Thomas Jefferson University

Brain Stimulation in Rehabilitation

Intensive Course in Transcranial Magnetic Stimulation

Harvard Medical School, CME

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Professor, Thomas Jefferson University, Philadelphia

Part 1: Background

Part 2: Technical Advances Improve Targeting

Part 3: TMS-Neuromodulation in Motor Recovery

Part 4: Conclusions

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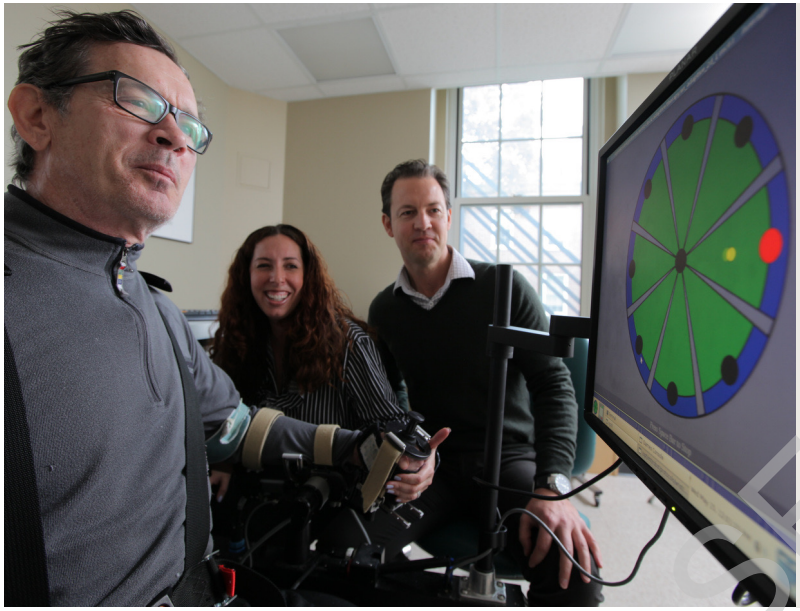
Rehabilitation

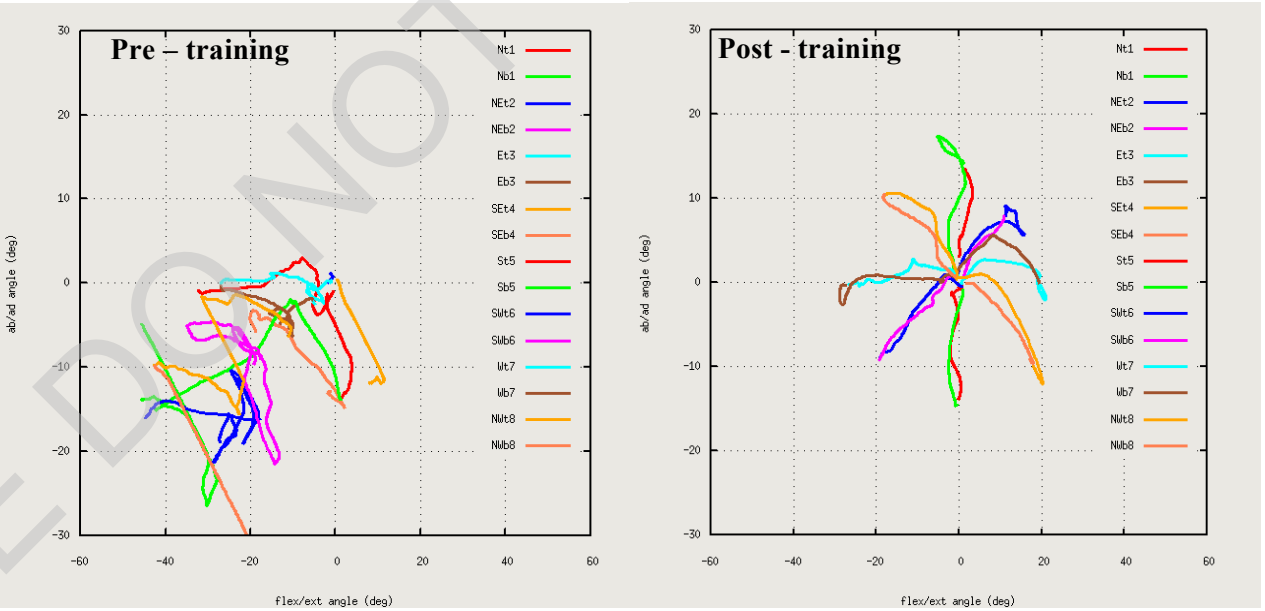
Marathon runner, Lawyer, Dad, in his 30s

Headache → stroke/coma
Upon waking, can't move one side of body

Robotics may help pave the way for regaining independent movement

Robotics may help pave the way for regaining independent movement





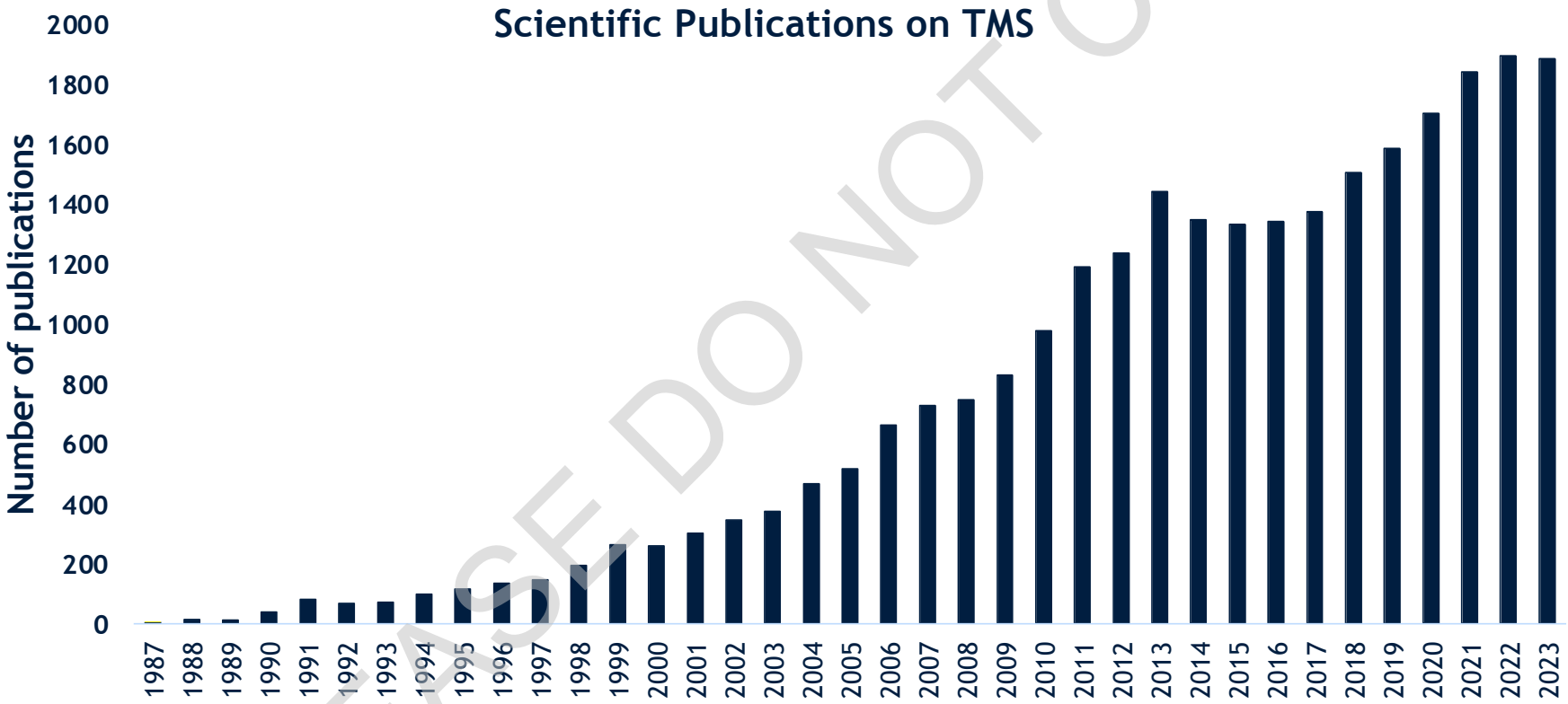
Digital gaming platforms

- Home-based telerehabilitation training produced substantial arm motor function gains on par with in-clinic rehabilitation.

- Intense telerehabilitation therapy is feasible, safe, and may improve outcomes early after stroke.

Cramer, et al. *JAMA Neurology* 2019; *Front. Neurology* 2021
Edwards, et al. *Neurorehabilitation & Neural Repair* 2023

Interest in TMS



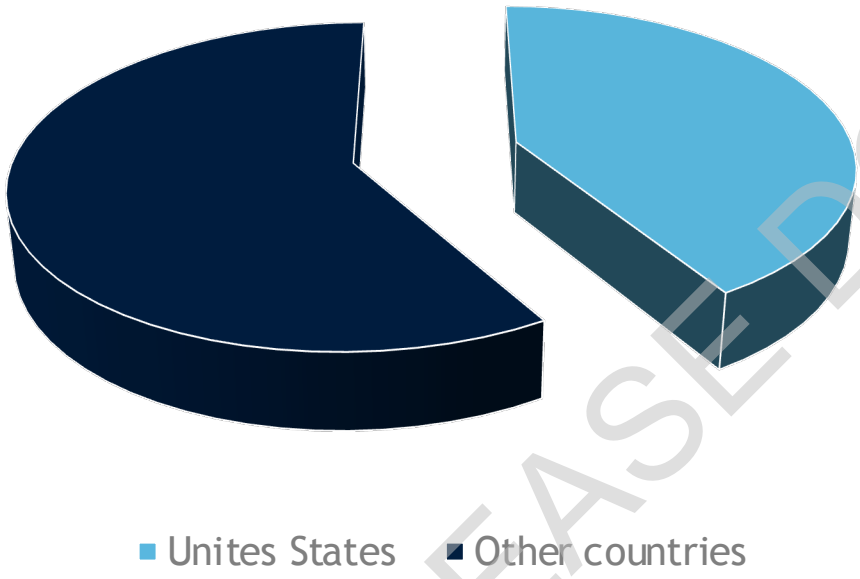
Source: PubMed, Search Terms: "Transcranial Magnetic Stimulation", Data as of March 29, 2024.

Large number of TMS clinical trials

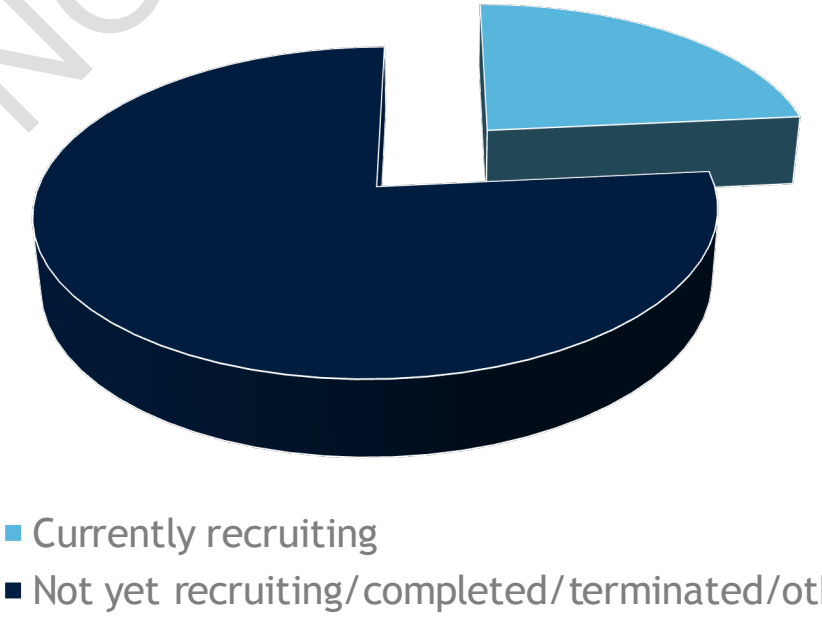
2,612 TMS clinical trials have been registered

- 1,079 (41%) are based in the United States
- 613 clinical trials are recruiting participants

Clinical Trials by Location

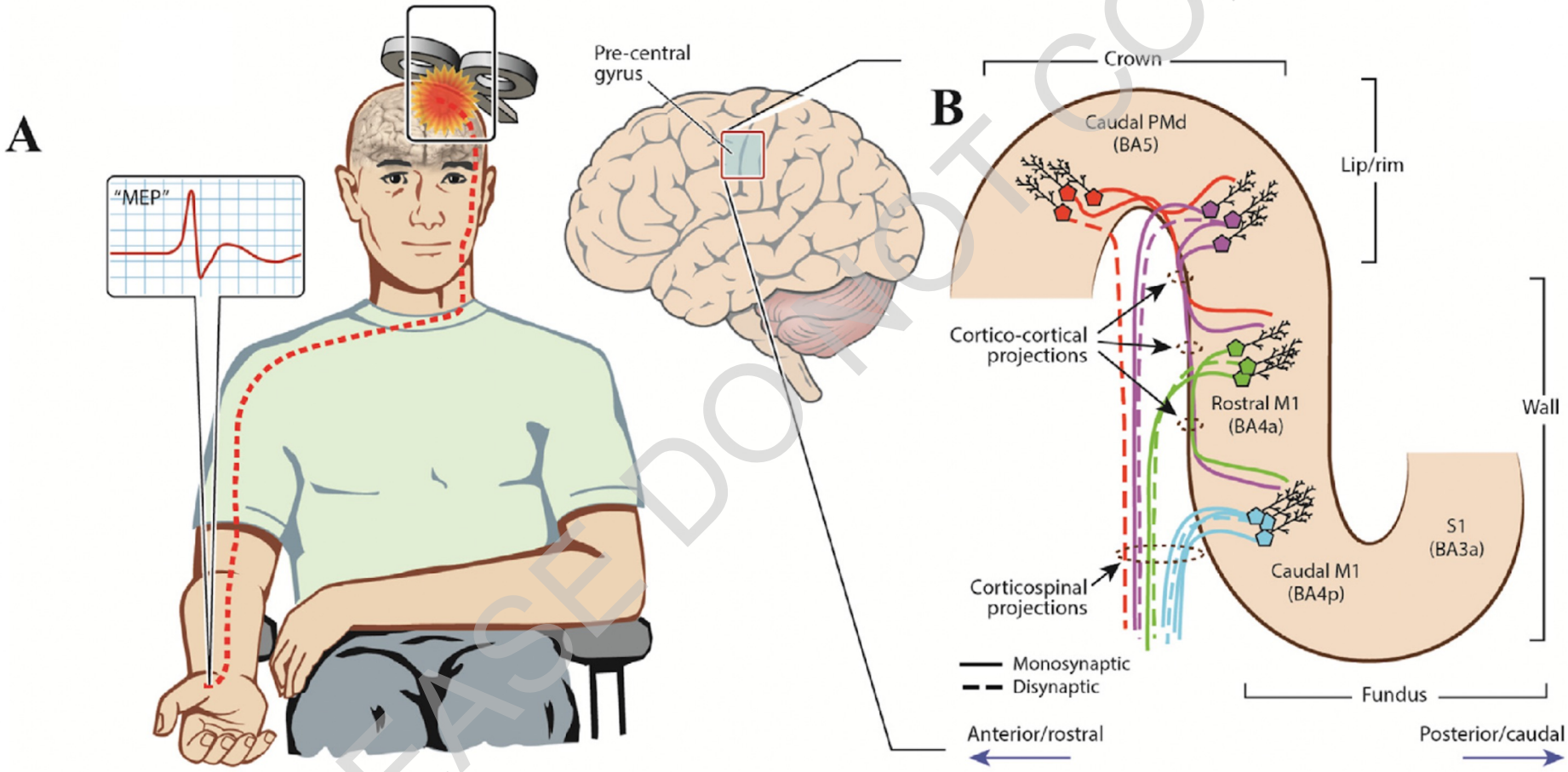


Clinical Trials by Status



Source: clinicaltrials.gov, Search Terms: "Transcranial Magnetic Stimulation", Data as of April 3, 2024.

Transcranial magnetic stimulation: Physics, Anatomy, Physiology



Diagnostic utility in neurological diseases

Clinical Neurophysiology 150 (2023) 131–175

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Review

Clinical diagnostic utility of transcranial magnetic stimulation in neurological disorders. Updated report of an IFCN committee

Steve Vucic [a,*], Kai-Hsiang Stanley Chen [b], Matthew C. Kiernan [c], Mark Hallett [d], David.H. Benninger [e], Vincenzo Di Lazzaro [f], Paolo M Rossini [g], Alberto Benussi [h], Alfredo Berardelli [i], Antonio Currà [j], Sandro M Krieg [k], Jean-Pascal Lefaucheur [l], Yew Long Lo [m], Richard A Macdonell [n], Marcello Massimini [o], Mario Rosanova [p], Thomas Picht [q], Cathy M Stinear [r], Walter Paulus [s], Yoshikazu Ugawa [t], Ulf Ziemann [u], Robert Chen [v]

Vucic et al., *Clinical Neurophysiology*, 2023; Chen et al., *Clinical Neurophysiology*, 2008

TMS is safe within the established safety recommendations

Clinical Neurophysiology 132 (2021) 269–306

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Review

Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines

Simone Rossi [a,*], Andrea Antal [b,c], Sven Bestmann [d], Marom Bikson [e], Carmen Brewer [f], Jürgen Brockmöller [g], Linda L. Carpenter [h], Massimo Cincotta [i], Robert Chen [j], Jeff D. Daskalakis [k], Vincenzo Di Lazzaro [l], Michael D. Fox [m,n,o], Mark S. George [p], Donald Gilbert [q], Vasilios K. Kimiskidis [r], Giacomo Koch [s], Risto J. Ilmoniemi [t], Jean Pascal Lefaucheur [u,v], Letizia Leocani [w], Sarah H. Lisanby [x,y,2], Carlo Miniussi [z], Frank Padberg [aa], Alvaro Pascual-Leone [ab,ac,ad], Walter Paulus [b], Angel V. Peterchev [ae], Angelo Quartarone [af], Alexander Rotenberg [ag], John Rothwell [d], Paolo M. Rossini [ah], Emiliano Santarnecchi [m], Mouhsin M. Shafi [m], Hartwig R. Siebner [ai,aj,ak], Yoshikatzu Ugawa [al], Eric M. Wassermann [am,2], Abraham Zangen [an], Ulf Ziemann [ao], Mark Hallett [ap,2,*],

Rossi et al., *Clinical Neurophysiology*, 2021; Rossi et al., *Clinical Neurophysiology*, 2009

Towards Phase III RCT / clinical efficacy

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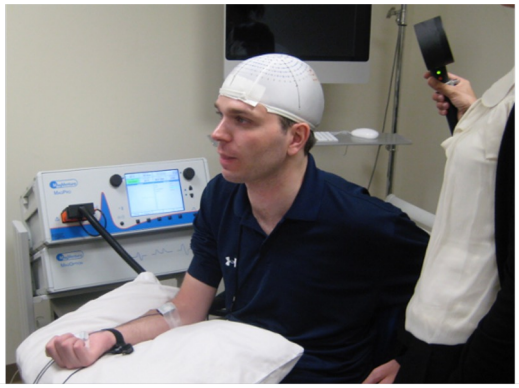
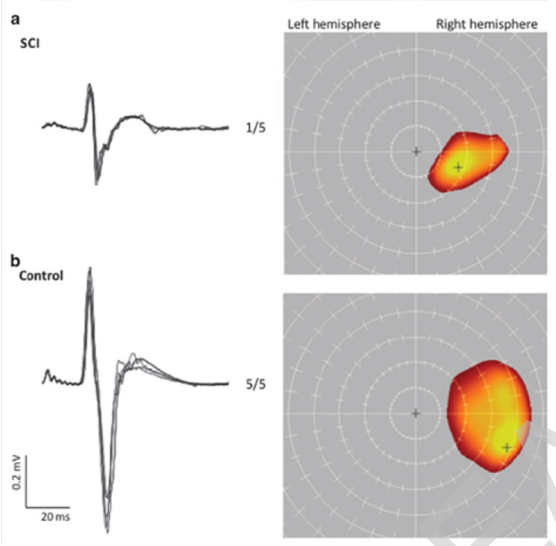
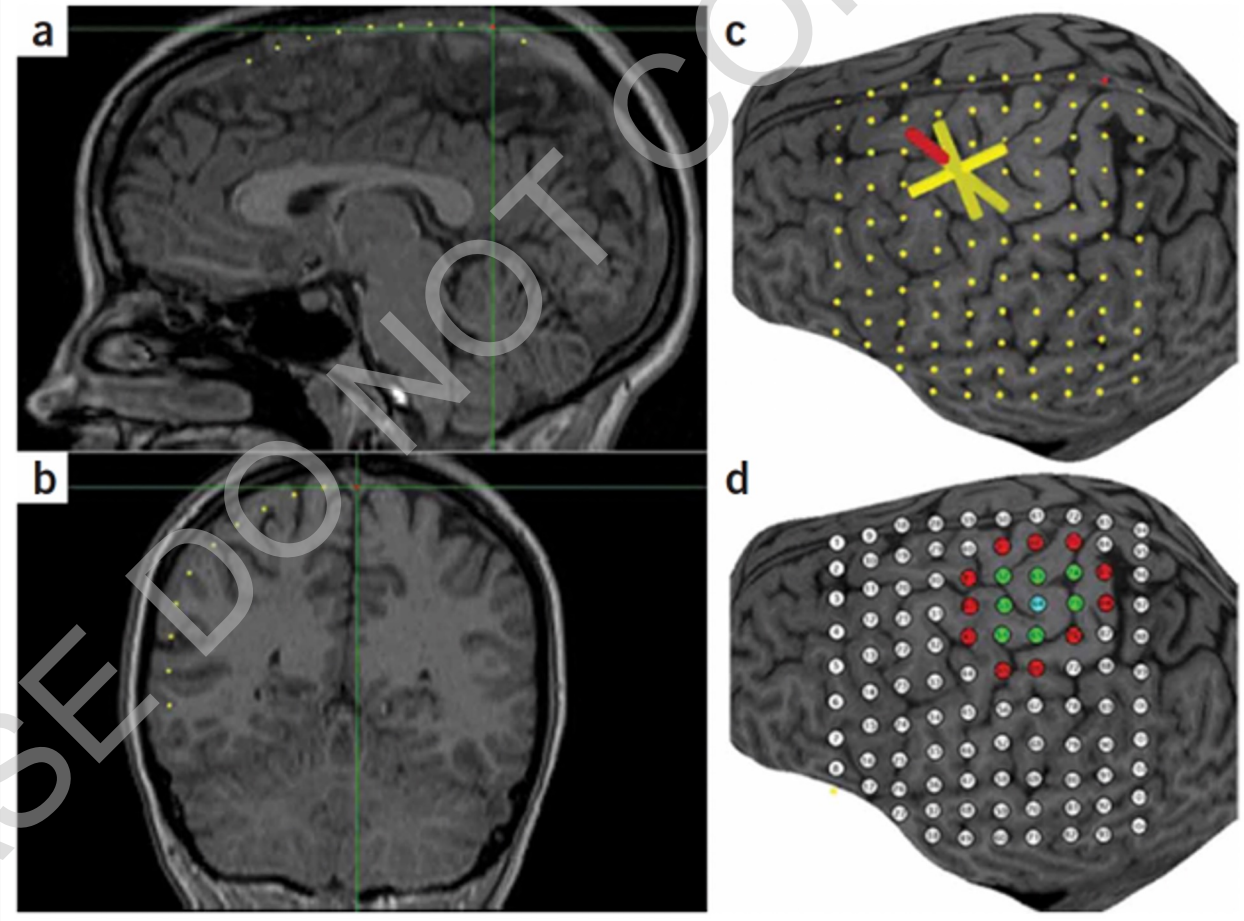
Historical – Mapping MEP to a scalp or cortical location



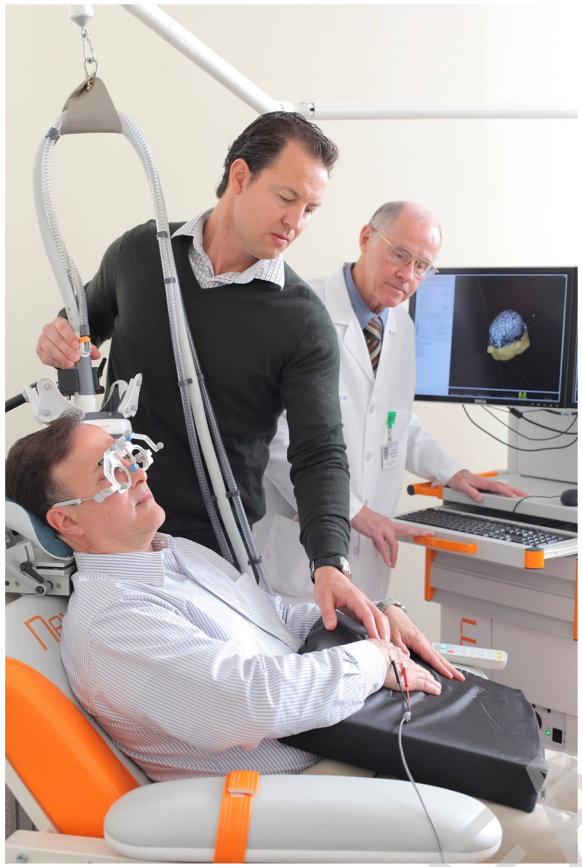


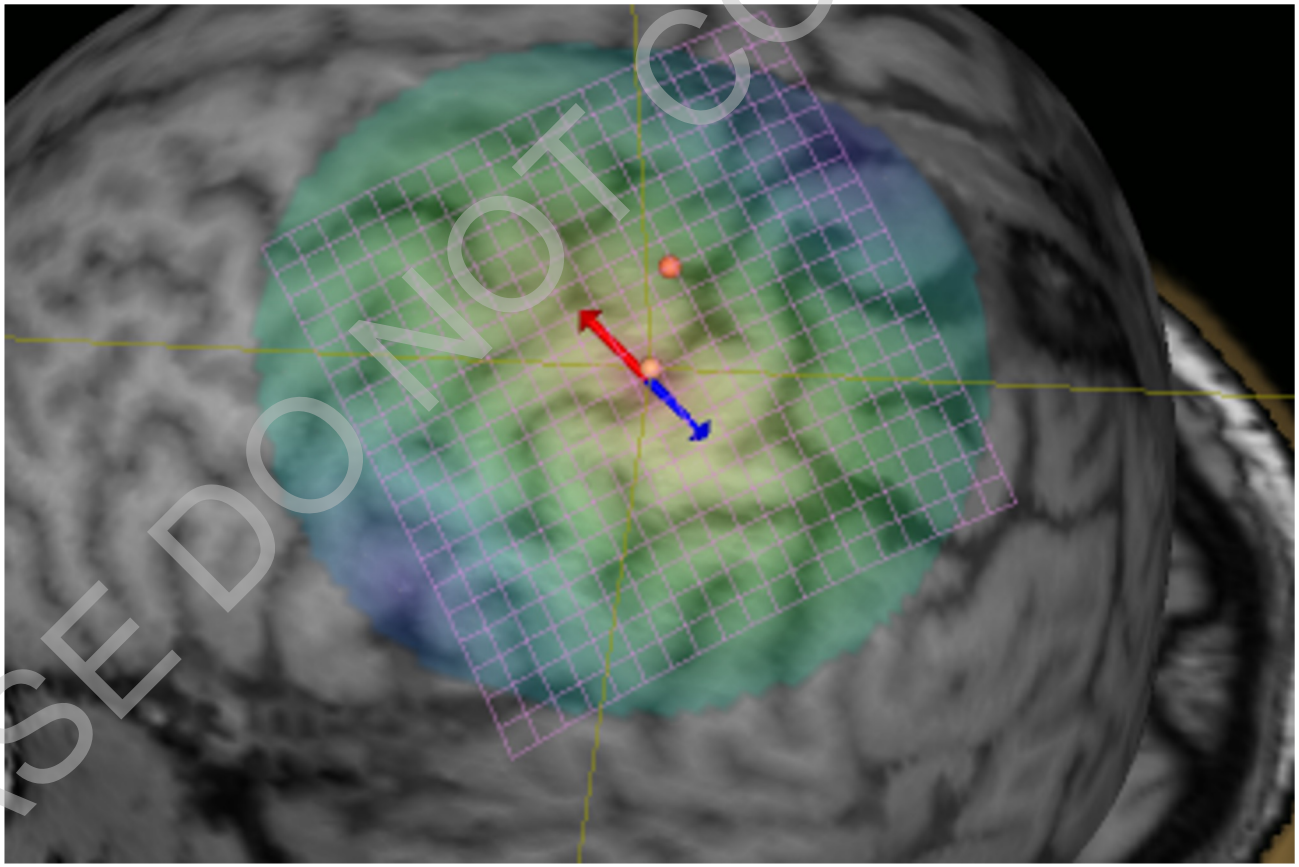
Cortes et al., *Spinal Cord*, 2017



Kleim et al., *Nature Protocols*, 2007

Precision motor mapping can inform brain ‘re-organization’ in recovery





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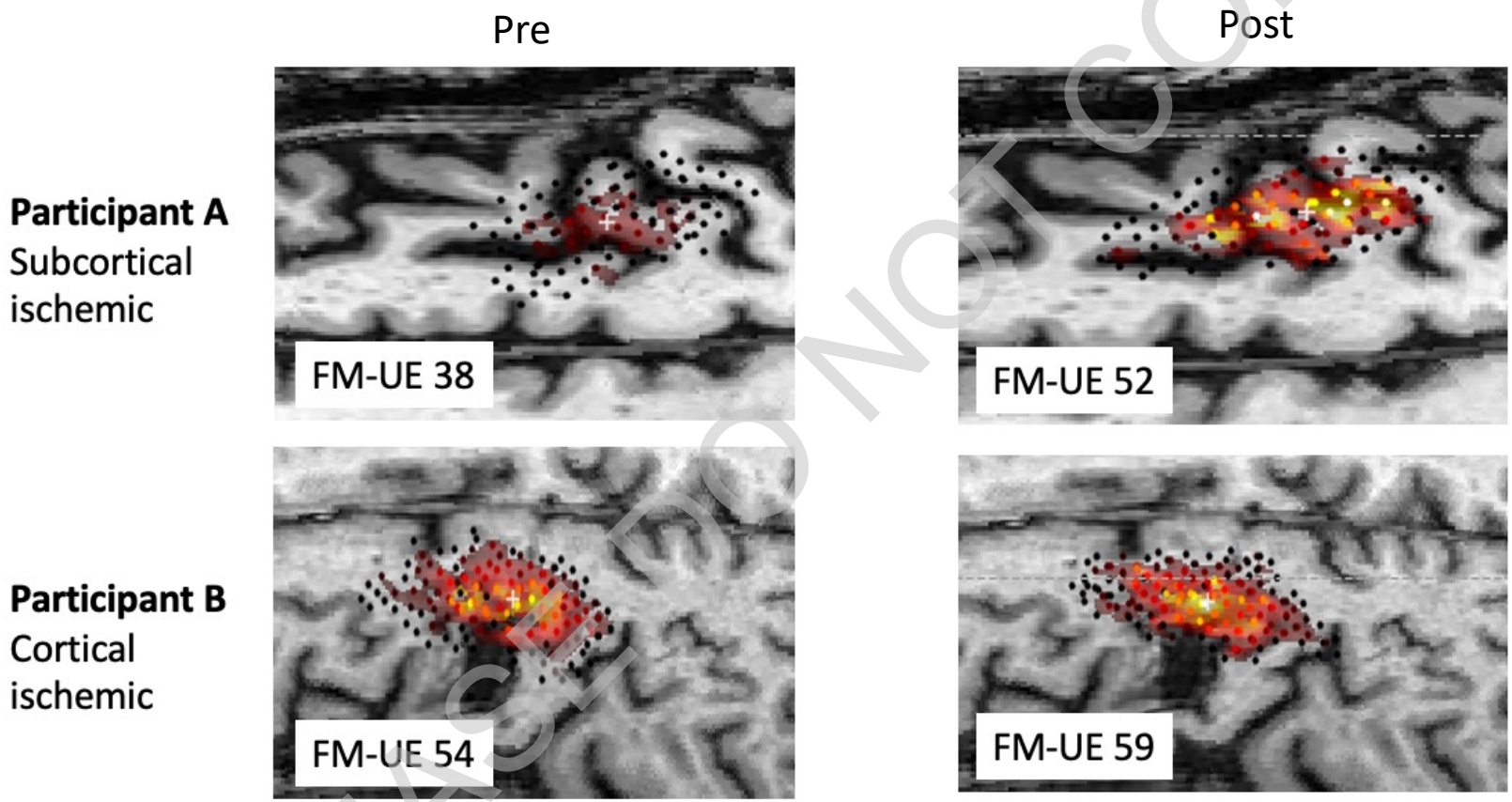
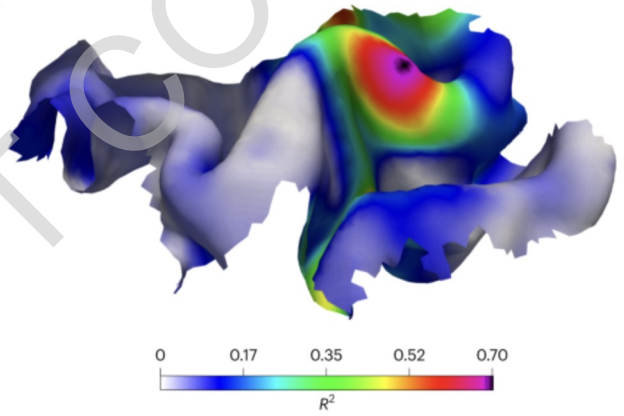


FM-UE: Fugl-Meyer Upper Extremity (Max 66)

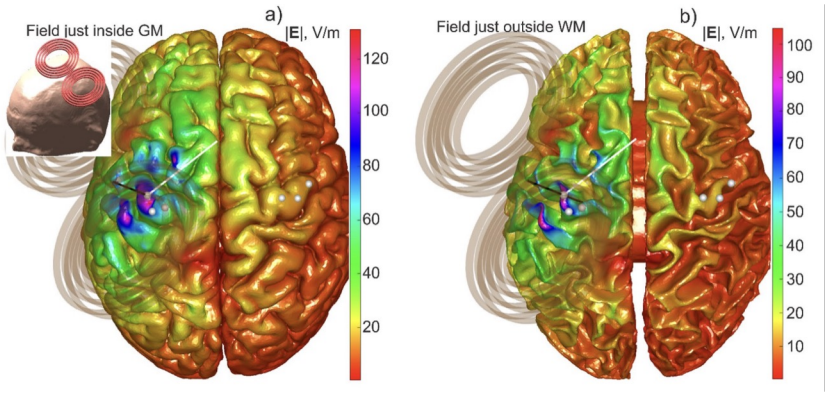
Contemporary - Mapping cortical electric fields to individual anatomy

TMS can be used to localize cortical muscle representations on the primary motor cortex for an individual.



Weise, et al., *Nature Protocols*, 2023

A fast, accurate TMS solver can determine TMS fields for any coil type in near-real time.



Makaroff, et al., *Scientific Reports*, 2023

Precision motor mapping can inform brain organization

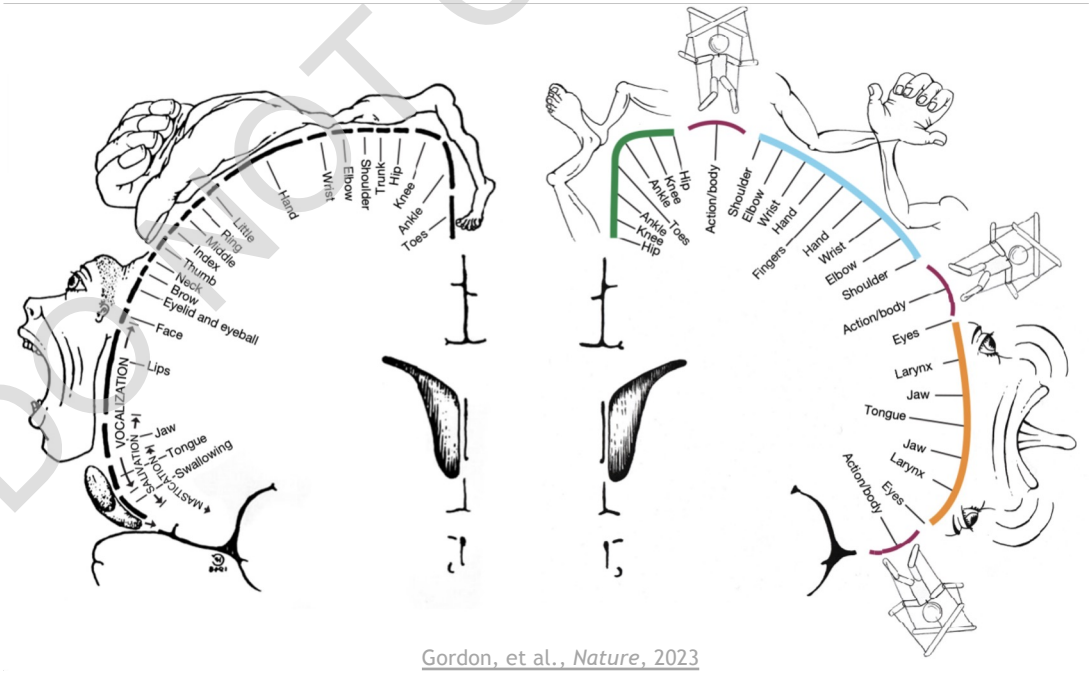
Famous 'homunculus' brain map redrawn to include complex movements

nature NEWS | 19 April 2023

Kozlov, *Nature News*, 2023

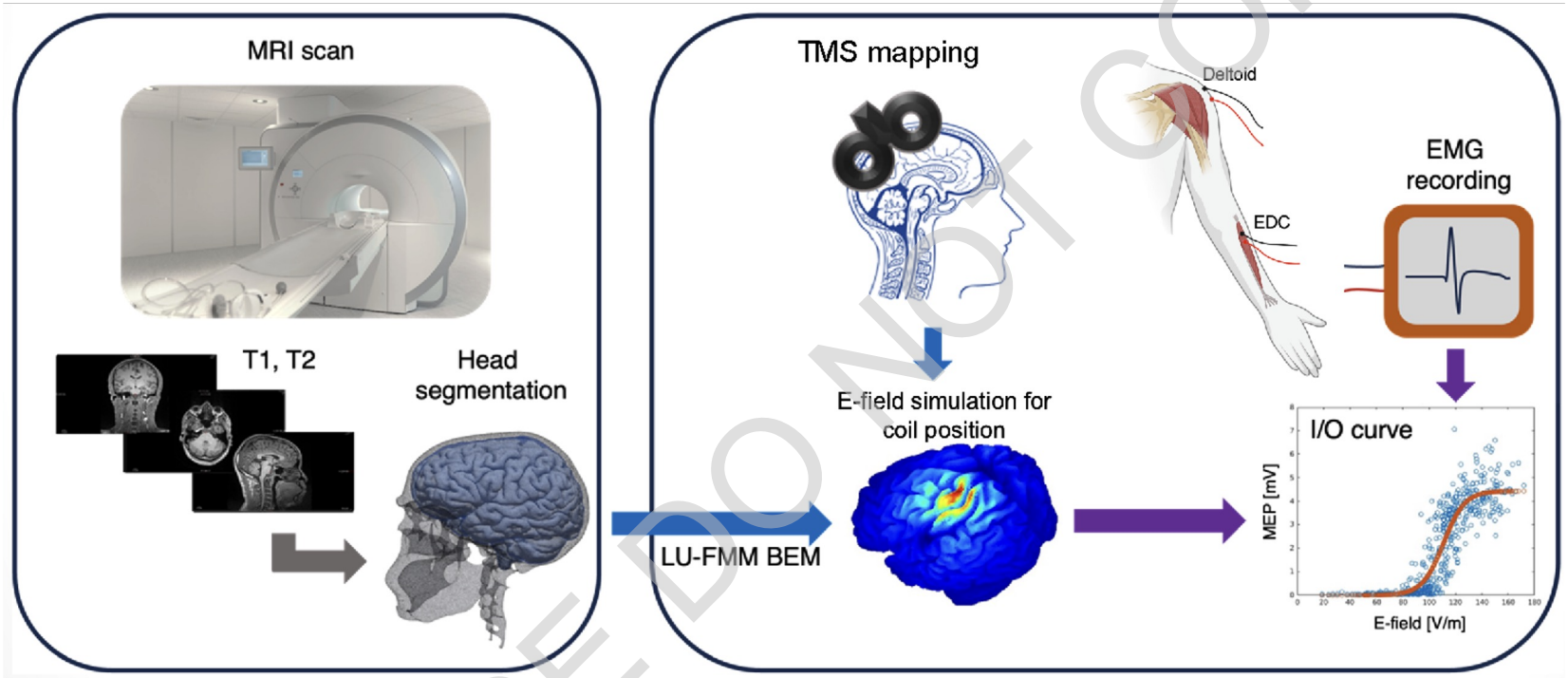
Penfield's homunculus (1948)

Integrate-isolate model (2022)



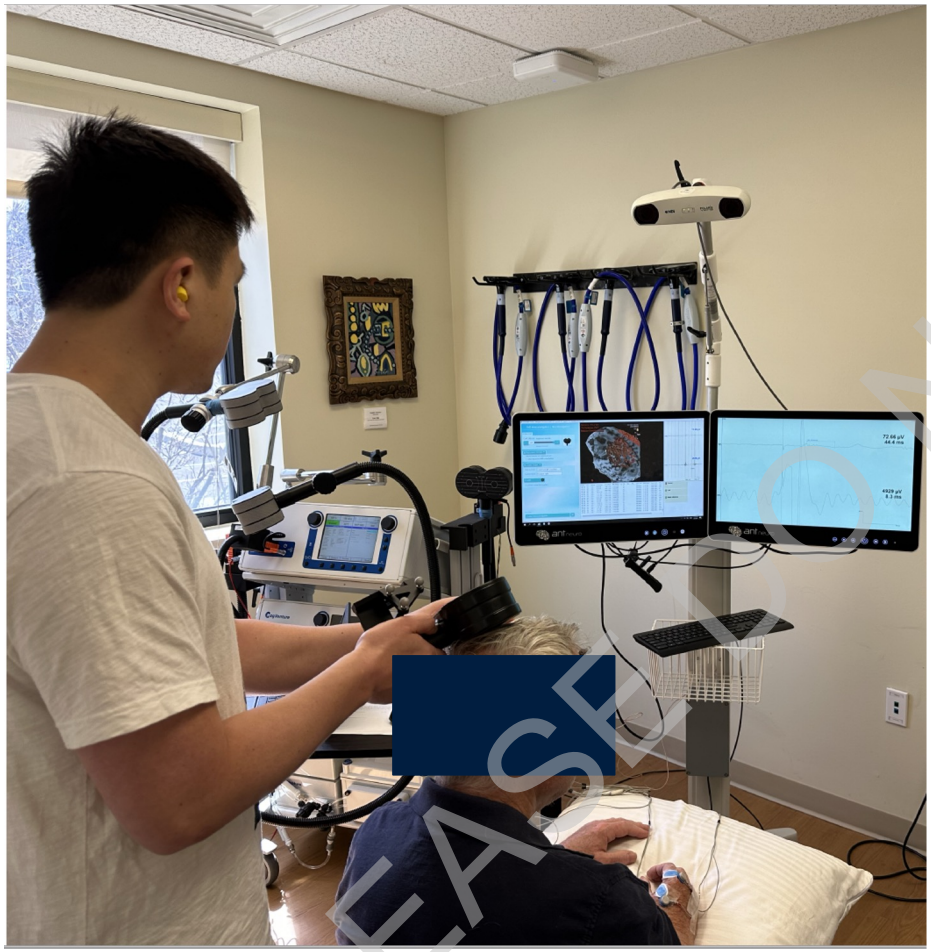
Gordon, et al., *Nature*, 2023

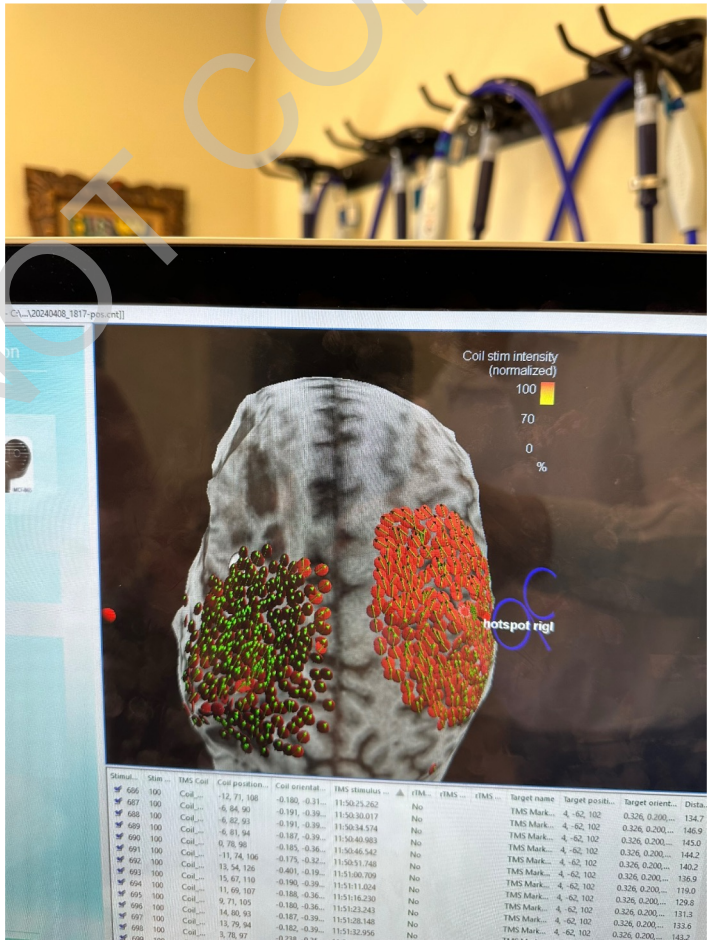
Workflow for mapping



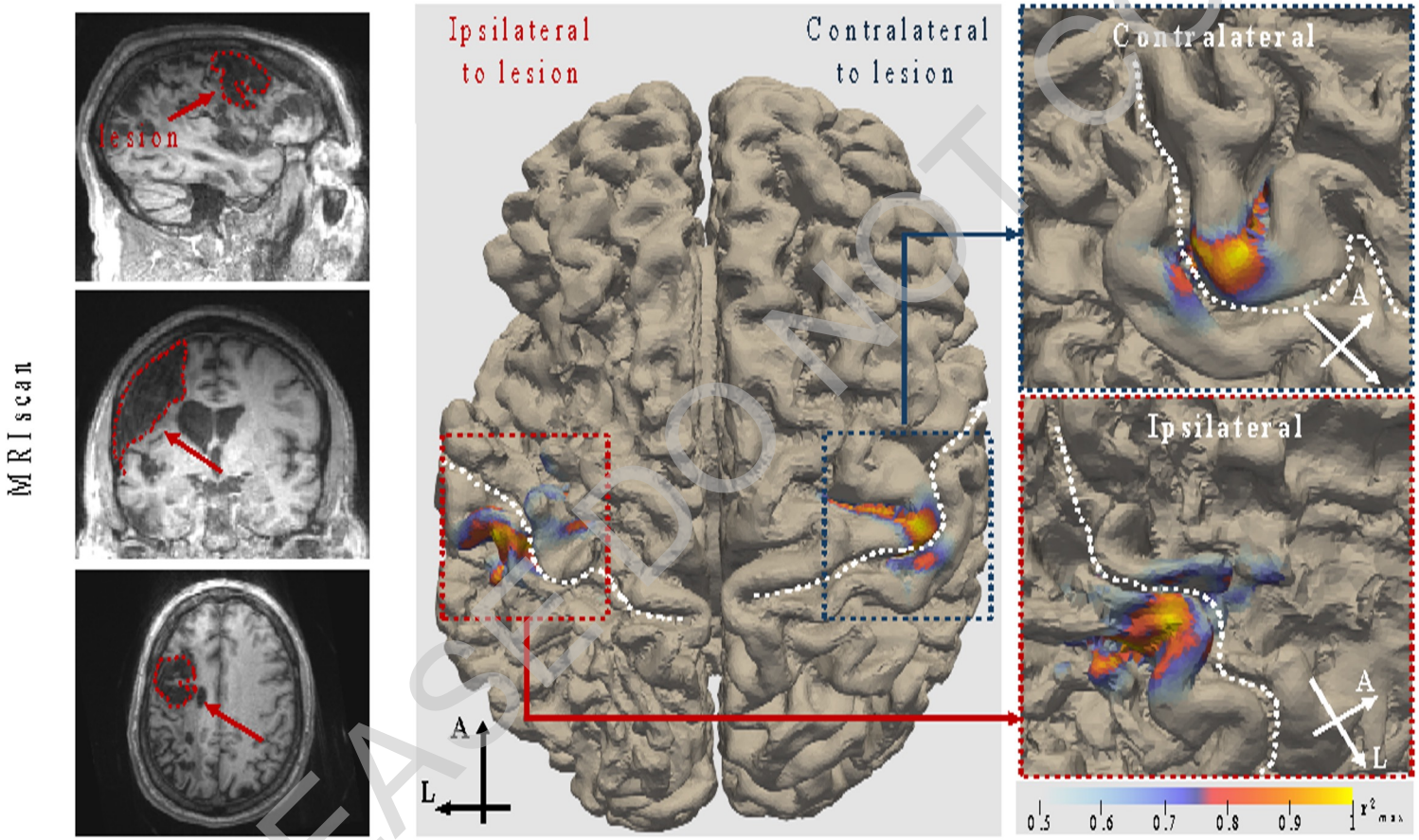
- The general experimental, modeling and analytical workflow for nTMS map and I/O curve generation.
- Left images prepare the subject-specific head (brain) model from anatomical MRI, then with TMS experimentation and corresponding brain electric field computation (center images), cortical E-field maps are generated, and input-output curves for target muscles (right images) are fit with a sigmoid function.

Identifying Rational targets





Stroke Mapping Case — for precision neuromodulation

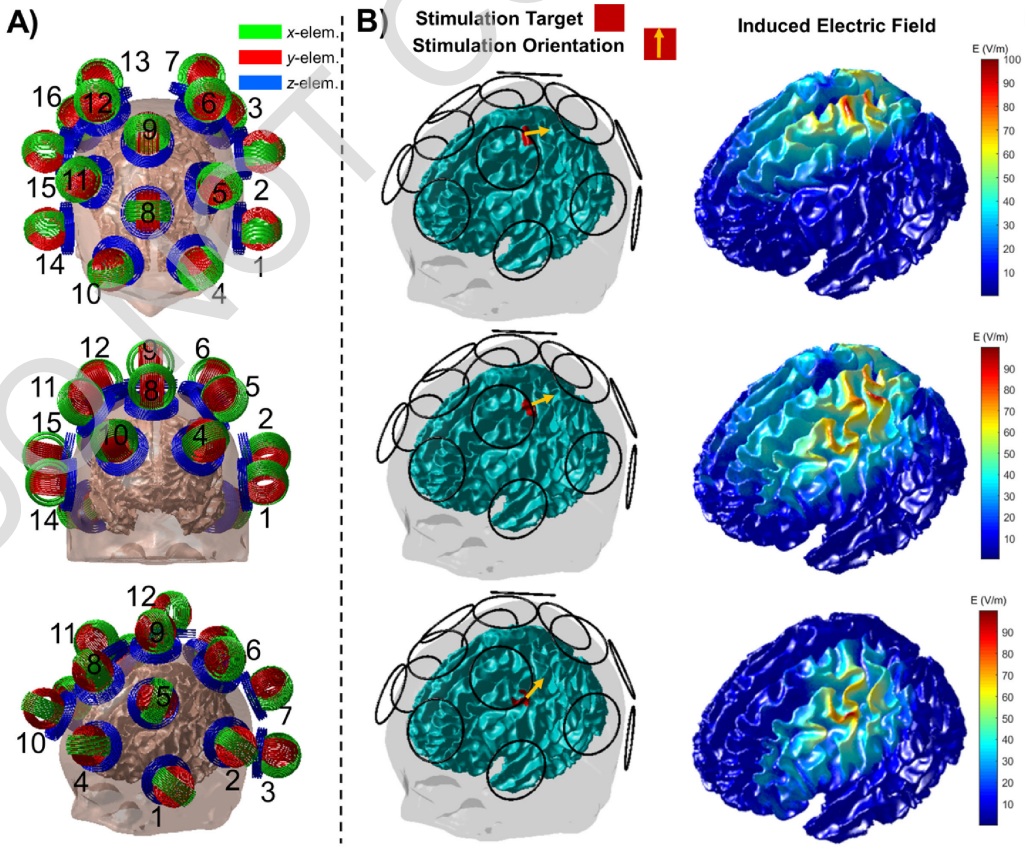


(courtesy of Drs. Evgenii Kim & Aapo Nummenmaa, Martinos Center/MGH TMS Lab)

Emerging tech: Robotics & multi-coil arrays

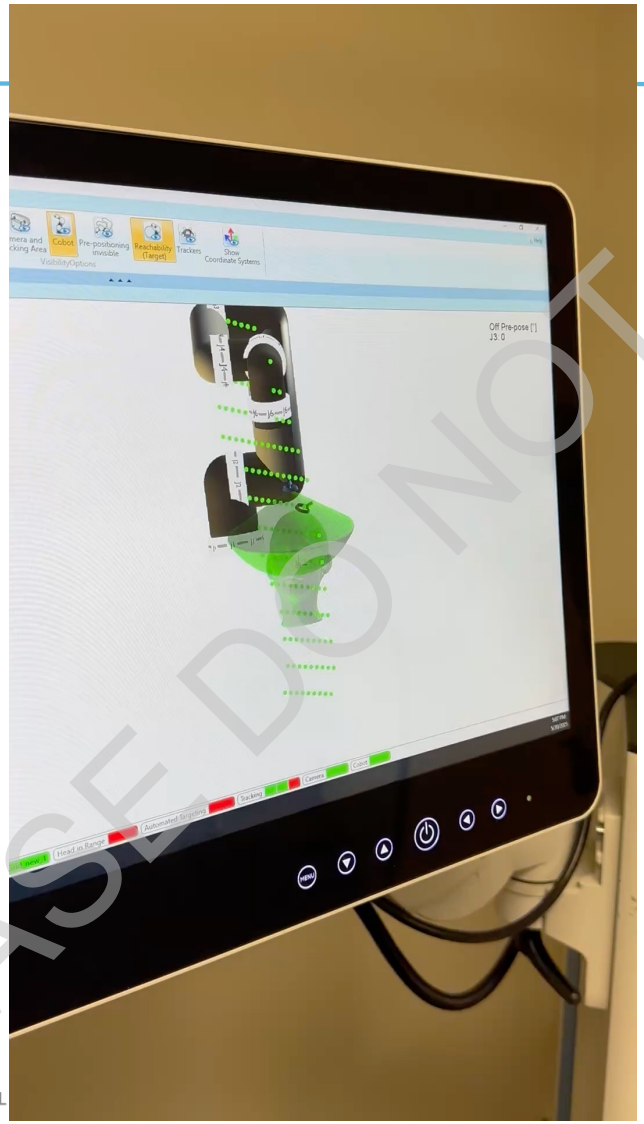
Robotic arm for automated targeting

Multi-coil array for e-field shaping, allows multiple targets



Navarro de Lara et al., *NeuroImage*, 2021; Daneshszand et al., *Brain Stimulation*, 2023

Emerging tech: Robotics



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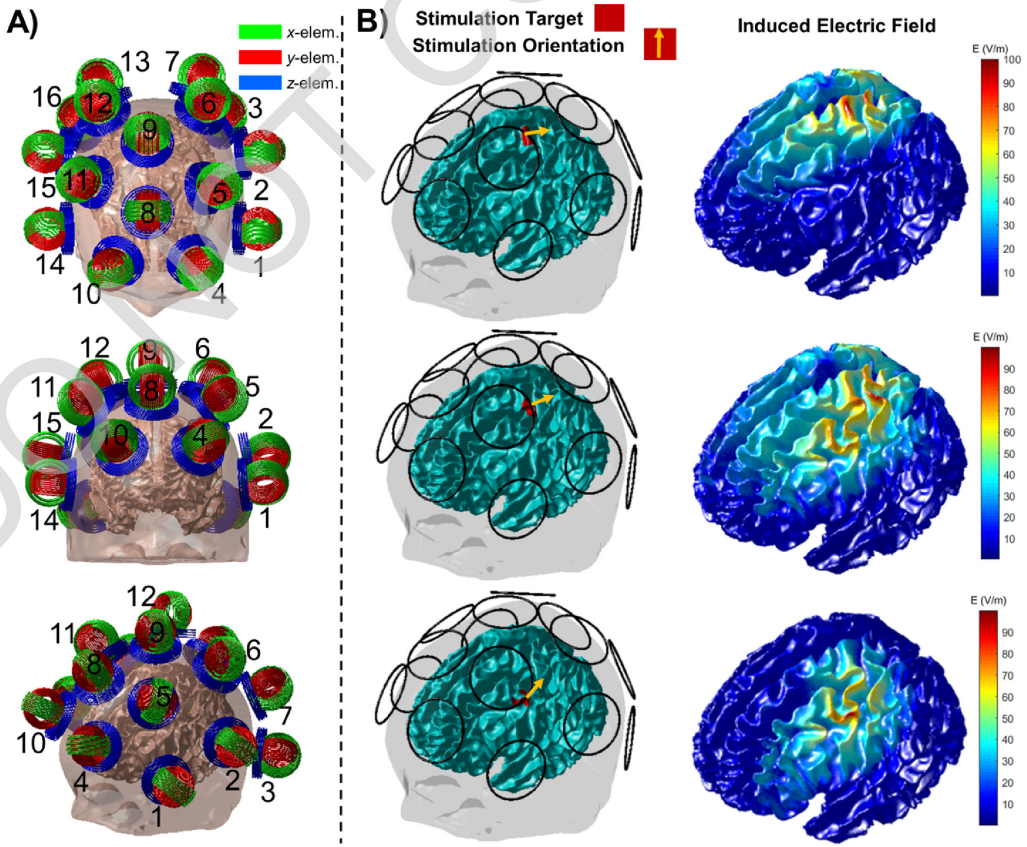

Navarro de Lara et al., *NeuroImage*, 2021; Daneshszand et al., *Brain Stimulation*, 2023

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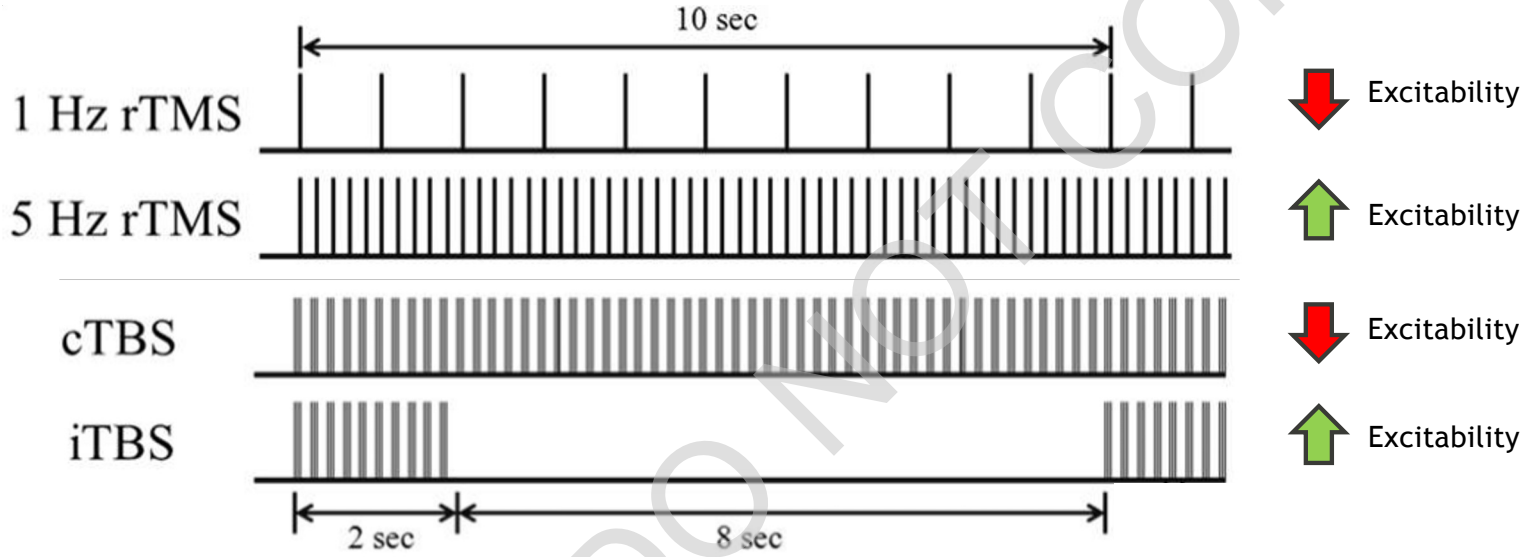
Common patterns of stimulation used for neuromodulation



Fang, et al., *J Med Biol Eng*, 2010

REVIEW ARTICLE

Assessing the mechanisms of brain plasticity by transcranial magnetic stimulation

Ali Jannati[1,2,3]✉, Lindsay M. Oberman[4], Alexander Rotenberg[1,2,3] and Alvaro Pascual-Leone[5,6,7]✉

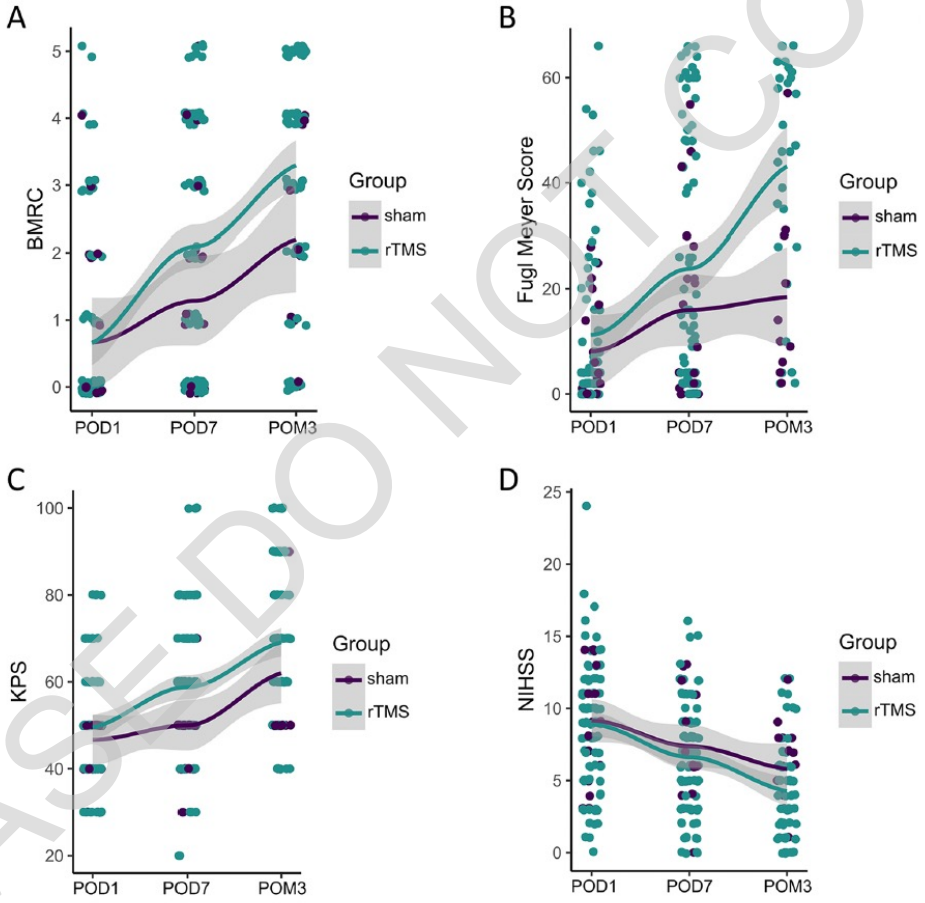
Neuropsychopharmacology **48**, 191–208 (2023) Jannati et al., *Neuropsychopharmacology*, 2023

Promising results for motor recovery in neurosurgery

Method:

- secondary analysis of two randomized and three one-arm studies in brain tumor patients with new/progressive postoperative paresis
- low frequency contralesional nrTMS or sham stimulation followed by physiotherapy

N= 135



Rosenstok et al, Journal of Neuro-Oncology (2025) 172:417–428

Promising results for stroke motor recovery

Stroke

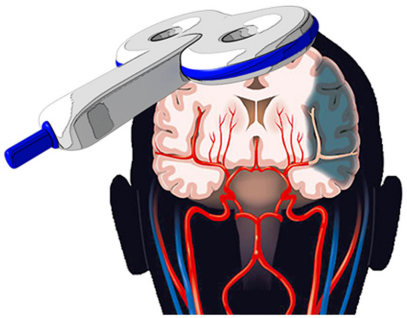
CLINICAL TRIAL

Continuous Theta-Burst Stimulation of the Contralesional Primary Motor Cortex for Promotion of Upper Limb Recovery After Stroke: A Randomized Controlled Trial

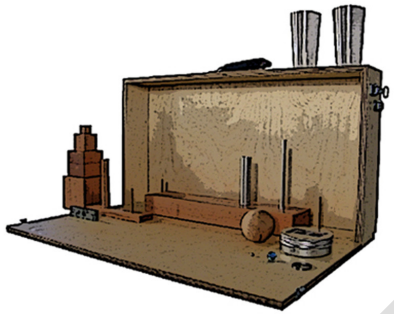
Jord J.T. Vink, MSc*; Eline C.C. van Lieshout, PhD*; Willem M. Otte, PhD; Ruben P.A. van Eijk, PhD; Mirjam Kouwenhoven, MD; Sebastiaan F.W. Neggers, PhD; H. Bart van der Worp, MD, PhD; Johanna M.A. Visser-Meily, MD, PhD; Rick M. Dijkhuizen, PhD

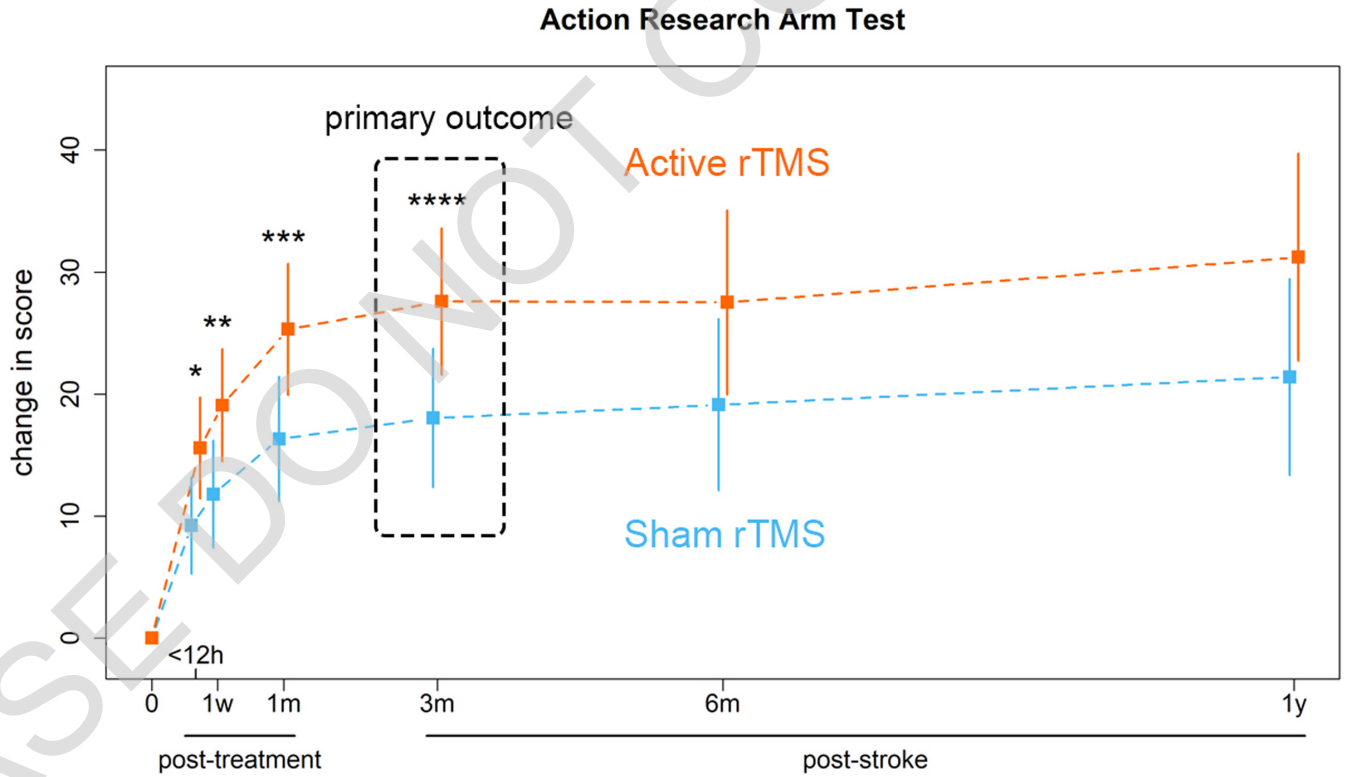
Promising results for stroke motor recovery

Intervention: Active versus sham inhibitory rTMS of the contralesional M1 combined with upper limb physical therapy



Primary outcome: Action Research Arm test at 3 months post-stroke





Interpreting contrasting findings

Stroke

CLINICAL TRIAL

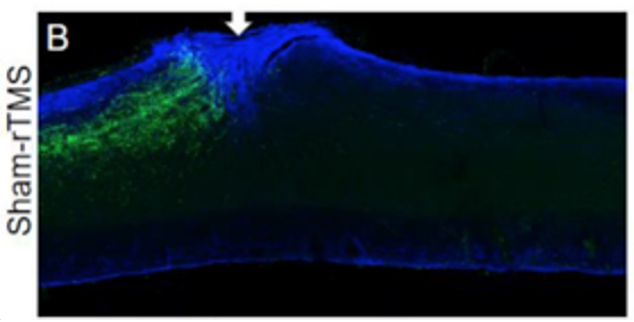
Electric Field Navigated 1-Hz rTMS for Poststroke Motor Recovery: The E-FIT Randomized Controlled Trial

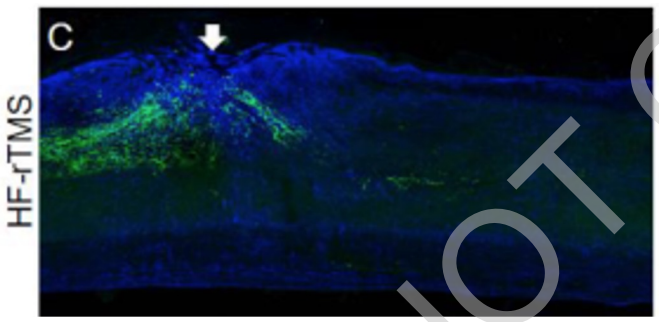
Dylan J. Edwards, PhD, PT; Charles Y. Liu, MD, PhD; Kari Dunning, PT, PhD; Felipe Fregni, MD, PhD; Jarmo Laine, MD; Benjamin E. Leiby, PhD; Lynn M. Rogers, PhD; Richard L. Harvey, MD

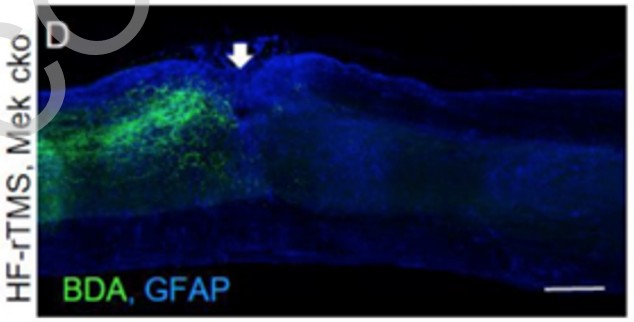
Edwards et al., *Stroke*, 2023

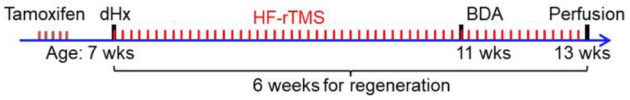
Di Pino, et al., *Nat Rev Neurol*, 2014 Di Pino, et al., *Clin Neurophysiol*, 2020 Lin & Baker, *Brain Stim*, 2022 Cole et al., *Am J Psychiatry*, 2020 Cole et al., *Am J Psychiatry*, 2022

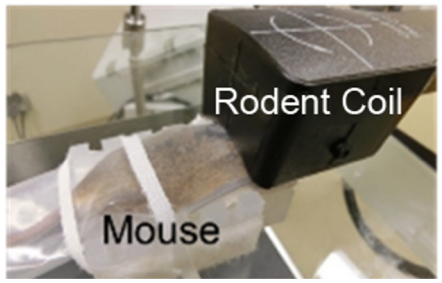
High frequency rTMS facilitates axon regeneration

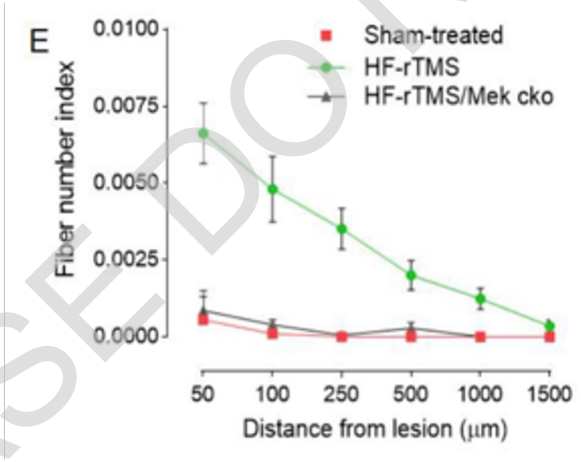


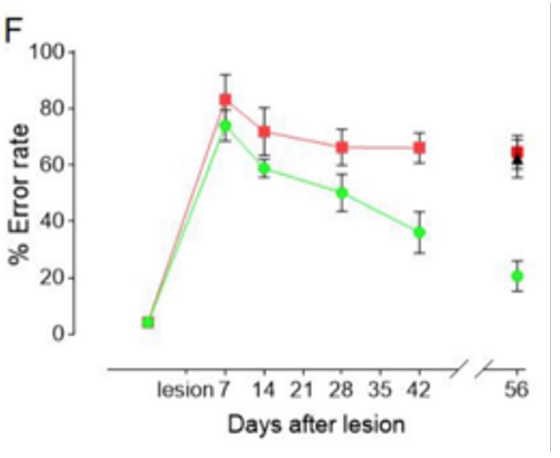




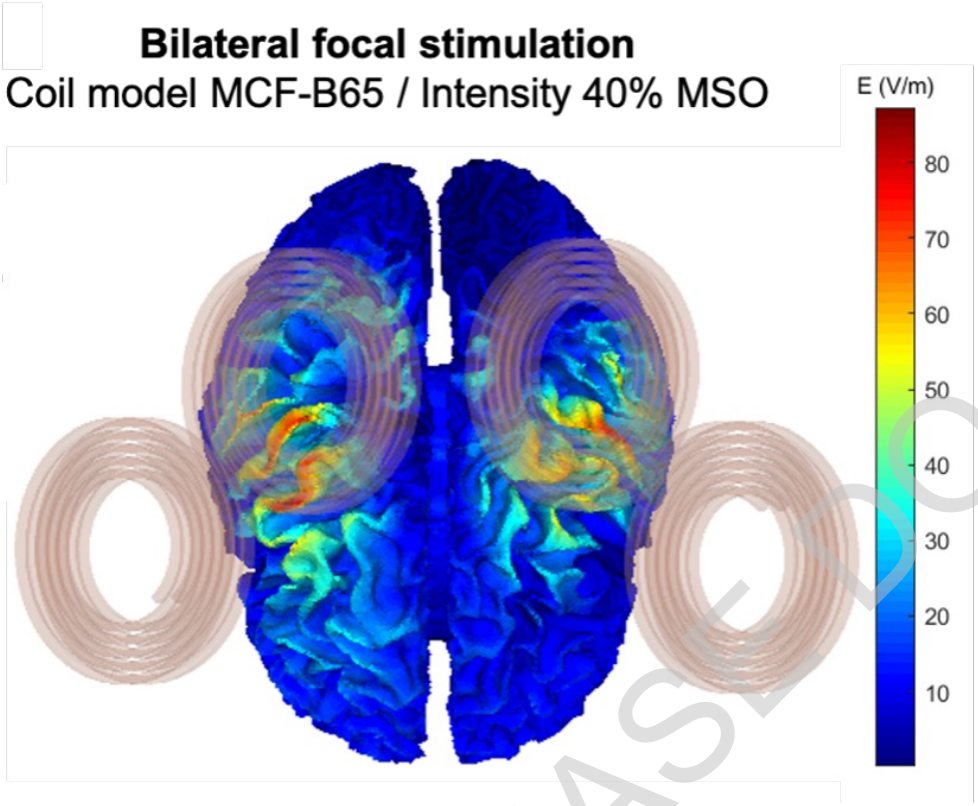








Translating HF-rTMS to human SCI - Phase 1 RCT commencing



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Conclusions

Advances in TMS electric field modeling & use of robotic positioning or multi-coil arrays can:

- enhance brain structure-function investigation
- improve targeting for neuromodulation with rTMS/TBS

Clinical & Translational studies are showing benefit for recovery of motor function

- starting early in recovery
- rational target and parameter selection based on contemporary theory, including use of network-based target selection

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Jefferson Moss Rehabilitation Research Institute
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Osborne Park, St. John of God, & Fiona Stanley Hospitals
Perron Institute for Neurological & Translational Science
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Jian Zhong, PhD

Exercise Medicine Research Institute
MSWA
NICHE/E-FIT Trial Investigators
Northstar.CA Trial Investigators
Neurotrauma Research Program
Research Participants
The SPIN Research Team

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Gary Thickbroom, PhD