TMS and Modeling

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COI Disclosure

- Potential conflicts of interest related to this presentation: None

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Abbreviations

- TMS: Transcranial magnetic stimulation
  - single-pulse (spTMS)
- tDCS / tACS: Transcranial direct / alternating current stimulation
- M1: Primary motor cortex
- EEG / MEG: Electro- and magnetoencephalography
- E-field / B-field: Electric field / Magnetic field
- MRI: Magnetic resonance imaging
- DTI: Diffusion tensor imaging
- GM / WM: Grey matter / White matter

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Modeling – What do you mean?

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Modeling – What do you mean?

= Where in the brain are we stimulating

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Modeling – What do you mean?

= Where in the brain are we stimulating

= How strongly are we stimulating

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Modeling – Why should we care?

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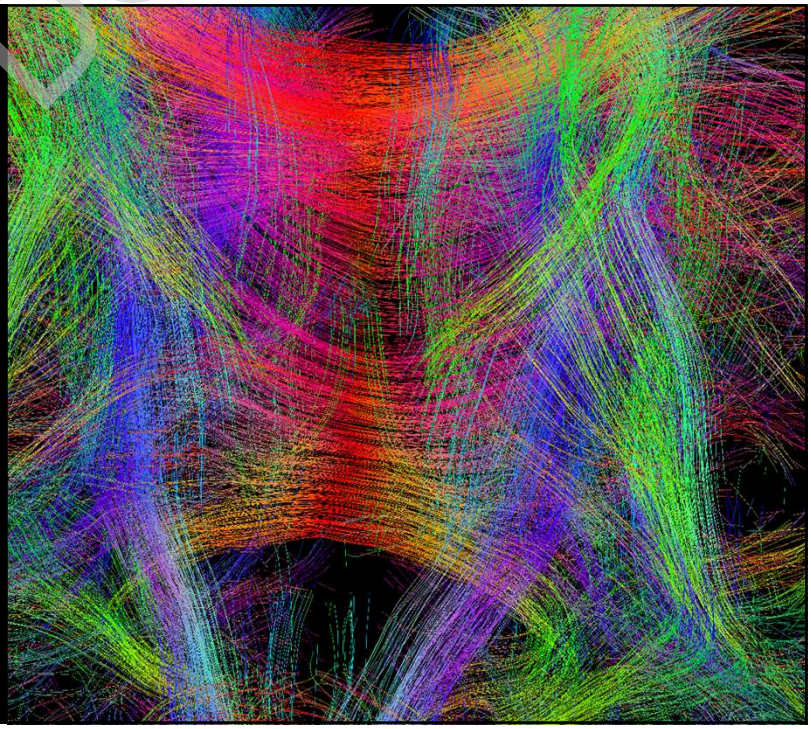
Improve safety



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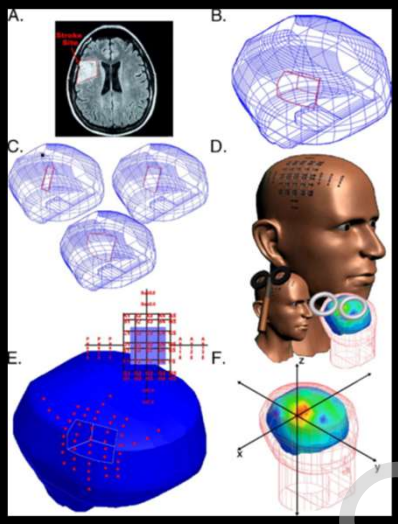
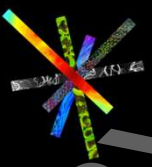
Brain lesions, skull defects, CSF cavities





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Wagner et al. (2006) Neuroimage 30:857-70

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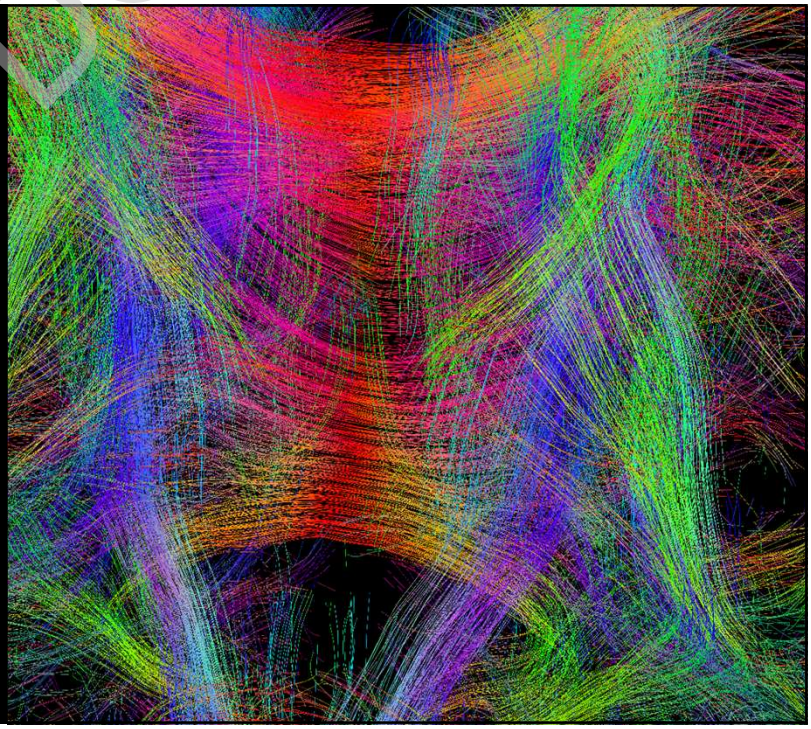
Improve treatment outcomes



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Which brain area am I stimulating?

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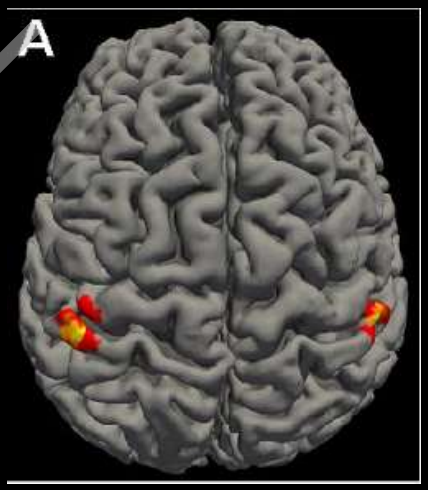
Which brain areas were TMS:d?



Nummenmaa, Stenroos, Ilmoniemi, Okada, Hämäläinen, Raij (2013) Clin Neurophysiol 124:1995-2007
Hernandez-Pavon, Schneider-Garces,, Begnoche, Miller, Raij (2023) Neuromodulation 26(4):745-54

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How strongly am I stimulating it?

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Which large-scale network am I dialing into?

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Am I stimulating a target that gives the best treatment outcome?

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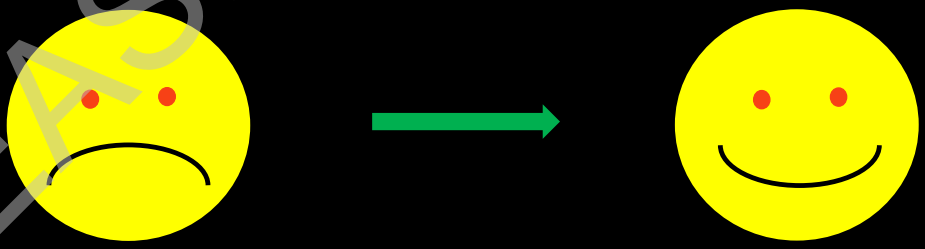
Let's use TMS to treat a patient with disorder X

TMS



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Where shall we place the coil?

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Where shall we place the coil?

Well, DLPFC of course!

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Where shall we place the coil?

Well, DLPFC of course!

I see. Are there other TMS clinics in town?

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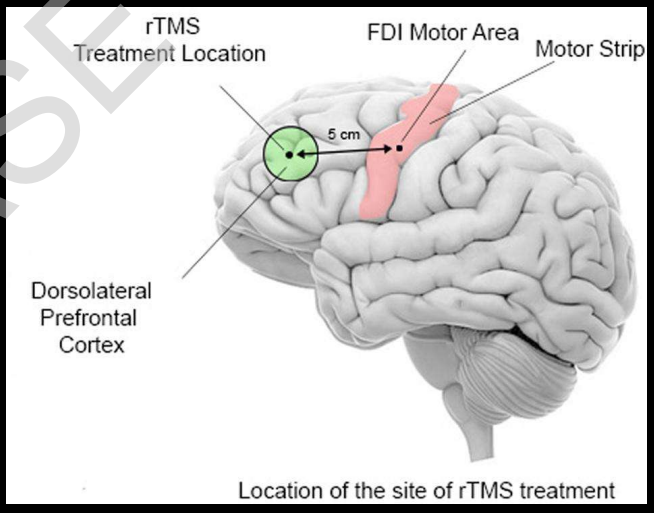
DLPFC 5-cm rule (functionally based – but on M1)



Pascual-Leone et al. (1996) Lancet 348:233-7

Sokhadze et al. (2018) Front Syst Neurosci 12:20

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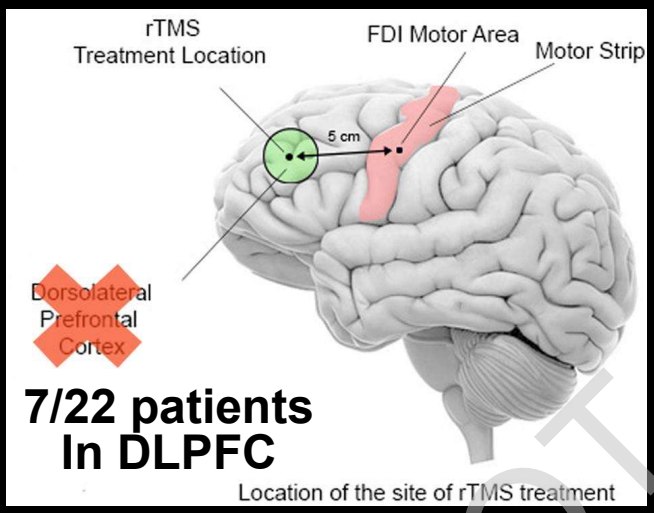
DLPFC 5-cm rule (functionally based – but on M1)



Herwig et al. (2001) Biol Psychiatry 50:58-61

Picture from: Sokhadze et al. (2018) Front Syst Neurosci 12:20

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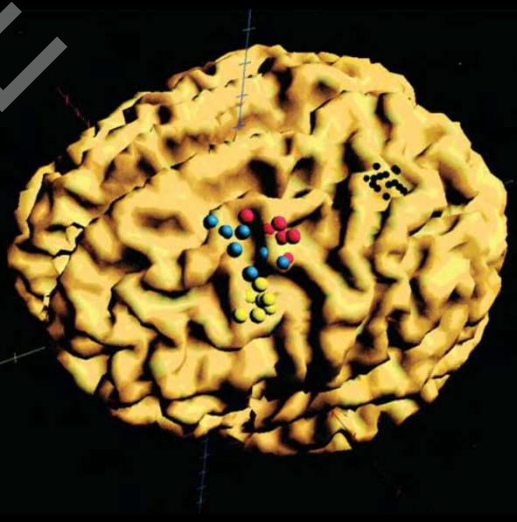
DLPFC 5-cm rule (functionally based – but on M1)



Variability across patients

Herwig, Padberg, Unger, Spitzer, Schönfeldt-Lecuona (2001) Biological Psychiatry 50(1):58-61

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MNI or Talairach coordinates

	Tx	Ty	Tz	MNIx	MNIy	MNIz	Treatment
DLPFC Regions[b]							
Study/Site							
Herwig *et al.* 2001 (37) 5 cm Stimulation Site	−42	17	52				
Herbsman *et al.* 2009 (36) 5 cm Stimulation Site	−42	20	49				
Herbsman *et al.* 2009 (36) 5 cm Sham Site	−39	17	47				
Average 5 cm Coordinates	−41	18	49	−41	16	54	
Herbsman *et al.* 2009 (36) Responders	−46	25	44	−46	23	49	
Herbsman *et al.* 2009 (36) Nonresponders	−41	19	50	−41	17	55	
Herwig *et al.* 2003 (43) EEG (F3) Site	−37	27	44	−37	26	49	
Rajkowska and Goldman-Rakic 1995 (54) BA46 Definition	−44	40	25	−44	40	29	
Rajkowska and Goldman-Rakic 1995 (54) BA9 Definition	−36	40	38	−36	39	43	
Paus *et al.* 2001 (25) TMS Target	−40	32	30	−40	31	34	
Cho and Strafella 2009 (53) TMS Target	−40	32	30	−40	31	34	
Fitgerald *et al.* 2009 (35) TMS Target	−46	45	35	−46	45	38	
Rusjan *et al.* 2010 (41) TMS Target	−50	31	32	−50	30	36	

Fox et al. (2012) Biological Psychiatry 72:595–603.

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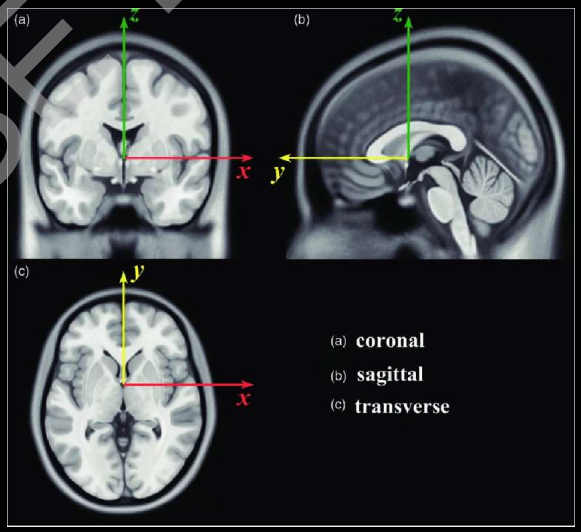
Talairach and MNI coordinate systems…



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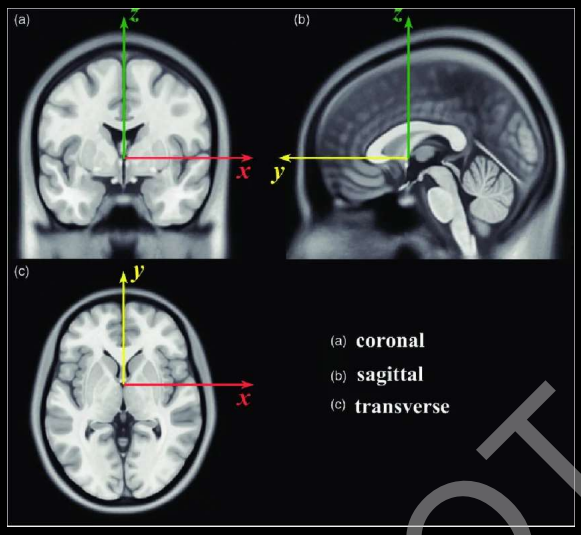
… do not accurately tell in which gyrus, sulcus, or BA we are



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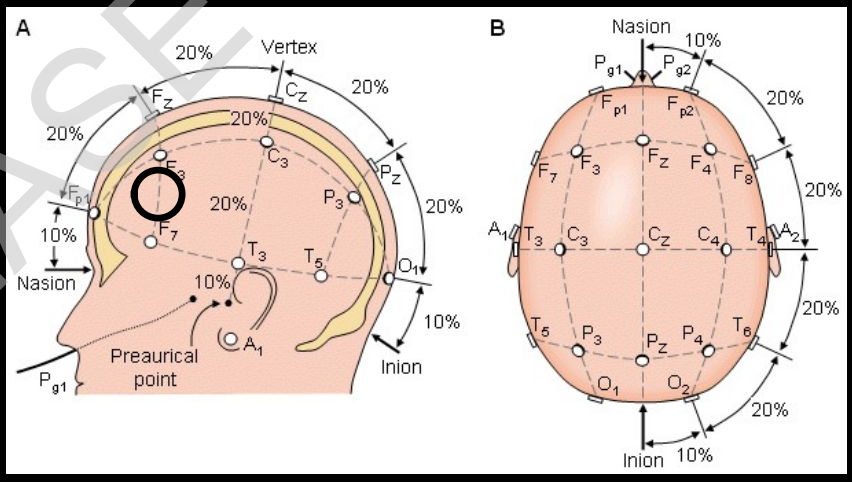
EEG International 10-20 System (F5, F3, F3-Beam)



Herwig et al. (2003) Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topography 16(2):95-9

Beam et al. (2020) An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimulation 2:50-4

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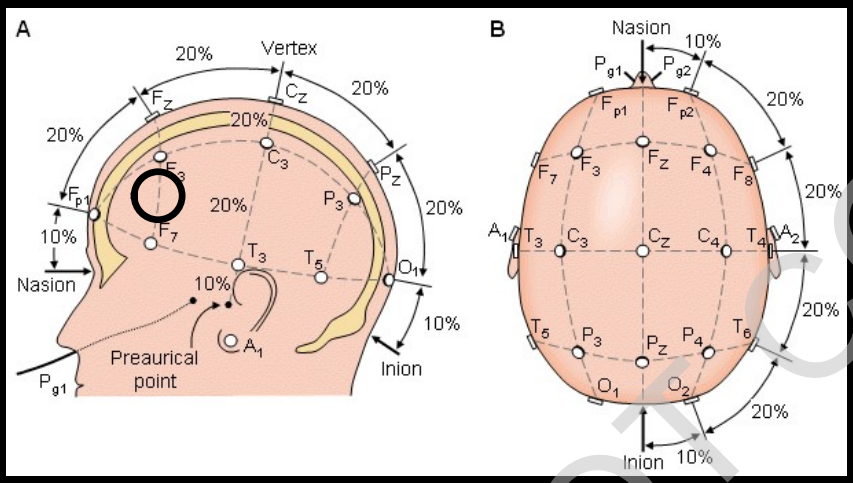
… but which gyrus is under F5? Or F3?



Herwig et al. (2003) Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topography 16(2):95-9

Beam et al. (2020) An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimulation 2:50-4

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MNI, Talairach, EEG electrode methods:

- ❑ Affordable (unless the treatment fails)
- ❑ Easy (no individual MRI or TMS navigator required)
- ❑ Are based on something else than cortical anatomy
- ❑ Give worse clinical outcomes?

- ❑ Why are we navigating in scalp-based coordinates if our goal is to target a specific brain area (brain coordinates)?

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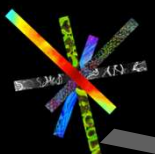
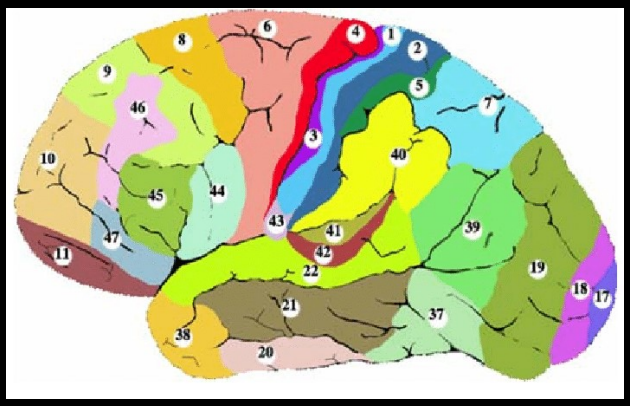
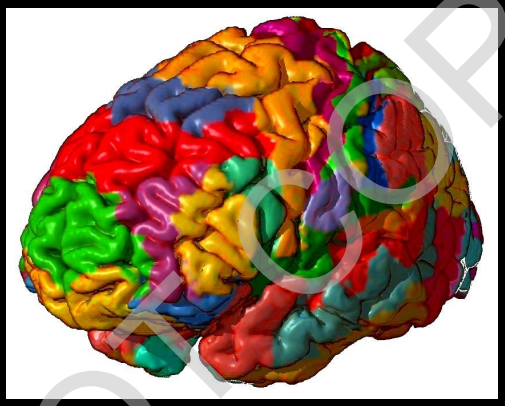
Cortical anatomy (BA9/BA46 junction, Ant MFG)







Fitzgerald et al. (2009) Neuropsychopharmacology 30:1255–62

Picture on left from: Vonsattel et al. (2009) Acta Neuropathol 115(5):509-32

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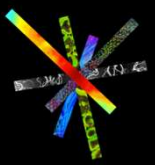
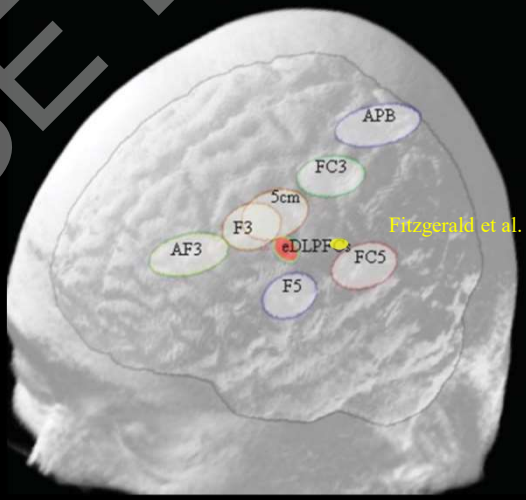
Cortical anatomy (BA9/BA46 junction, Ant MFG)





Fitzgerald et al. 2009 (Approximate)

Fitzgerald et al. (2009) A Randomized Trial of rTMS Targeted with MRI Based Neuro-Navigation in Treatment-Resistant Depression. Neuropsychopharmacology 30:1255–62

Rusjan et al. (2010) Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. Human Brain Mapping 31(11):643-52

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Hypotheses:

1. Some cortical anatomy targets are better than others
2. Treatment outcomes depend on targeting a “good” cortical anatomy area
3. The “good” cortical areas are similar across patients
4. We can identify the best target using modeling

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Given our hypotheses:

We need to use individual cortical anatomy to target a specific cortical anatomy location (MRI, TMS navigation device).

MNI, Talairach, or scalp based methods do not tell us about the individual anatomy.

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Methods

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From TMS coil location to stimulated brain area

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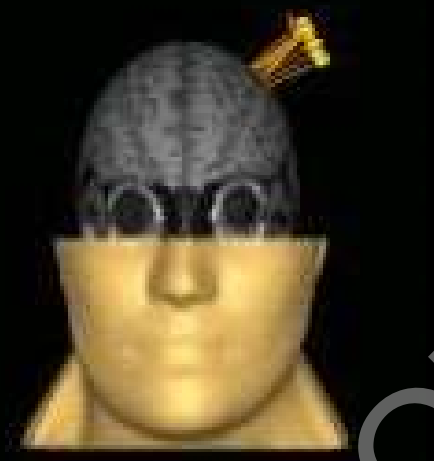
1. Ball-and-stick estimates



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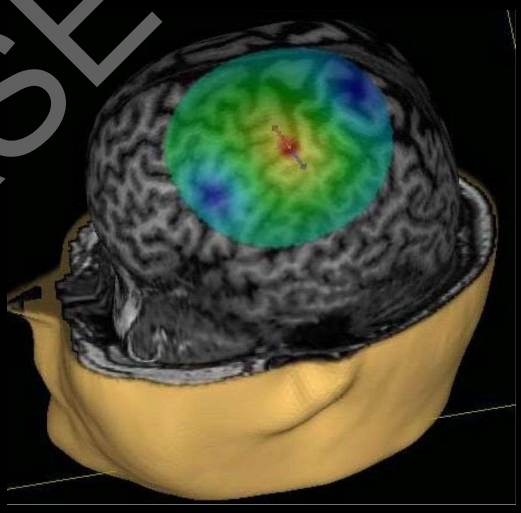
2. Simple TMS E-fields



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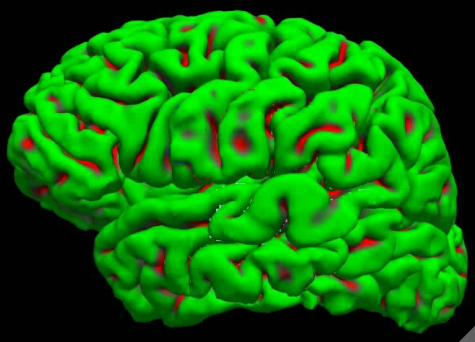
3. The actual cortical surface



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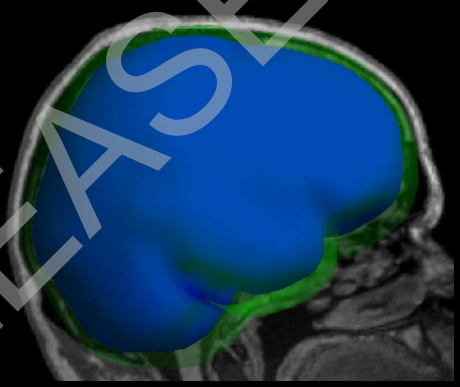
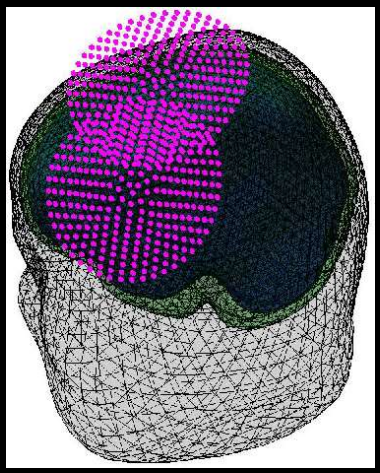
+ Realistic head model + coil model





Nummenmaa et al. (2013) Clin Neurophysiol 124:1995-2007

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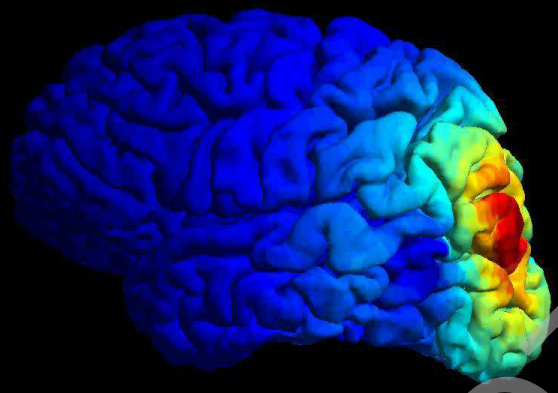
TMS-induced cortical E-fields



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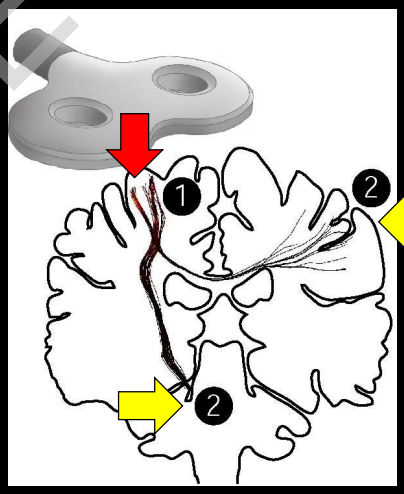
Primary + Secondary activations



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Diana, Raij, Melis, Nummenmaa, Leggio, Bonci (2017) Nature Reviews Neuroscience 18:685-

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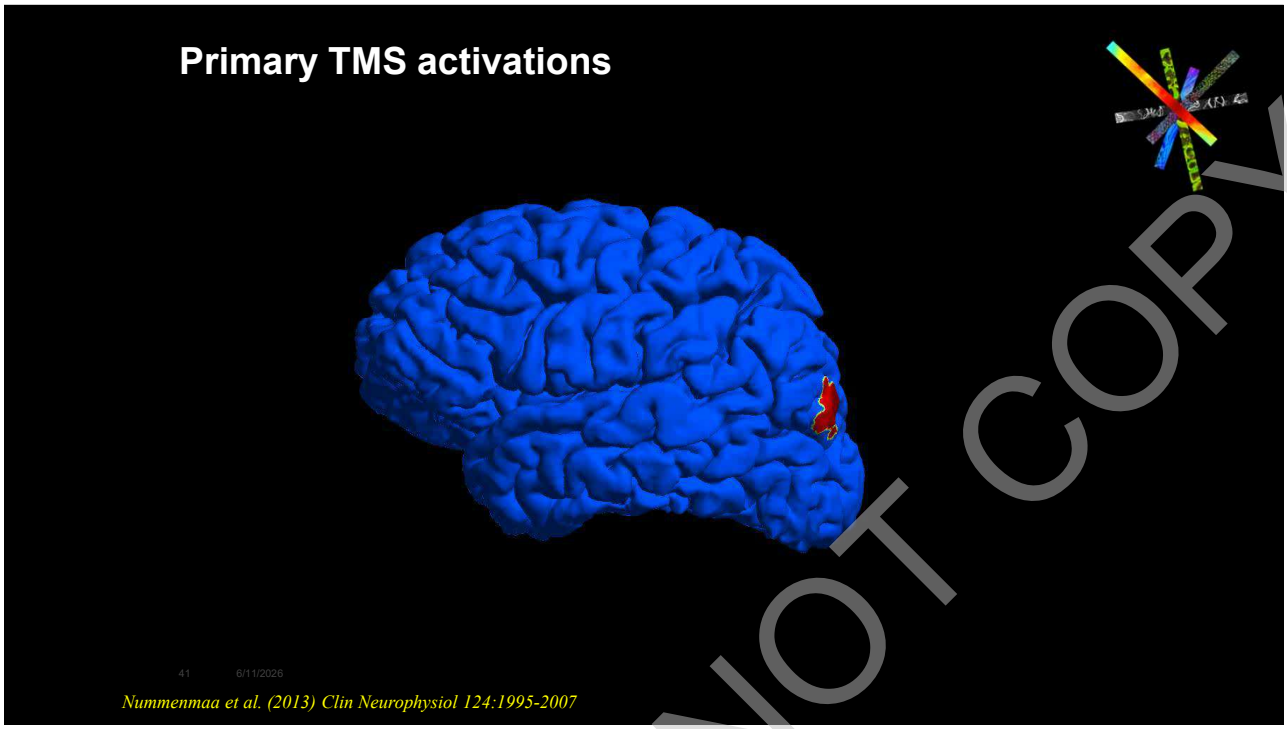

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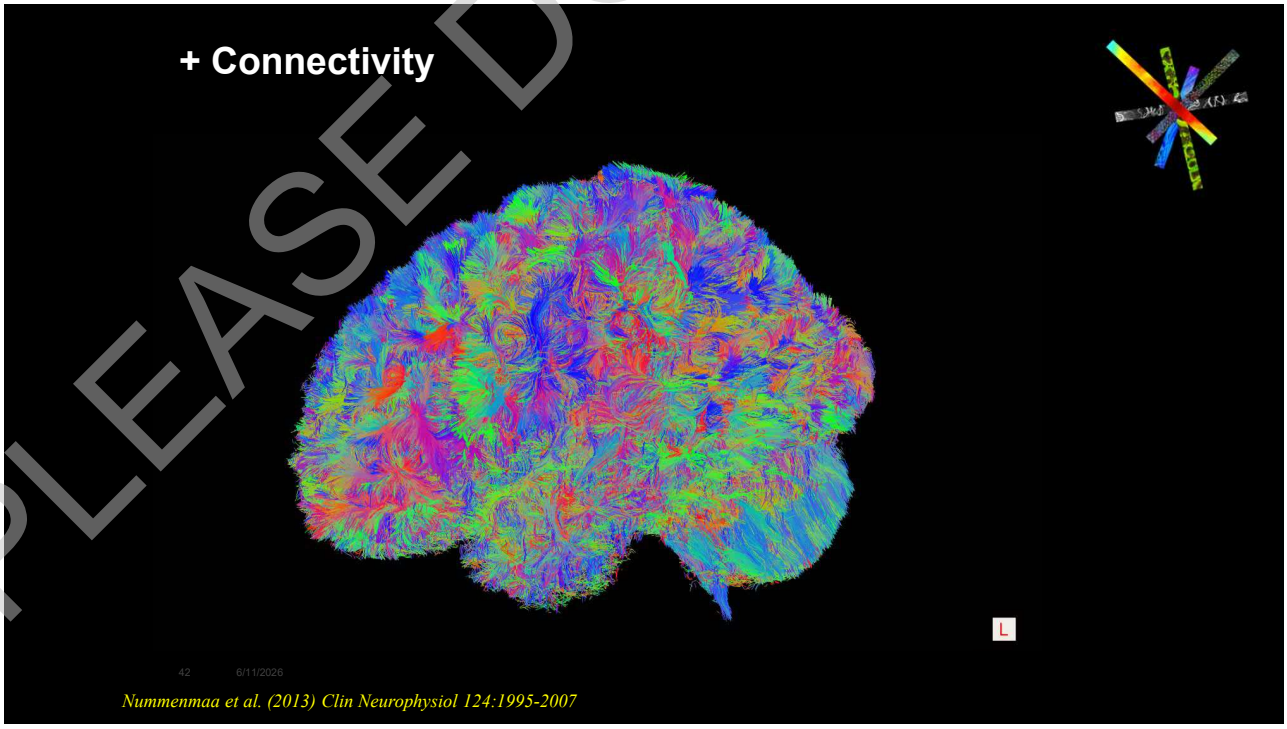

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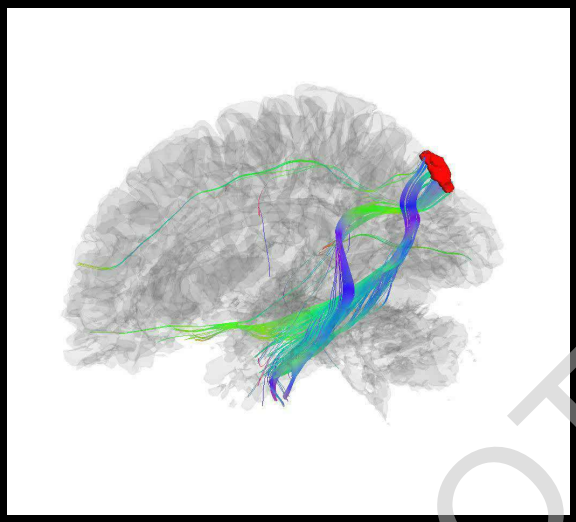
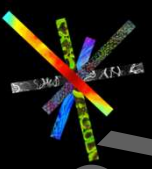
= Network-level TMS navigation





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Do we need individual MRIs?

Cortical folding anatomy is individual. So, yes.

To align gyri/sulci accurately across subjects, it is necessary to extract the individual cortical surfaces (FreeSurfer)

The elastic (non-linear) morph function between the cortical surfaces is also automatically computed by FreeSurfer

Fischl, Sereno, Tootell, Dale (1999) Hum Brain Mapp 8(4):272-84

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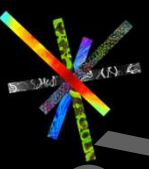
For TMS targeting, how should we spatially align brains across individual subjects?



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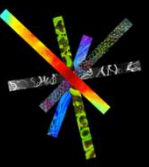
Remember TMS is a superficial stimulation method



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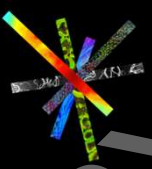
Remember TMS is a superficial stimulation method



Therefore, the cortical surface is the relevant navigational space

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Natively surface-based intersubject brain alignment methods

Surface-based morphing (+ 3D volumetric morphing)

FreeSurfer cortical parcellation

Widely used in fMRI and MEG/EEG for 20+ years but, so far, more rarely in TMS

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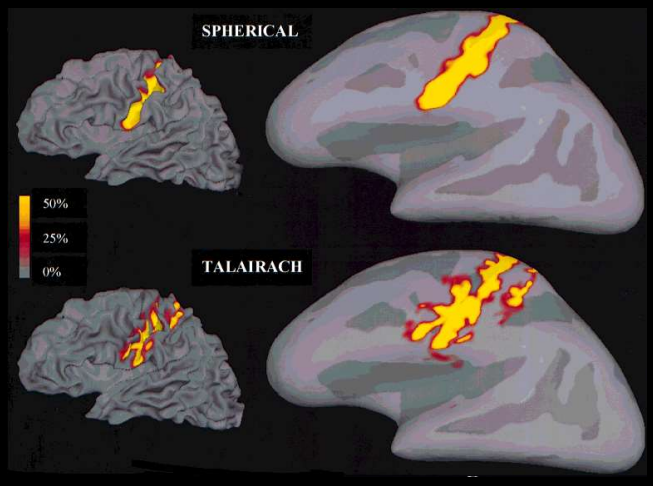

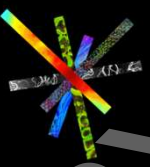

Cortical surface averaging

Volumetric averaging

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Fischl et al. (1999) Human Brain Mapping 8(4):272-84; Fischl (2012) Freesurfer. Neuroimage 62:774-81.

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How does aligning (morphing) cortical surfaces across patients work?

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Surface non-linear registration

Fischl, Sereno, Tootell, Dale (1999) Hum Brain Mapp 8:272-284

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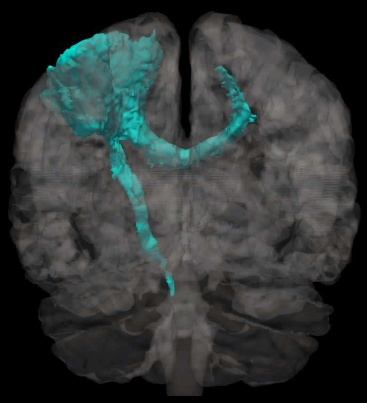
3D volumetric morphing



Postelnicu, Zollei, Fischl (2012) IEEE Trans Med Imaging 28:508-22

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How will we use this knowledge?

Example 1: Let's find out where we should stimulate to alleviate symptoms of X

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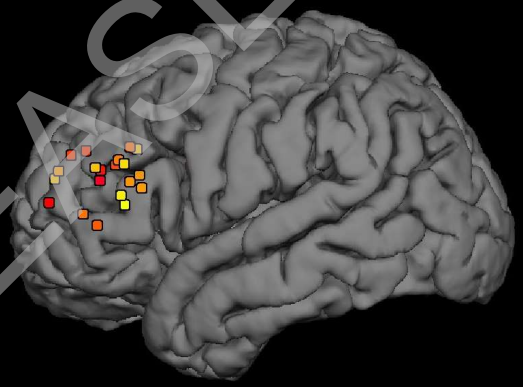
Individual E-field maxima

A. E-field maxima



MNI [-50, 30, 36] (Rusjan)

107 180 V/m

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Raij, Schneider-Garces, Srivatsan, Terraneo, Gallimberti, Bonci, Phan, Ahveninen, Nummenmaa (2026) Submitted

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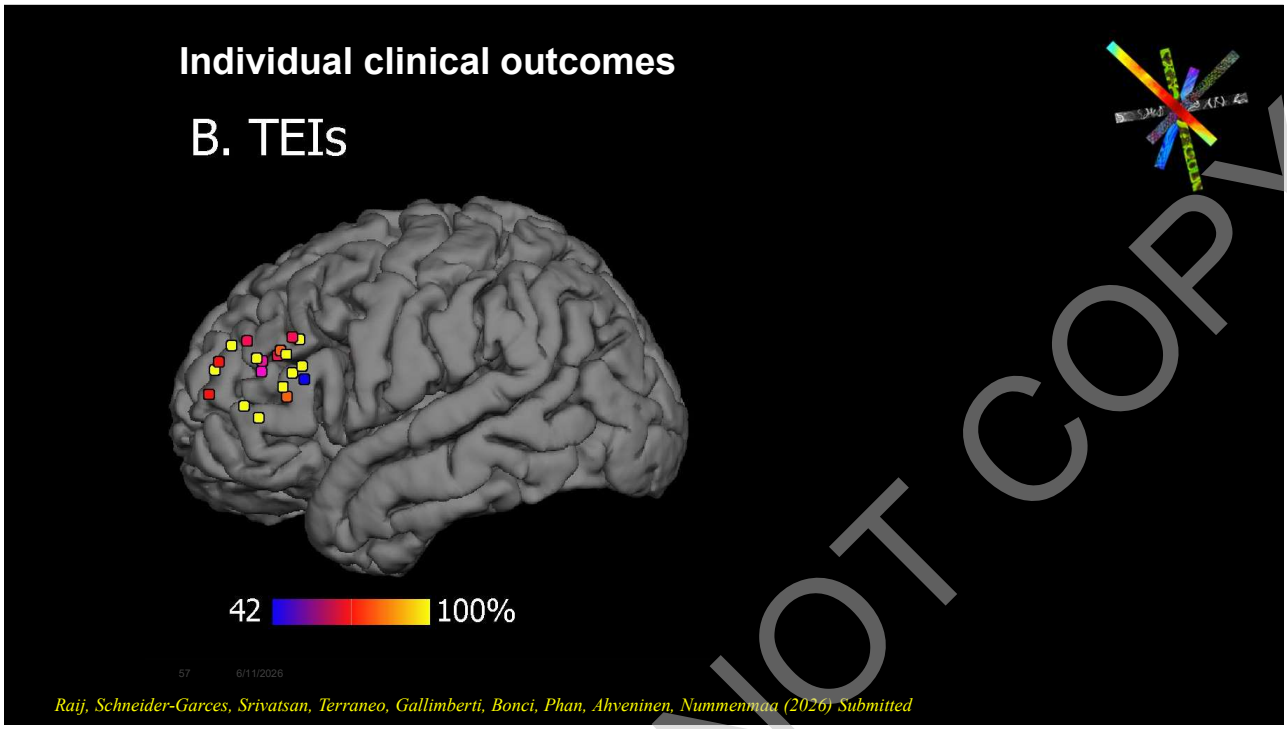

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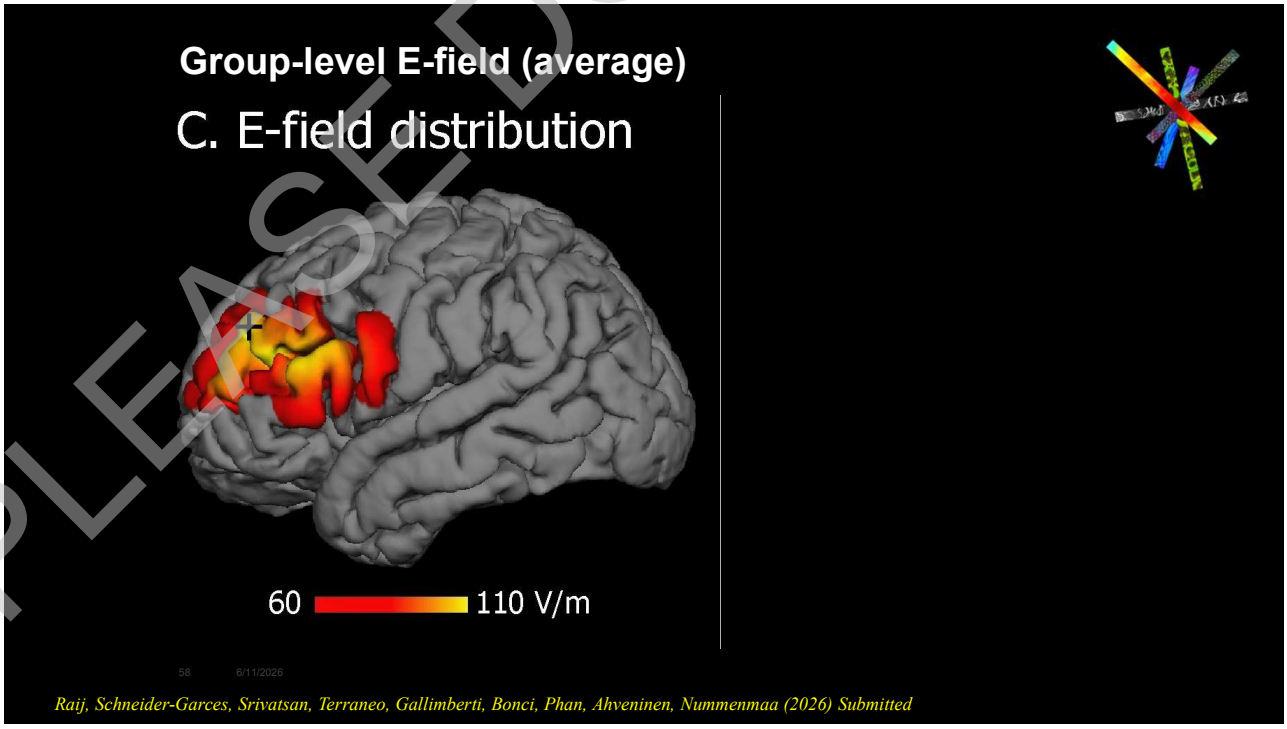

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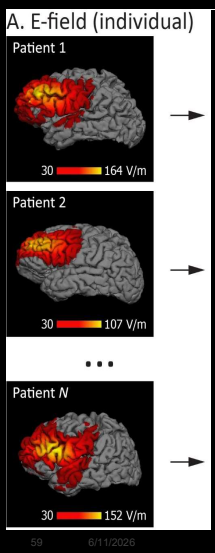
1. Stimulate N patients, compute individual E-fields



Raij, Schneider-Garces, Srivatsan, Terraneo, Gallimberti, Bonci, Phan, Ahveninen, Nummenmaa (2026) Submitted

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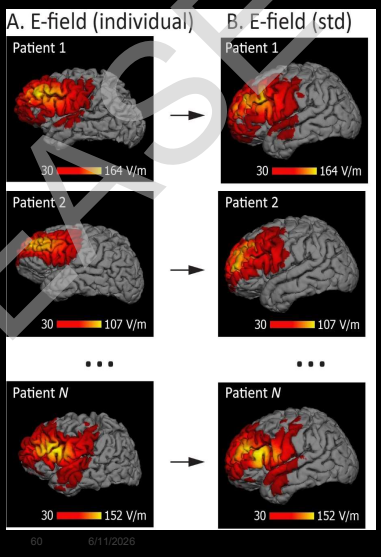
2. Morph individual E-fields to a standard brain



Raij, Schneider-Garces, Srivatsan, Terraneo, Gallimberti, Bonci, Phan, Ahveninen, Nummenmaa (2026) Submitted

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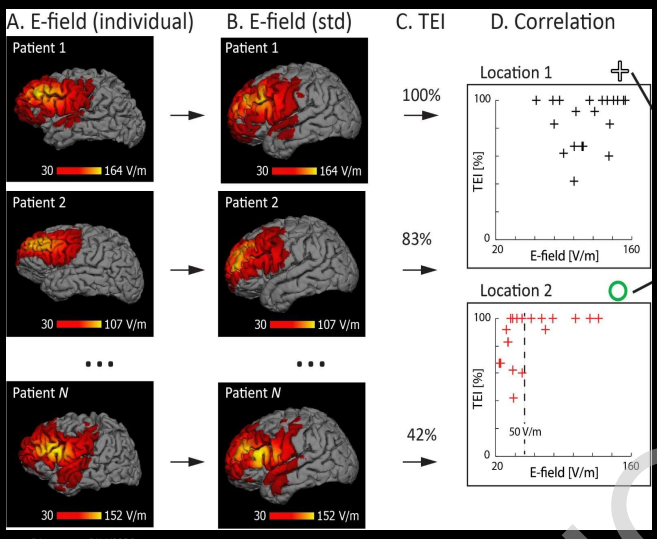
3. Relationship between E-fields and outcomes



Raij, Schneider-Garces, Srivatsan, Terraneo, Gallimberti, Bonci, Phan, Ahveninen, Nummenmaa (2026) Submitted

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4. Use statistical methods to reveal significance

Unpublished results removed

Raij, Schneider-Garces, Srivatsan, Terraneo, Gallimberti, Bonci, Phan, Ahveninen, Nummenmaa (2026) Submitted

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Next, we plug in connectivity from TMS targets

Example 2: Let's find out where the connections go in patients that improve *vs.* those that do not

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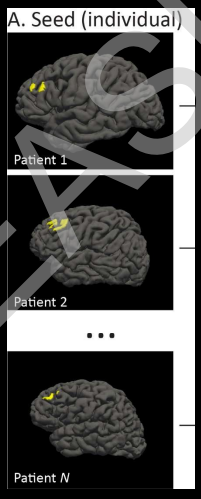
1. Individual E-field maxima -> seeds



Raij, Schneider-Garces, Begnoche, Gallimberti, Phan, Srivatsan, Terraneo, Bonci, Nummenmaa (2026) Submitted

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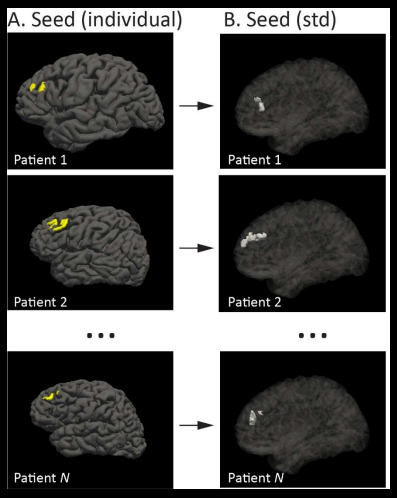
2. Morph individual seeds to standard brain



Unpublished results removed

65 6/11/2026

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65

3. Relationship between seed connectivity and outcomes

Unpublished results removed

66 6/11/2026

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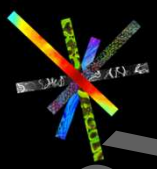
4. Use statistical methods to reveal significance



Unpublished results removed

Raij, Schneider-Garces, Begnoche, Gallimberti, Phan, Srivatsan, Terraneo, Bonci, Nummenmaa (2026) Submitted

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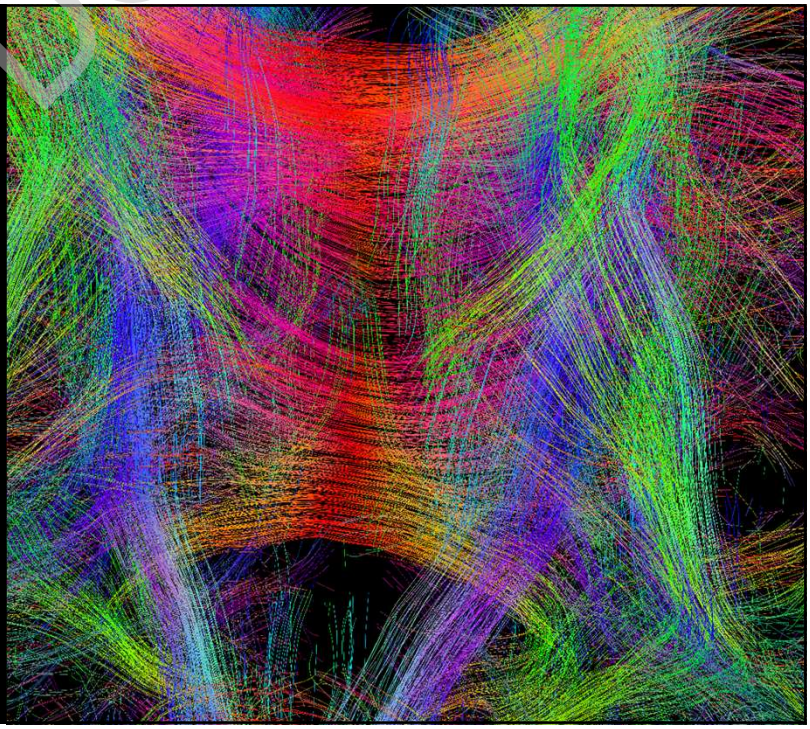
Improve non-clinical studies



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Prove that the intended targets were activated

69 6/11/2026

Ahveninen et al. (2013) Nature Communications 4:2585

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Examine which brain areas were responsible for the experimental effects

70 6/11/2026

Raij, Nummenmaa, Marin, Porter, Furtak, Setsompop, Milad (2018) Biological Psychiatry 84(2):129-37

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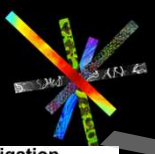
Quality control: TMS coil center and tilt

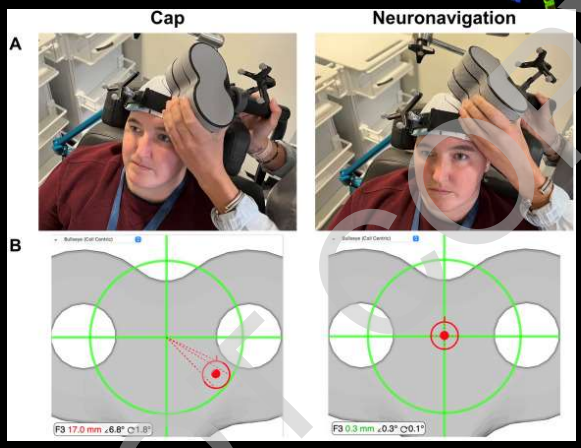


TMS coil center should be on the scalp tangential to the local head curvature.

Common mistakes:

- ❑ Gap
- ❑ Incorrect roll
- ❑ Incorrect pitch

Always save your navigator data for every treatment pulse, every session. This will tell you if something went wrong and allows analyses as above.



Caulfield et al., (2022) Brain Stimulation 15(5):1192-1205

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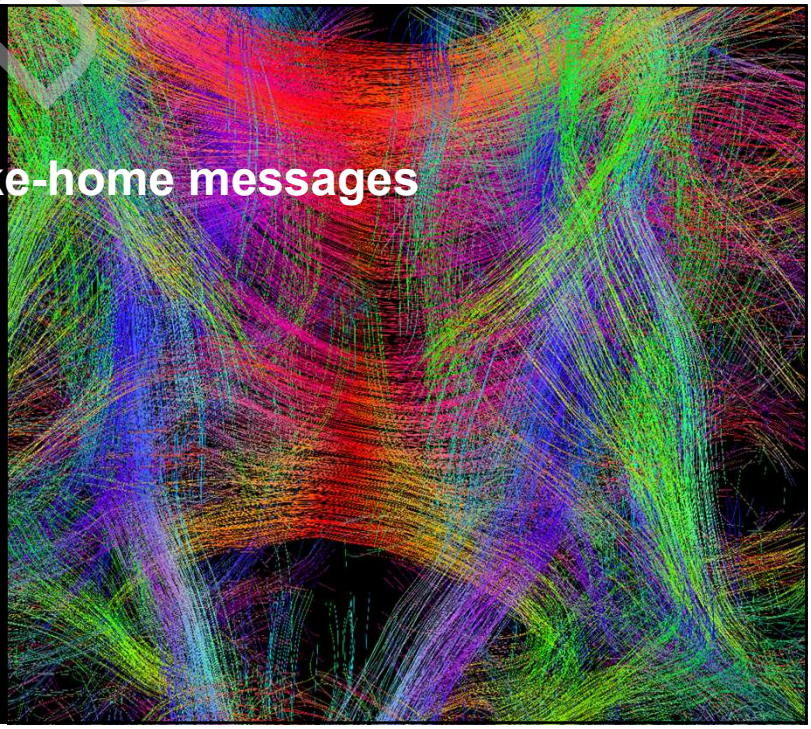
Take-home messages



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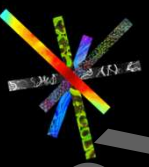
TMS and modeling: Take-home messages



- ❑ Helpful and sometimes critically important
- ❑ Calculate TMS E-fields (intensity at each location)
- ❑ Examine where E-fields activate neuronal tissue and where the activations spread
- ❑ Correlate the E-field and connectivity results with outcomes

Requires the following key data:

1. Where the TMS coil and head were located (navigator)
2. Individual head model (volume conductor, from MRI)
3. Individual brain anatomy (from MRI)

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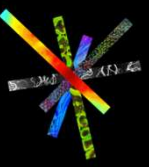
Techniques, software



- ❑ Finite element method (FEM)
- Free (SimNIBS, DUNEuro, SciRun, ROAST)
- Commercial (e.g., Ansys Maxwell, COMSOL, Sim4Life)

- ❑ Boundary element method (BEM)

- ❑ BEM with the Fast Multipole Method (BEM-FMM)

Nummenmaa, Stenroos, Ilmoniemi, Okada, Hamalainen, and Raij (2013) Clin Neurophysiol 124:1995-2007

Makarov, Wartman, Daneshzand, Fujimoto, Raij, and Nummenmaa (2020) J Neural Eng 17(4):046023

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- Aapo Nummenmaa (MGH)
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- Padma Sundaram (MGH)

Questions or comments
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UG3EB034875 (AN)
R01EB035484 (SM)
P41EB015896 (BR)

NIH National Institute of Neurological Disorders and Stroke

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