TMS and Modeling

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1 10/24/2024

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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 magnetoencephalogaphy
- 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?

How the TMS-induced E-fields influence the brain

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Modeling – Why should we care?

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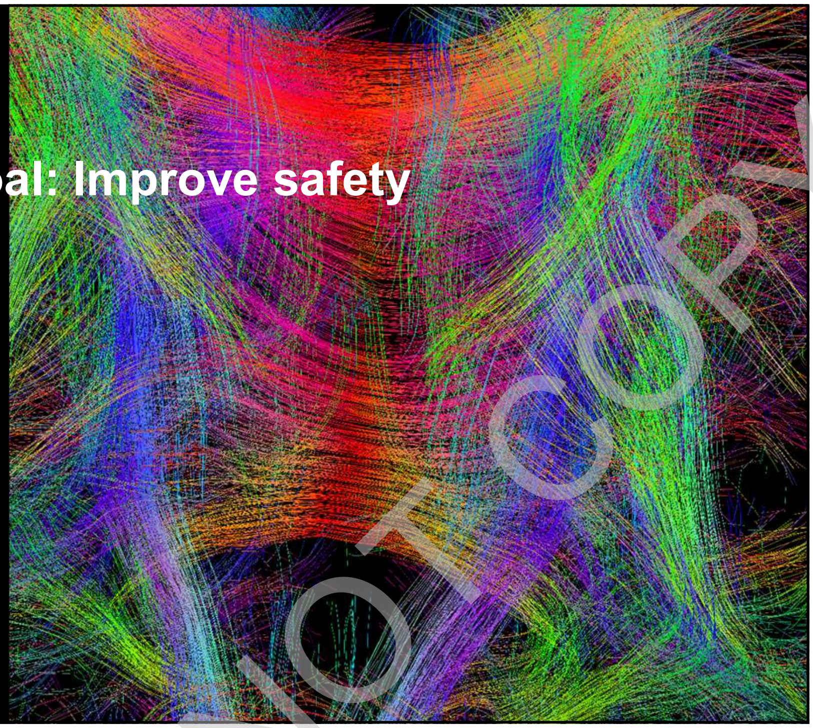
Goal: Improve safety



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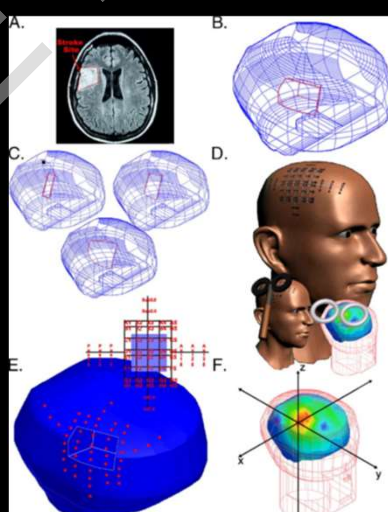
Brain lesions, skull defects, CSF cavities



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

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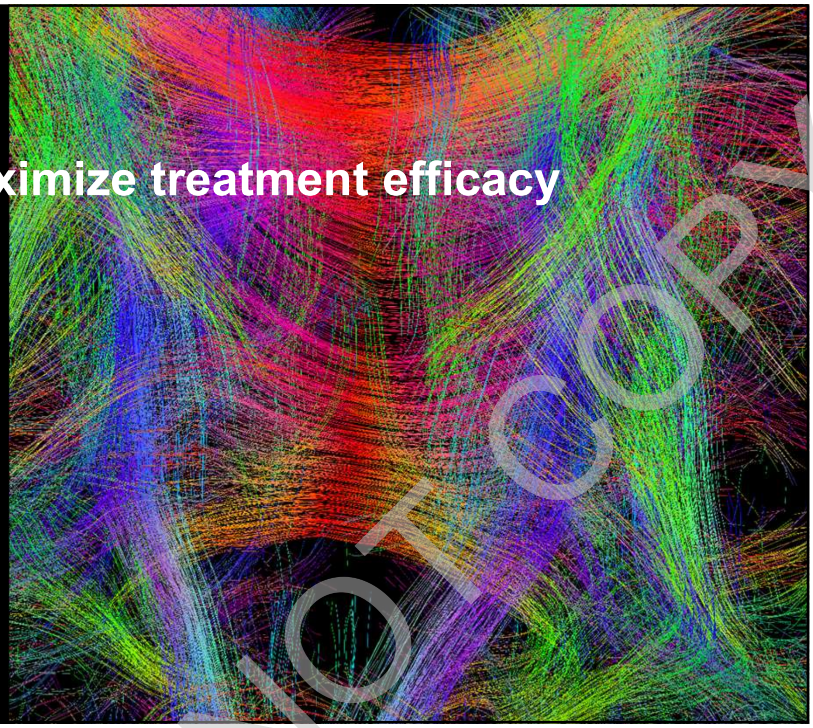
Goal: Maximize treatment efficacy



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Which brain area am I stimulating?

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How strongly am I stimulating it?

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From TMS coil location to stimulated brain area

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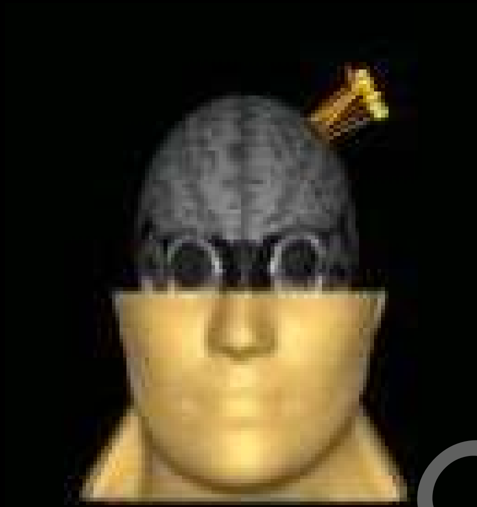
1. Ball-and-stick estimates



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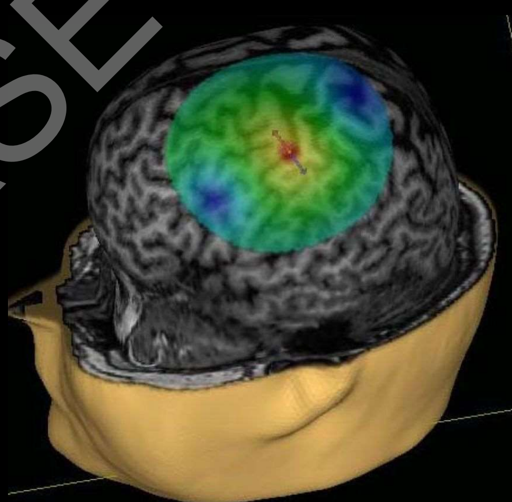
2. Simple TMS E-fields



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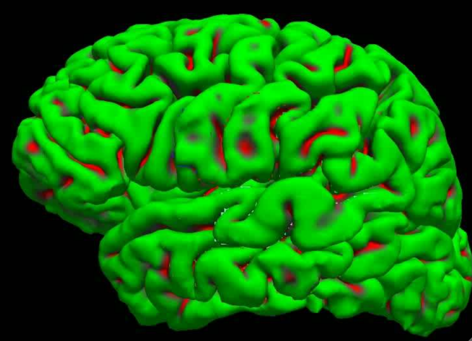
3. More realistic E-fields



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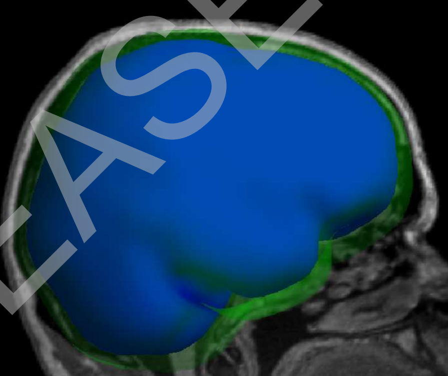
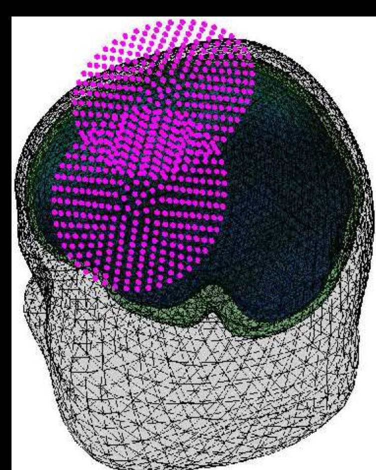
= Realistic head model + coil model





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

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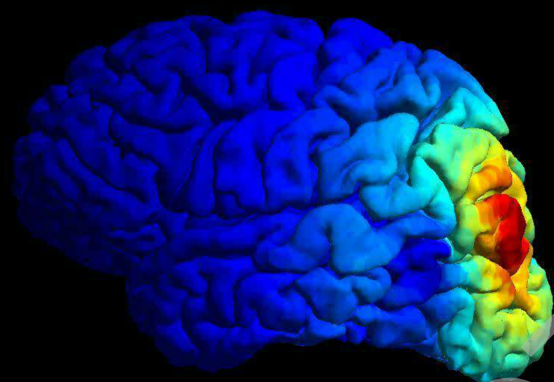
TMS-induced cortical E-fields



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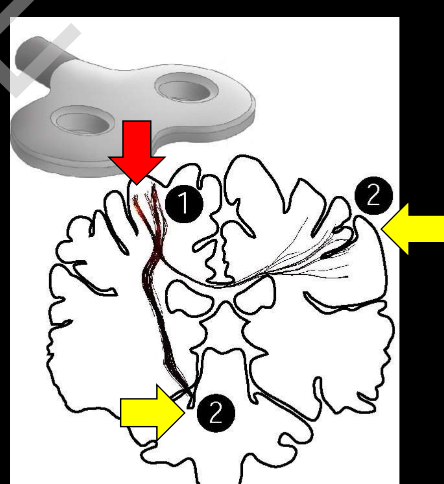
Primary + Secondary activations



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

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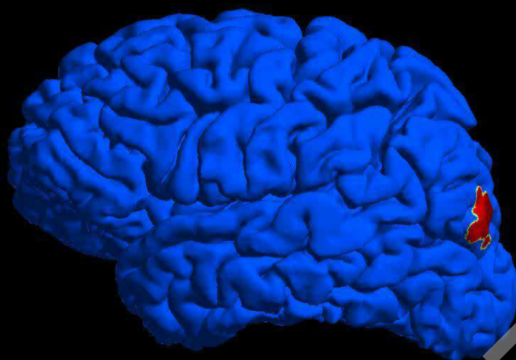
Primary TMS activations



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

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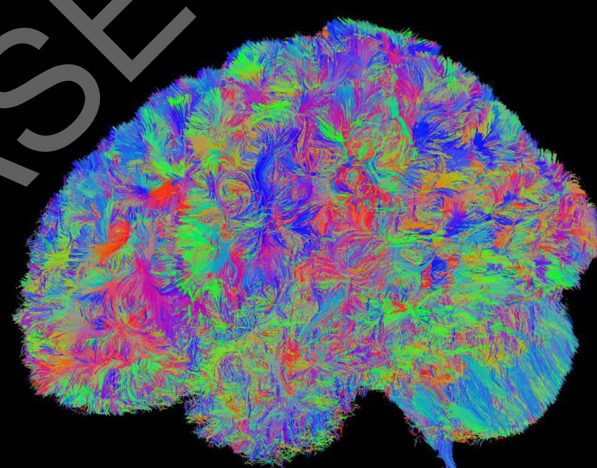
+ Connectivity



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

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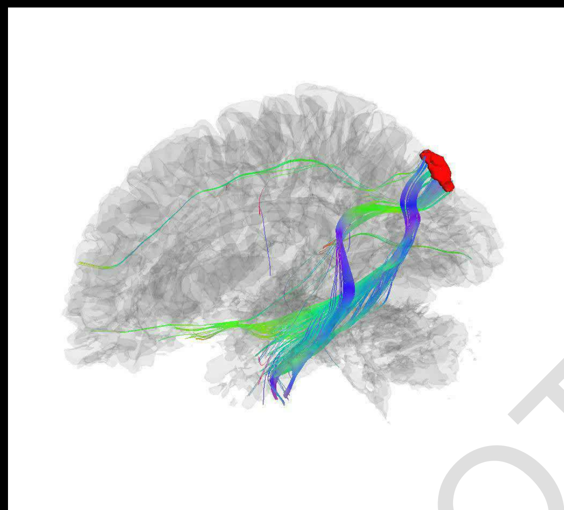
= Network-level TMS navigation



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How will we use this knowledge?

Example 1: Let's find out where we should stimulate

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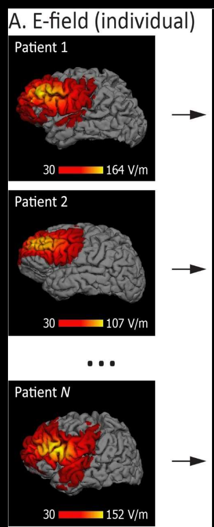
1. Stimulate patients, compute individual E-fields



… Some slides removed, yet unpublished data

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How will we use this knowledge?

Example 2: Let's find out where the connections go

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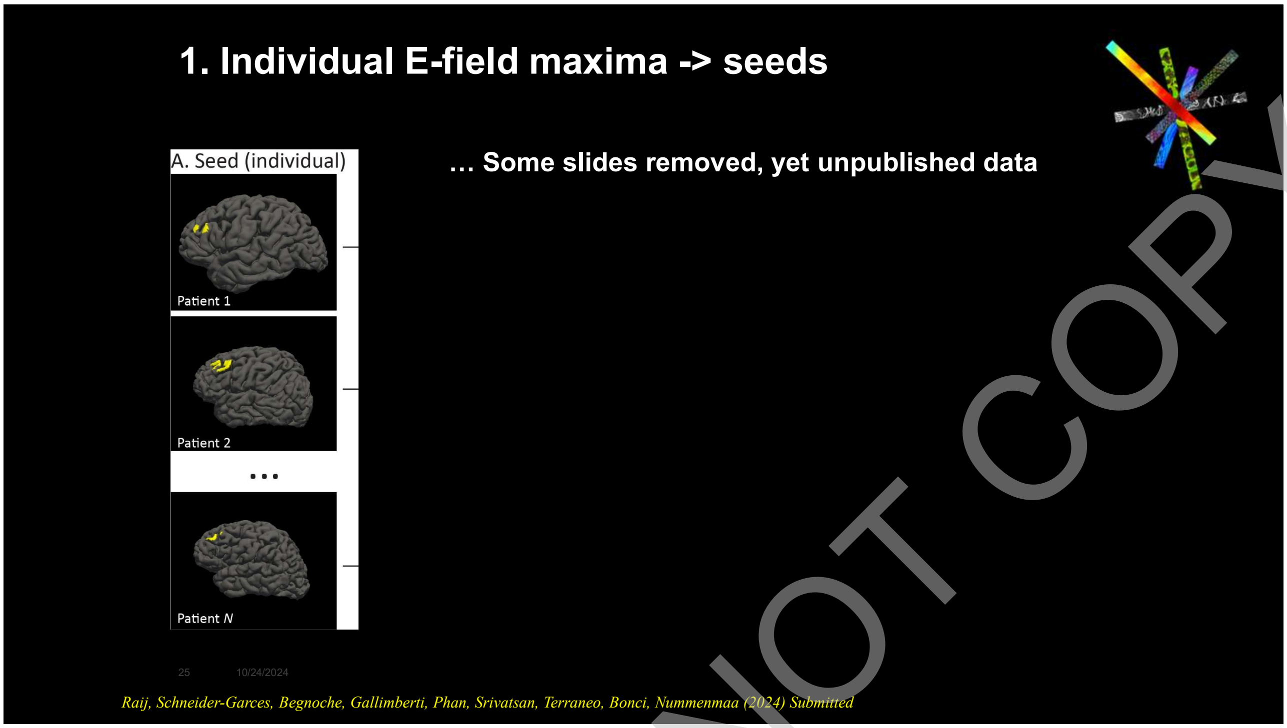
1. Individual E-field maxima -> seeds
A. Seed (individual)
Patient 1
Patient 2
…
Patient N
… Some slides removed, yet unpublished data
Raij, Schneider-Garces, Begnoche, Gallimberti, Phan, Srivatsan, Terraneo, Bonci, Nummenmaa (2024) Submitted
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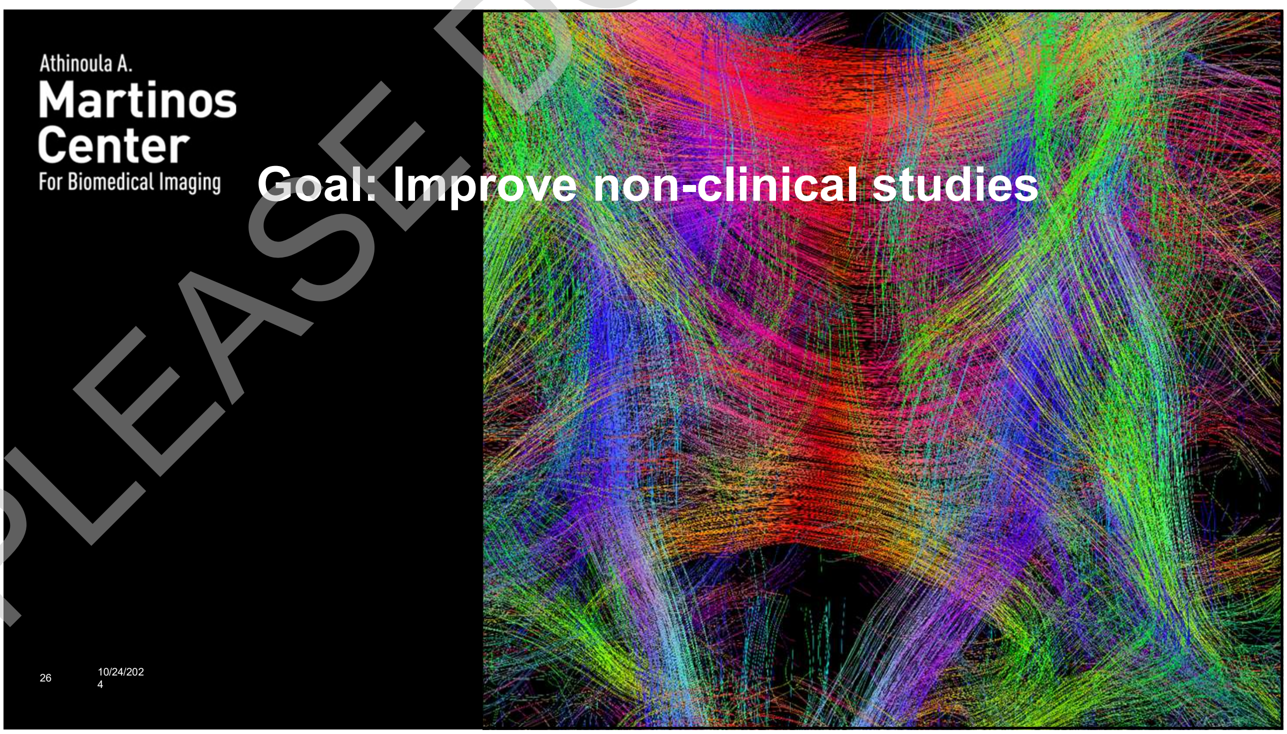
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Goal: Improve non-clinical studies
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Prove that the intended targets were activated

nature COMMUNICATIONS

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 Ahveninen[1], Samantha Huang[1], Aapo Nummenmaa[1], John W. Belliveau[1,2], An-Yi Hung[1], Iiro P. Jääskeläinen[3], Josef P. Rauschecker[4], Stephanie Rossi[1], Hannu Tiitinen[3] & Tommi Raij[1]

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

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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

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Raij, Nummenmaa, Marin, Porter, Furtak, Setsompop, Milad (2018) Biological Psychiatry

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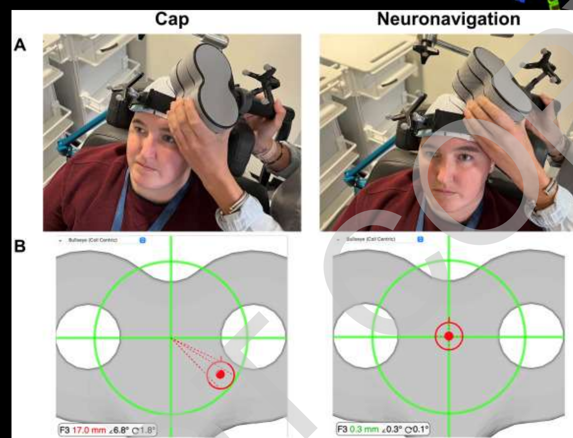
Quality control: TMS coil center and tilt

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

Common mistakes:

- ❑ Gap
- ❑ Incorrect roll
- ❑ Incorrect pitch

These influence the E-field maximum location and intensity, leading to loss of activation, or activation of different areas and mechanisms than intended.



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

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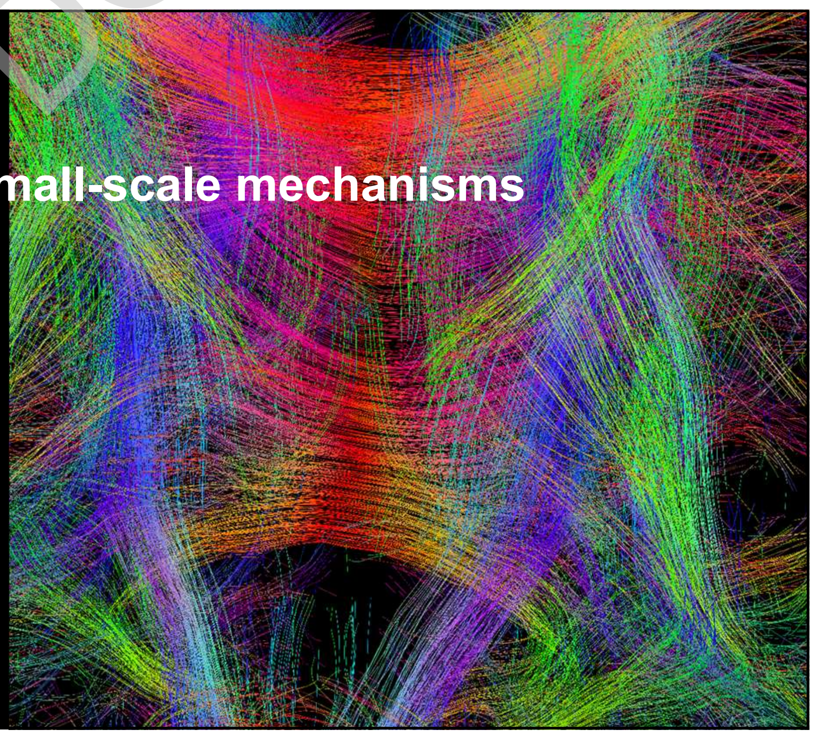
Goal: Small-scale mechanisms



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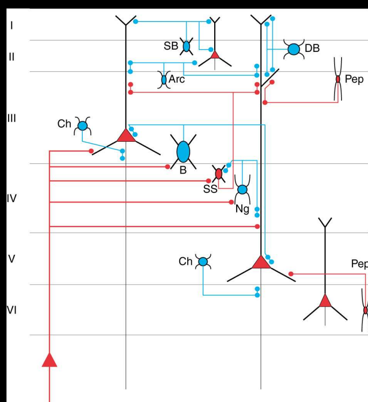
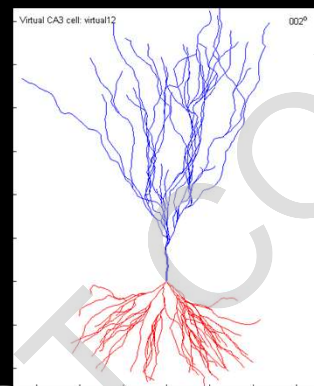
… at different spatial resolutions:

Mesoscopic



Microscopic



Source:
http://www.krasnow.gmu.edu/alexei/cinema/virt3/intro.html

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Nummenmaa et al. (2013) Clin Neurophysiol 124:1995-2007; Mountcastle (1998) Perceptual Neuroscience; Diana et al., (2017) Nat Rev Neurosci 18(11):685-93

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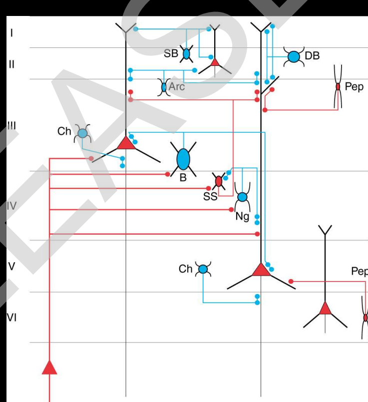
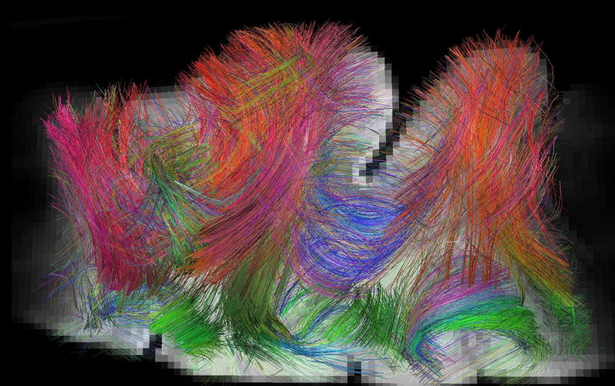
… in two different types of brain tissue:

Grey matter



White matter



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Nummenmaa et al. (2013) Clin Neurophysiol 124:1995-2007; Mountcastle (1998) Perceptual Neuroscience; Diana et al., (2017) Nat Rev Neurosci 18(11):685-93

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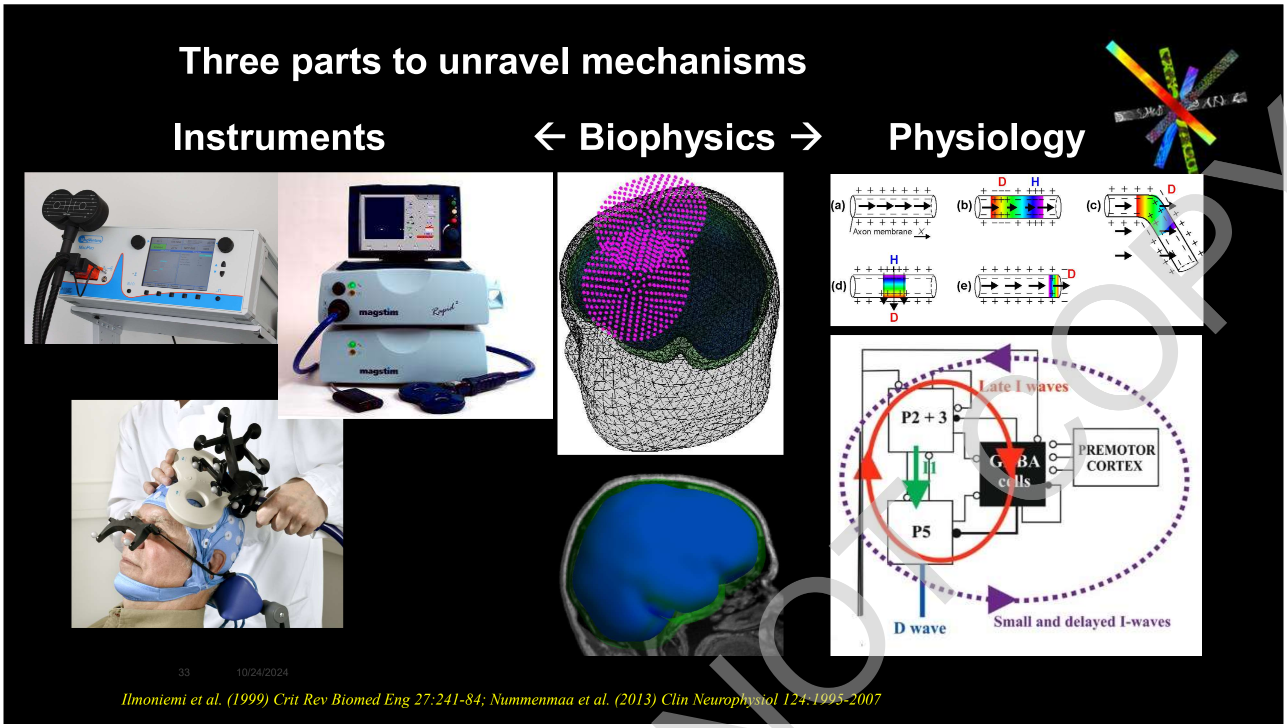

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Modeling: Microscopic level

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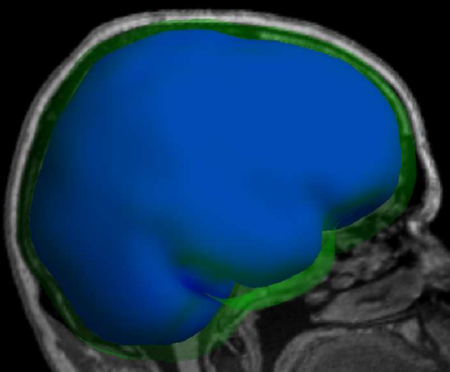
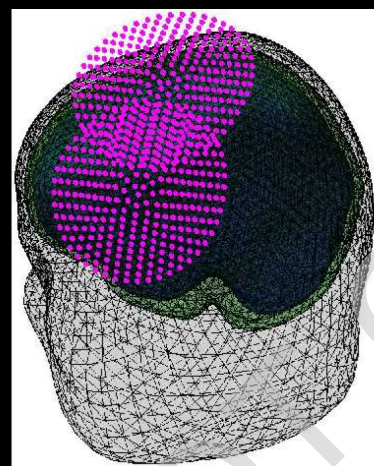
Still need to include macroscopic facts (volume conductor, TMS coil properties) into account





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

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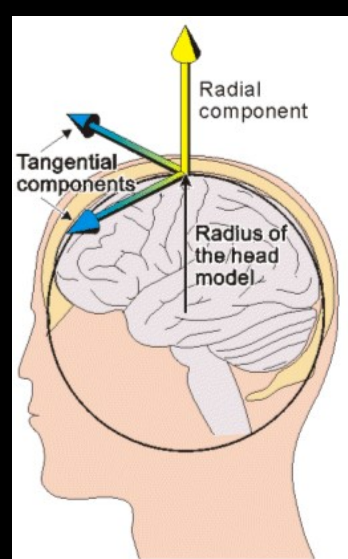
Orientations of TMS-induced currents

In a spherically symmetrical homogenous volume conductor (~ human head), TMS induces only tangential primary E-fields.

Nothing radial. No matter how we tilt the TMS coil.



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

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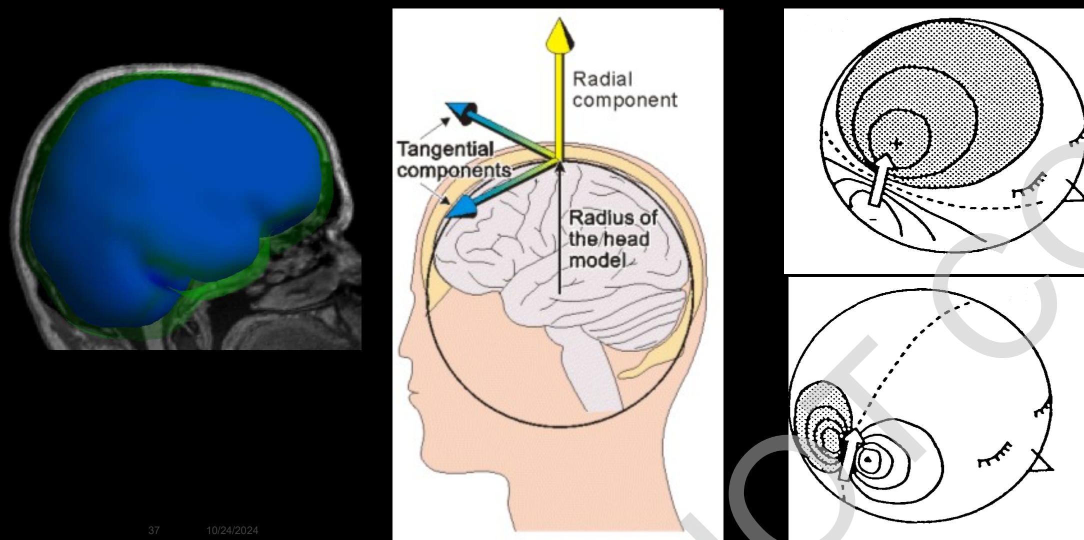
… and differences for magnetic *vs.* electrical stimulation

The skull | **Radial E-fields** | **90 degrees rotation**



Niedermeyer 1996 EEG book; Ilmoniemi et al. (1999) Crit Rev Biomed Eng 27:241-84; Nummenmaa et al. (2013) Clin Neurophysiol 124:1995-2007

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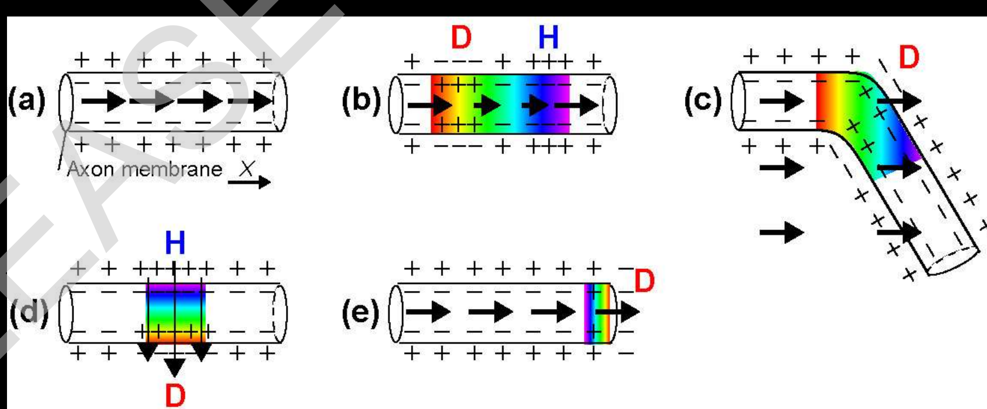
Microscopic effects in GM and WM axons: Passive



Ilmoniemi et al. (1999) Crit Rev Biomed Eng 27:241-84

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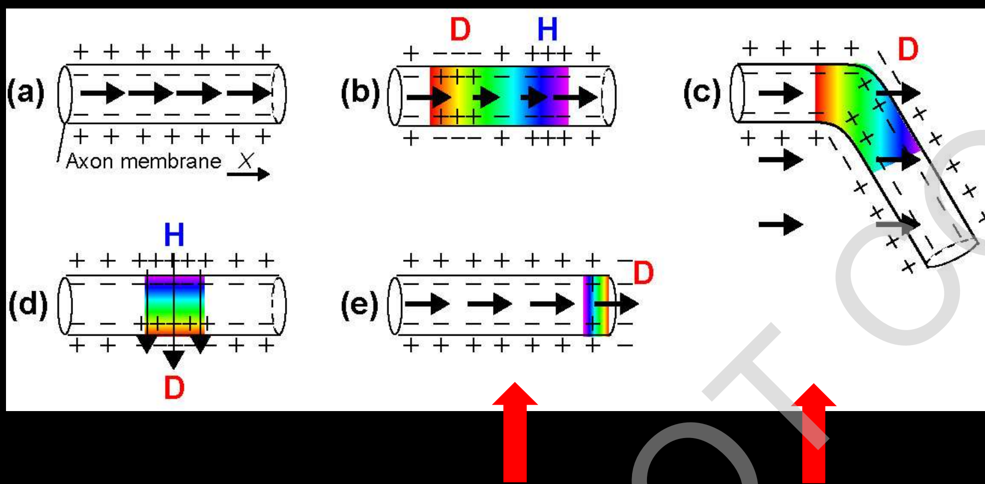
Microscopic effects in GM and WM axons: Passive



Ilmoniemi et al. (1999) Crit Rev Biomed Eng 27:241-84

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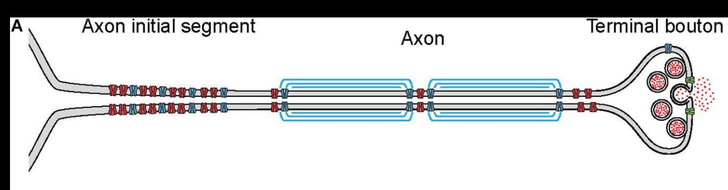
Microscopic effects in GM and WM axons: Active

The density of voltage-gated channels varies across the neuron

Thus, E-field evoked action potentials are initiated preferentially at:

- ❑ Axon hillock
- ❑ Nodes of Ranvier
- ❑ Axonal curves
- ❑ Axon terminals (synapses)



Siebner et al., (2022) Clin Neurophysiol 140:59-97

Burke and Bender (2019) Front Cell Neurophysiol 13:221

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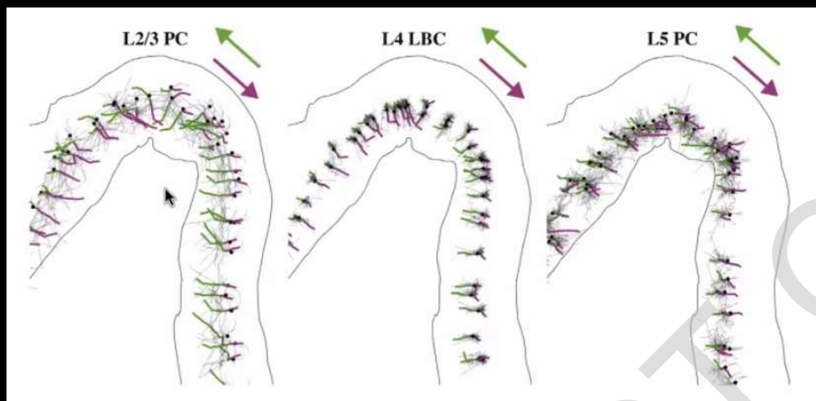
E-field microscopic effects in GM axonal arbors



TMS activates axonal terminations aligned to local E-field direction

Aberra et al., (2020) Brain Stimul 13:175-189; Siebner et al., (2022) Clin Neurophysiol 140:59-97

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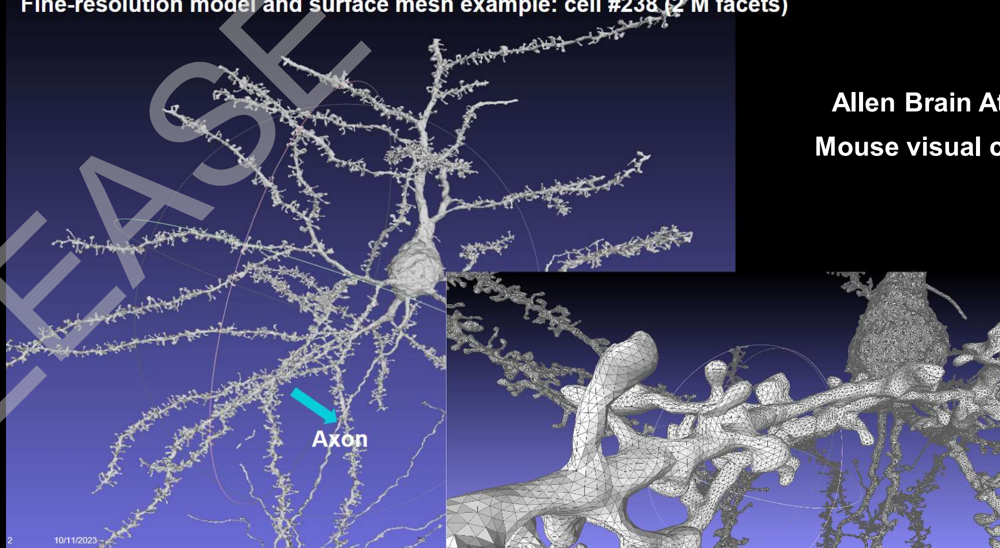
Microscopic effects in GM

Fine-resolution model and surface mesh example: cell #238 (2 M facets)



Allen Brain Atlas:
Mouse visual cortex

Miles, Noetscher, Qi, Weise, Knösche, Nummenmaa, Makaroff (2023) Brain and Human Body Modeling Conference, Boston, MA

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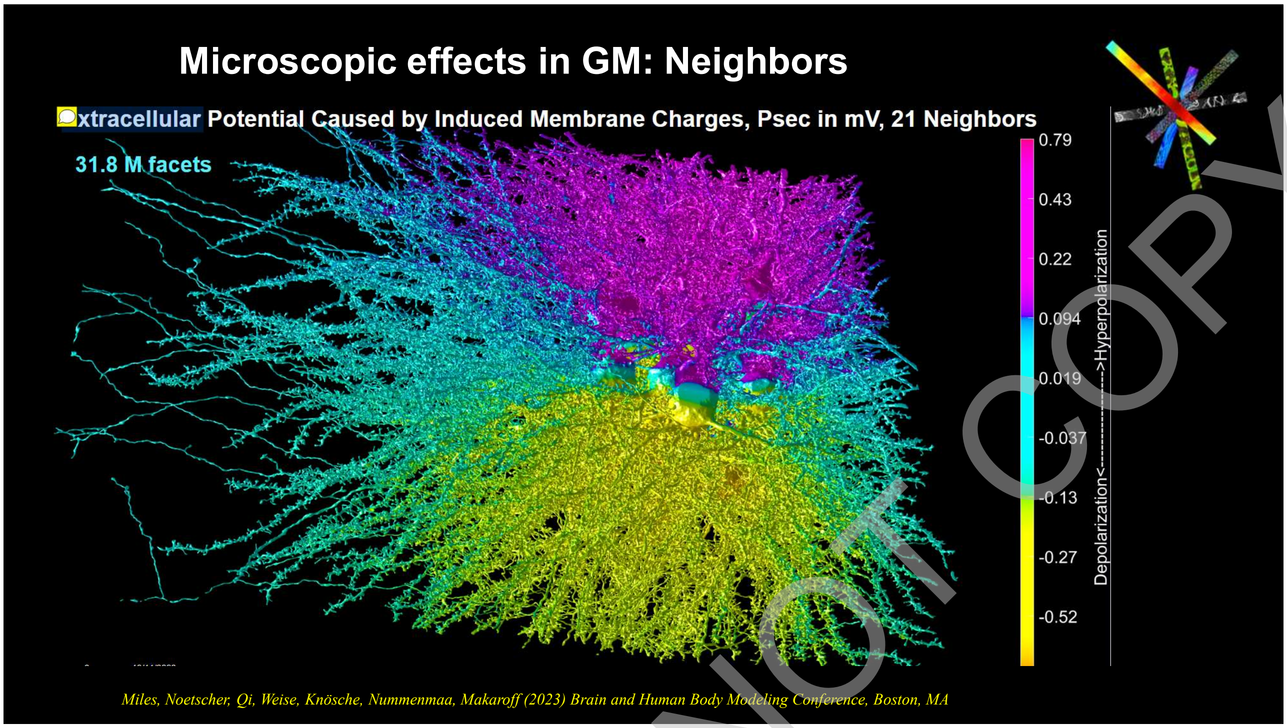
Microscopic effects in GM: Neighbors
Extracellular Potential Caused by Induced Membrane Charges, Psec in mV, 21 Neighbors
31.8 M facets
0.79
0.43
0.22
0.094
0.019
-0.037
-0.13
-0.27
-0.52
Depolarization<---------->Hyperpolarization
Miles, Noetscher, Qi, Weise, Knösche, Nummenmaa, Makaroff (2023) Brain and Human Body Modeling Conference, Boston, MA

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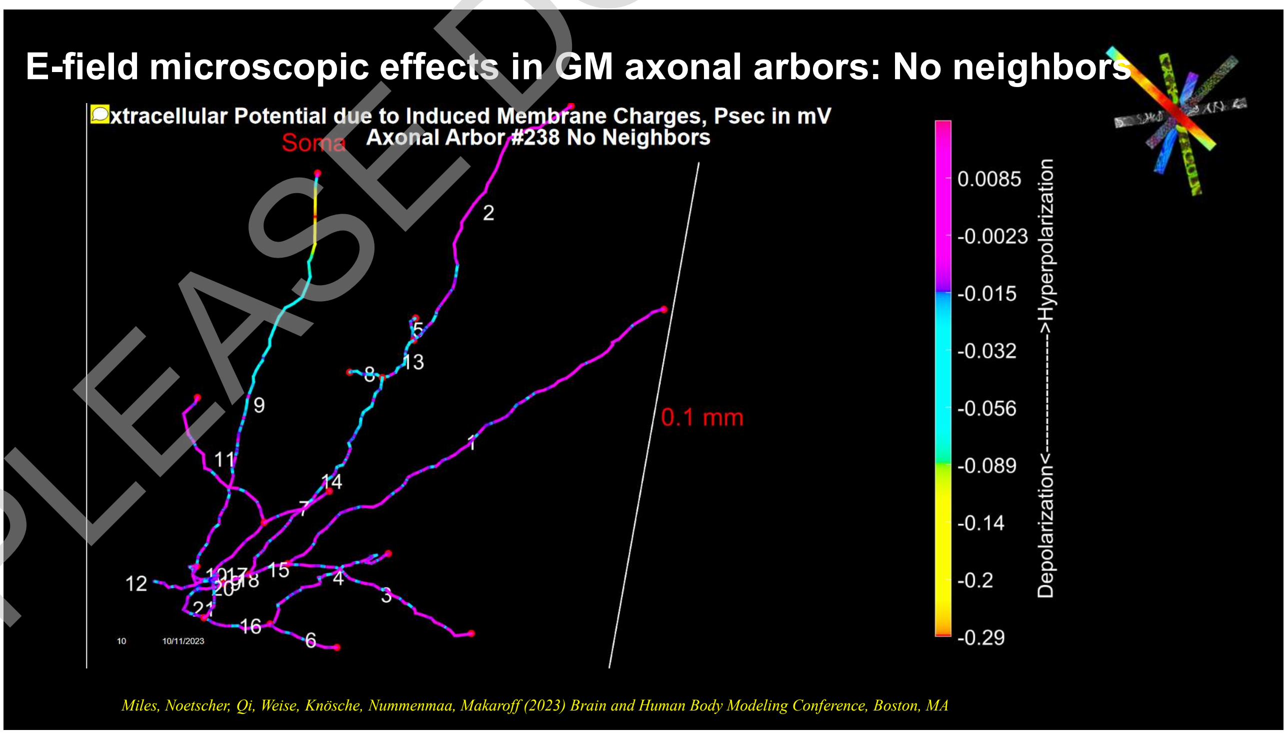
E-field microscopic effects in GM axonal arbors: No neighbors
Extracellular Potential due to Induced Membrane Charges, Psec in mV
Axonal Arbor #238 No Neighbors
Soma
0.1 mm
0.0085
-0.0023
-0.015
-0.032
-0.056
-0.089
-0.14
-0.2
-0.29
Depolarization<---------->Hyperpolarization
10/11/2023
Miles, Noetscher, Qi, Weise, Knösche, Nummenmaa, Makaroff (2023) Brain and Human Body Modeling Conference, Boston, MA

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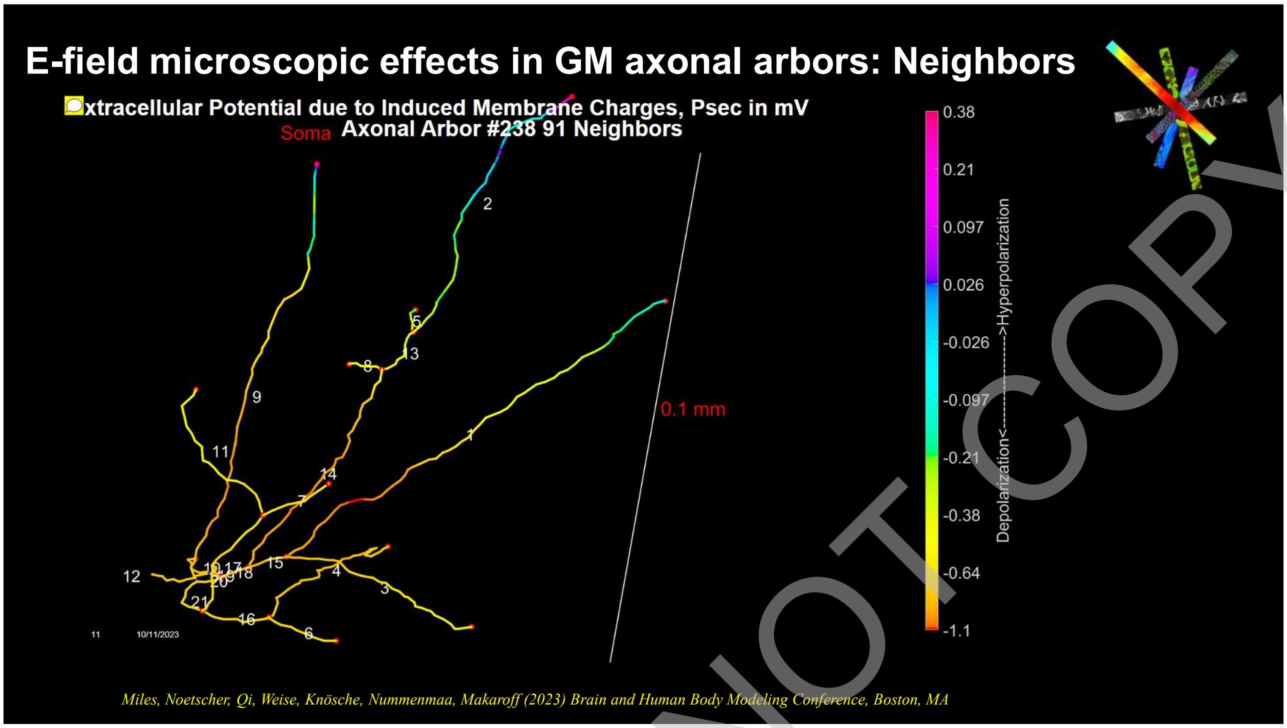
E-field microscopic effects in GM axonal arbors: Neighbors
Extracellular Potential due to Induced Membrane Charges, Psec in mV
Soma
Axonal Arbor #238 91 Neighbors
0.1 mm
0.38
0.21
0.097
0.026
-0.026
-0.097
-0.21
-0.38
-0.64
-1.1
Depolarization<------------->Hyperpolarization
Miles, Noetscher, Qi, Weise, Knösche, Nummenmaa, Makaroff (2023) Brain and Human Body Modeling Conference, Boston, MA

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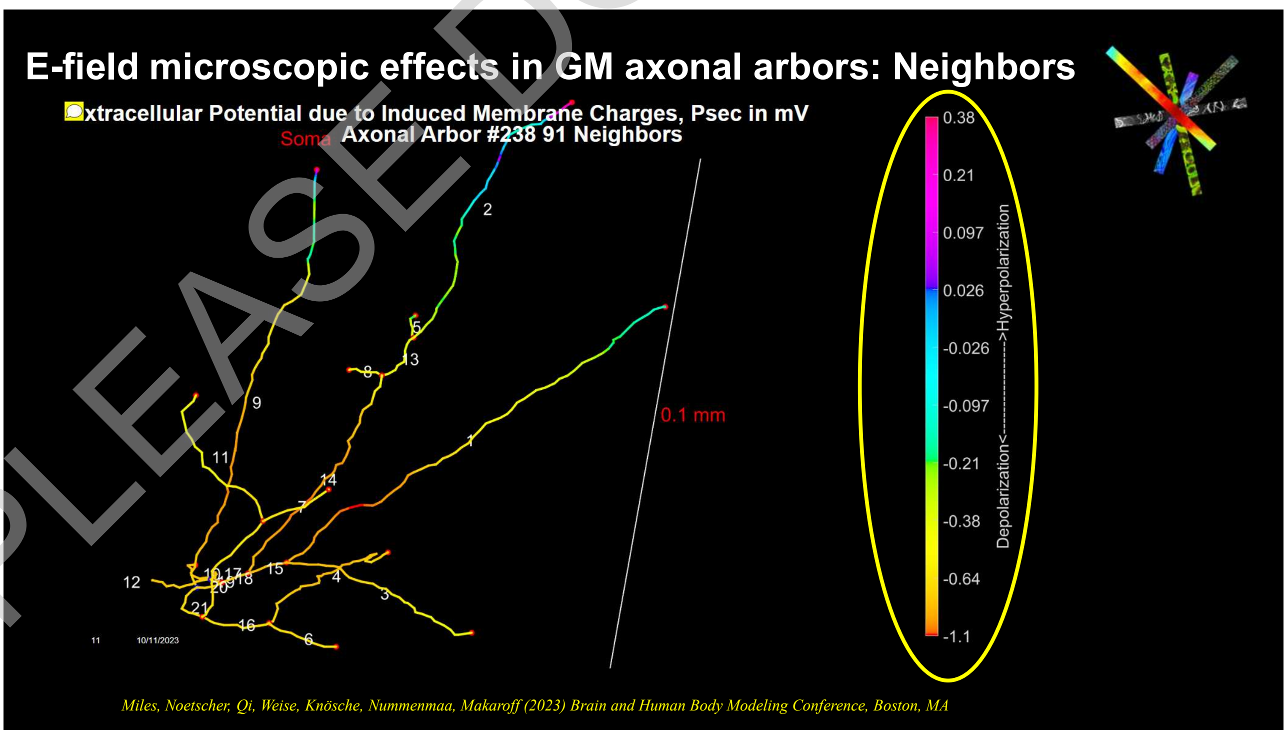
E-field microscopic effects in GM axonal arbors: Neighbors
Extracellular Potential due to Induced Membrane Charges, Psec in mV
Soma
Axonal Arbor #238 91 Neighbors
0.1 mm
0.38
0.21
0.097
0.026
-0.026
-0.097
-0.21
-0.38
-0.64
-1.1
Depolarization<------------->Hyperpolarization
Miles, Noetscher, Qi, Weise, Knösche, Nummenmaa, Makaroff (2023) Brain and Human Body Modeling Conference, Boston, MA

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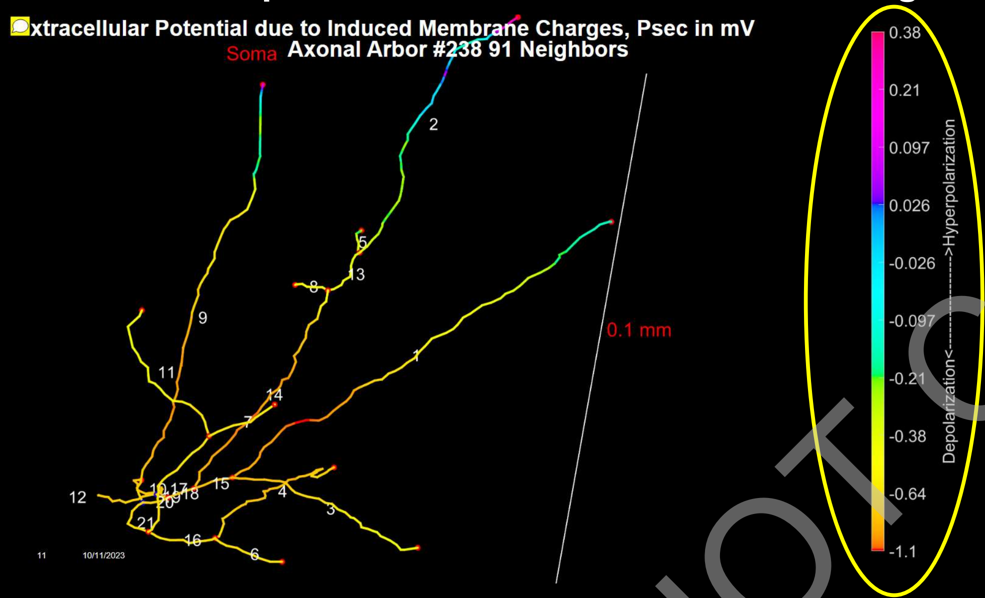
E-field microscopic effects in GM axonal arbors: Neighbors



~Two-fold increase in activating function

Miles, Noetscher, Qi, Weise, Knösche, Nummenmaa, Makaroff (2023) Brain and Human Body Modeling Conference, Boston, MA

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Mesoscopic level

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Mesoscopic level:

Grey Matter (GM)

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Cortical columns and intracortical circuits

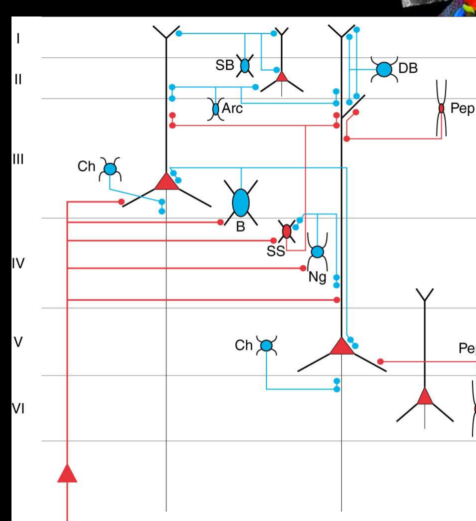
Pyramidal neurons (output units)

Interneurons

TMS/TES induced electric currents permeate the entire scene, causing local hyper- and depolarizations

This triggers cascades of action potentials from all cell types

However, typical recordings detect pyramidal neuron outputs (*e.g.,* MEPs) only



Mountcastle (1998) Perceptual Neuroscience

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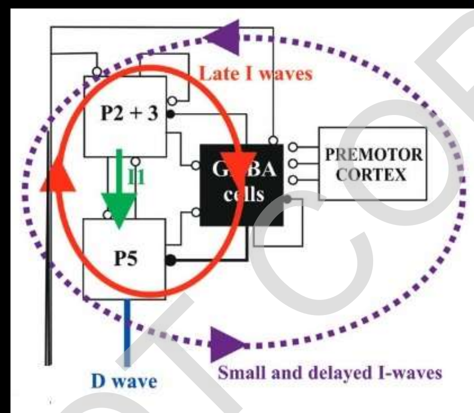
D-waves and I-waves

D-waves: Direct activation of pyramidal neurons

I-waves: Interneurons are activated, leading to indirect activation of pyramidal neurons

Pyramidal neurons and interneurons have different activation thresholds and preferred orientations for the activating current

➔ We can ~independently evoke D-waves or I-waves, to study some clinically relevant features (*e.g.,* grey matter abnormalities, white matter lesions)



Terao & Ugawa (2002) J Clin Neurophysiol 19:322-43; Douglas et al., (1989) Neural Comp 1:480-488; Di Lazzaro (2013) Handbook of Clinical Neurology 116: Brain Stimulation

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Mesoscopic level:

White Matter (WM)

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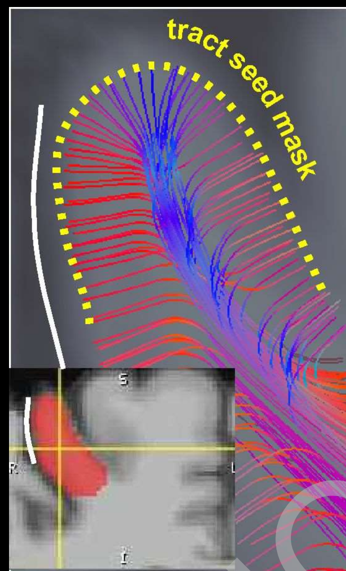
Effects in WM



Nummenmaa, McNab, Savadiev, Okada, Hamalainen, Wang, Wald, Pascual-Leone, Wedeen, and Raij (2014) Brain Stimulation 7(1):80-4

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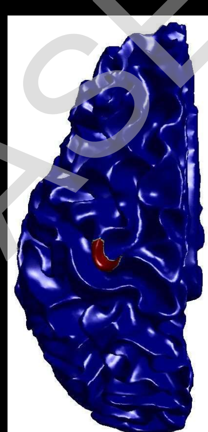
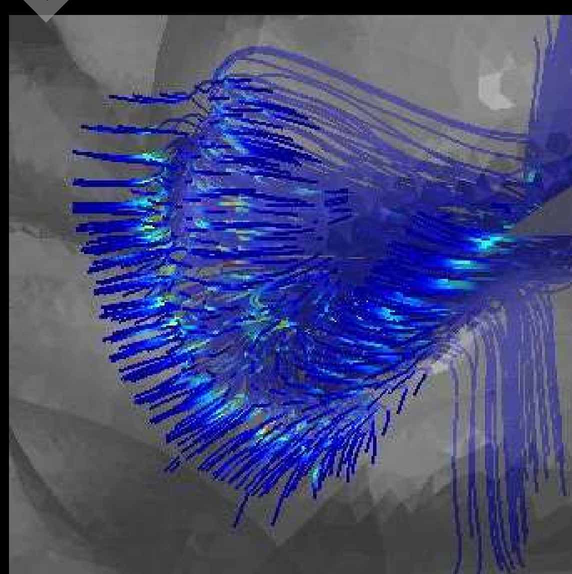
Effects in WM





Nummenmaa, McNab, Savadiev, Okada, Hamalainen, Wang, Wald, Pascual-Leone, Wedeen, and Raij (2014) Brain Stimulation 7(1):80-4

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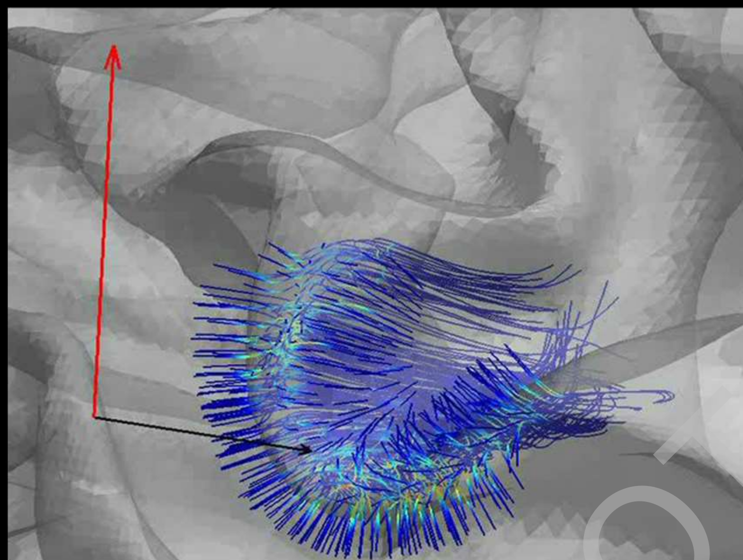
Effects in WM



Nummenmaa, McNab, Savadiev, Okada, Hamalainen, Wang, Wald, Pascual-Leone, Wedeen, and Raij (2014) Brain Stimulation 7(1):80-4

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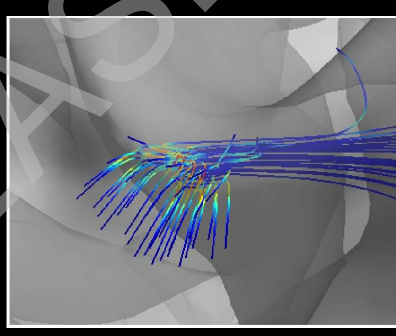
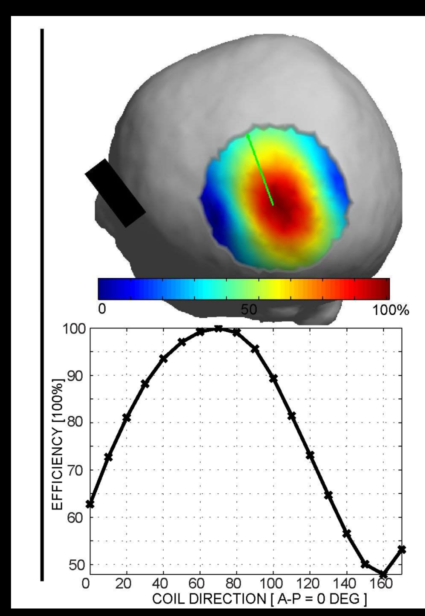
Effects in WM





Nummenmaa, McNab, Savadiev, Okada, Hamalainen, Wang, Wald, Pascual-Leone, Wedeen, and Raij (2014) Brain Stimulation 7(1):80-4

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Techniques and software

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Techniques, software, what data do I need

- ❑ 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)

Macroscopic-scale modeling requires the following data:

1. Where my TMS coil was located (navigator devices)
2. Individual head model (volume conductor, from MRI)
3. Individual brain anatomy (from MRI)

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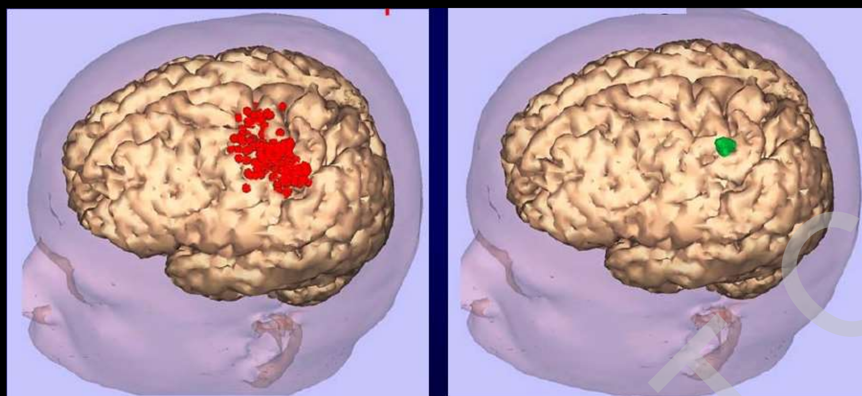
Do we need TMS navigators?



Gugino et al (2001) Clin Neurophysiol 112:1781-92

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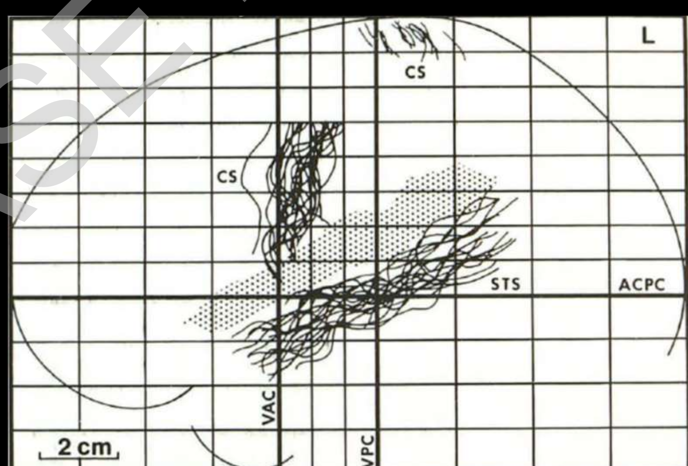
Do we need individual MRIs for the TMS navigators?



Szikla et al (1977) in Tamraz & Comair (2000); Ono et al (1990)

Steinmetz, Fürst, Freund (1990) AJNR Am J Neuroradiol 11:1123-30

Pascual-Leone, Bartrez-Faz, Keenan (1999) Philos Trans R Sec Lond B Biol Sci 354:1229-38

Fox, Buckner, Liu, Chakravarty, Lozano, Pascual-Leone (2014) PNAS 111:E4367-75

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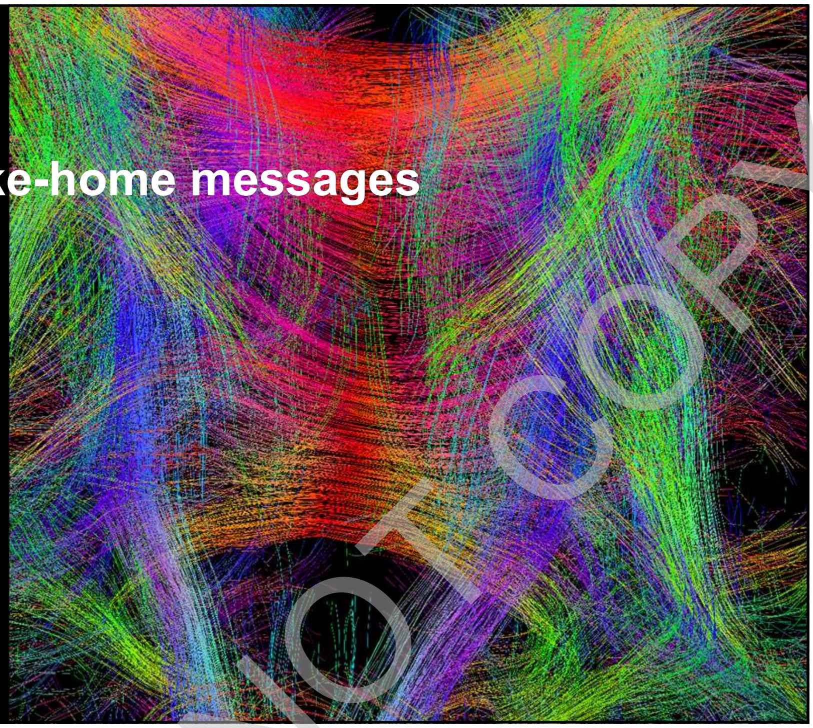
Take-home messages



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TMS and modeling: Take-home messages

- ❑ Helpful and sometimes critically important
- ❑ Calculate TMS E-fields (intensity at each location)
- ❑ Macroscopic scale
- ❑ Micro- and mesoscopic level studies
- ❑ Examine where and how E-fields activate neuronal tissue

At the macroscopic level, requires the following key data:

1. Where my TMS coil was located (navigator devices)
2. Individual head model (volume conductor, from MRI)
3. Individual brain anatomy (from MRI)

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Thank you

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

Questions or comments

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