The Future of TMS

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Alexander Rotenberg, MD, PhD



TMS Course - Harvard Medical School

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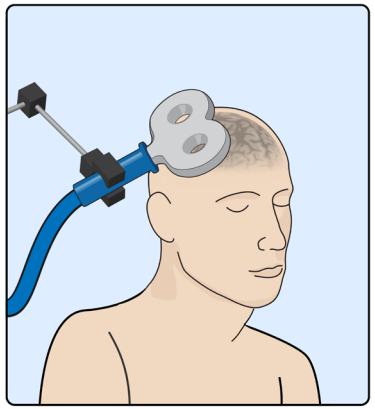
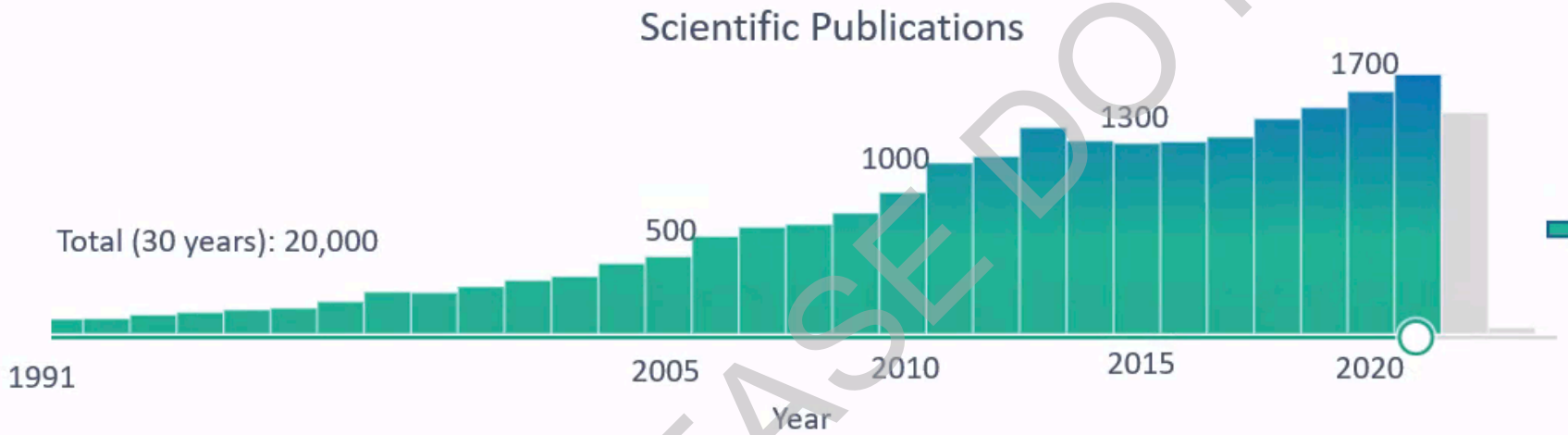


Transcranial Magnetic Stimulation (TMS)



FDA clearances

- 2008 Major depression disorder (MDD)
- 2009 Cortical mapping
- 2013 Migraine with aura
- 2015 Obsession compulsory disorder (OCD)
- 2020 Smoking cessation
- 2021 Anxiety comorbidity with MDD

(Cohen, Samantha L., et al., 2022)

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TMS in Medication-Resistant Depression

Real Clinical Impact !

- >600 systems in clinical use in the US
- 250 days/year & 5 patients/day

= *750,000 treatments per year*

- approx. 25 sessions/Rx/patient

= *30,000 patients/year*

- 30% remission

= *9,000 patients in remission/year*

➢ *25 patients in remission/day*

Covered by Medicare
& most health insurance plans in the US

Covered by health insurance in

- Canada
- Australia
- New Zealand
- Japan
- UK

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TMS in Medication-Resistant Depression

Real Clinical Impact !

- 60% + responders
- After a treatment course (of up to 6 weeks) benefit lasts on average 5 months
- In case of relapse, response to new treatment course is at least as good as initial response in >90% of cases [Kelly et al. J Neuropsych Clin Neurosci 2017]
- Maintenance is possible

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Present

Helping Patients

However……40% do NOT respond

We have yet to realize the promise of (noninvasive) neuromodulation





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(Noninvasive) Neuromodulation does not represent a treatment for an illness,

but offers **tool** that allows modulation of the neural substrate of **symptoms and disabilities** caused by brain illnesses or dysfunctions

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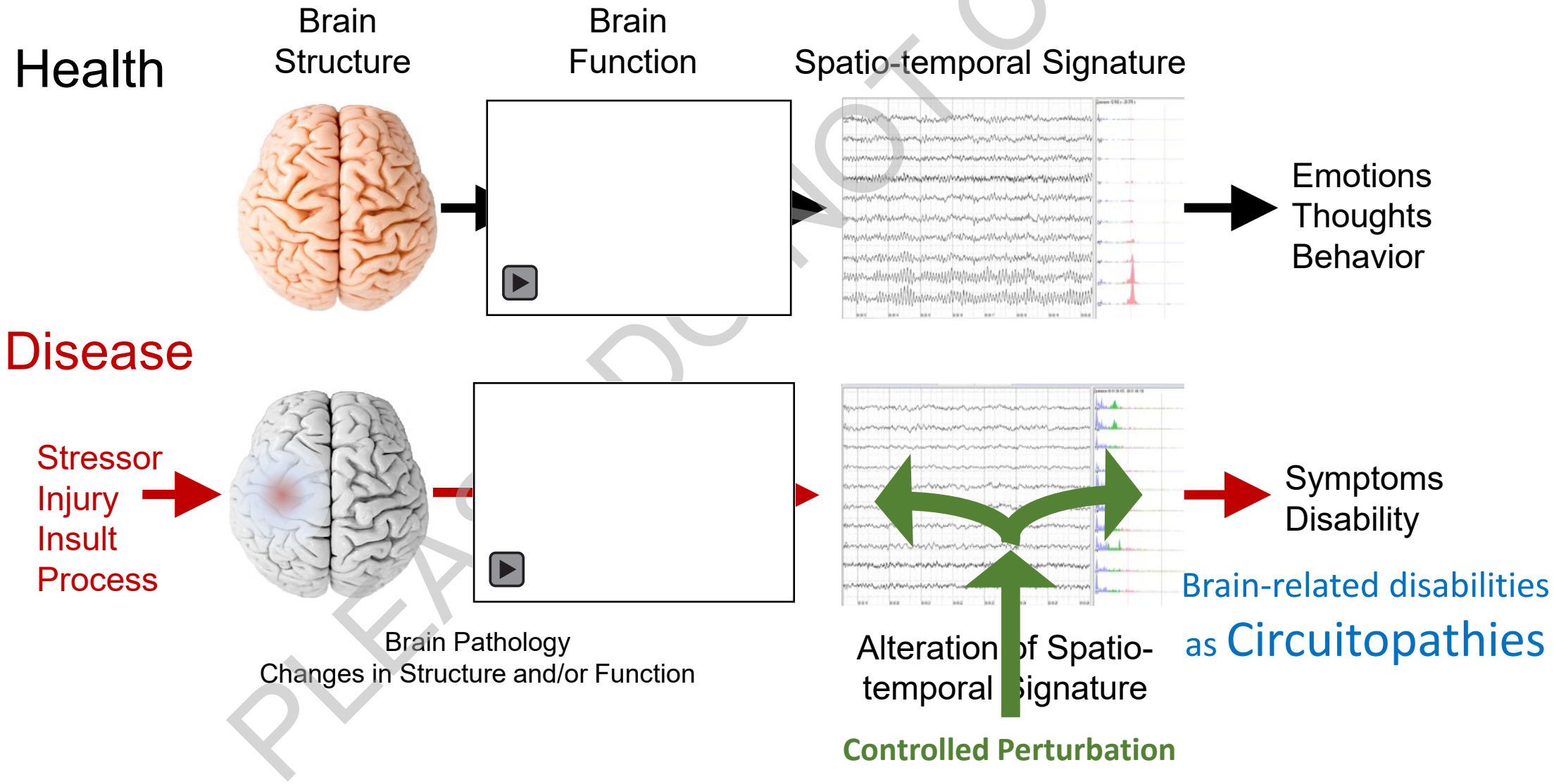
Spatio-Temporal Signatures of Brain-Related Disabilities



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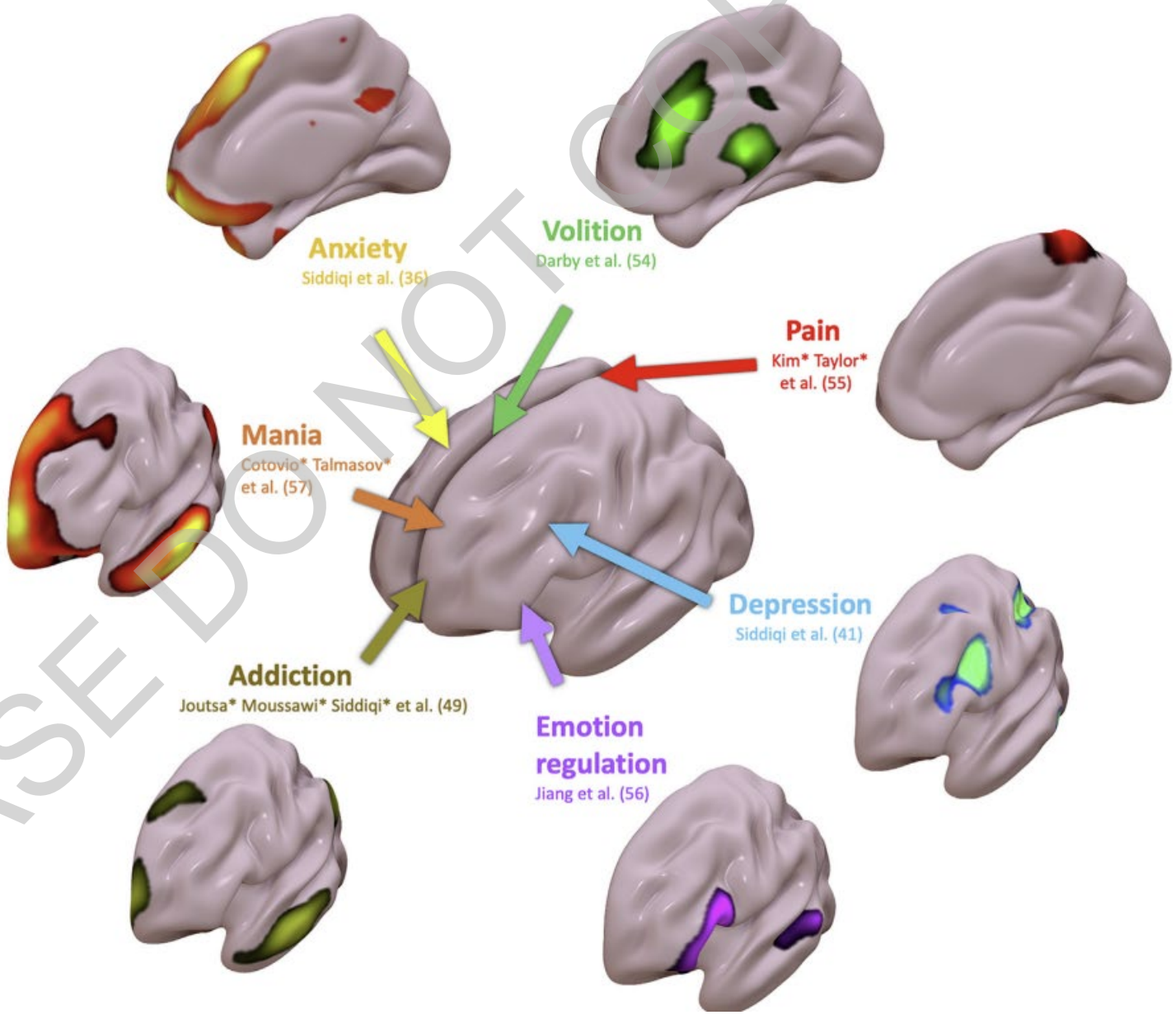
Symptom-specific targeting



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Siddiqi and Fox 2024 Biol Psych

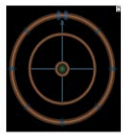
Precision Medicine Symptom-Based Approach



Imaging Service
- Collect specified imaging protocol



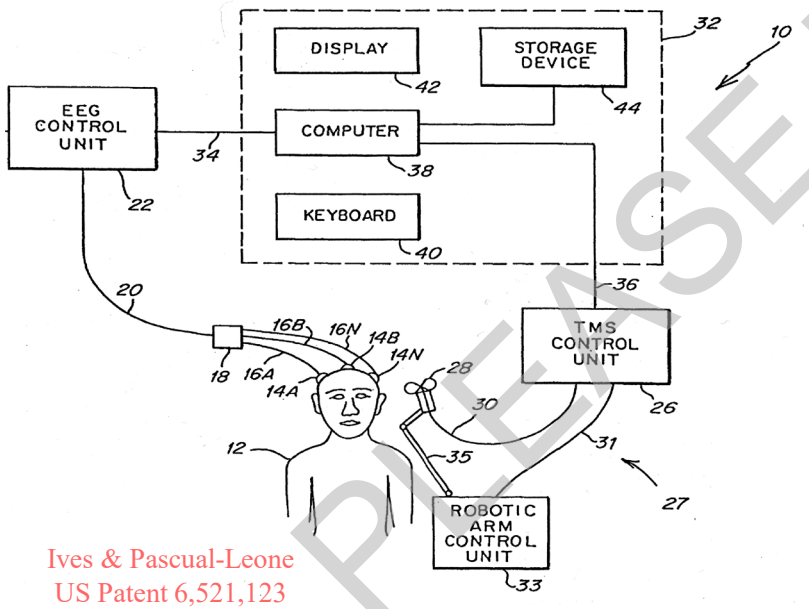




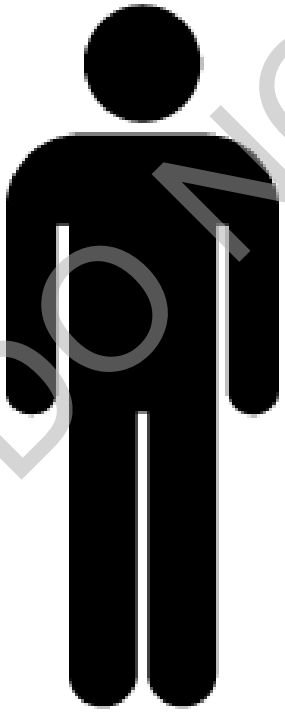
TMS Clinic
- Targeting Tool

Central Processing Core
- rsfcMRI Analysis
- Identify Cortical Target

Pascual-Leone & Fox – US 61/648,032
Docket # B0662.70083US00



Ives & Pascual-Leone
US Patent 6,521,123



1. Define and target symptoms/disabilities - rather than diagnostic entities
2. Identify physiologic biotypes / biomarkers
3. Personalize the intervention (brain target, stimulation parameters, etc)
4. Measure the physiologic impact to assess effect
5. Adjust intervention, and iteratively optimize algorithm (close loop)

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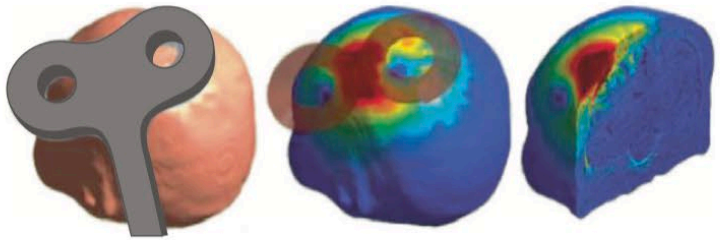
Spatial precision

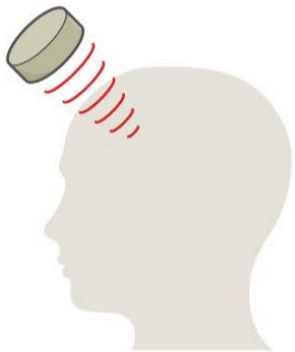
Imaging-guided targeting



Electric field modeling

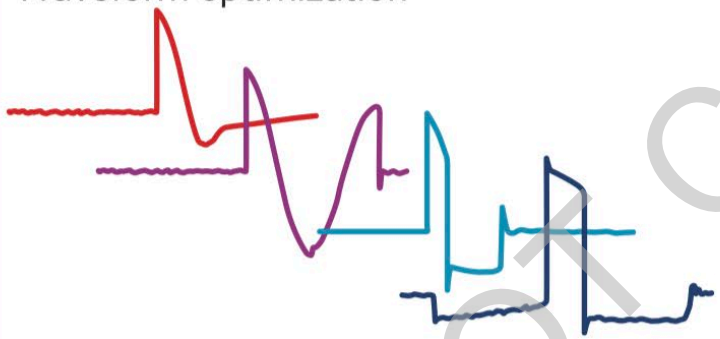


Focal/multifocal stimulation

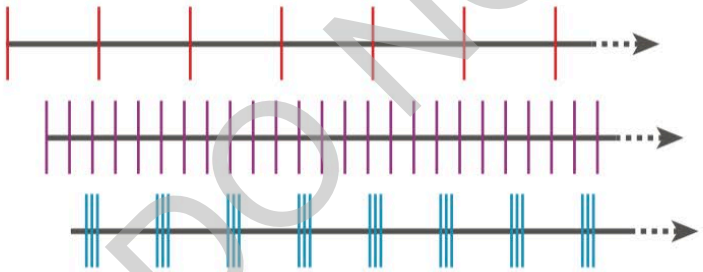


Temporal precision

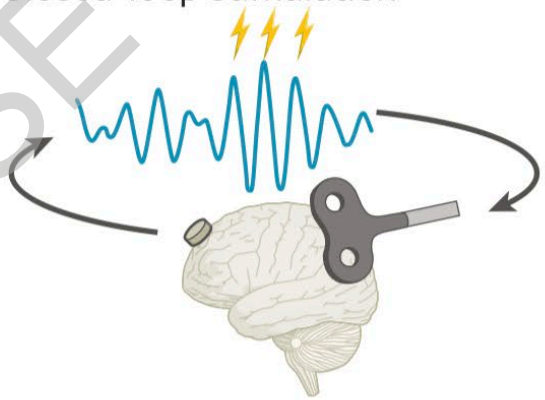
Waveform optimization



Patterned stimulation

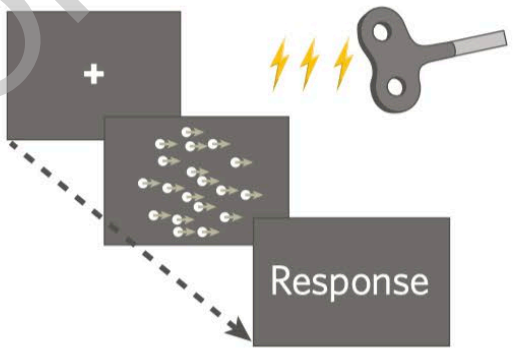


Closed-loop stimulation

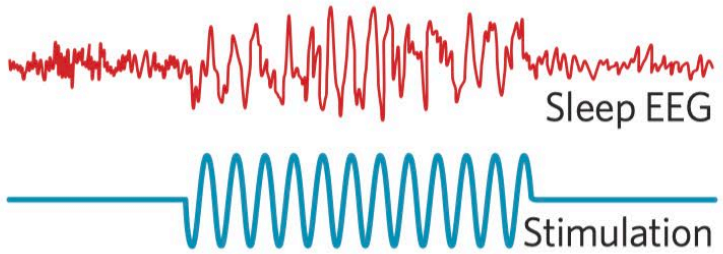


Contextual precision

Online stimulation



Biological rhythm



Combinatorial therapy



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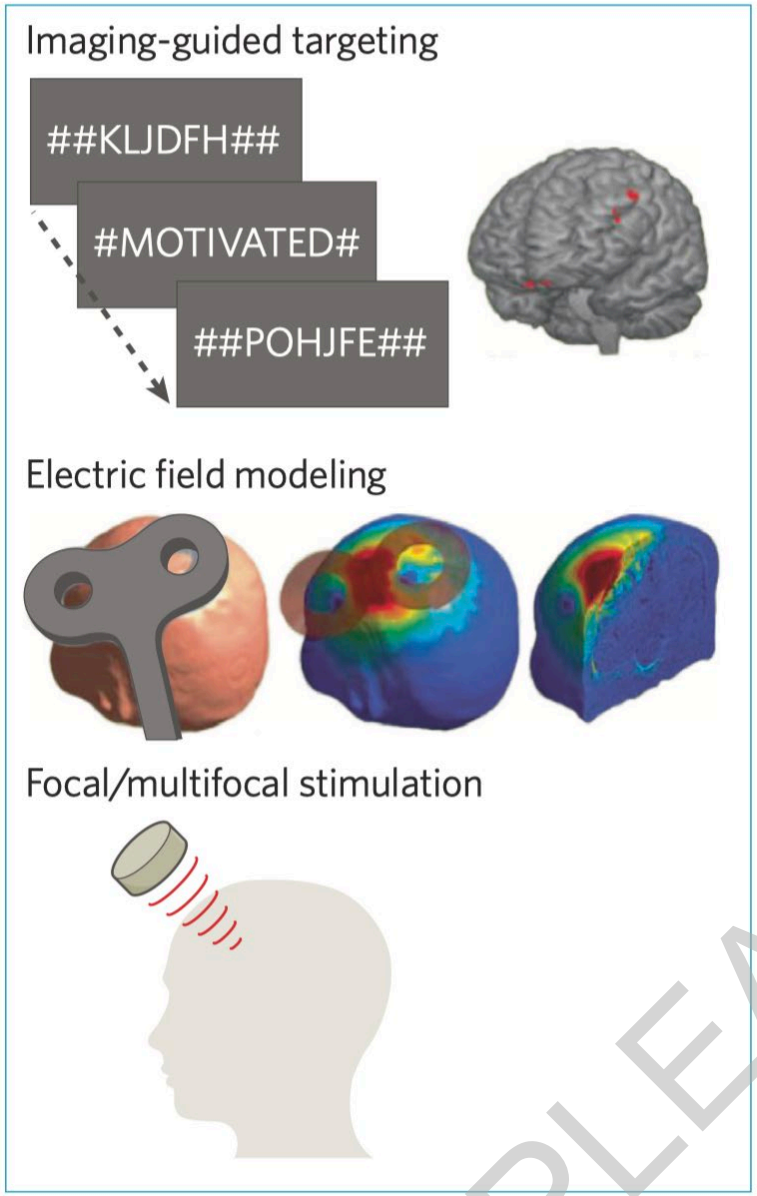
Jannati et al. Neuropsychopharmacology 2023

Jannati et al. Neuropsychopharmacology 2023
Cappon & Pascual-Leone Am J Psych 2024



1. Know where to target: MRI-guided TMS
2. Keep target consistent: Robot-assisted TMS
3. Make target smaller: Micro TMS
4. Modulate entire network: Multifocal NIBS

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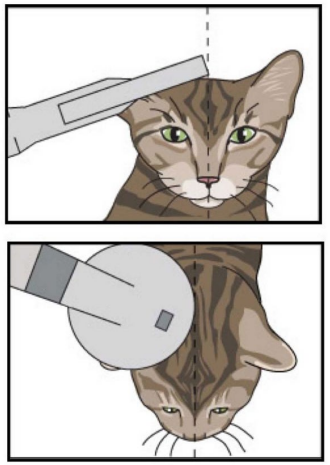
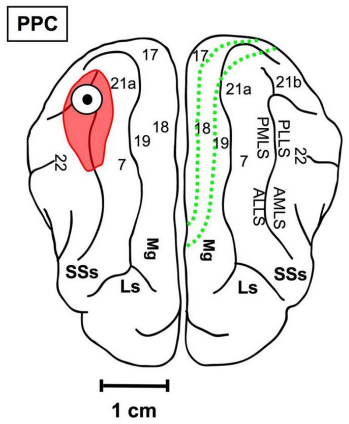
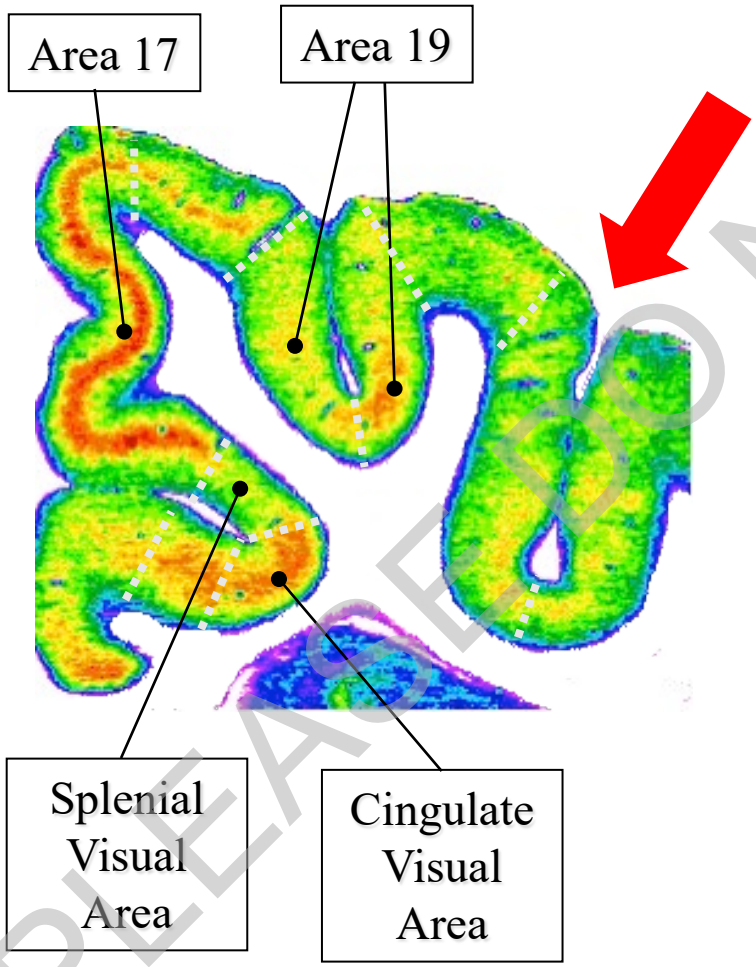
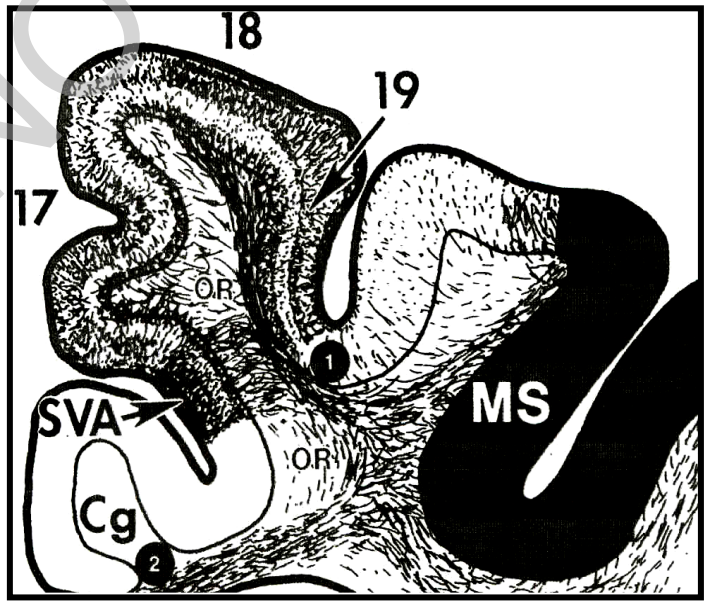
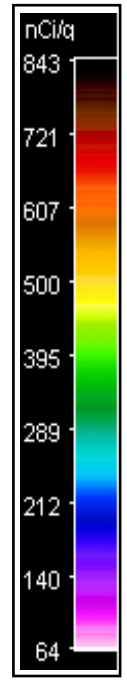
NiBS modulates activity in brain networks & the effects depend on connectivity











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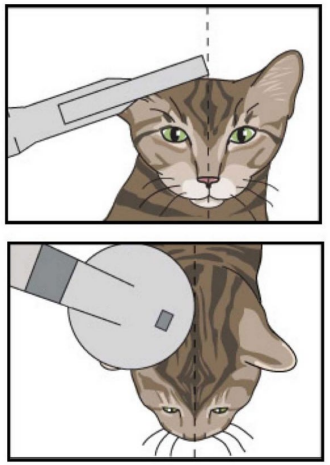
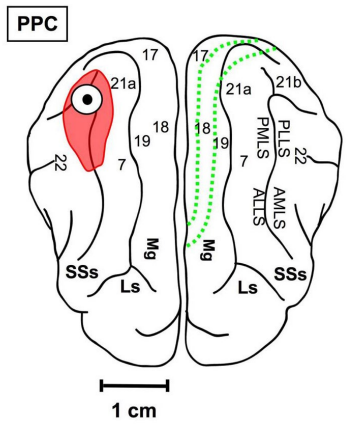
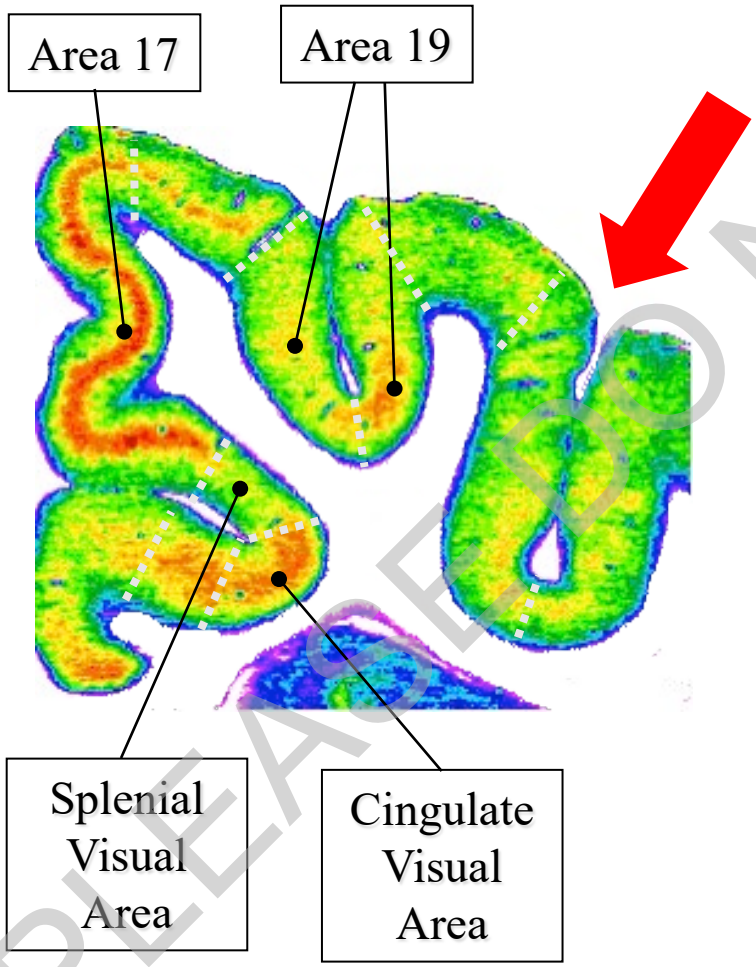
Valero-Cabre et al *Exp Brain Res 2005, 2006*

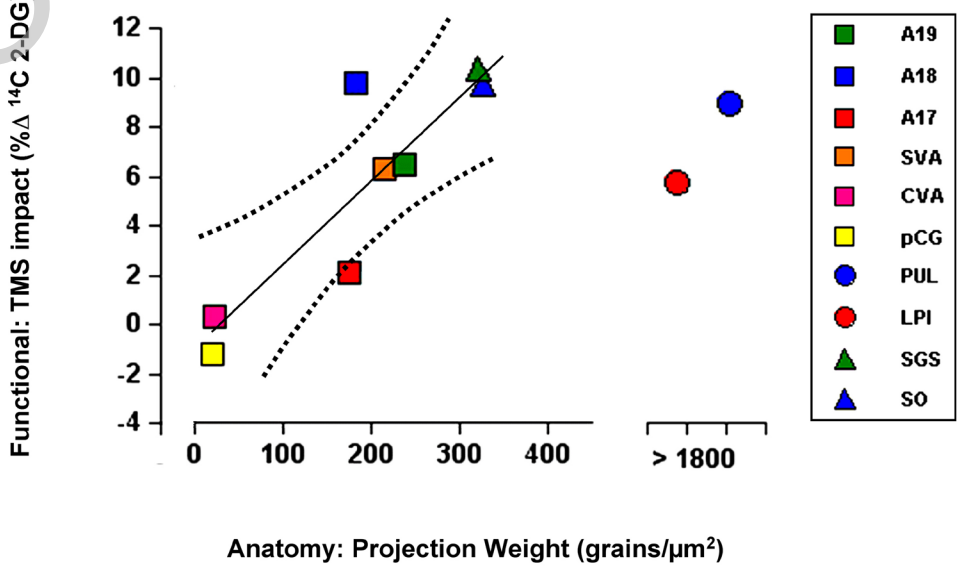


NiBS modulates activity in brain networks & the effects depend on connectivity









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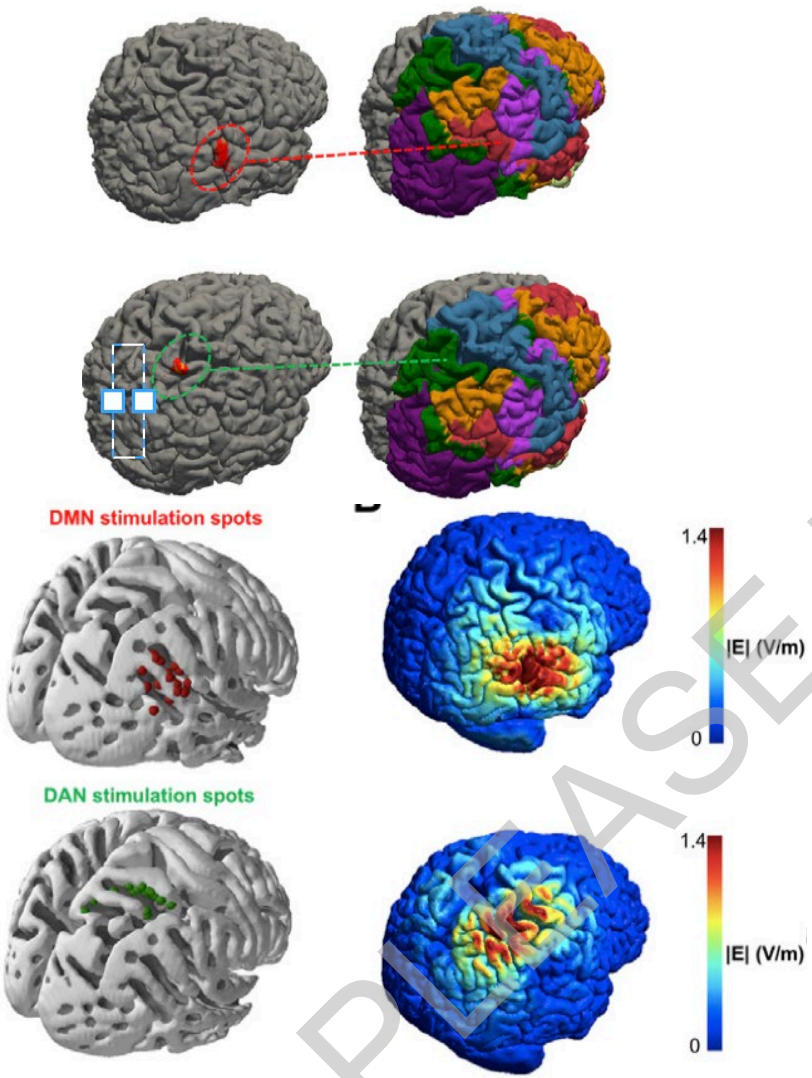
Valero-Cabre et al *Exp Brain Res 2005, 2006*

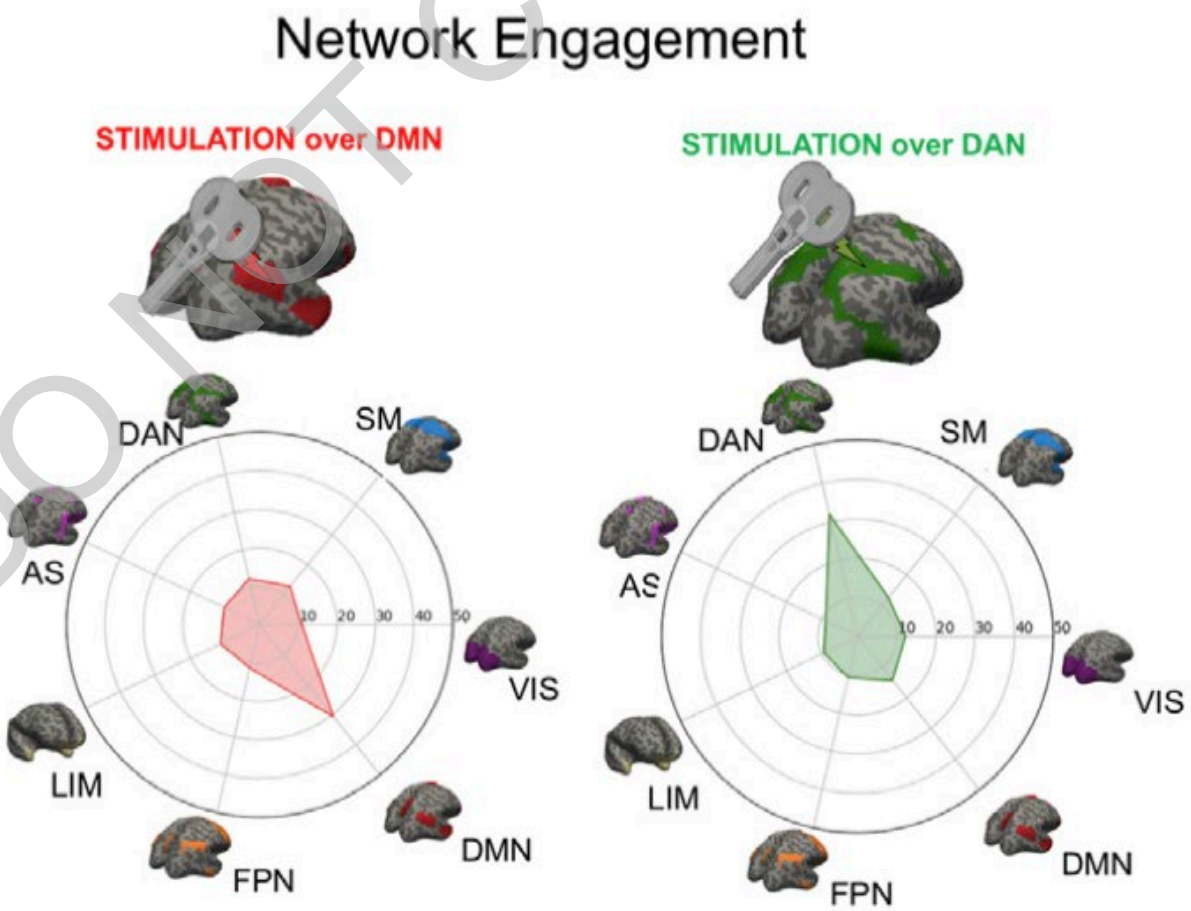


Davide Momi

Impact on specific brain networks

Momi et al. Neuroimage 2021





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Robot-guided TMS

- Target different network nodes in specific order and timing
- Adaptive close loop system

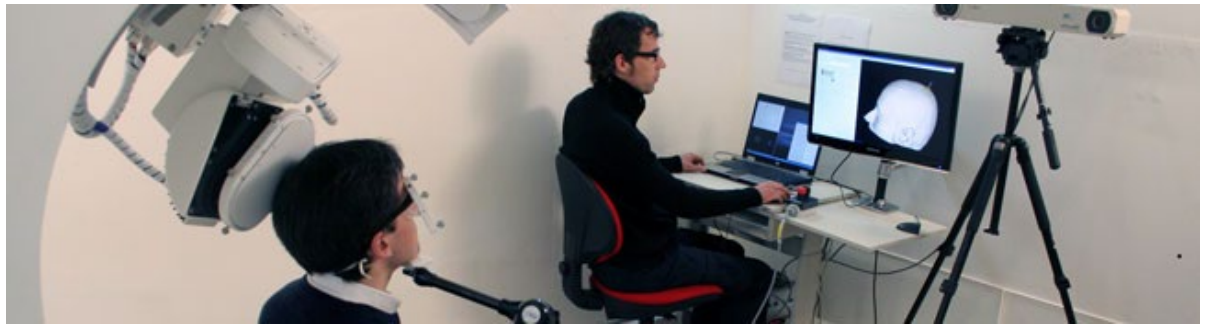
Axilum Robotics

FDA cleared
CE mark









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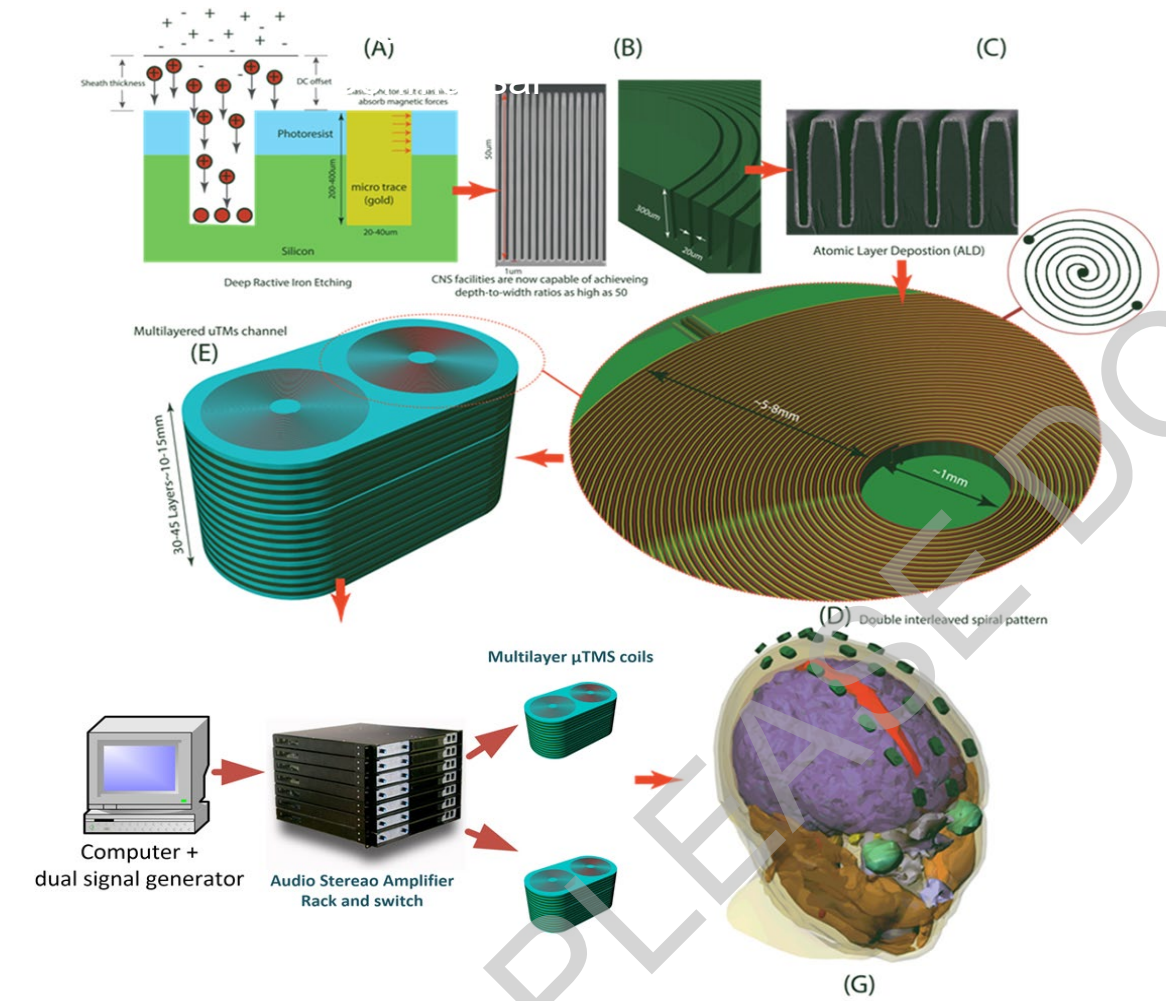
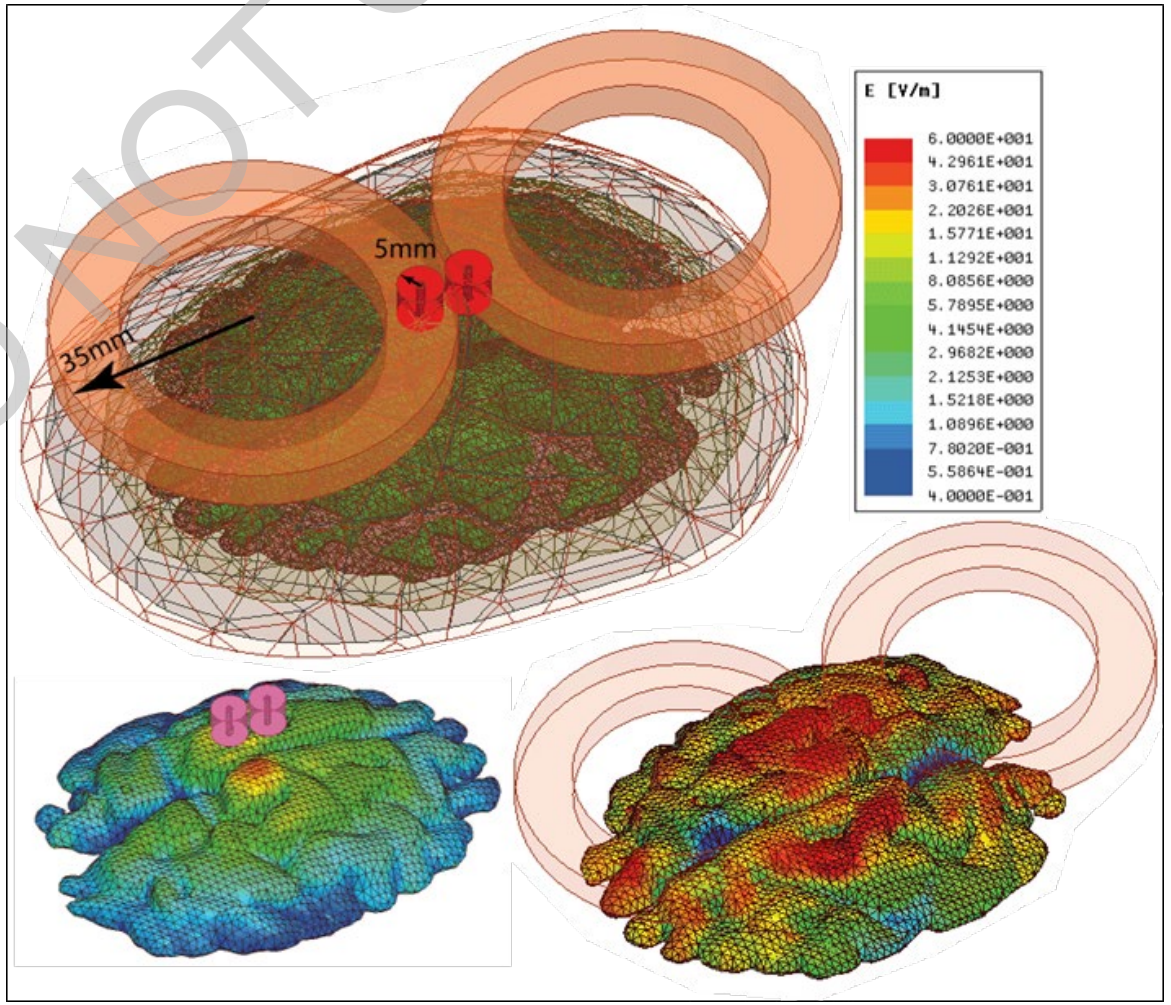
Giorgio Bonmassar

µTMS

Colella et al Annu Int Conf IEEE Eng Med Biol Soc. 2019
Colella et al Med Phys. 2023





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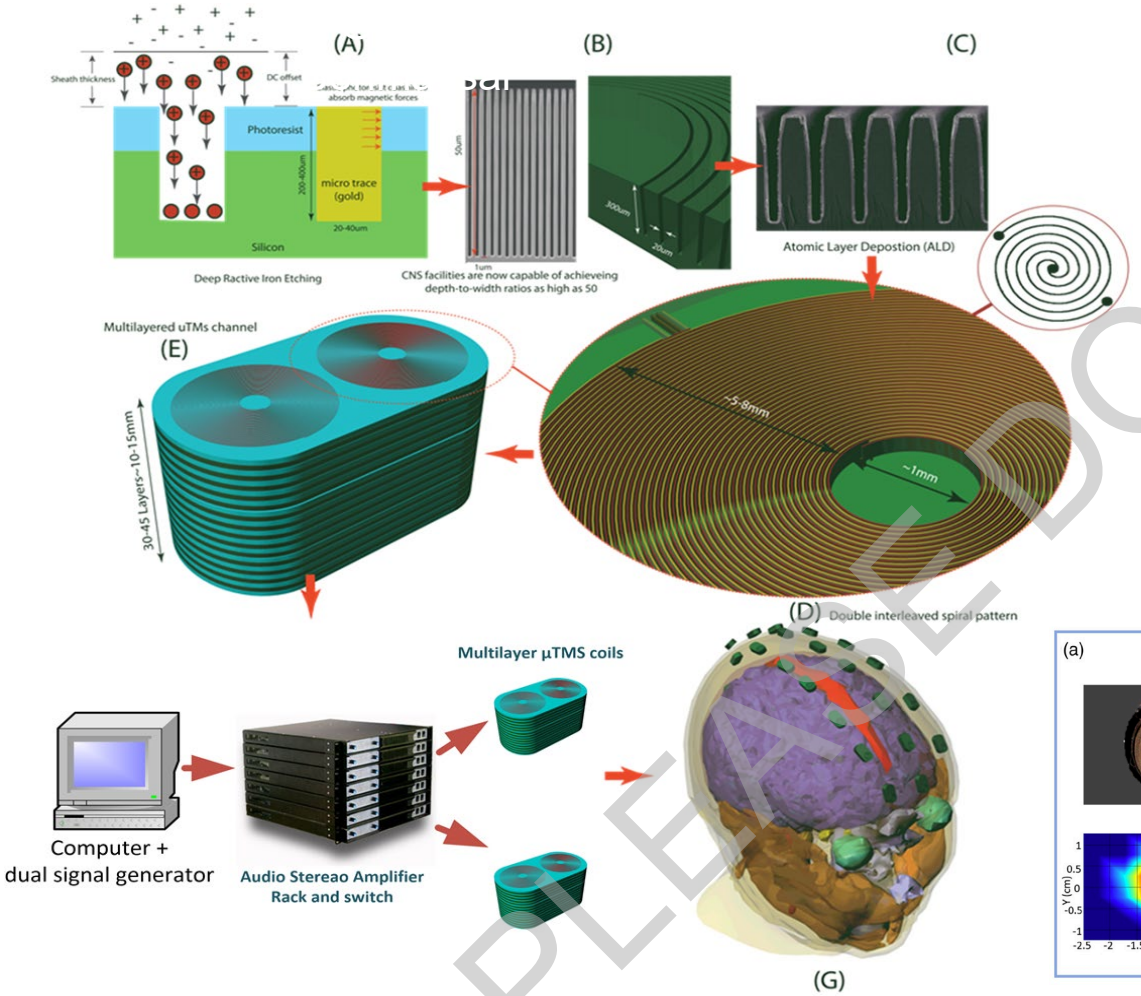
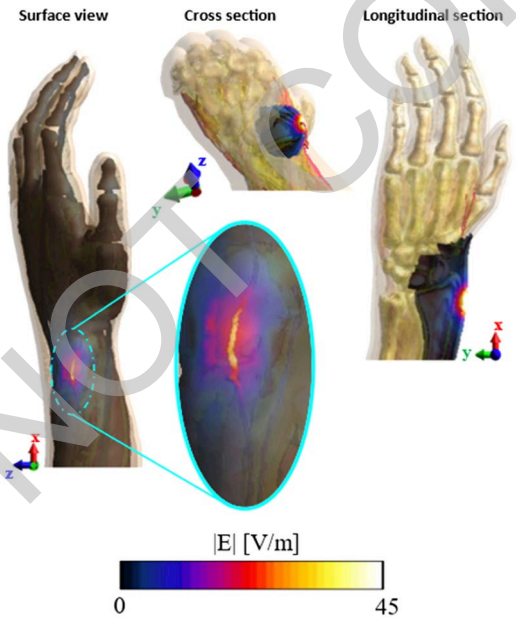
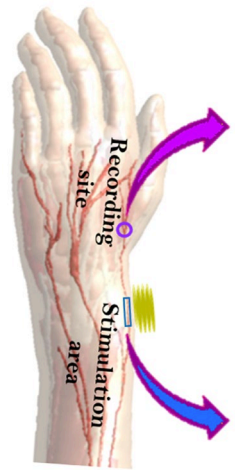
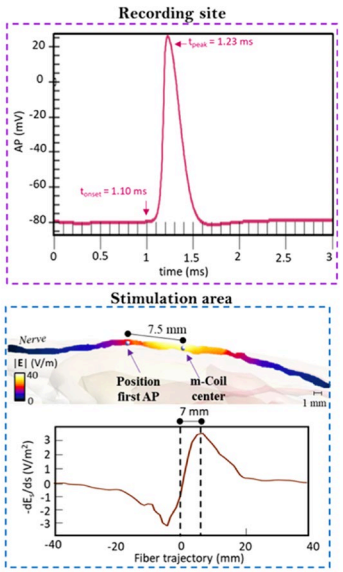
µTMS

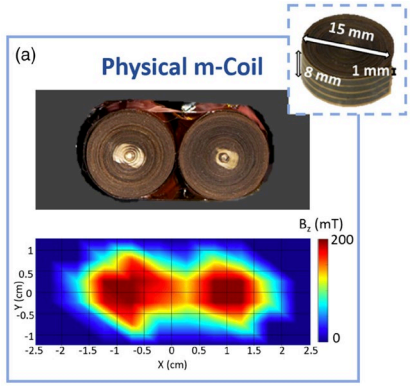
Colella et al. *Annu Int Conf IEEE Eng Med Biol Soc.* 2019
Colella et al. *Med Phys.* 2023

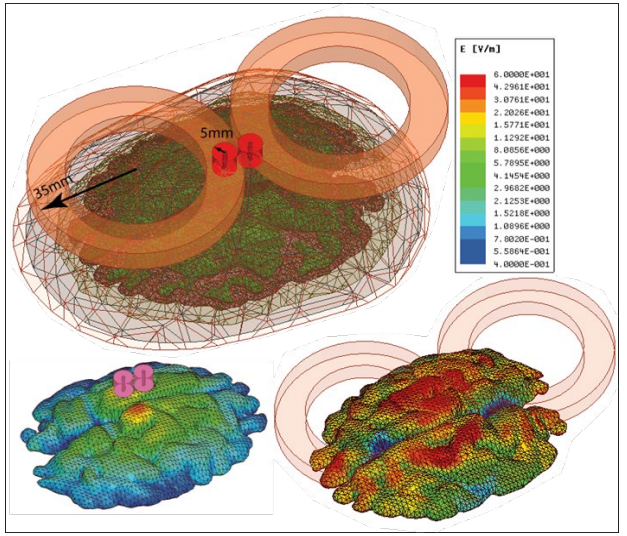












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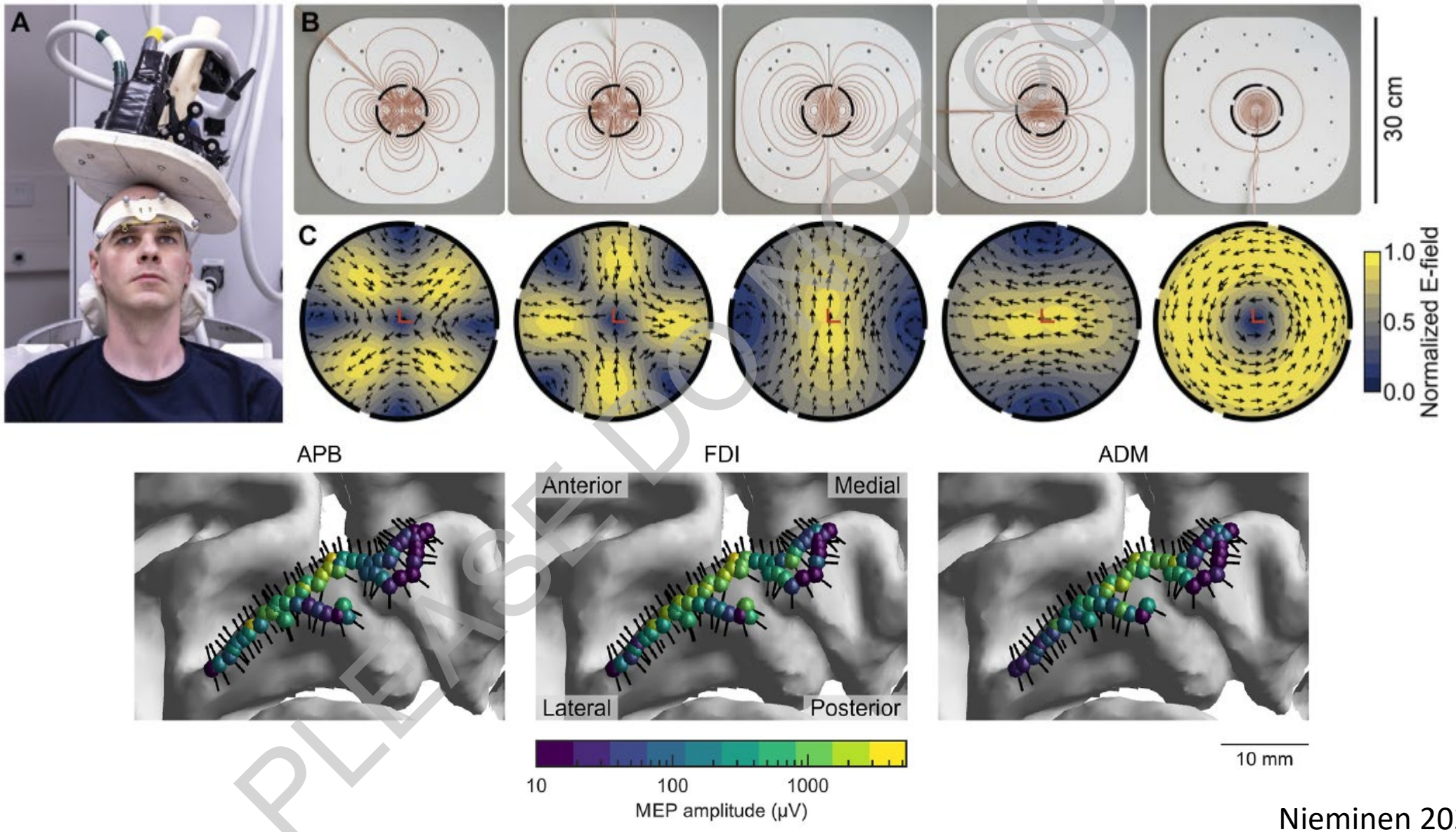
Multi-locus TMS



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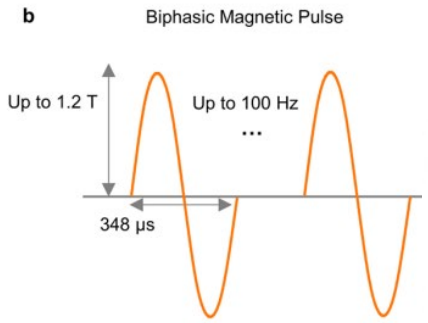
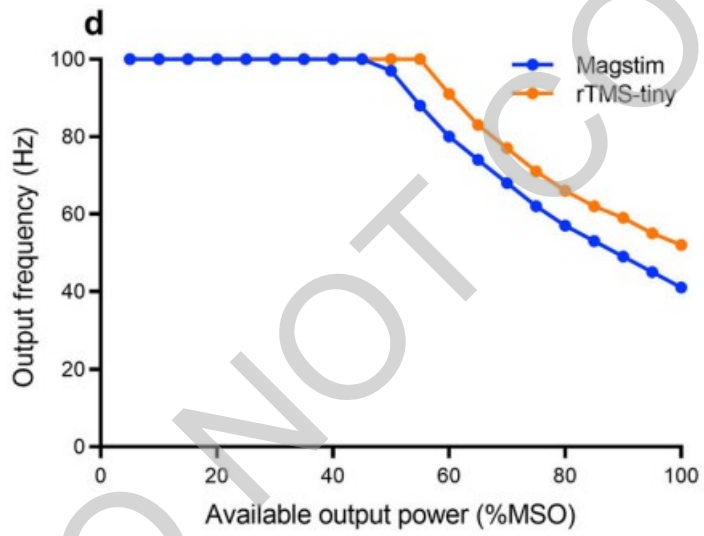
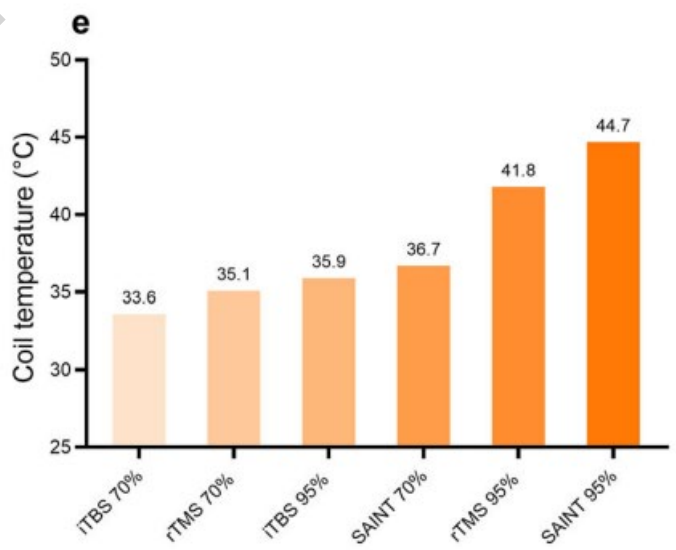
Nieminen 2022 Br Stim

Portable TMS



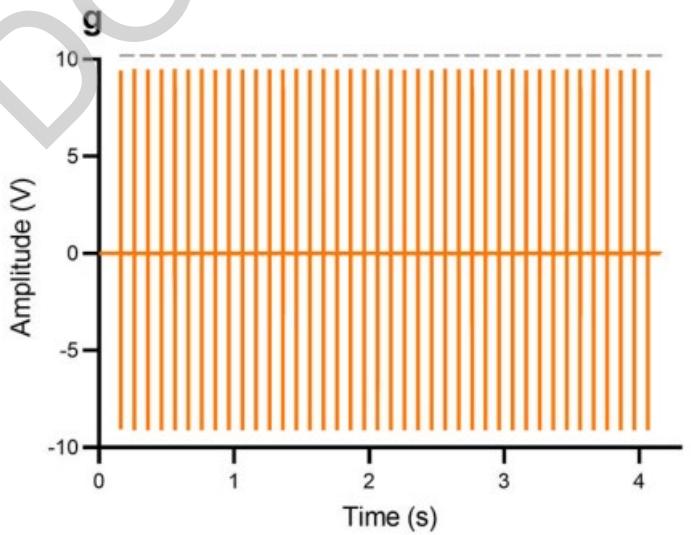


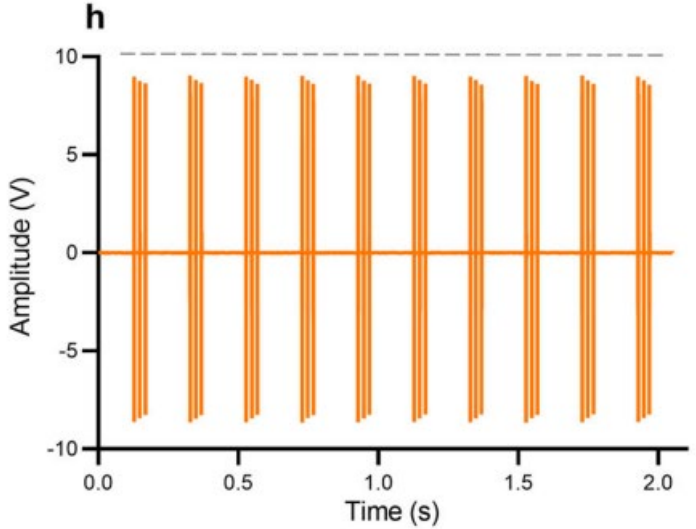












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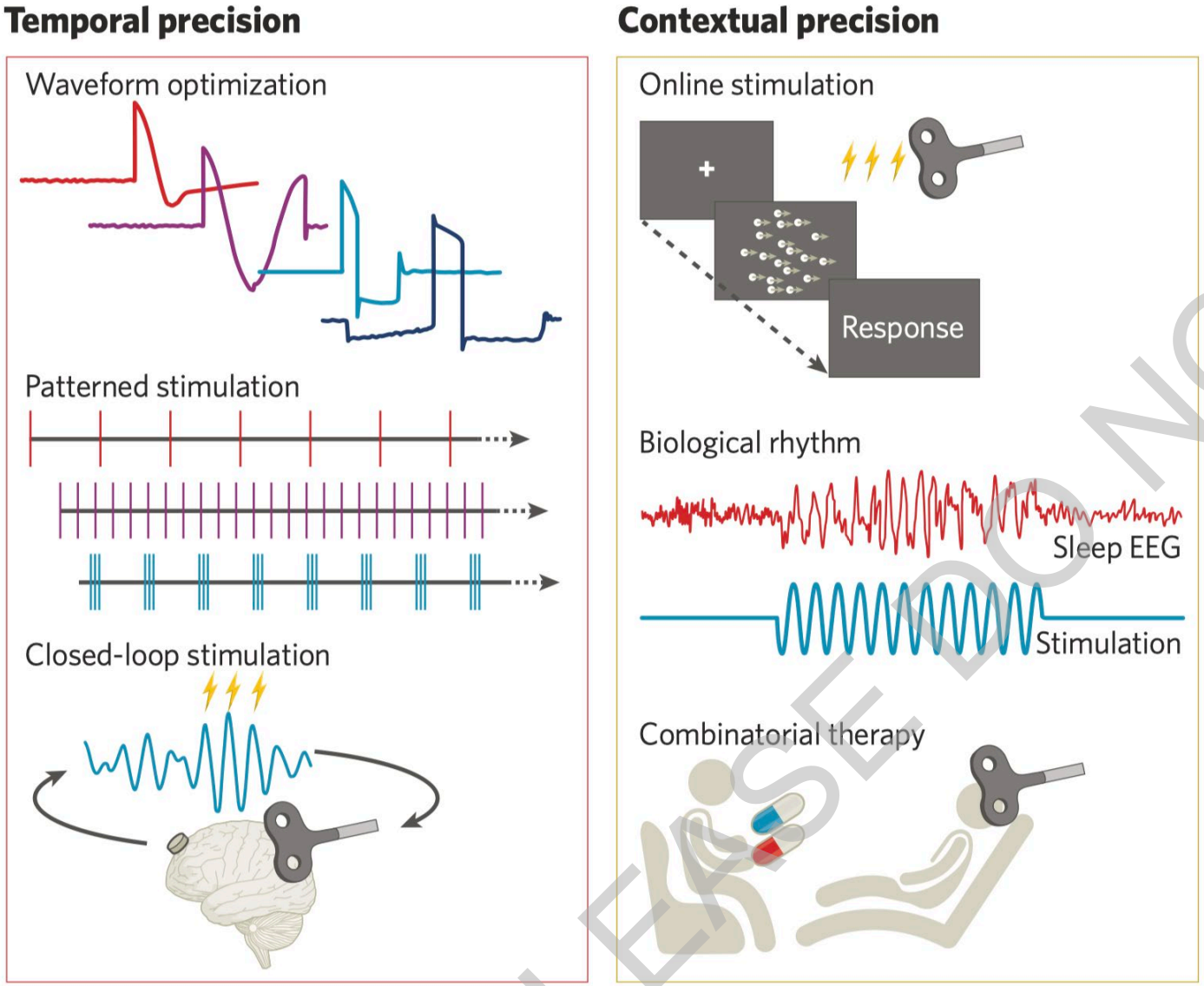
Qi 2025 Nature Communications

Jannati et al. Neuropsychopharmacology 2023
Cappon & Pascual-Leone Am J Psych 2024



1. Individualize stimulation parameters
   - Measure neurophysiologic effect

2. Leverage State-dependency effects
   - Combine with other interventions / medications

3. Design improved stimulators

4. Optimize stimulation protocols

5. Stimulate at right time
   - Oscillations specific stimulation
   - Closed loop stimulation

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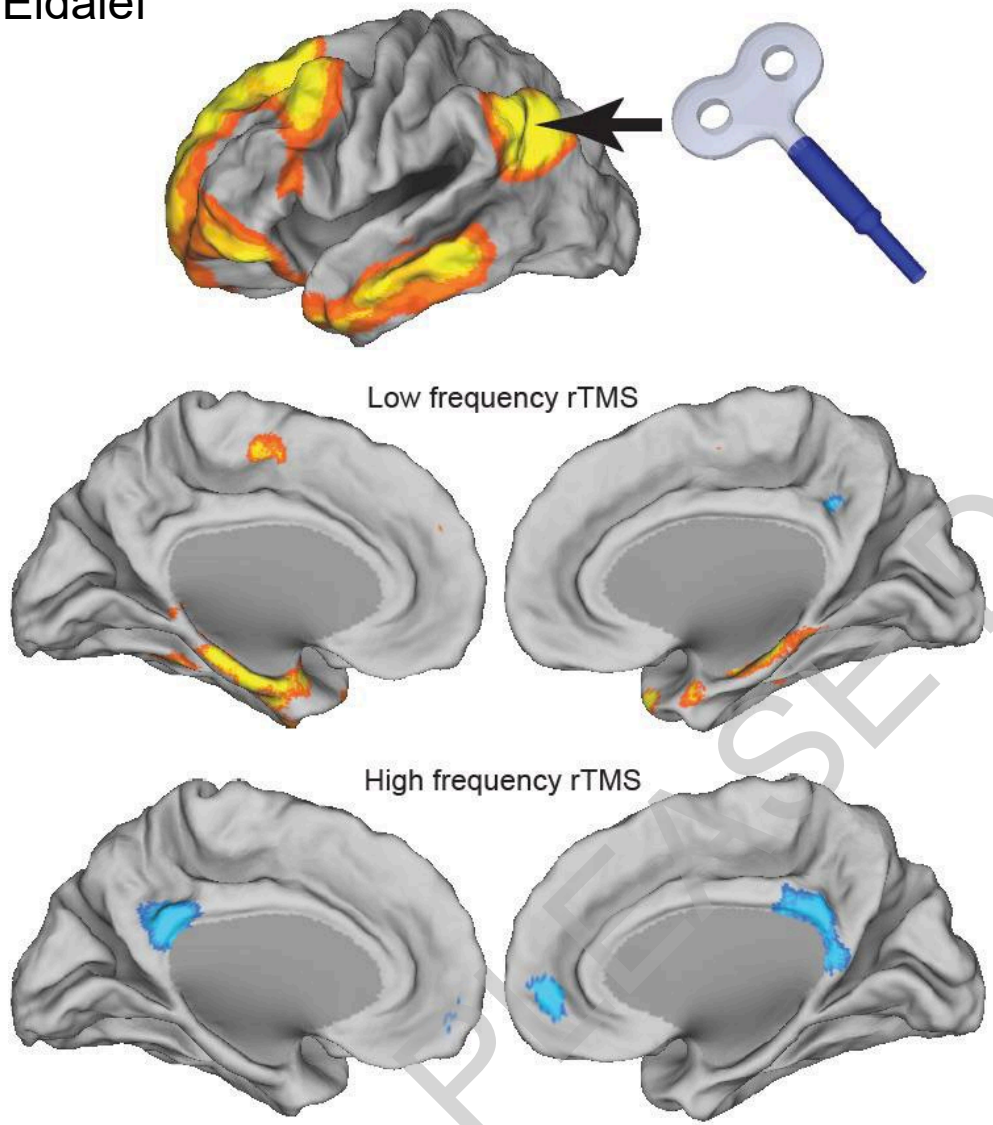
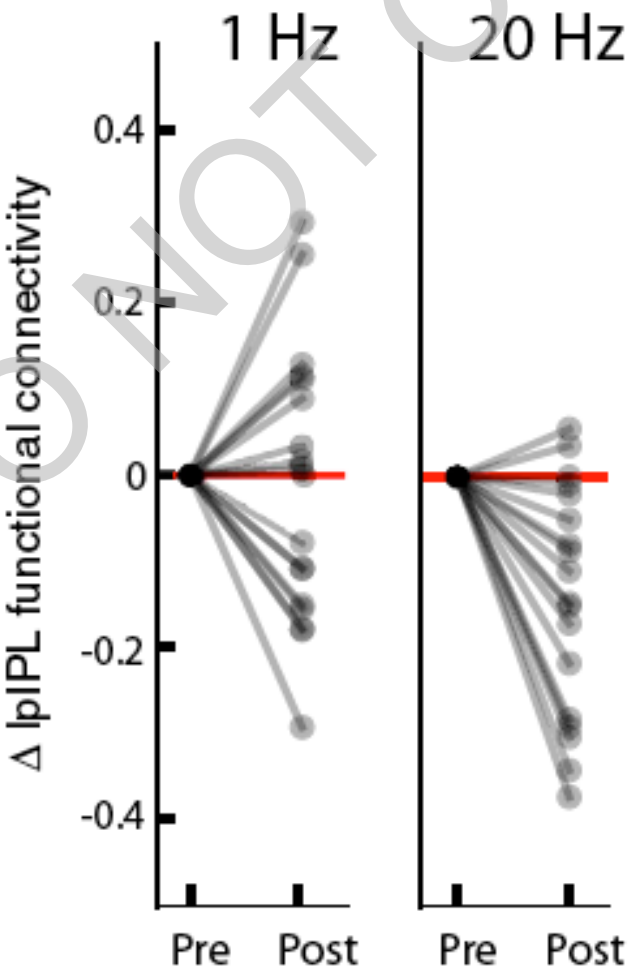
Variability of Physiologic Effects



Mark Eldaief





Need to Measure!

Neurophysiologic monitoring:
fMRI – EEG – etc

Define dose
Enable close-loop

Eldaief et al *PNAS*, 2011

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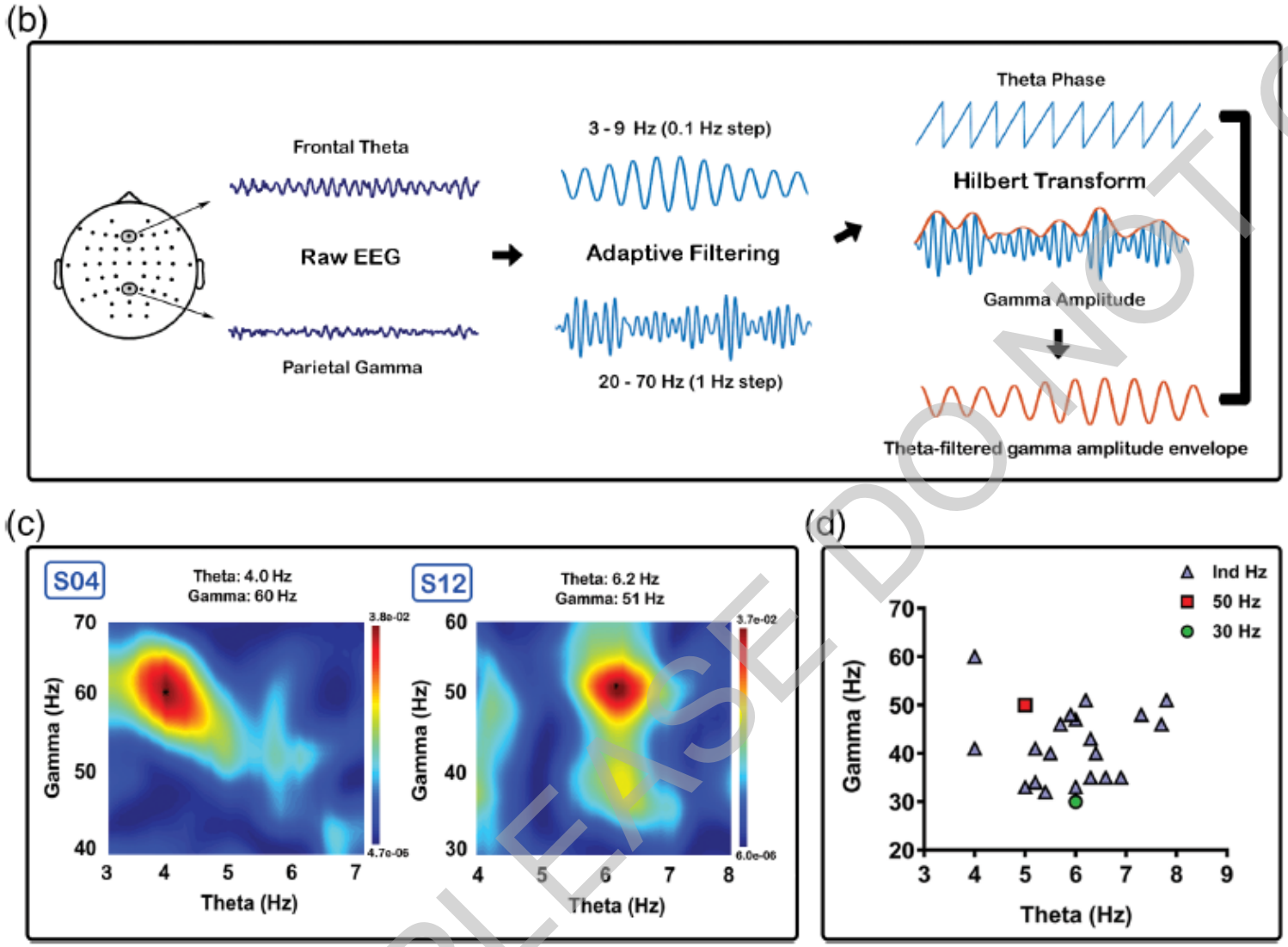
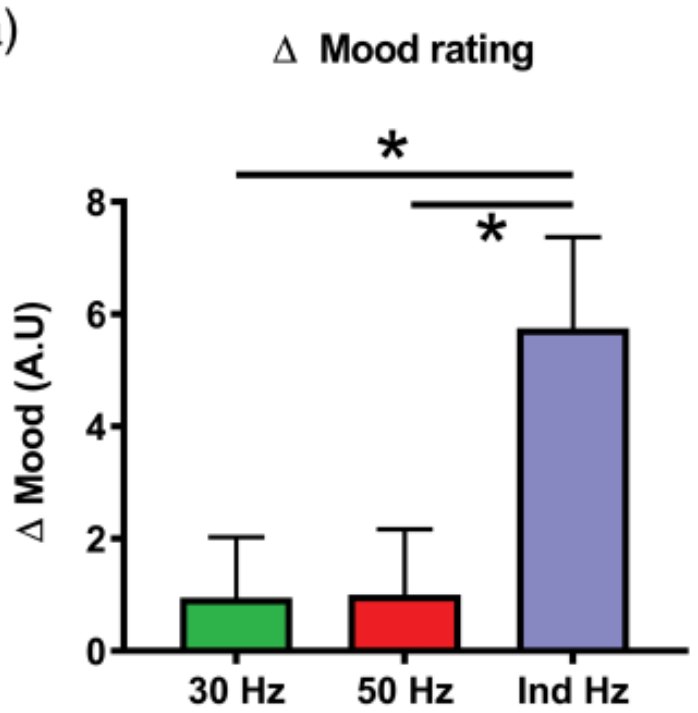
Personalized parameters





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Chung 2019 HumBrMap



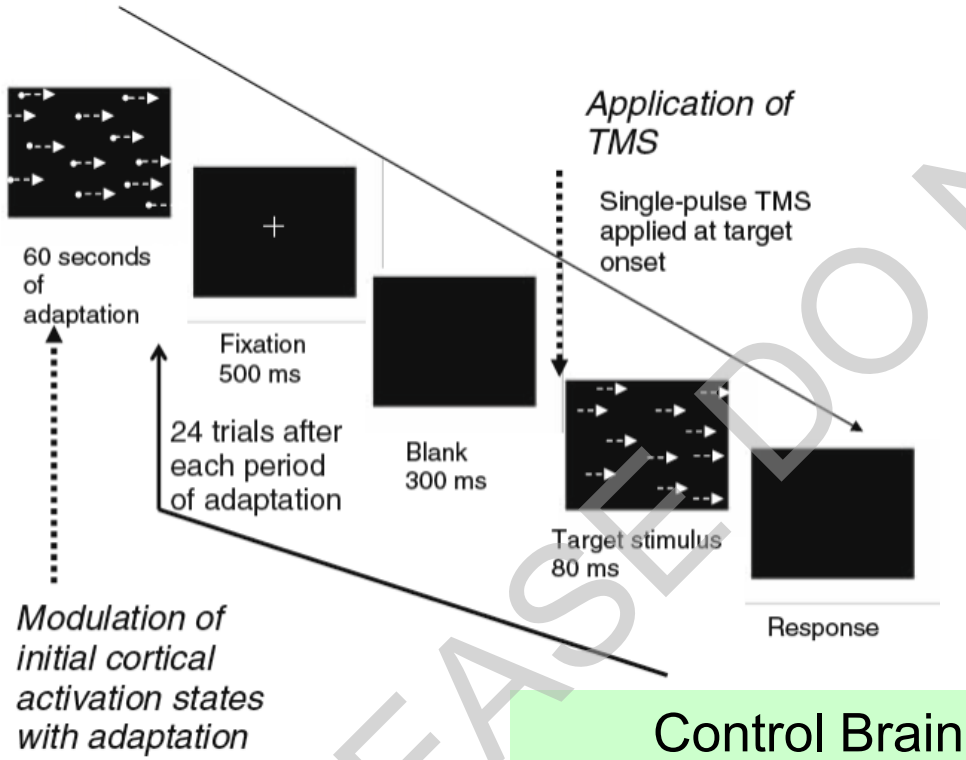
Zaira Cattaneo

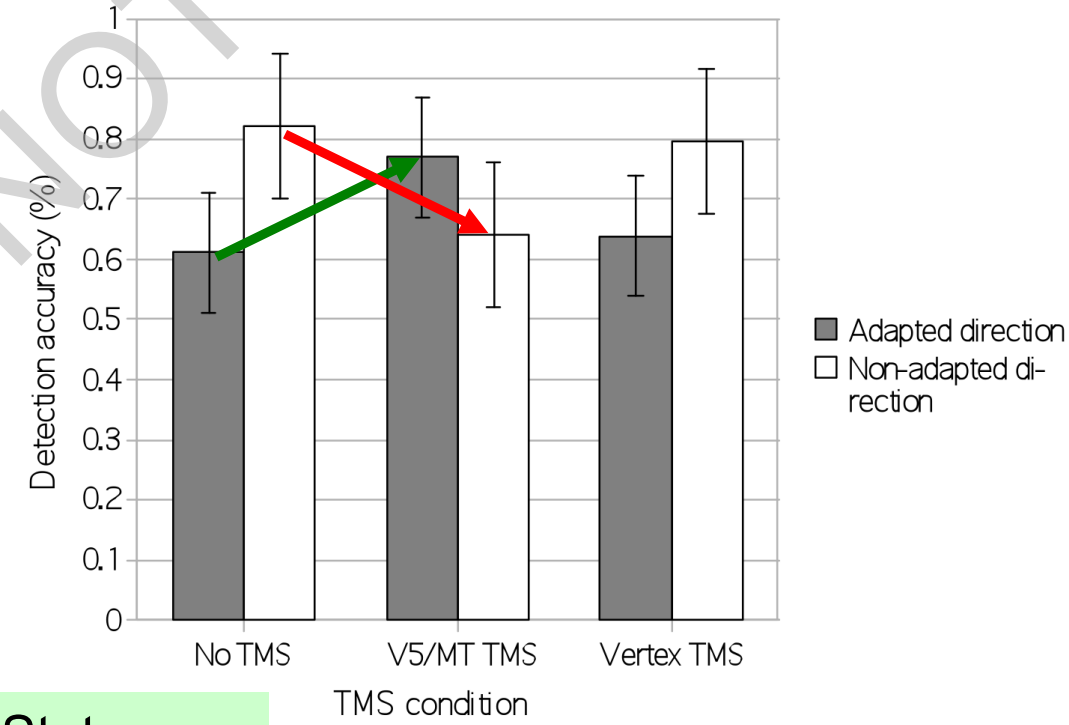


Juha Silvanto

State Dependency For Specific Neural Populations

TMS-adaptation paradigm and motion direction discrimination in visual area V5/MT





Control Brain State

Consistency and Greater Specificity of Effect

TMS disrupts non-adapted but improves adapted direction discrimination

Cattaneo & Silvanto *Neurosci Lett* 08

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Brain Topogr (2008) 21:1–10
DOI 10.1007/s10548-008-0067-0

REVIEW ARTICLE

State-Dependency of Transcranial Magnetic Stimulation

Juha Silvanto · Alvaro Pascual-Leone

Concurrent TMS stimulation with
Cognitive Training in Dementia



NEURONIX
INTEGRATING NEUROLOGICAL SOLUTIONS

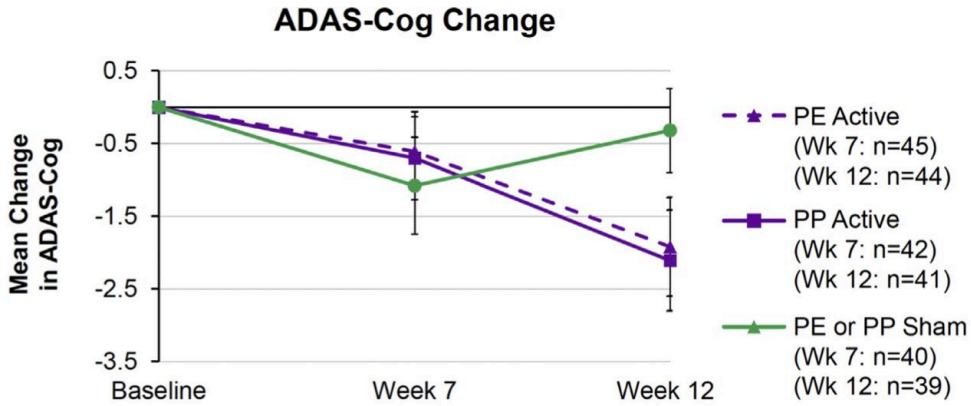
Sabbagh et al *Alzheimer's & Dementia* 2019



FDA-Approval for OCD
Provocation task + TMS

Brainsway

- How create an 'optimal' state ?
- When to couple brain stimulation with state modification ?



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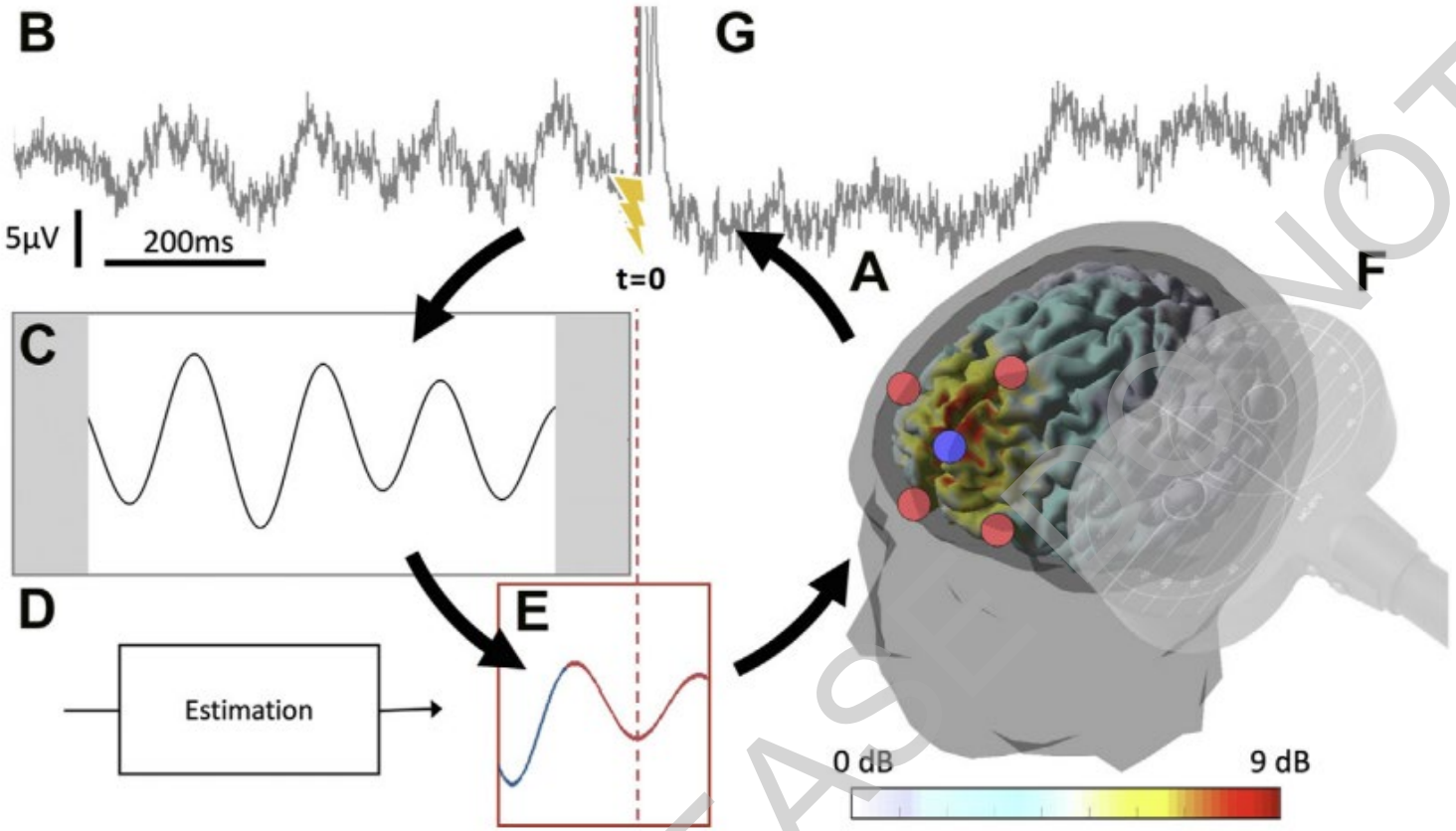
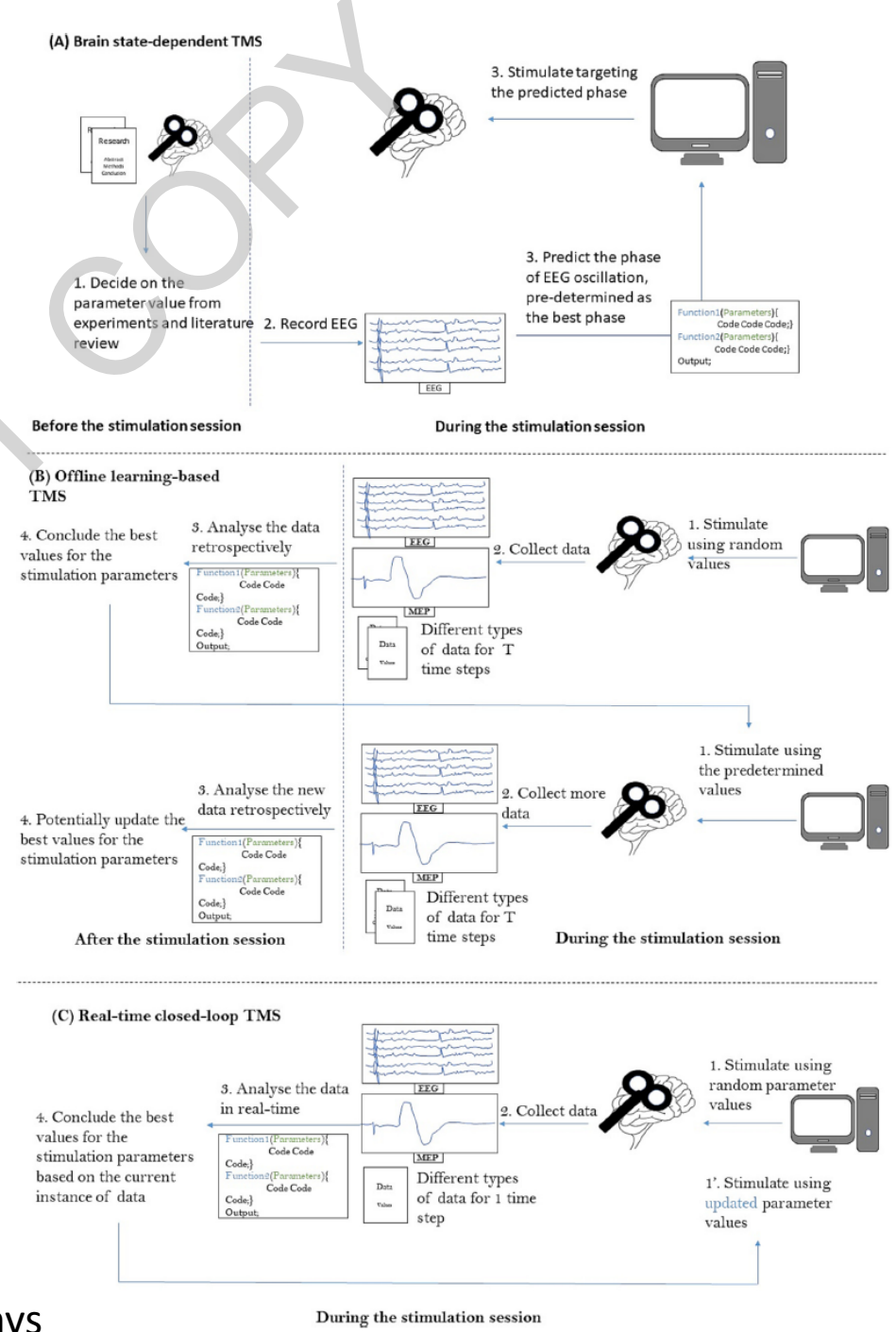
Closed-loop EEG-TMS modulation





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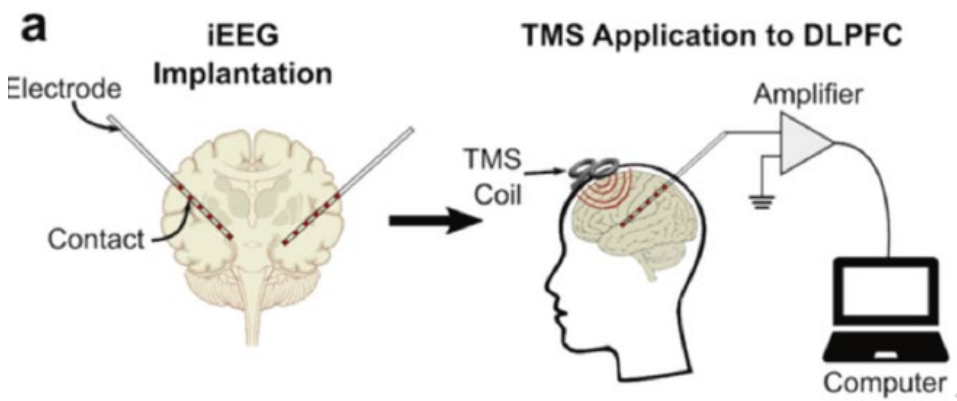
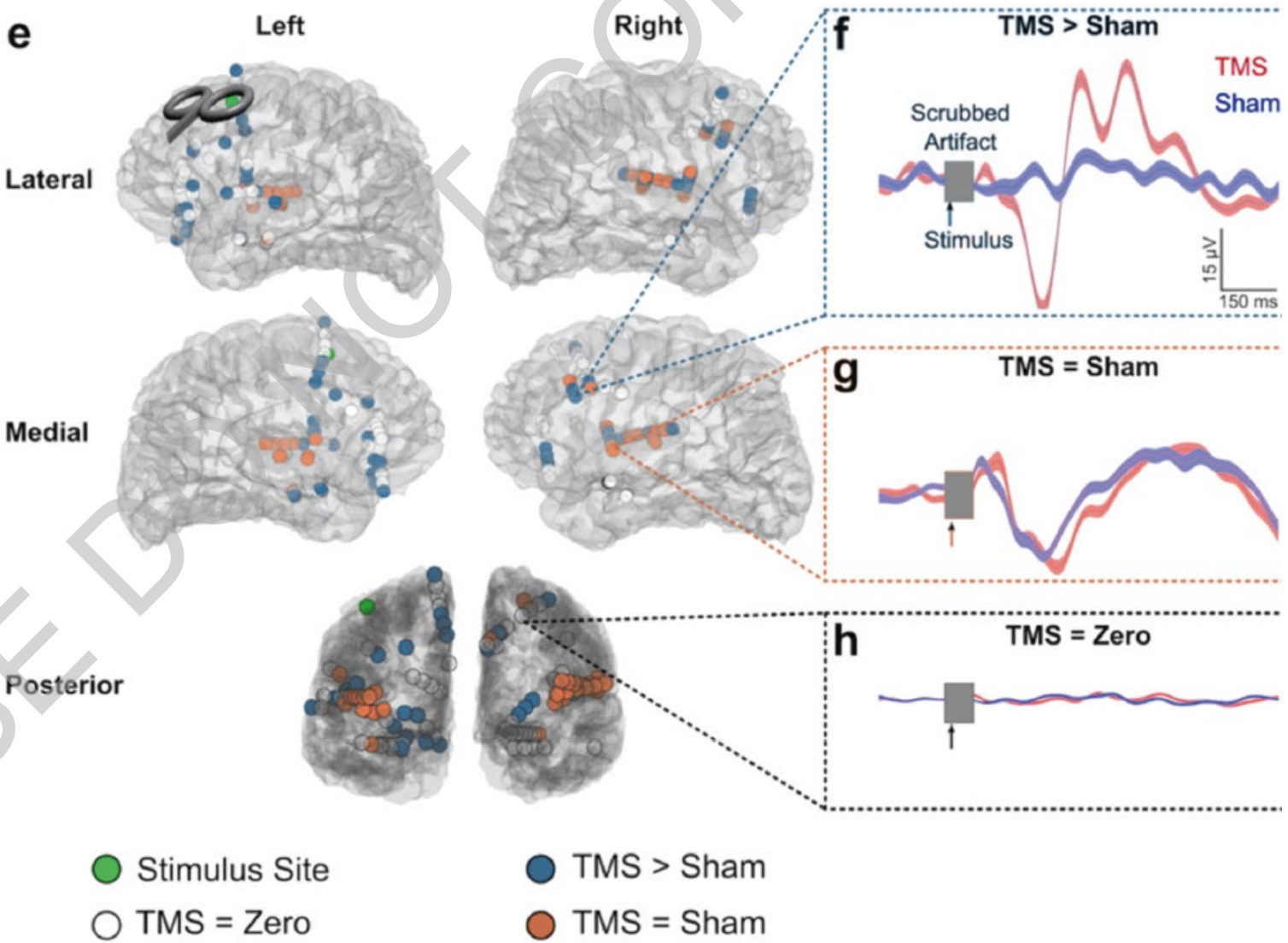
Left: Zrenner & Ziemann BiolPsych 2024; Right: Humaidan 2024 Clin Neurophys

Intracranial EEG validated approaches and mechanisms





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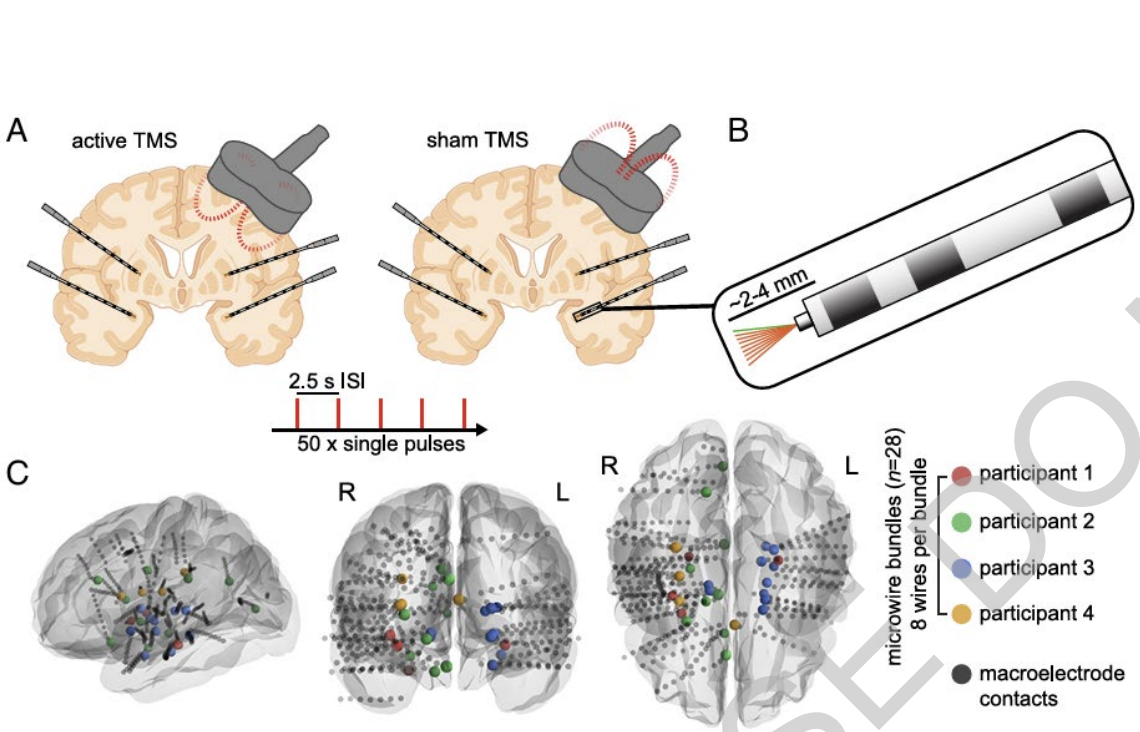
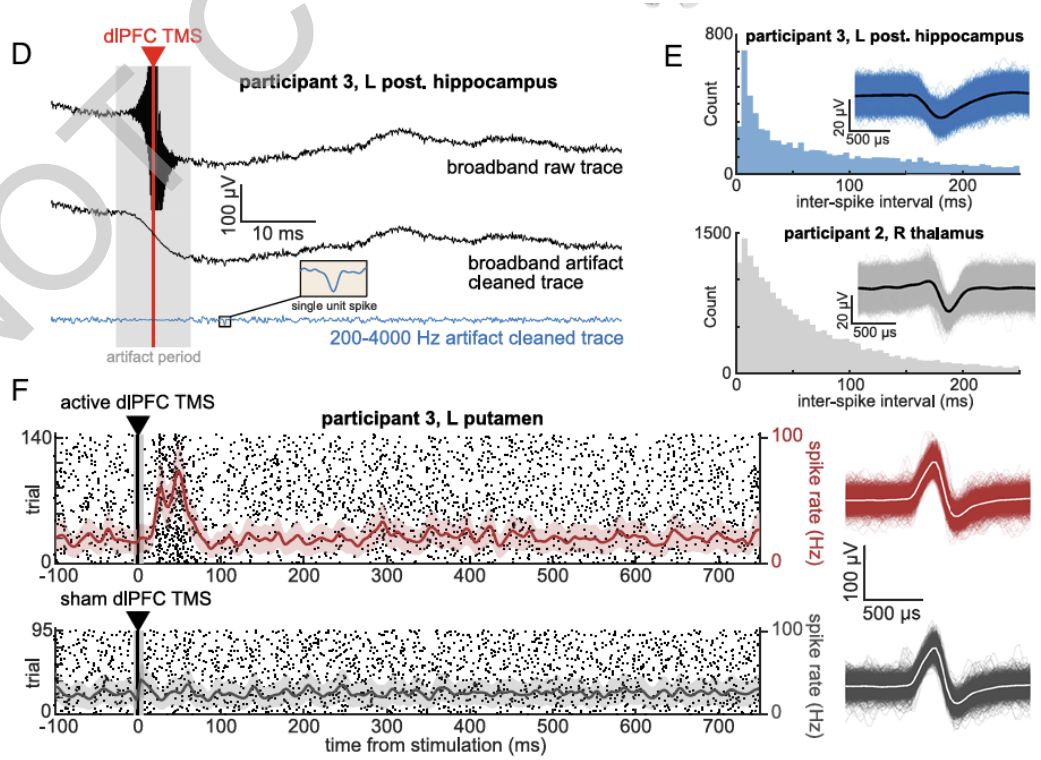
Wang et al 2024, Molecular Psychiatry

Intracranial single cell recordings enable deeper mechanistic insight





Dickey et al. 2026, PNAS

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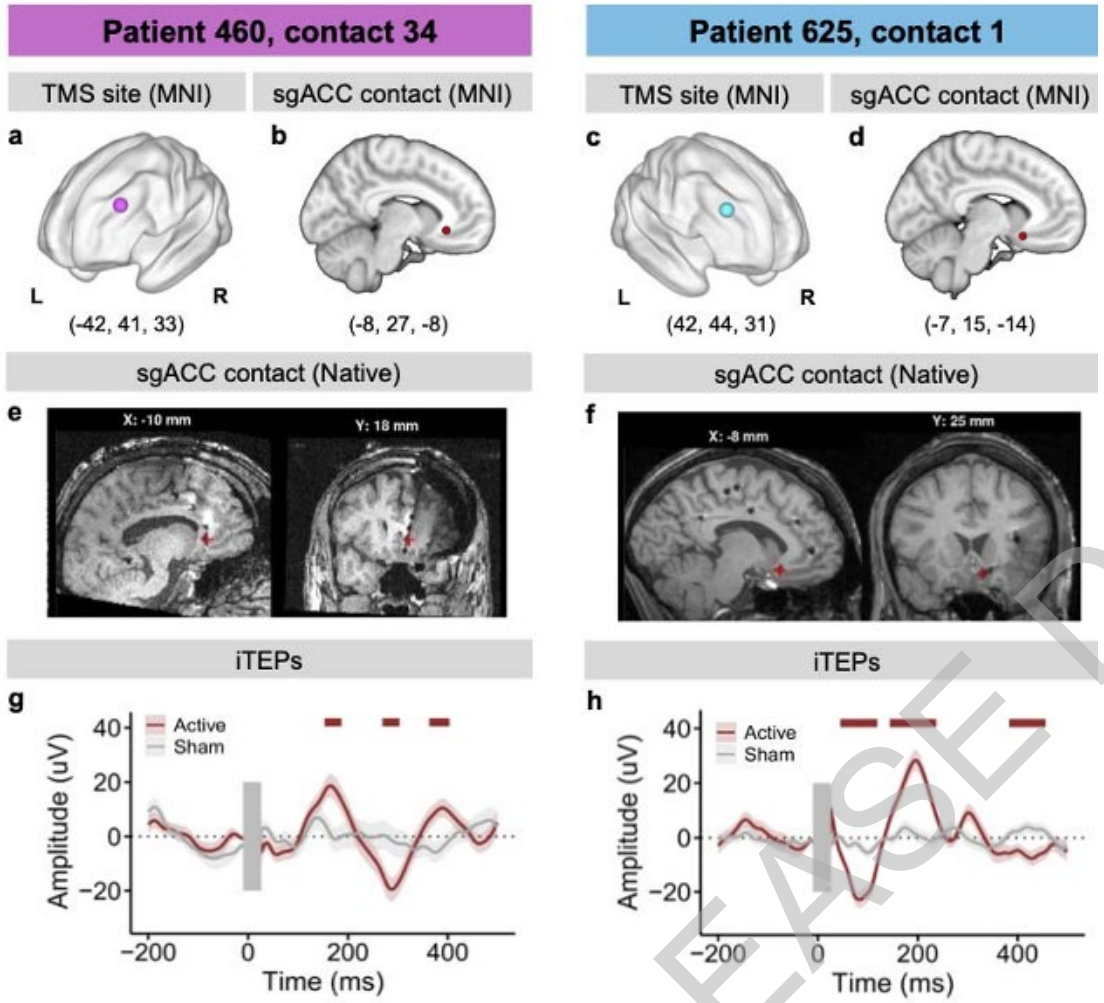
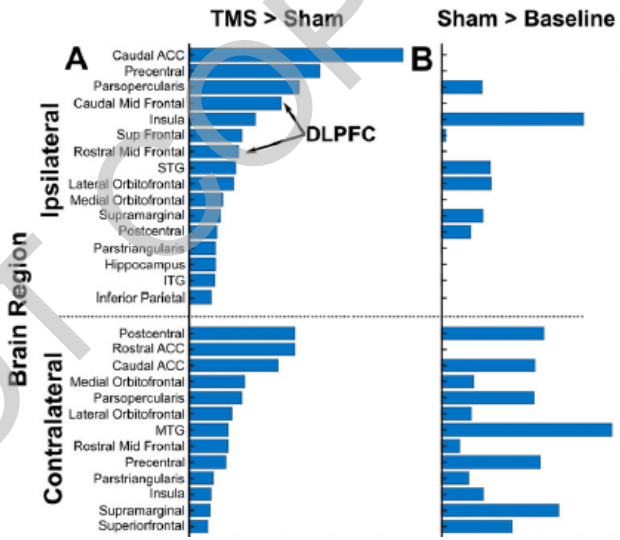
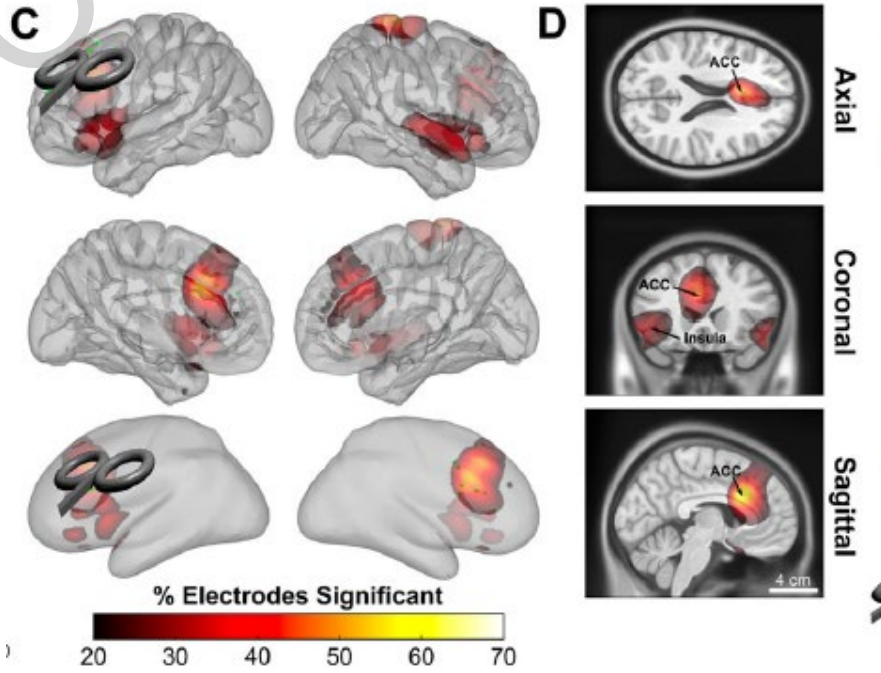
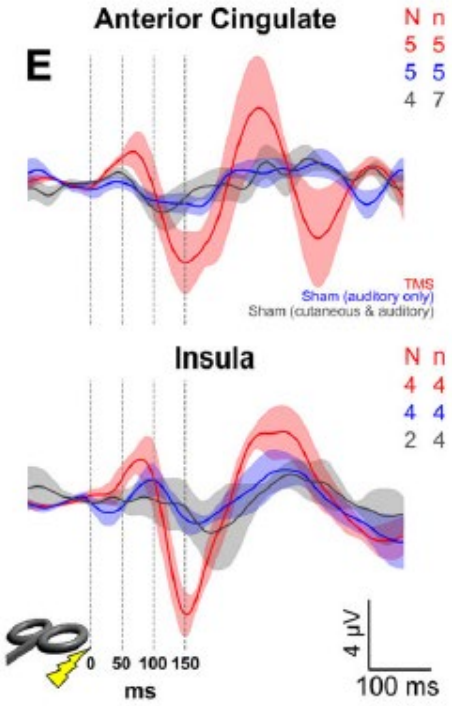
LDLPFC Stimulation activates sgACC … but also a number of other regions!









Left: Trapp 2024 Biorxiv; Right: Wang 2024 Mol Psych

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Accelerated TBS (SAINT)

B

Day 1	Day 2	Day 3	Day 4	Day 5
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
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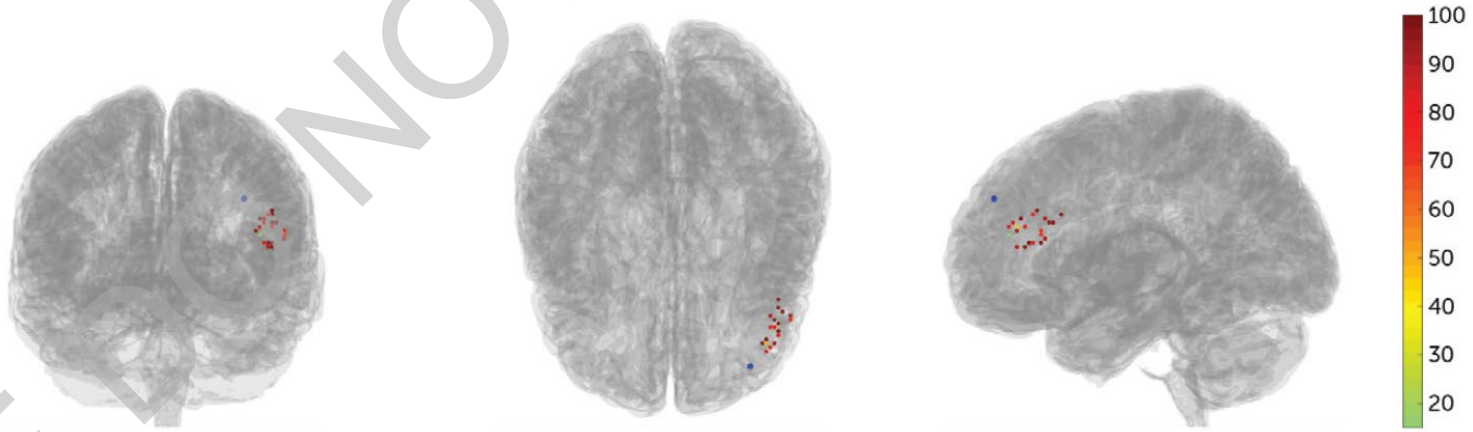

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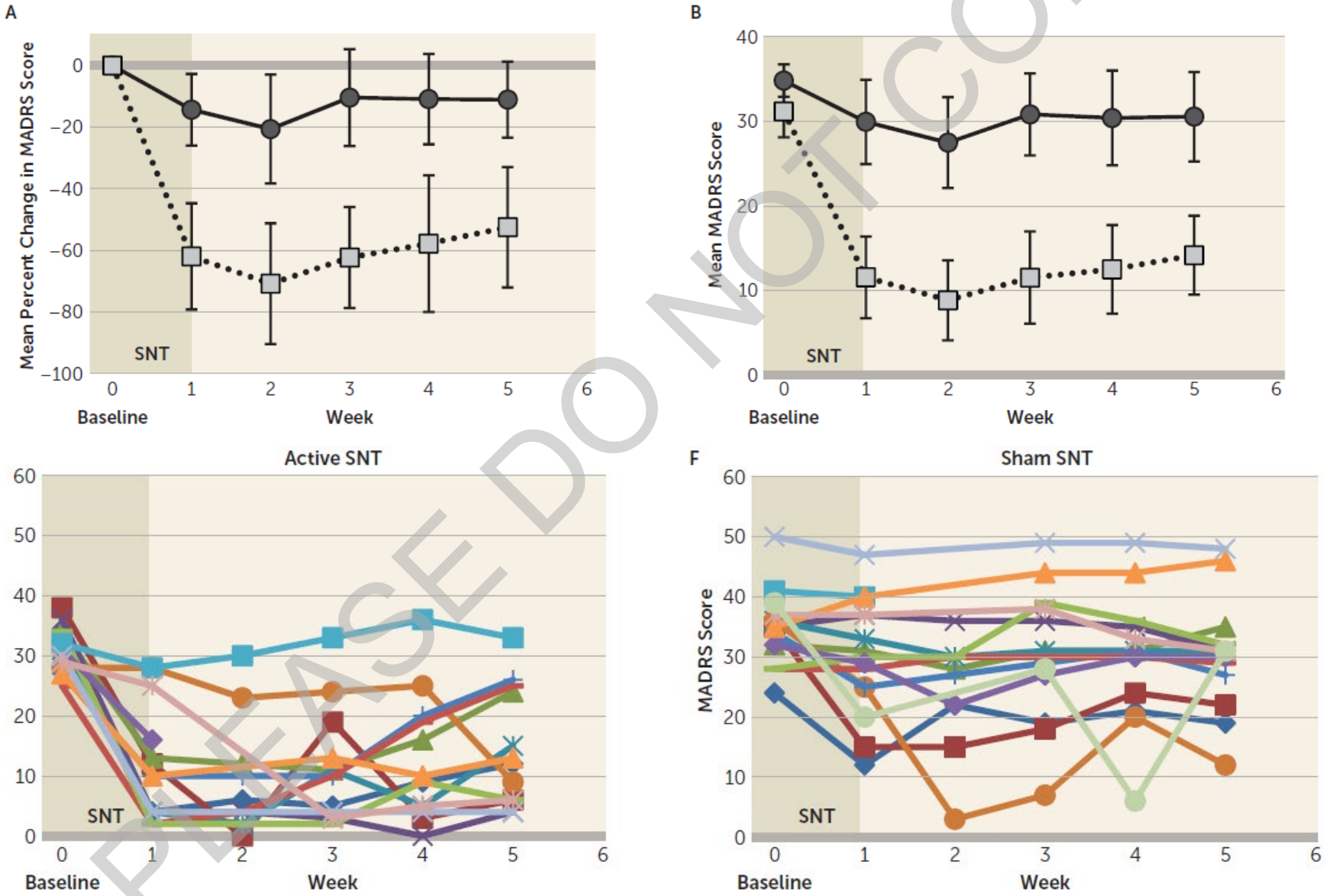
Cole 2020 Am Jour Psych

Accelerated TBS (SAINT) results



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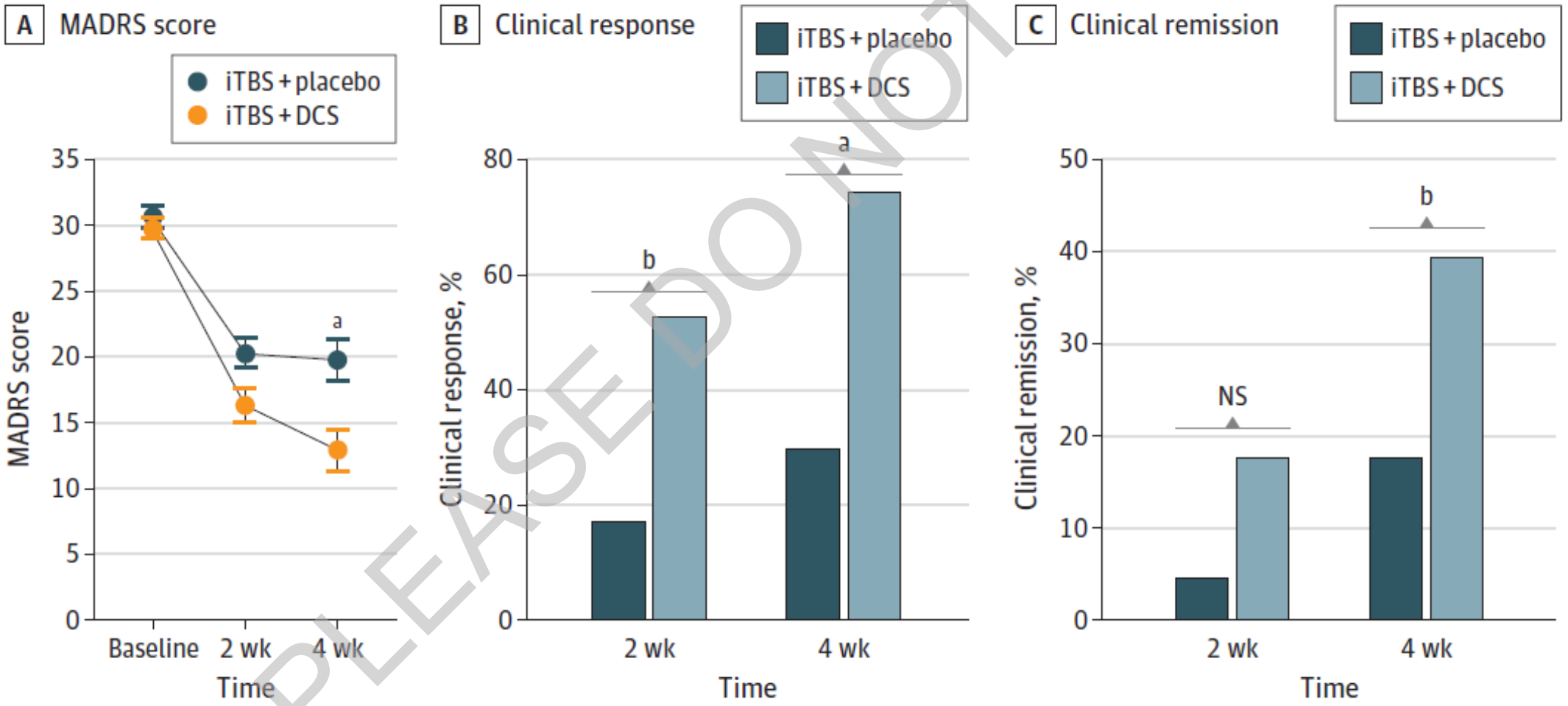
Cole 2022 AJP

TMS + drugs

JAMA Psychiatry | Original Investigation

Efficacy of Adjunctive D-Cycloserine to Intermittent Theta-Burst Stimulation for Major Depressive Disorder
A Randomized Clinical Trial

Jaeden Cole, BSc; Maya N. Sohn, BSc; Ashley D. Harris, PhD; Signe L. Bray, PhD; Scott B. Patten, MD, PhD; Alexander McGirr, MD, PhD



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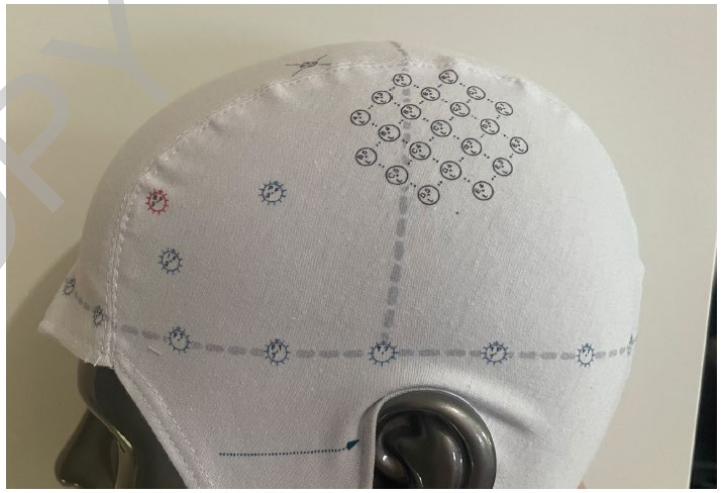
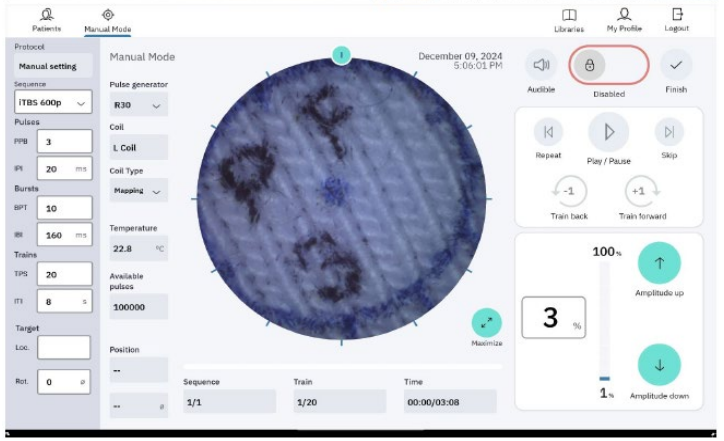
One-D TMS: Accelerated TBS + drugs

- 32 patients, open-label study
- Single dose of d-cycloserine 125mg, 50-70 min prior to TMS
- Single dose lisdexamfetamine 20mg
- 20 sessions of iTBS: 5/50 Hz, 2s-on 8s-off, 600 pulses total, 120% RMT, every 30 minuts
- Target Siddiqi 2021 target (MN -46, 9, 31) using scalp heuristics
- Used Magventure R30 with Ampa L-coil
- No specific instructions to patients









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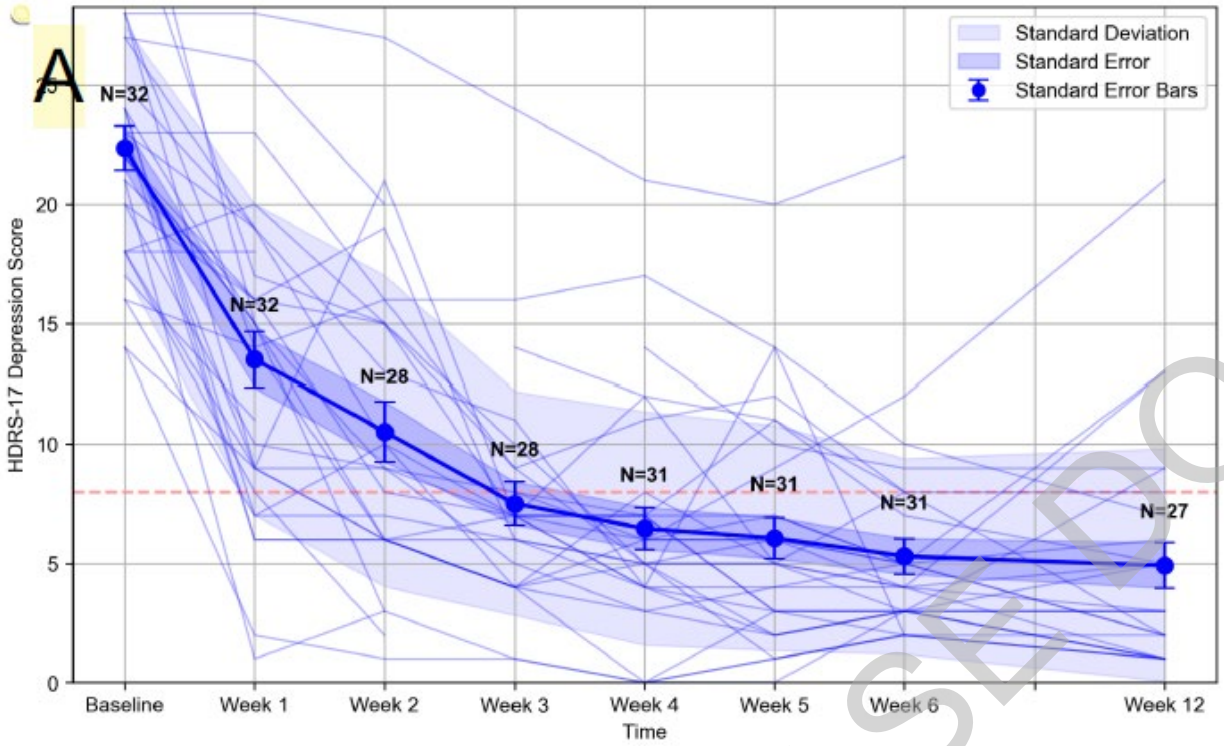
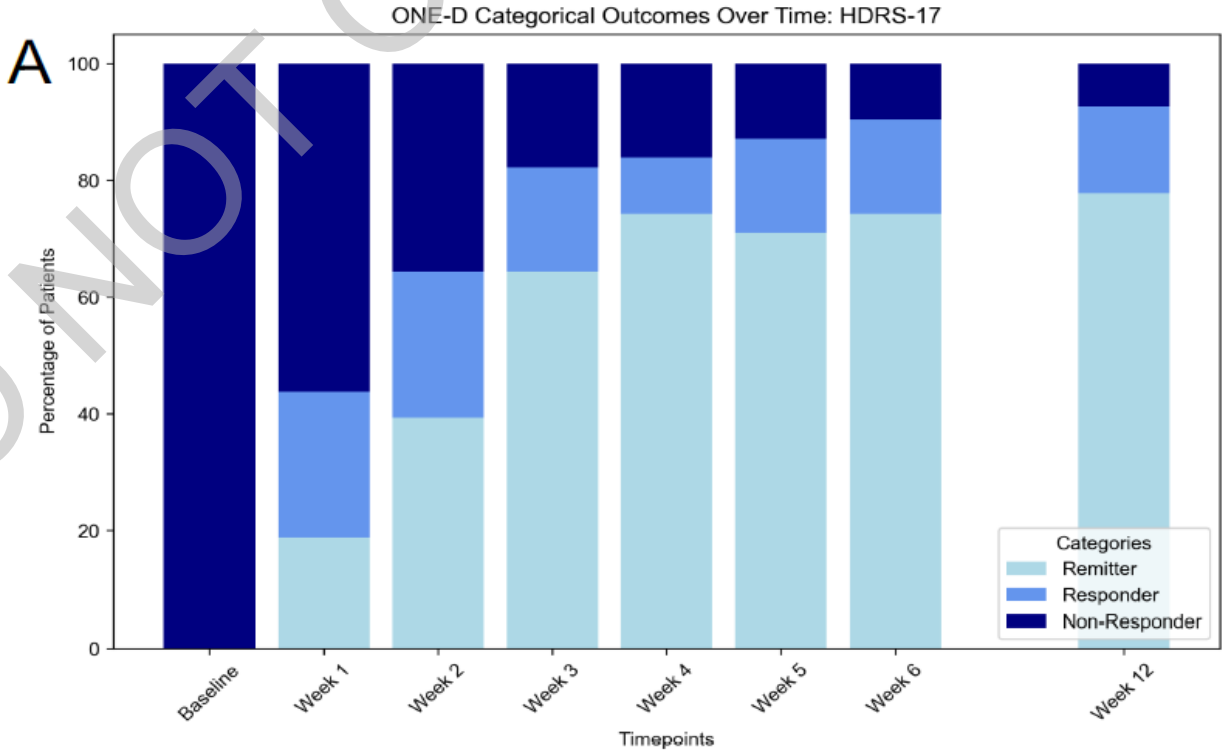
Vaughn 2025 Bioarxiv

One-D results





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