

TMS and Modeling

Tommi Raij, MD, PhD

Associate Professor of Radiology, Harvard Medical School

Director, TMS Clinical Research
MGH/MIT/HMS Martinos Center for Biomedical Imaging
Boston, MA, USA

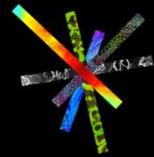


1 2/27/2026

1

COI Disclosure

Potential conflicts of interest related to this presentation: None

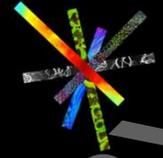


2 2/27/2026

2

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



3

Modeling – What do you mean?

= Where in the brain are we stimulating

Modeling – Why should we care?

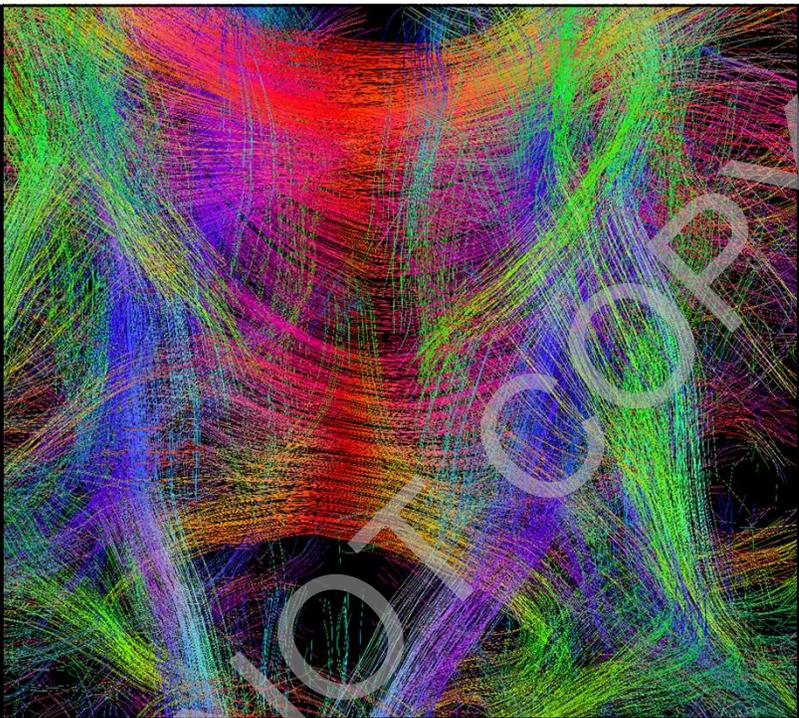
4 2/27/2026



4

Athinoula A.
Martinos Center
For Biomedical Imaging

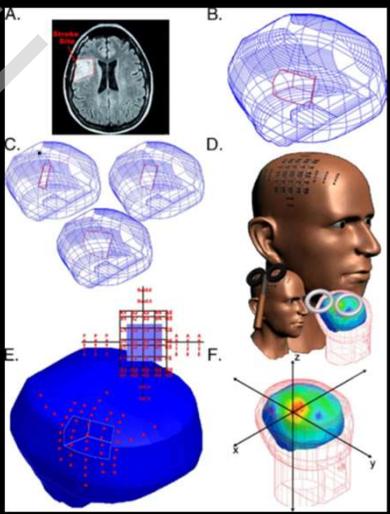
Improve safety



5 2/27/2026

5

Brain lesions, skull defects, CSF cavities



A. B.
C. D.
E. F.

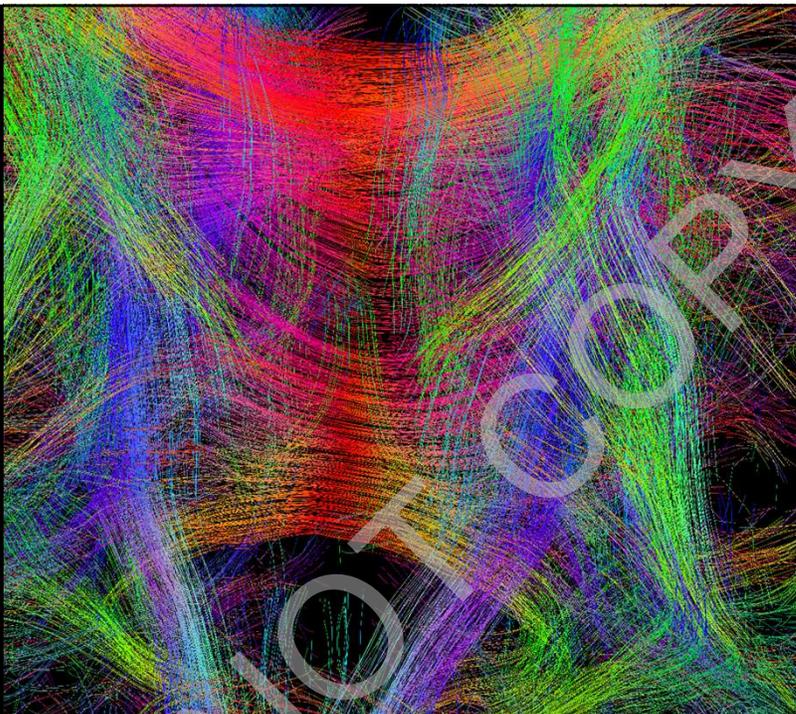
6 2/27/2026

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

6

Athinoula A.
Martinos Center
For Biomedical Imaging

**Improve
treatment
outcomes**



7 2/27/2026

7

**Which brain areas am I stimulating?
How strongly am I stimulating them?
Which large-scale networks am I dialing into?
Am I stimulating a target that gives the best
treatment outcome?**

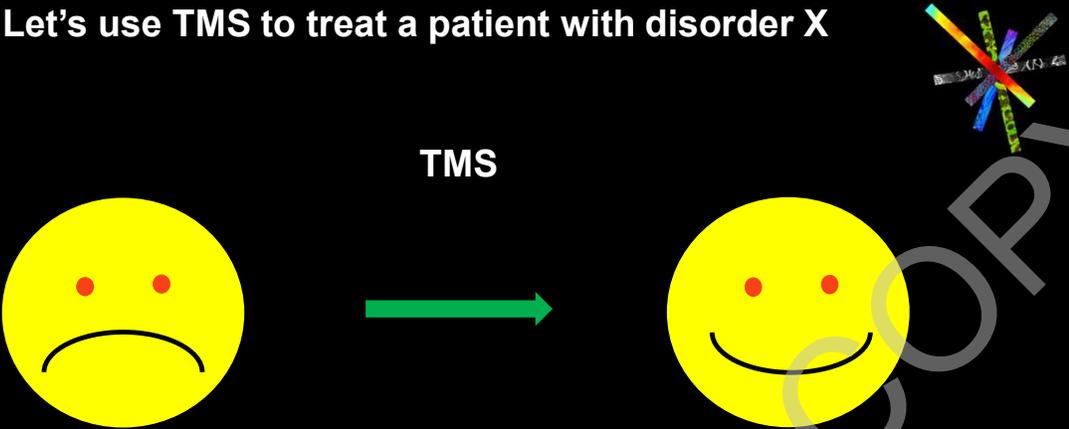


8 2/27/2026

Athinoula A.
Martinos Center
For Biomedical Imaging

8

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



TMS

9 2/27/2026

9

Where shall we place the coil?

Well, DLPFC of course!

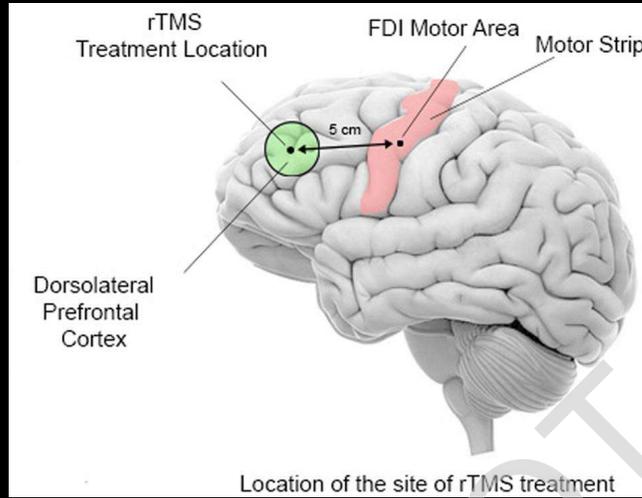
I see. Are there other TMS clinics in town?



10 2/27/2026

10

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



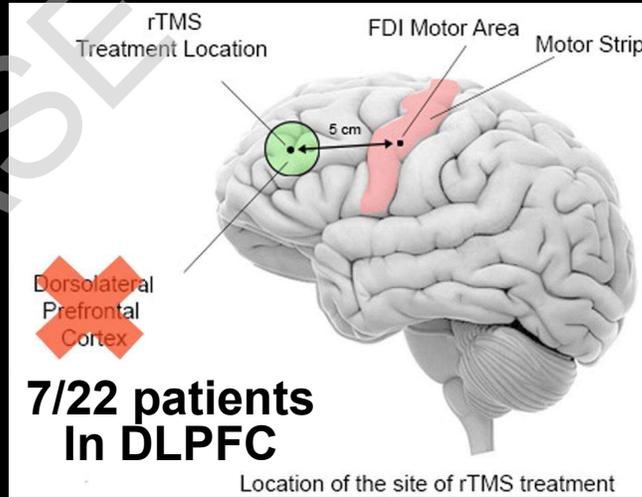
Pascual-Leone et al. (1996) Lancet 348:233-7

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

11 2/27/2026

11

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



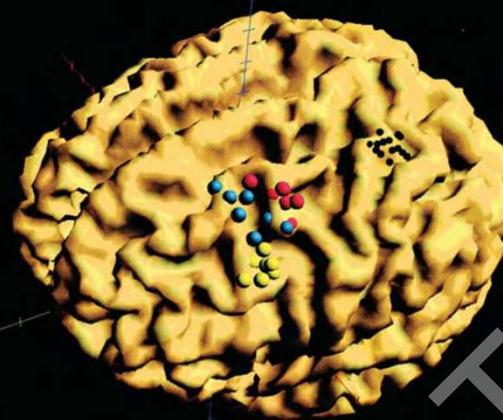
Herwig et al. (2001) Biol Psychiatry 50:58-61

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

12 2/27/2026

12

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



Variability across patients

13 2/27/2026 Herwig, Padberg, Unger, Spitzer, Schönfeldt-Lecuona (2001) *Biological Psychiatry* 50(1):58-61

13

MNI or Talairach coordinates

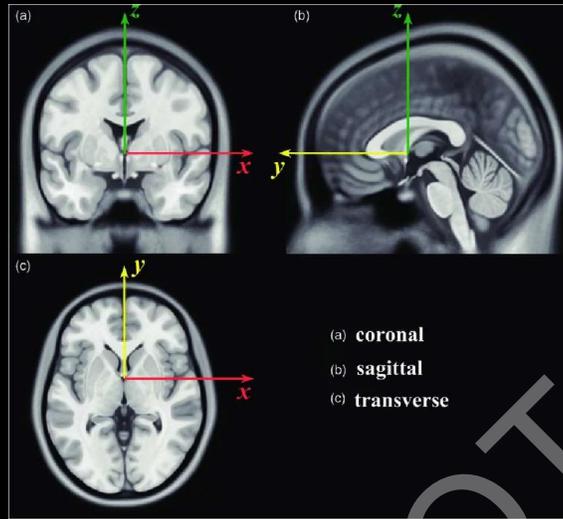
	Tx	Ty	Tz	MNIx	MNIy	MNIz	Treatment
DLPFC Regions^b							
Study/Site							
Herwig <i>et al.</i> 2001 (37) 5 cm Stimulation Site	-42	17	52				
Herbsman <i>et al.</i> 2009 (36) 5 cm Stimulation Site	-42	20	49				
Herbsman <i>et al.</i> 2009 (36) 5 cm Sham Site	-39	17	47				
Average 5 cm Coordinates	-41	18	49	-41	16	54	
Herbsman <i>et al.</i> 2009 (36) Responders	-46	25	44	-46	23	49	
Herbsman <i>et al.</i> 2009 (36) Nonresponders	-41	19	50	-41	17	55	
Herwig <i>et al.</i> 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 <i>et al.</i> 2001 (25) TMS Target	-40	32	30	-40	31	34	
Cho and Strafella 2009 (53) TMS Target	-40	32	30	-40	31	34	
Fitzgerald <i>et al.</i> 2009 (35) TMS Target	-46	45	35	-46	45	38	
Rusjan <i>et al.</i> 2010 (41) TMS Target	-50	31	32	-50	30	36	

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

14 2/27/2026

14

Talairach and MNI coordinate systems...



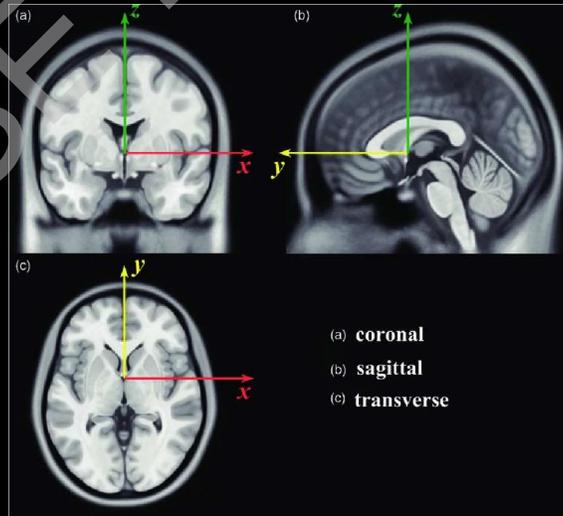
Picture from: Wang et al. (2016) *Textile Res J* 86(3):318-24.



15 2/27/2026

15

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



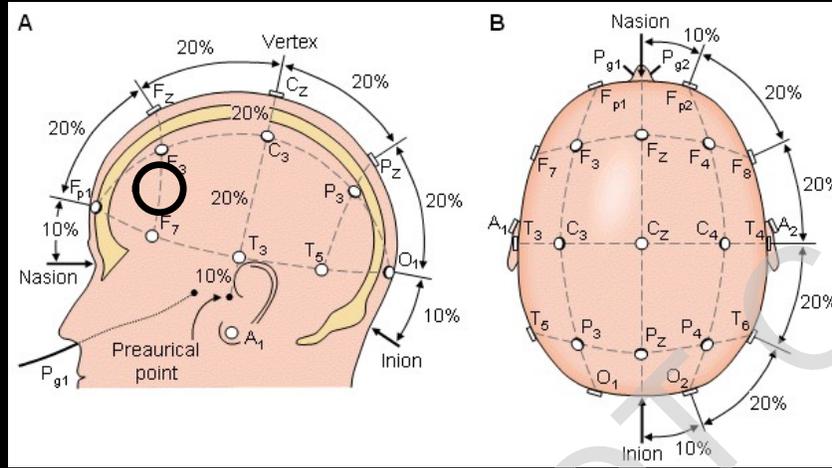
Picture from: Wang et al. (2016) *Textile Res J* 86(3):318-24.



16 2/27/2026

16

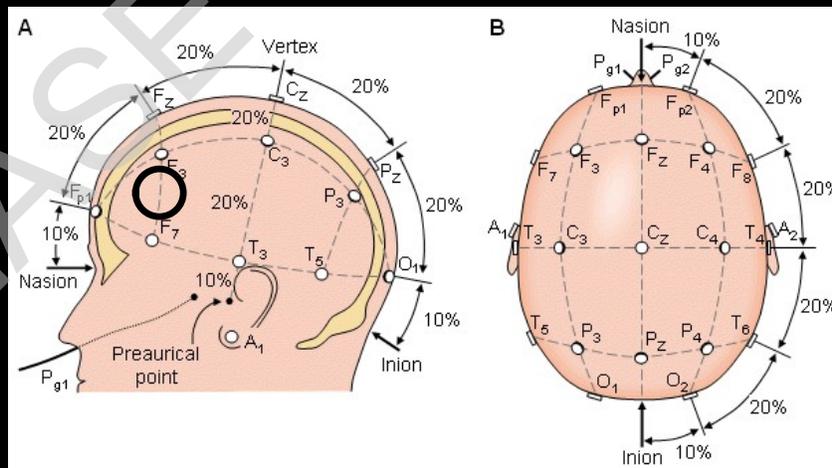
EEG International 10-20 System (F5, F3, F3-Beam)



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

17

... but which gyrus in my patient is under F5? Or F3?

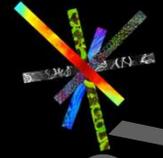


Herwig et al. (2003) Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topography* 16(2):95-9
 Beam et al. (2020) An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimulation* 2:50-4

18

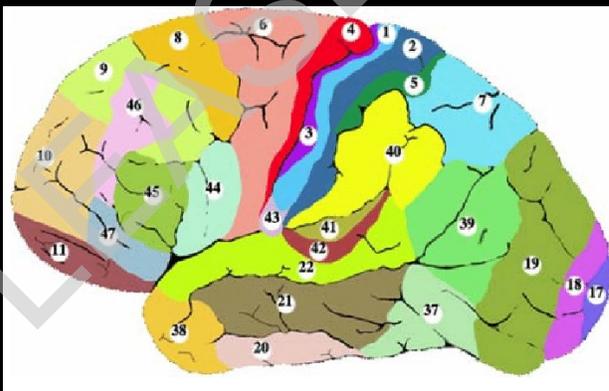
MNI, Talairach, EEG electrode methods:

- Affordable (unless the treatment fails)
- Easy (no individual MRI or TMS navigator required)
- Are based on something else than cortical anatomy
- Appear to give worse clinical outcomes
- Why are we navigating on the scalp if our goal is to target a specific brain area?



19

Cortical anatomy (BA9/BA46 junction, Ant MFG)

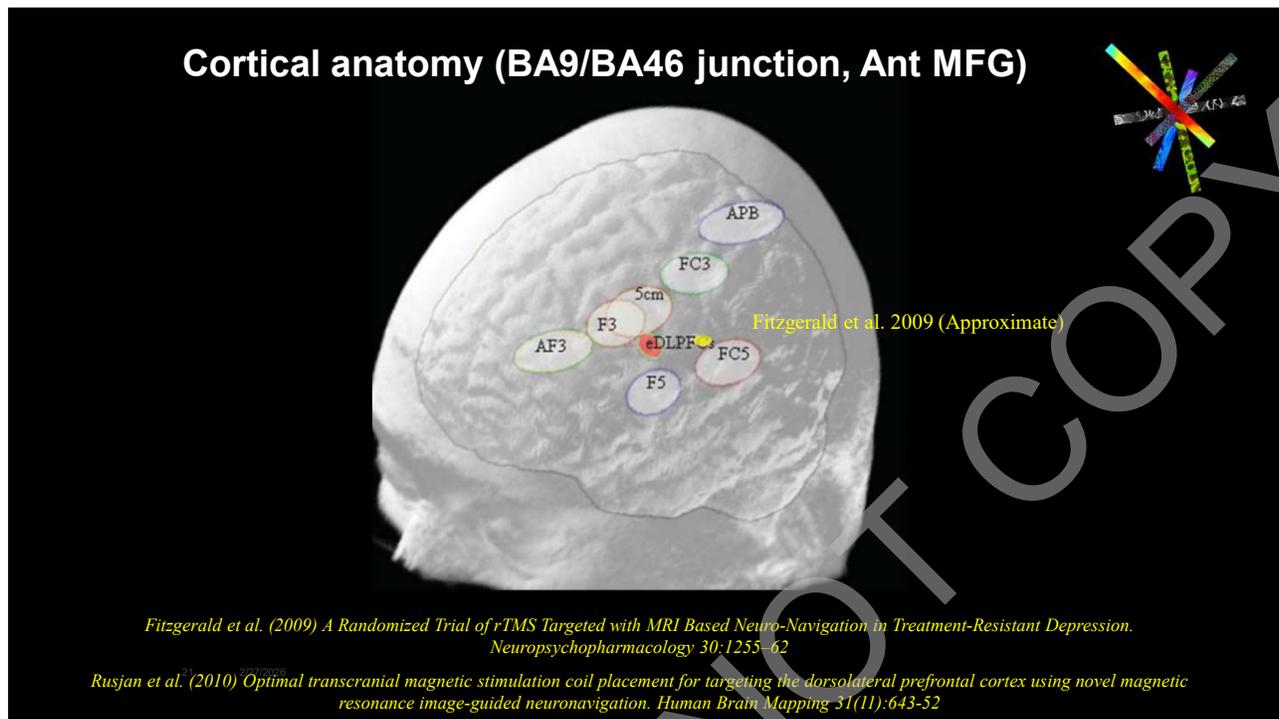


Fitzgerald et al. (2009) Neuropsychopharmacology 30:1255-62

20 2/27/2026

Picture on left from: Vonsattel et al. (2009) Acta Neuropathol 115(5):309-32

20



21

Hypotheses:

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

22 2/27/2026

Athenaia A.
Martinos Center
For Biomedical Imaging

22

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 enough about the individual anatomy.

23 2/27/2026



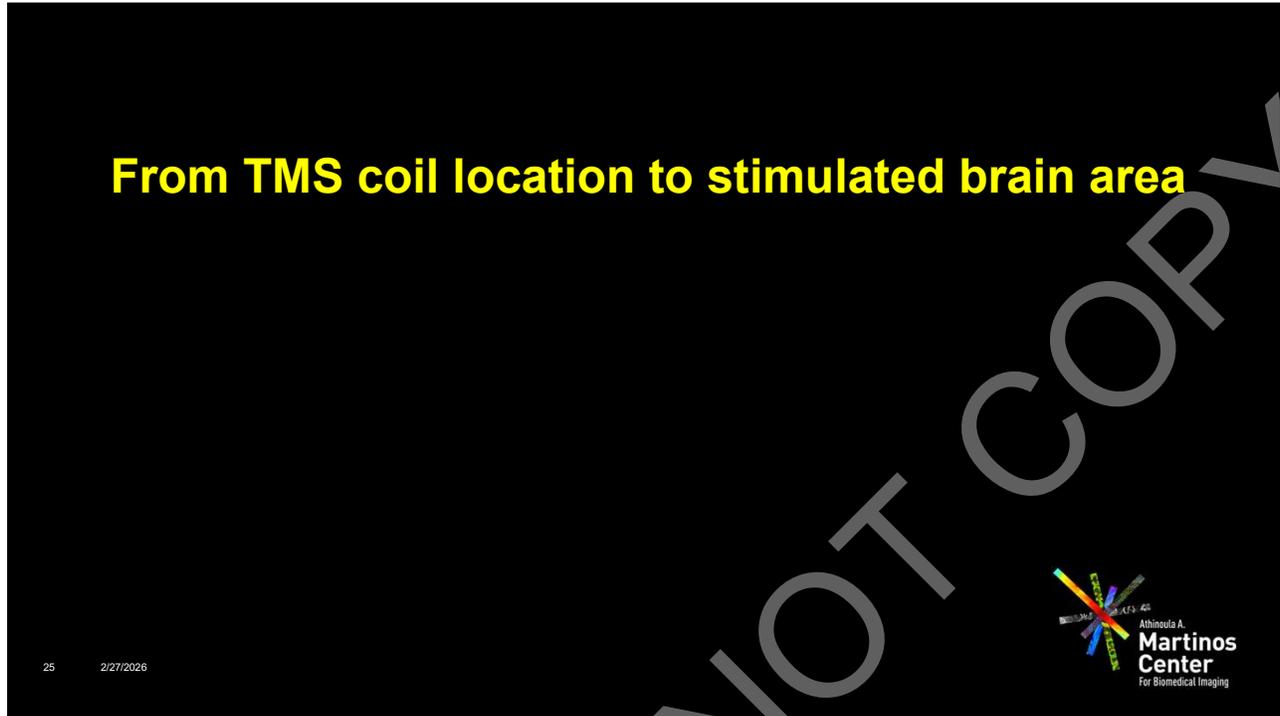
23

Methods

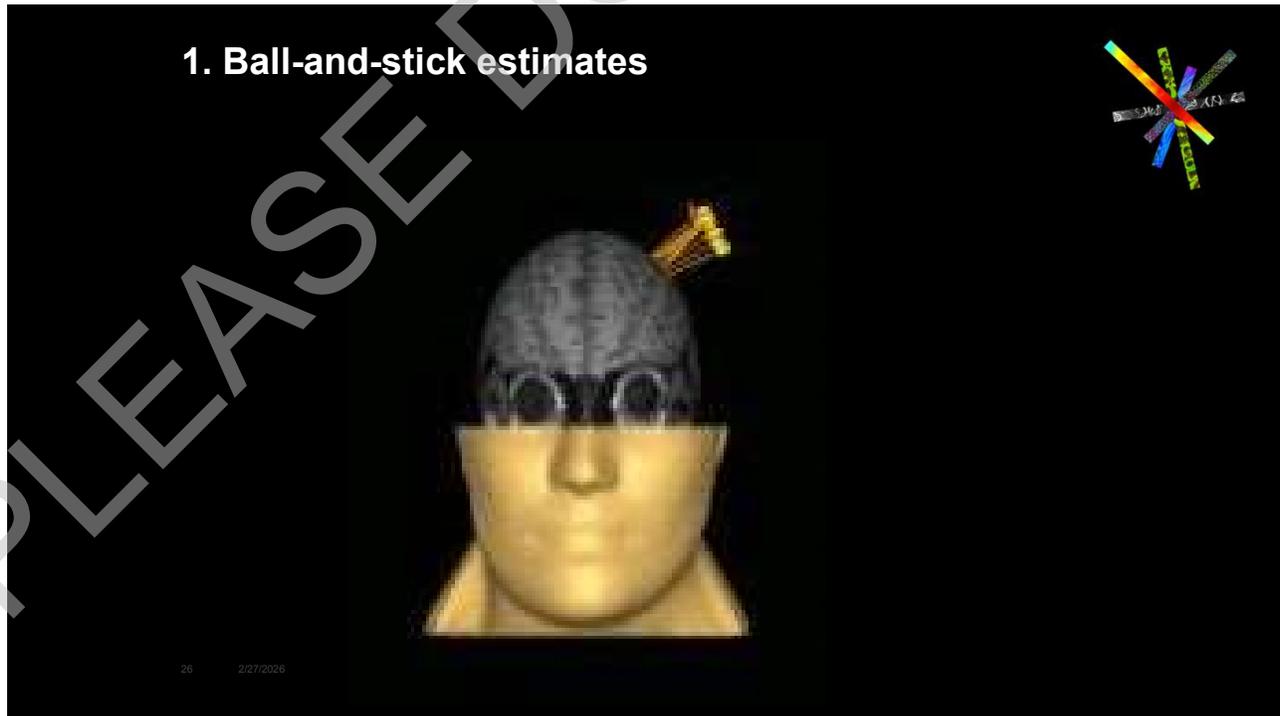
24 2/27/2026



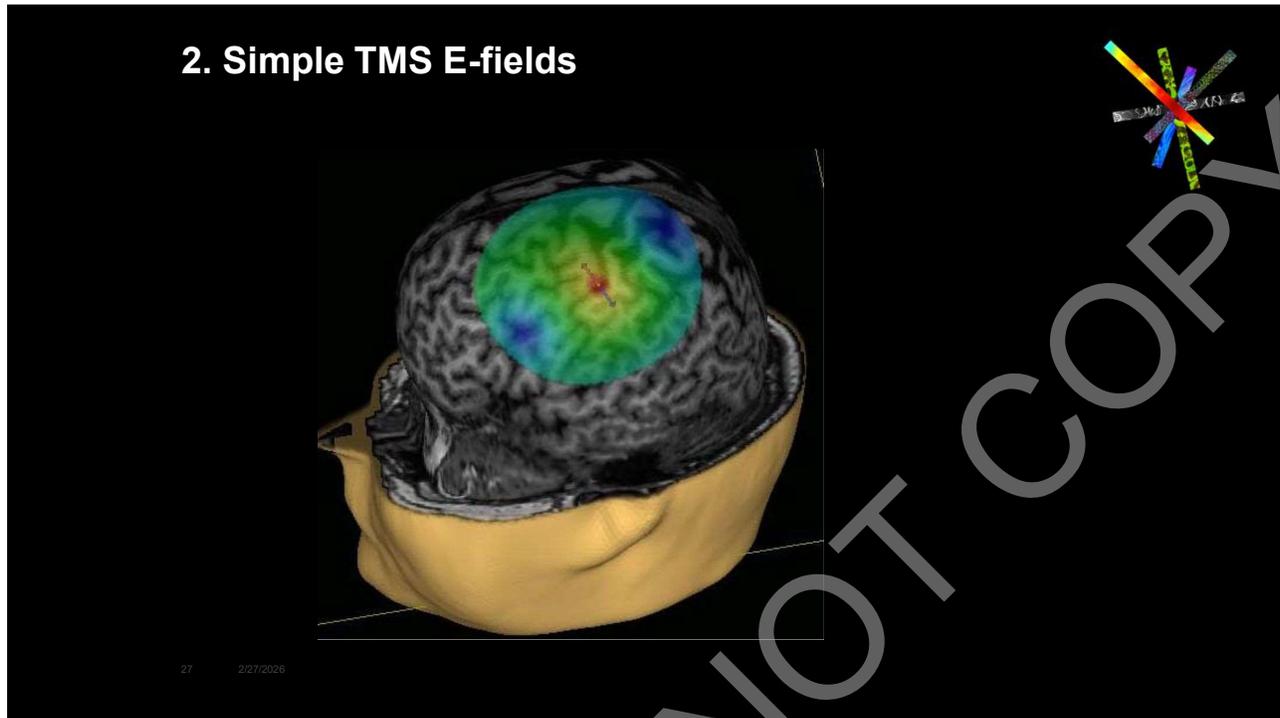
24



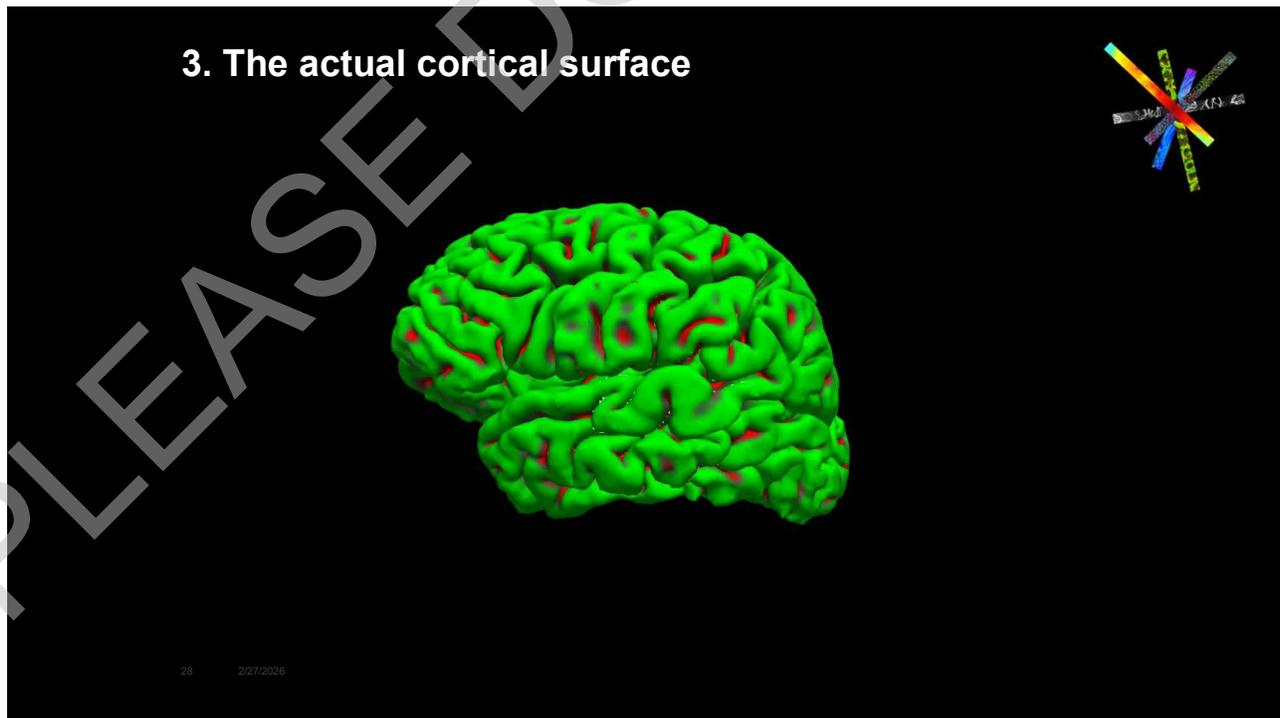
25



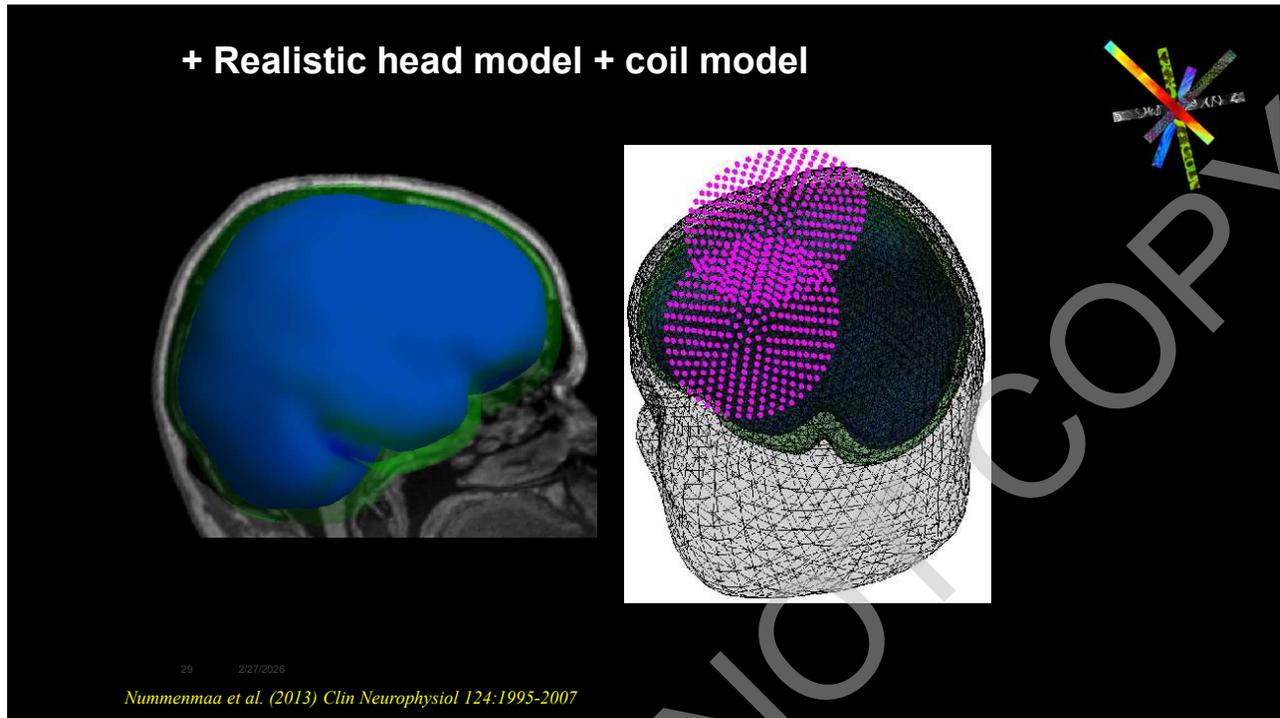
26



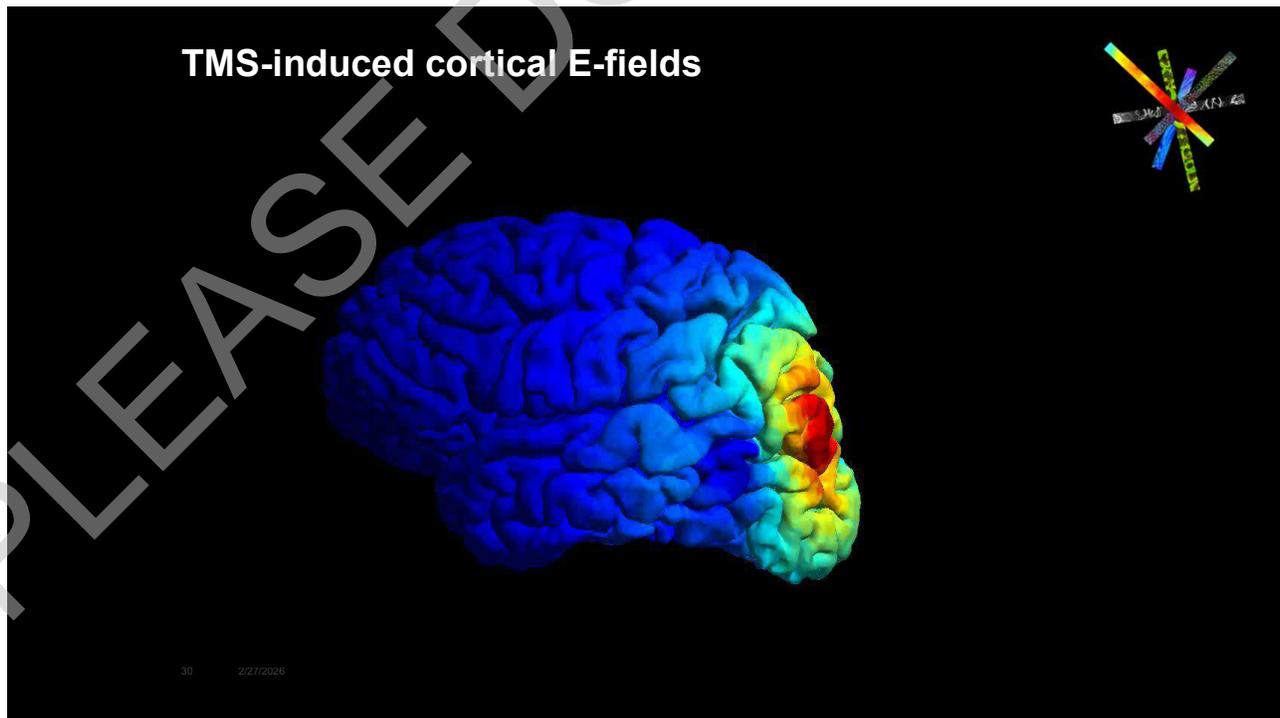
27



28

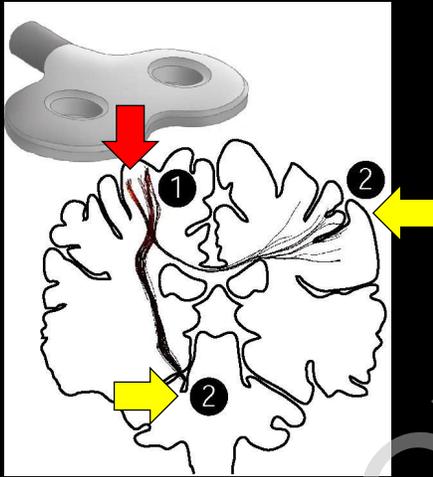


29



30

Primary + Secondary activations



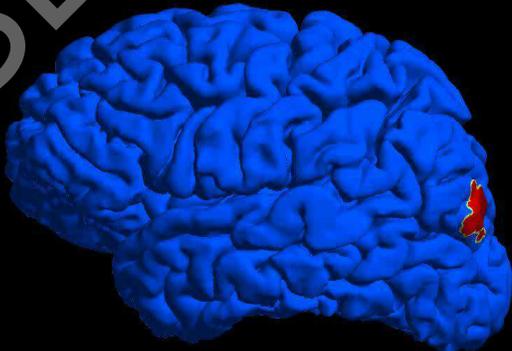
The diagram shows a lateral view of the brain with a TMS coil positioned above it. A red arrow points to region 1, and yellow arrows point to region 2. A colorful asterisk-like graphic is in the top right corner.

31 2/27/2026

Diana, Raj, Melis, Nummenmaa, Leggio, Bonci (2017) Nature Reviews Neuroscience 18:685-93

31

Primary TMS activations

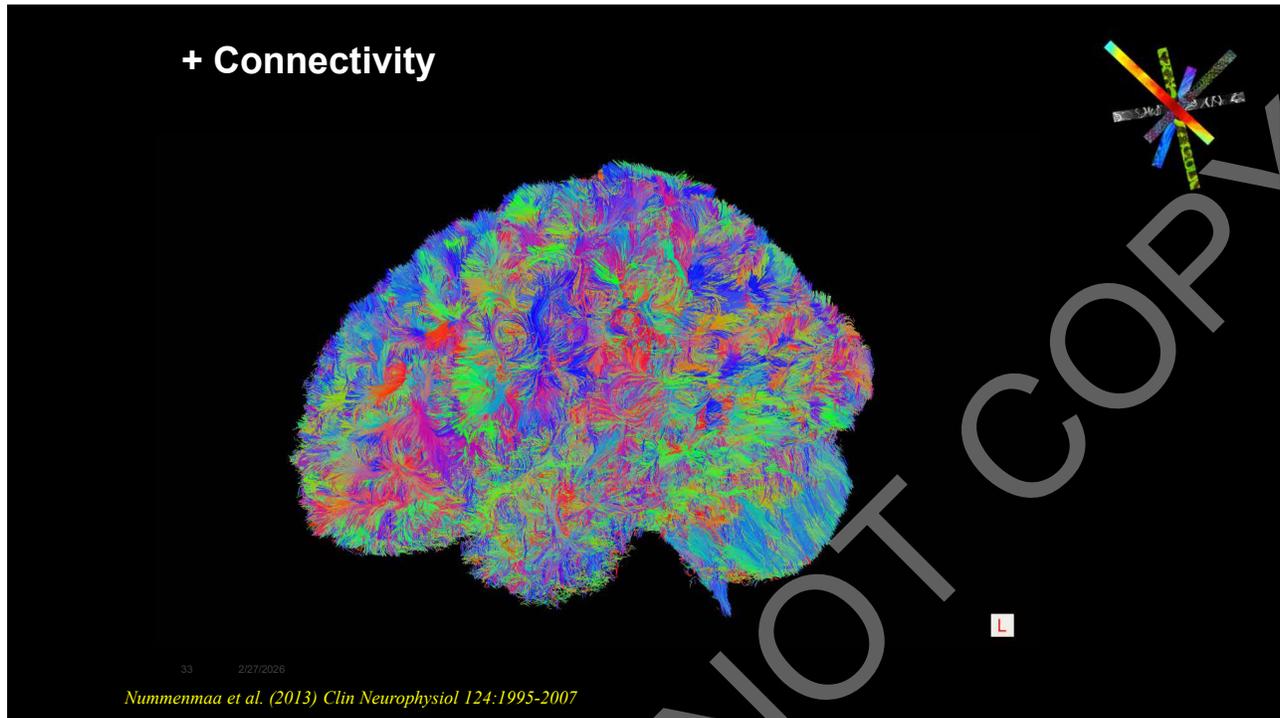


A 3D model of a human brain with a small red area on the lateral surface. A colorful asterisk-like graphic is in the top right corner.

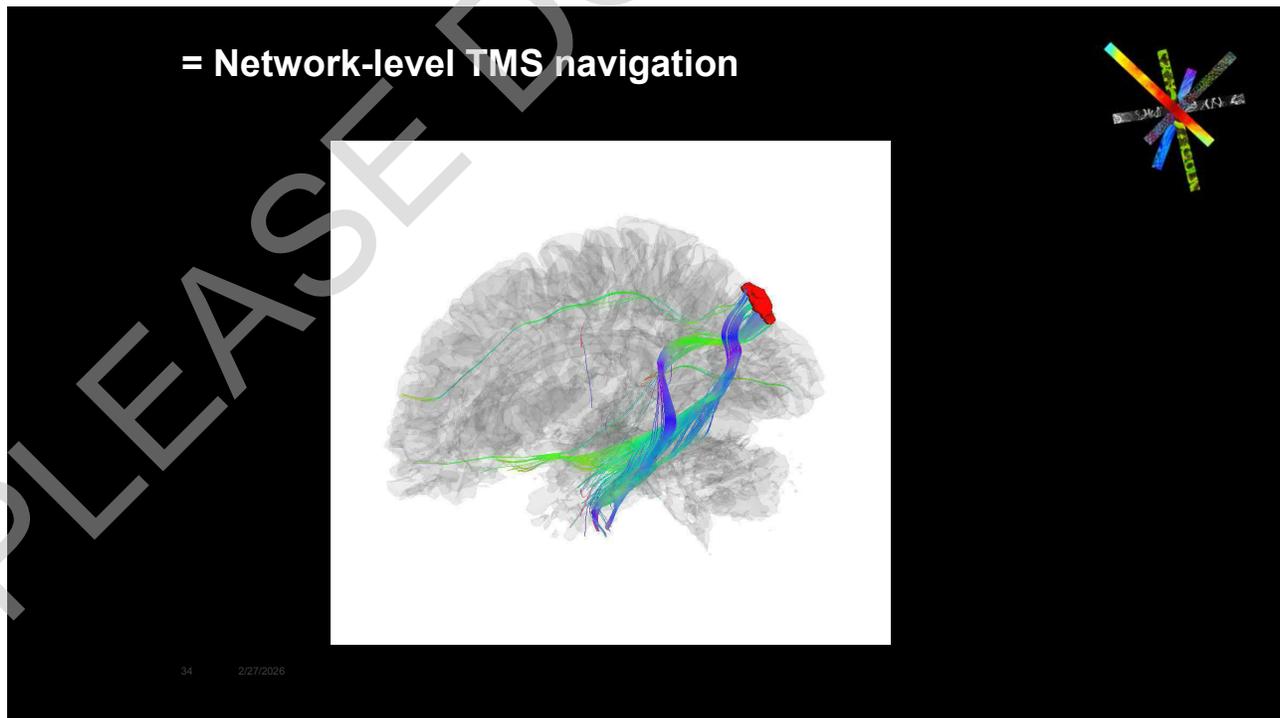
32 2/27/2026

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

32



33



34

Do we need individual MRIs?

Individual cortical folding anatomy. 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

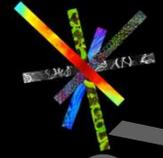
35

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



36

Remember TMS is a superficial stimulation method



37

Remember TMS is a superficial stimulation method



Therefore, the cortical surface is the relevant navigational space

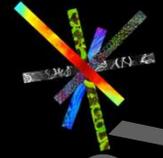
38

Natively surface-based intersubject brain alignment methods

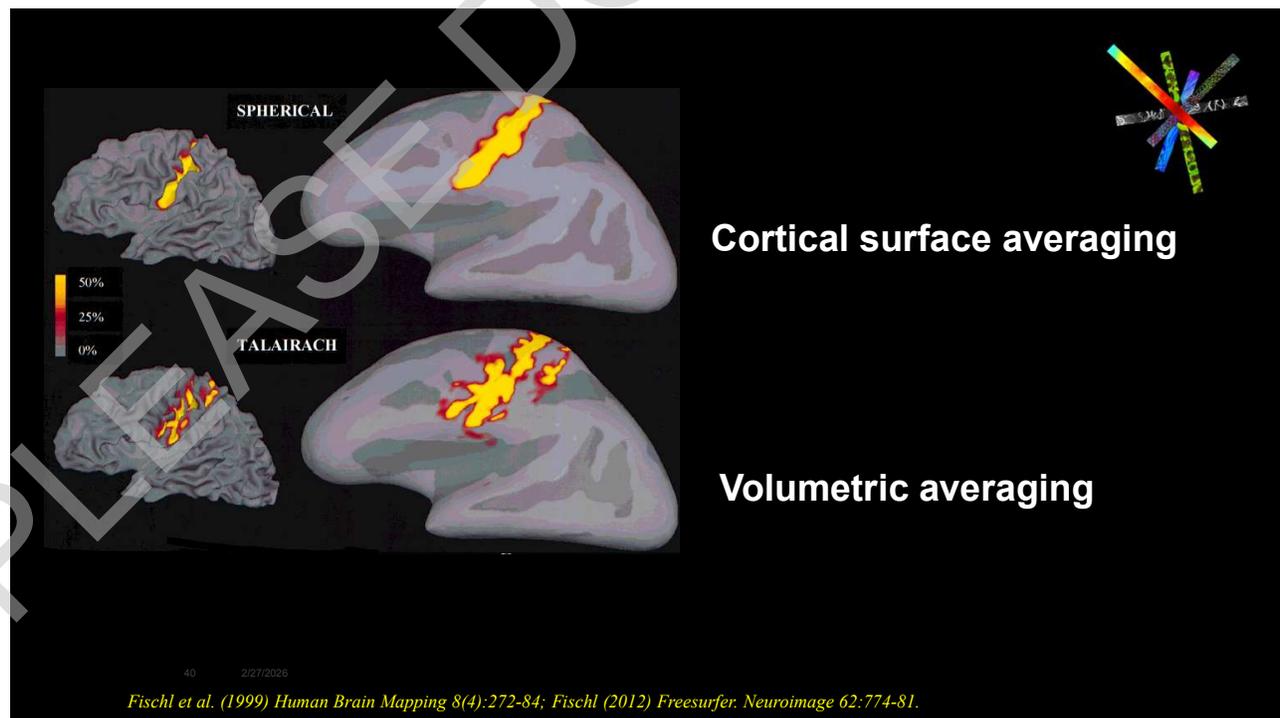
Surface-based morphing (+ 3D volumetric morphing)

FreeSurfer cortical parcellation

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

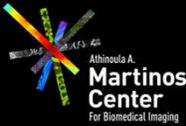


39



40

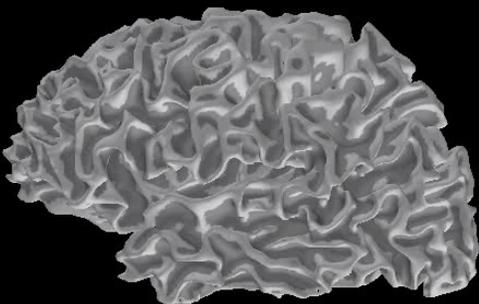
How does aligning (morphing) cortical surfaces across patients work?



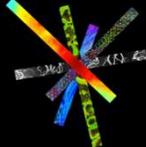
41 2/27/2026

41

Surface-based morphing



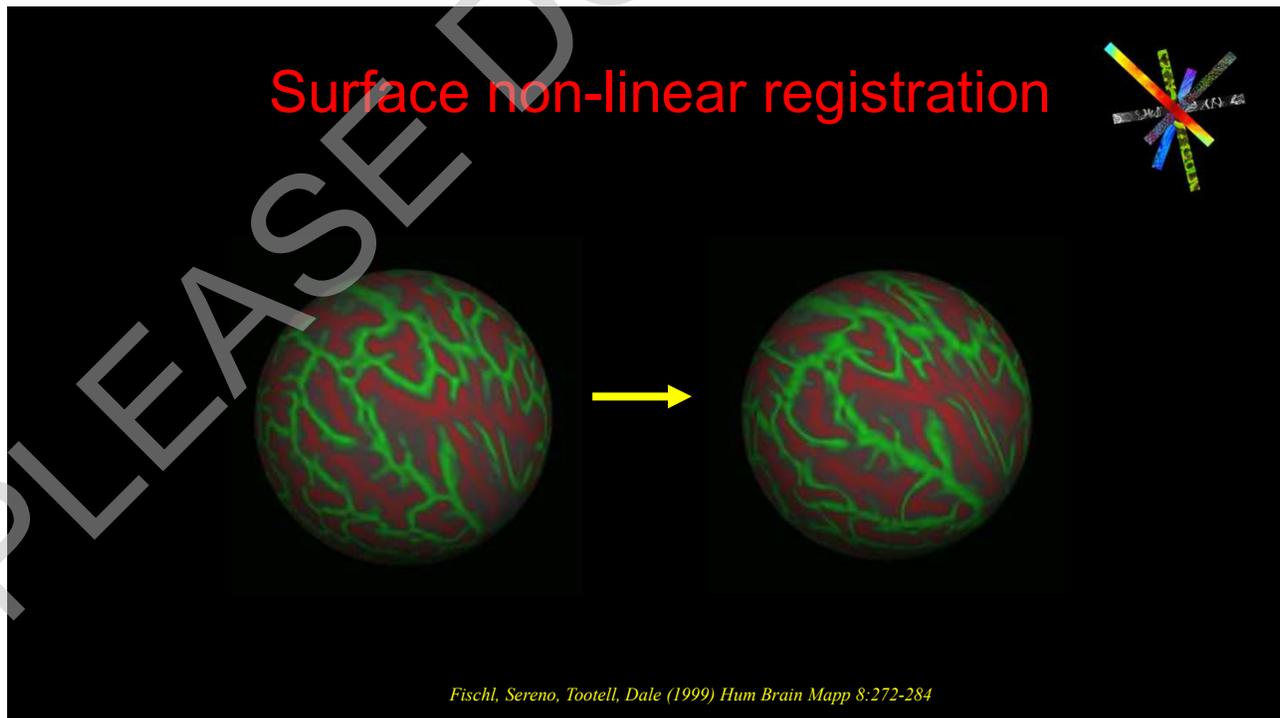
No data loaded.



42

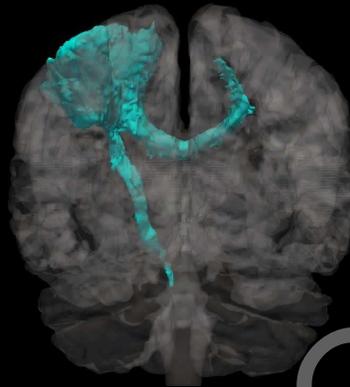


43



44

3D volumetric morphing



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

45

How will we use this knowledge?

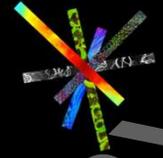
Example 1: Let's find out where we should stimulate to alleviate symptoms of X

46 2/27/2026



46

Individual E-field maxima



[Currently unpublished data removed here]

47 2/27/2026

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

47

Individual clinical outcomes



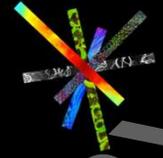
[Currently unpublished data removed here]

48 2/27/2026

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

48

Group-level E-field (average)



[Currently unpublished data removed here]

49 2/27/2026

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

49

1. Stimulate N patients, compute individual E-fields



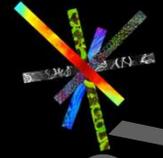
[Currently unpublished data removed here]

50 2/27/2026

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

50

2. Morph individual E-fields to a standard brain



[Currently unpublished data removed here]

51 2/27/2026

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

51

3. Relationship between E-fields and outcomes



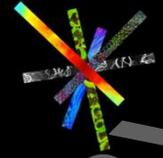
[Currently unpublished data removed here]

52 2/27/2026

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

52

4. Use statistical methods to reveal significance



[Currently unpublished data removed here]

53 2/27/2026

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

53

Next, we plug in connectivity from TMS targets

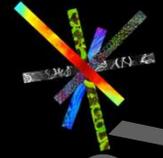
**Example 2: Let's find out where the connections go
in patients that improve vs. those that do not**

54 2/27/2026



54

1. Individual E-field maxima -> seeds



[Currently unpublished data removed here]

55 2/27/2026

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

55

2. Morph individual seeds to standard brain



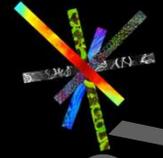
[Currently unpublished data removed here]

56 2/27/2026

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

56

3. Relationship between seed connectivity and outcomes



[Currently unpublished data removed here]

57 2/27/2026

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

57

4. Use statistical methods to reveal significance



[Currently unpublished data removed here]

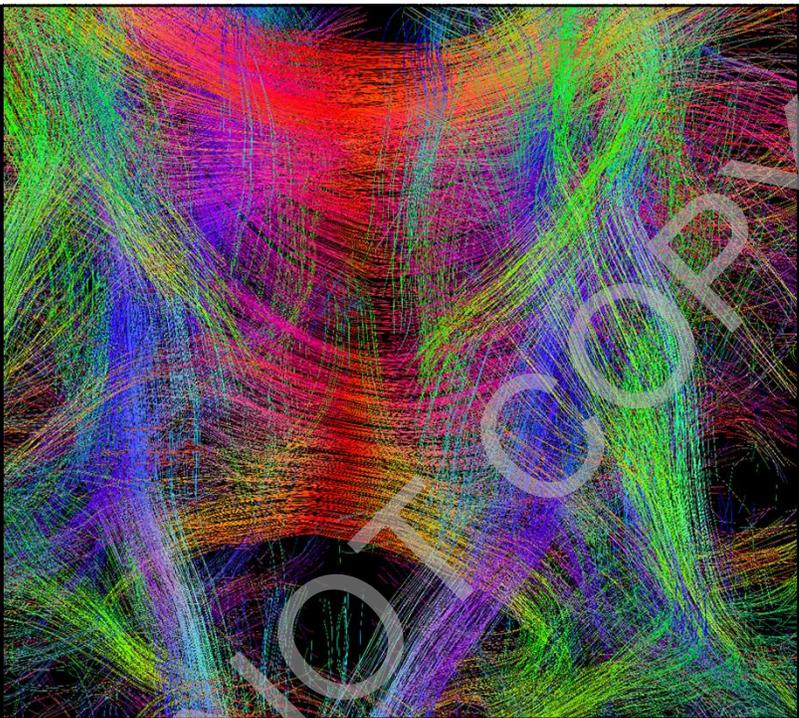
58 2/27/2026

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

58

Athinoula A.
Martinos Center
 For Biomedical Imaging

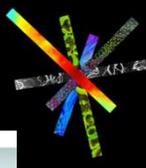
Improve non-clinical studies



59 2/27/2026

59

Prove that the intended targets were activated





ARTICLE

Received 20 May 2013 | Accepted 10 Sep 2013 | Published 14 Oct 2013 DOI: 10.1038/ncomms3585

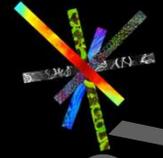
Evidence for distinct human auditory cortex regions for sound location versus identity processing

Jyrki Ahveninen¹, Samantha Huang¹, Aapo Nummenmaa¹, John W. Belliveau^{1,2}, An-Yi Hung¹, Iiro P. Jääskeläinen³, Josef P. Rauschecker⁴, Stephanie Rossi¹, Hannu Tiitinen³ & Tommi Raij¹

60 2/27/2026 *Ahveninen et al. (2013) Nature Communications 4:2585*

60

Examine which brain areas were responsible for the experimental effects



ARTICLE IN PRESS

Archival Report

Biological Psychiatry

Prefrontal Cortex Stimulation Enhances Fear Extinction Memory in Humans

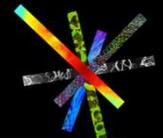
Tommi Raij, Aapo Nummenmaa, Marie-France Marin, Daria Porter, Sharon Furtak, Kawin Setsompop, and Mohammed R. Milad

61 2/27/2026

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

61

Quality control: TMS coil center and tilt

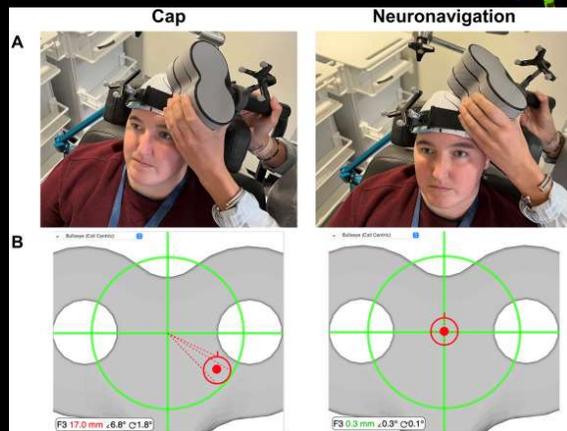


TMS coil center should be on the scalp tangential to the local head curvature.

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

62

Athinoula A.
Martinos Center
For Biomedical Imaging

Take-home messages



63 2/27/2026

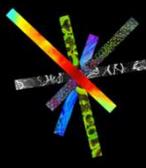
63

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)

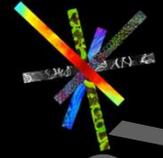


64

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



65

Thank you

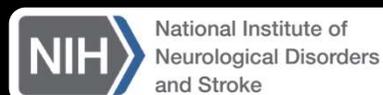
- Aapo Nummenmaa (MGH)
- Sergey Makaroff (WPI/MGH)
- Padma Sundaram (MGH)

Questions or comments

- raij@nmr.mgh.harvard.edu

Funding

R01NS126337 (TR)
 R01MH128421 (AN)
 R01DC020891 (AN)
 UG3EB034875 (AN)
 R01EB035484 (SM)
 P41EB015896 (BR)



66