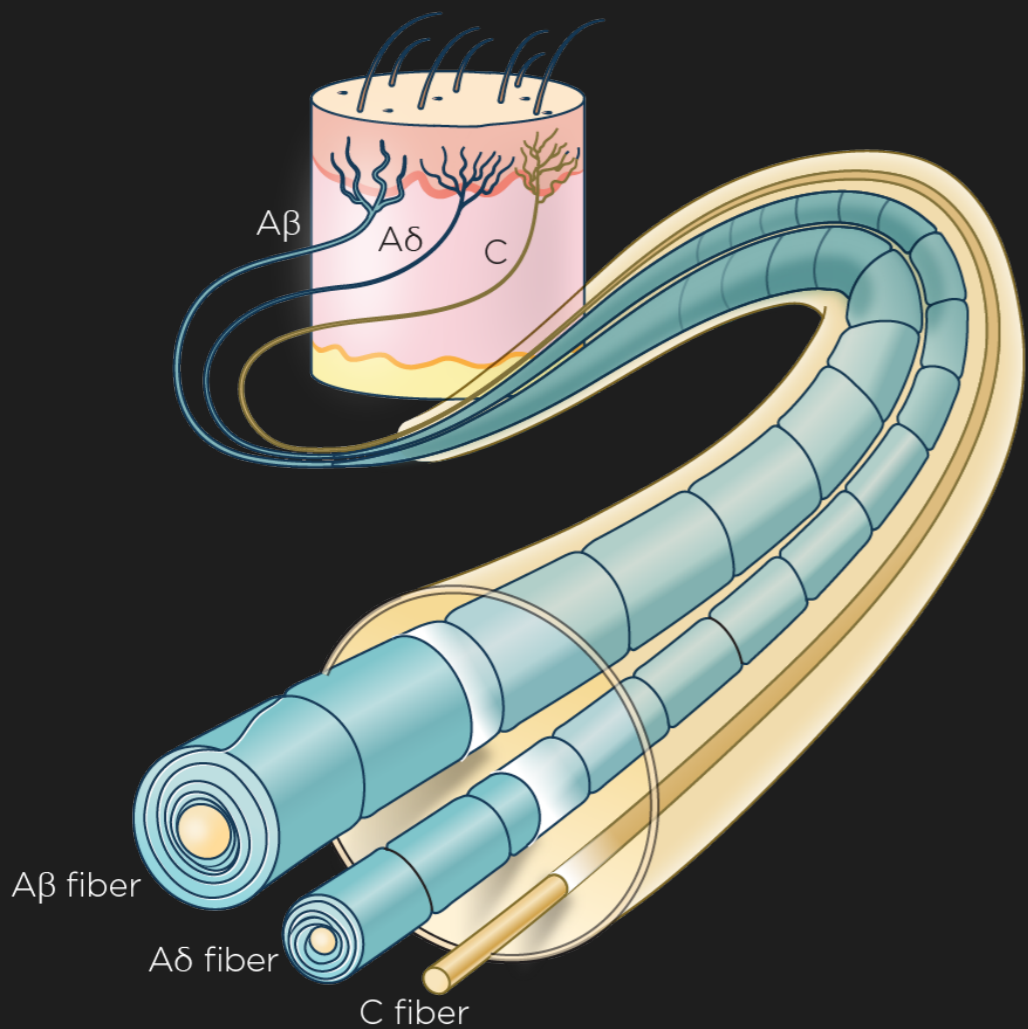
Concurrent cutaneous electrical stimulation



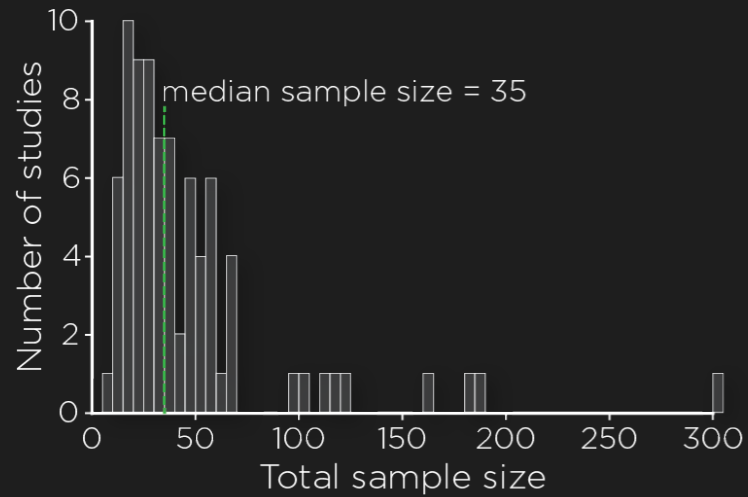


Why pulse shape matters... strength-duration properties of sensory fibers

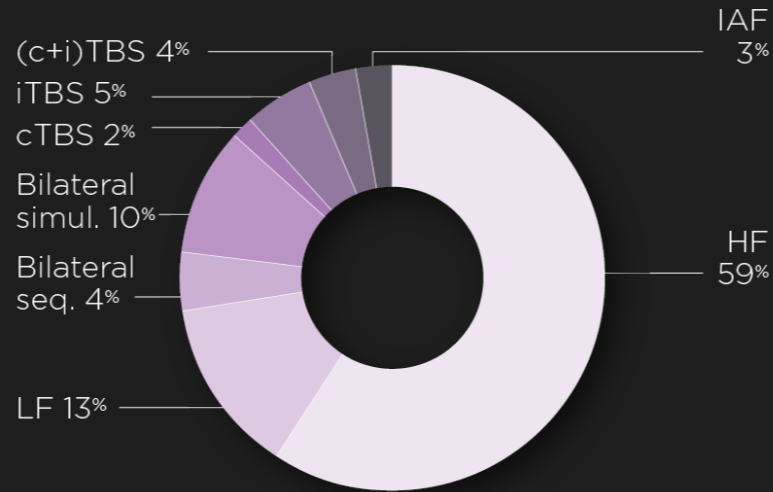




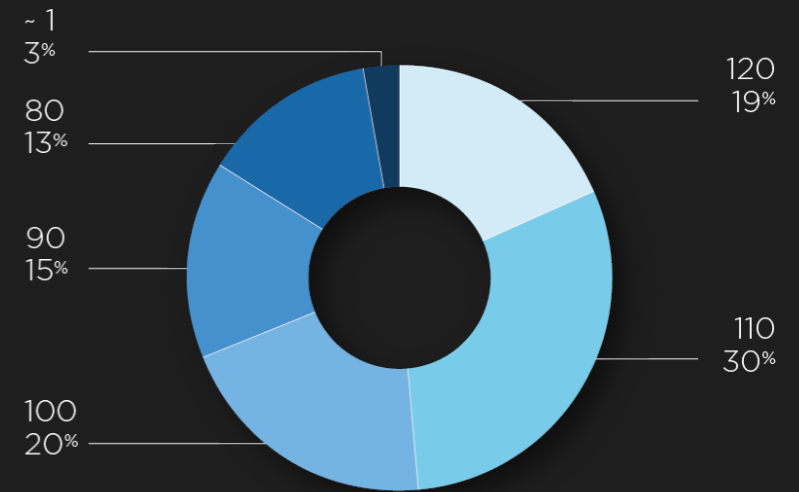
A. Sample size



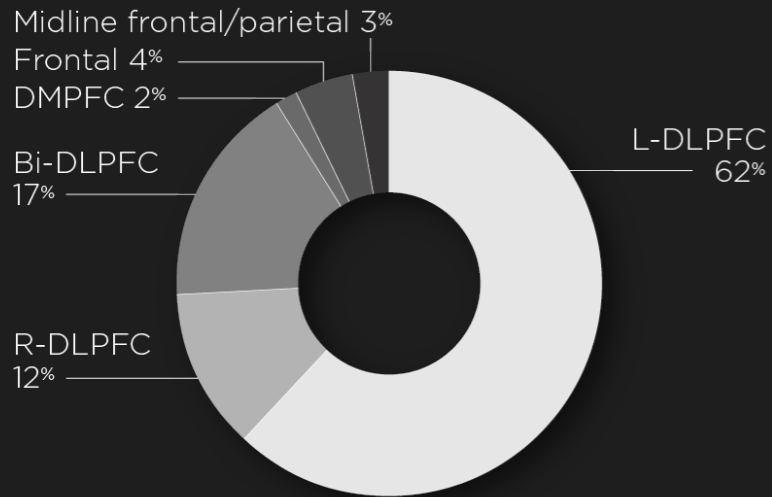
B. Stimulation protocol



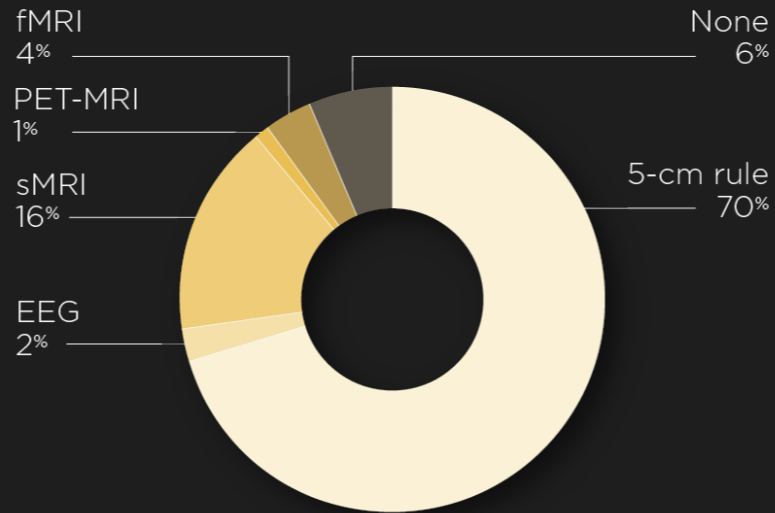
C. Intensity (% threshold)



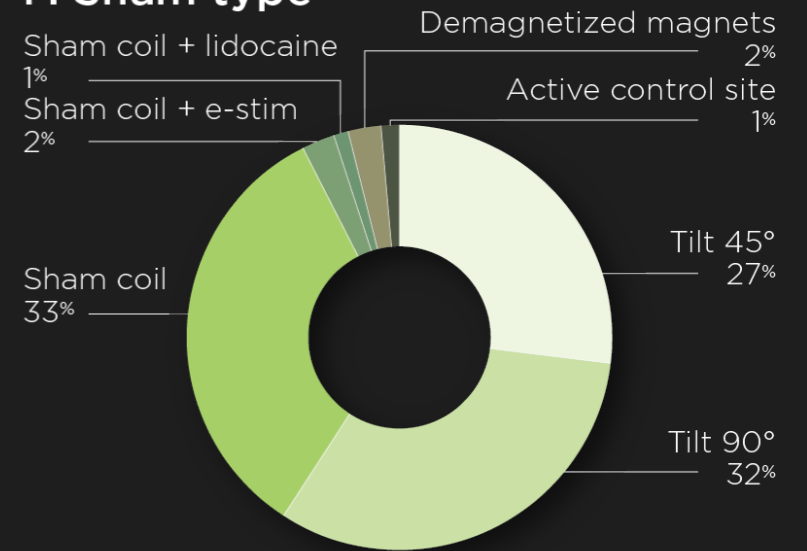
D. Stimulation site



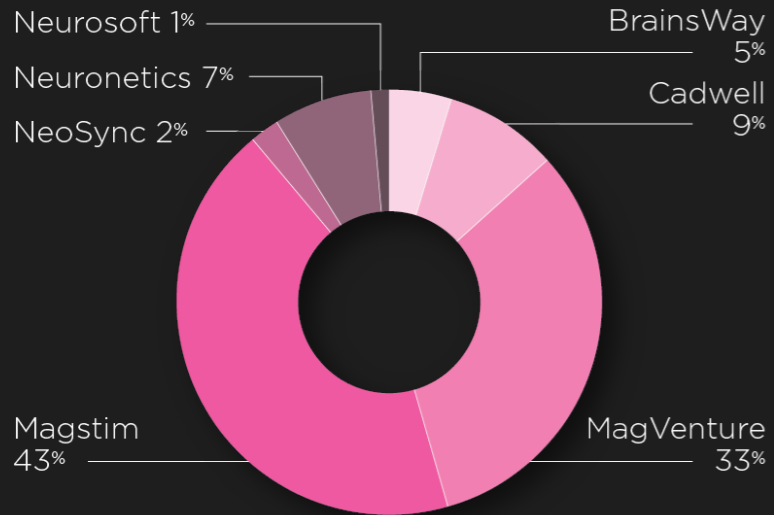
E. Targeting approach



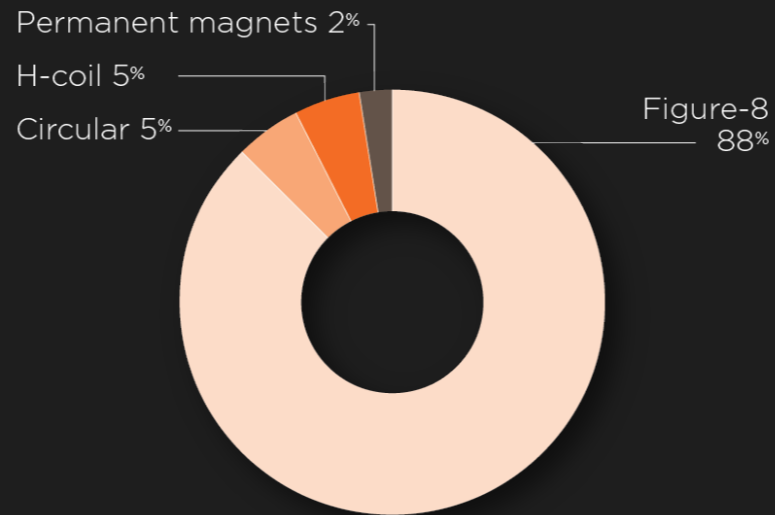
F. Sham type



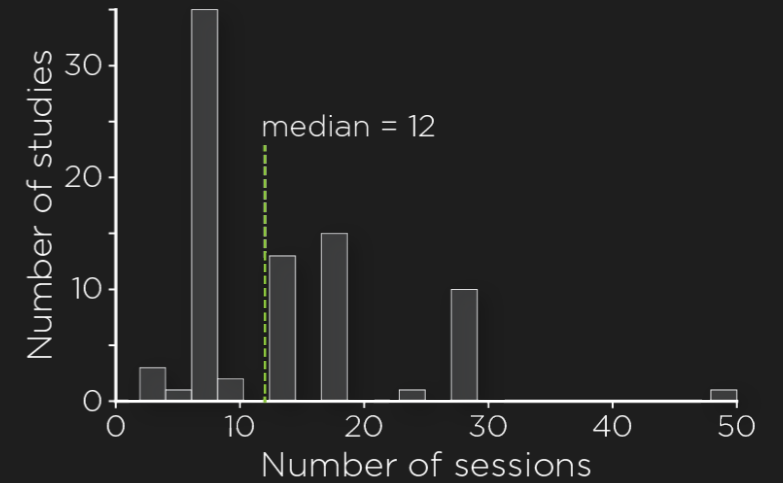
G. Stimulator/Manufacturer

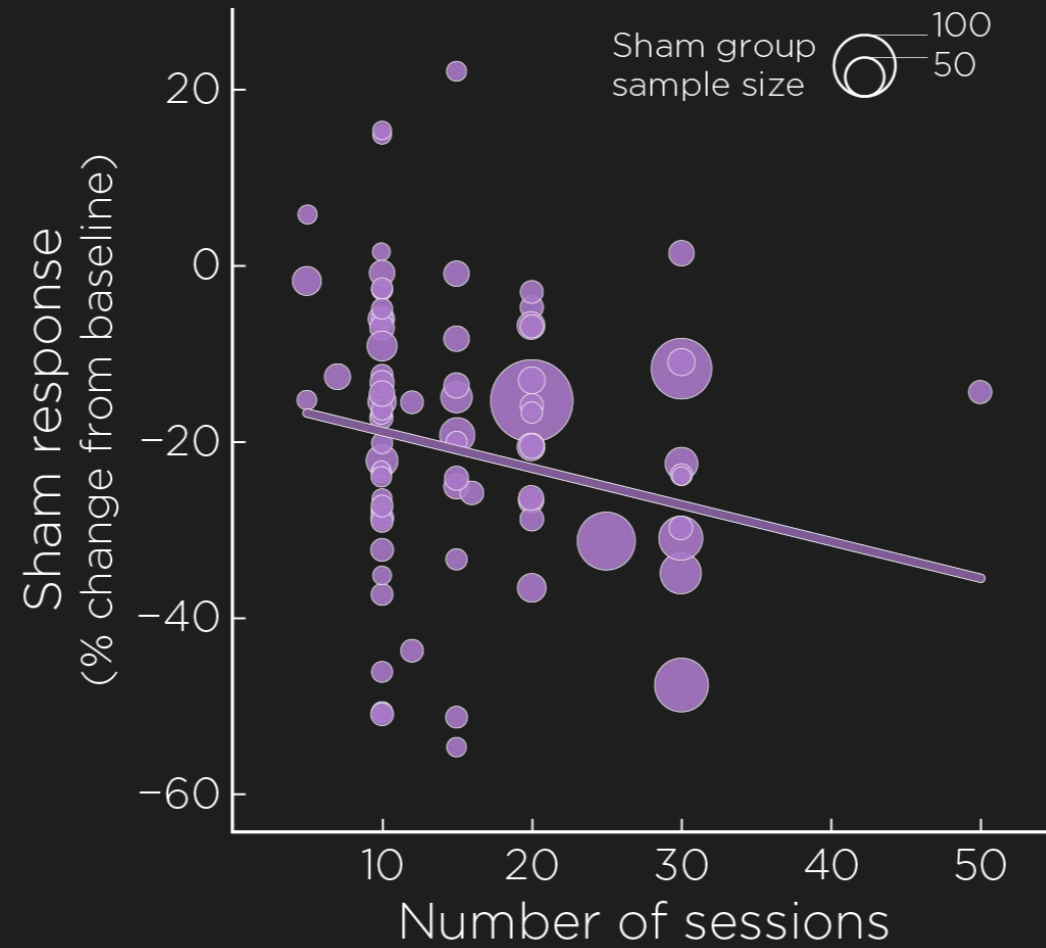


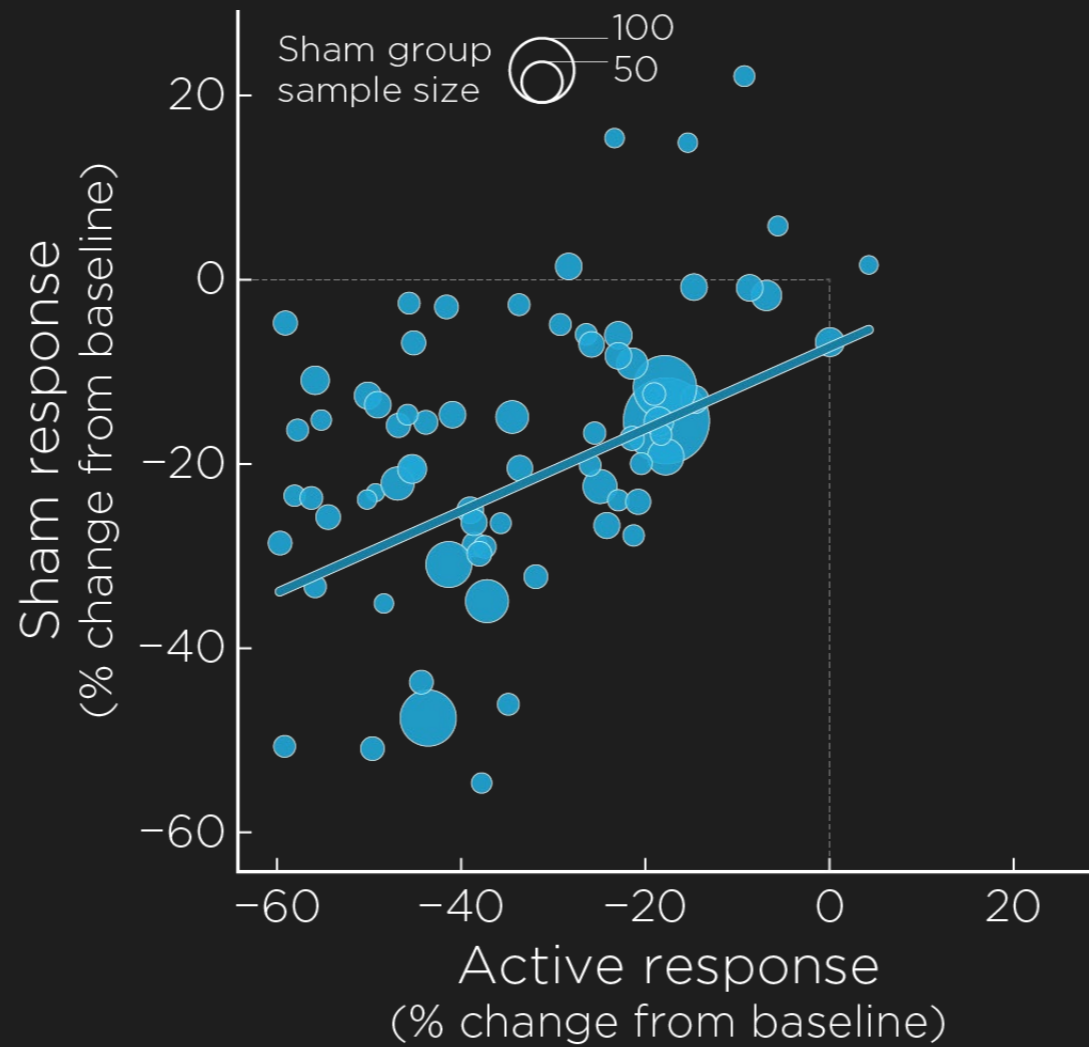
H. Coil type

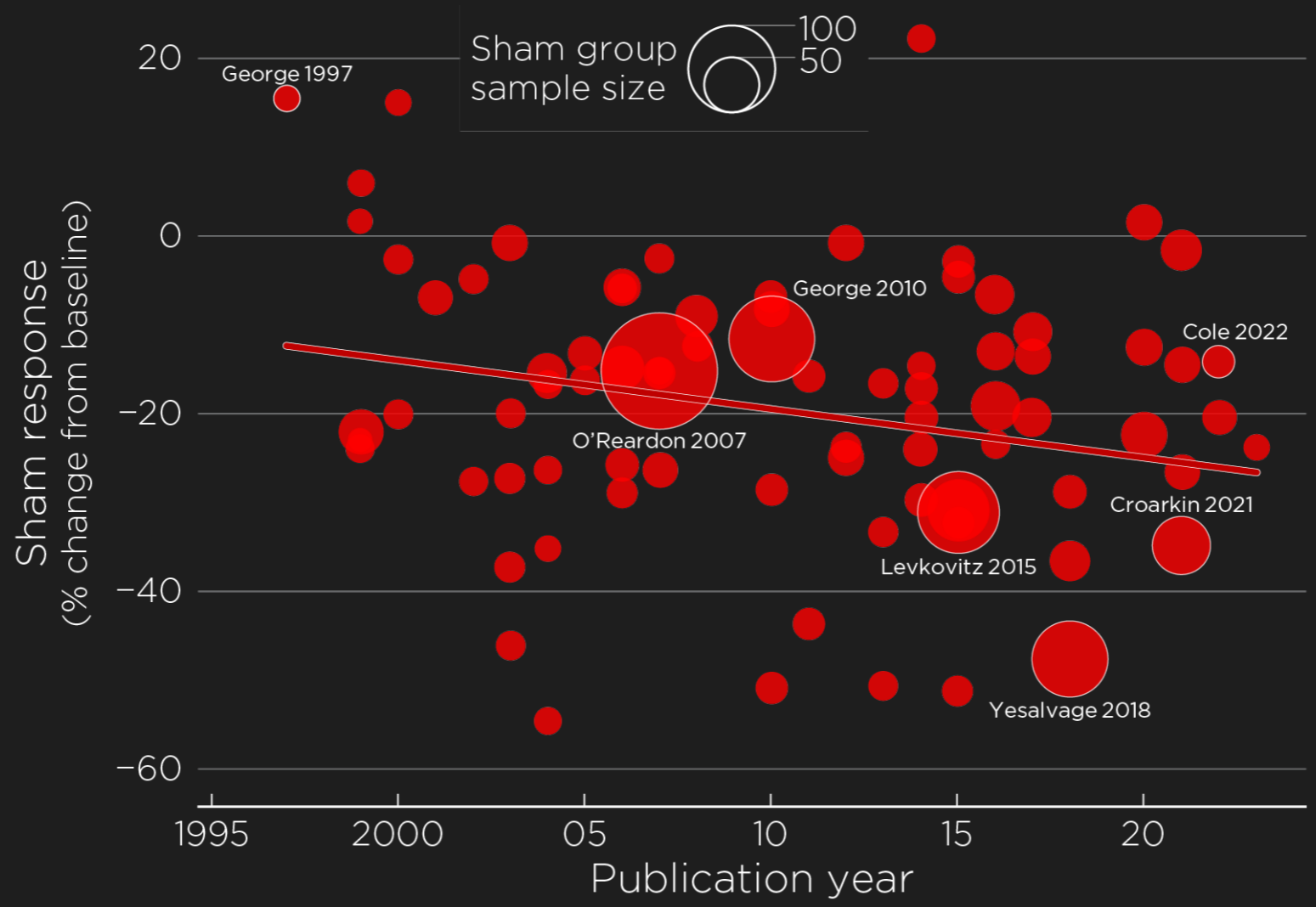


I. Number of sessions

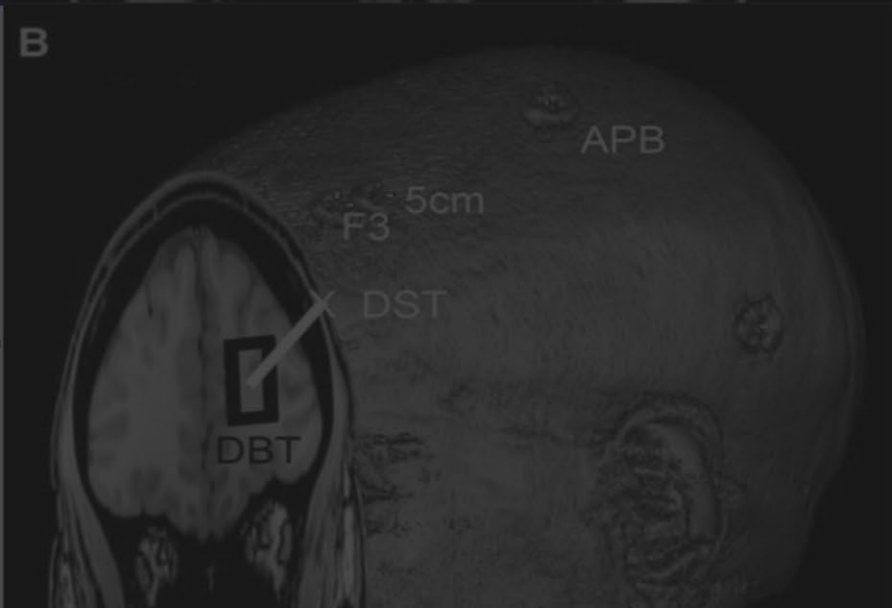
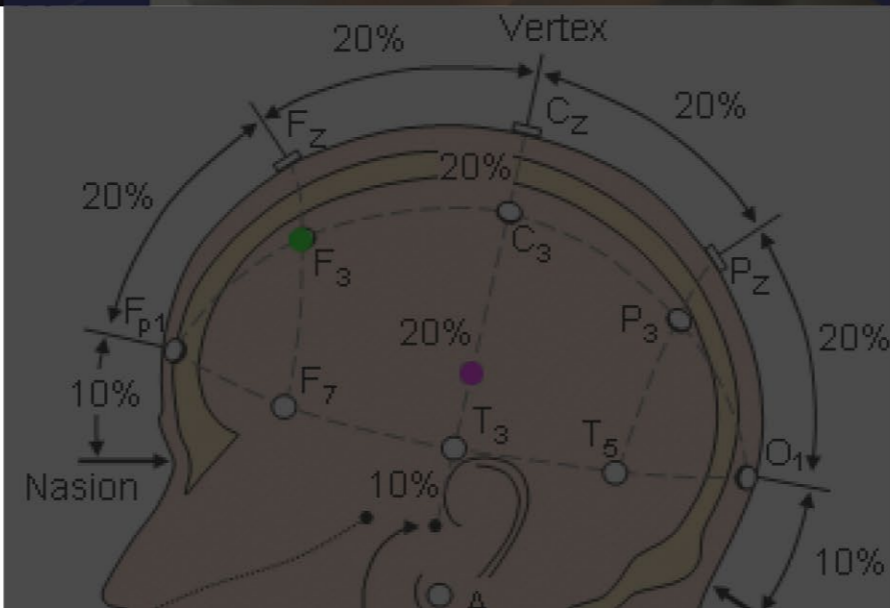
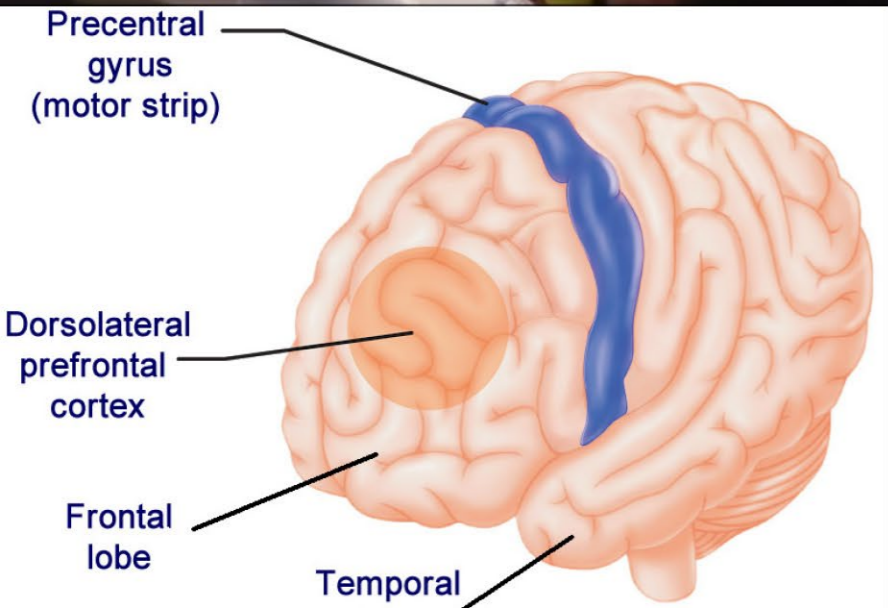
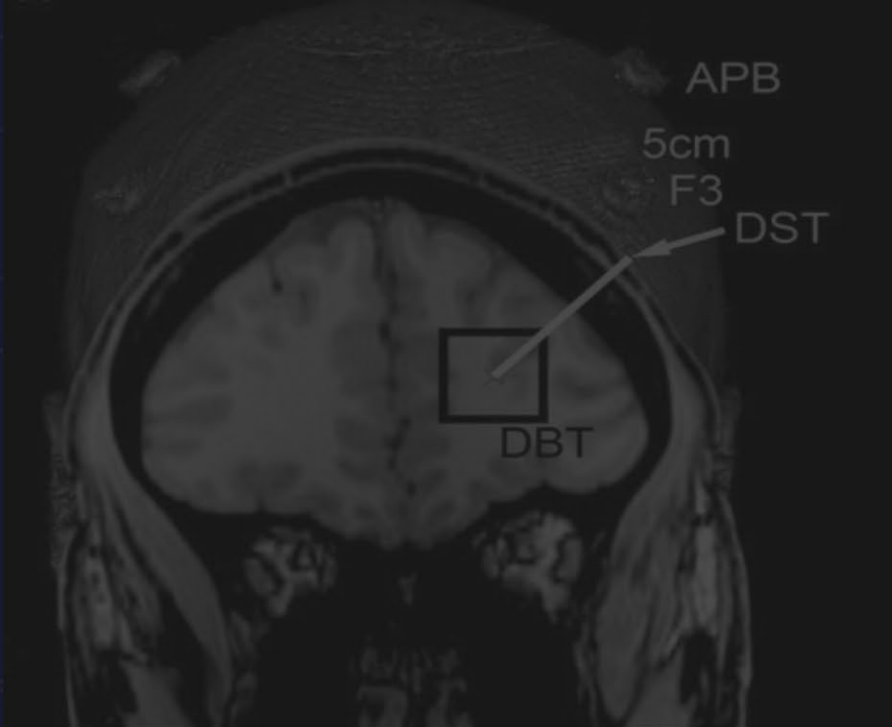
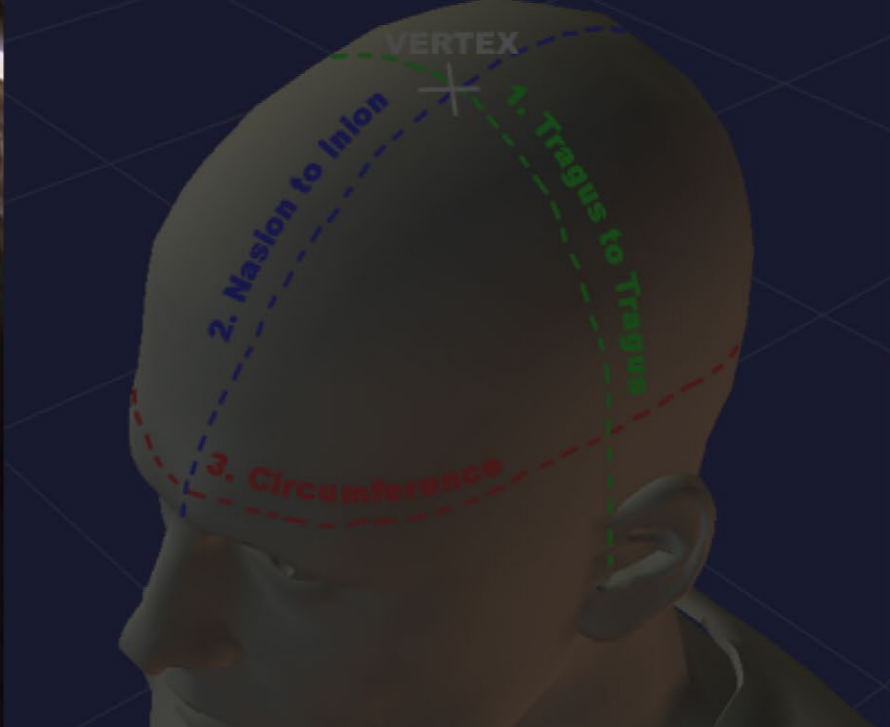


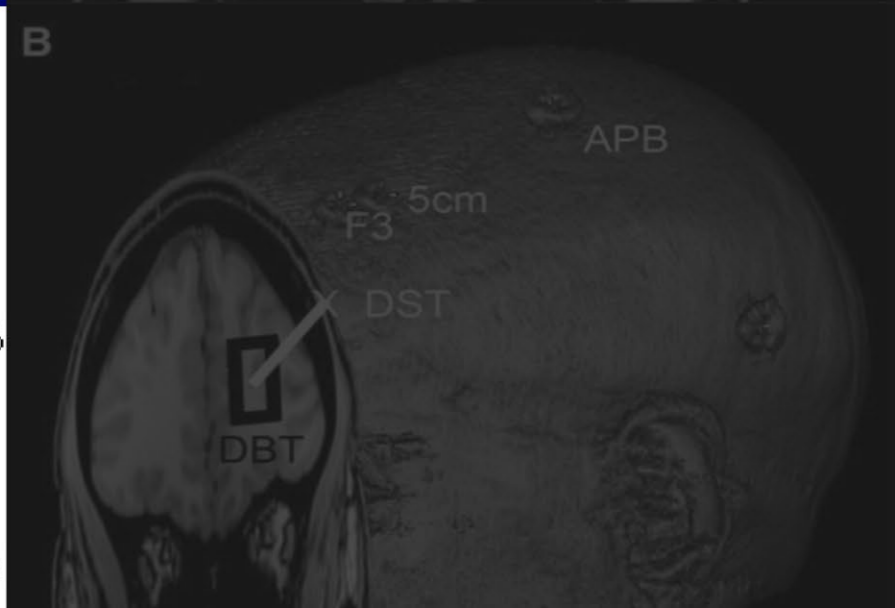
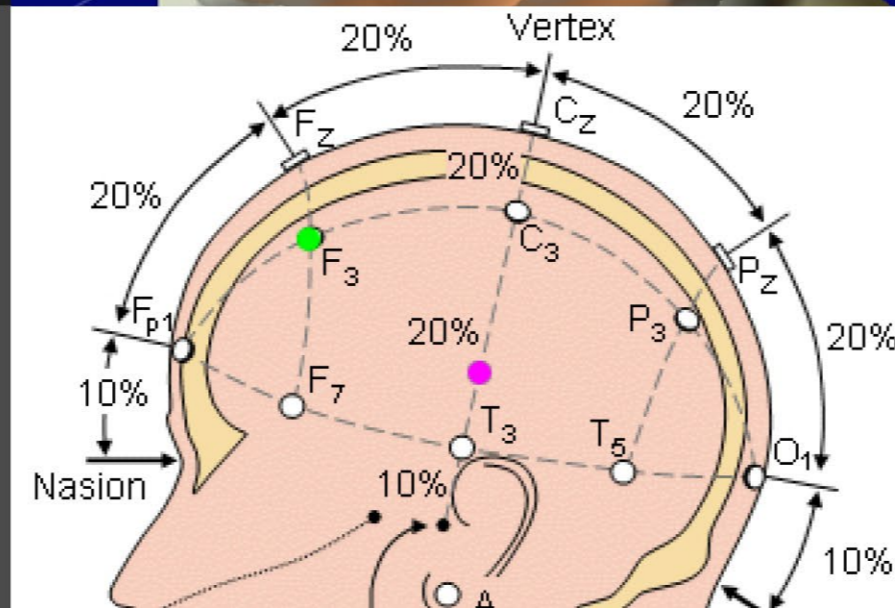
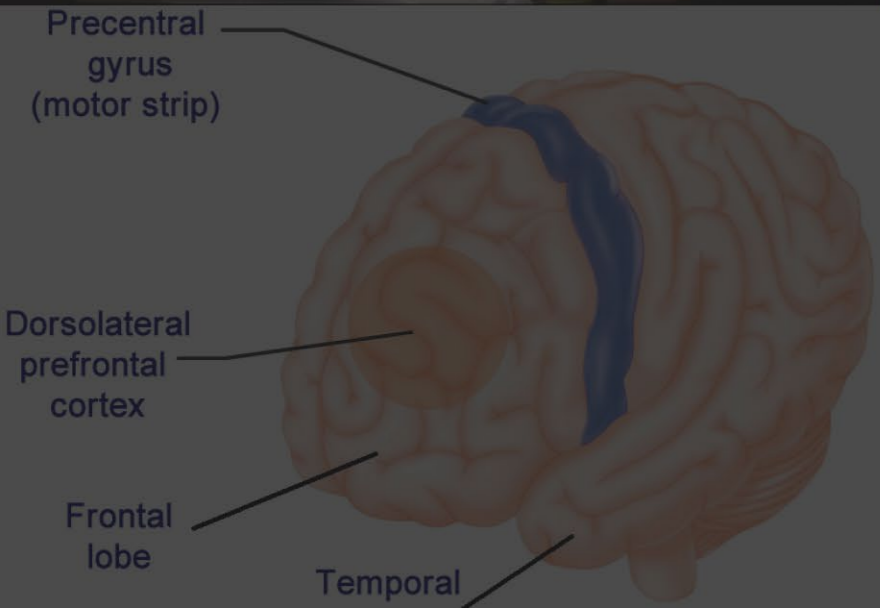
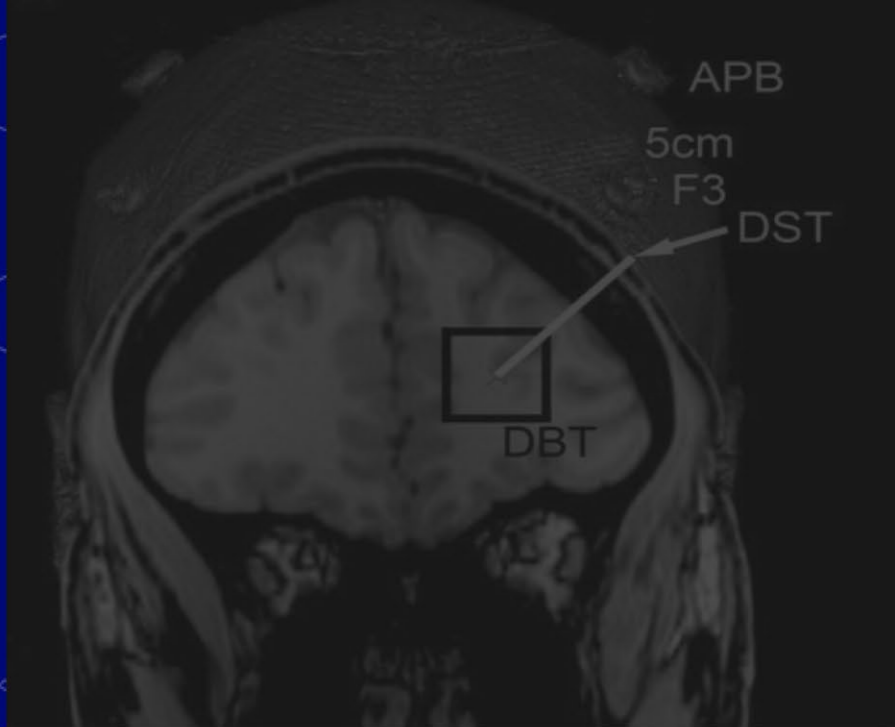
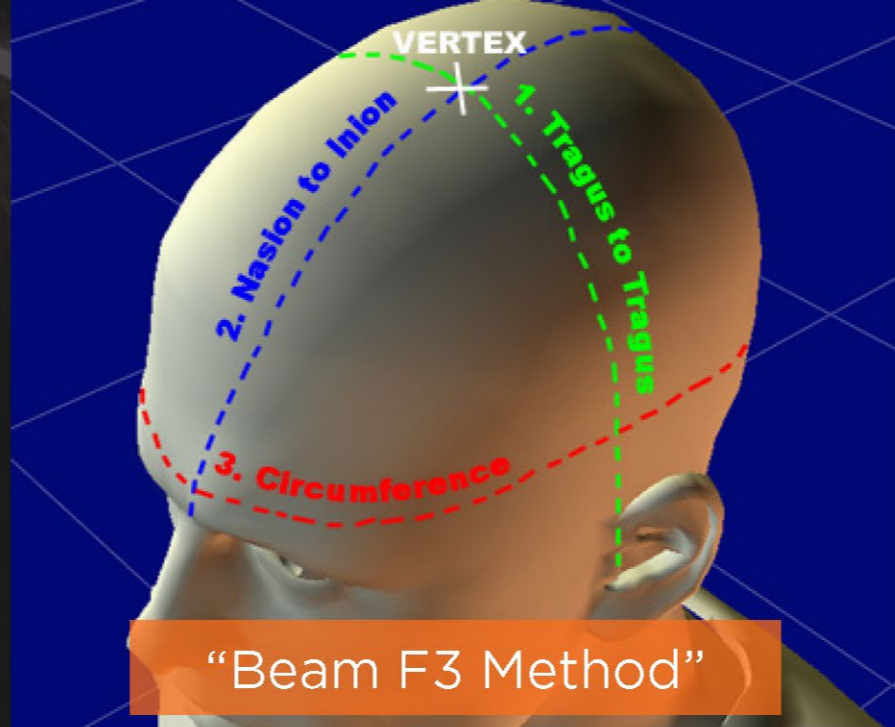


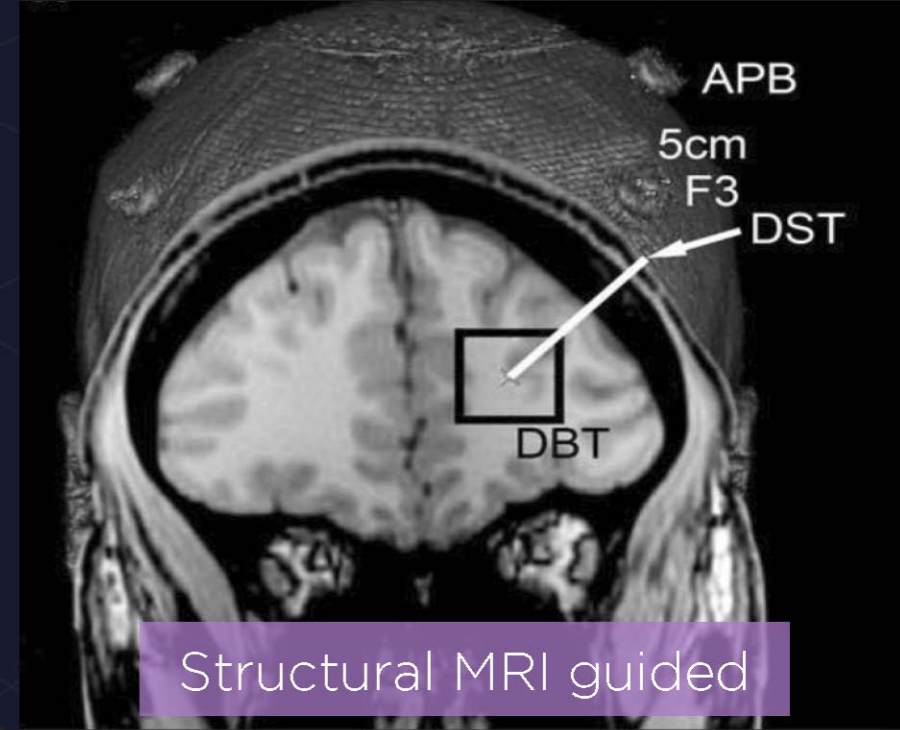
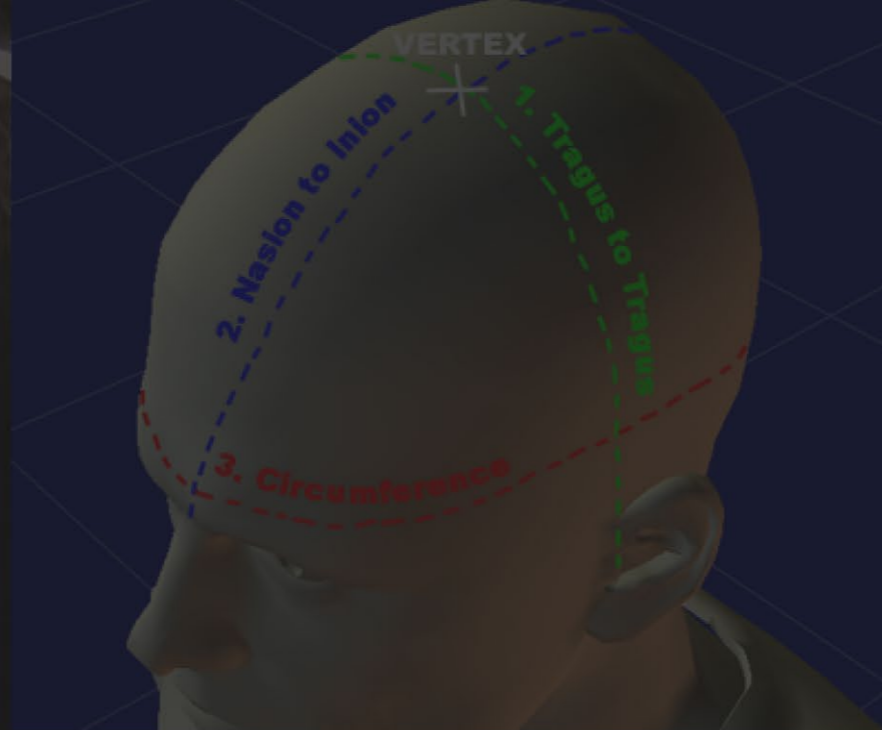




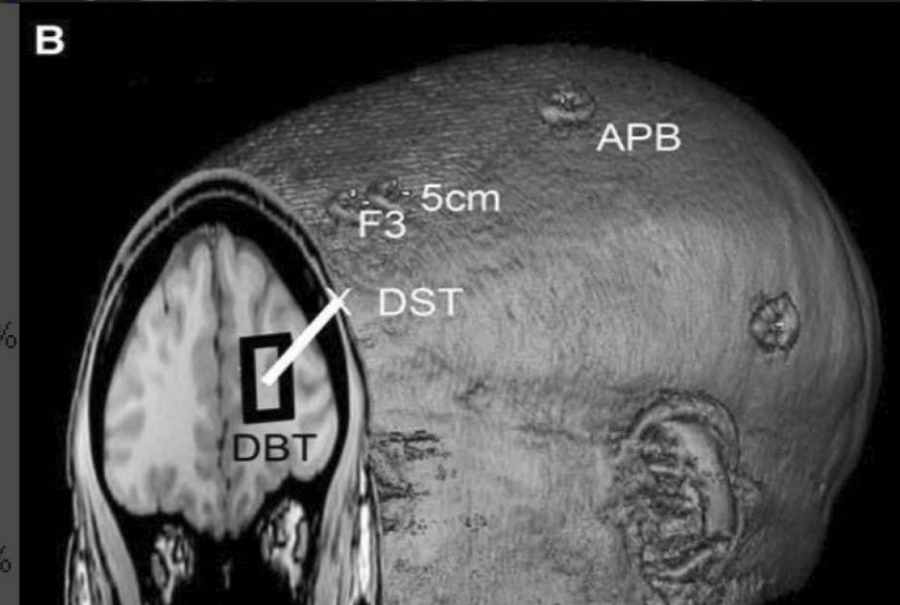
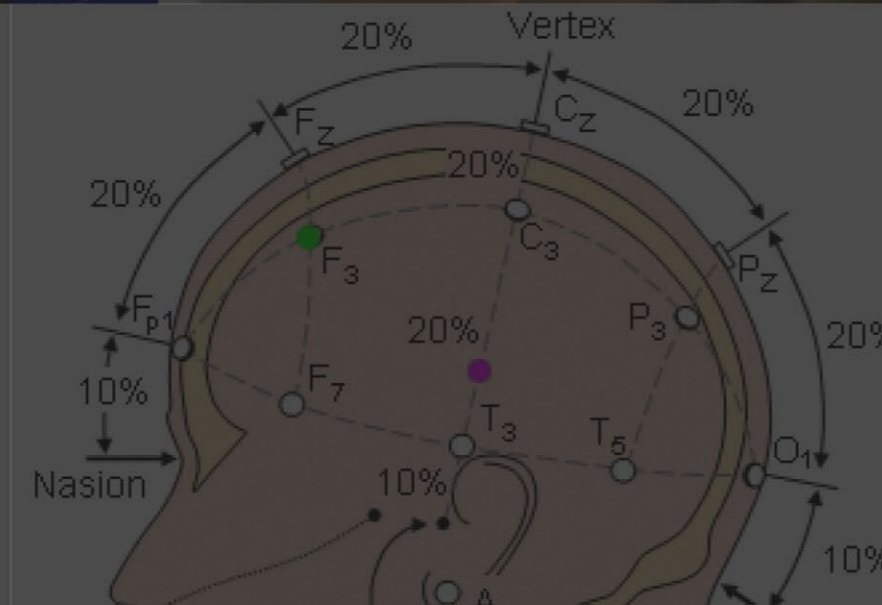
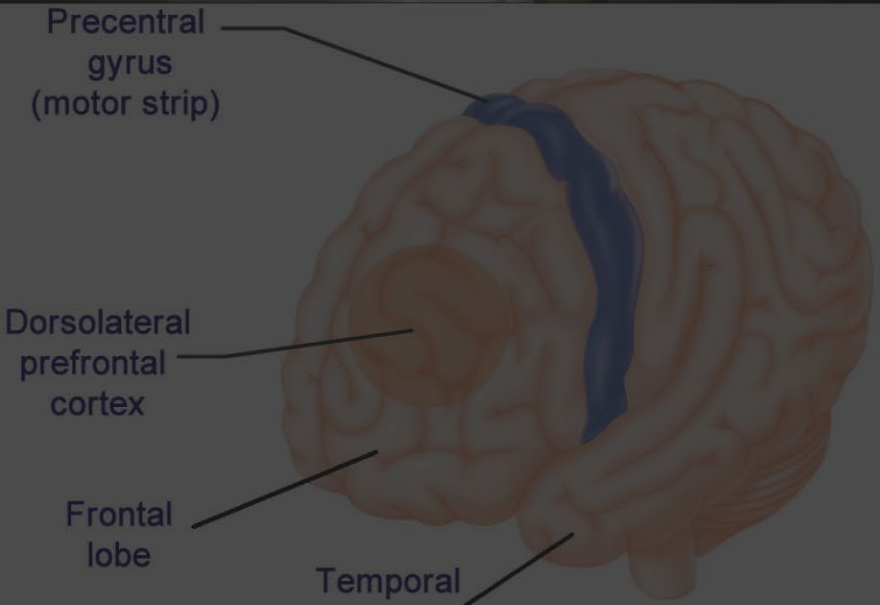
“Future studies should focus on ~~strategies to reduce the placebo response~~ and **examine the optimal dosing of TMS** for adolescents with TRD.

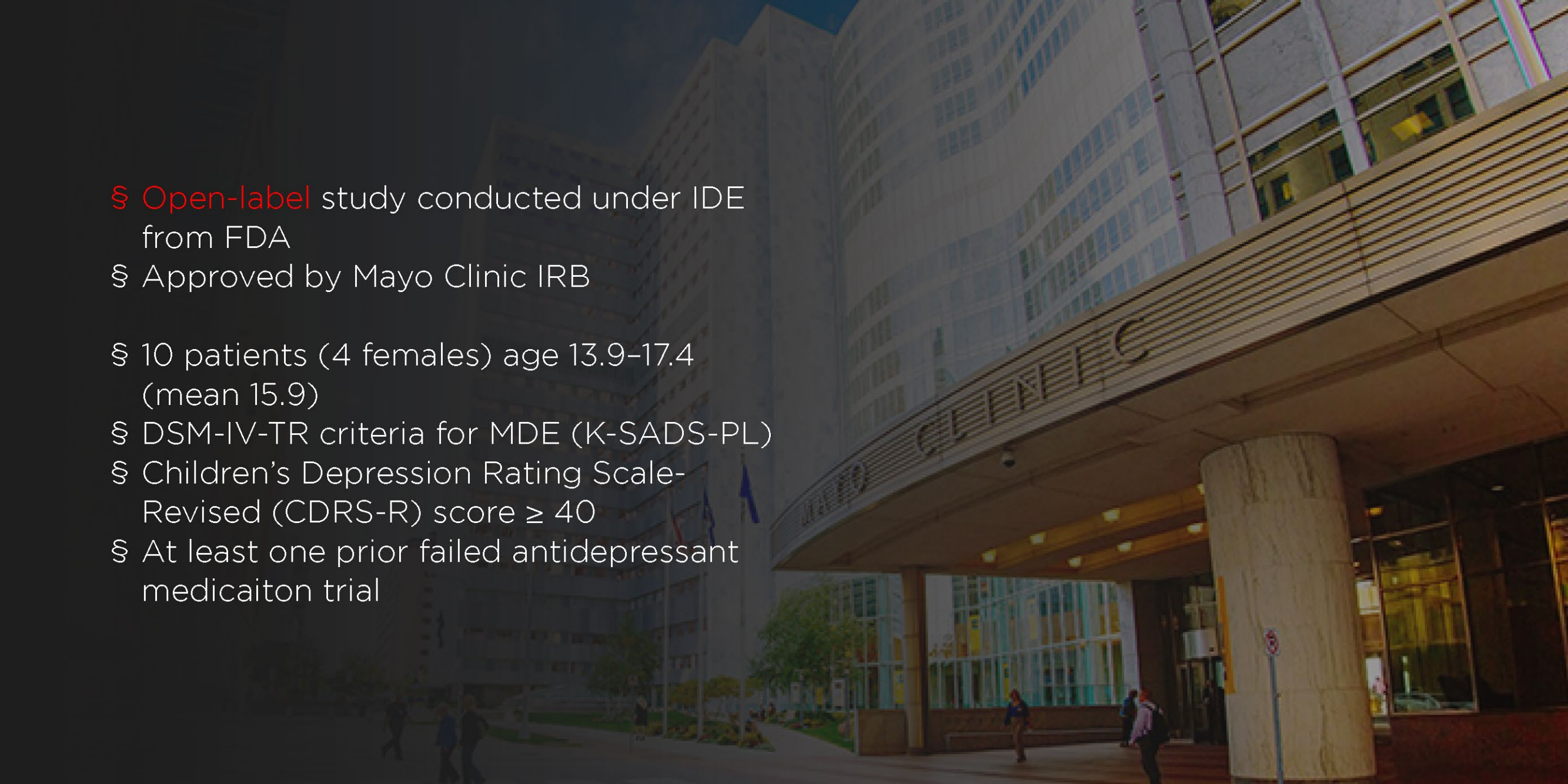






Structural MRI guided



The background image shows the exterior of a large, modern building, identified as the Mayo Clinic by the signage above the entrance. The building has a curved facade with many windows, some of which are illuminated from within. The sky is a deep blue, suggesting dusk or dawn. In the foreground, there are some people walking and a few trees. The overall scene is a professional and institutional setting.

§ **Open-label** study conducted under IDE from FDA

§ Approved by Mayo Clinic IRB

§ 10 patients (4 females) age 13.9–17.4 (mean 15.9)

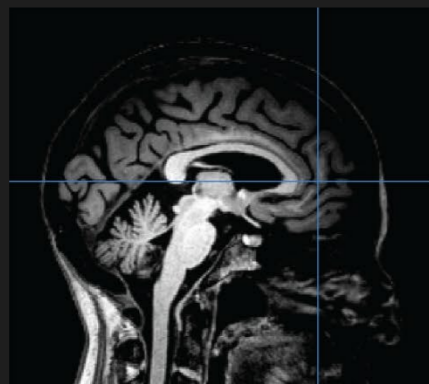
§ DSM-IV-TR criteria for MDE (K-SADS-PL)

§ Children's Depression Rating Scale-Revised (CDRS-R) score ≥ 40

§ At least one prior failed antidepressant medication trial



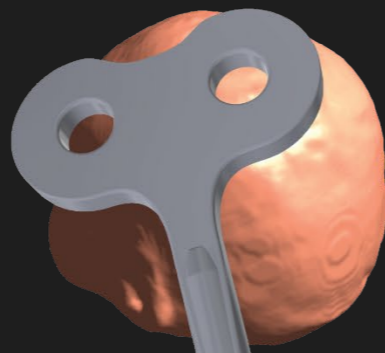
- § Individual left DLPFC target localized using structural MRI (DLPFC Scalp Target: DST)
- § 10-Hz rTMS delivered using NeuroStar Therapy System, at intensity of 120% Standard Motor Threshold
- § 5 days per week, over 6–8 weeks, up to 30 sessions
- § Computational electric field modeling...



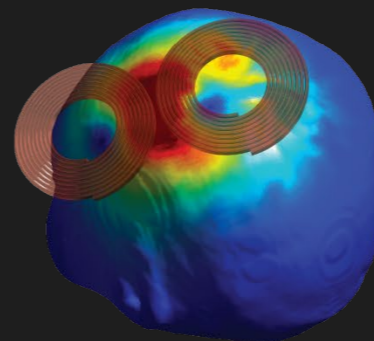
individual MRI



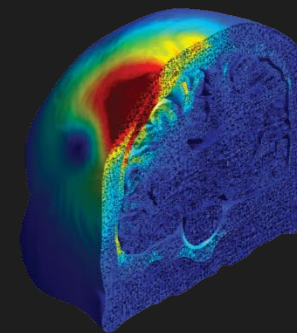
tissue segmentation



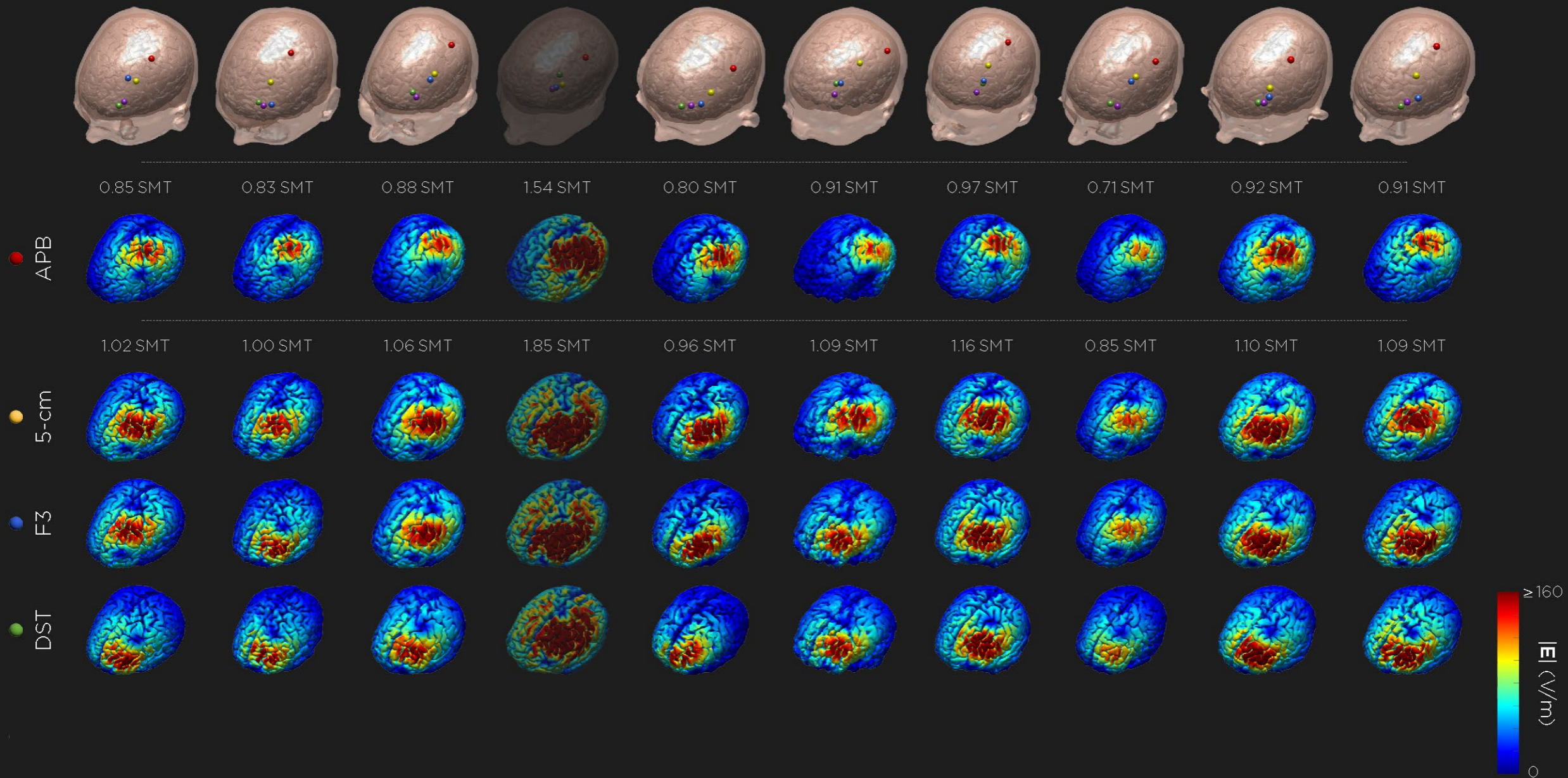
3D head model &
coil model

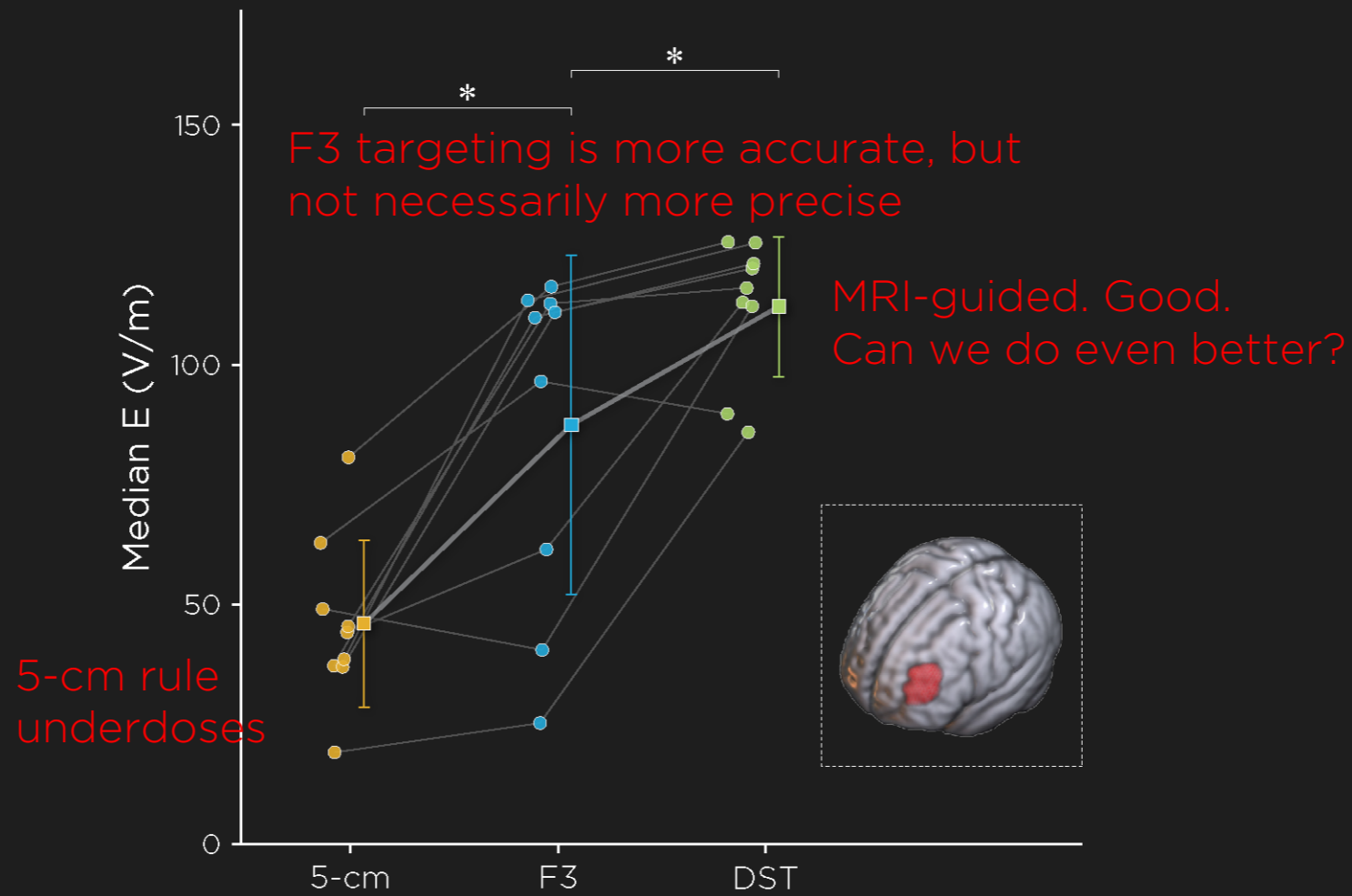


finite element solver



electric field analysis







OPEN ACCESS

EDITED BY
 Mikhail A. Lebedev,
 Lomonosov Moscow State University, Russia

REVIEWED BY
 Jack Jiaqi Zhang,
 Hong Kong Polytechnic University,
 Hong Kong SAR, China
 Shaw-Ji Chen,
 Taitung MacKay Memorial Hospital, Taiwan

*CORRESPONDENCE
 Davin K. Quinn
 ✉ dquinn@salud.unm.edu

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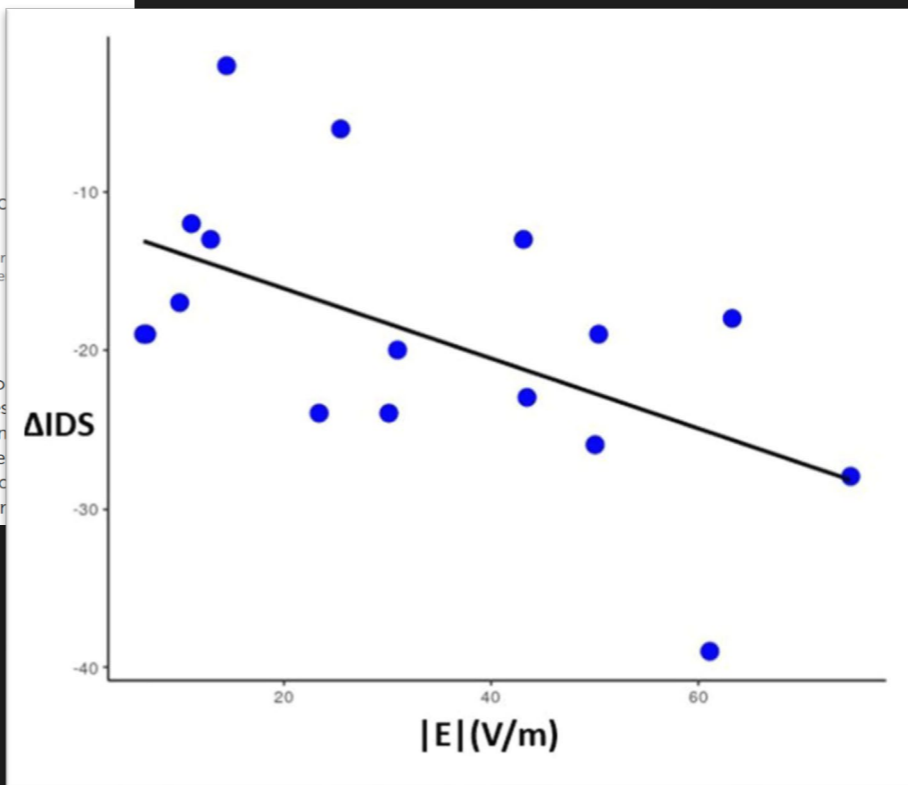
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 Olmstead, Yang, Price, Bowers-Wu, Durham,
 Hazlewood, Farrar, Miller, Lloyd, Garcia, Ojeda,

Electric field distribution predicts efficacy of accelerated intermittent theta burst stimulation for late-life depression

Davin K. Quinn^{*k}, Joel Upston¹, Thomas R. Jones¹, Benjamin C. Gibson², Tessa A. Olmstead¹, Justine Yang¹, Allison M. Price³, Dorothy H. Bowers-Wu¹, Erick Durham⁴, Shawn Hazlewood¹, Danielle C. Farrar¹, Jeremy Miller¹, Megan O. Lloyd¹, Crystal A. Garcia¹, Cesar J. Ojeda¹, Brant W. Hager¹, Andrei A. Vakhtin⁵ and Christopher C. Abbott¹

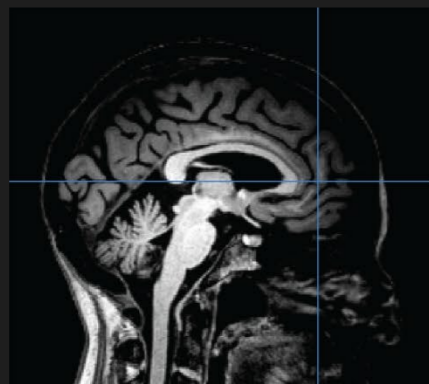
¹Department of Psychiatry and Behavioral Sciences, UNM, Albuquerque, NM, United States, ²Department of Psychology, University of New Mexico, Albuquerque, NM, United States, ³Department of Surgery, UNM, Albuquerque, NM, United States, ⁴Department of Psychiatry, Texas Tech University, El Paso, TX, United States, ⁵Mind Research Network, Albuquerque, NM, United States

Introduction: Repetitive transcranial magnetic stimulation (rTMS) is a promising intervention for late-life depression (LLD) but may have lower rates of response and remission owing to age-related brain changes. In particular, rTMS electric field strength may be attenuated by cortical atrophy in the prefrontal cortex. To identify clinical characteristics and treatment parameters associated with response, we undertook a pilot study of accelerated fMRI-guided intermittent theta burst stimulation (ITBS) for LLD. We hypothesized that electric field distribution (EFD) would predict response to ITBS. We measured EFD in 15 patients with LLD using a realistic head model. EFD was measured at the site of the prefrontal cortex (PFC) and at the site of the motor cortex (MC). We found that EFD at the PFC was significantly lower than EFD at the MC. EFD at the PFC was significantly lower in patients who did not respond to ITBS compared to patients who did respond to ITBS. EFD at the PFC was significantly lower in patients who did not respond to ITBS compared to patients who did respond to ITBS. EFD at the PFC was significantly lower in patients who did not respond to ITBS compared to patients who did respond to ITBS.



-40

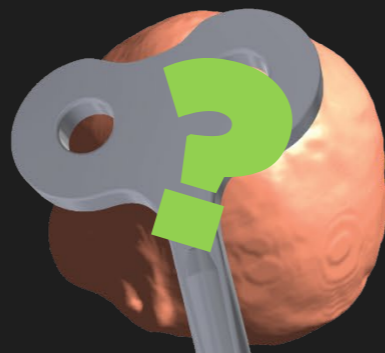
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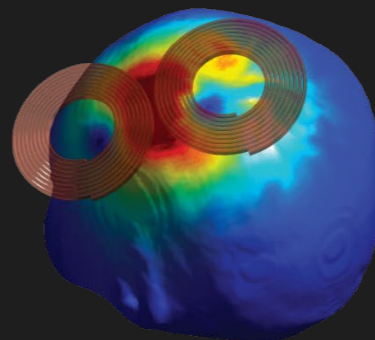
individual MRI



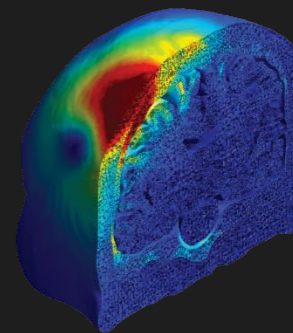
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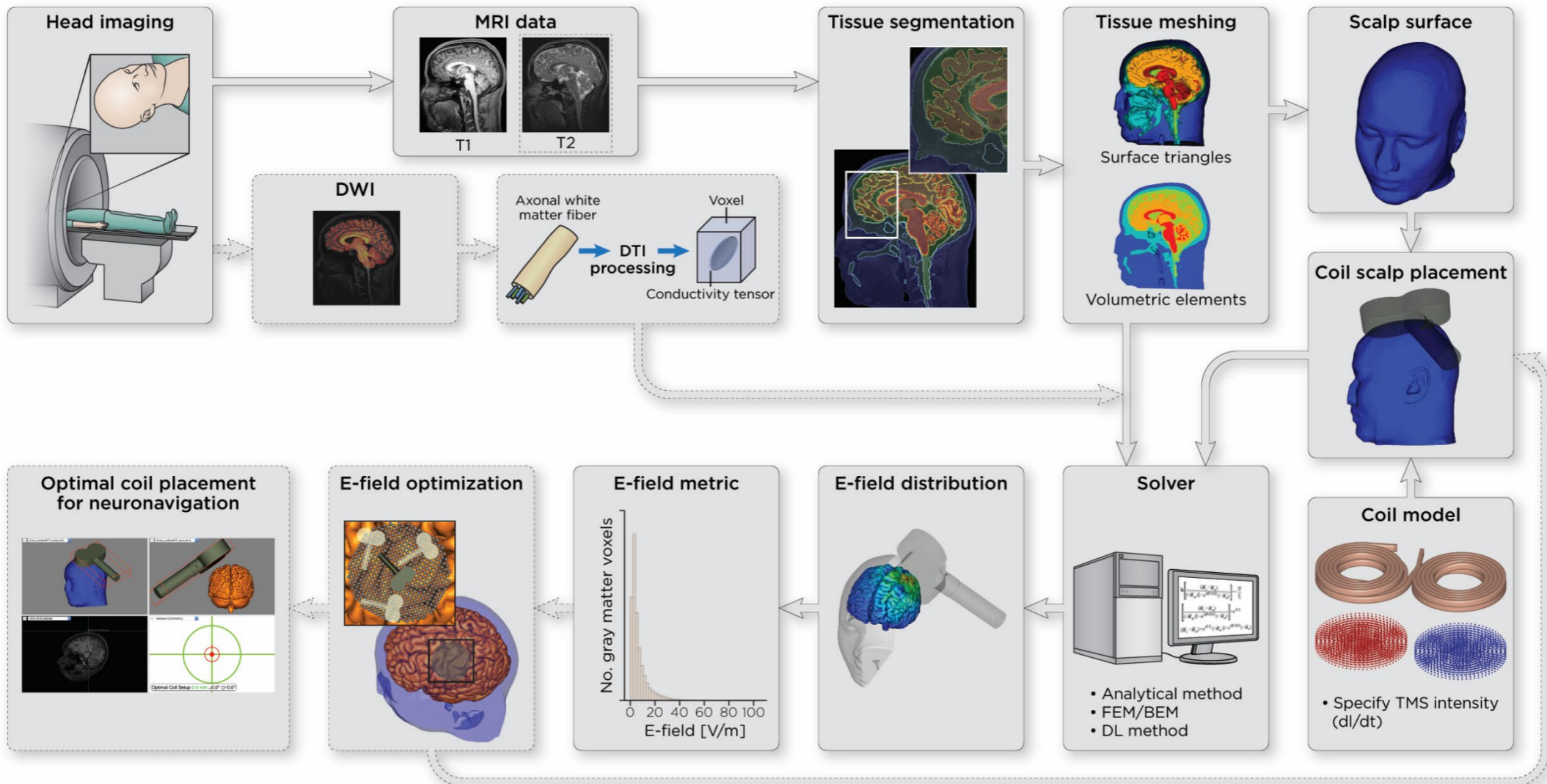
3D head model & coil model

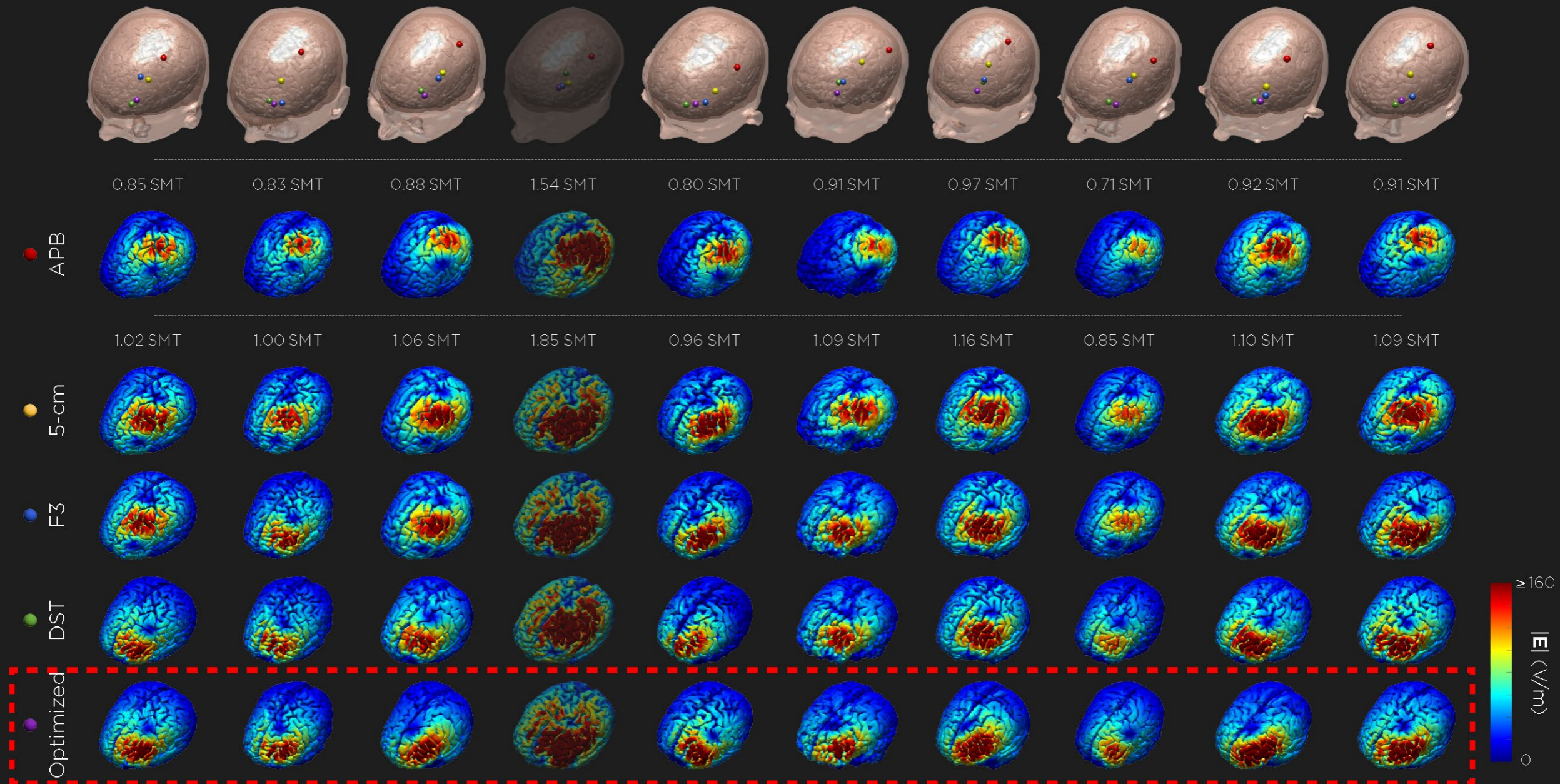


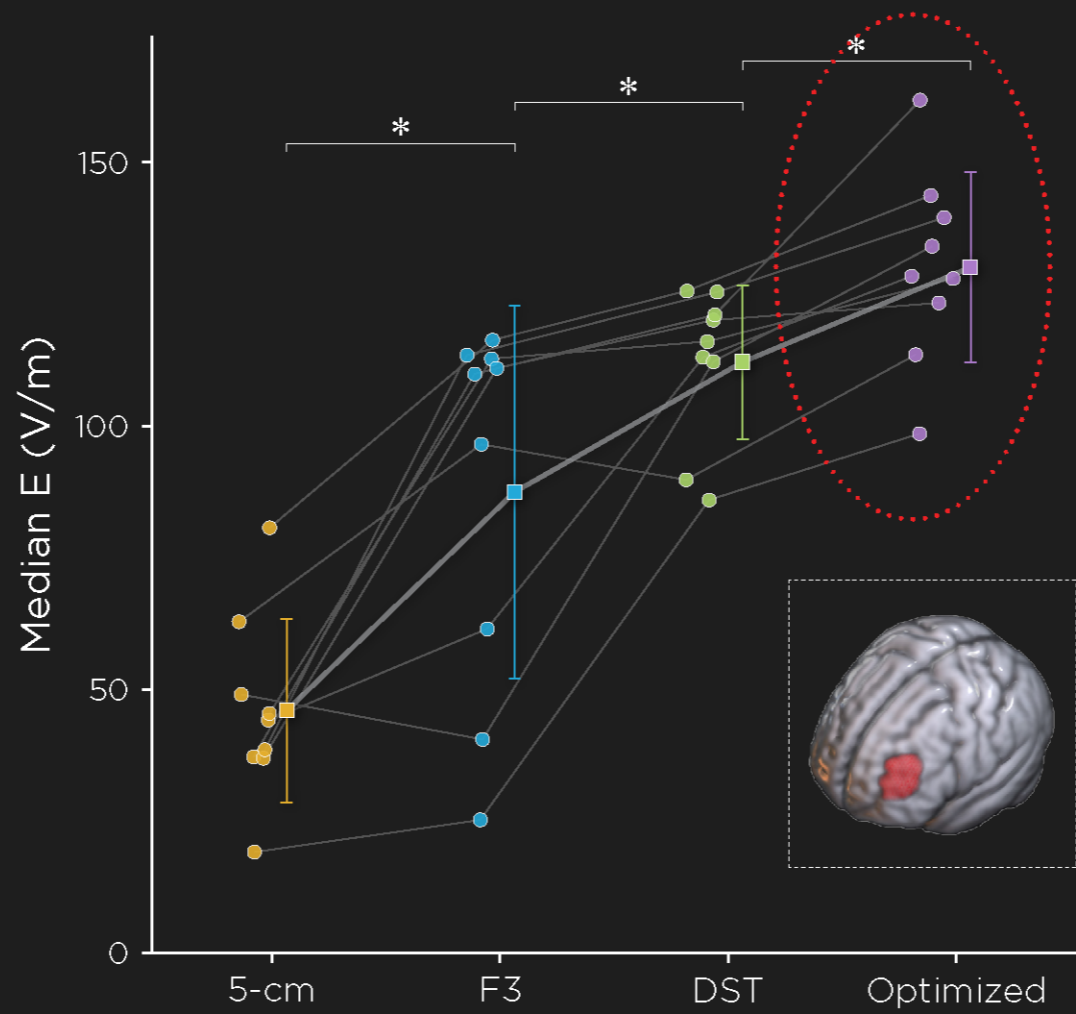
finite element solver

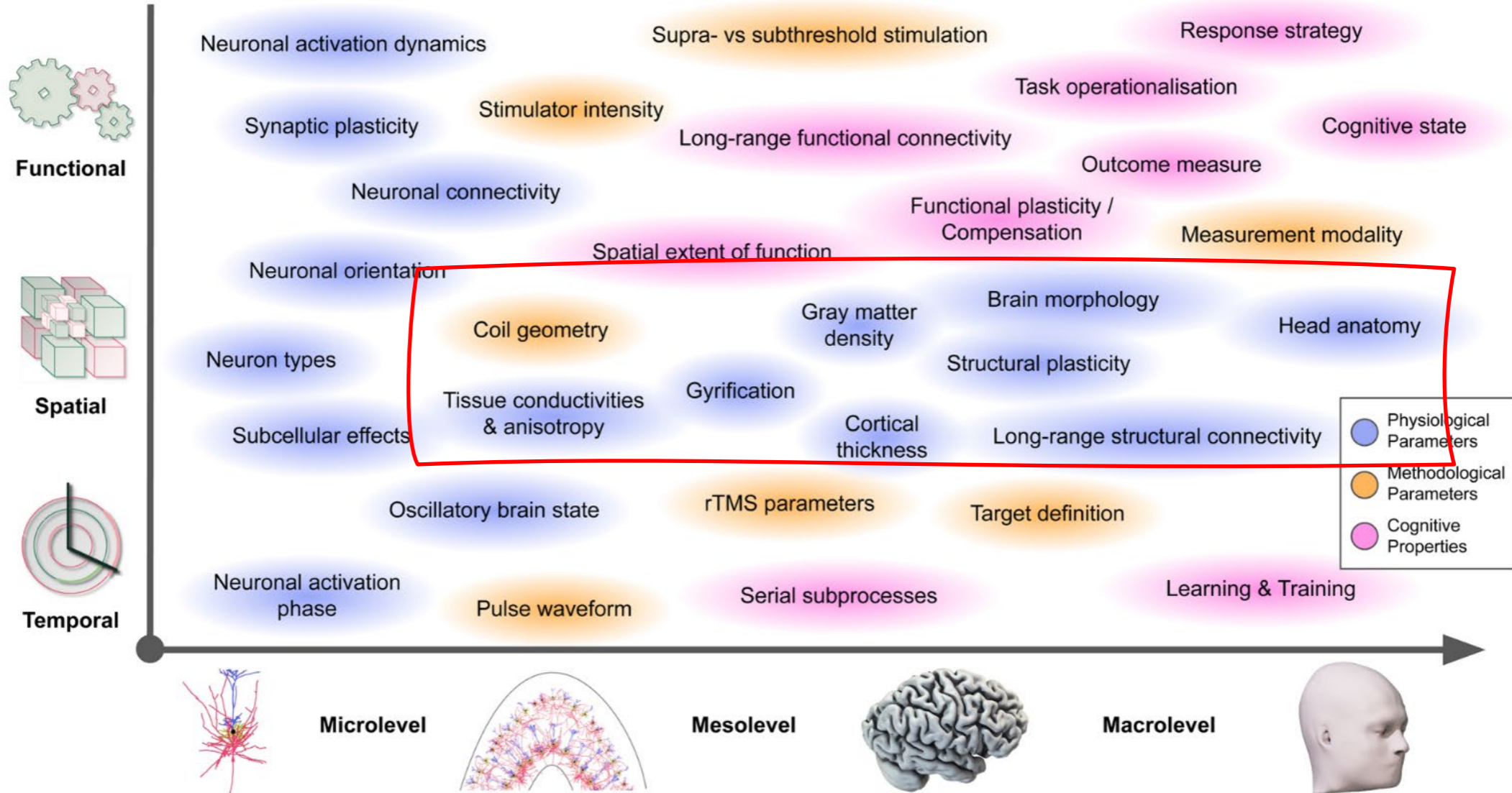


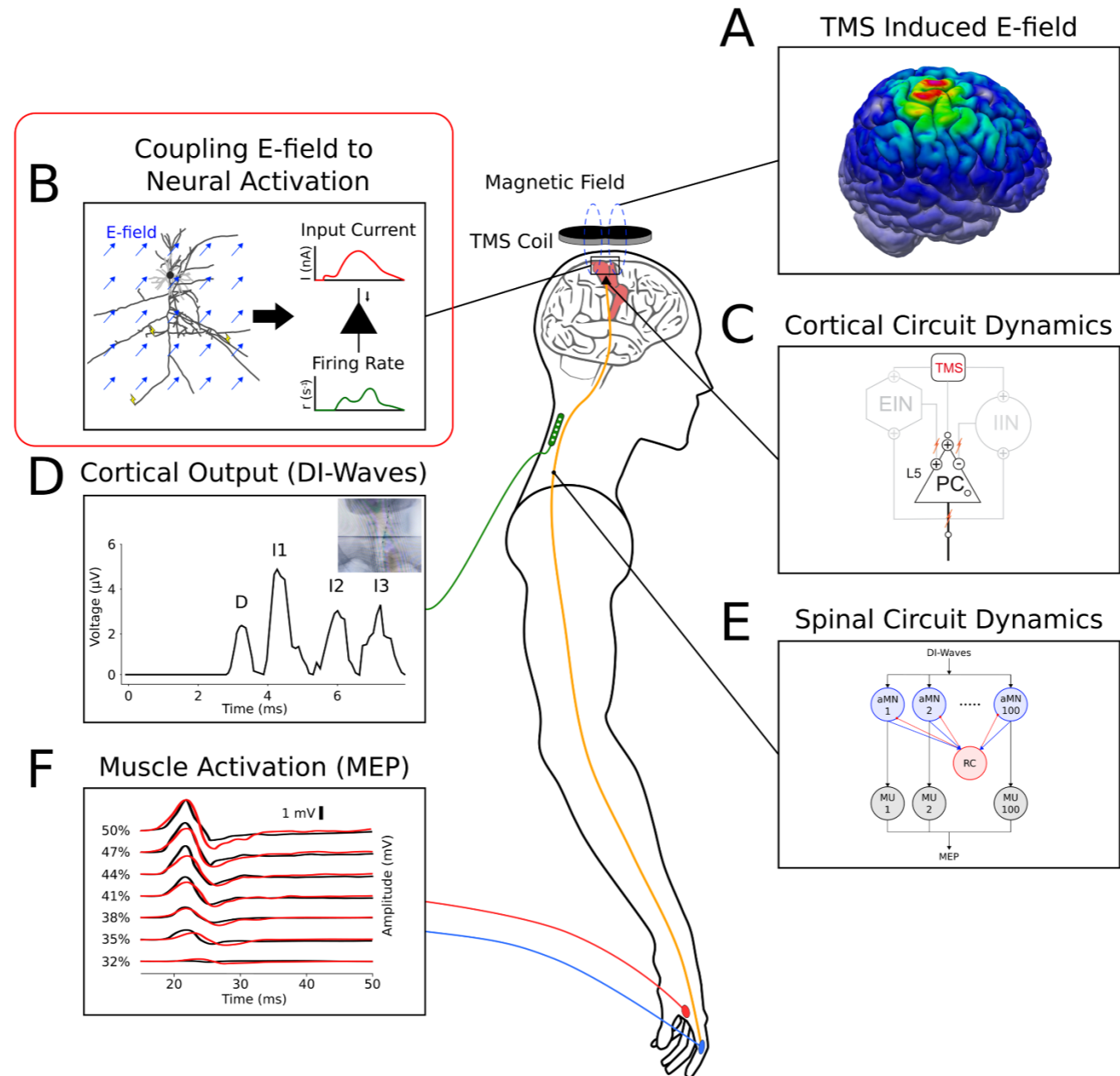
electric field analysis



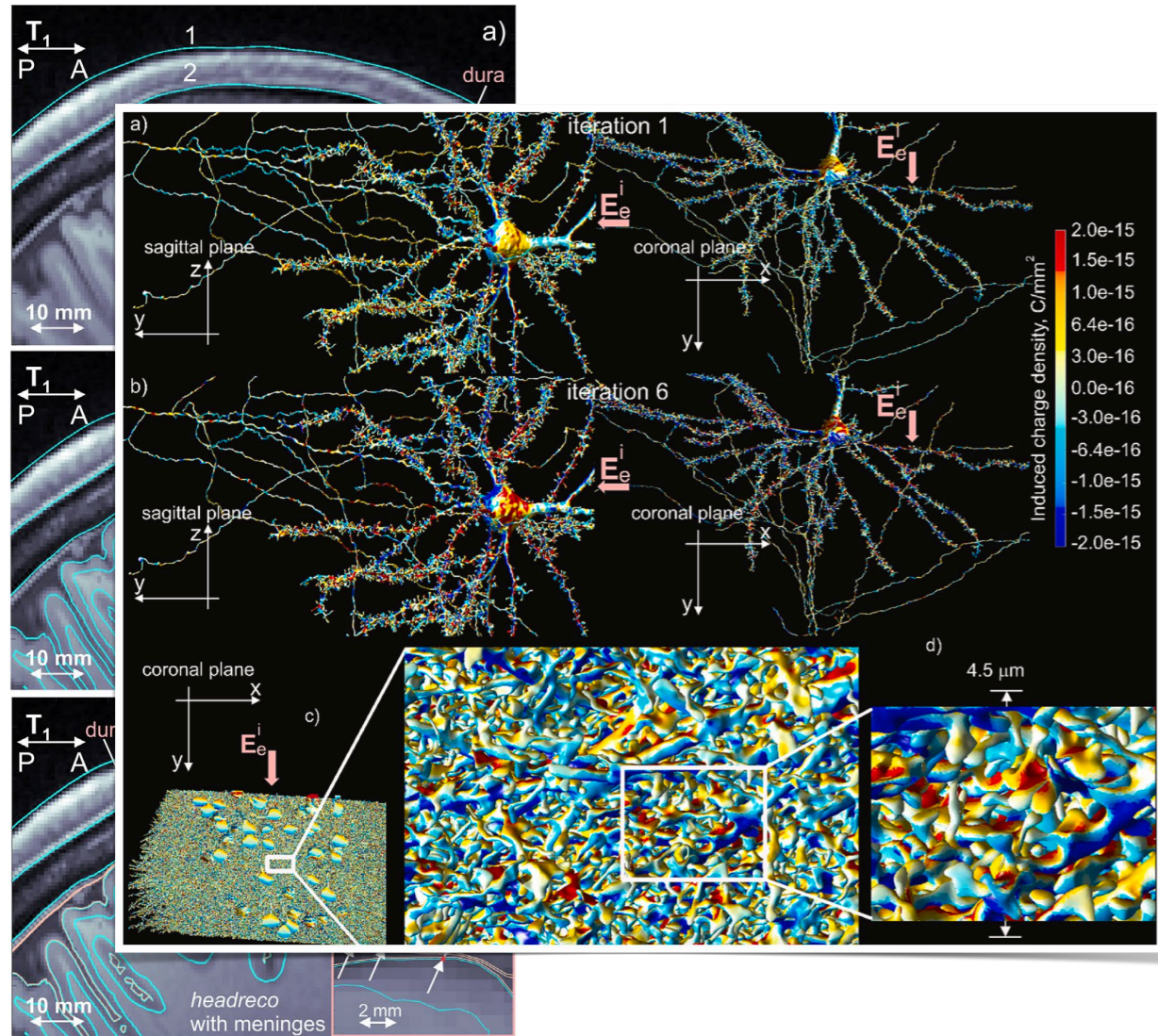






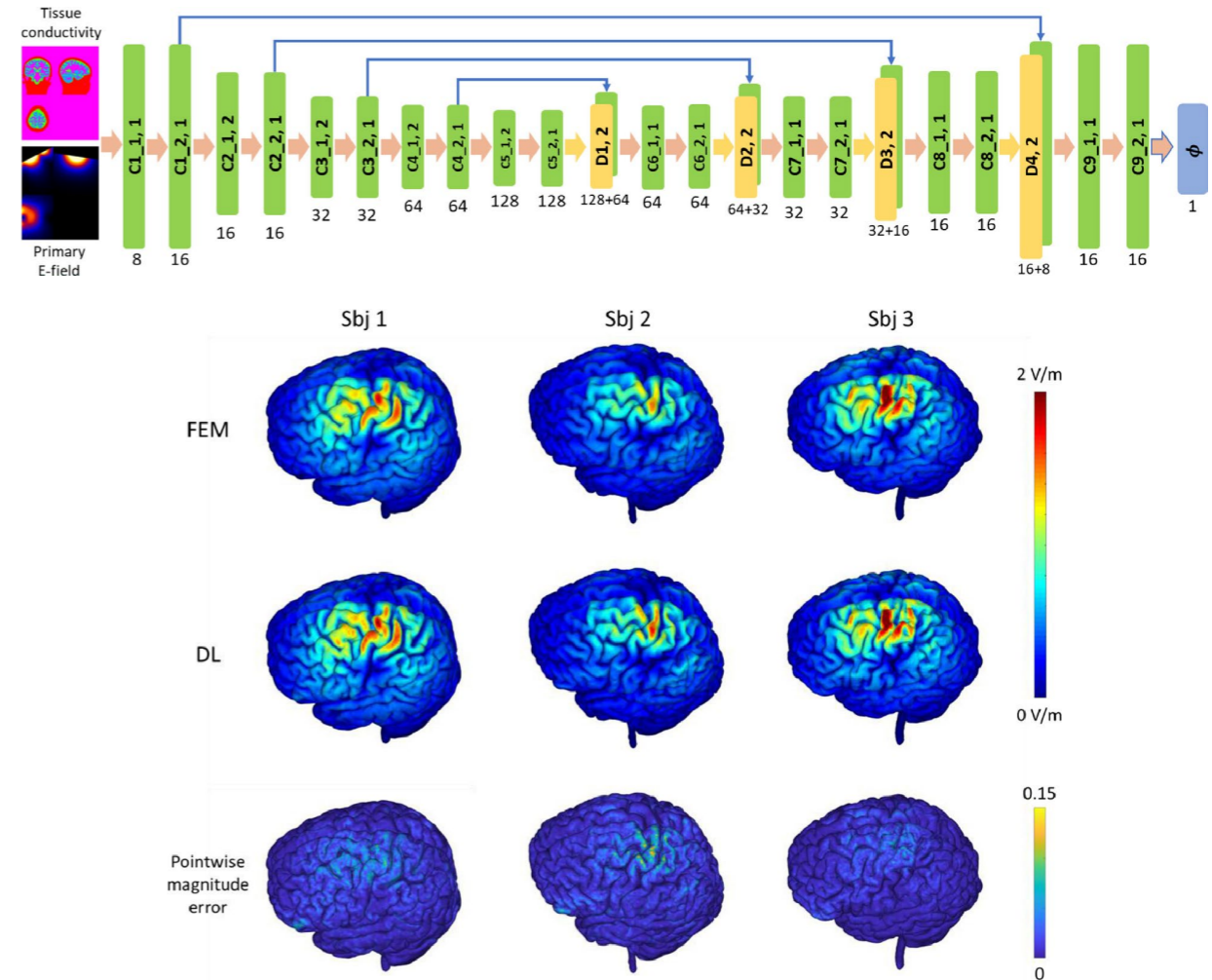


More detailed

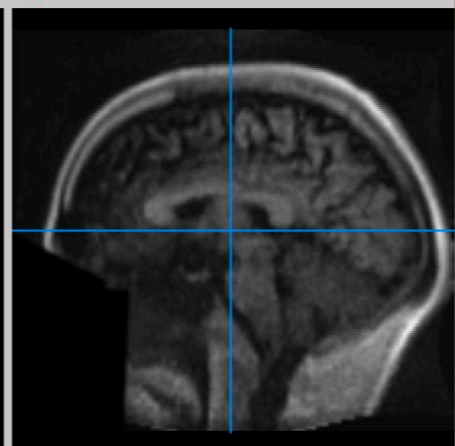
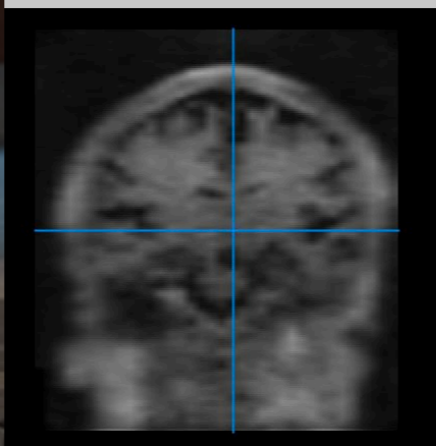
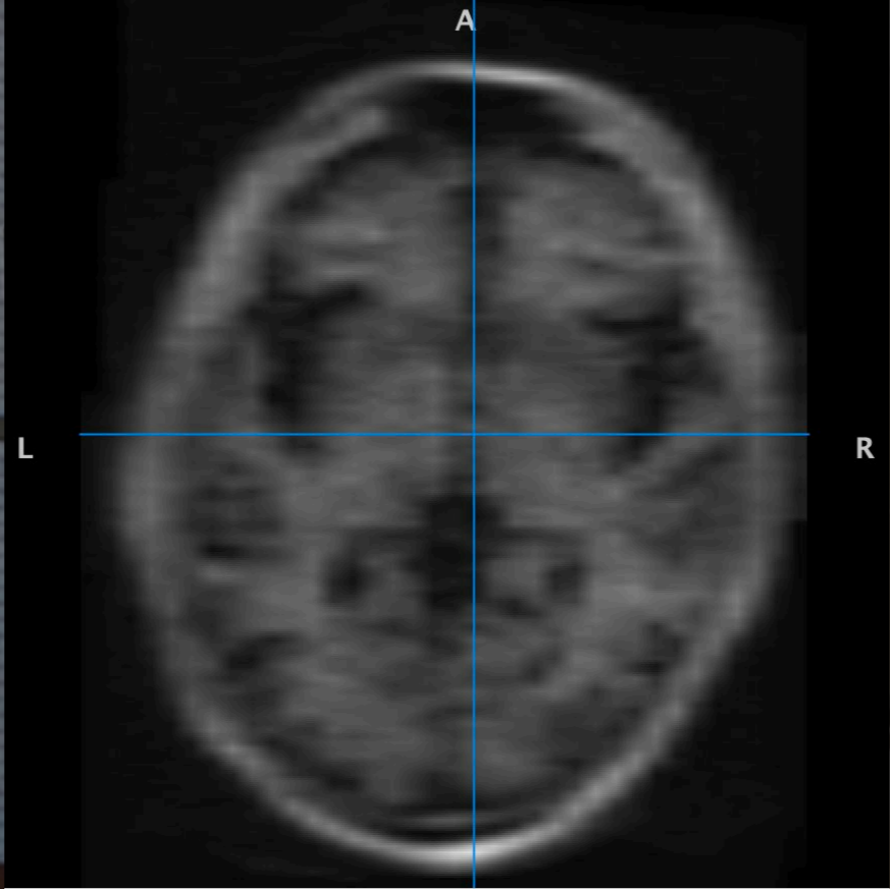


Weise, et al.; Qi et al; Makaroff et al.

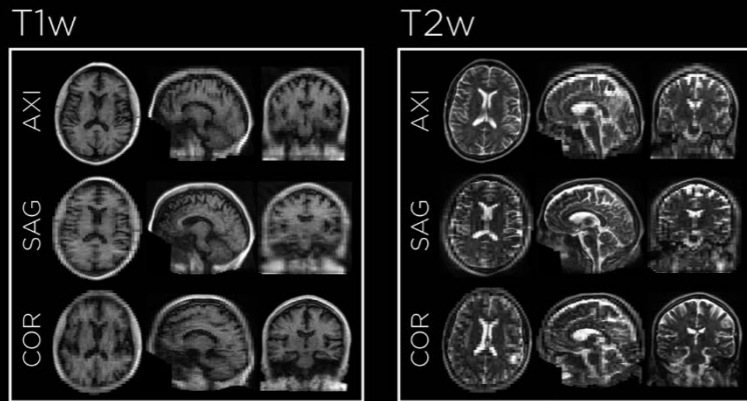
And faster



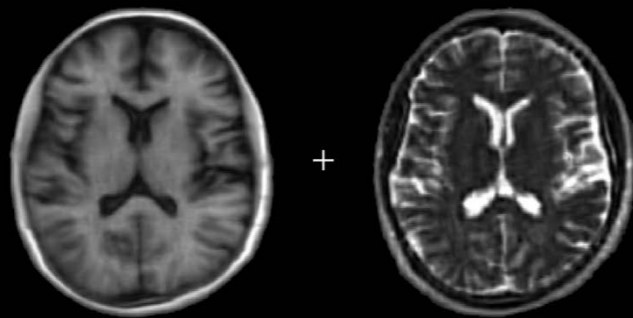
Li, et al. *Neuroimage*, 264:119705, 2022



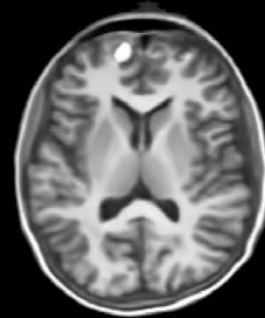
64 mT



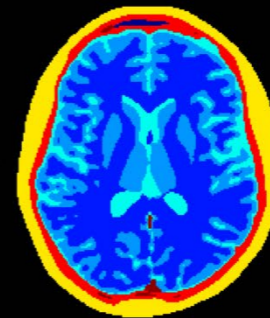
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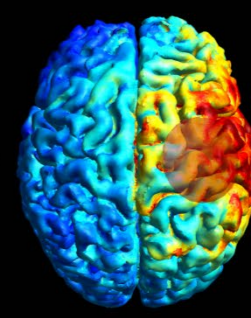
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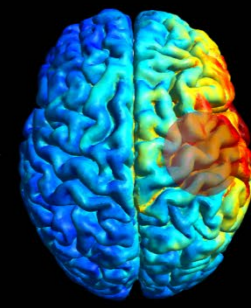
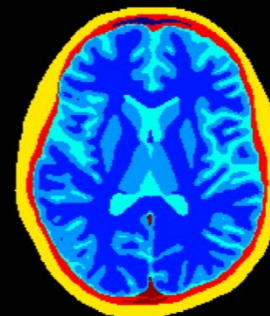
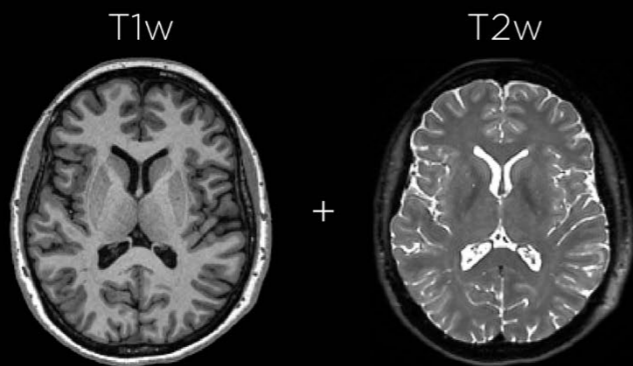
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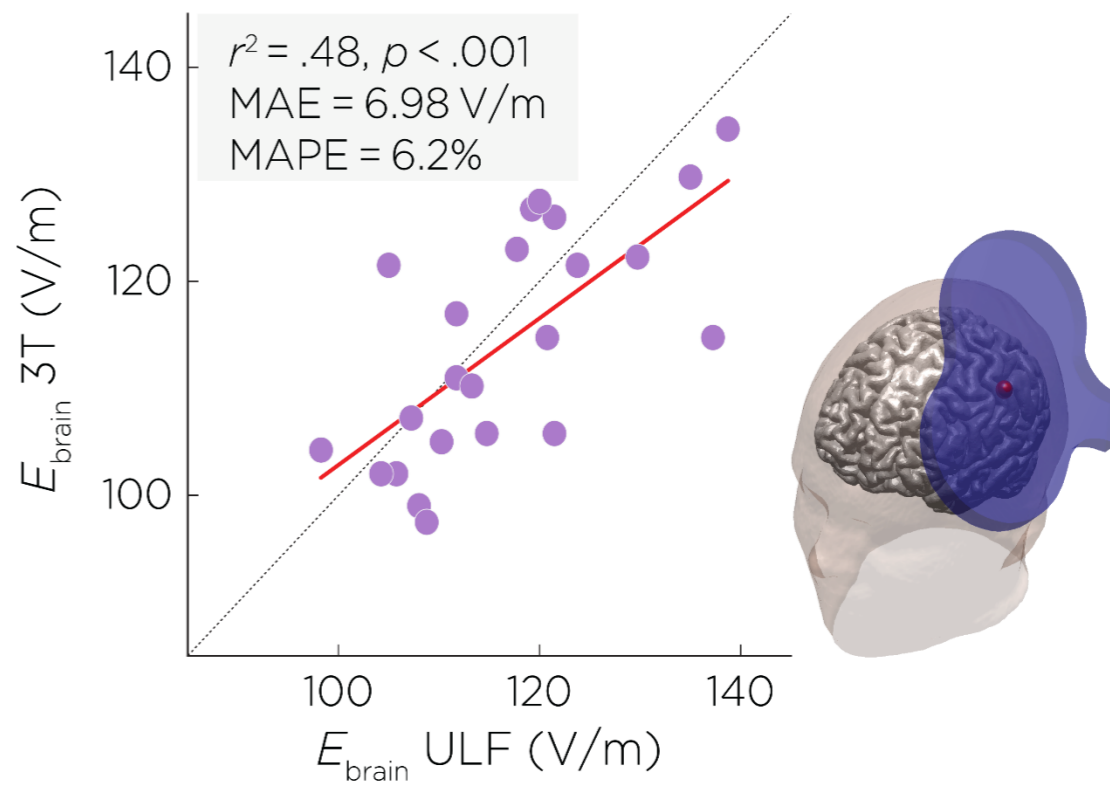
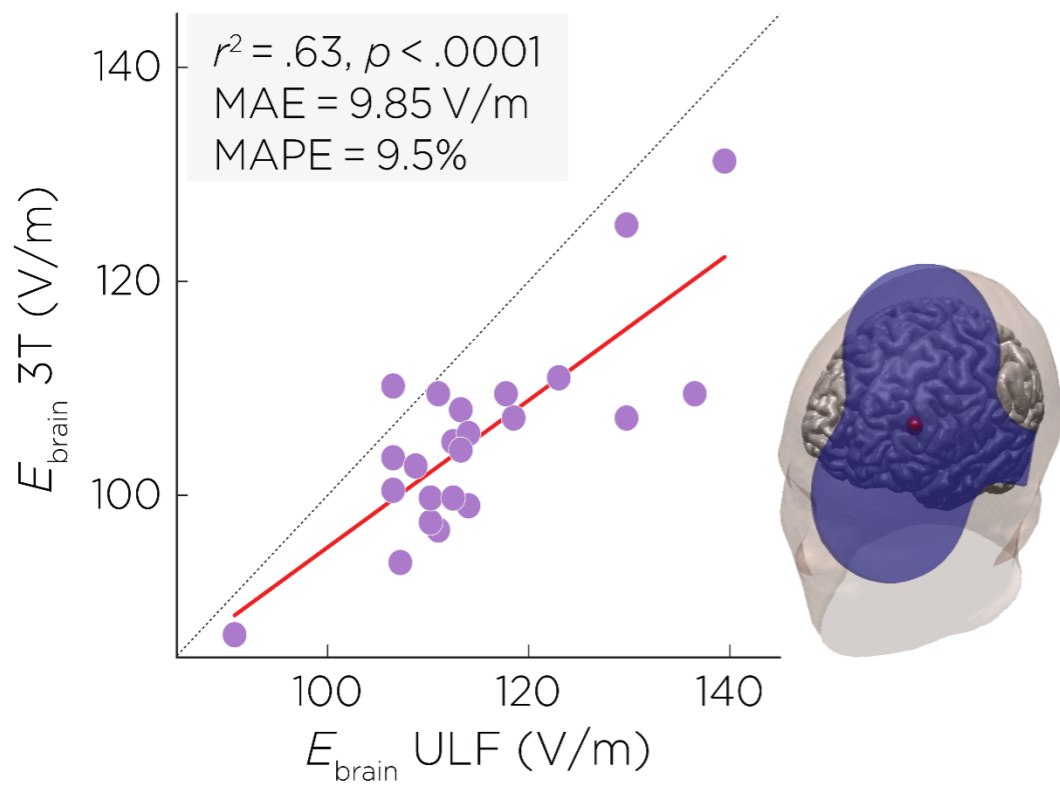


E-field
(SimNIBS)



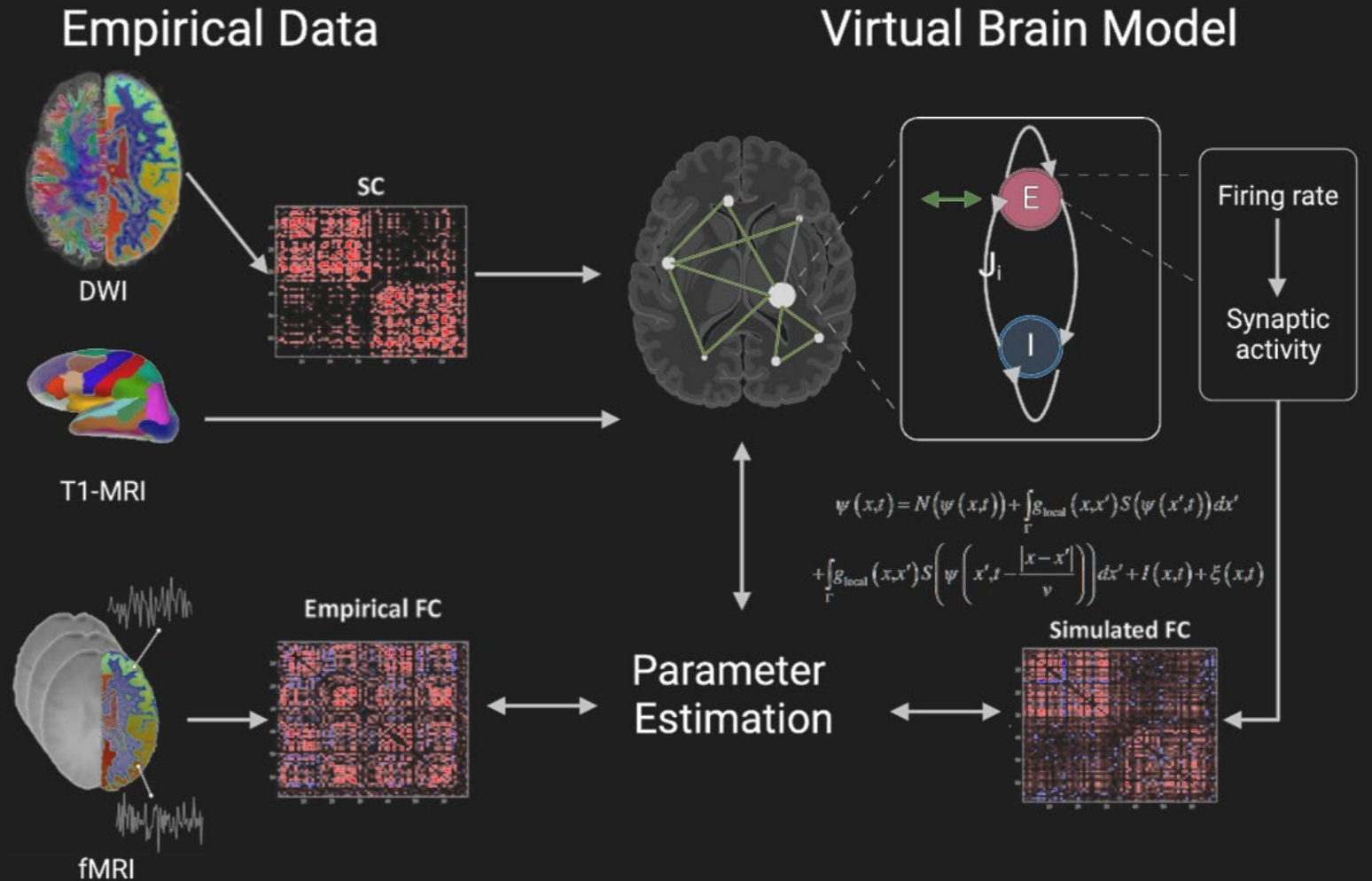
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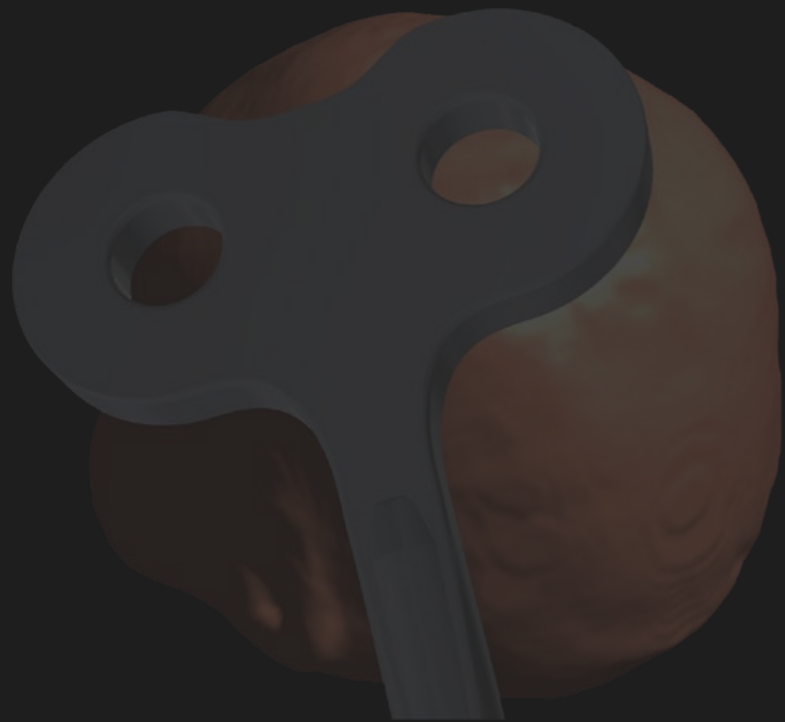




Future work: Generative models for targeting

- Get ULF images, perform super-resolution image reconstruction
- Make structural connectome from DTI
- Embed neural mass models at each parcellation node
- Structural connectivity weighted network defines inter-node coupling
- Use foundation fMRI model's learned latent-representations of resting-state dynamics to infer subject-specific parameters
- Simulate resting-state FC between DLPFC and sgACC to identify treatment target
- E-field modeling to optimize coil placement





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