

Neuromodulation and Interventional Psychiatry

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Laboratory for Circuit Neuroscience and Neuromodulation

MGH Transcranial Magnetic Stimulation clinical service

Mass General Brigham, Harvard Medical School

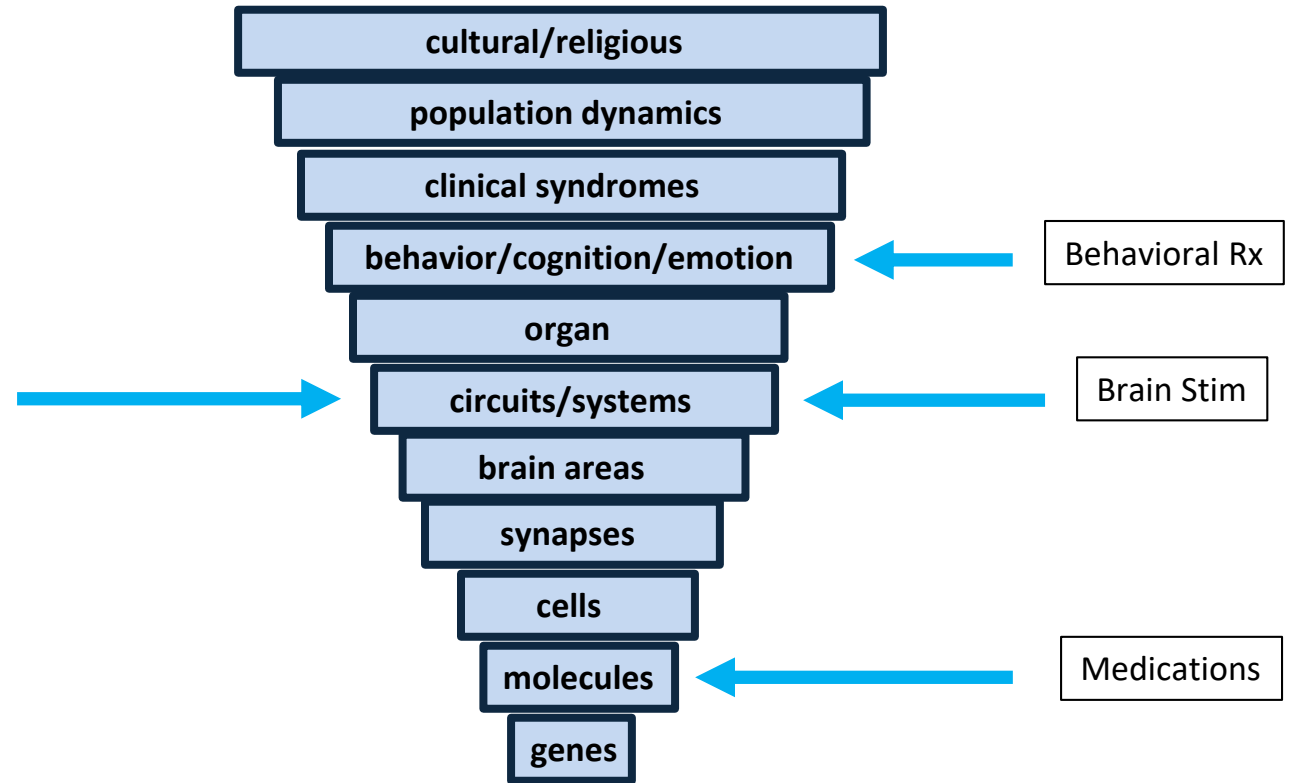
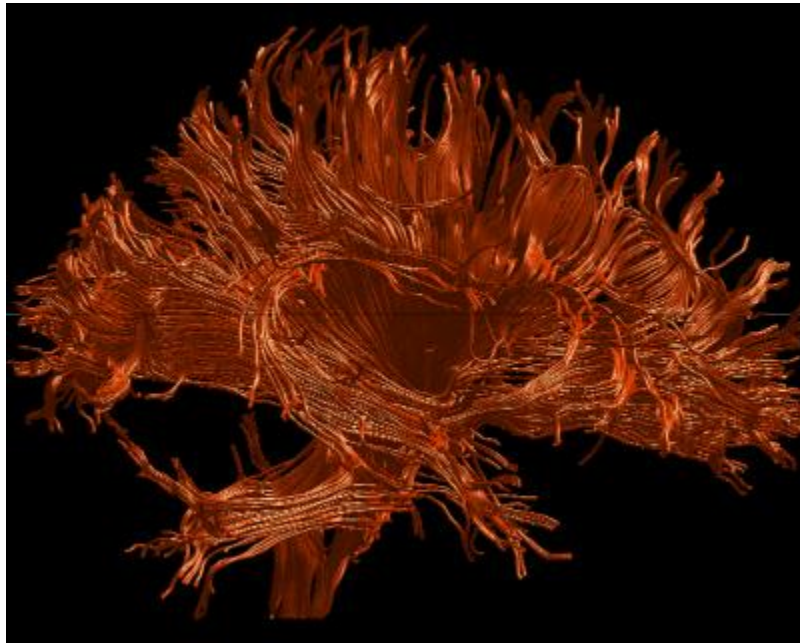
Disclosures

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- Consultant: Neuroelectrics, Fisher Wallace

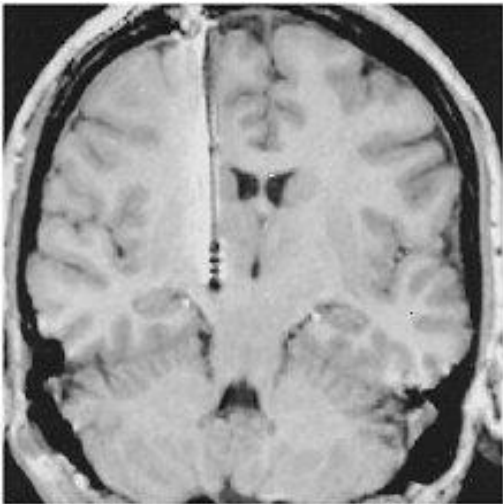
Neuropsychiatry and Circuitopathies



Neuromodulation Technologies

Invasive

Deep Brain Stimulation (DBS)
Vagal Nerve Stimulation (VNS)
Responsive Neurostimulation (RNS)

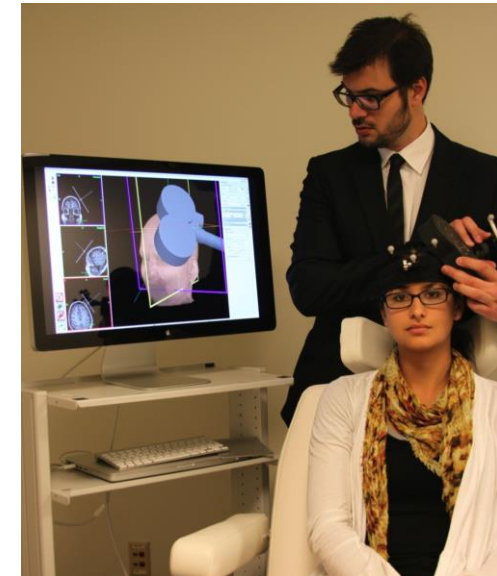


Convulsive

Electroconvulsive Therapy (ECT)
Magnetic Seizure Therapy (MST)



Transcranial Magnetic Stimulation (TMS)
Transcranial Direct Current Stim. (tDCS)
Noninvasive VNS
External Trigeminal Nerve Stim. (eTNS)
EEG Neurofeedback

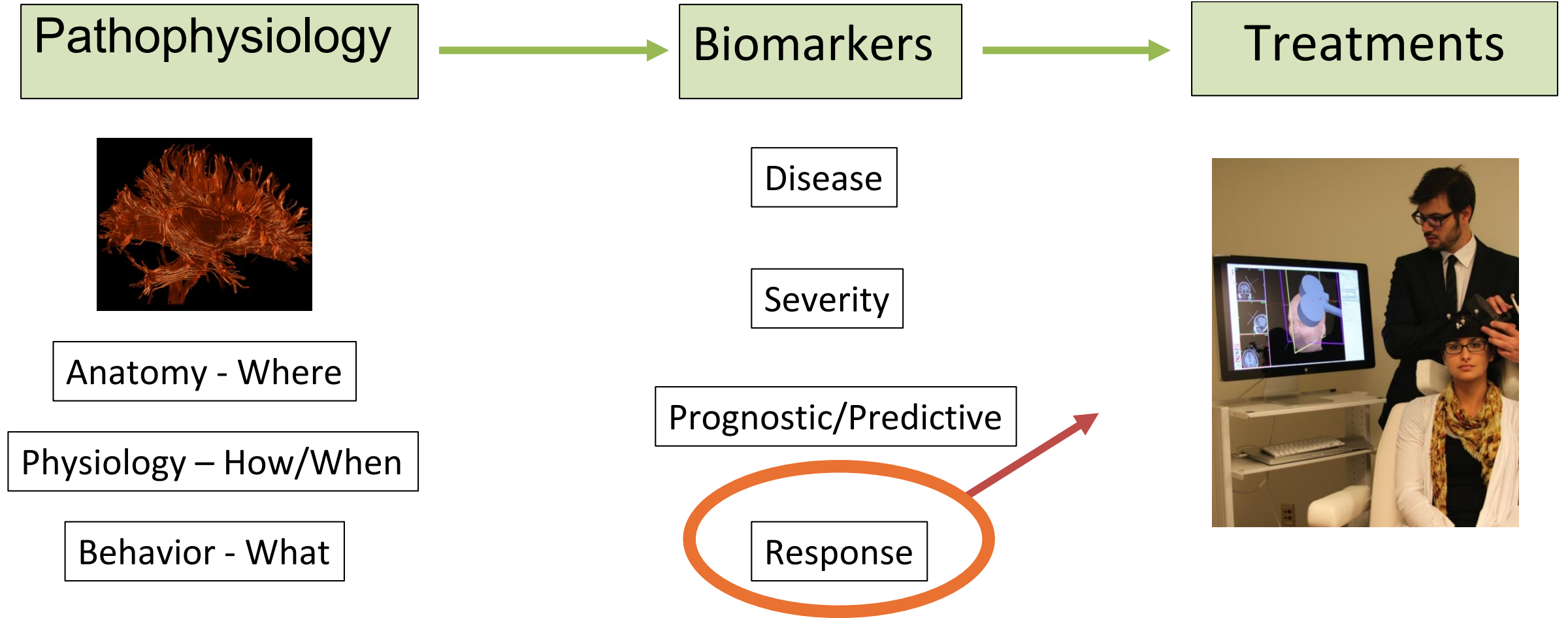


Device Neuromodulation and the FDA

DEVICE	CONDITION
Deep Brain Stimulation	Chronic Pain (revoked)
	Parkinson's Disease
	Essential Tremor
	Dystonia (HDC)
	Epilepsy
	OCD
Responsive Neurostimulation	Focal Epilepsy
Vagus Nerve Stimulation	Epilepsy
	TRD
	Stroke Motor Rehabilitation (Arm)
Noninvasive VNS	Migraine (acute; preventive)
	Cluster Headache

DEVICE	CONDITION
Electroconvulsive Therapy	MDE (unipolar, bipolar)
	Catatonia
	Mania and Schizophrenia off class II label (2018)
Transcranial Magnetic Stimulation	TRD (adults and adolescents)
	Migraine (acute with aura, preventive)
	OCD
	Smoking Cessation
Transcranial Direct Current Stim	MDD (home-based)
EEG Neurofeedback	PTSD symptoms
Trigeminal Nerve Stimulation	Pediatric ADHD
	Migraine (acute; preventive)

Treatment Development for Circuit Therapeutics

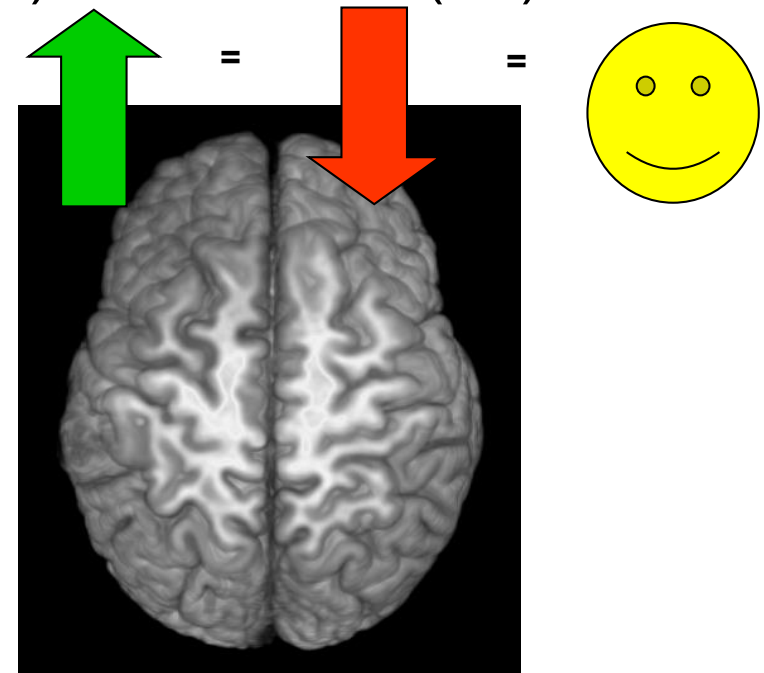


Biomarker-driven Rx development in MDD

- 1990s: Early PET data identified hypometabolic frontal lobes in Depression, with additional hemispheric (frontal) asymmetry
- 1990s: rTMS can selectively increase (HF) or decrease (LF) cortical excitability

Depression Rx Strategy:

- Left: High Frequency (5-20 Hz)
- Right: Low Frequency (1 Hz)



Initial evidence: DLPFC-TMS improves depression

NeuroReport 6, 1853–1856 (1995)

Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression

**Mark S. George,^{1,2}
Eric M. Wassermann,³
Wendol A. Williams,⁴ Ann Callahan,¹
Terence A. Ketter,¹ Peter Basser,⁵
Mark Hallett⁵ and Robert M. Post¹**

¹Biological Psychiatry Branch, National Institute of Mental Health; ²Dept Psychiatry, Radiology and Neurology, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425-0720; ³Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders; ⁴NIAA; ⁵Biomedical Engineering and Instrumentation Program, NCRR; National Institutes of Health, Bethesda, MD 20897, USA

THE LANCET

Early report

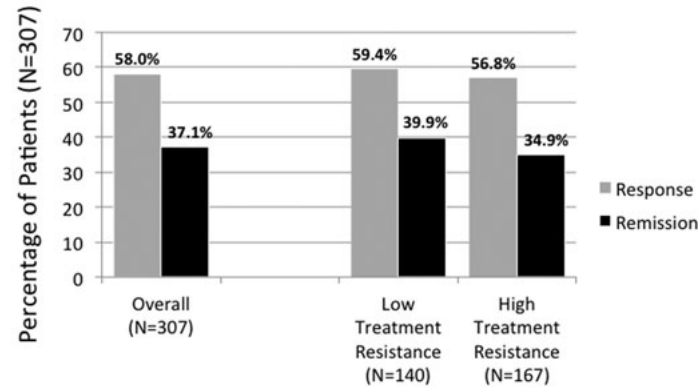
Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression

Alvaro Pascual-Leone, Belen Rubio, Federico Pallardó, Maria Dolores Catalá

Lancet 1996; 347: 233–37

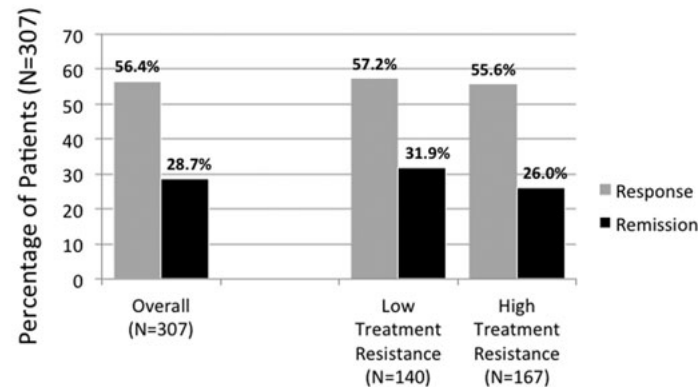
MDD Effectiveness Naturalistic Studie

CGI-S Outcomes



LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

PHQ-9 Outcomes

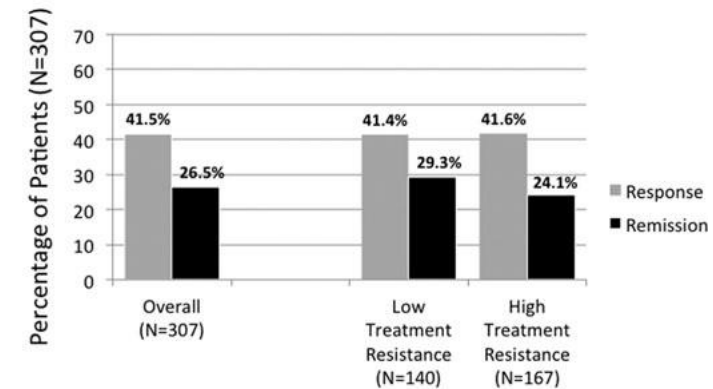


LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

Carpenter et al. 2012

- 339 patient with MDD naïve to TMS
- Concurrent medications/therapy
- Response Rate: 41.5-58%
- Remission Rate: 26.5-37.1%
- Age and severity predict outcome
- Treatment-resistant not a predictor

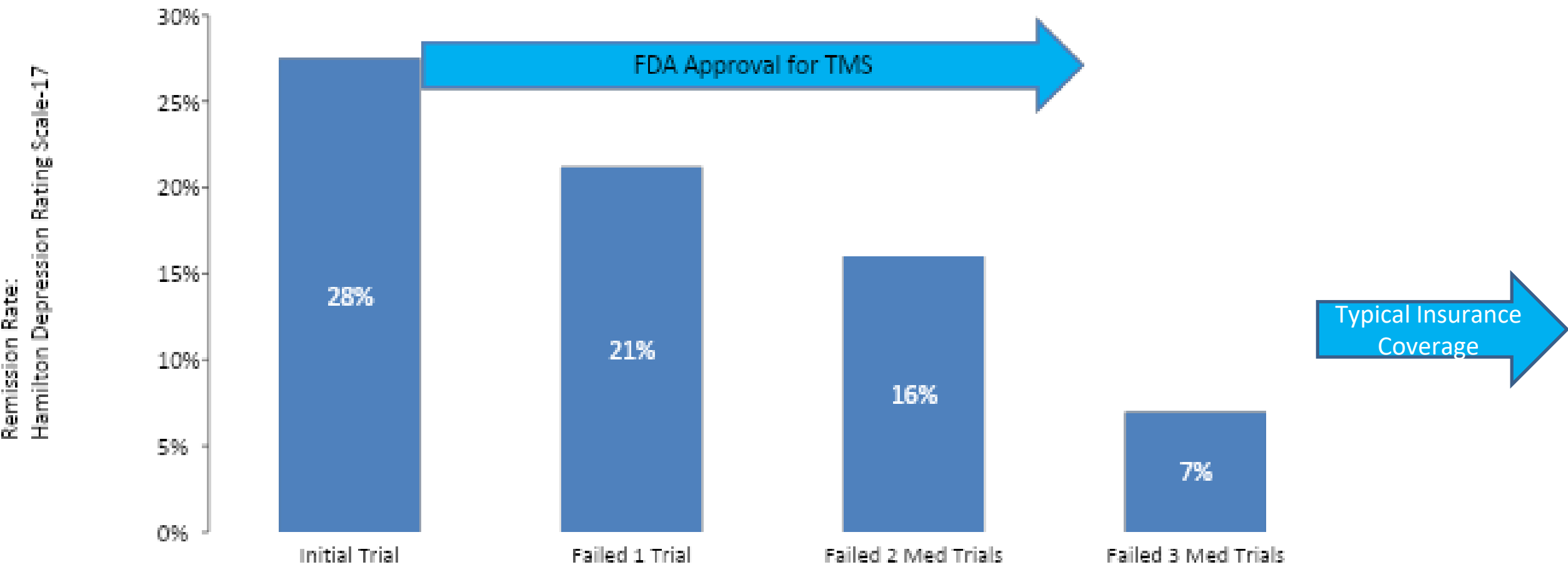
IDS-SR Outcomes



LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

Why Consider TMS treatment for Depression?

STAR*D Study: Depression Treatment Outcomes



Likelihood of achieving remission drops with each subsequent medication trial

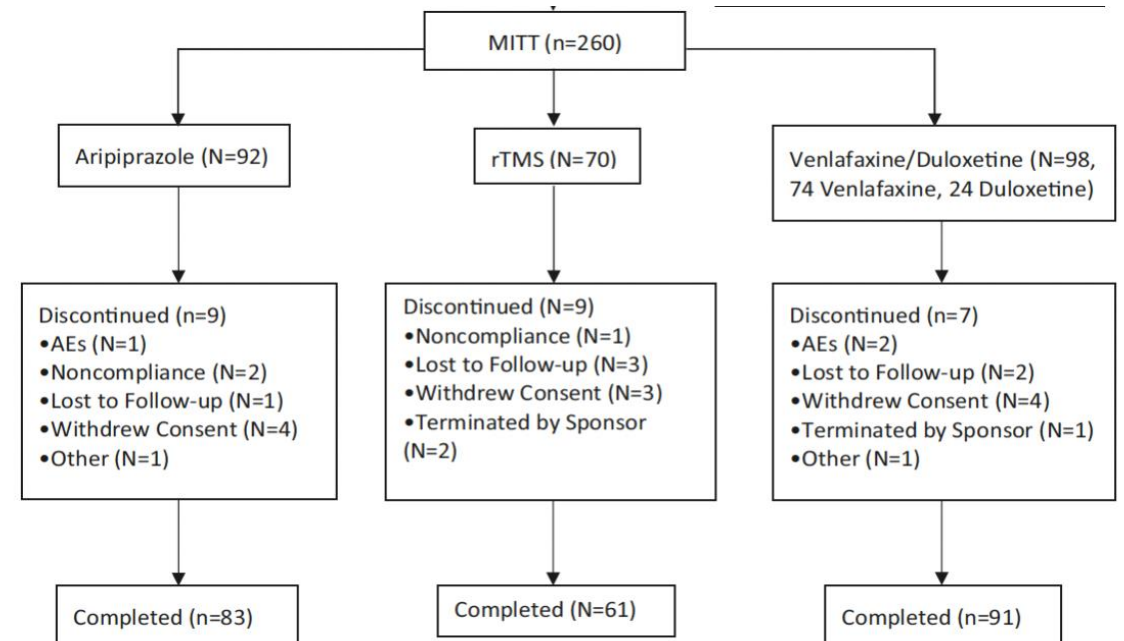
Rush AJ et al. Am J Psych 163:1905-1917, 2006

TRD: switching SNRI vs augmenting atypicals vs TMS

Comparative effectiveness research trial for antidepressant incomplete and non-responders with treatment resistant depression (ASCERTAIN-TRD) a randomized clinical trial

George I. Papakostas¹✉, Madhukar H. Trivedi², Richard C. Shelton³, Dan V. Iosifescu⁴, Michael E. Thase⁵, Manish K. Jha², Sanjay J. Mathew⁶, Charles DeBattista⁷, Mehmet E. Dokucu⁸, Olga Brawman-Mintzer⁹, Glenn W. Currier¹⁰, William Vaughn McCall¹¹, Mandana Modirrousta¹², Matthew Macaluso^{3,13}, Alexander Bystritsky¹⁴, Fidel Vila Rodriguez¹⁵, Erik B. Nelson¹⁶, Albert S. Yeung¹, Anna Feeney¹, Leslie C. MacGregor¹, Thomas Carmody² and Maurizio Fava¹

Mol. Psychiatry,
2024



TRD: switching SNRI vs augmenting atypicals vs TMS

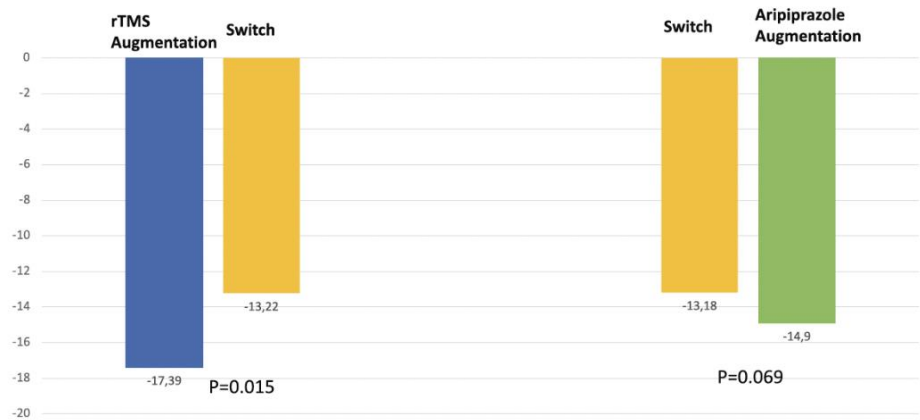


Fig. 2 Model adjusted change in MADRS scores. MADRS Montgomery Asberg Depression Rating Scale, rTMS Repetitive Transcranial Magnetic Stimulation. Alpha = 0.025.

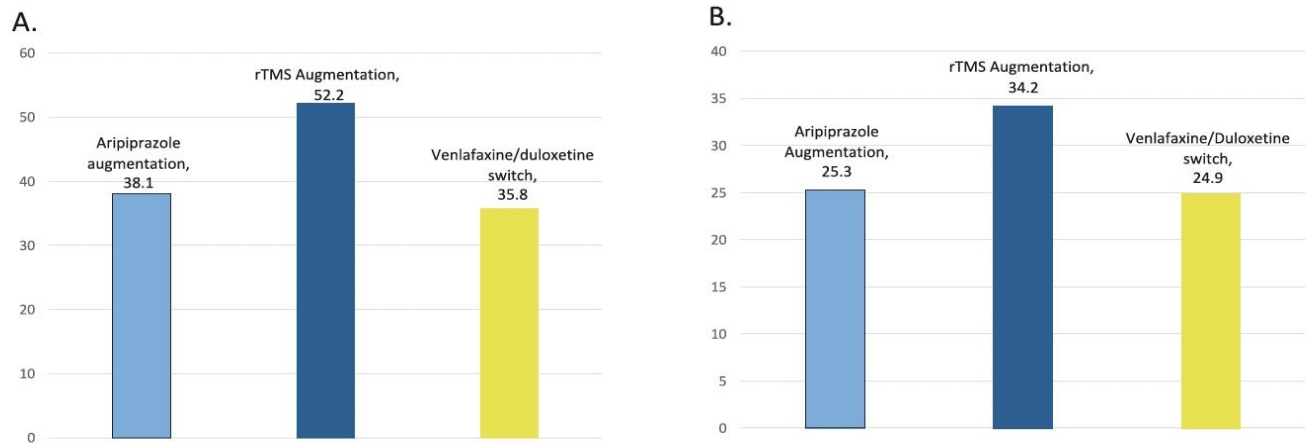


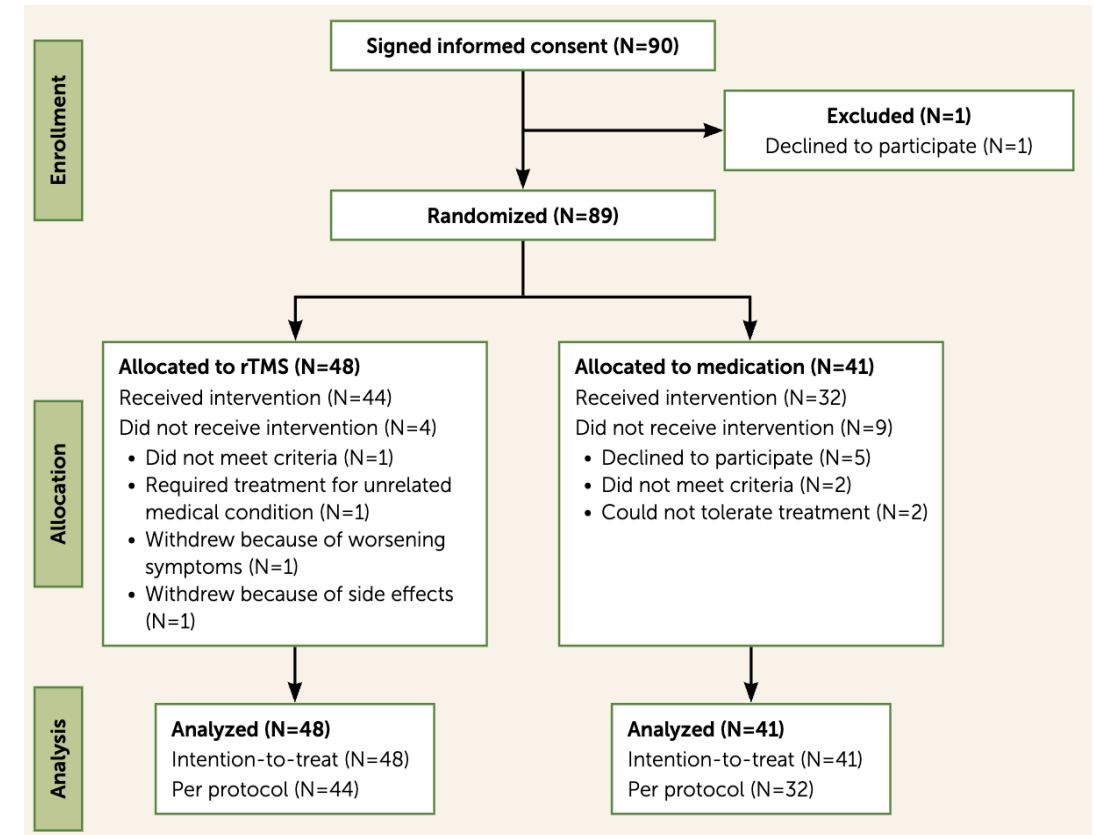
Fig. 4 MADRS response and remission rates comparing different study arms. A MADRS response rates (%); B MADRS remission rates (%). MADRS Montgomery-Asberg Depression Rating Scale (MADRS), rTMS Repetitive Transcranial Magnetic Stimulation; y-axis = % response/remission, x-axis = study arms.

Replication: TMS augmentation > med switching

rTMS as a Next Step in Antidepressant Nonresponders: A Randomized Comparison With Current Antidepressant Treatment Approaches

Iris Dalhuisen, Ph.D., Iris van Oostrom, Ph.D., Jan Spijker, M.D., Ph.D., Ben Wijnen, Ph.D., Eric van Exel, M.D., Ph.D., Hans van Mierlo, M.D., Ph.D., Dieuwertje de Waardt, M.D., Ph.D., Martijn Arns, Ph.D., Indira Tendolkar, M.D., Ph.D., Philip van Eijndhoven, M.D., Ph.D.

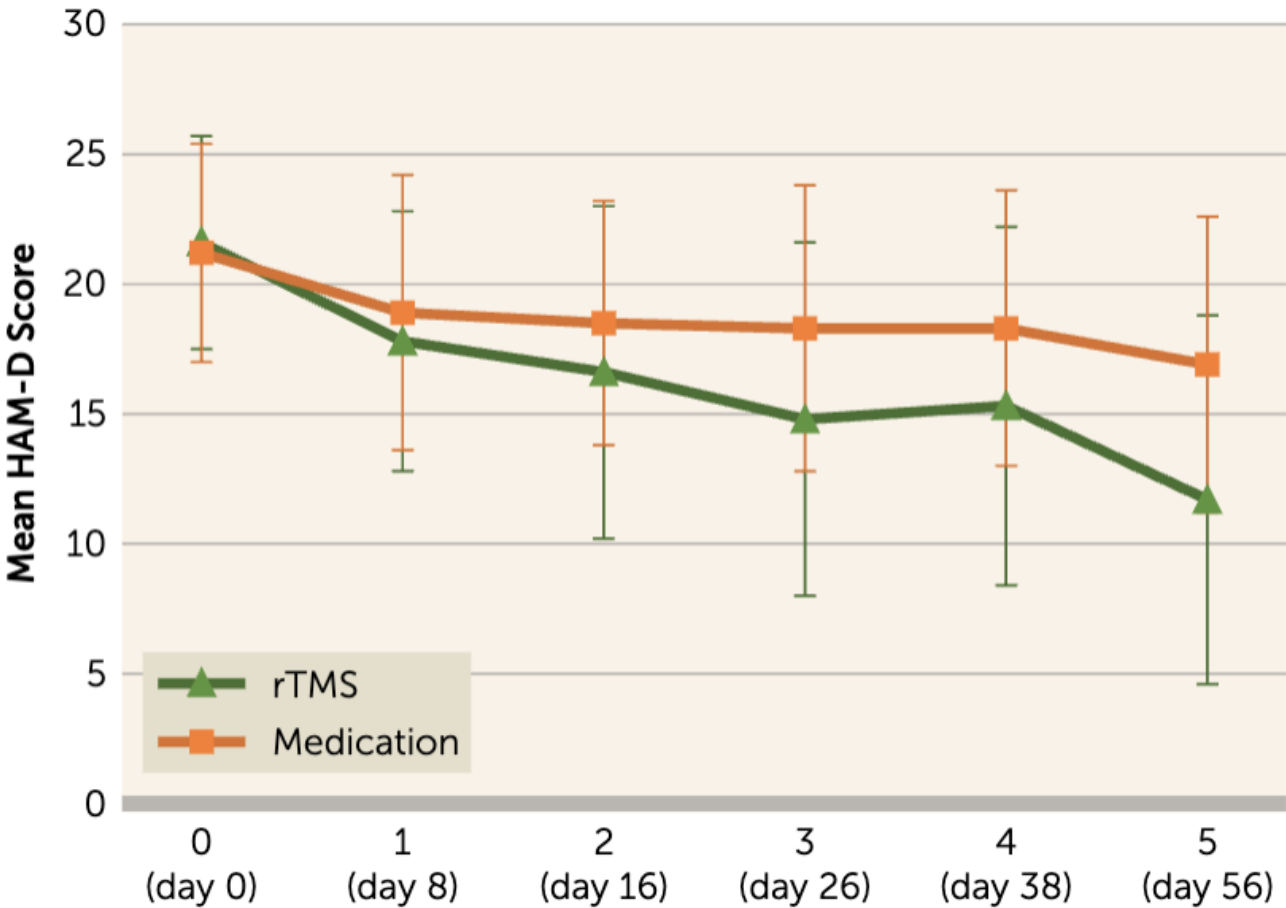
Am J Psychiatry,
2024



Replication: TMS augmentation > med switching

rTMS as a Next Step in Antidepressant Nonresponders: A Randomized Comparison With Current Antidepressant Treatment Approaches

Am J Psychiatry,
2024



TMS as first line therapy?

FULL ACCESS | Interventional Psychiatry | Published Date: 29 September 2022

TMS Should Be Considered as First-Line Treatment for Moderate to Severe Major Depressive Disorder

Richard A. Bermudes, M.D. | [AUTHORS INFO & AFFILIATIONS](#)

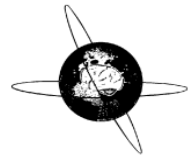
Publication: Psychiatric News • Volume 57, Number 10 • <https://doi.org/10.1176/appi.pn.2022.10.8.27>



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Clinical Neurophysiology

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



Opinion Paper

Should rTMS be considered a first-line treatment for major depressive episodes in adults?

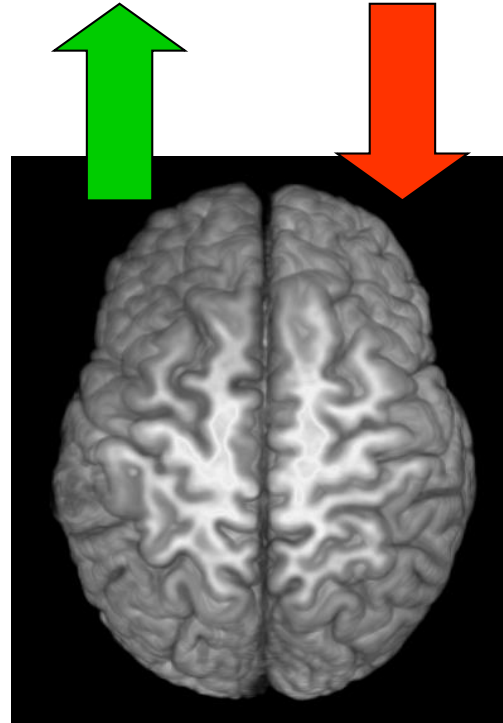
Sean J. O'Sullivan^{a,b,*}, Derrick M. Buchanan^b, Jean-Marie V. Batail^{c,d}, Nolan R. Williams^b



TMS Protocols for MDD

Left DLPFC excitation:
High Frequency (5-20 Hz)

- 10Hz
- 120% motor threshold
- 3000 pulses/session (15-38min)
- 30 sessions: 1 daily over 6wks



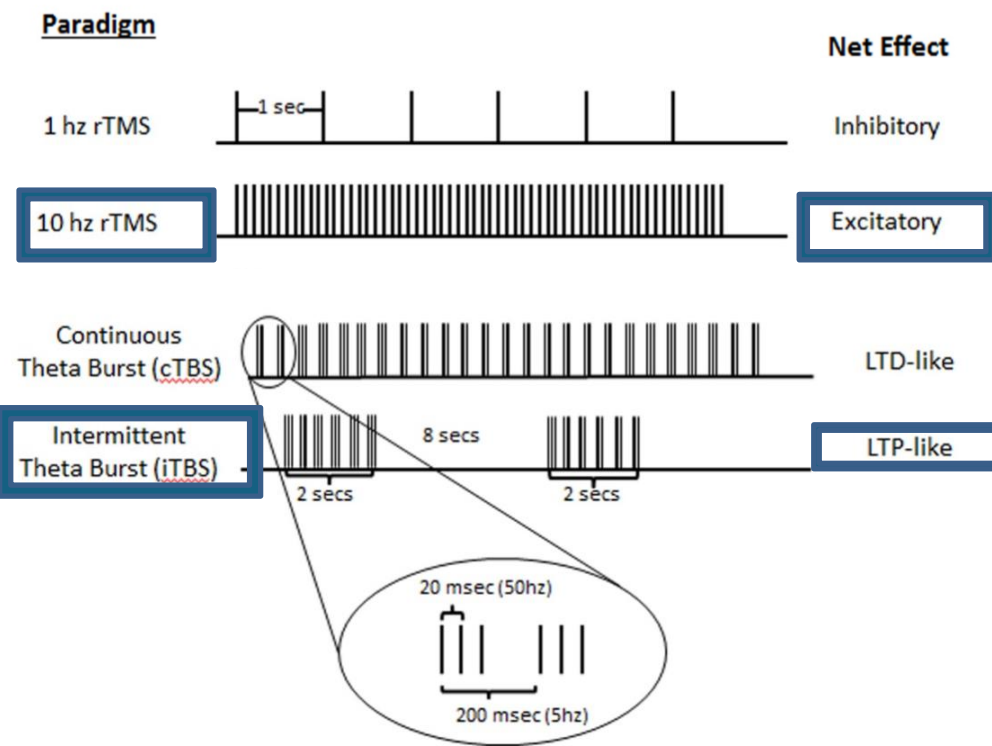
Right DLPFC inhibition:
Low Frequency (1 Hz)

- 1Hz
- 110-120% motor threshold
- 1200-1800 p/session (20-30min)
- 30 sessions: 1 daily over 6 wks

New Protocols: Theta Burst Stimulation (TBS)

Frequency determines excitatory vs. inhibitory effects

MDD: 10 Hz L-DLPFPC



- Shorter duration
- Longer-lasting physiological and cognitive effects are established in mechanistic studies

FDA-cleared: TBS for MDD

Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial



Daniel M Blumberger, Fidel Vila-Rodriguez, Kevin E Thorpe, Kfir Feffer, Yoshihiro Noda, Peter Giacobbe, Yuliya Knyahnytska, Sidney H Kennedy, Raymond W Lam, Zafiris J Daskalakis, Jonathan Downar

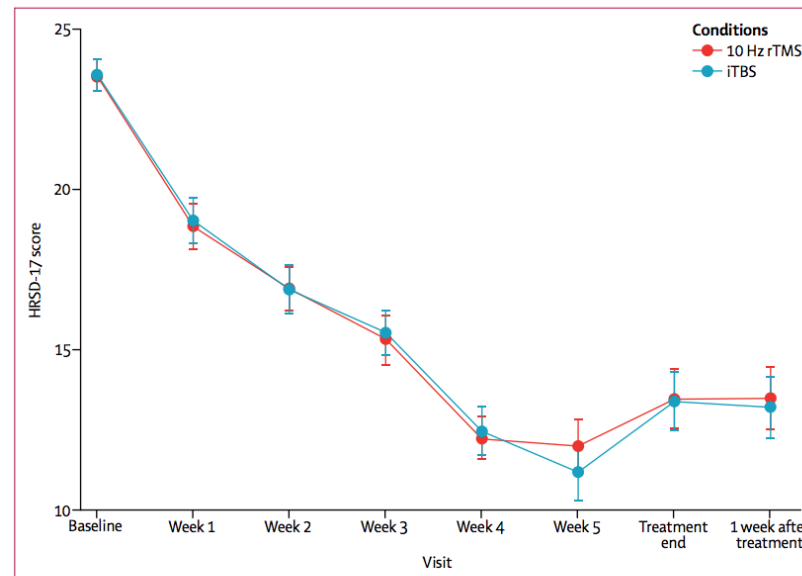


Figure 3: Change in HRSD-17 scores over time, comparing the 10 Hz rTMS and iTBS treatment groups
Data are mean scores with lower and upper 90% CIs.

Response Rate: 39%-49%
Remission Rate: 20%-32%

FDA cleared in 2018

Accelerated TMS

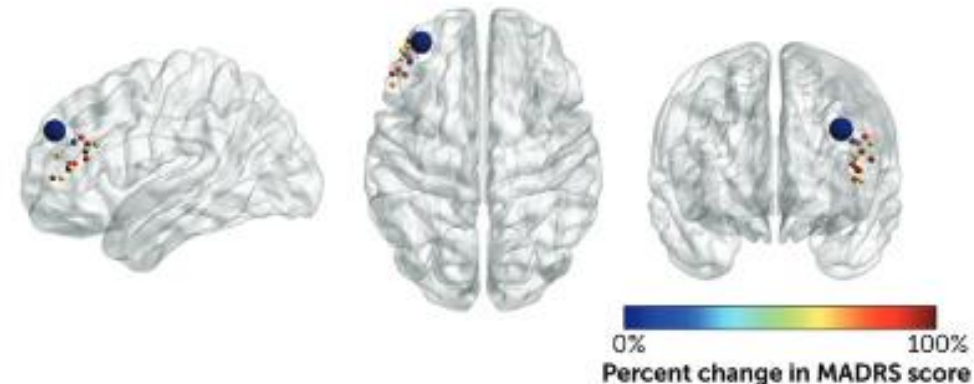
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fcMRI-guided Accelerated TBS for MDD

Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial



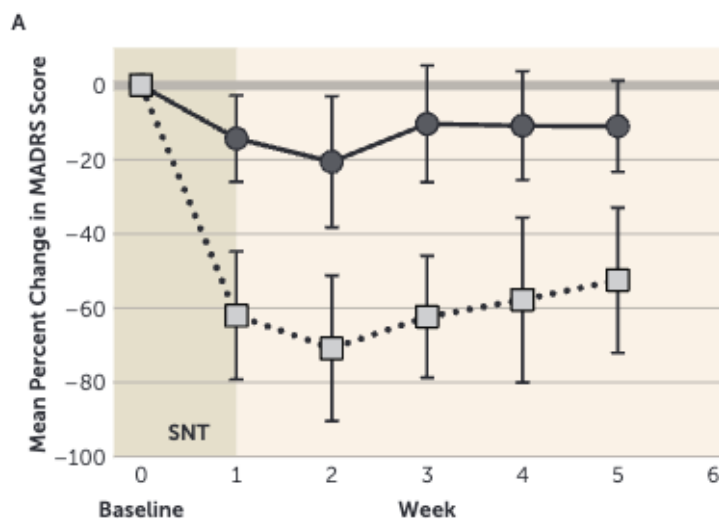
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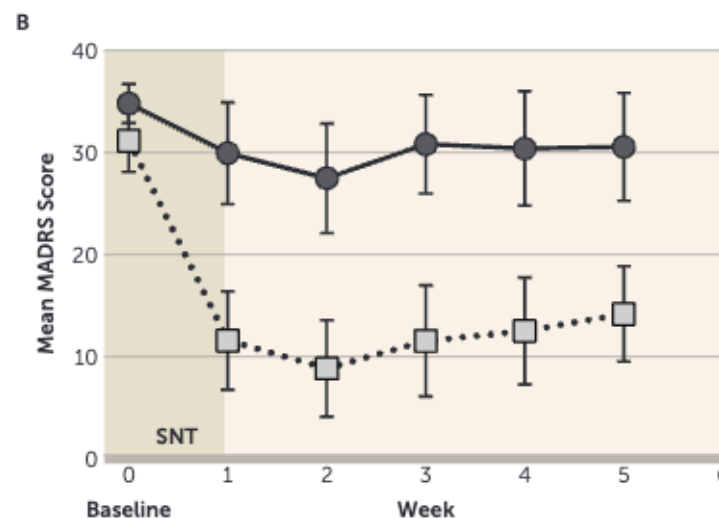
^a The location of the F3 coordinate (shown in dark blue) is based on the work of Okamoto et al. (59). The colors of the targets represent the maximum percentage change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) score.

fMRI-guided Accelerated TBS for MDD

Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial



Active: 62.0%, 70.9%, 62.4%, 57.8%, 52.5%
Sham: 14.3%, 20.6%, 10.4%, 10.9%, 11.1%



Interim Analysis: 30 patients (aim was 60)
Cohen's d > 0.8 ? Study ended

85.7% response rate
78.6% remission rate

FDA cleared in 2022

SNT for Bipolar Depression

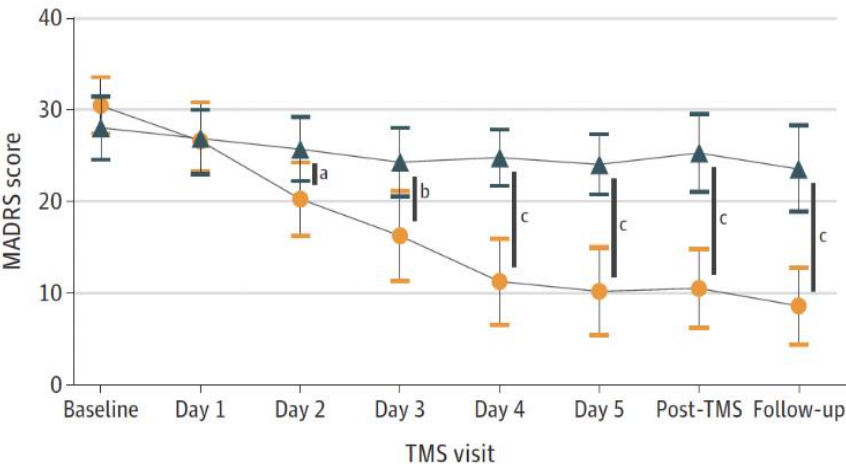
JAMA Psychiatry | Brief Report 2024

Accelerated Intermittent Theta-Burst Stimulation and Treatment-Refractory Bipolar Depression

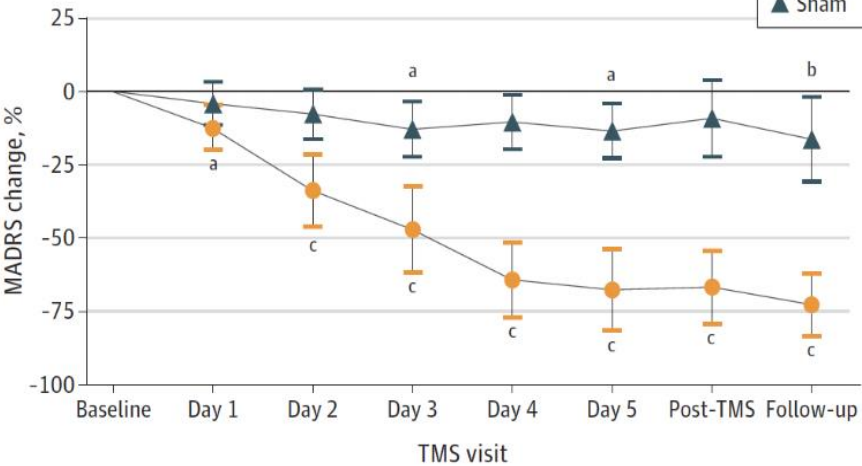
A Randomized Clinical Trial

Yvette I. Sheline, MD; Walid Makhoul, MD; Alexandra S. Batzdorf, BA; Frederick J. Nitchie, MS; Kevin G. Lynch, PhD; Robin Cash, PhD; Nicholas L. Balderston, PhD

A Between-group raw score differences



B Within-group percentage change from baseline



Baseline characteristic	Participants ^a	
	Sham (n = 12)	Active (n = 12)
Age, mean (SD), y	43.6 (19.2)	43.1 (15.2)
Sex		
Female	6 (50)	6 (50)
Male	6 (50)	6 (50)
Diagnosis		
Bipolar II	11 (92)	11 (92)
Bipolar I	1 (1)	1 (1)
Trials, mean (SD), No.		
Antidepressant	5.1 (1.8)	4.9 (1.6)
Augmentation	1.4 (0.8)	1.1 (0.9)
Pharmacotherapy		
Lithium	3 (25)	5 (42)
Anticonvulsants (lamotrigine, depakote)	11 (92)	5 (42)
SSRIs (citalopram, sertraline, and fluoxetine)	2 (17)	3 (25)
SNRIs (venlafaxine, duloxetine)	2 (17)	0 (0)
Other antidepressants (bupropion)	2 (17)	1 (8)
Hormone supplement (cytomel)	0	2 (17)
Atypical antipsychotics (cariprazine, lurasidone, quetiapine, aripiprazole)	4 (33)	7 (58)
Psychiatric comorbidities		
Anxiety	4 (33)	5 (42)
PTSD	3 (25)	2 (17)
ADHD	3 (25)	3 (25)

But...

Repetitive transcranial magnetic stimulation (rTMS) in bipolar disorder: A systematic review

Gerasimos Konstantinou^{1,2}  | Jeanette Hui¹ | Abigail Ortiz^{1,3} | Tyler S. Kaster^{1,2} |
Jonathan Downar^{1,4} | Daniel M. Blumberger^{1,2} | Zafiris J. Daskalakis^{1,2,5}

“The current data regarding the application of rTMS in BD patients remain limited. More adequately powered sham-controlled studies are required to verify its efficacy. Large-scale clinical trials are needed to also determine whether its effects extend to manic and mixed episodes, as well as its role in mood stabilization and amelioration of suicidal behavior.”

Biomarker-Driven Treatment Development



Invited Commentary | Psychiatry

Therapeutic Neuromodulation for Bipolar Disorder—The Case for Biomarker-Driven Treatment Development

Joan A. Camprodon, MD, MPH, PhD

Augmentation of TMS with “neuroplastogens”

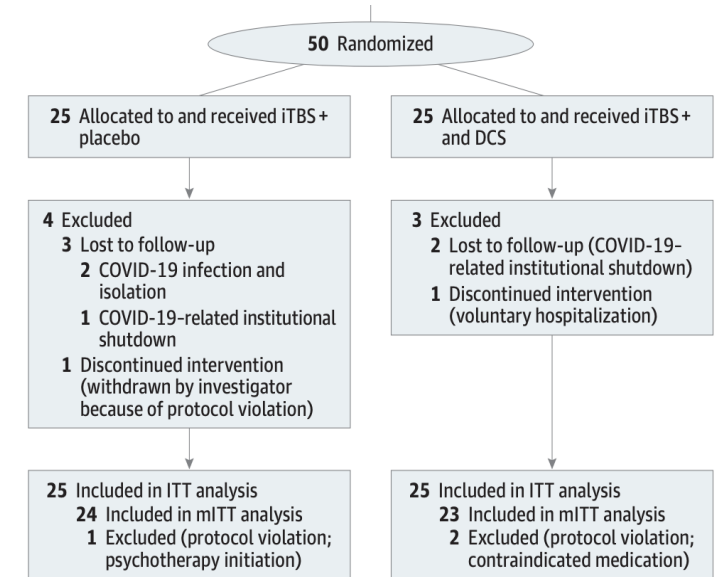
JAMA Psychiatry | [Original Investigation](#)

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

D-cycloserine (NMDA partial agonist): 100mg, 60min pre-TMS, first 2 weeks only

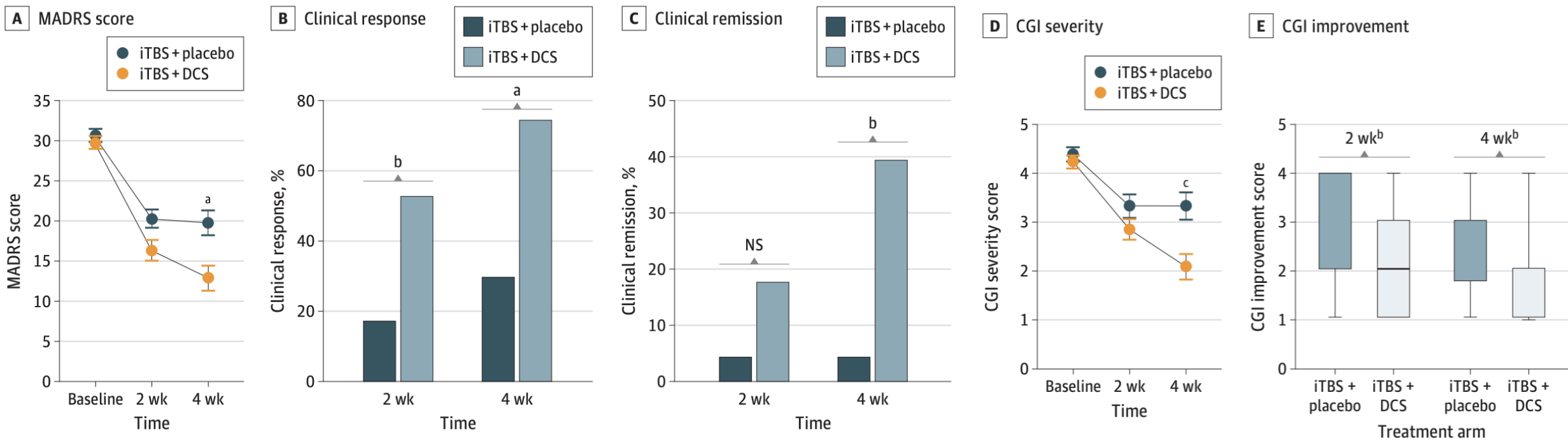
TMS: iTBS, 600 pulses 80%MT, F3Beam, 4 weeks/20 daily sessions



Augmentation of TMS with “neuroplastogens”

JAMA Psychiatry | Original Investigation

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



Rapid Treatments for Depression

fMRI-guided accelerated TMS

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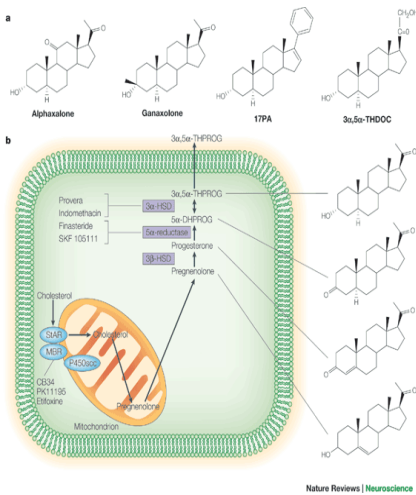
Electroconvulsive Therapy (ECT)



(Es)ketamine



Neurosteroids



Brexanolone IV
Zuranolone PO

Psychedelics



Interventional Psychiatry

Interventional Neuropsychiatry: new subspecialty?



Precision Neuromodulation: Beyond Personalized Protocols

fMRI-guided accelerated TMS

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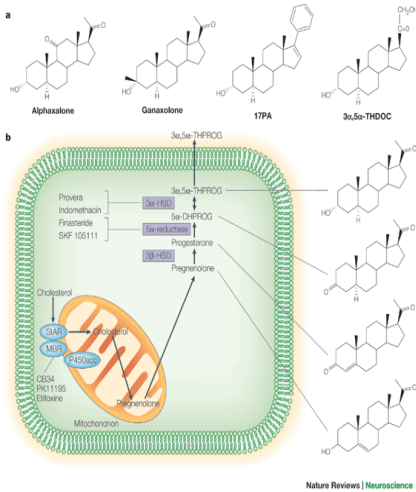
Electroconvulsive Therapy (ECT)



(Es)ketamine



Neurosteroids



Brexanolona IV
Zuranolona PO

Psychedelics



Who should get what when?

Biomarker-Informed Precision Treatment Selection

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Does 18 Hz deep TMS benefit a different subgroup of depressed patients relative to 10 Hz rTMS? The role of the individual alpha frequency

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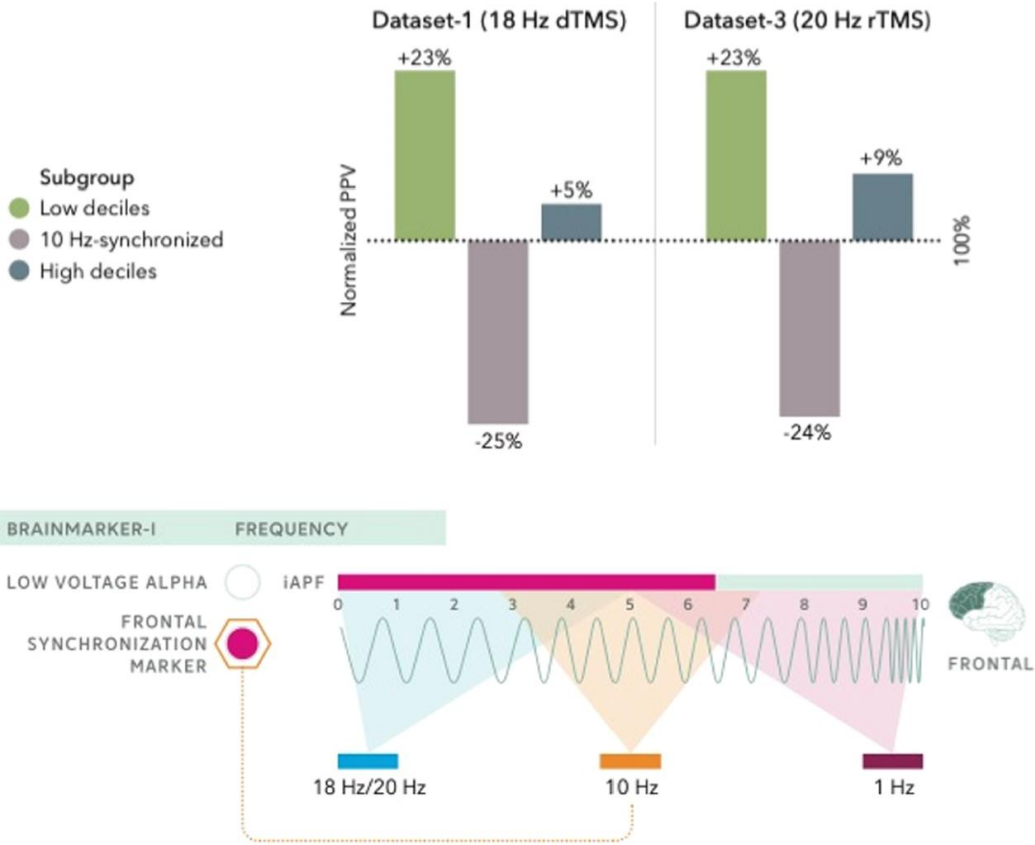


Fig. 4. Subgroup analyses and stratification recommendation. Results of the PPV/nPPV analyses of Dataset-1 and -3. The low decile subgroup presented with highest remission rates compared to the 10 Hz-synchronized and high decile subgroups (top). Taken together with the previous findings of treatment stratification with Brainmarker-I regarding 10 Hz and 1 Hz rTMS (Voetterl et al., 2023a), patients falling in the low decile subgroup are suggested to be stratified to 18 or 20 Hz TMS, the 10 Hz-synchronized subgroup to 10 Hz and the high decile subgroup to 1 Hz TMS (bottom).

Thanks!



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