TMS in the Age of Experimental Medicine and Precision Neuromodulation

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Disclosures

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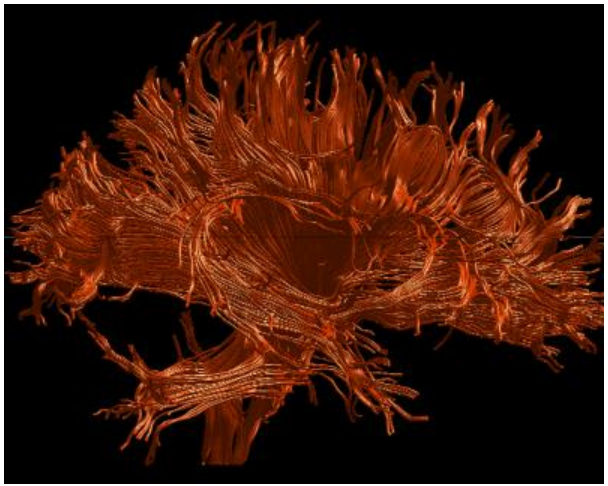
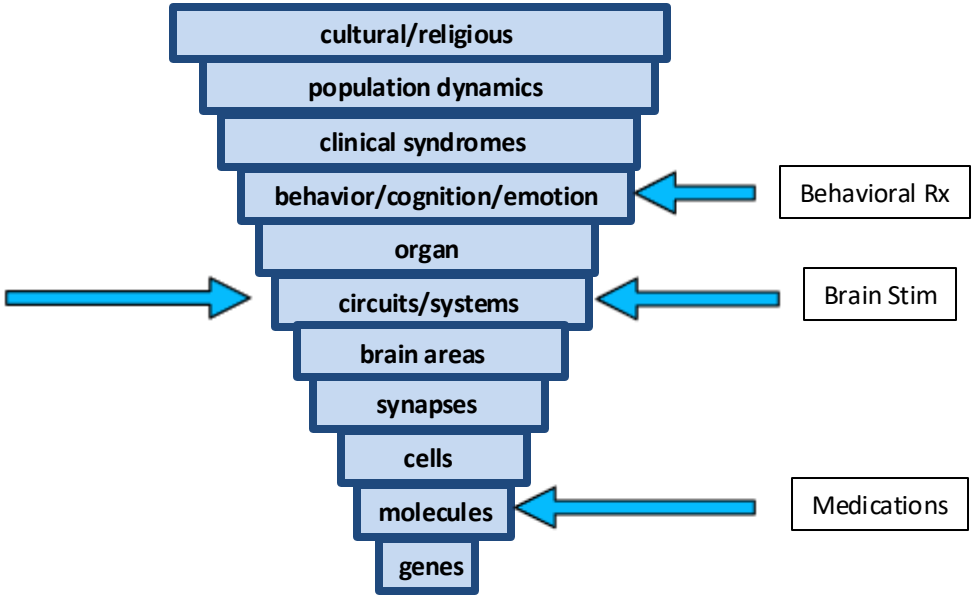
- Scientific Advisory Board: Hyka, Flow Neuroscience
- Consultant: Mifu Technologies, Neuroelectrics, LivaNova

Neuropsychiatry and Circuitopathies





Treatment Development in NM: a Focus on Circuits

Pathophysiology → Biomarkers → Treatments

Behavior

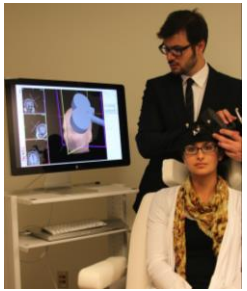
Circuits → Anatomy
Circuits → Physiology

Disease

Severity

Prognostic/Predictive

Response



Biomarker-driven Rx development in MDD

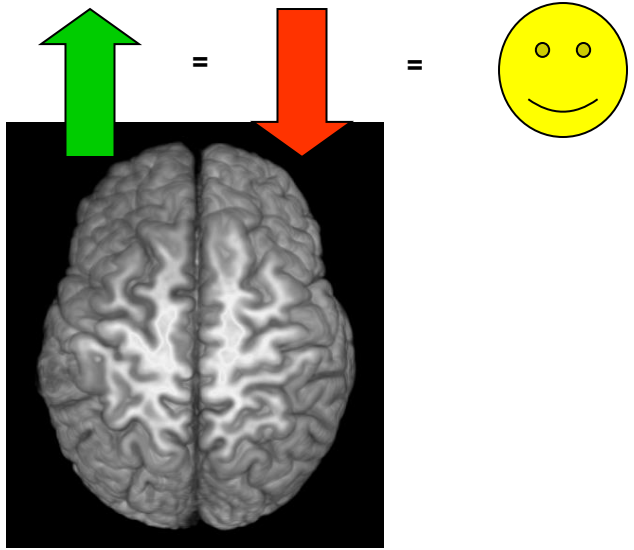
- 1990s: Early PET data identified hypometabolic frontal lobes in Depression, with additional hemispheric (frontal) asymmetry

- 1990s: rTMS can selectively increase (HF) or decrease (LF) cortical excitability

Depression Rx Strategy:

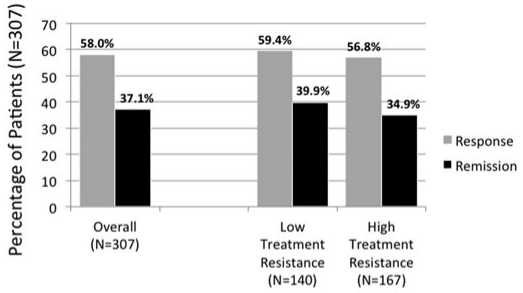
-Left: High Frequency (5-20 Hz)

-Right: Low Frequency (1 Hz)



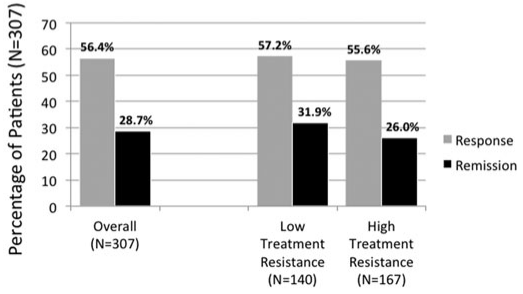
MDD Effectiveness Naturalistic Studies

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

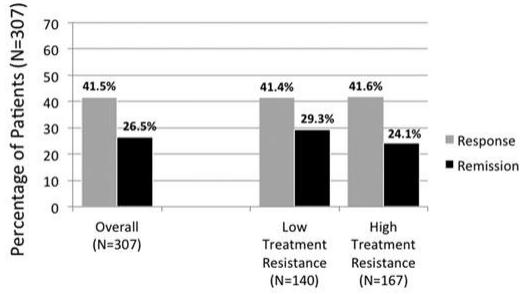


LOCF Analysis of intent-to-treat population
Please see text for definitions of response, remission and treatment resistance level

Carpenter et al. 2012

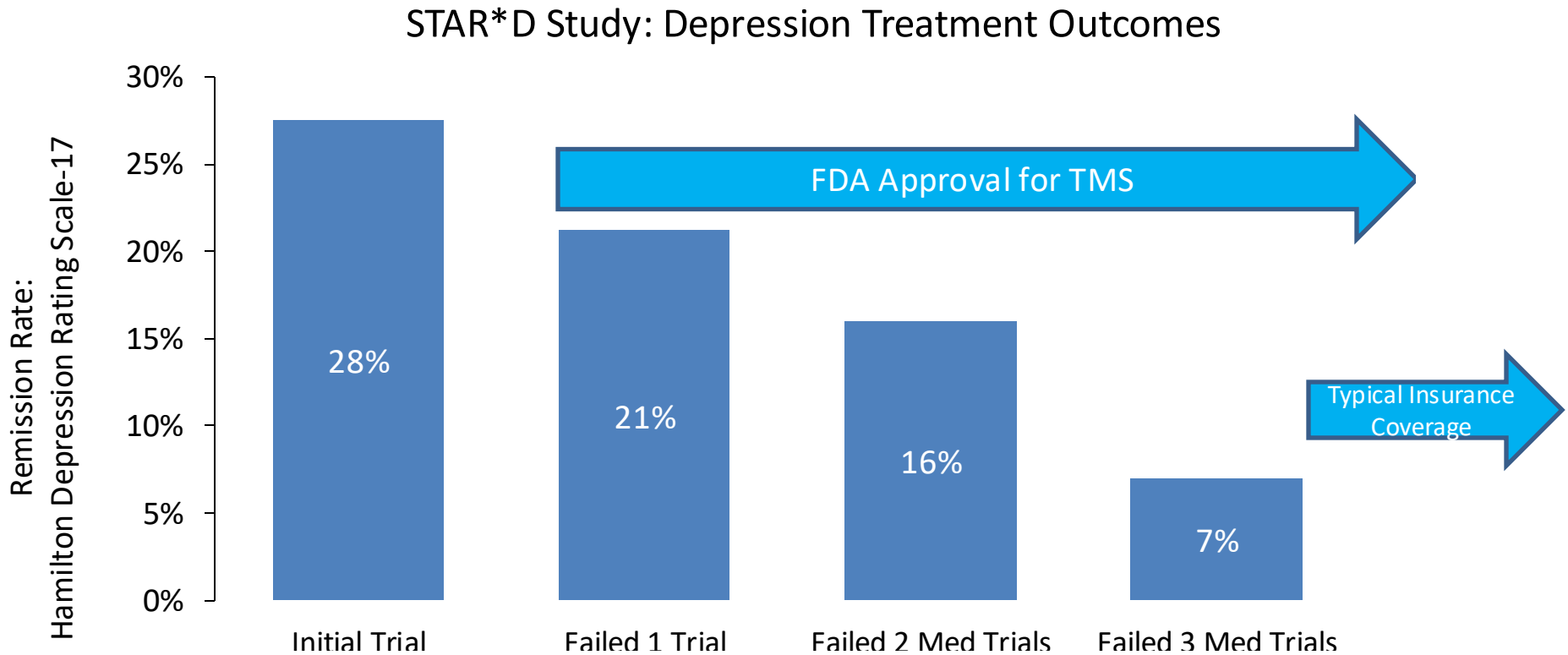
- 339 patient with MDD naïve to TMS
- Concurrent medications/therapy
- Response Rate: 41.5-58%
- Remission Rate: 26.5-37.1%
- Age and severity predict outcome
- Treatment-resistant not a predictor

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?



Likelihood of achieving remission drops with each subsequent medication trial

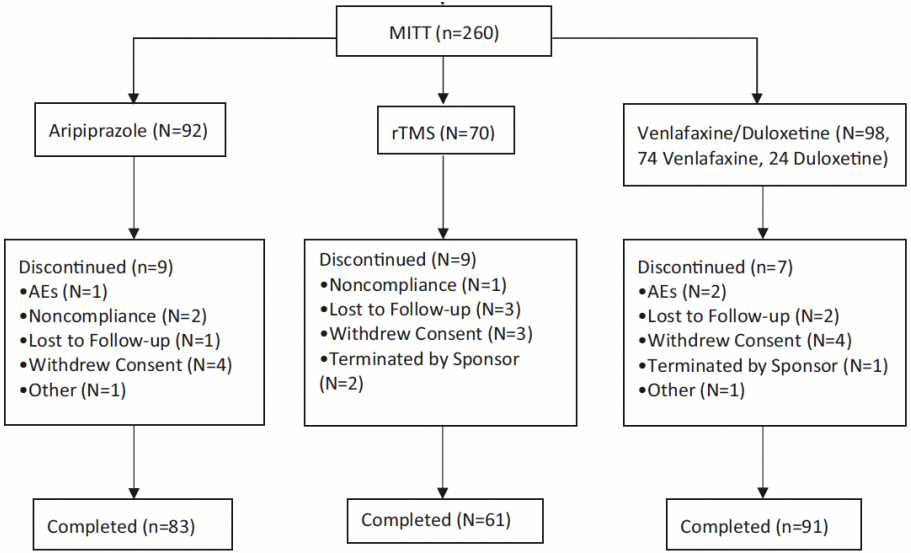
Rush AJ et al. Am J Psych 163:1905-1917, 2006

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. Papakostas[1]✉, Madhukar H. Trivedi[2], Richard C. Shelton[3], Dan V. Iosifescu[4], Michael E. Thase[5], Manish K. Jha[2], Sanjay J. Mathew[6], Charles DeBattista[7], Mehmet E. Dokucu[8], Olga Brawman-Mintzer[9], Glenn W. Currier[10], William Vaughn McCall[11], Mandana Modirrousta[12], Matthew Macaluso[3,13], Alexander Bystritsky[14], Fidel Vila Rodriguez[15], Erik B. Nelson[16], Albert S. Yeung[1], Anna Feeney[1], Leslie C. MacGregor[1], Thomas Carmody[2] and Maurizio Fava[1]

Mol. Psychiatry, 2024



TRD: switching SNRI vs augmenting atypicals vs TMS

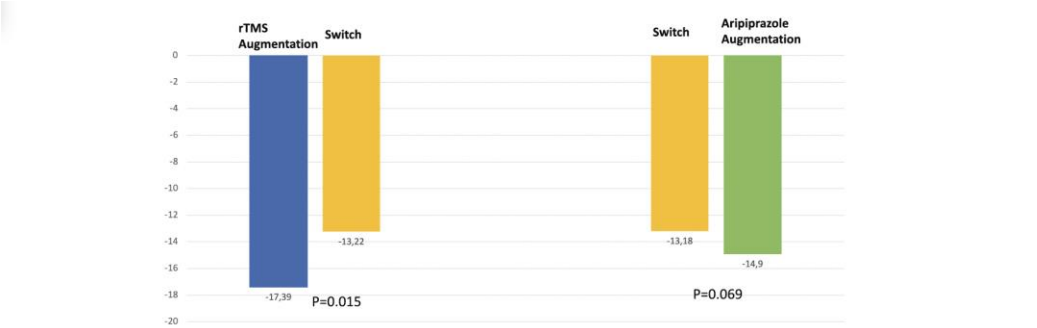


Fig. 2 Model adjusted change in MADRS scores. MADRS Montgomery Asberg Depression Rating Scale, rTMS Repetitive Transcranial Magnetic Stimulation. Alpha = 0.025.

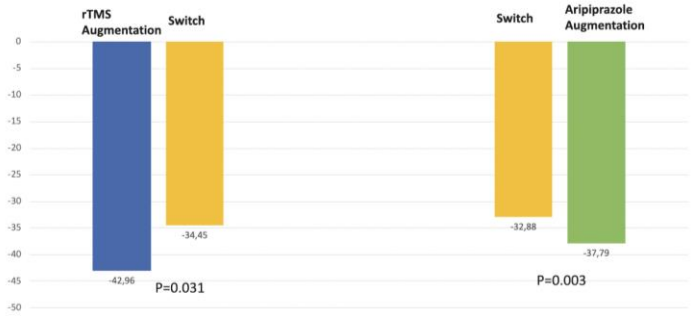


Fig. 3 Model adjusted change in SDQ scores. SDQ Symptoms of Depression Questionnaire, rTMS Repetitive Transcranial Magnetic Stimulation. Alpha = 0.025.

TRD: switching SNRI vs augmenting atypicals vs TMS

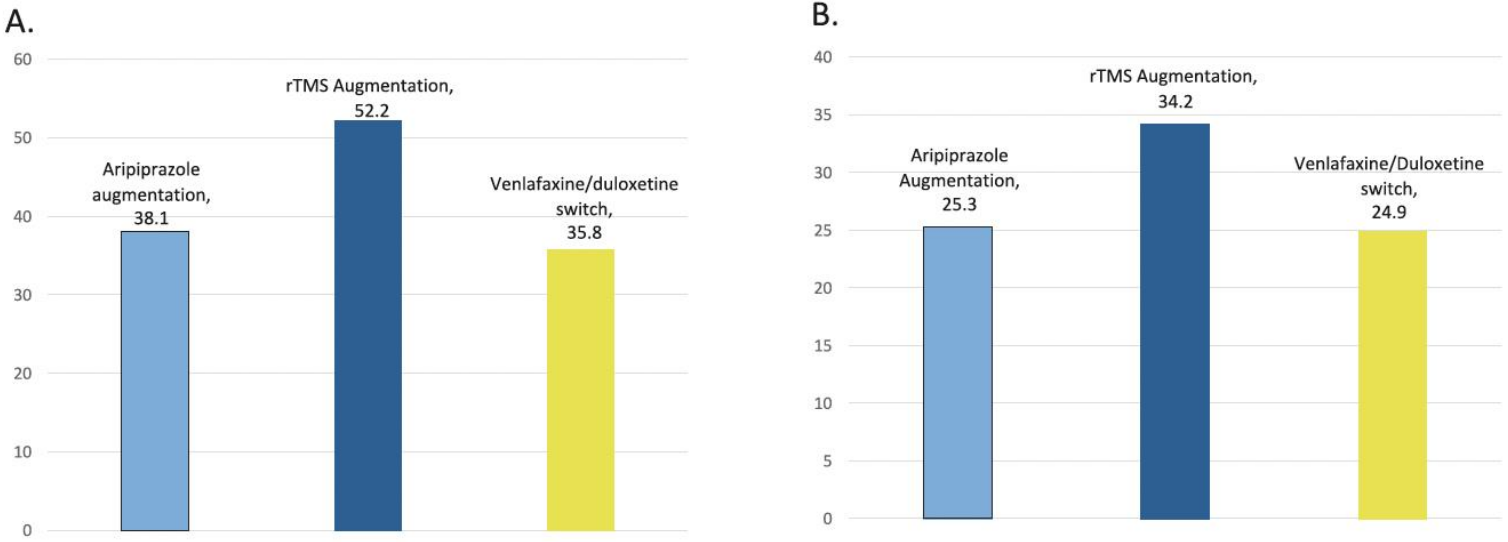


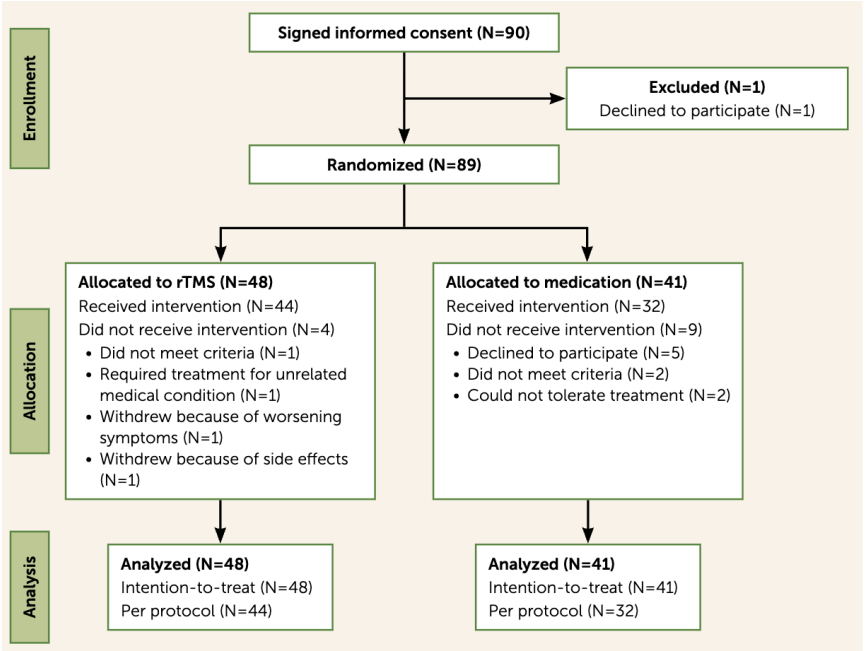
Fig. 4 MADRS response and remission rates comparing different study arms. A MADRS response rates (%); **B** MADRS remission rates (%). MADRS Montgomery-Asberg Depression Rating Scale (MADRS), rTMS Repetitive Transcranial Magnetic Stimulation; y-axis = % response/remission, x-axis = study arms.

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



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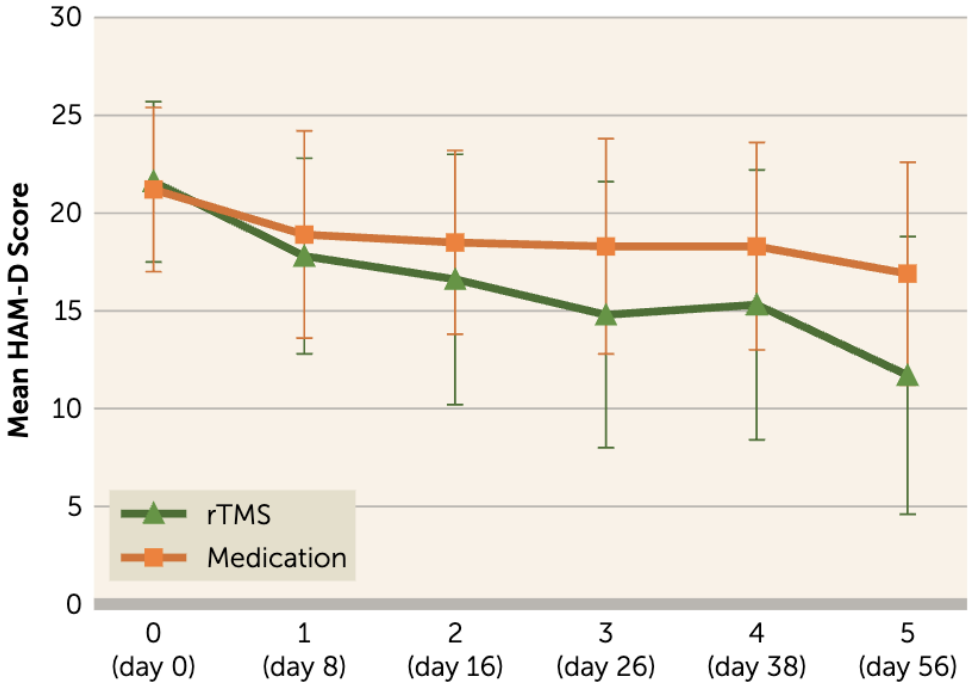
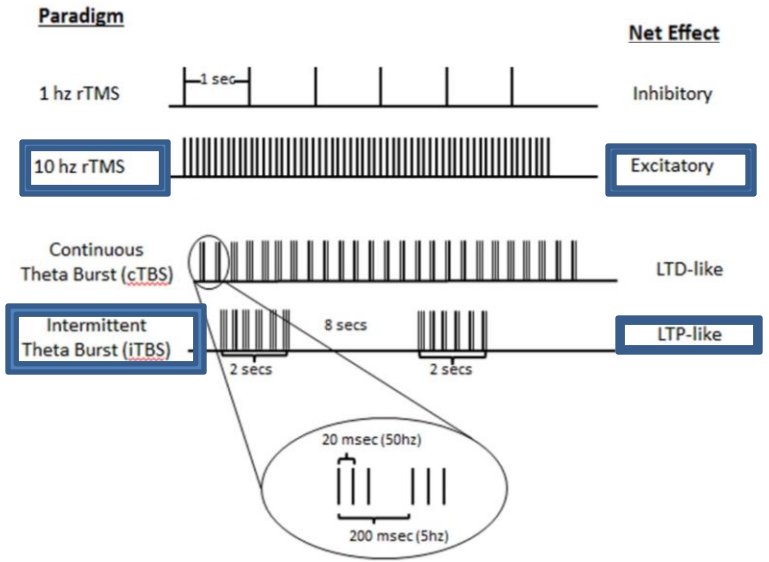


New Protocols: Theta Burst Stimulation (TBS)

MDD: 10 Hz L-DLPFPC

Frequency determines excitatory vs. inhibitory effects



- 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

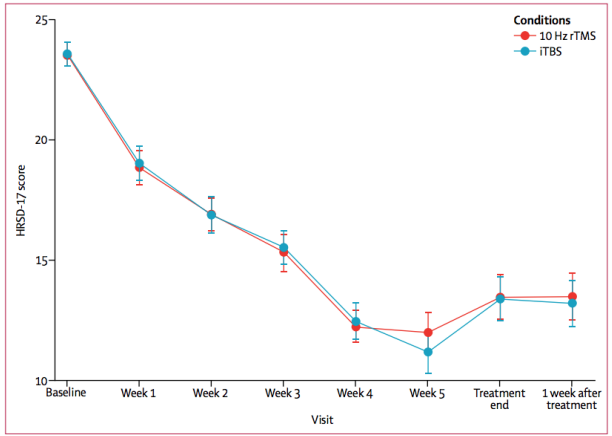


***Figure 3*: Change in HRSD-17 scores over time, comparing the 10 Hz rTMS and iTBS treatment groups**
Data are mean scores with lower and upper 90% CIs.

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

FDA cleared in 2018

Accelerated TMS

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
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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
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iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
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50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI

fcMRI-guided Accelerated TBS for MDD

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

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
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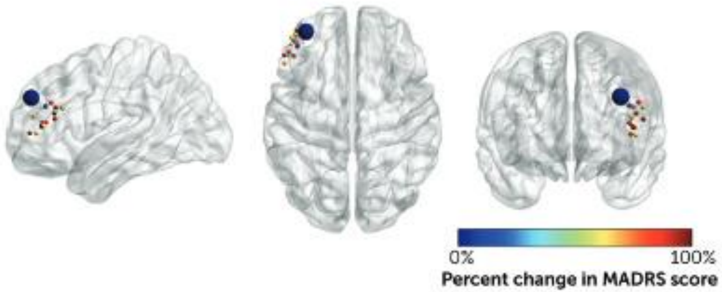
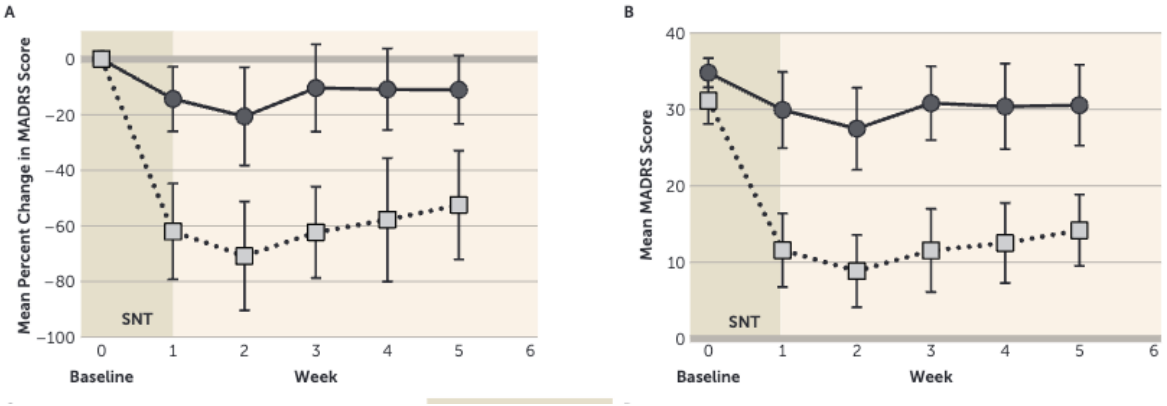


[a] The location of the F3 coordinate (shown in dark blue) is based on the work of Okamoto et al. (59). The colors of the targets represent the maximum percentage change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) score.

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

Rapid Treatments for Depression

fMRI-guided accelerated TMS

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
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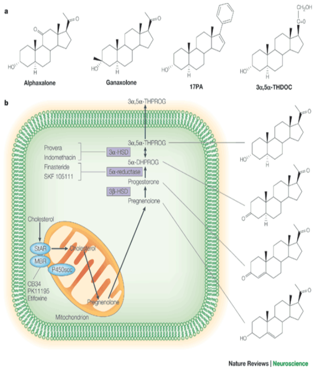
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI

Electroconvulsive Therapy (ECT)

(Es)ketamine

Neurosteroids



Brexanolone IV
Zuranolone PO

Psychedelics

Interventional Psychiatry

Interventional Neuropsychiatry: new subspecialty?

Brain Stimulation 18 (2025) 298–305

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

Towards accredited clinical training in brain stimulation: Proceedings from the brain stimulation subspecialty summits

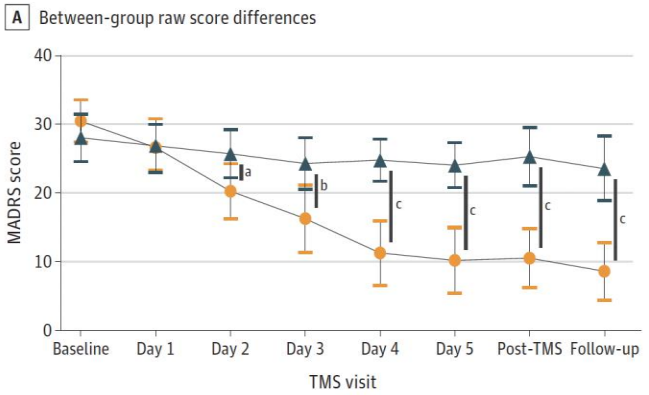
Shan H. Siddiqi [a,b,c,d,*], Leo Chen [e,f], Nicholas T. Trapp [g,h], Noreen Bukhari-Parlakturk [i,j], Joseph J. Taylor [a,b,d], Aaron D. Boes [h,k], Joshua C. Brown [c,d,l], Tracy Barbour [d,m], Joan A. Camprodon [d,m], Michael D. Fox [a,b,d,n], Brian H. Kopell [o], Carlene MacMillan [p,q,r], Alfonso Fasano [s,t,u,v], Robert S. Fisher [w], Ziad Nahas [x], Gonzalo J. Revuelta [y,z], Patricio Riva-Posse [aa], John D. Rolston [a,d,bb], Katherine Scangos [cc,dd], Mouhsin M. Shafi [d,ee], Andrew H. Smith [o], Joshua Wong [ff], Casey H. Halpern [q], Helen S. Mayberg [gg], Nolan R. Williams [hh]

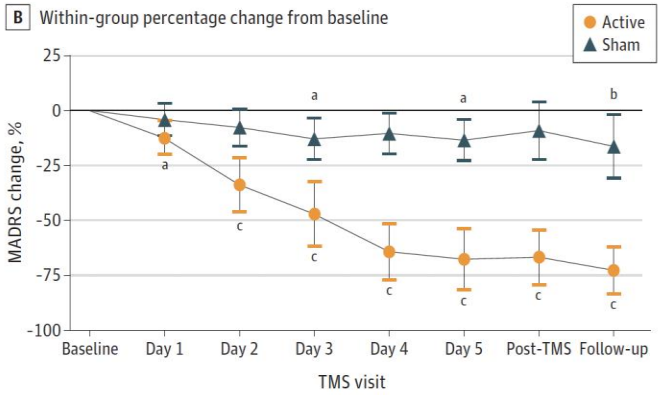
SNT for Bipolar Depression

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





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 Hui[1] | 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

JAMA Network | Open

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”

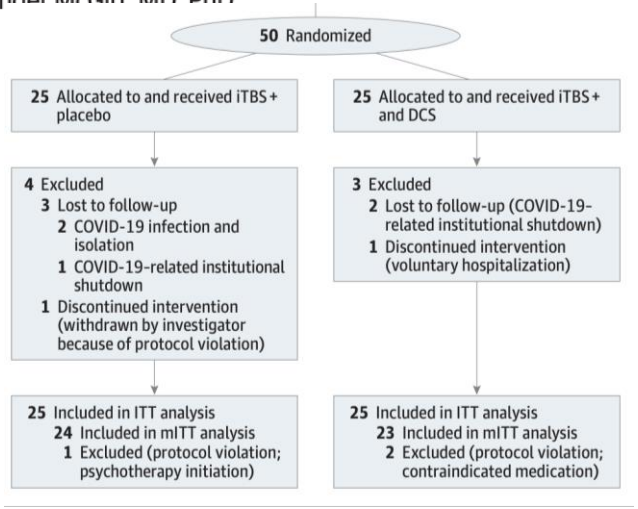
JAMA Psychiatry | Original Investigation

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”

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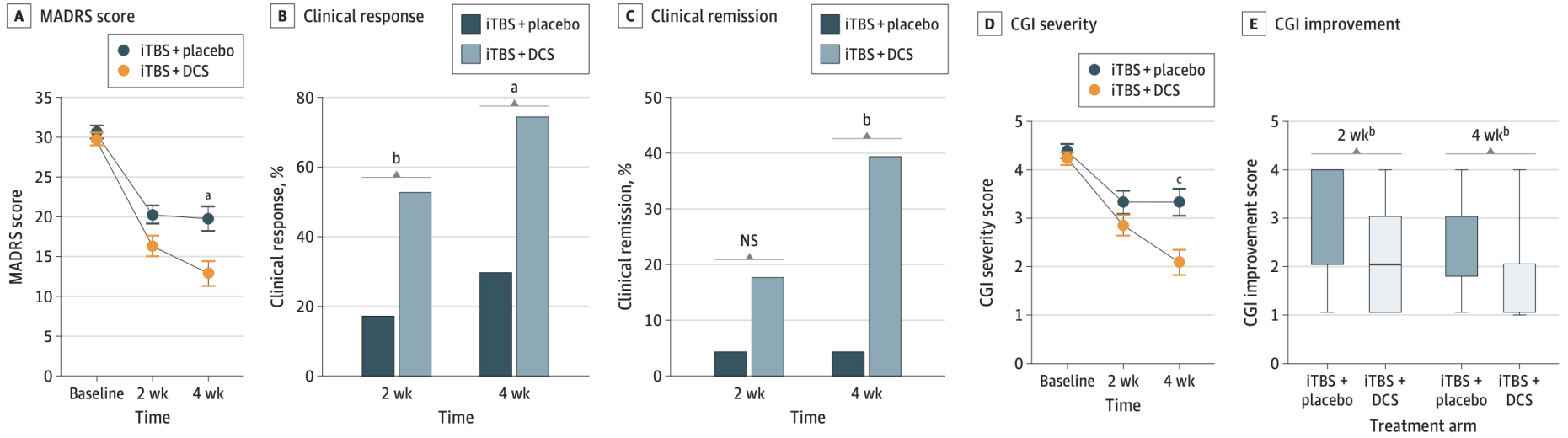
A Randomized Clinical Trial



Precision Neuromodulation: Beyond Personalized Protocols

fMRI-guided accelerated TMS

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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
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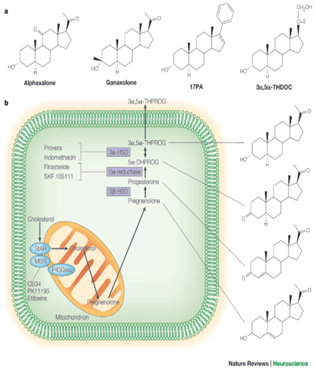
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI

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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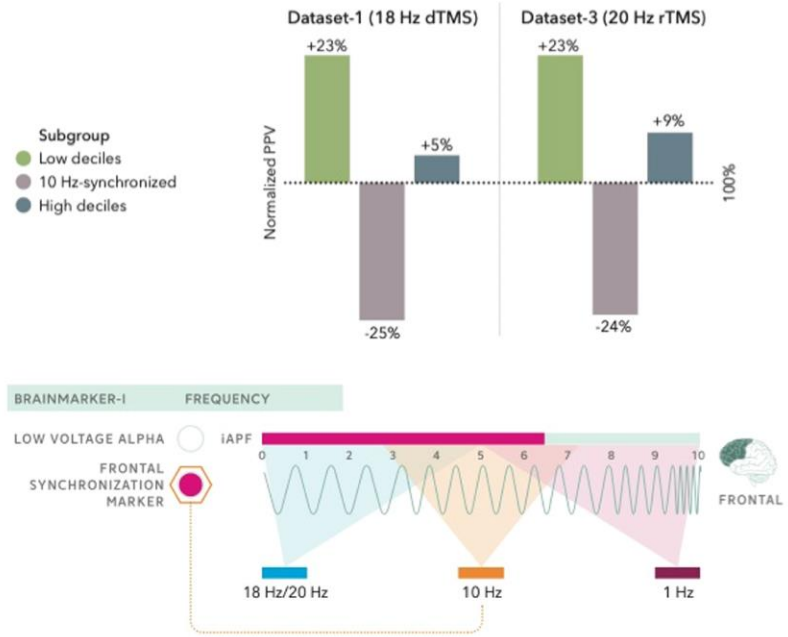

Fig. 4. Subgroup analyses and stratification recommendation. Results of the PPV/nPPV analyses of Dataset-1 and −3. The low decile subgroup presented with highest remission rates compared to the 10 Hz-synchronized and high decile subgroups (top). Taken together with the previous findings of treatment 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!