

# The Future of TMS

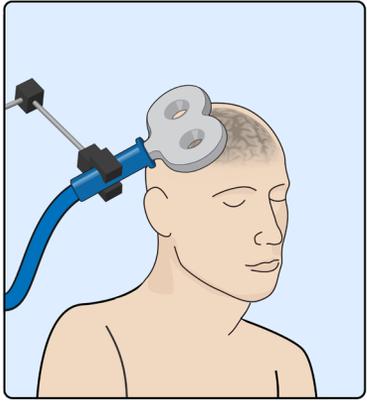
Alvaro Pascual-Leone, MD, PhD

Mouhsin Shafi, MD, PhD

Alexander Rotenberg, MD, PhD



TMS Course - Harvard Medical School



## 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)

# 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

# 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

**Present** Helping Patients  
However.....40% do NOT respond

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



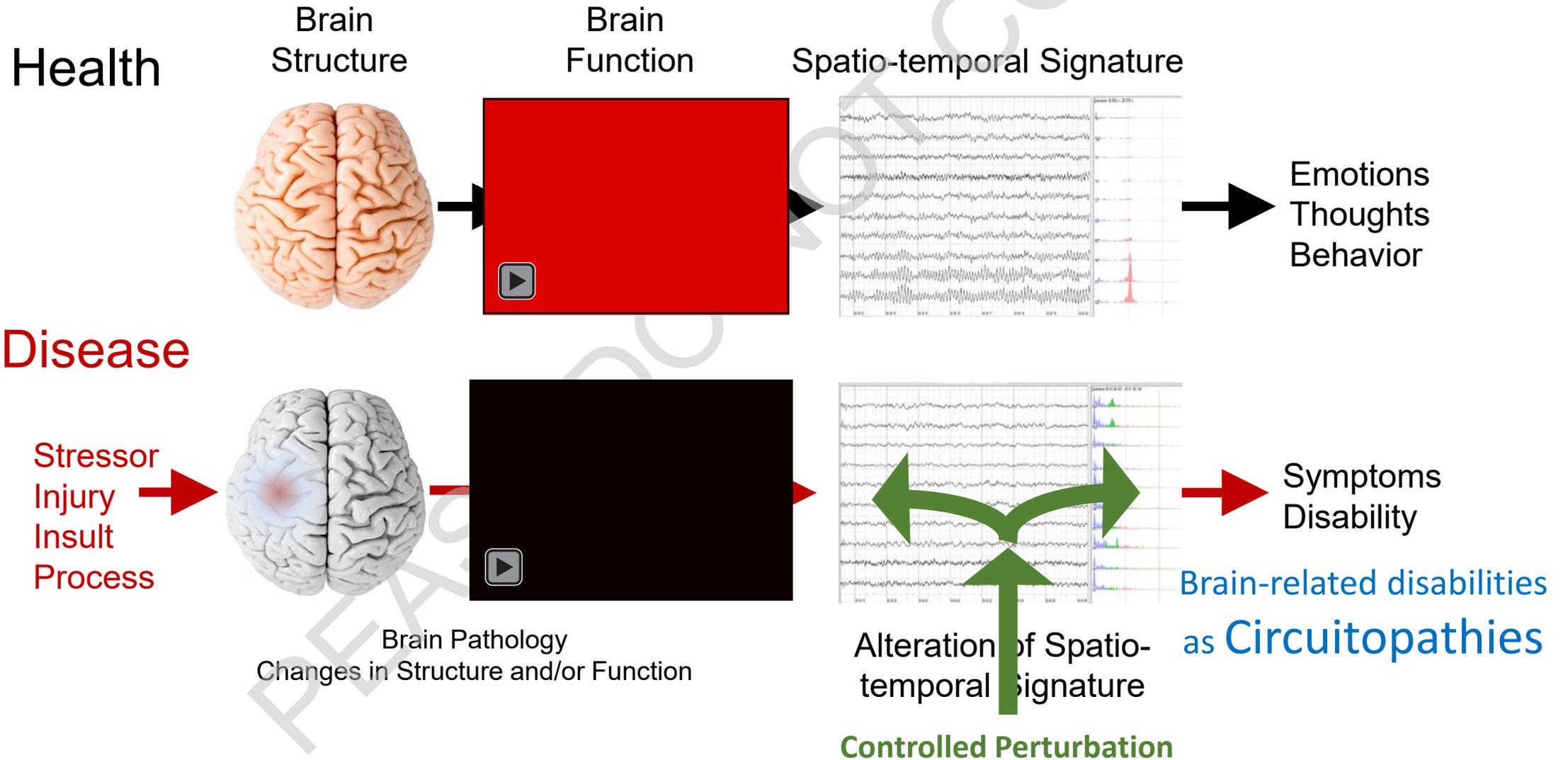
PLEASE DO NOT COPY

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

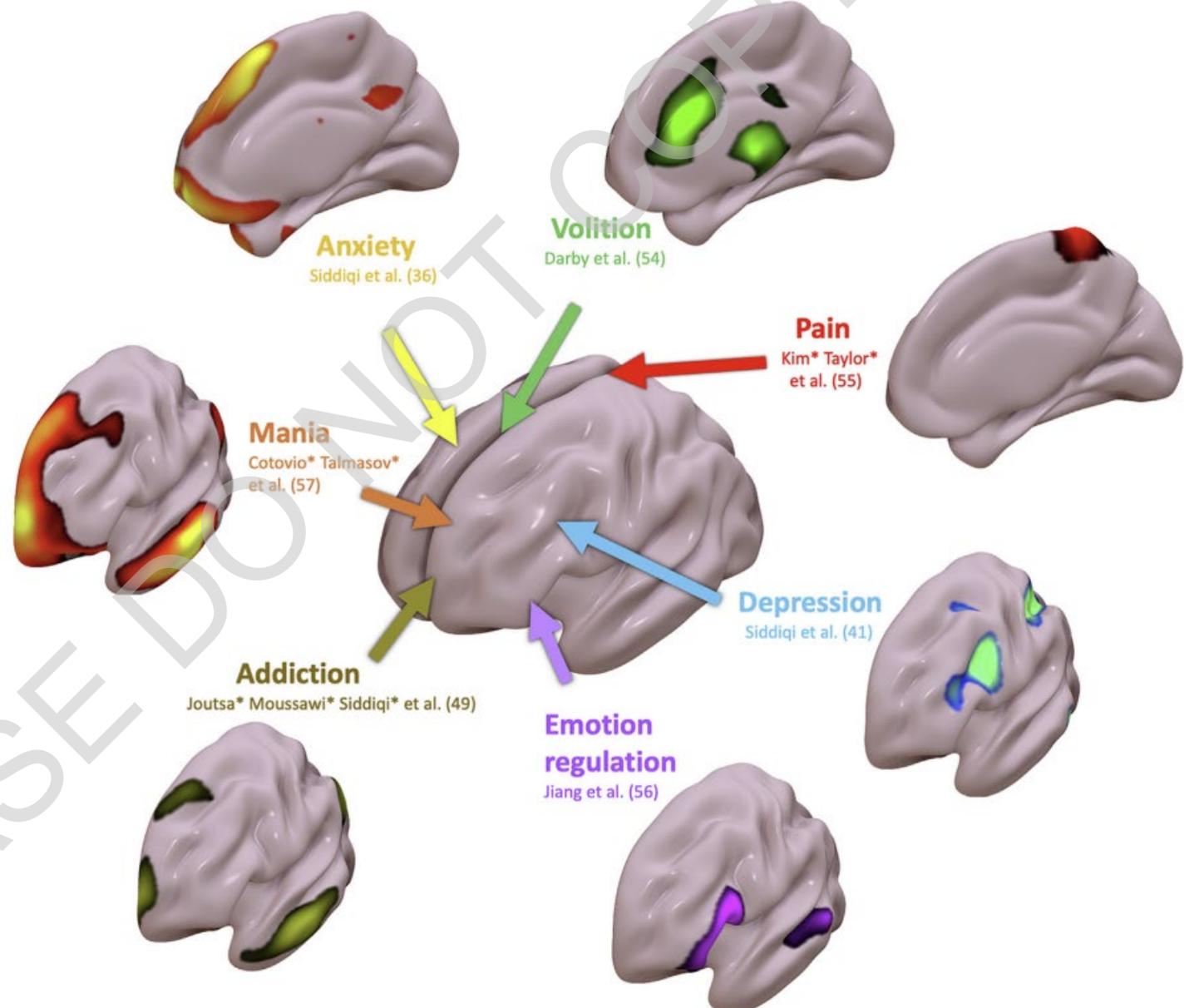
but offers **tool** that allows modulation of the neural substrate of **symptoms and disabilities** caused by brain illnesses or dysfunctions



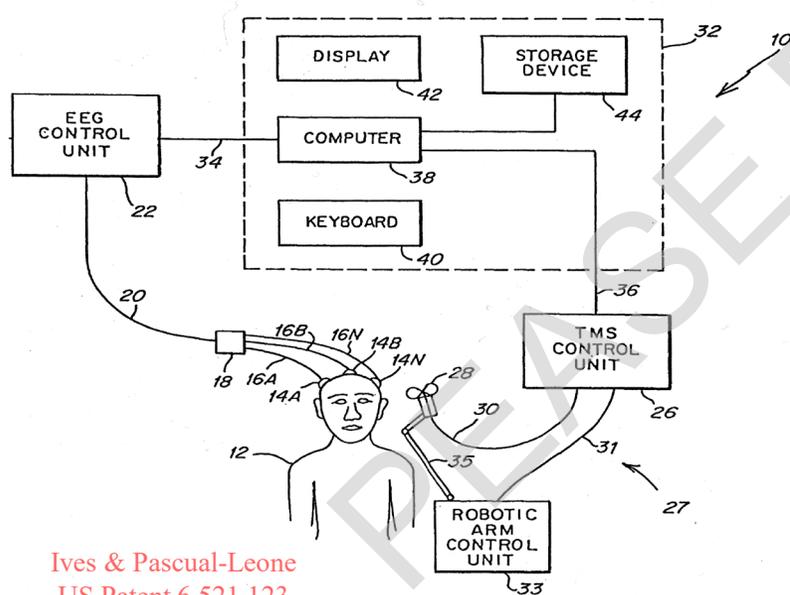
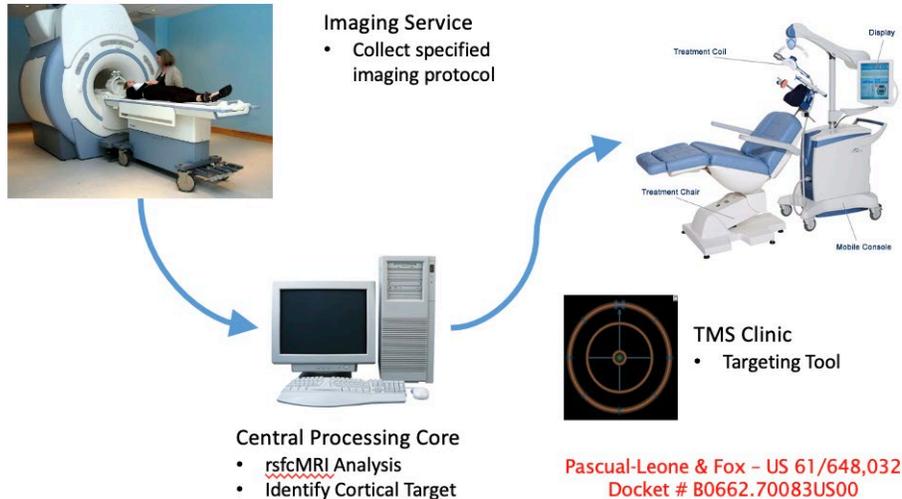
# Spatio-Temporal Signatures of Brain-Related Disabilities



# Symptom-specific targeting



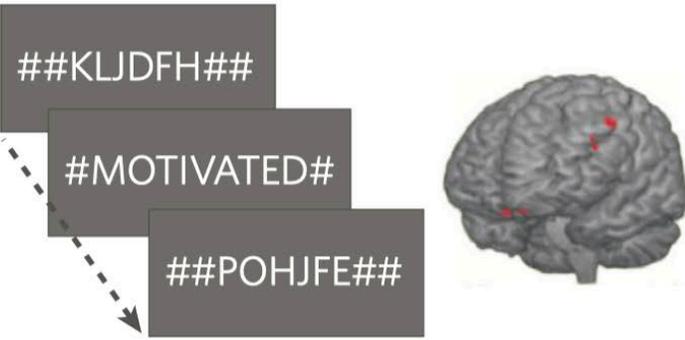
# Precision Medicine Symptom-Based Approach



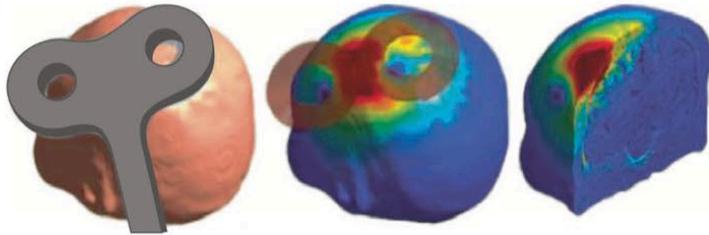
1. Define and target symptoms/disabilities - rather than diagnostic entities
2. Identify physiologic biotypes / biomarkers
3. Personalize the intervention (brain target, stimulation parameters, etc)
4. Measure the physiologic impact to assess effect
5. Adjust intervention, and iteratively optimize algorithm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

## Spatial precision

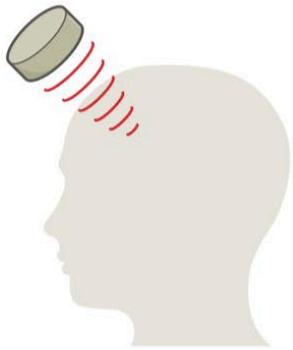
Imaging-guided targeting



Electric field modeling

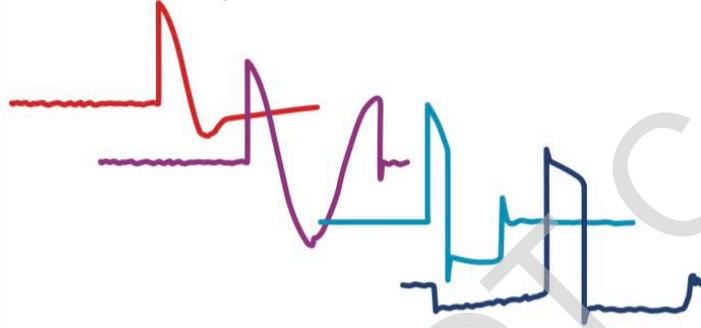


Focal/multifocal stimulation

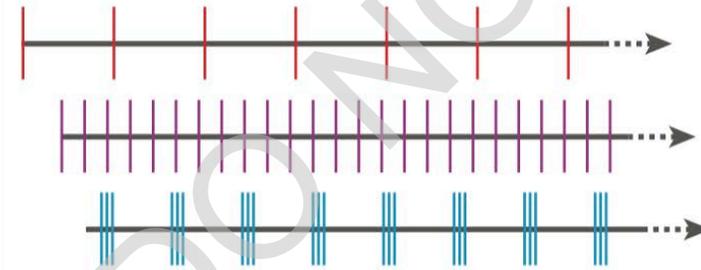


## Temporal precision

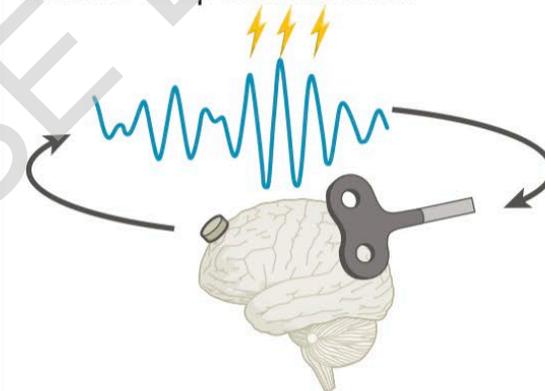
Waveform optimization



Patterned stimulation

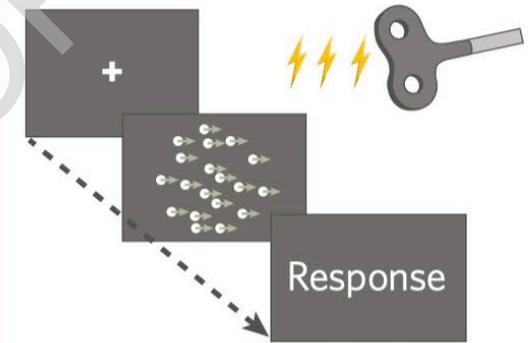


Closed-loop stimulation

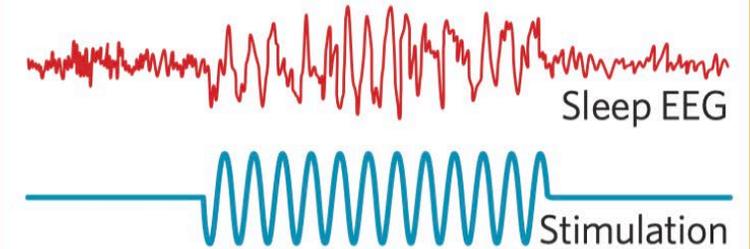


## Contextual precision

Online stimulation



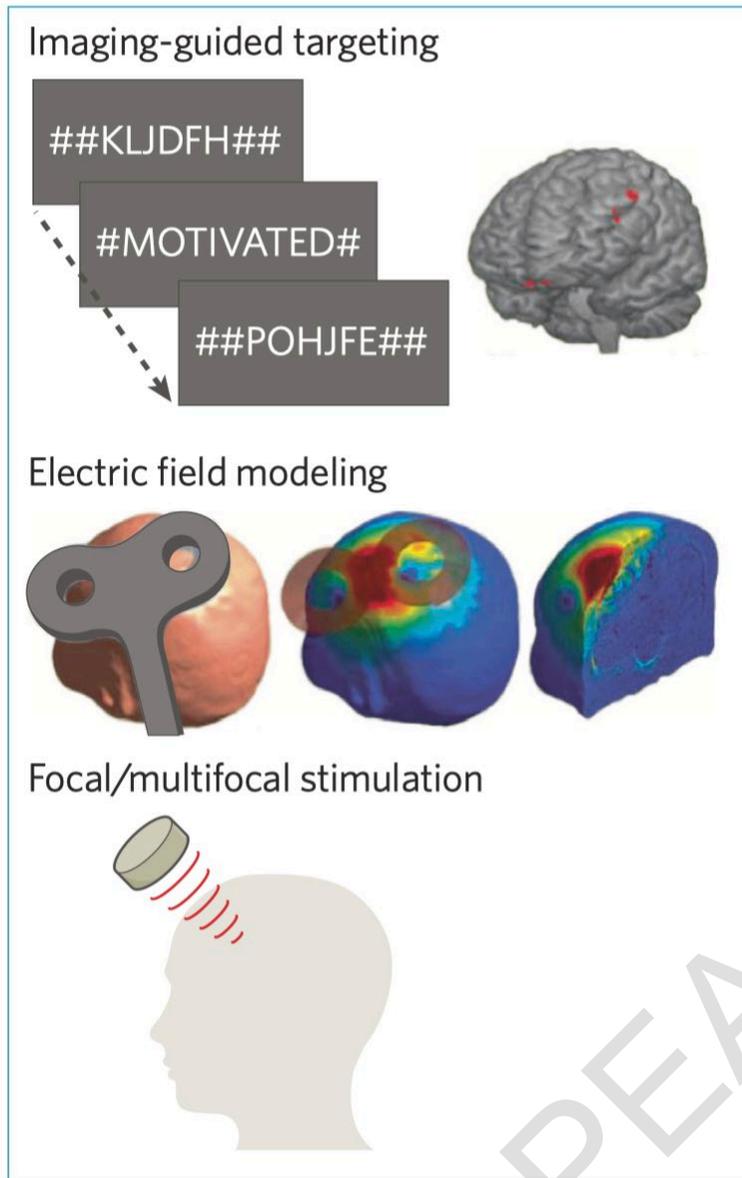
Biological rhythm



Combinatorial therapy



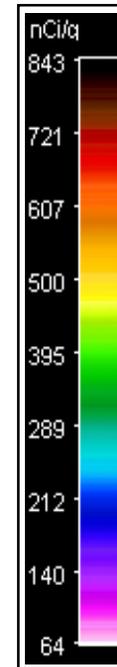
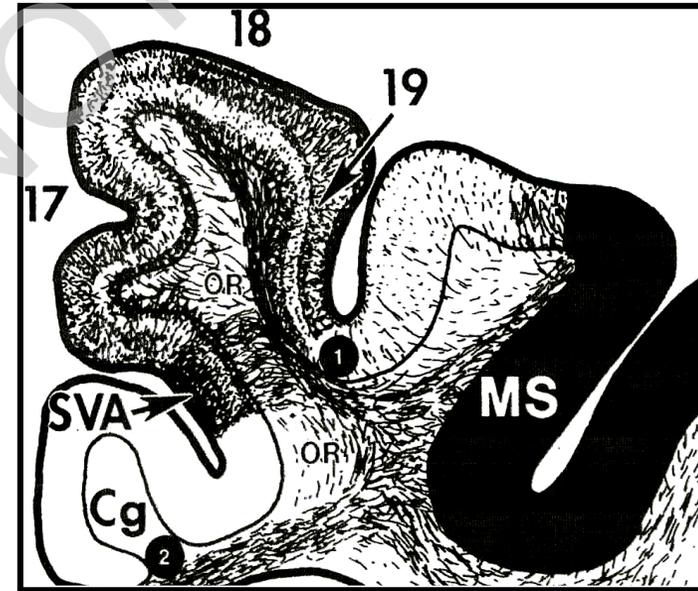
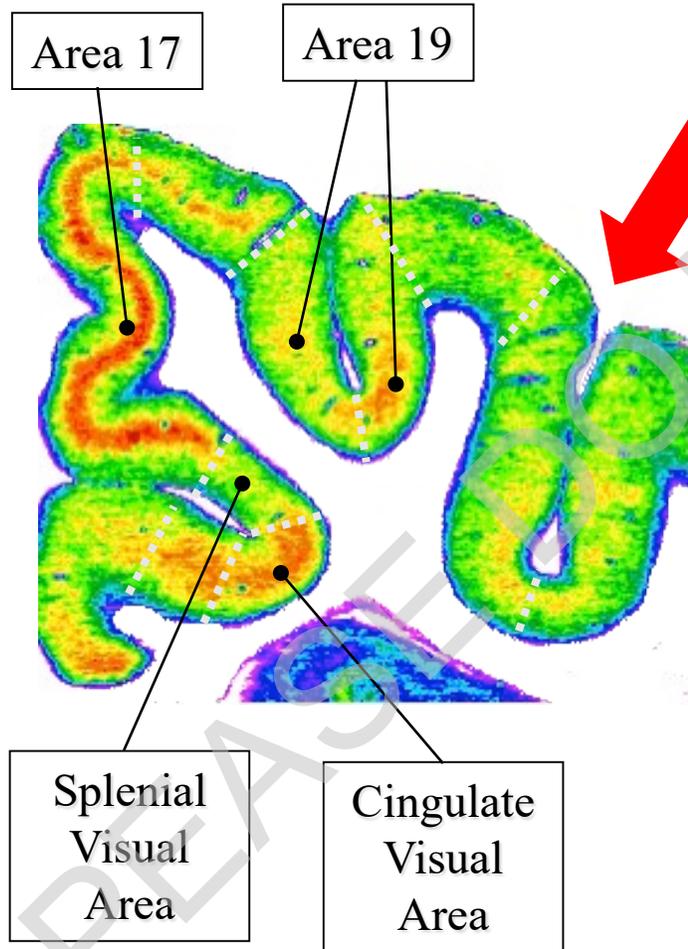
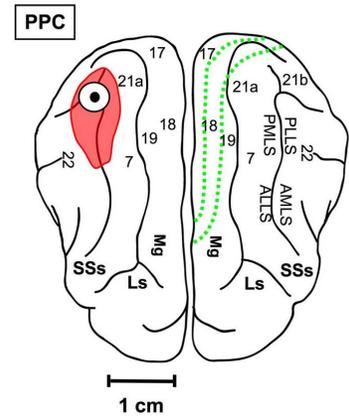
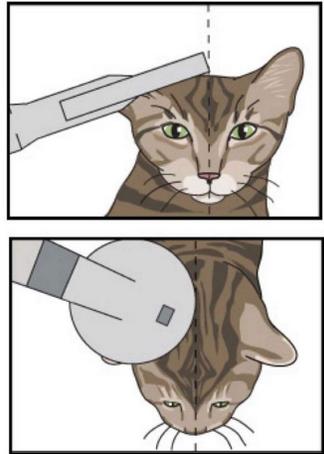
## Spatial precision



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

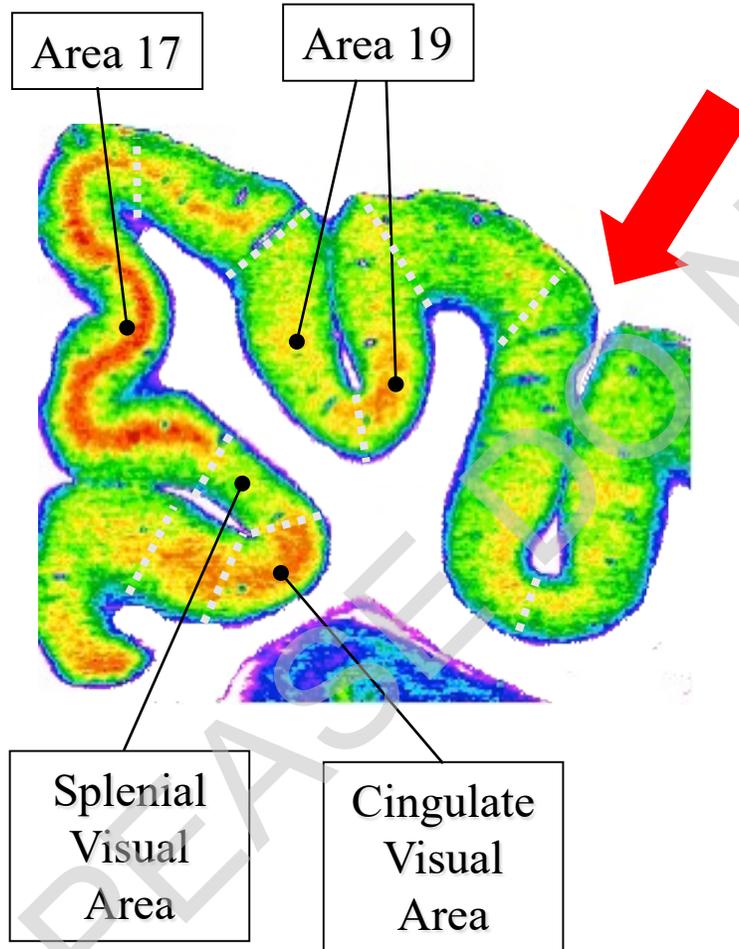
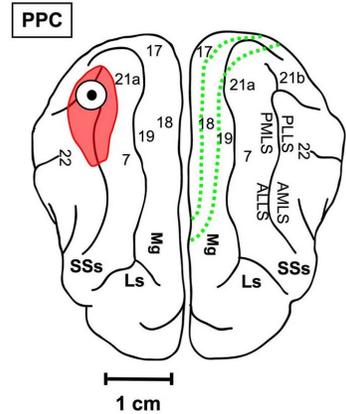
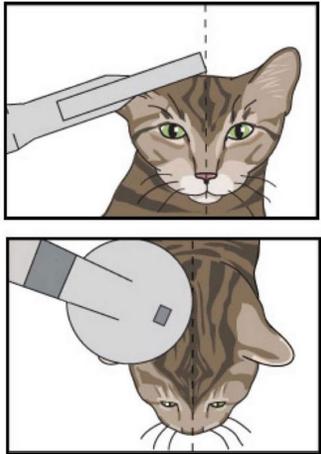


# NiBS modulates activity in brain networks & the effects depend on connectivity

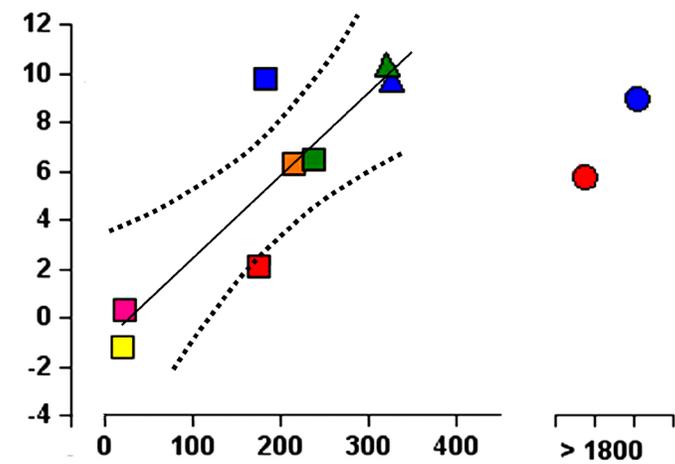




# NiBS modulates activity in brain networks & the effects depend on connectivity



Functional: TMS impact (% $\Delta$   $^{14}\text{C}$  2-DG)



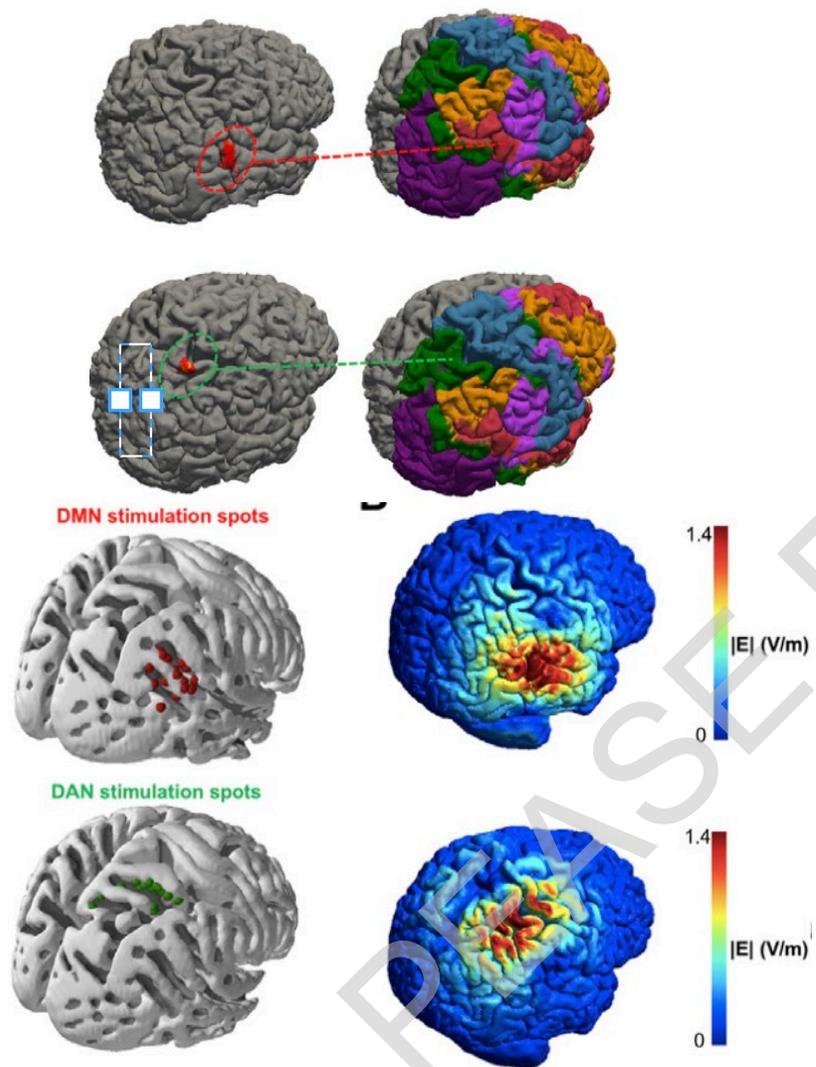
Anatomy: Projection Weight (grains/ $\mu\text{m}^2$ )

- A19
- A18
- A17
- SVA
- CVA
- pCG
- PUL
- LPI
- ▲ SGS
- ▲ SO

# Impact on specific brain networks



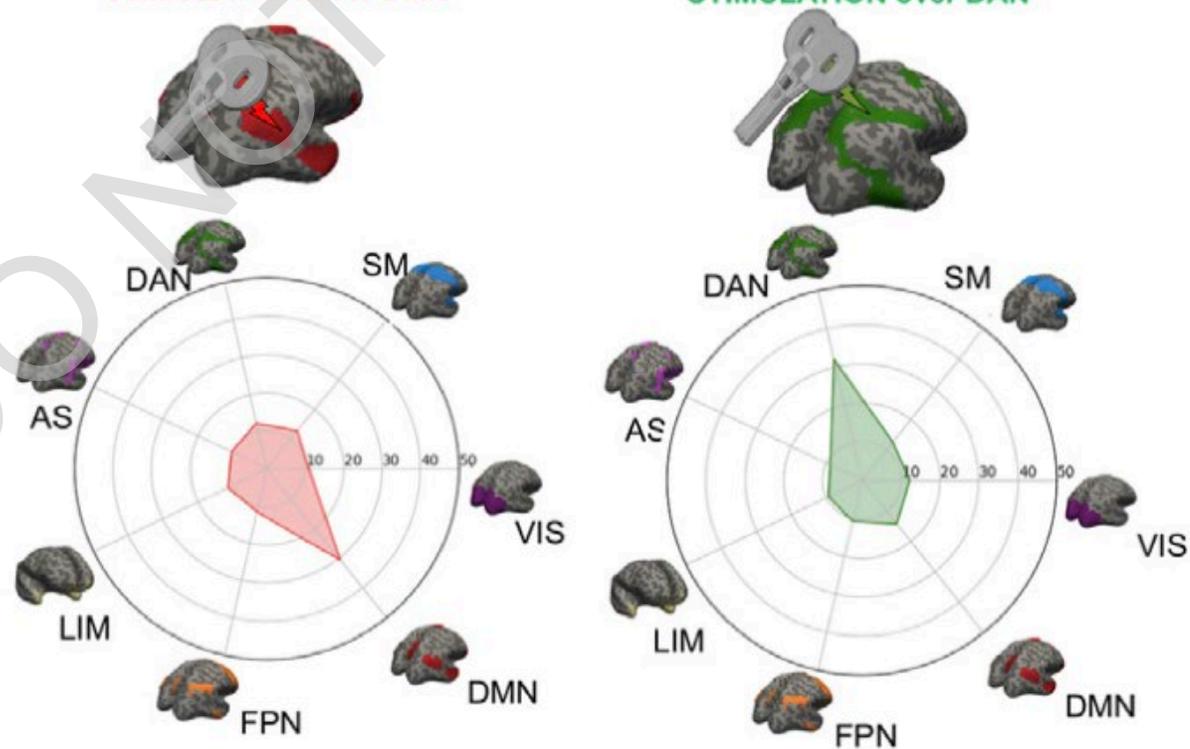
Davide Momi

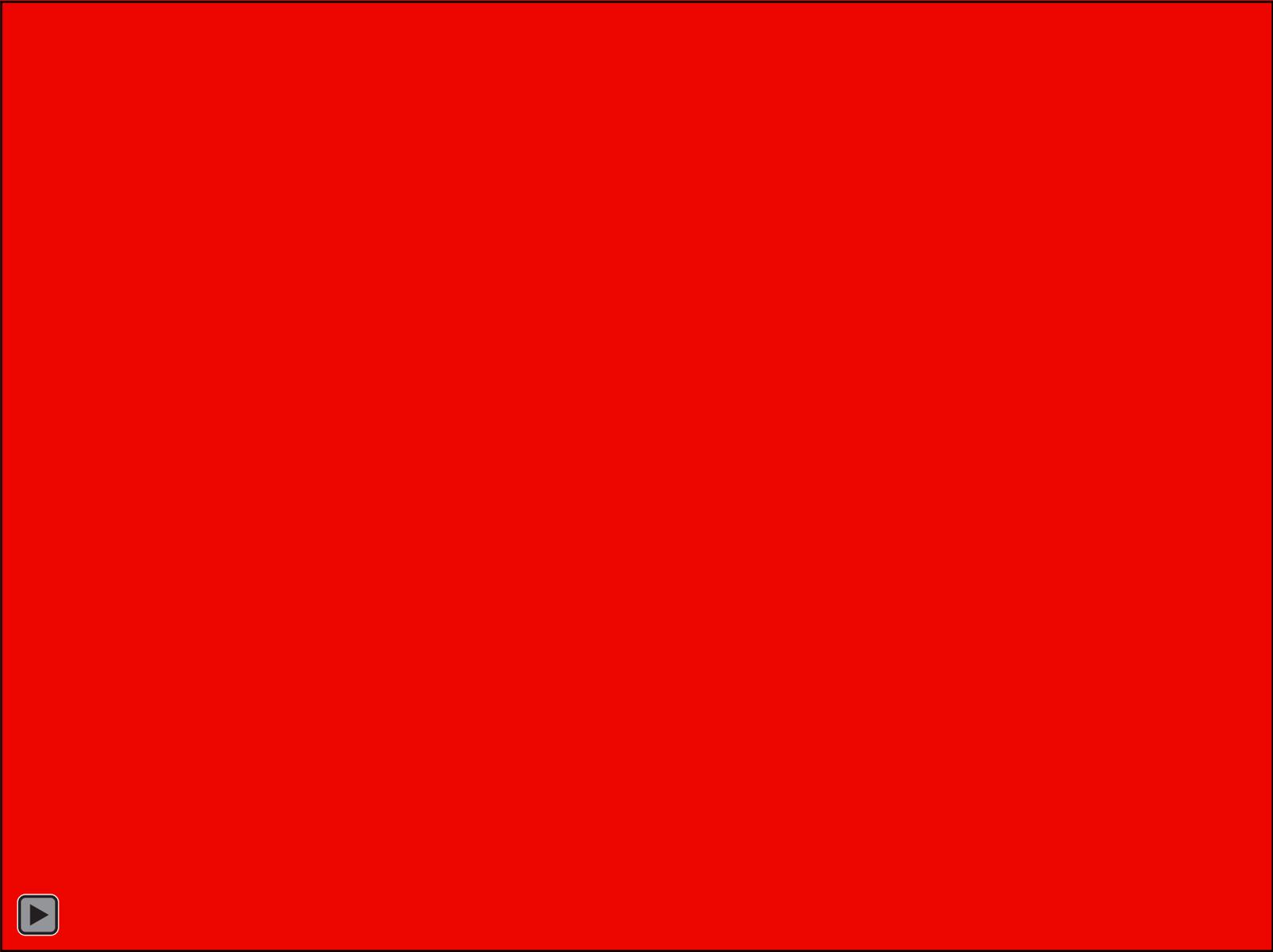


## Network Engagement

STIMULATION over DMN

STIMULATION over DAN





# Robot-guided TMS

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



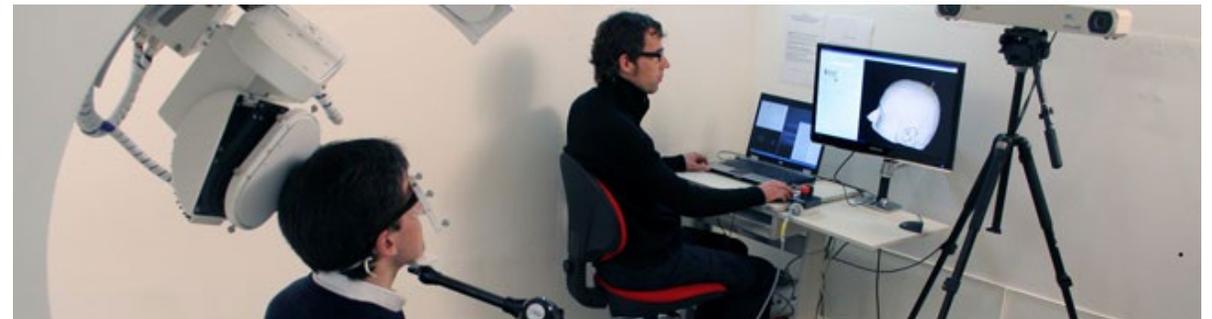
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CE mark



Axilum Cobot



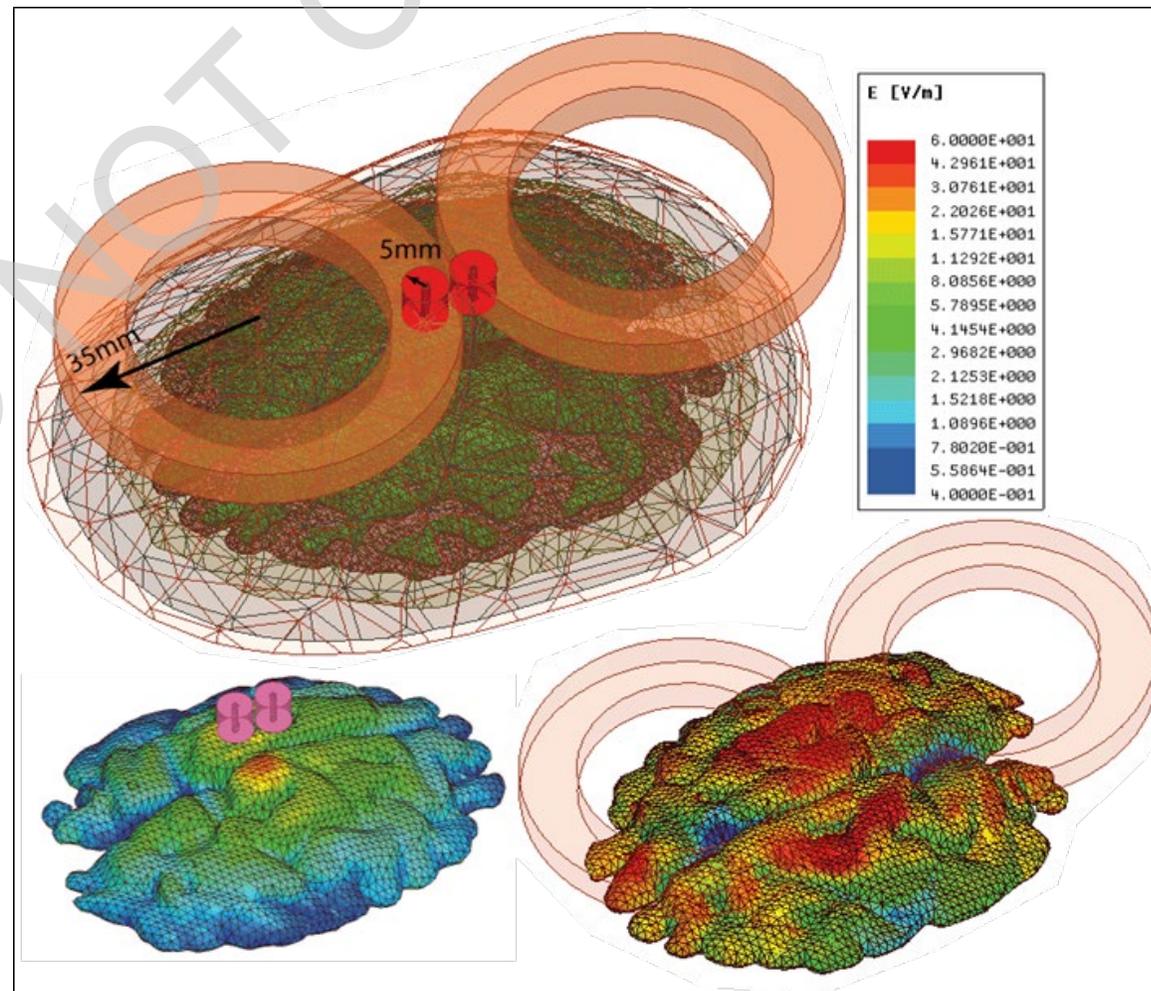
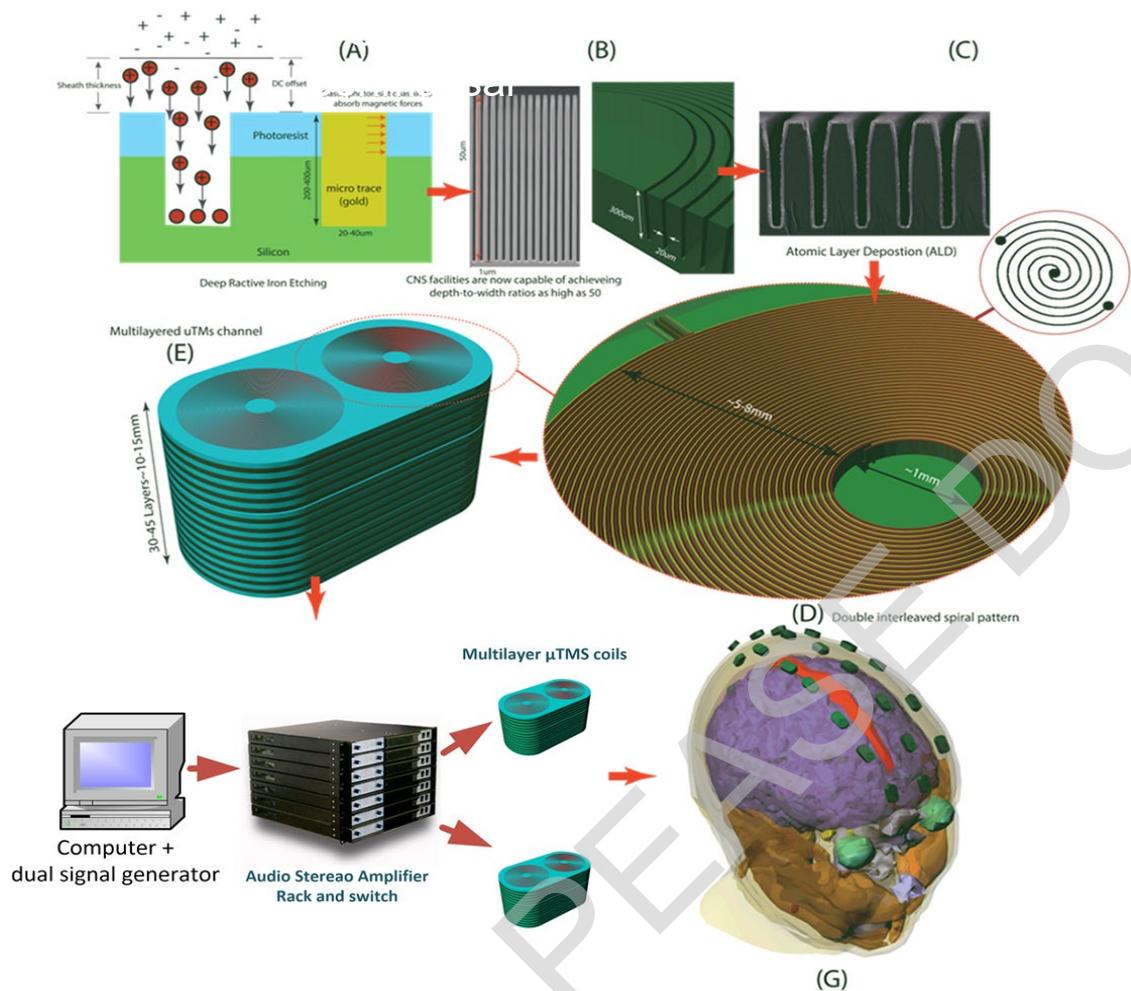
Axilum Robot





Giorgio Bonmassar

# $\mu$ TMS



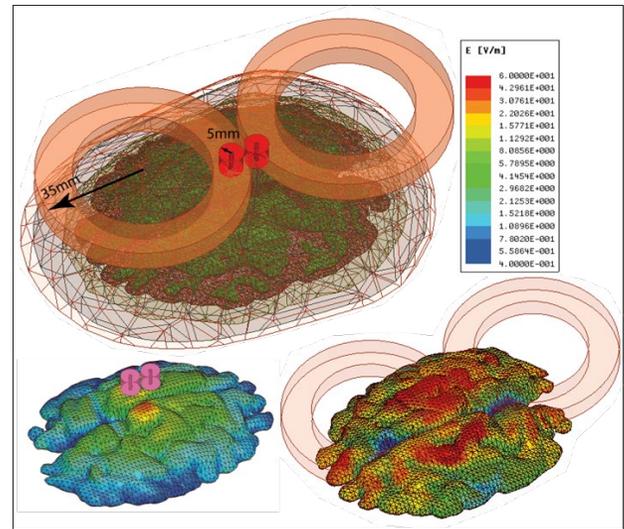
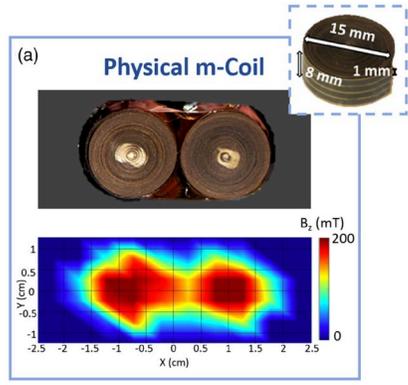
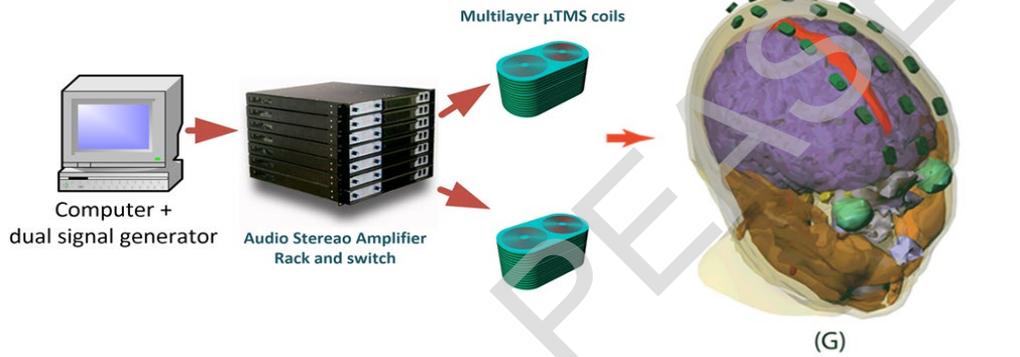
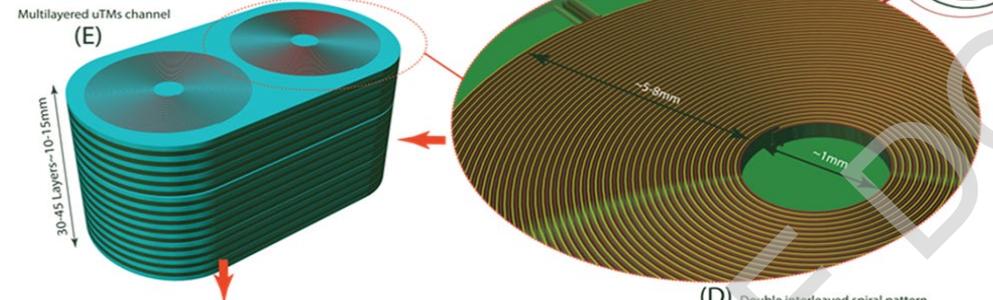
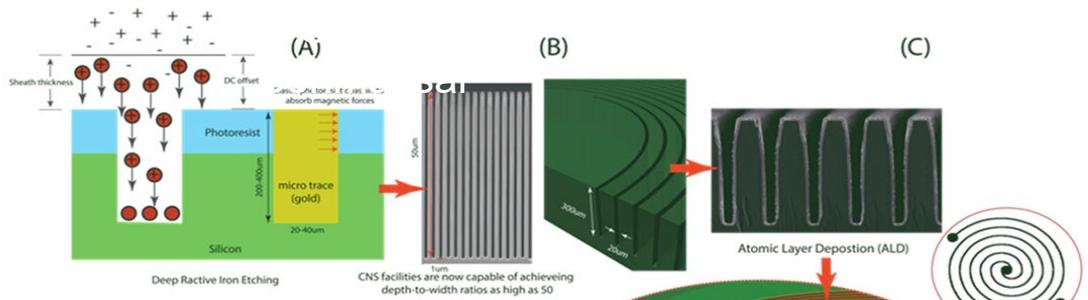
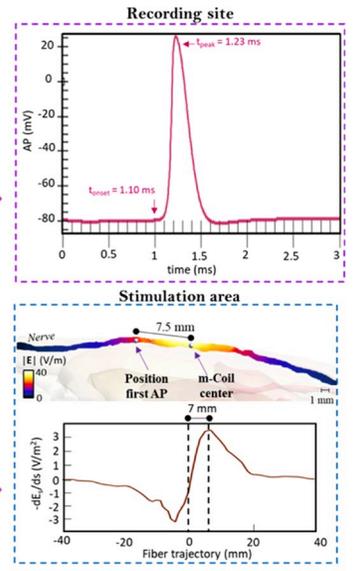
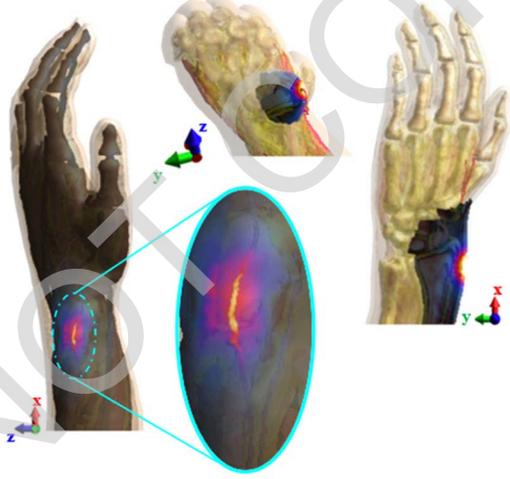


Giorgio Bonmassar

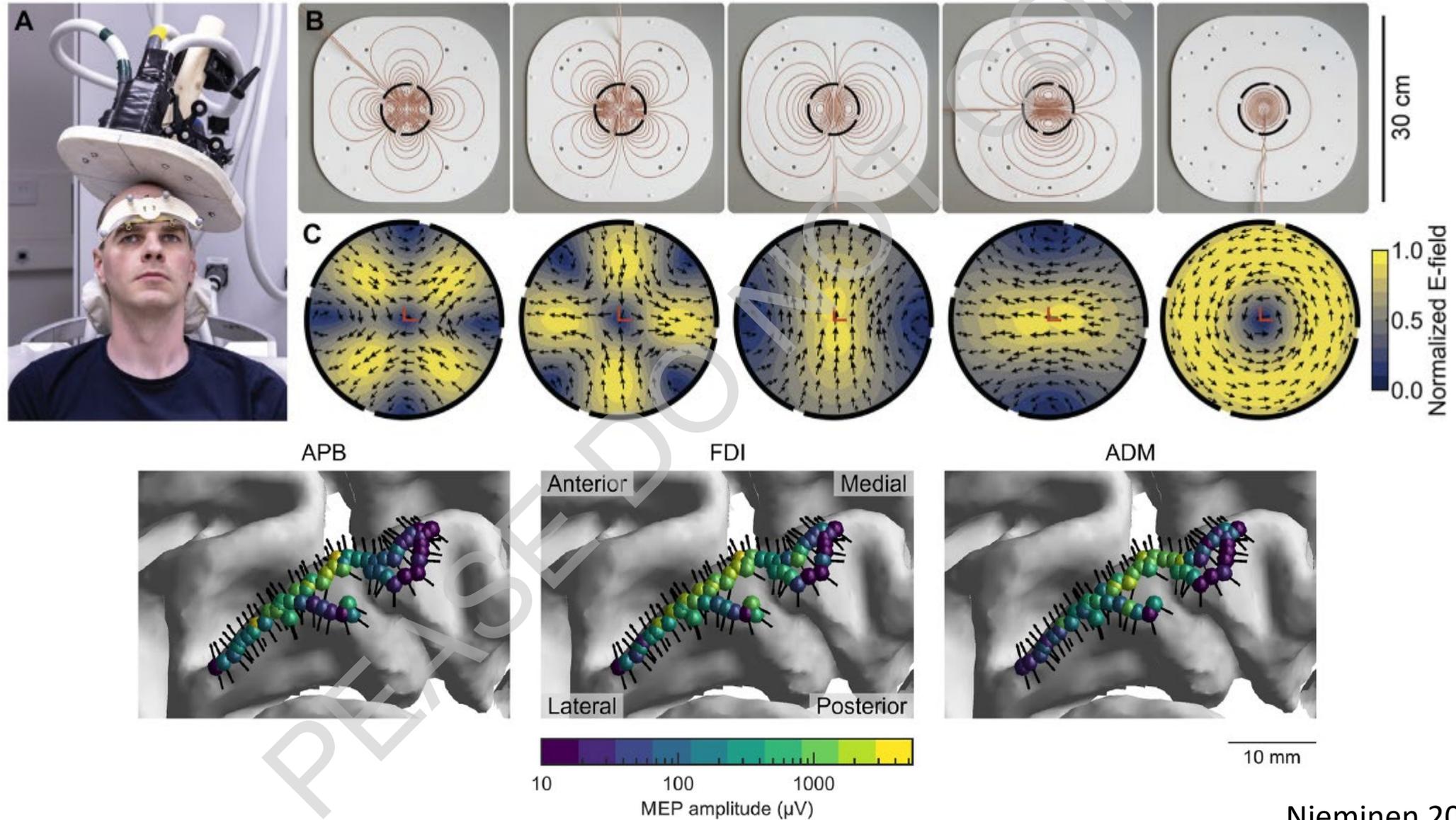
# $\mu$ TMS

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

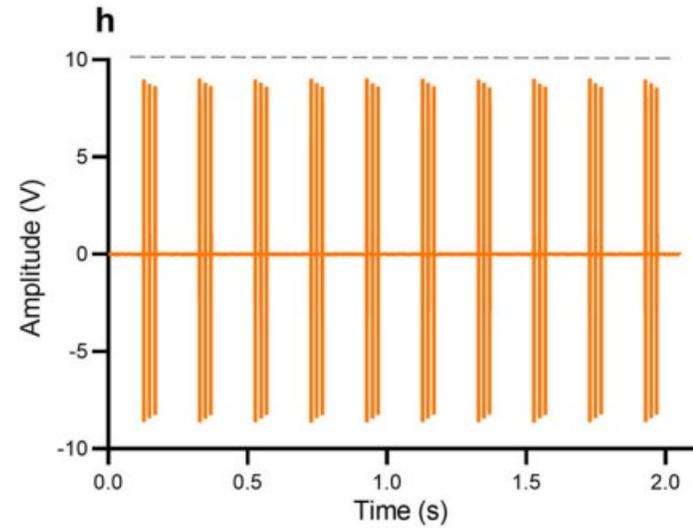
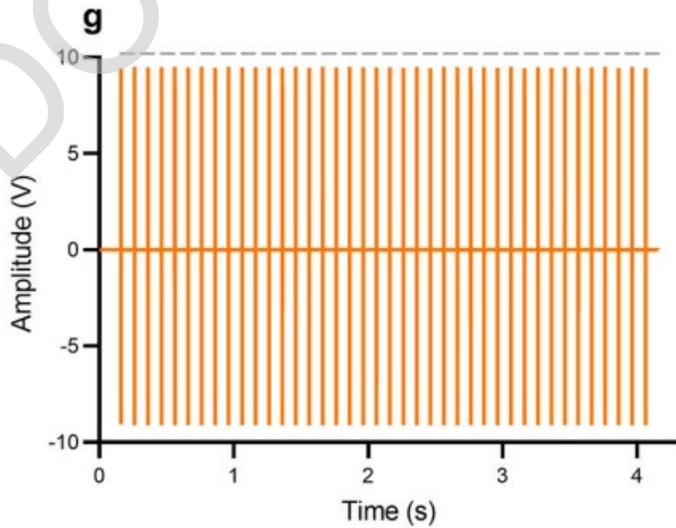
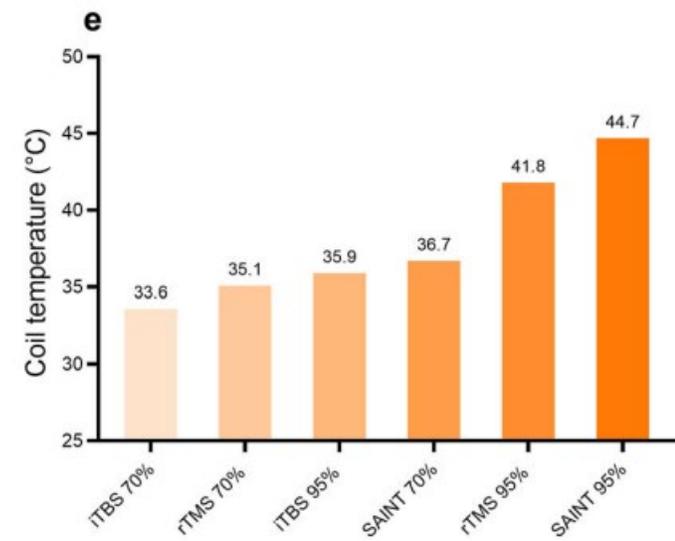
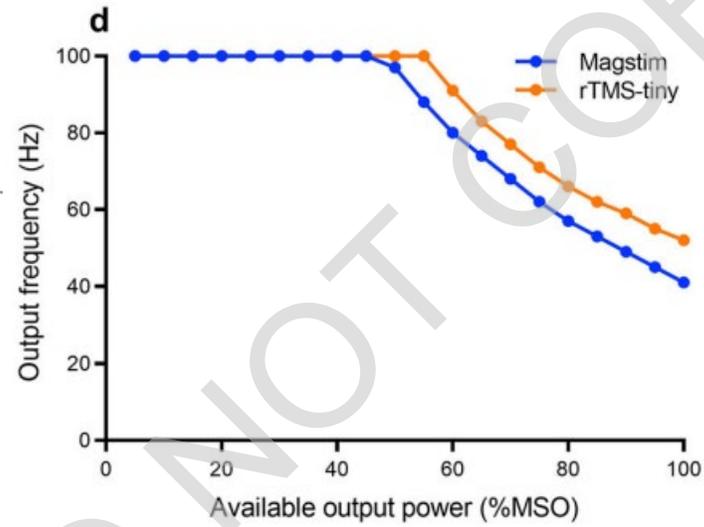
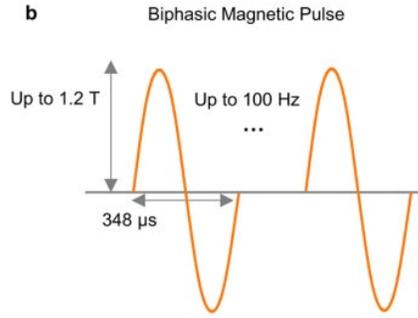
Surface view    Cross section    Longitudinal section



# Multi-locus TMS

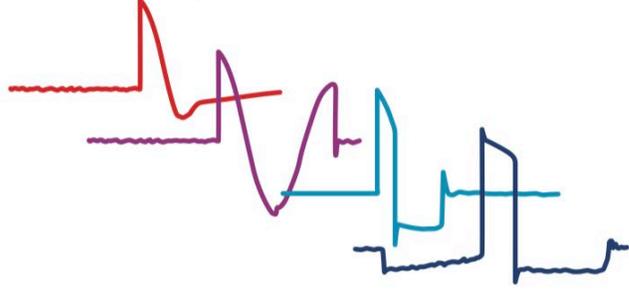


# Portable TMS

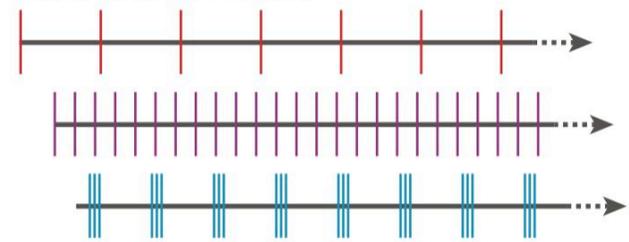


## Temporal precision

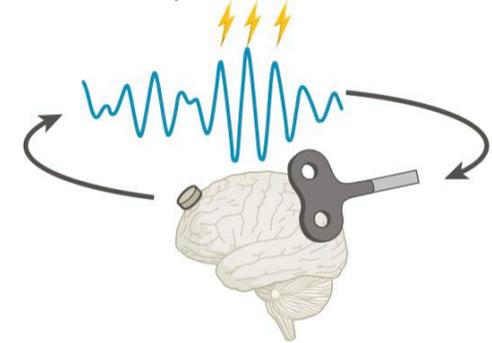
### Waveform optimization



### Patterned stimulation

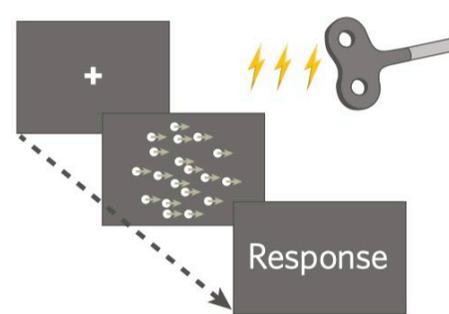


### Closed-loop stimulation

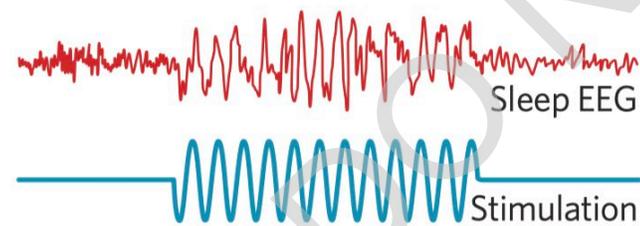


## Contextual precision

### Online stimulation



### Biological rhythm



### Combinatorial therapy

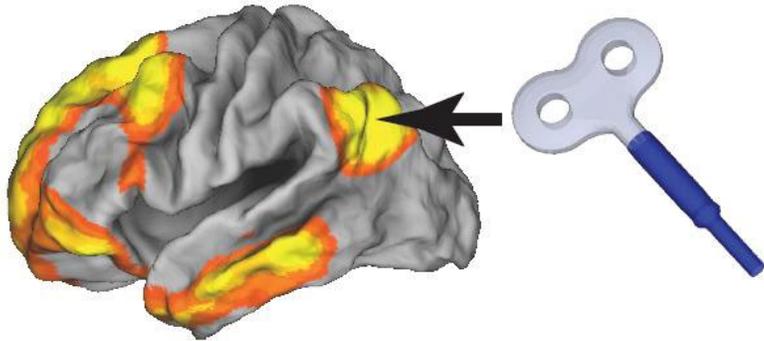


1. Individualize stimulation parameters
  - Measure neurophysiologic effect
2. Leverage State-dependency effects
  - Combine with other interventions / medications
3. Design improved stimulators
4. Optimize stimulation protocols
5. Stimulate at right time
  - Oscillations specific stimulation
  - Closed loop stimulation

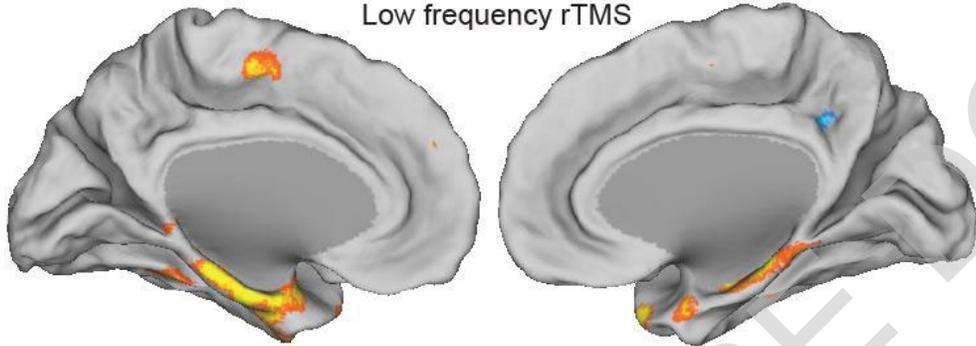
# Variability of Physiologic Effects



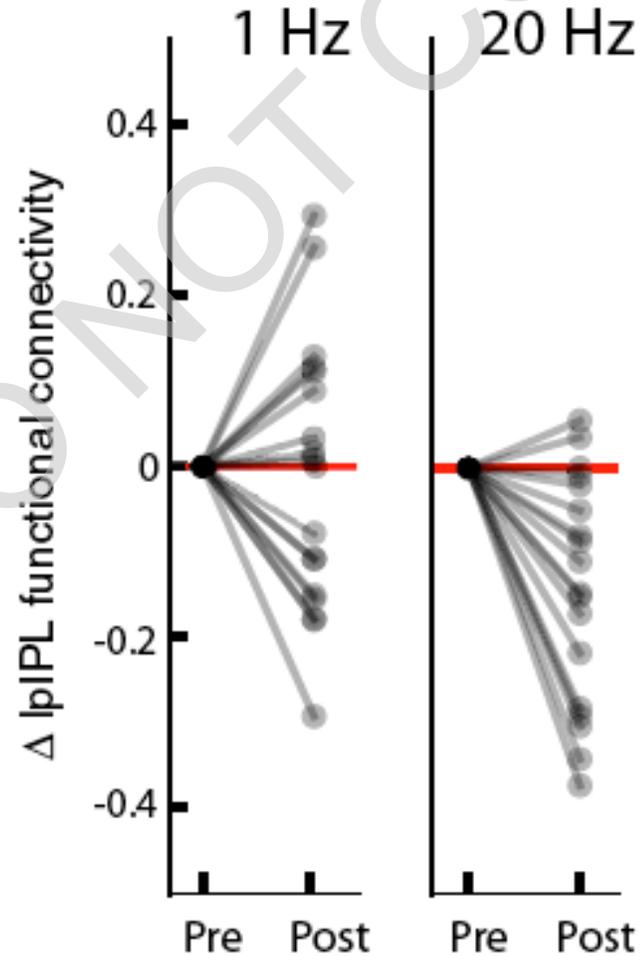
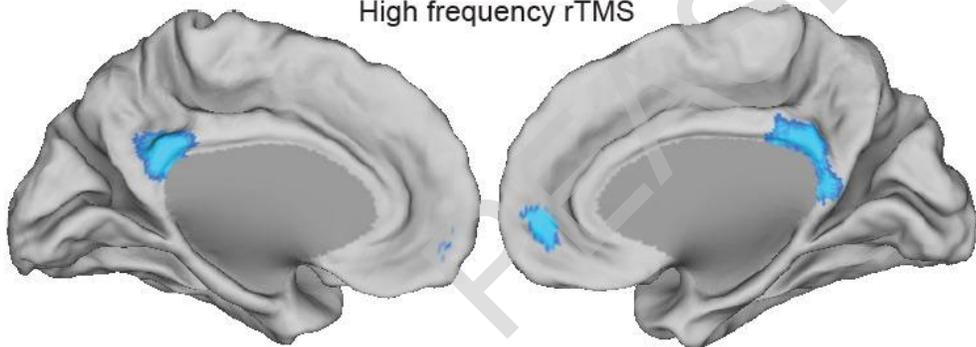
Mark Eldaief



Low frequency rTMS



High frequency rTMS

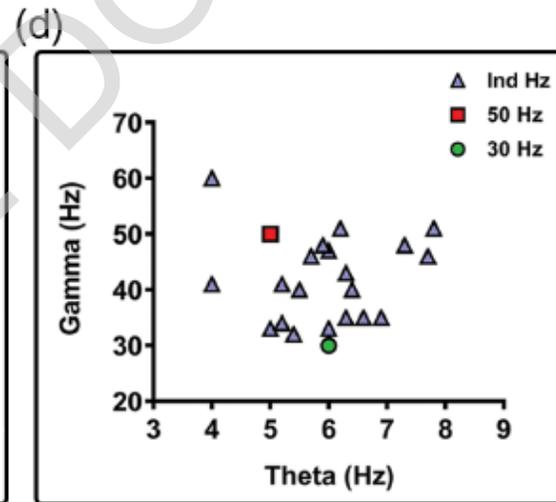
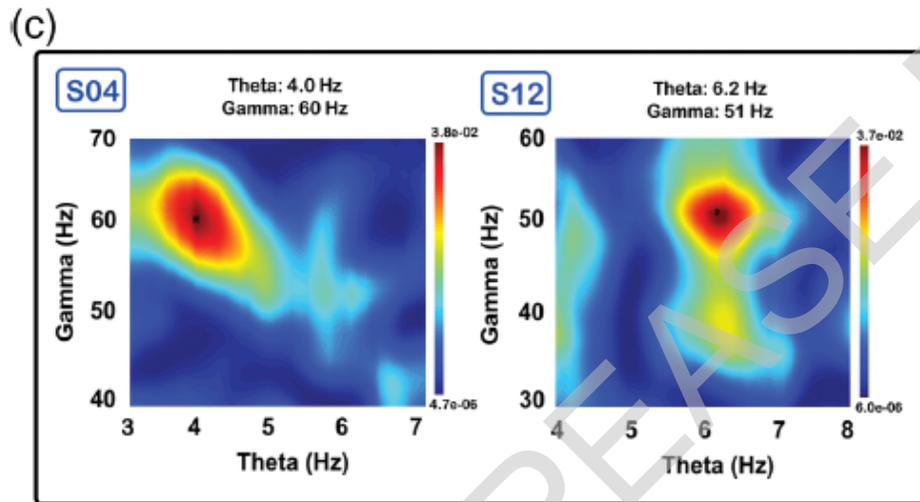
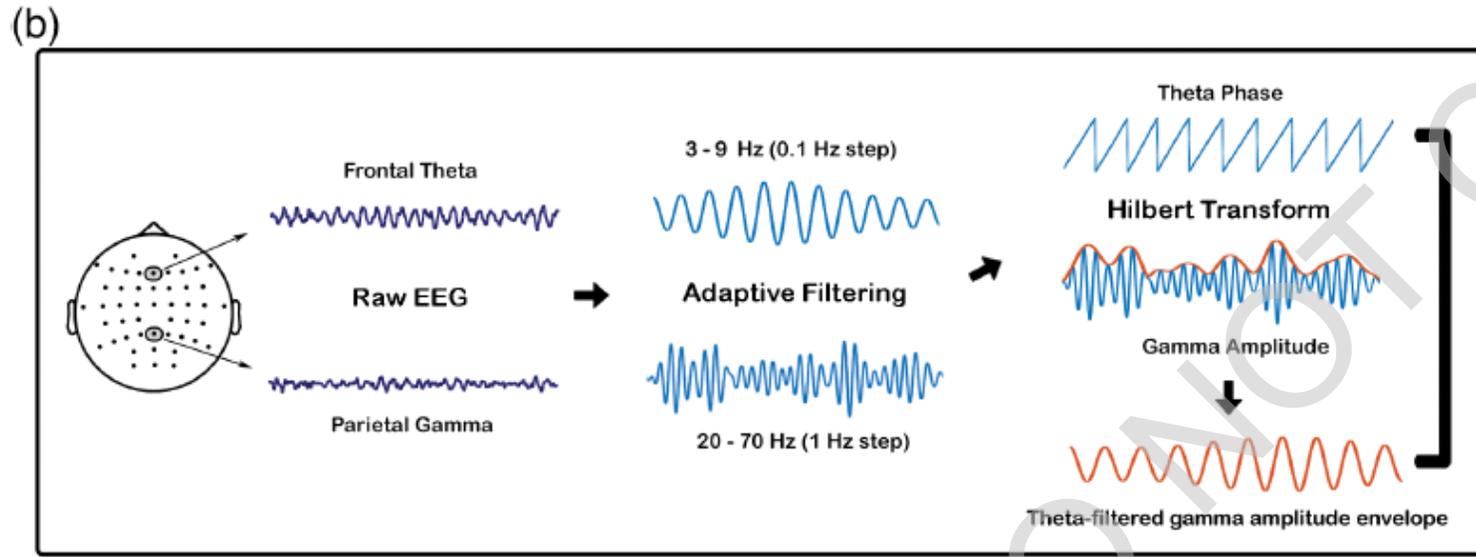


Need to Measure!

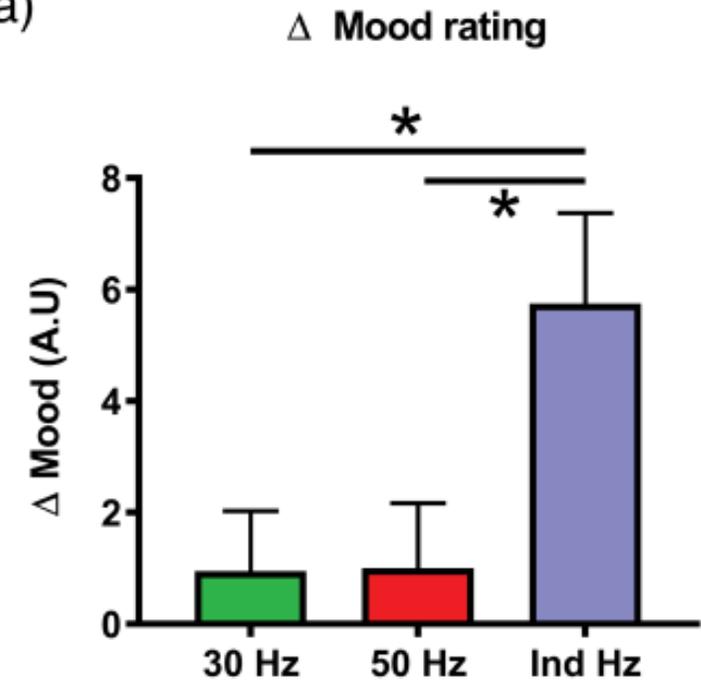
Neurophysiologic monitoring:  
fMRI - EEG - etc

Define dose  
Enable close-loop

# Personalized parameters



(a)





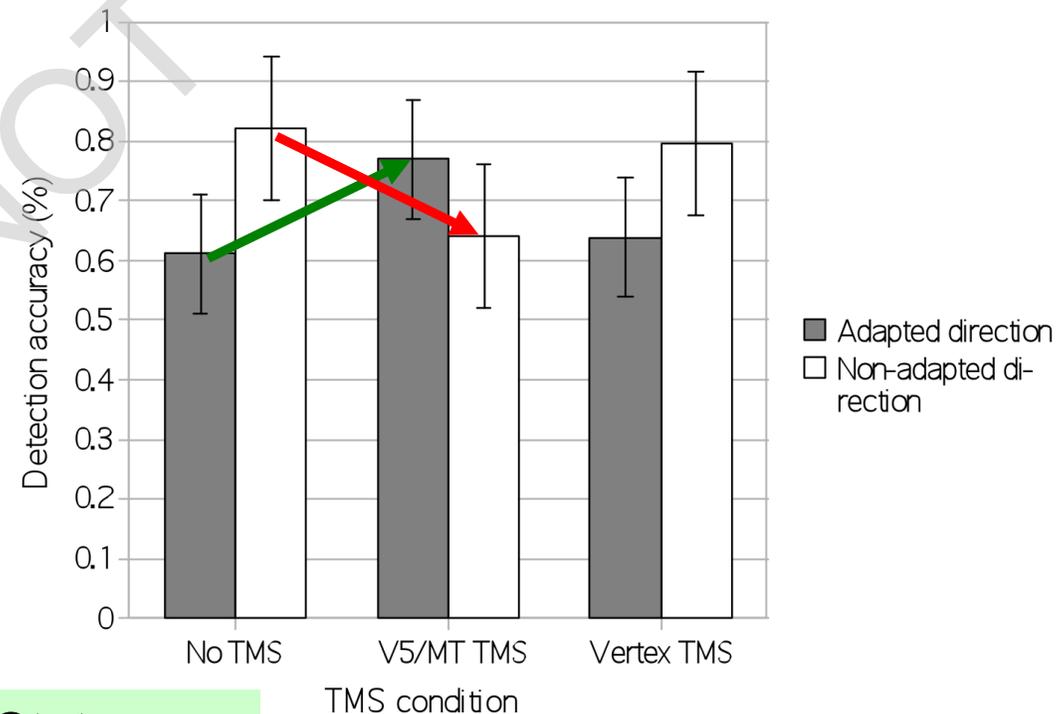
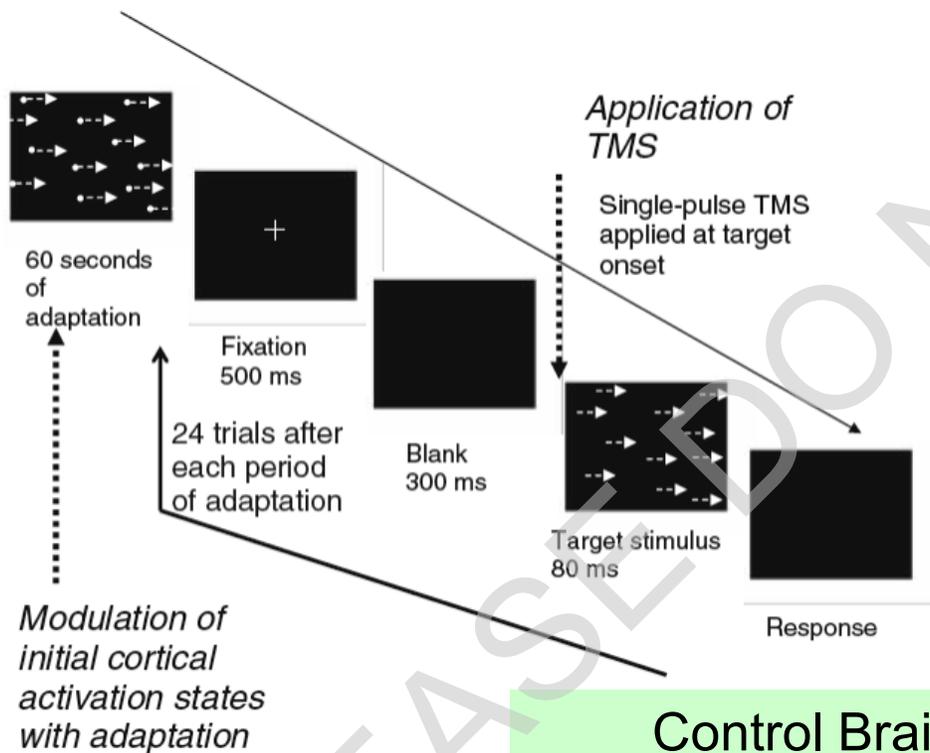
Zaira  
Cattaneo



Juha  
Silvanto

# State Dependency For Specific Neural Populations

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



Consistency and Greater Specificity of Effect

TMS disrupts non-adapted but improves adapted direction discrimination

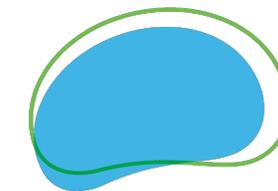
# State-Dependency of Transcranial Magnetic Stimulation

Juha Silvanto · Alvaro Pascual-Leone

## Concurrent TMS stimulation with Cognitive Training in Dementia



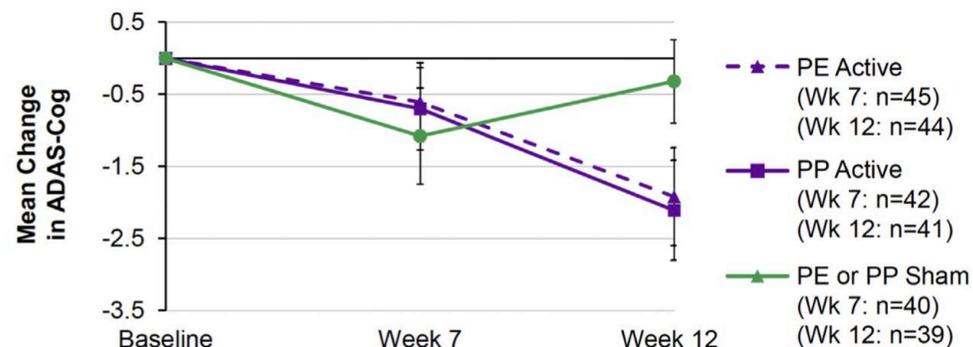
FDA-Approval for OCD  
Provocation task + TMS



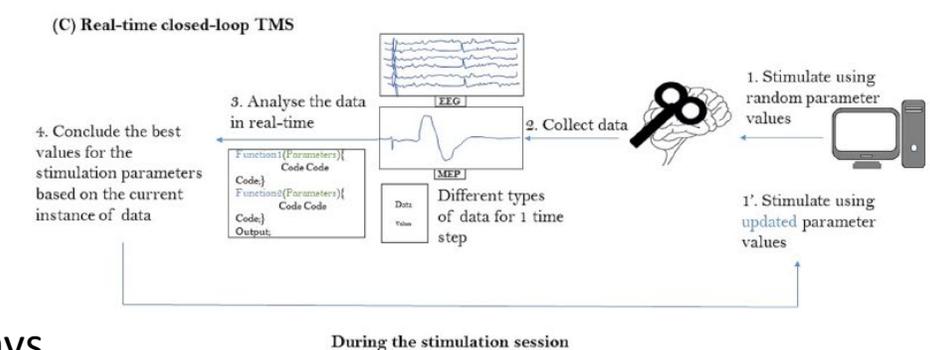
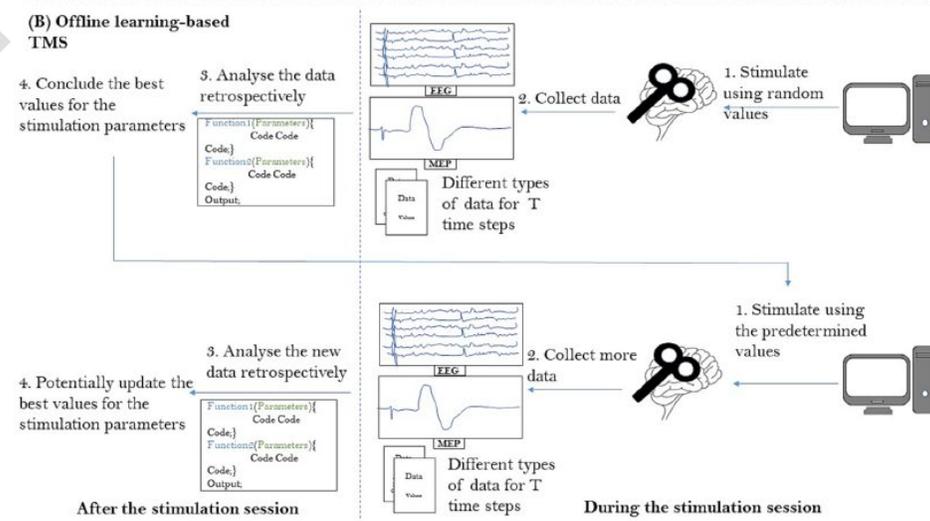
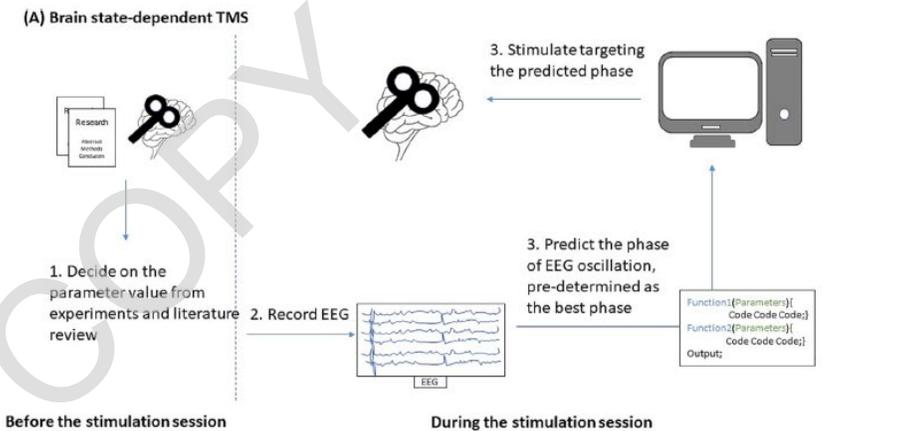
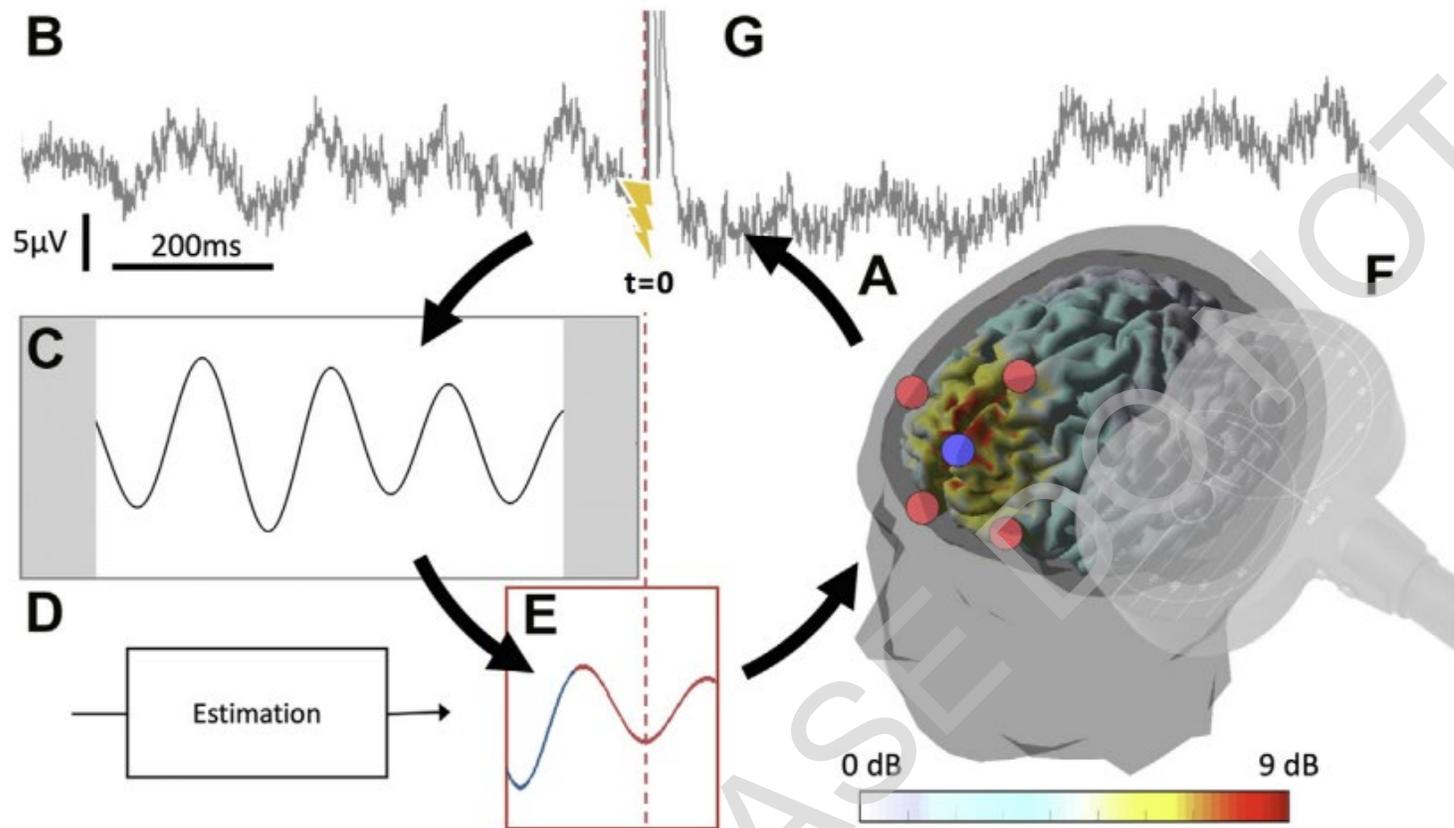
Brainsway

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

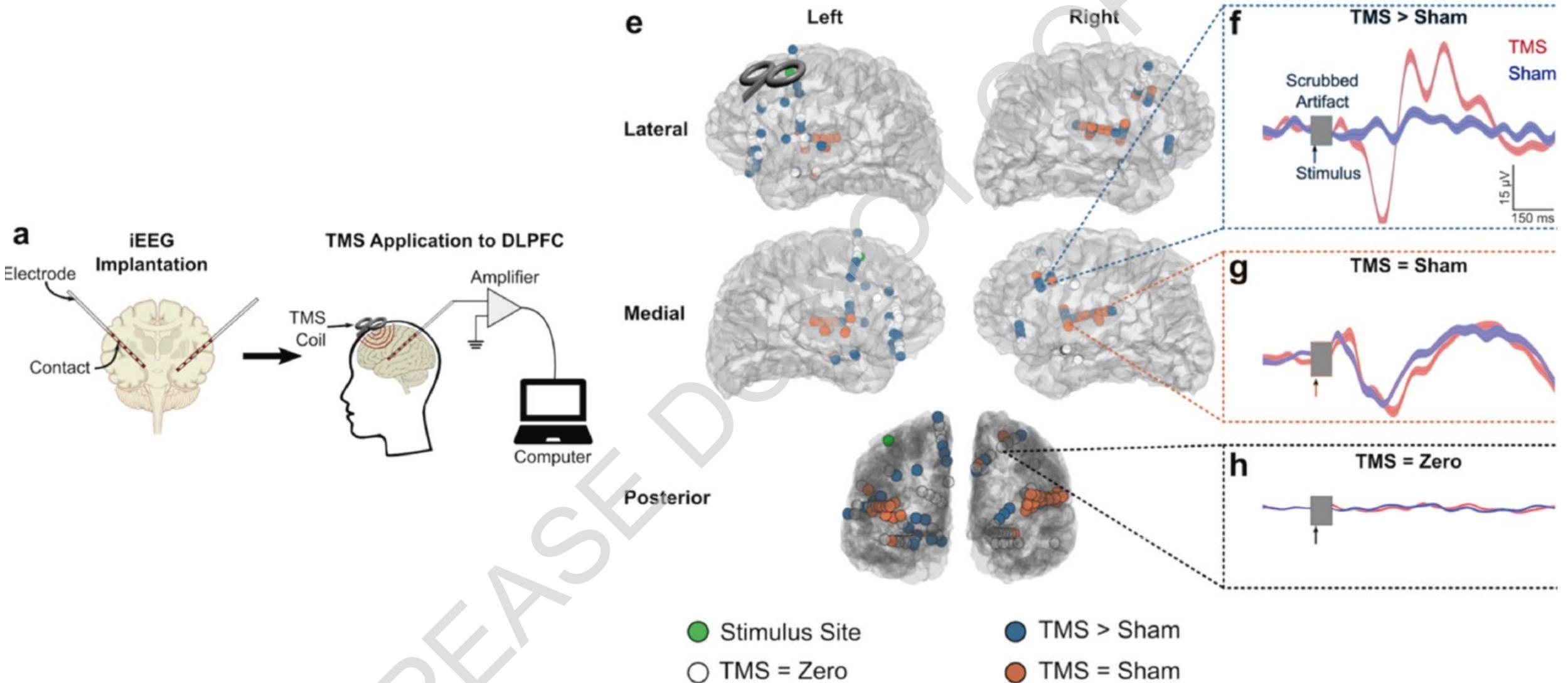
ADAS-Cog Change



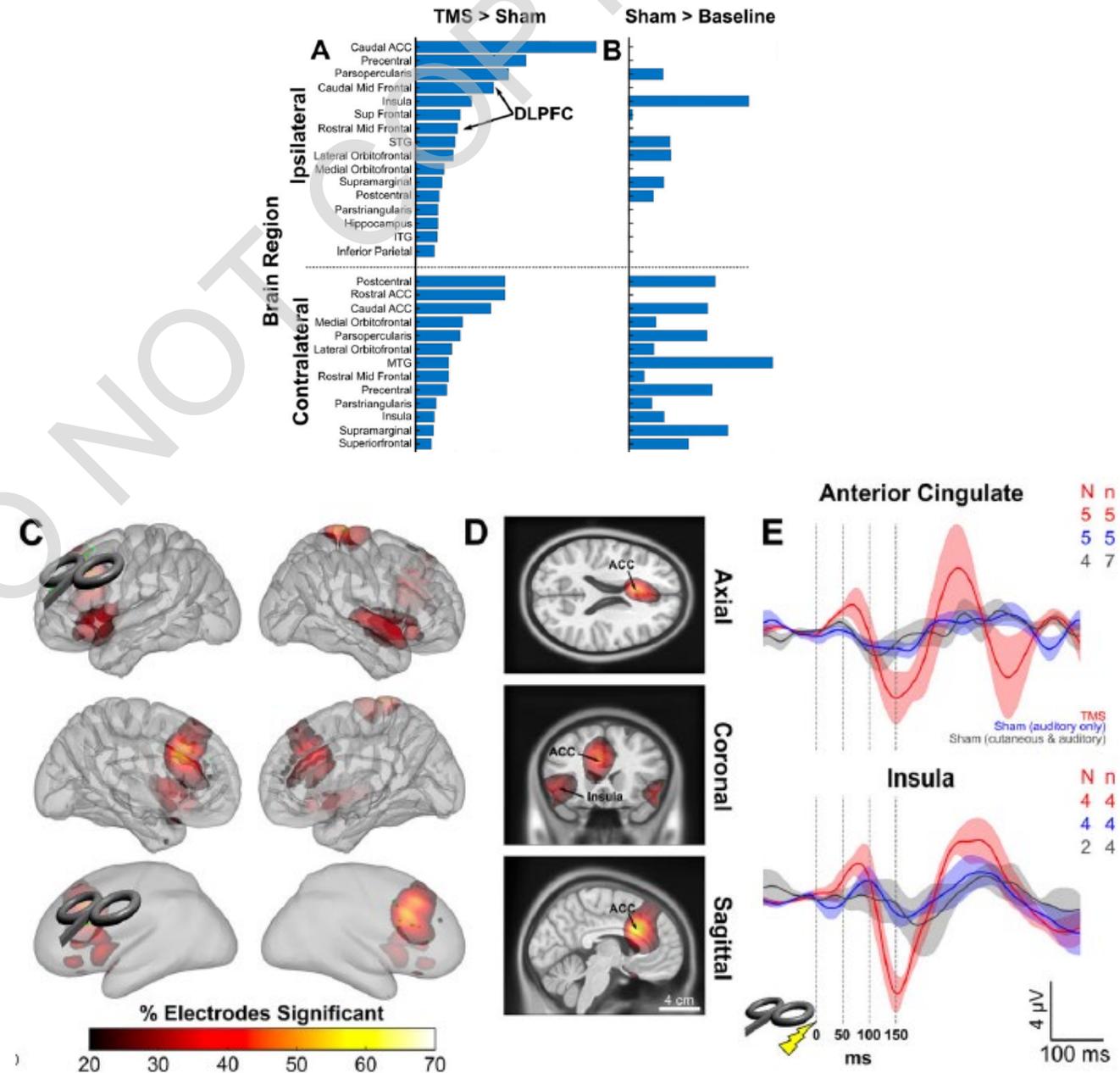
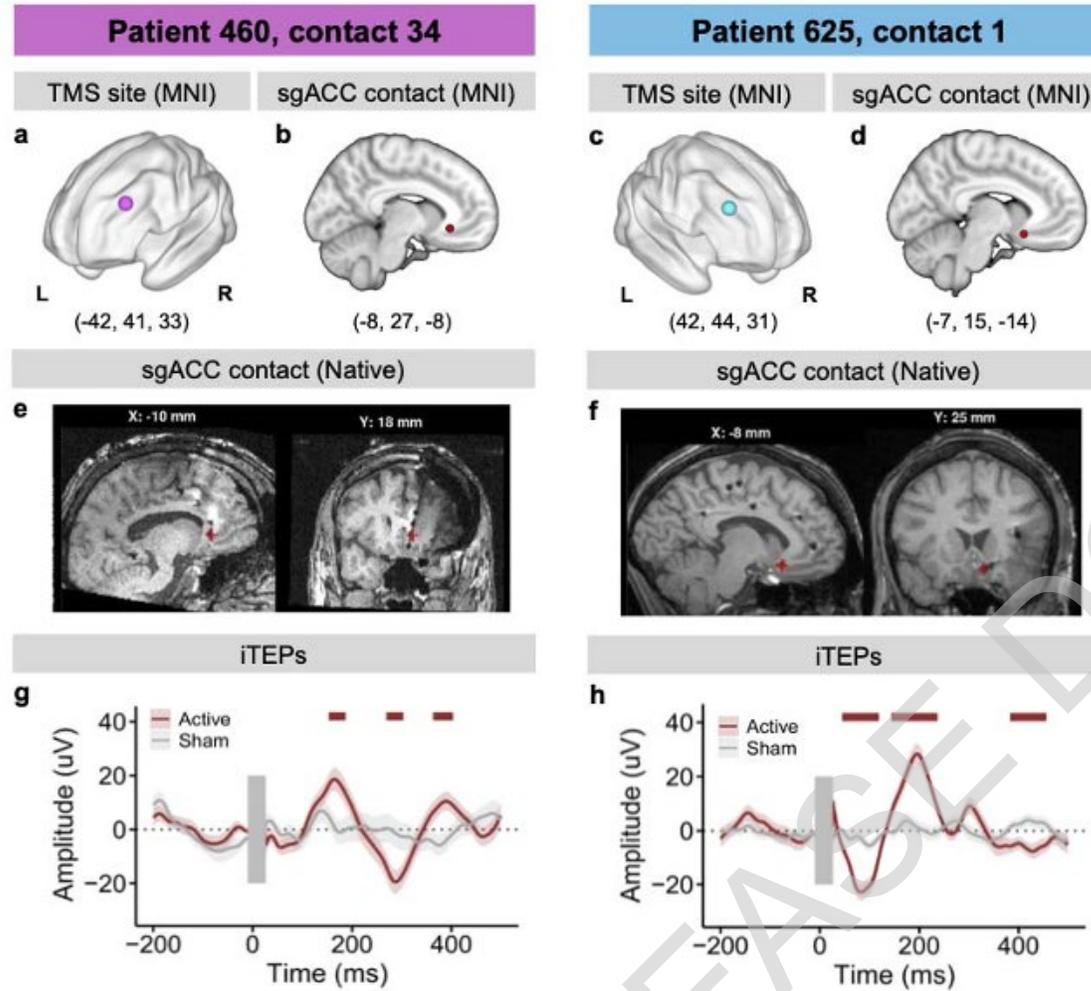
# Closed-loop EEG-TMS modulation



# Intracranial EEG validated approaches and mechanisms



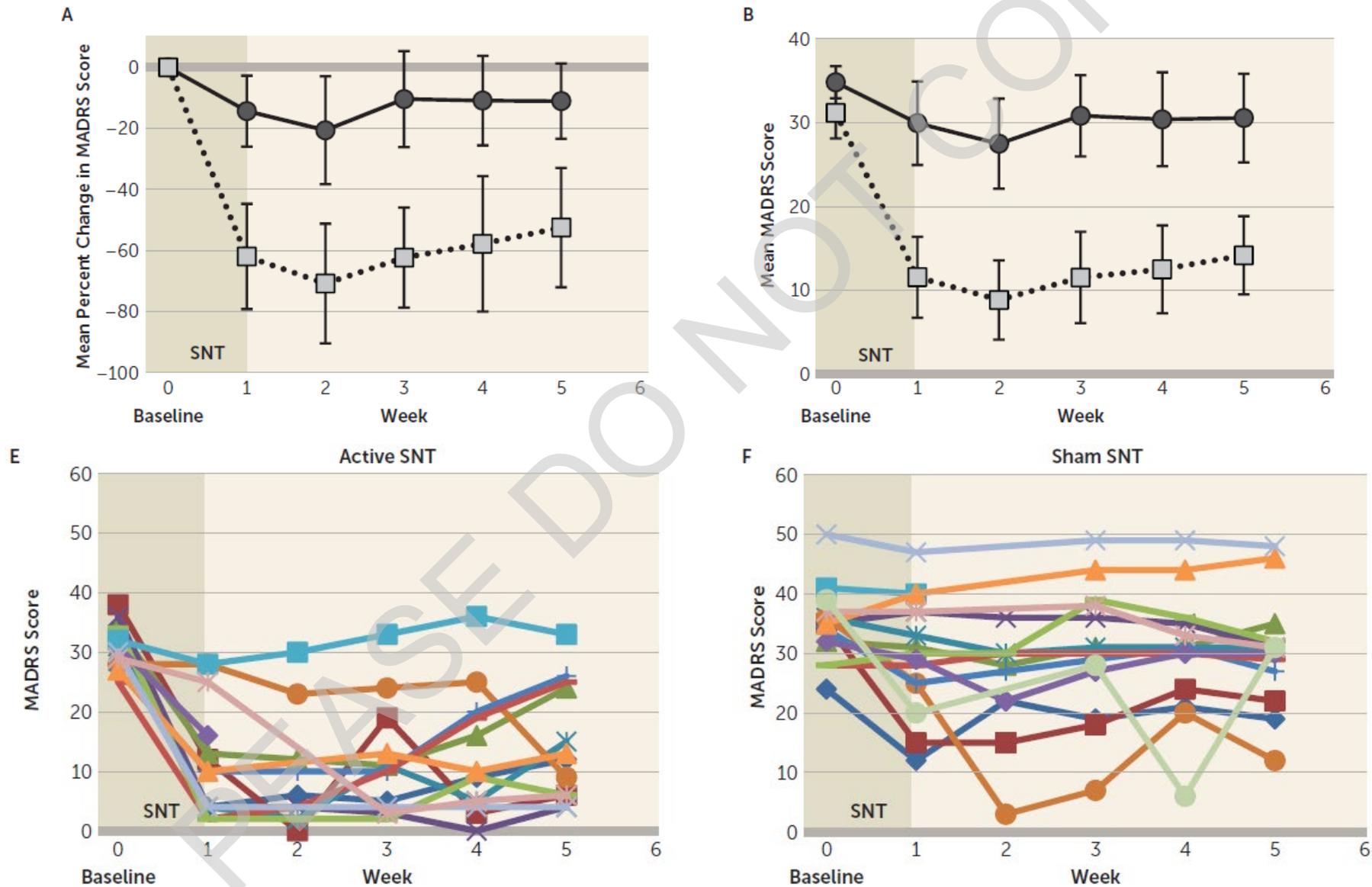
# LDLPFC Stimulation activates sgACC ... but also a number of other regions!



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



# Accelerated TBS (SAINT) results



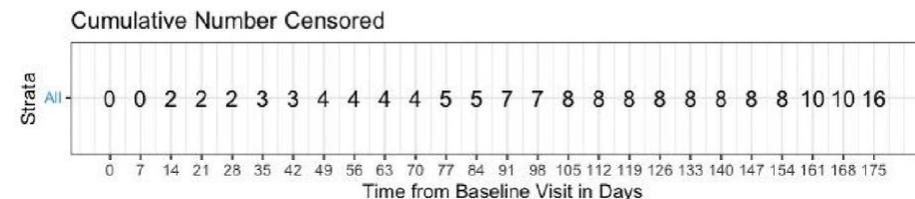
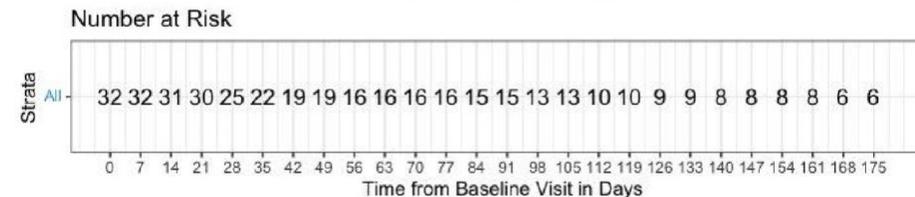
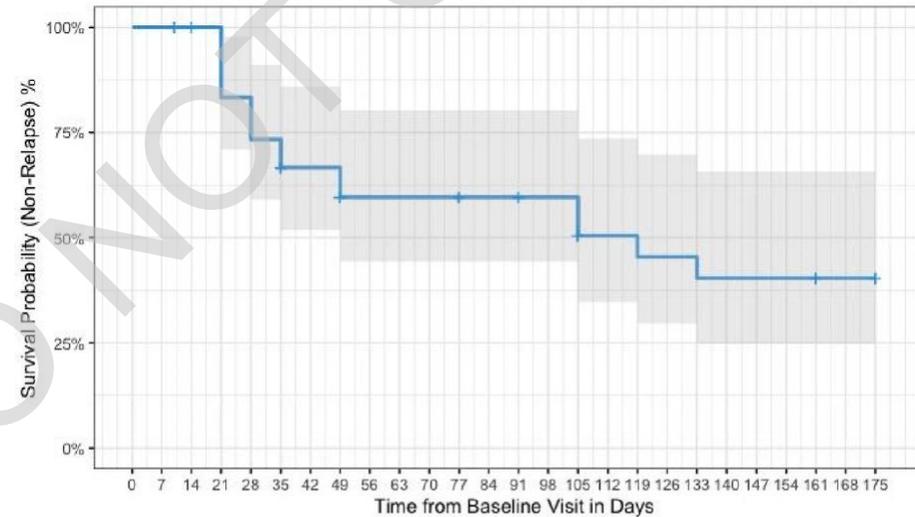
# Durability of SAINT?

- Geoly 2025: Evaluated 46 participants from prior SAINT studies who entered 4-week controlled follow-up, followed by “naturalistic” follow-up out to 24 weeks.
- 32/46 participants (69.6%) were in remission at end of acute treatment period, 37/46 (80.4%) were responders

**Table 2**

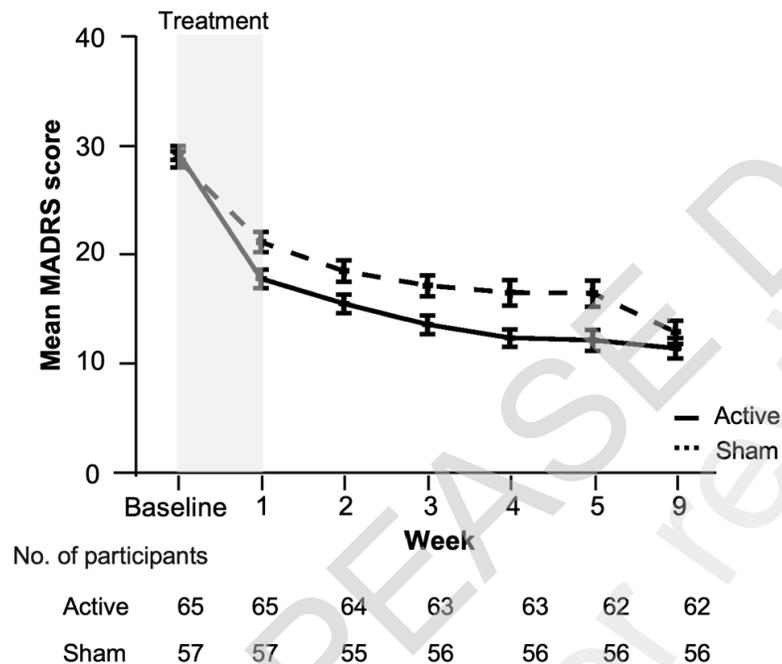
SNT remission and response rates over follow-up period.

Follow-up		Remission   Response		
Criteria	Participants	2-Week	4-Week	12-Week
<b>Remission</b>	<b>All</b>	56.5 % (26/46)	45.7 % (21/46)	32.6 % (15/46)
	<b>Acute Remitters</b>	78.1 % (25/32)	62.5 % (20/32)	46.9 % (15/32)
<b>Response</b>	<b>All</b>	65.2 % (30/46)	63.0 % (29/46)	37.0 % (17/46)
	<b>Acute Responders</b>	78.4 % (29/37)	75.7 % (28/37)	43.2 % (16/37)



# But is SAINT really that effective?

- Recent multi-site randomized trial out of China randomized 130 participants to receive a SAINT-like protocol
  - Reported using identical inclusion/exclusion criteria
  - Treated with “SNT parameters”: **90% RMT**, 1800 pulses per session, 10 sessions per day with 50-minute ISI, 5 consecutive days to **individualized DLPFC target**



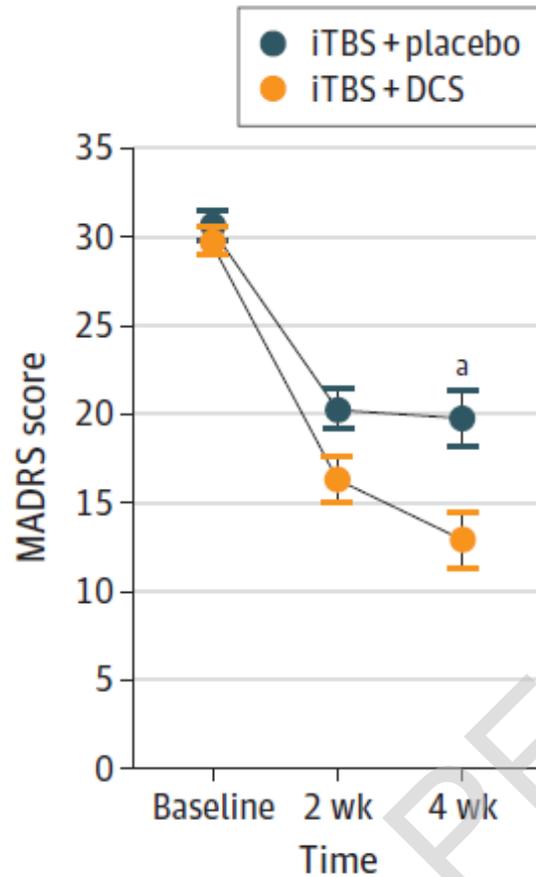
	Active	Sham	Active vs Sham	
			Relative risk, 95% CI	P value
<b>Responders</b>				
Week 1	20/65(30.8%)	9/57(15.8%)	1.95, [0.97, 3.93]	.062
Week 2	31/64(48.4%)	13/55(23.6%)	2.05, [1.20, 3.51]	.009
Week 3	37/63(58.7%)	19/56(33.9%)	1.73, [1.13, 2.63]	.011
Week 4	40/63(63.5%)	23/56(41.1%)	1.55, [1.07, 2.23]	.019
Week 5	41/62(66.1%)	26/56(46.4%)	1.42, [1.02, 1.99]	.037
Week 9	44/62(71.0%)	37/56(66.1%)	1.07, [0.84, 1.37]	.569
<b>Remitters</b>				
Week 1	9/65(13.9%)	3/57(5.3%)	2.63, [0.75, 9.25]	.132
Week 2	16/64(25.0%)	7/55(12.7%)	1.96, [0.87, 4.42]	.103
Week 3	22/63(34.9%)	9/56(16.1%)	2.17, [1.09, 4.32]	.027
Week 4	22/63(34.9%)	11/56(19.6%)	1.78, [0.95, 3.33]	.073
Week 5	24/62(38.7%)	13/56(23.2%)	1.67, [0.94, 2.95]	.079
Week 9	34/62(54.8%)	25/56(44.6%)	1.23, [0.85, 1.78]	.274

# TMS + drugs

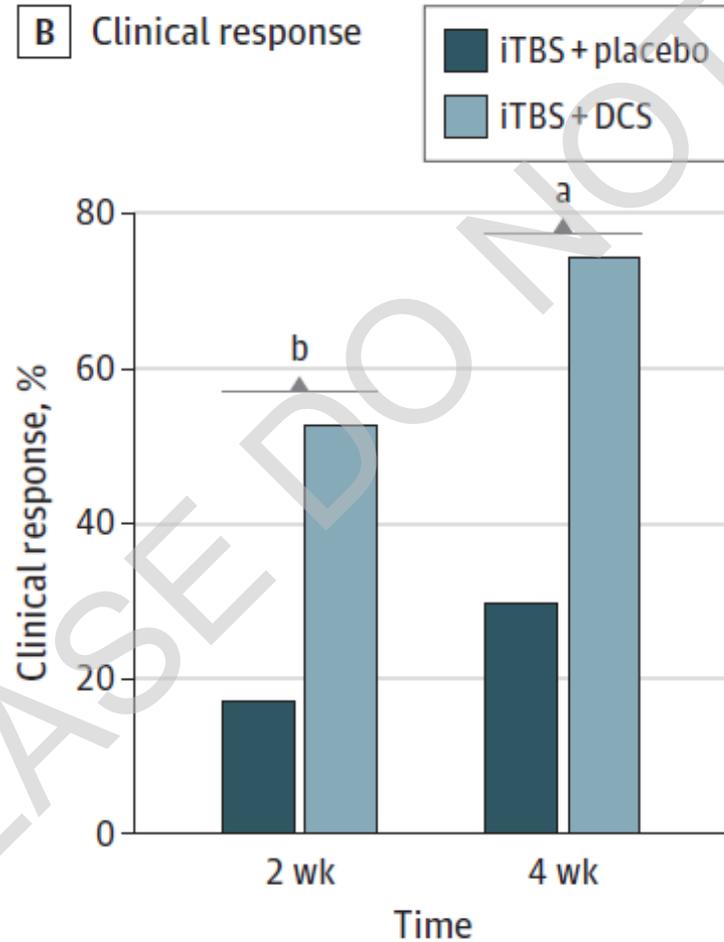
## Efficacy of Adjunctive D-Cycloserine to Intermittent Theta-Burst Stimulation for Major Depressive Disorder A Randomized Clinical Trial

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

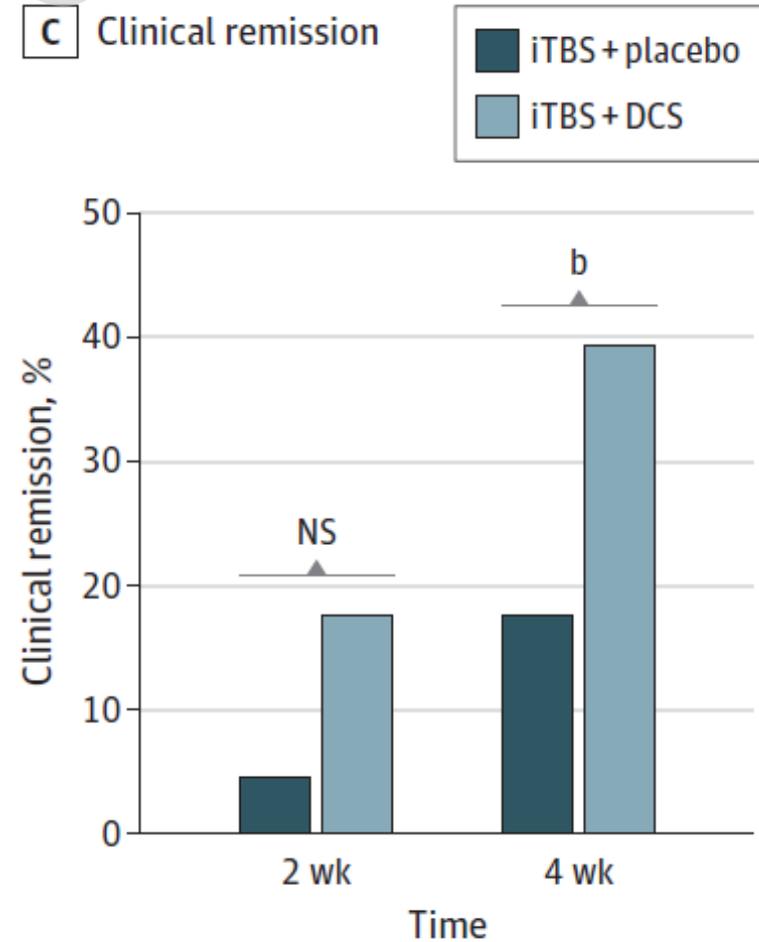
**A** MADRS score



**B** Clinical response

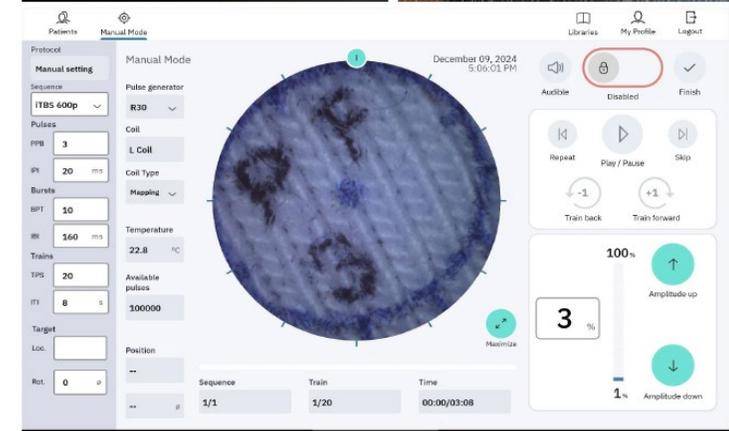
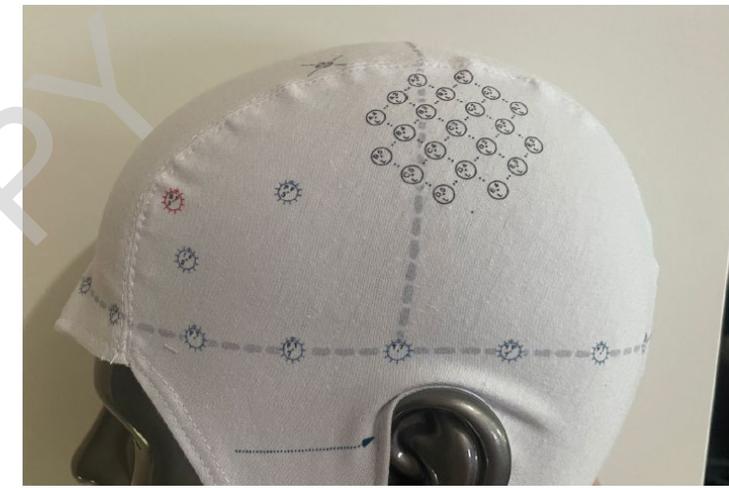


**C** Clinical remission

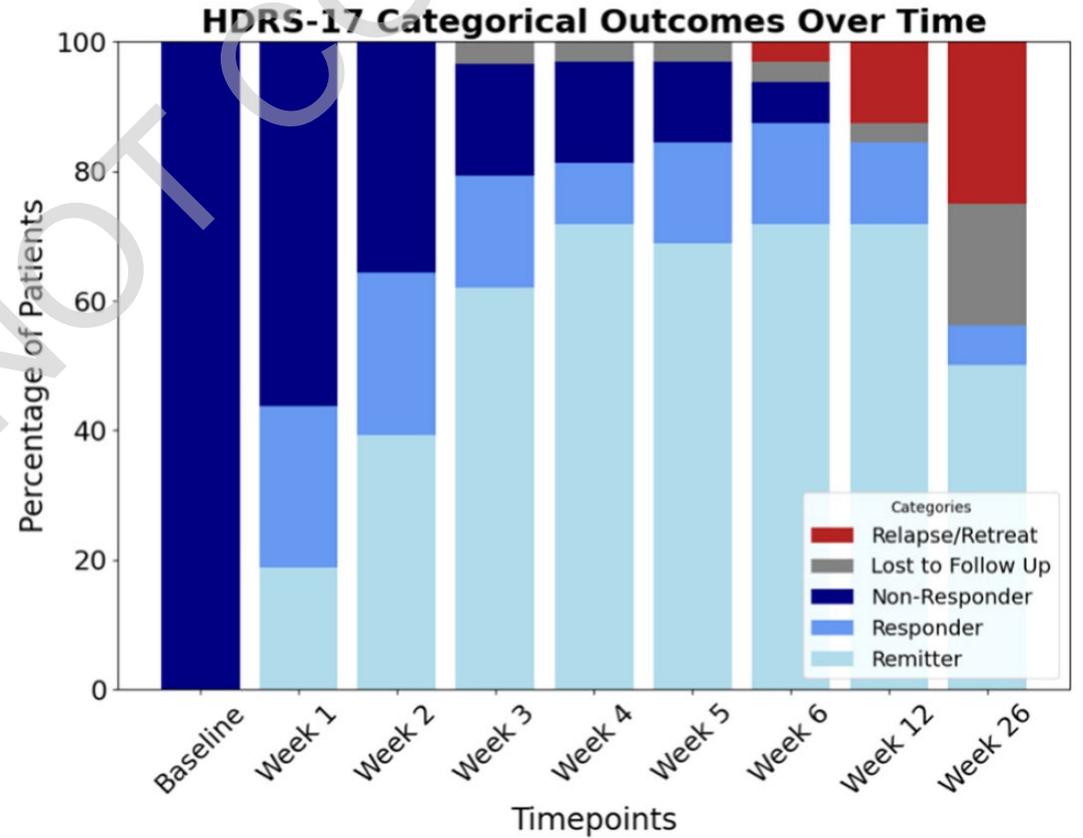
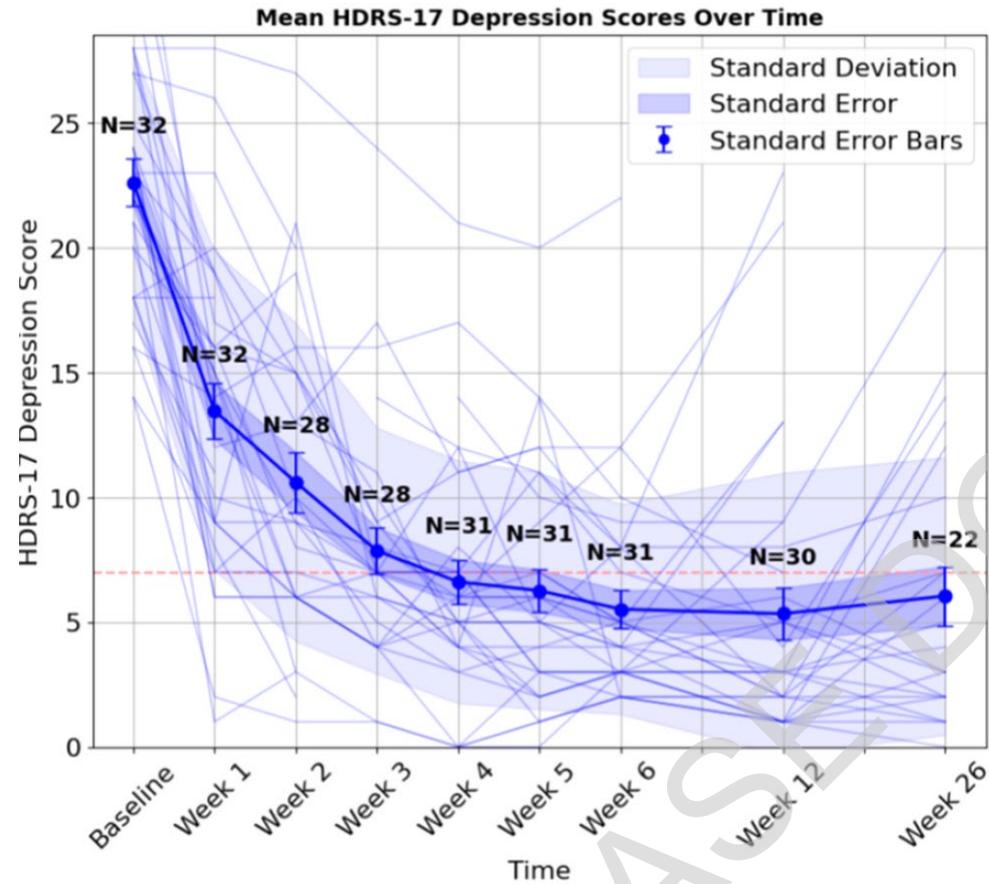


# One-D TMS: Accelerated TBS + drugs

- 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 minutes
- Target Siddiqi 2021 target (MN -46, 9, 31) using scalp heuristics
- Used Magventure R30 with Ampa L-coil
- No specific instructions to patients

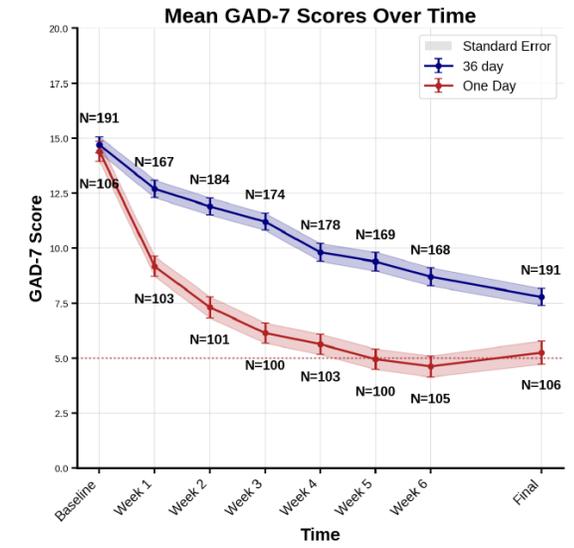
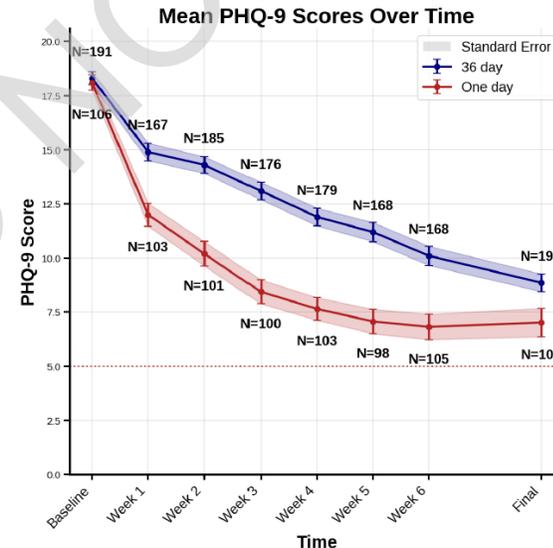
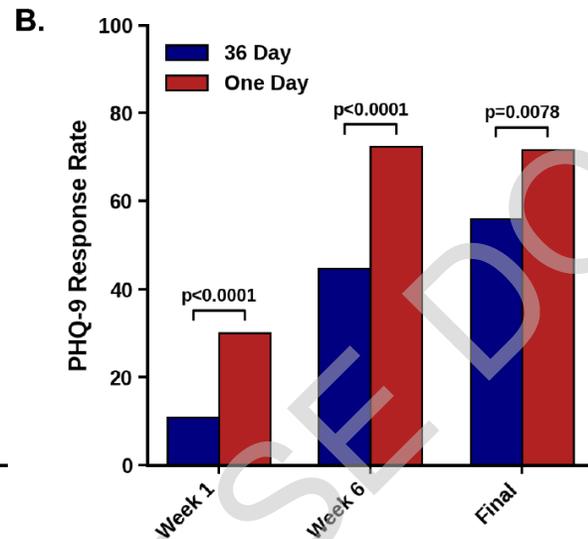
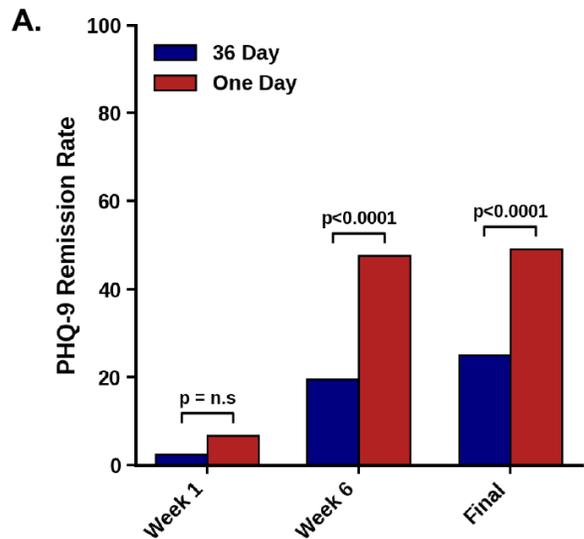


# One-D results



# Another case-series of OneD

- Berlow 2026 (preprint): 114 patients received a one-day pharmacologically augmented accelerated TBS protocol
- Did propensity matching to compare to patients who received conventional (36-session) rTMS



Final remission and response rates were 49.1% / 71.7% for one-day protocol, 25.1% / 56.0% for conventional rTMS

# Other Noninvasive Devices?

nature medicine

Article

<https://doi.org/10.1038/s41591-024-03305>

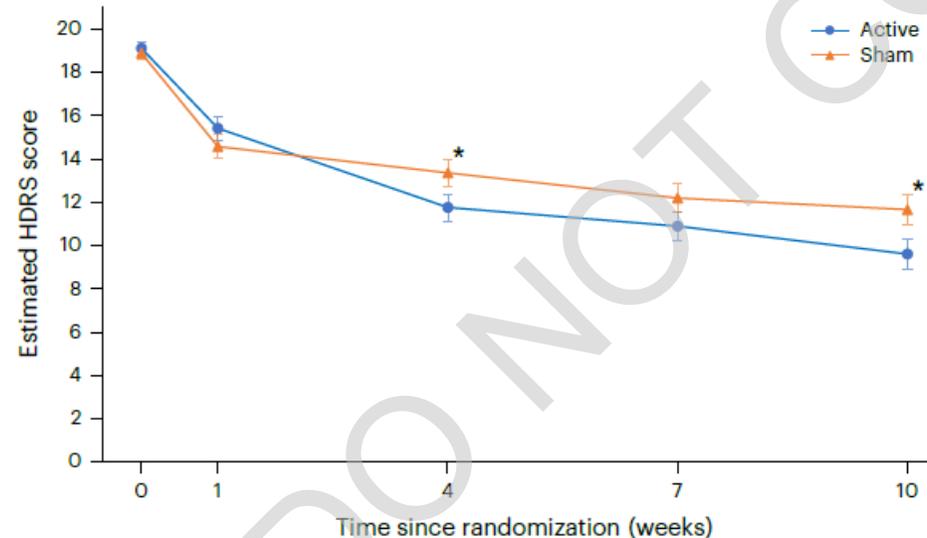
## Home-based transcranial direct current stimulation treatment for major depressive disorder: a fully remote phase 2 randomized sham-controlled trial



Figure 1. The Flow FL-100 Headset

- A sham-controlled RCT evaluating whether **home-based** bilateral frontal tDCS can improve symptoms of depression in patients with Major Depressive Disorder
- 2 sites (London, Texas)
- Randomized 174 participants with MDD “of at least moderate severity” to tDCS (Anode LDLPFC, cathode RDLPFC; 2mA; 30 min), 5 sessions per week for 3 weeks followed by 3 sessions/wk for 7 weeks
- Primary outcome measure change in HDRS-17 score with real vs sham stimulation at 10 weeks

# Effective for depression!



- At week 10, HDRS decrease of  $9.41 \pm 6.25$  points in active versus  $7.14 \pm 6.10$  points in sham ( $p = 0.012$ )
  - Also significant difference at week 4 but not week 7
- Response rate (50%) of 58.4% in active vs 37.8% in sham ( $p = 0.017$ )
- Remission rate ( $\text{HDRS} \leq 7$ ) 44.9% in active vs 21.8% in sham ( $p = 0.004$ )

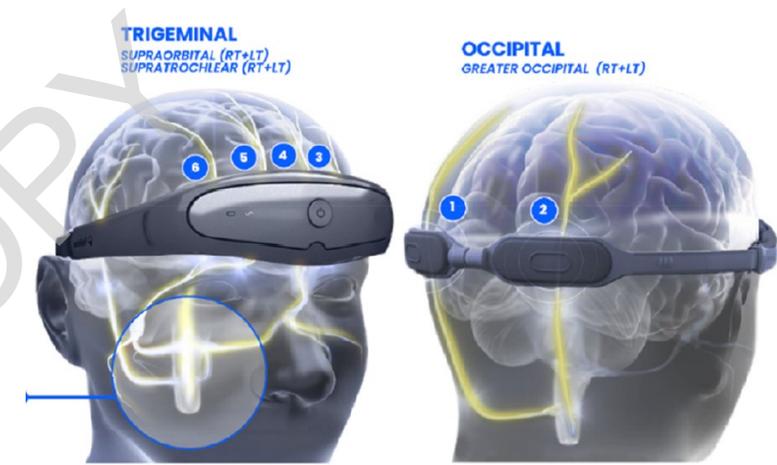
# But a very different population than TMS trials

- HDRS inclusion score only > 15
- Excluded patients with treatment-resistant depression!
- Excluded participants on benzodiazepines or ASMs
- Excluded anyone who had **ever** been admitted to hospital for depression

Characteristic	Active	Sham
Number of participants	87	87
Age	37.09±11.14	38.32±10.92
Sex		
Women	54 (62)	66 (76)
Ethnicity		
Asian	9 (10)	2 (2)
Black or African American	3 (3)	1 (1)
Native Hawaiian or Other	0 (0)	0 (0)
White	72 (83)	73 (84)
Other	3 (3)	11 (13)
Missing	0 (0)	0 (0)
Educational level		
Lower than high school or secondary school	1 (1)	0 (0)
Some college education	18 (21)	19 (22)
Diploma	9 (10)	7 (8)
Bachelor's or Professional Degree	37 (43)	37 (43)
Master's or Doctoral Degree	22 (25)	23 (26)
Preferred not to answer/missing	0 (0)	1 (1)
Age of onset of MDD, years	22.08±9.68	22.40±8.78
Previous number of episodes	4.11 (0-30)	4.80 (0-30)
Previous number of suicide attempts	0.10 (0-2)	0.16 (0-2)
First episode of MDD	18 (21)	10 (11)

Clinical ratings		
HDRS	19.18±2.83	18.92±2.63
HDRS severity:		
Moderate (HDRS score: 16-18)	45 (52)	45 (52)
Severe (HDRS score: 19-22)	29 (33)	33 (38)
Very severe (HDRS score: 23 or greater)	13 (15)	9 (10)
MADRS	24.72±4.68	23.87±5.49
MADRS-s	26.77±6.90	25.67±6.34
HAM-A	15.45±4.61	14.25±4.57
YMRS	2.10±1.72	1.92±1.58
EQ-5D-3L	0.75±0.13	0.75±0.14
RAVLT	57.92±11.15	58.51±13.40
SDMT	52.26±10.13	50.40±10.14
Taking antidepressant medication		
Selective serotonin reuptake inhibitor	40 (46)	35 (40)
Nonselective monoamine reuptake inhibitor	1 (1)	3 (3)
Other antidepressant medications	18 (21)	17 (20)
Taking combination of antidepressant medications		
In psychotherapy during the trial	12 (14)	14 (16)
In psychotherapy and taking antidepressant medication	6 (7)	12 (14)
No antidepressant medication or psychotherapy during the trial	25 (29)	32 (37)

# Trigeminal and occipital stim?



- Randomized, multi-site (13 sites) clinical trial in USA and Israel. Randomized 124 patients with unipolar MDD to real vs sham stimulation
- 22-70 years old, failed 1-4 prior antidepressant meds or had undergone at least 2 inadequate trials in the current episode
- HDRS-21 score > 19
- 8-week double-blind phase, self-administer treatments **2x/day for 40 min per session 5-7 days per week (!!!)**
- Primary outcome change in HDRS17 (not 21?) at week 8.
- mITT population required 70% prescribed stimulation time

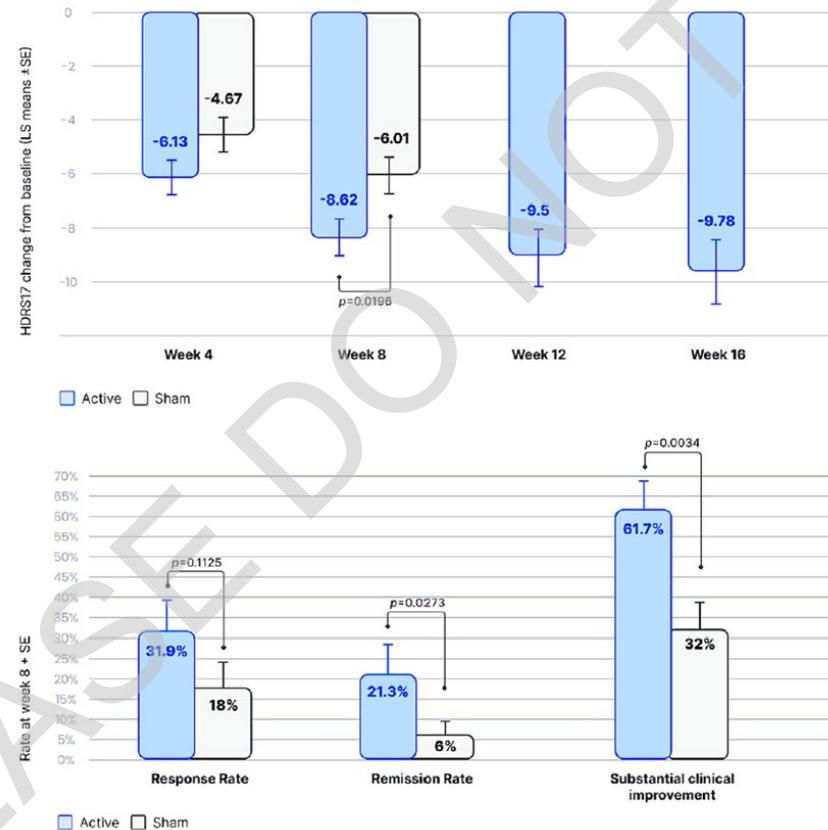
# Effective for MDD

- Albeit with lower response / remission rates compared to TMS ...

**Table 2**  
MDD Treatment History and Baseline Depression Severity (mITT sample).

	Active (n = 47)	Sham (n = 50)	p-Value <sup>a</sup>
Age at Onset of first MDD Episode (Years), Mean (SD)	25.3 (13.40)	26.5 (13.91)	0.6574
Lifetime # MDD Episodes, Mean (SD)	9.2 (8.47)	10.1 (9.24)	0.6006
Current Episode Duration (Months), Mean (SD)	13.8 (8.25)	14.2 (7.45)	0.7915
Failed Adequate Trials in Current Episode, Mean (SD)	1.7 (0.89)	1.9 (0.89)	0.2269
Inadequate/Intolerable Trials in Current Episode, Mean (SD)	0.1 (0.49)	0.1 (0.50)	0.9025
Antidepressant Medication in Current Episode, n (%)	47 (100)	50 (100)	1.000
TMS in current episode, n (%)	1 (2.1)	6 (12.0)	0.1126
Psychotherapy in current episode, n (%)	30 (47)	31 (62.0)	0.8521
Other treatment in current episode, n (%)	1 (2.1)	3 (6.0)	0.6178
HDRS17 total score, Mean (SD)	21.6 (2.87)	22.1 (3.07)	0.4251
HDRS21 total score, Mean (SD)	23.1 (3.03)	23.6 (2.99)	0.4201
MADRS total score, Mean (SD)	29.7 (5.47)	30.4 (5.04)	0.5030
CGI-Severity Rating, Mean (SD)	4.8 (0.69)	4.8 (0.56)	0.8304

<sup>a</sup> t-test or chi-square comparing groups, as appropriate.



Outcomes following double blind phase and during open-label phase (mITT).

	Week 8	Week 12	Week 16	p-value (week 8-16)
<b>HDRS17 change from baseline, LSmeans [CI]</b>	-8.36 [-10.37; -6.35]	-9.50 [-11.67; -7.32]	-9.78 [-12.21; -7.34]	0.1105 <sup>a</sup>
<b>HDRS17 Response Rate</b>	31.1 % (14/45)	46.5 % (20/43)	48.8 % (20/41)	0.0215 <sup>b</sup>
<b>HDRS17 Remission Rate</b>	22.2 % (10/45)	25.6 % (11/43)	31.7 % (13/41)	0.2329 <sup>b</sup>
<b>HDRS17 Clinically Substantial Improvement</b>	62.2 % (28/45)	60.5 % (26/43)	70.7 % (29/41)	0.2293 <sup>b</sup>