Thomas Jefferson University

Brain Stimulation in Rehabilitation

Intensive Course in Transcranial Magnetic Stimulation

Harvard Medical School, CME

Dylan J. Edwards, PhD
Nancy W. Shrier Director, Jefferson Moss Rehabilitation Research Institute
Professor, Thomas Jefferson University, Philadelphia

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Precision Neuromodulation

Predicting response to rTMS might be best understood using a precision medicine approach:

"The right treatment, for the right patient, at the right time"

Of the many factors that influence outcome in rTMS, the highest priority are:

- **what brain target/s (based on lesion)**
- **how to hit the target (dose at correct brain node)**
- **inhibition or excitation effect desired**
- **timing (what stage of recovery, what type of physical therapy)**

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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



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Robotics may help pave the way for regaining independent movement







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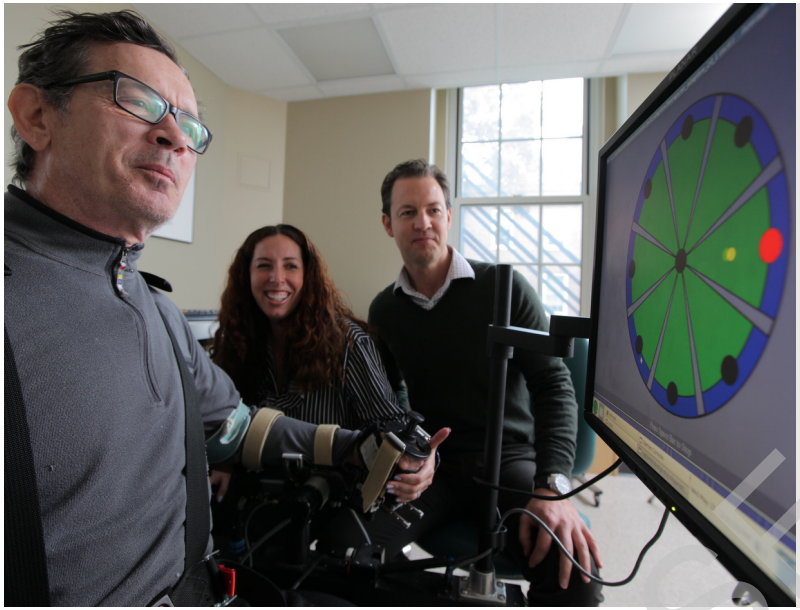
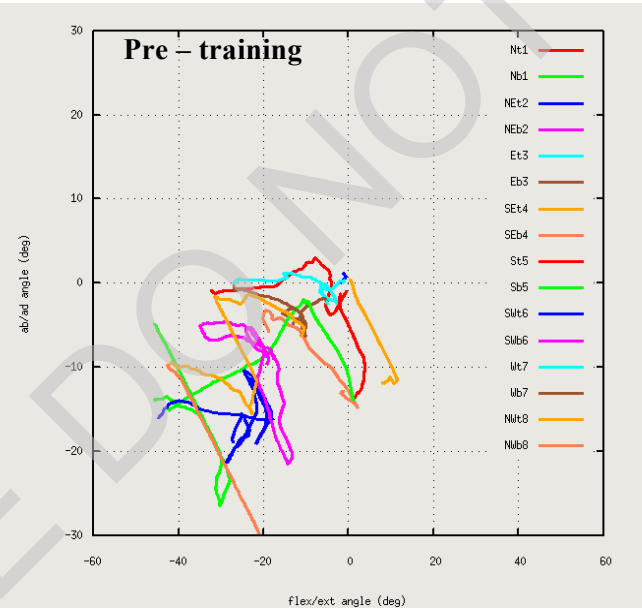
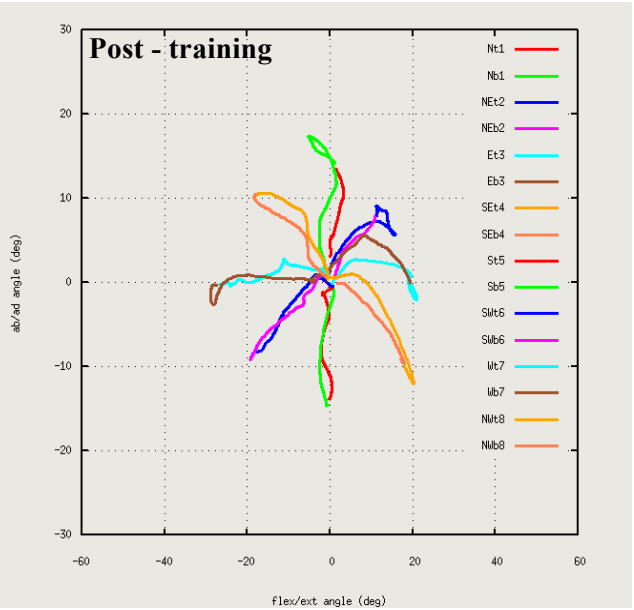
Robotics may help pave the way for regaining independent movement







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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.





NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY
Funded by a Grant from the National Institutes of Health

ClinicalTrials.gov ID
NCT06682429

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

Jefferson Moss Rehabilitation Research Institute

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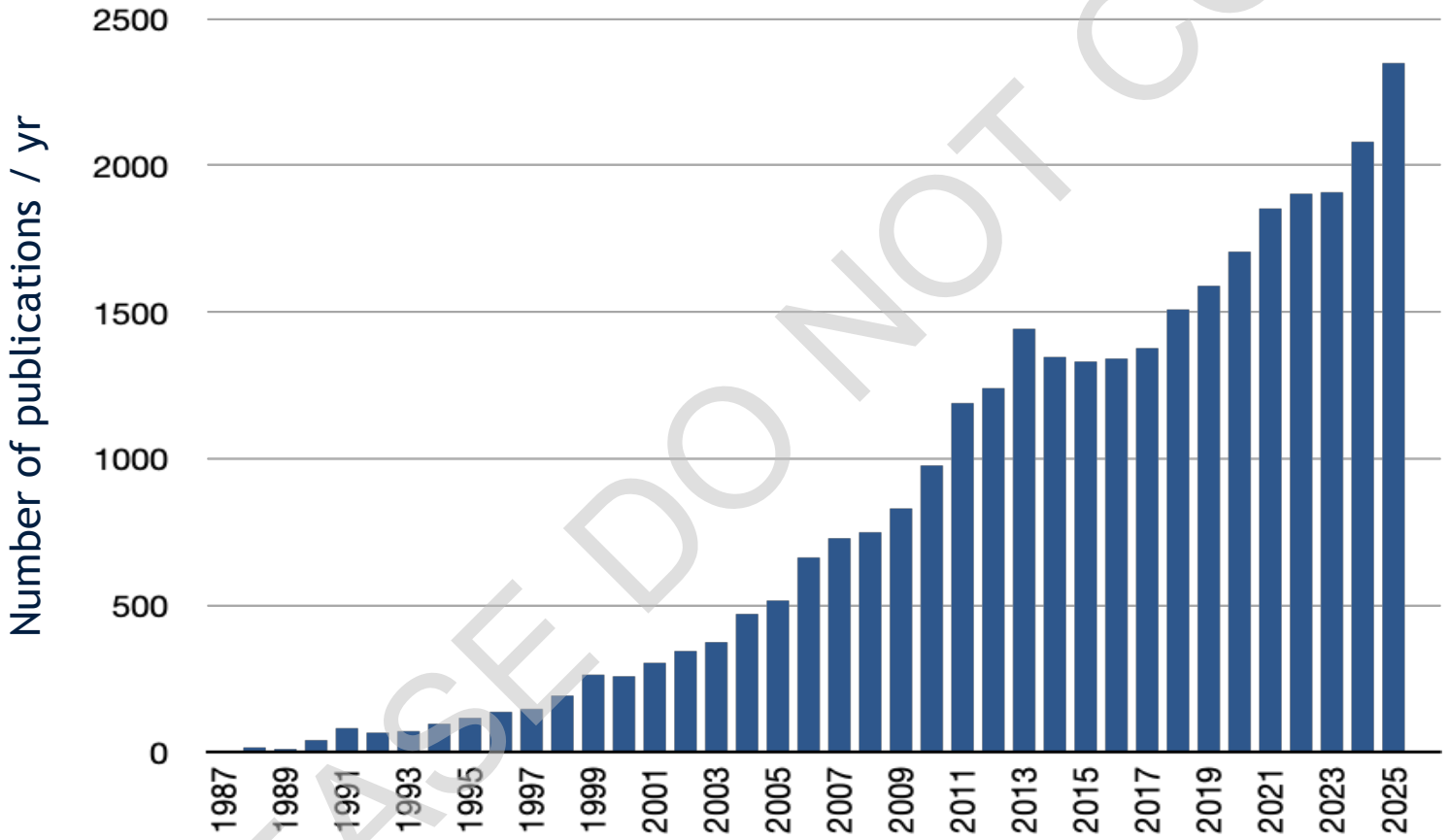
Interest in TMS - Scientific Publications



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

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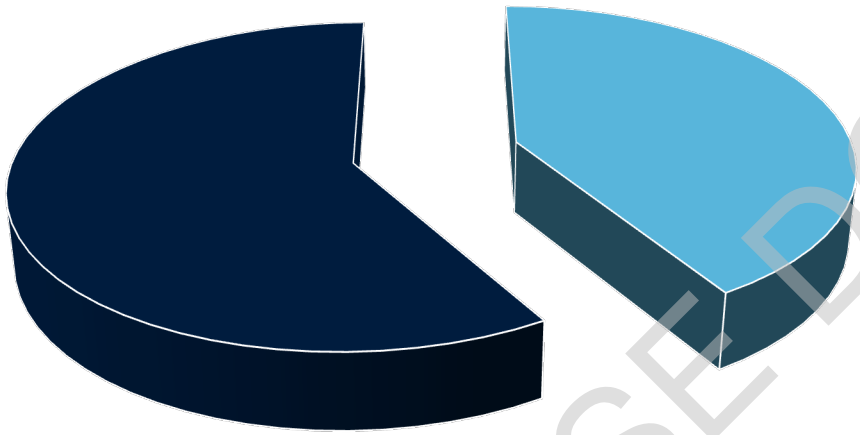
Large number of TMS clinical trials

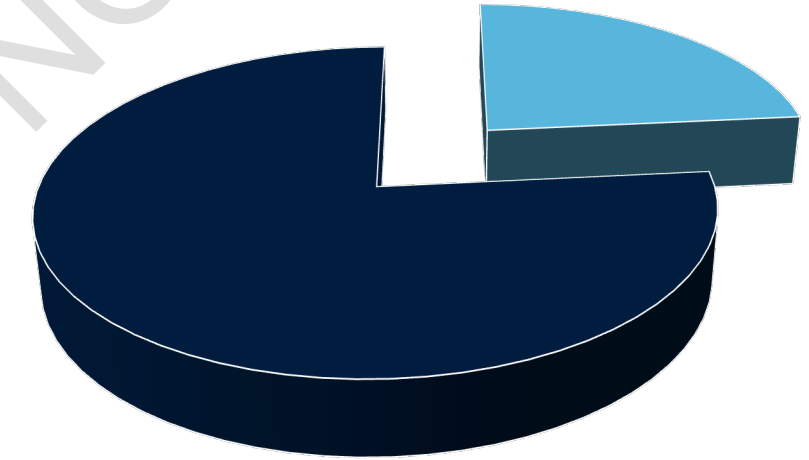
2,612 TMS clinical trials have been registered

- 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.

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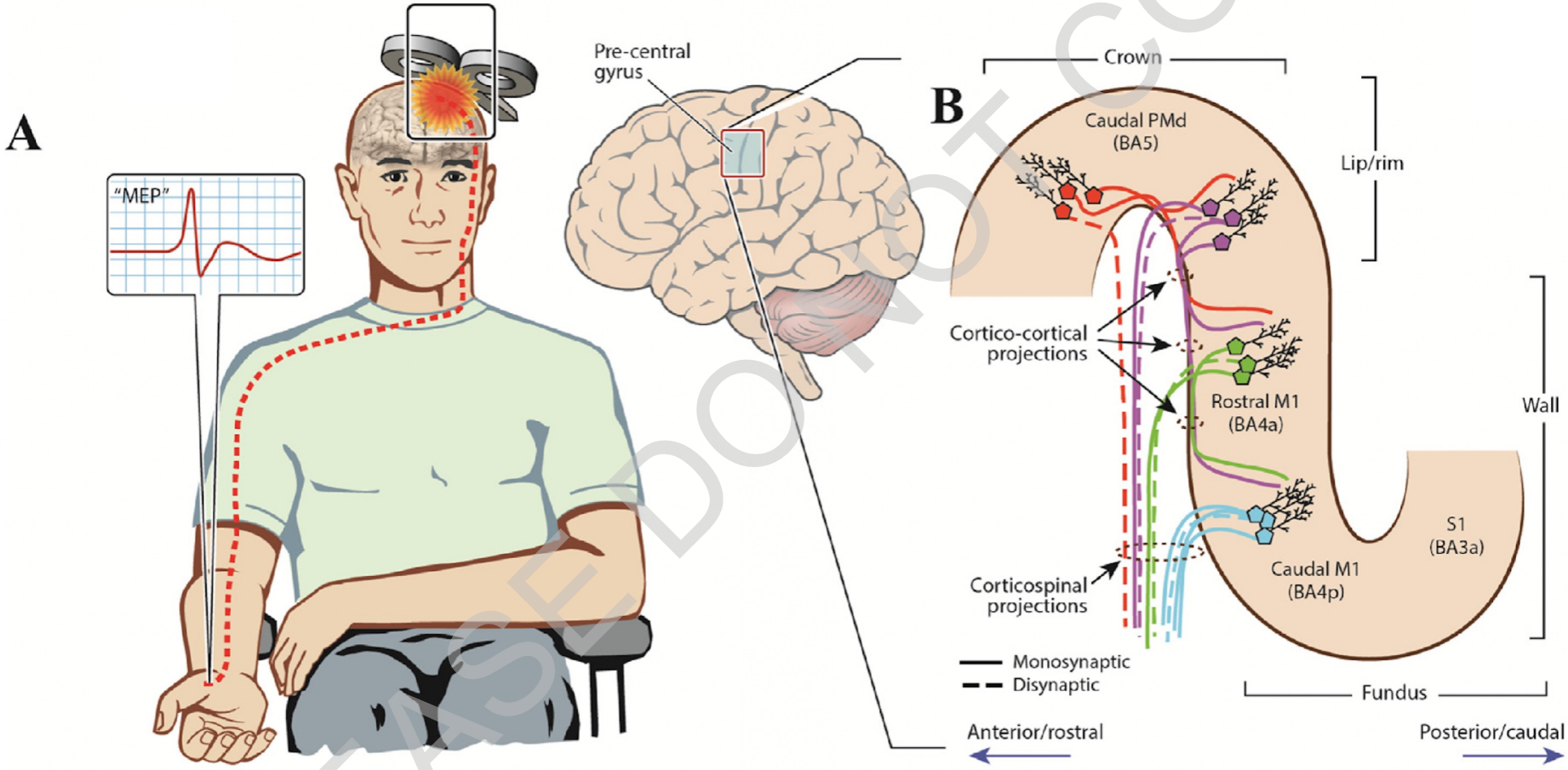
Transcranial magnetic stimulation: Physics, Anatomy, Physiology



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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

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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

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Towards Phase III RCT / clinical efficacy

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Part 1: Background

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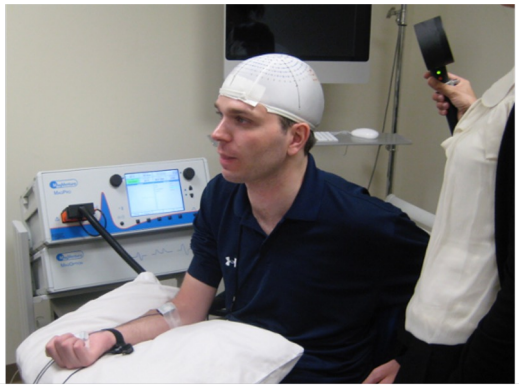
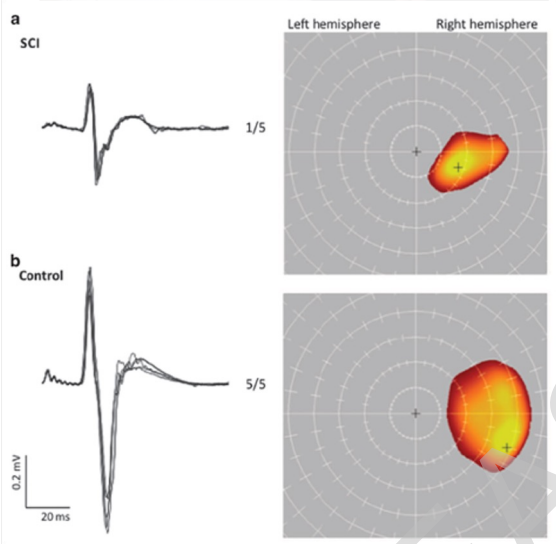
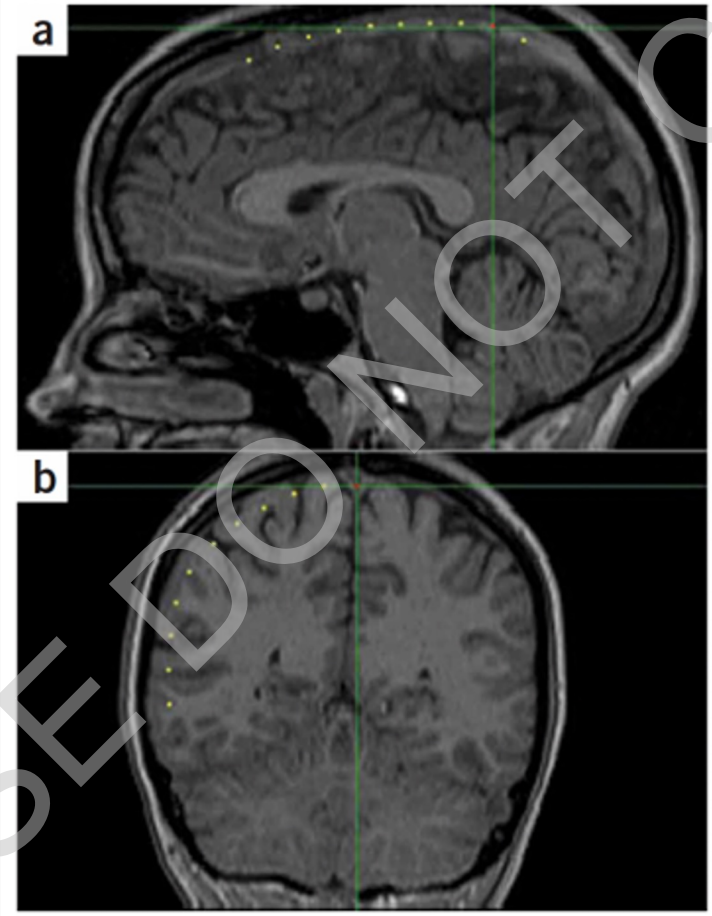
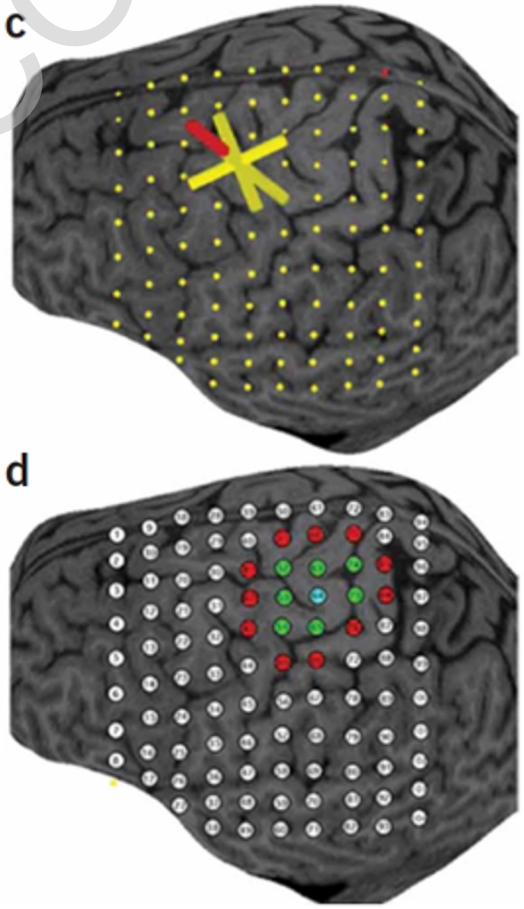
Historical – Mapping MEP to a scalp or cortical location





Cortes et al., *Spinal Cord*, 2017





Kleim et al., *Nature Protocols*, 2007

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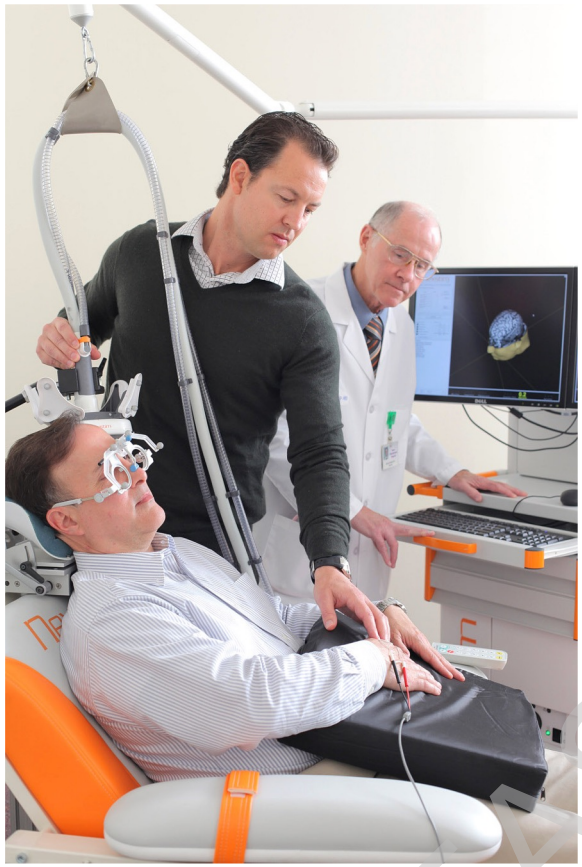
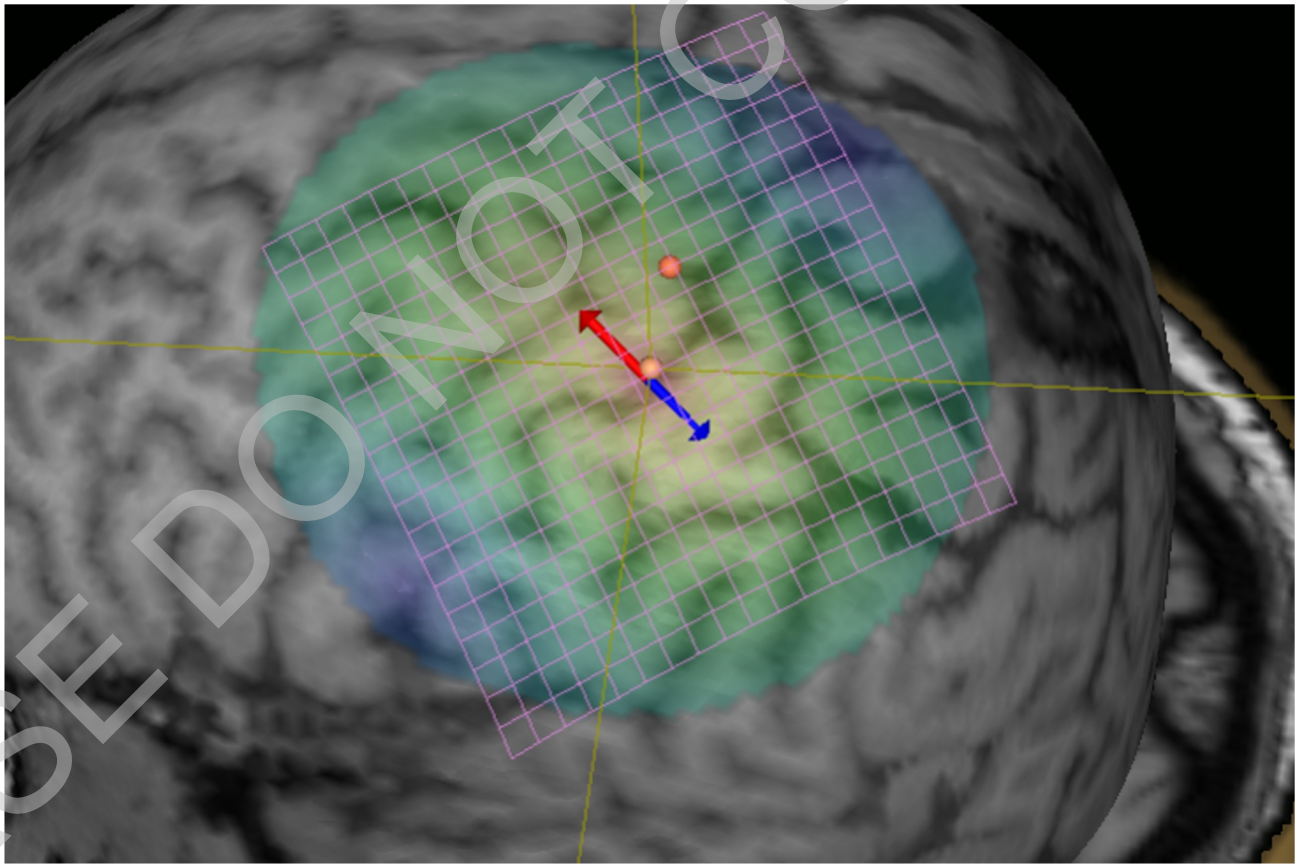
Precision motor mapping can inform brain ‘re-organization’ in recovery





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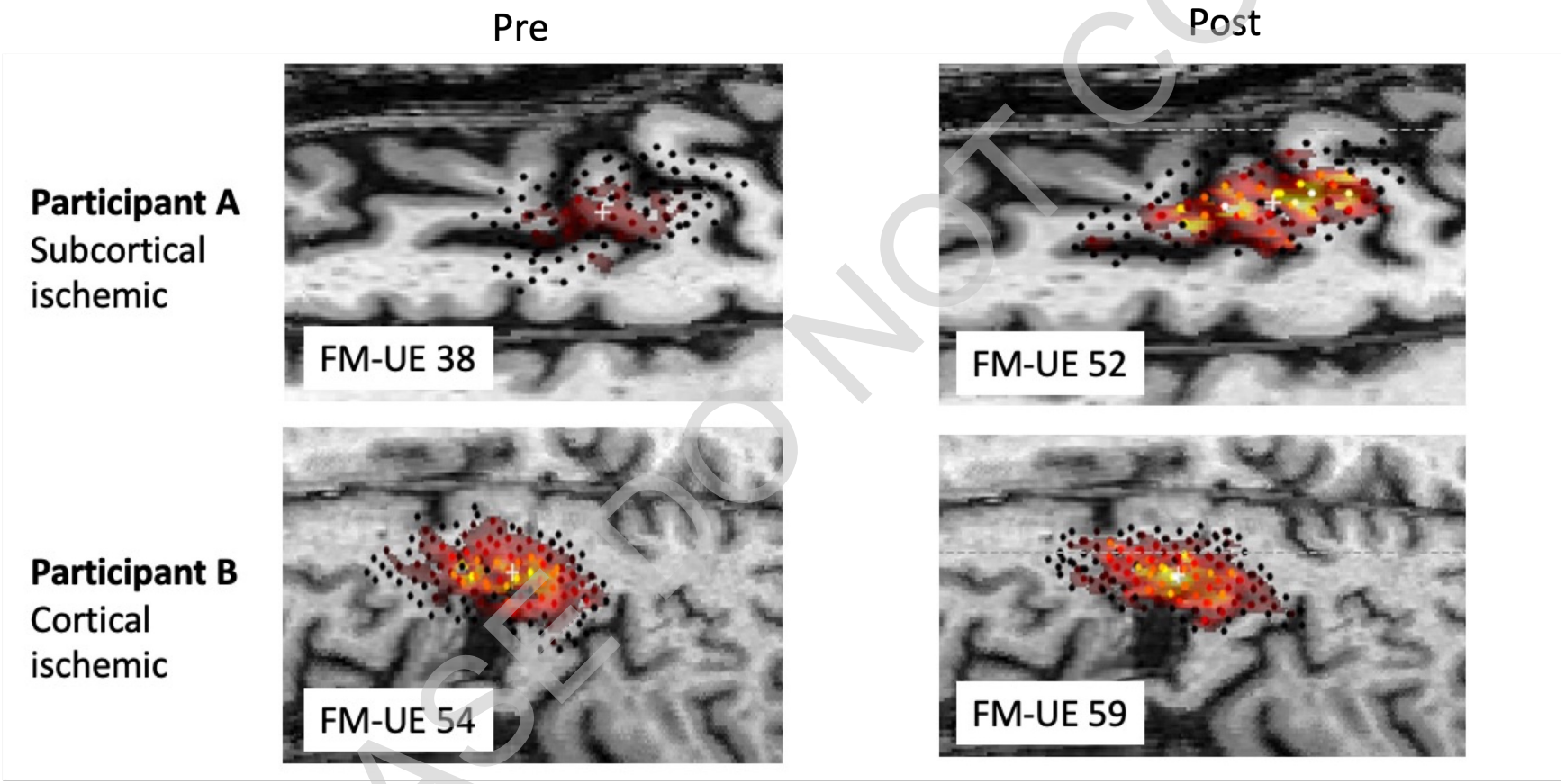

FM-UE: Fugl-Meyer Upper Extremity (Max 66)

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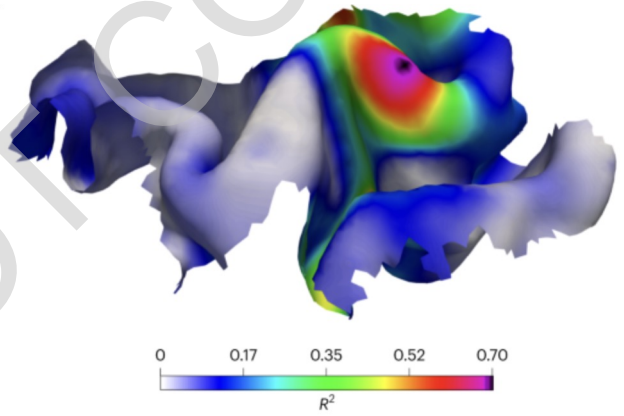
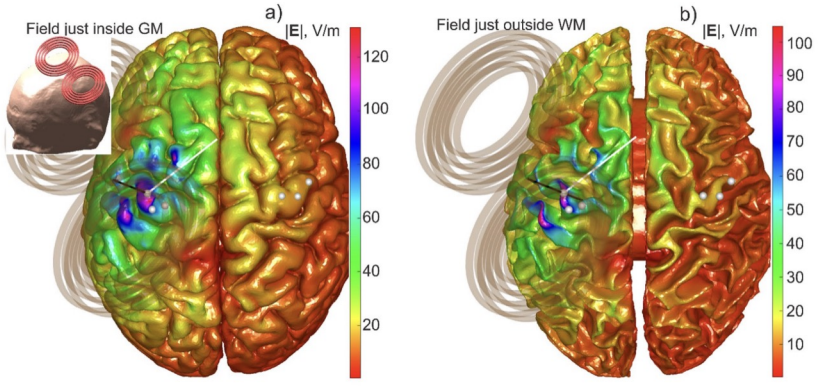
Contemporary - Mapping cortical electric fields to individual anatomy

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

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Precision motor mapping can inform brain organization

Famous 'homunculus' brain map redrawn to include complex movements

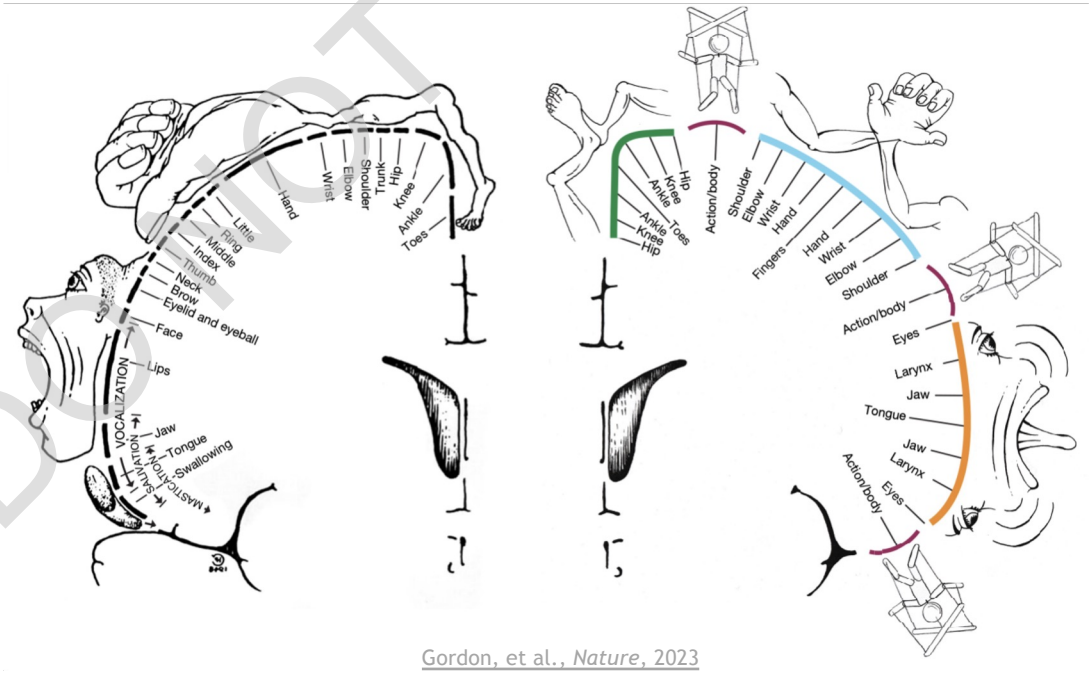


nature NEWS | 19 April 2023

Kozlov, *Nature News*, 2023

Penfield's homunculus (1948)

Integrate-isolate model (2022)



Gordon, et al., *Nature*, 2023

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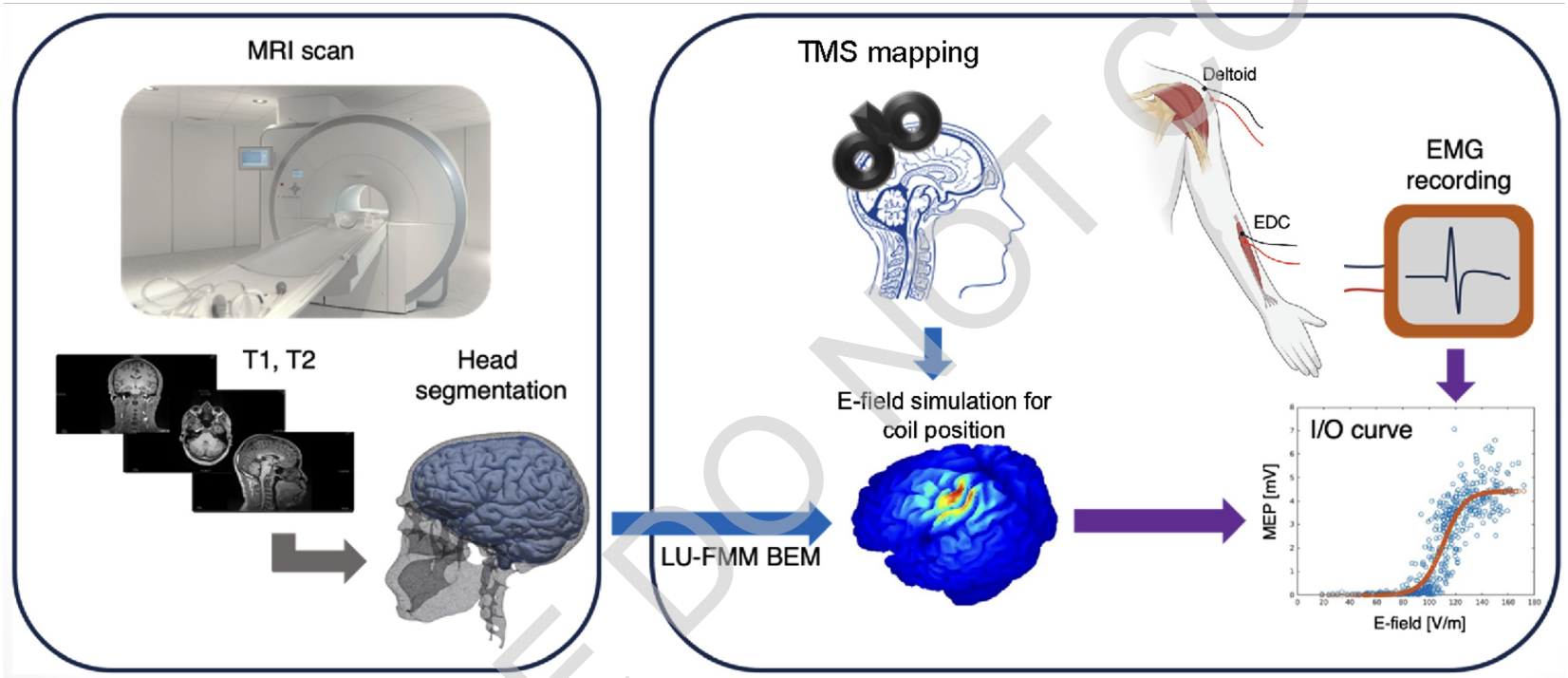
Workflow for mapping



- 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.

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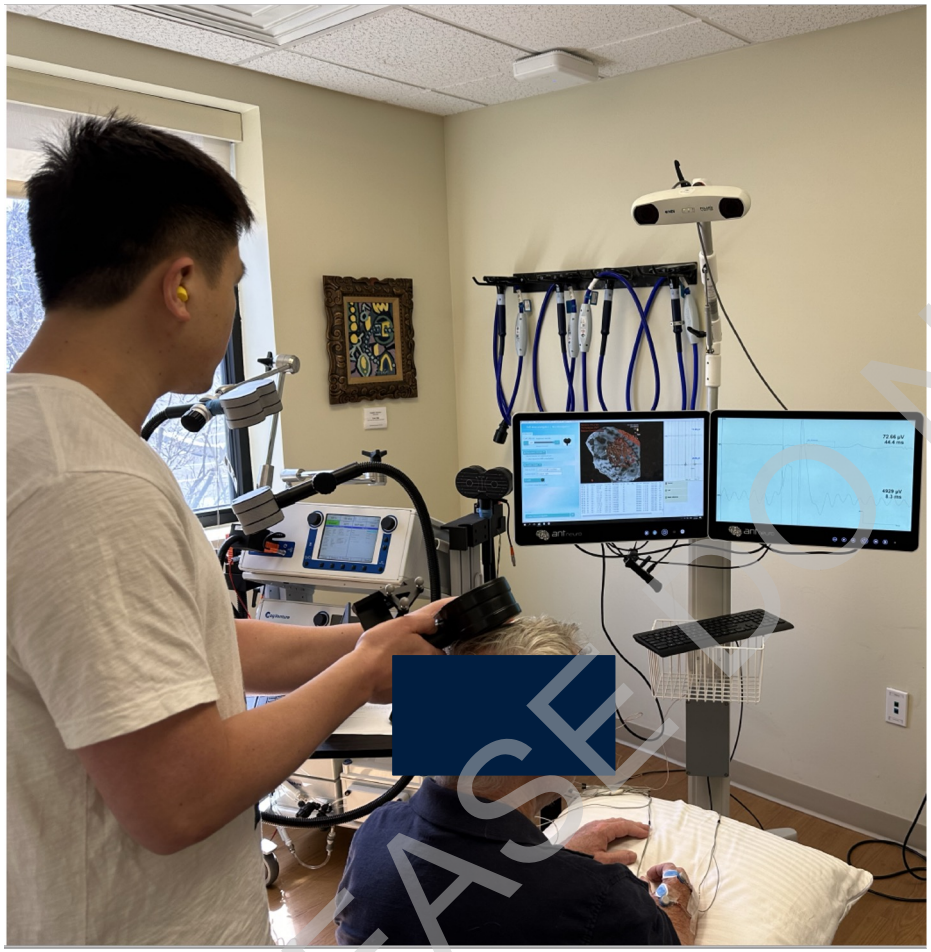
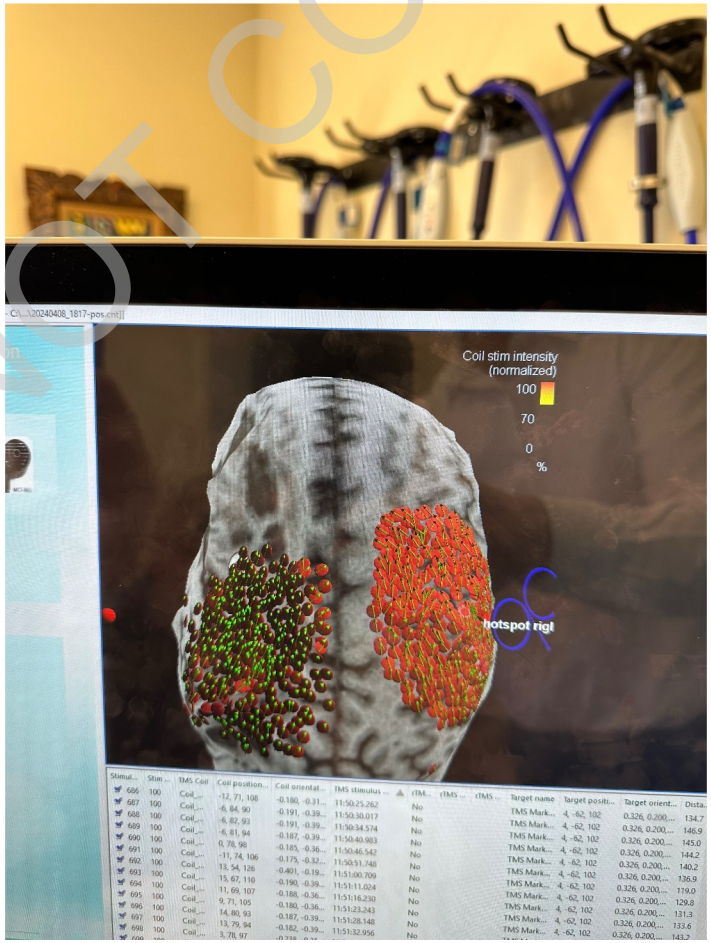
Identifying Rational targets





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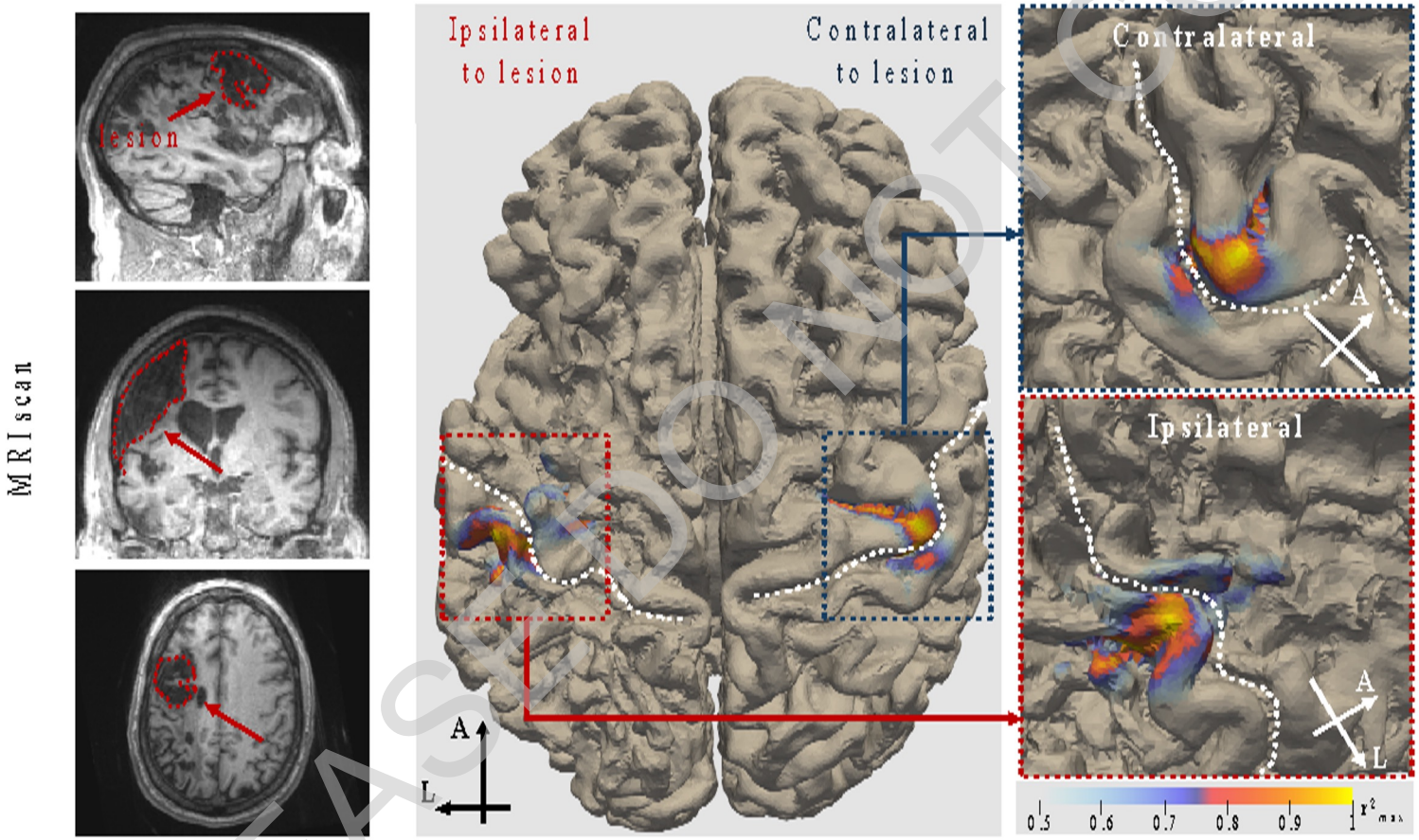
Stroke Mapping Case — for precision neuromodulation



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

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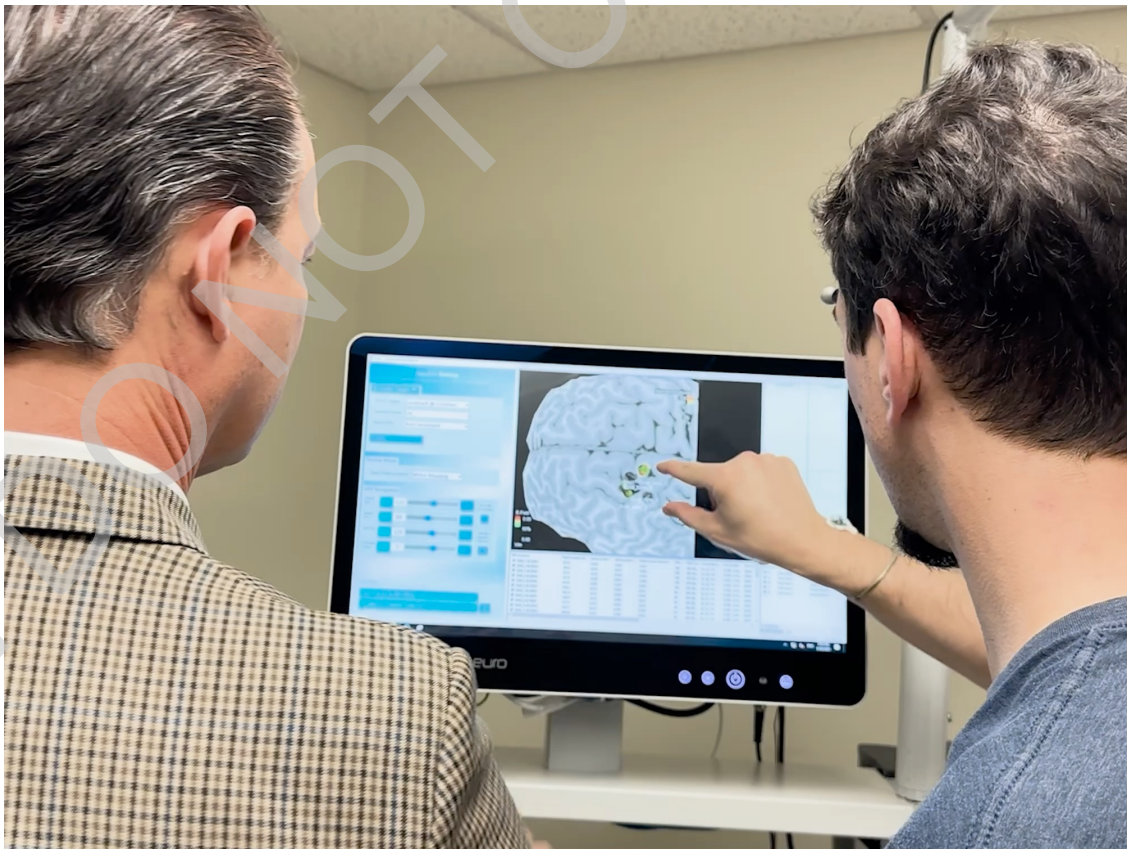
Emerging tech: Robotics & multi-coil arrays

Robotic arm for automated targeting





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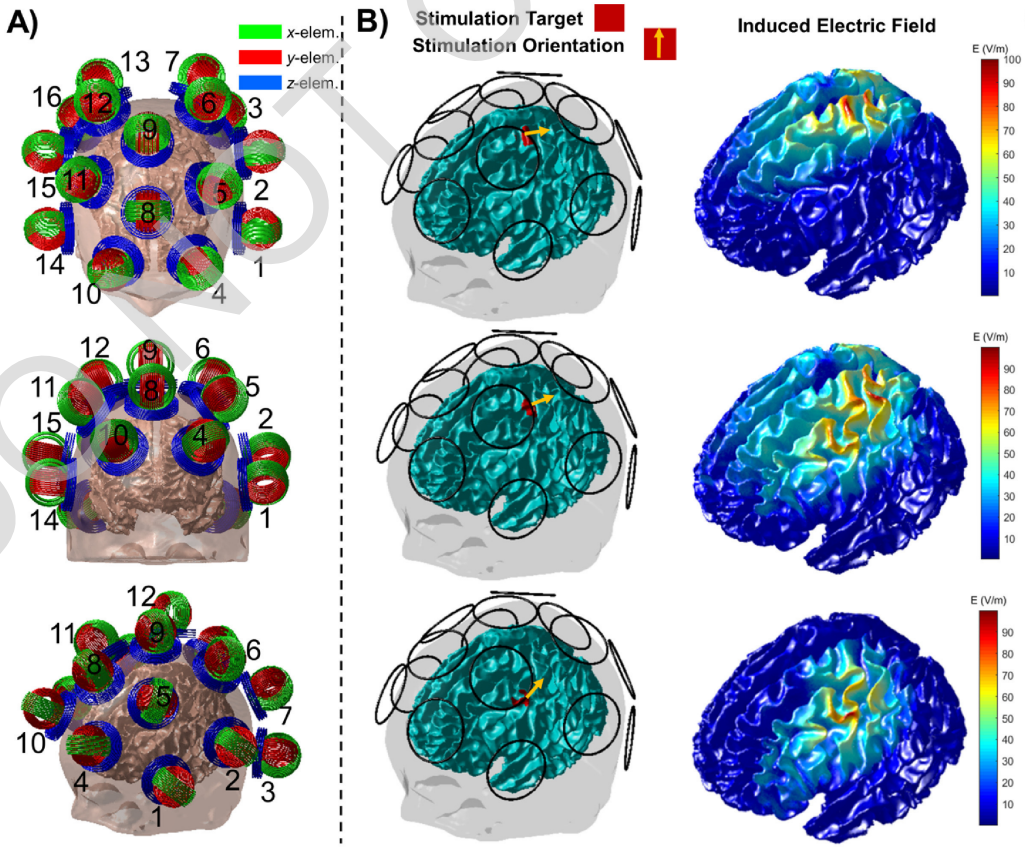
Emerging tech: Robotics & multi-coil arrays

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

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Part 1: Background

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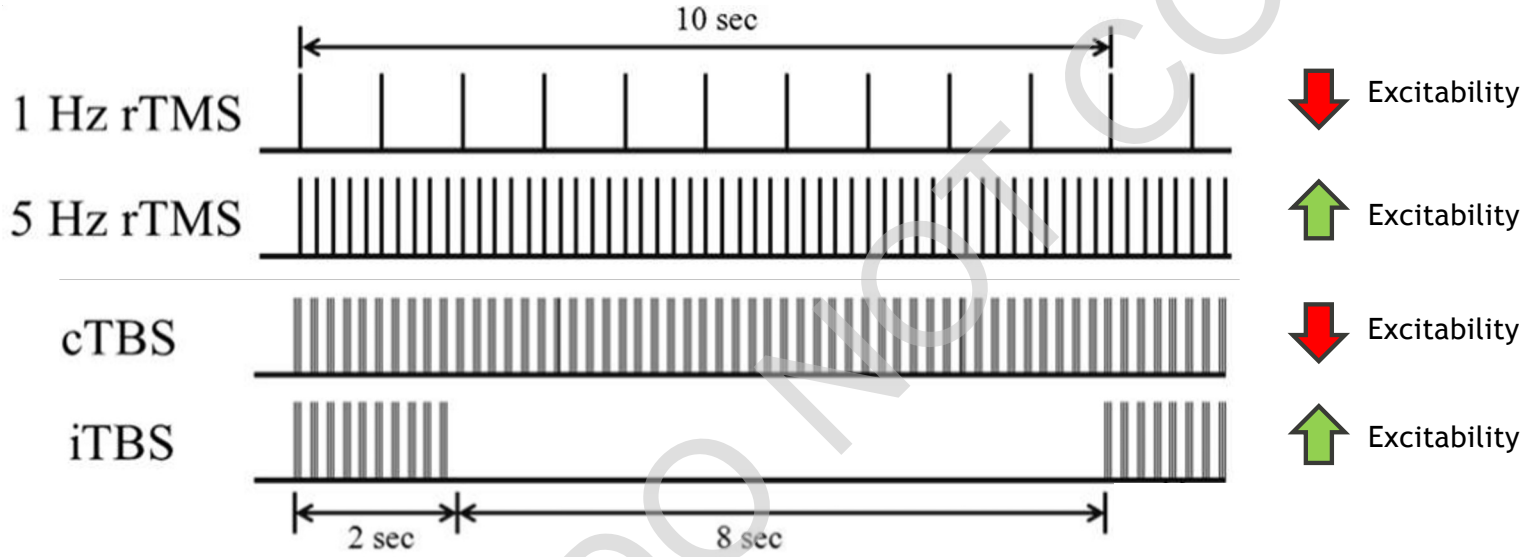
Common patterns of stimulation used for neuromodulation



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

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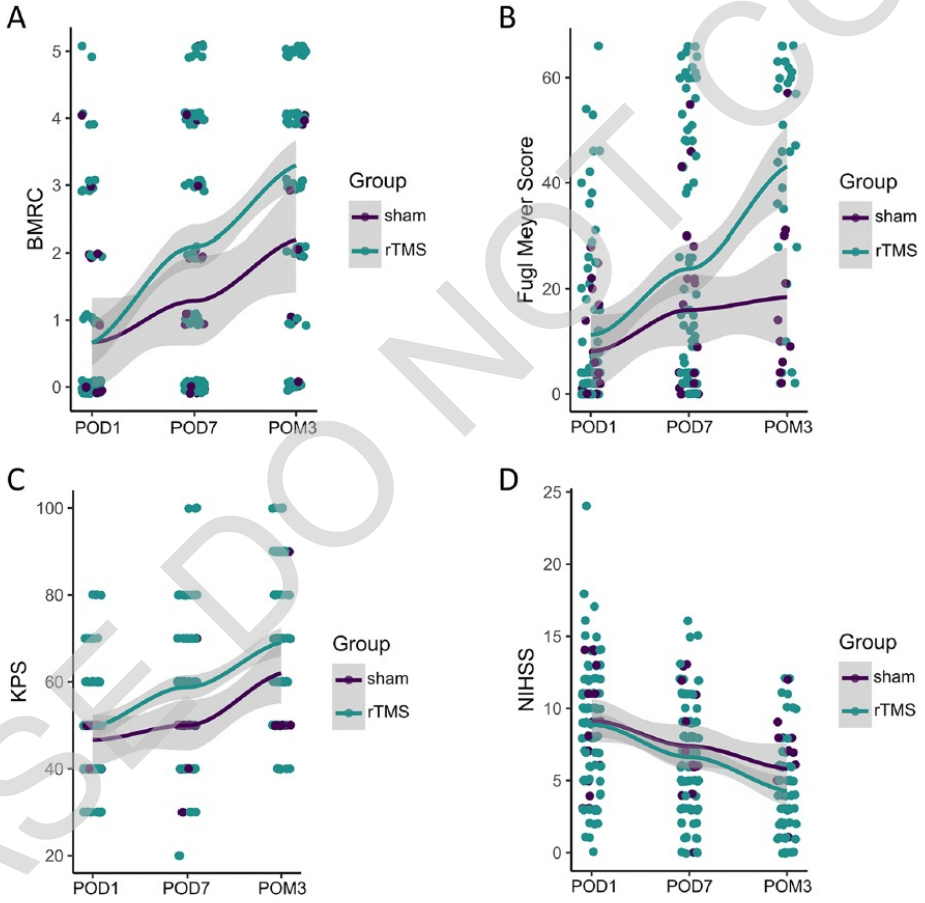
Promising results for motor recovery in neurosurgery

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

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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

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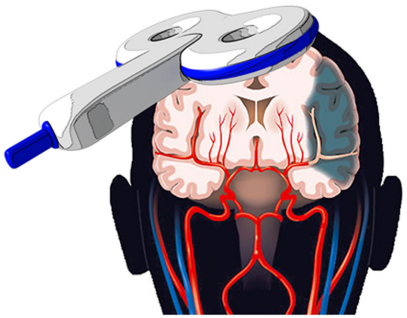
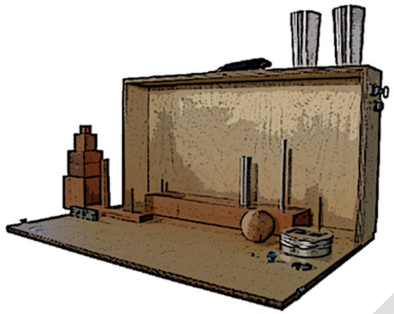
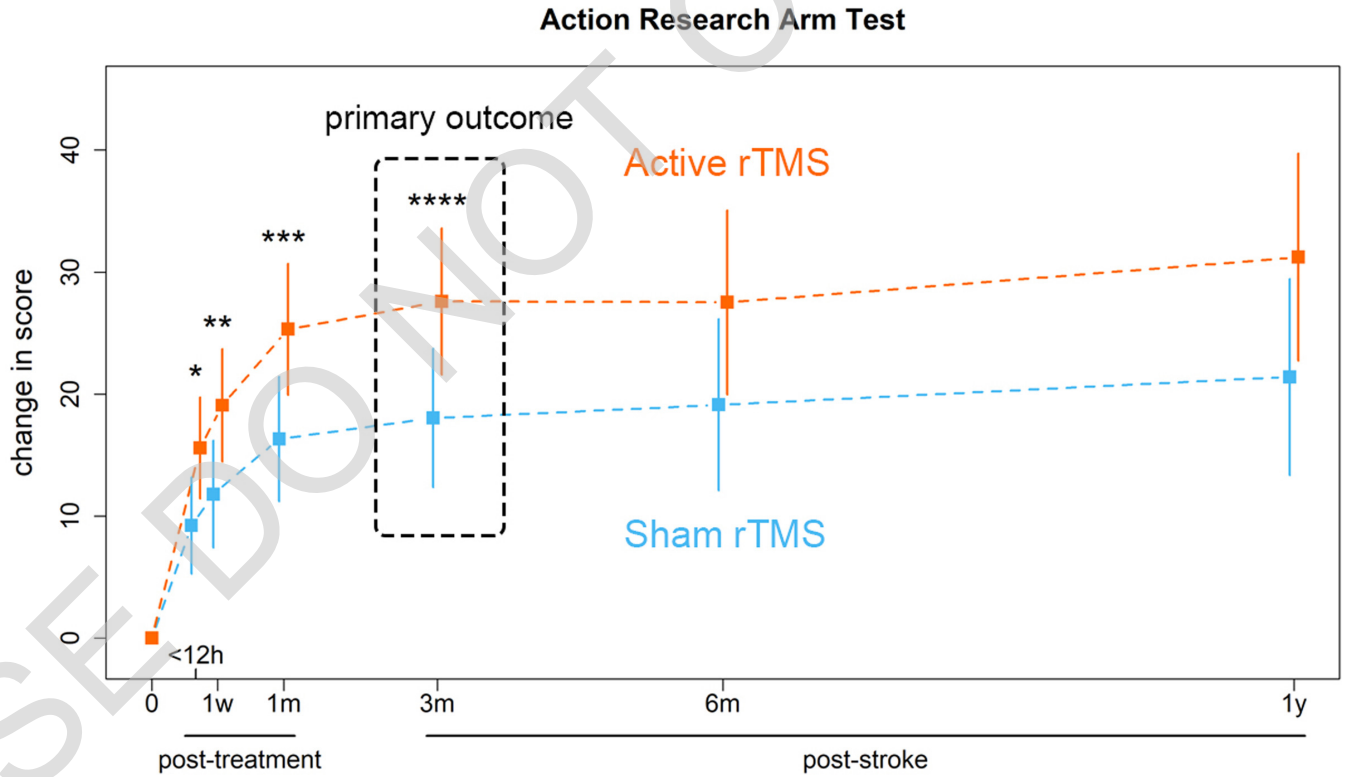
Promising results for stroke motor recovery

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





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Vink et al., *Stroke*, 2023

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

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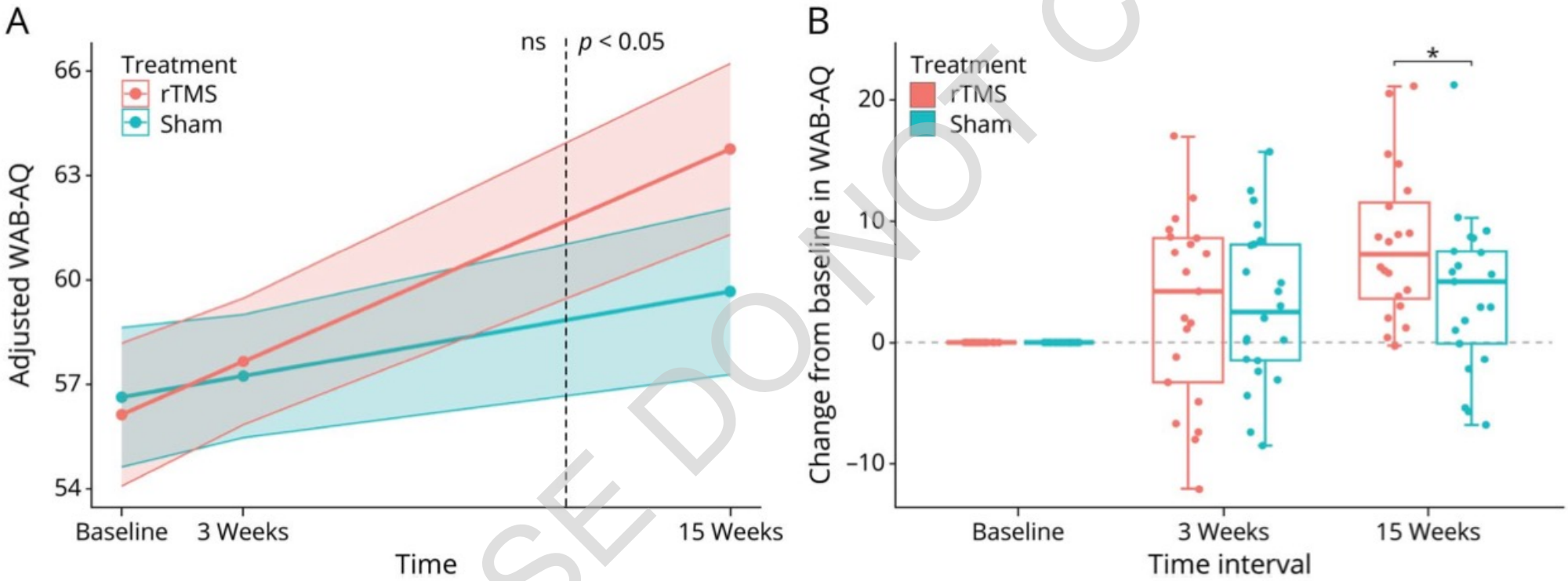
1Hz rTMS improves post-stroke aphasia



Neurology®

Low et al, 2025

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Neuromodulation vs Regeneration/Repair

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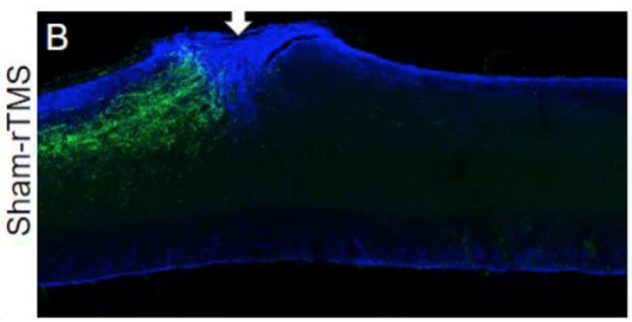
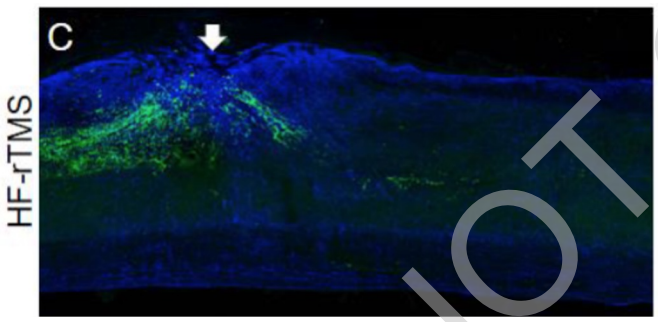
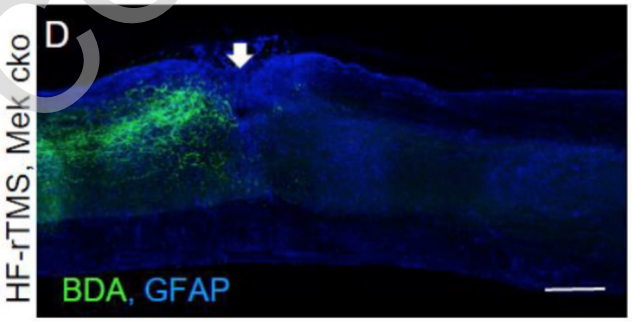
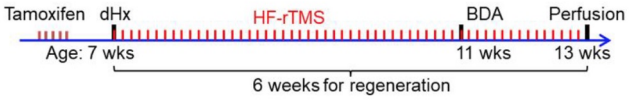
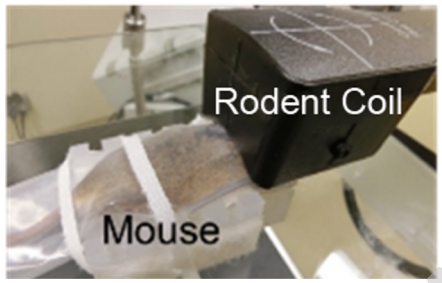
High frequency rTMS facilitates axon regeneration

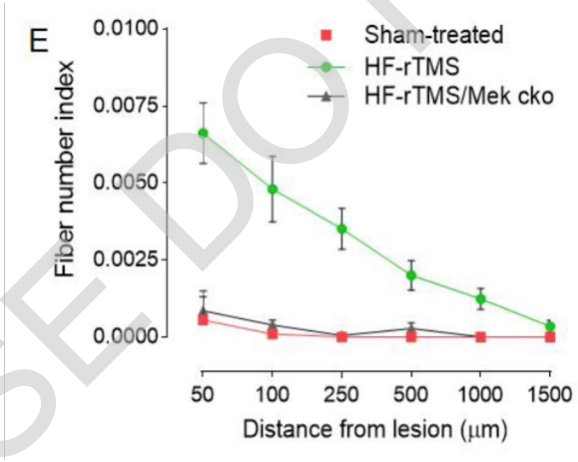


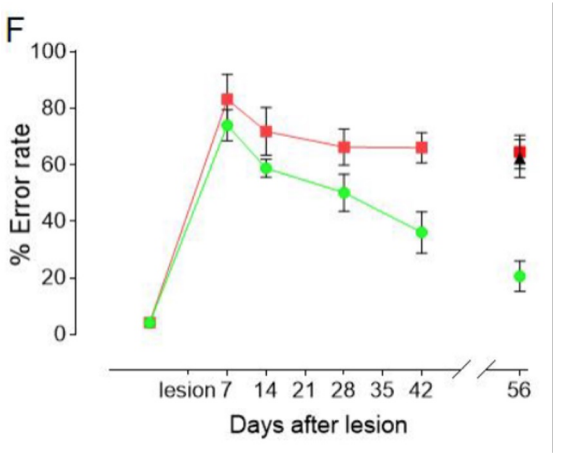












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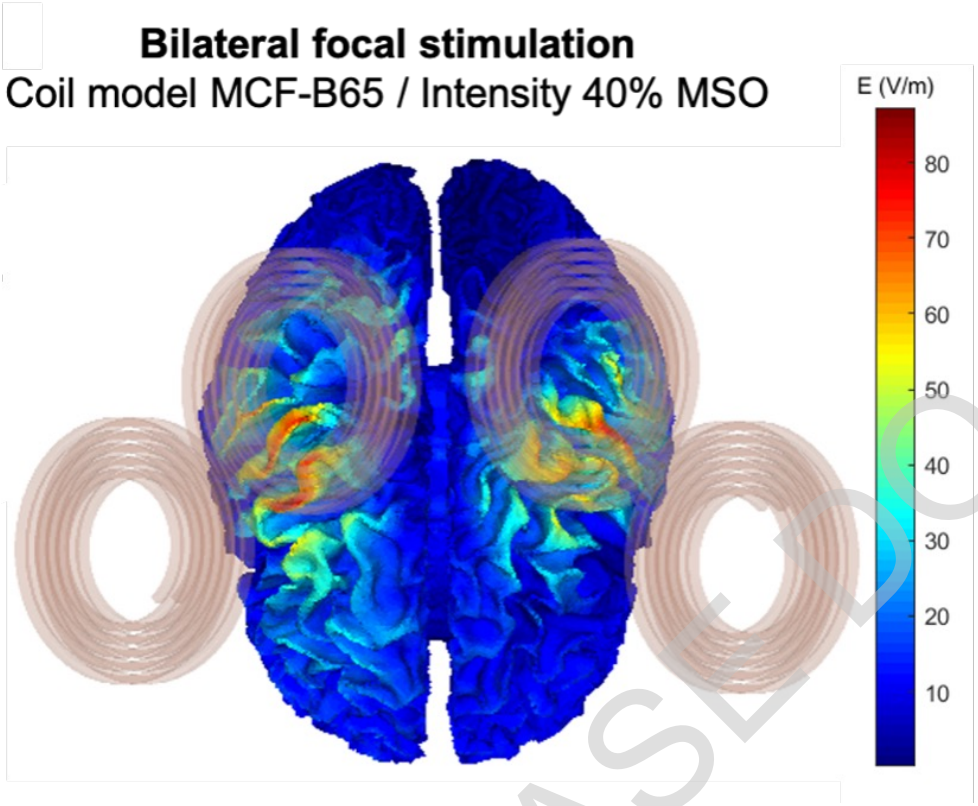
Translating HF-rTMS to human SCI - Phase 1 RCT commencing





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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 for motor
- rational target and parameter selection based on contemporary theory, including use of network-based target selection

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Acknowledgements

Funding and Support:

Canadian Institutes of Health Research
National Institutes of Health
New York State PART and IDEAS Grants
Pennsylvania Department of Health

Foundations
Adelson, Burke, Skirball, Train-the-Brain
Chernowitz Medical Research Foundation

Industry Support
ANT Neuro
Ekso Bionics
TRCare
Nexstim Ltd., Finland

Philanthropy
Nancy Wachtel Shrier Directorship, Jefferson Moss Rehabilitation Research Institute

Organizations:

Burke Neurological Institute / Weill Cornell Medicine
Edith Cowan University
Einstein Healthcare Network
Jefferson Moss Rehabilitation Research Institute
Martinos Center / MGH / Harvard University
Osborne Park, St. John of God, & Fiona Stanley Hospitals
Perron Institute for Neurological & Translational Science
Thomas Jefferson University
UCLA/CalRehab

Colleagues, current and former lab staff:

Amanda Bernstein, BE
Amy Bialek, MS, PT
Marom Bikson, PhD
Francesco Boato, PhD
Johanna Chang, SLP
Mar Cortes, MD
Bruce Dobkin, MD
Carolin Dohle, MD
Taiza Edwards, PT, PhD
Felipe Fregni, MD, PhD
Mena Garcia-Vega, PT
Linda Gerber, PhD
Xiaofei Guan, MD, PhD
Gavin Hsu, PhD candidate
Marco Iacoboni, MD
Evgenii Kim, PhD
Tomoko Kitago, MD
John Krakauer, MD
Hermano Krebs, PhD
Amy Kucyeski, PhD
Sapna Kumar, PhD
Sergey Makarov, PhD
Ken Nosaka, PhD
Aapo Nummenmaa, PhD
Clara Oromendia, PhD
Alvaro Pascual-Leone, MD, PhD
Lucas Parra, PhD
Heather Pepper Lane, MA
Raj Ratan, MD PhD
Michael Reding, MD
Jennifer Roger, PhD
Avrielle Rykman Peltz, MA
Heidi Schambra, MD
Joshua Silerstein, BS
Barby Singer, PT, PhD
Janet Taylor, MD, PhD
Gary Thickbroom, PhD
Zoe Tsagaris, MS, OTR/L
Onno van Der Groen, PhD
Kirsten van Rijn, PT
Bruce Volpe, MD
Susan Wortman-Jutt, SLP
Helma Zanders, MS, PT
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

Presentation Insights:

Steve Cramer, MD
Sapna Kumar, PhD
Marie McNeely, PhD
Gary Thickbroom, PhD

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