JAMA Psychiatry | Brief Report

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

IMPORTANCE Bipolar disorder (BD) is chronic and disabling, with depression accounting for the majority of time with illness. Recent research demonstrated a transformative advance in the clinical efficacy of transcranial magnetic stimulation for treatment-resistant major depressive disorder (MDD) using an accelerated schedule of intermittent theta-burst stimulation (aiTBS), but the effectiveness of this treatment for treatment-refractory BD is unknown.

OBJECTIVE To evaluate the effectiveness of aiTBS for treatment-refractory BD.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial, conducted from March 2022 to February 2024, included individuals with treatment-resistant BD with moderate to severe depressive episodes referred from the Penn Bipolar outpatient clinic. Included patients had 2 or more prior failed antidepressant trials by Antidepressant Treatment History Form criteria and no other primary psychiatric diagnosis, were receiving a mood stabilizer for 4 or more weeks, and had a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 20 or higher.

INTERVENTION Prior to treatment, resting-state functional magnetic resonance imaging was used to compute personalized left dorsolateral prefrontal cortex target by connectivity to subgenual anterior cingulate cortex. Patients were randomized 1:1 to 10 sessions per day of imaging-guided active or sham aiTBS for 5 days with 1 session per hour at 90% resting motor threshold for 90 000 pulses total.

MAIN OUTCOME AND MEASURES The main outcome was repeated MADRS scores before and after treatment.

RESULTS A total of 24 participants (12 [50%] female; 12 [50%] male; mean [SD] age, 43.3 [16.9] years) were randomized to active (n = 12) or sham (n = 12) aiTBS. All participants completed treatment and 1-month follow-up. MADRS scores were significantly lower in the active group (mean [SD], 30.4 [4.8] at baseline; 10.5 [6.7] after treatment) than in the sham group (28.0 [5.4] at baseline; 25.3 [6.7] after treatment) at treatment end (estimated difference, −14.75; 95% CI, −19.73 to −9.77; $P < .001$; Cohen d, −2.19).

CONCLUSION AND RELEVANCE In this randomized clinical trial, aiTBS was more effective than sham stimulation for depressive symptom reduction in patients with treatment-resistant BD. Further trials are needed to determine aiTBS durability and to compare with other treatments.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05228457

Supplemental content

Author Affiliations: Center for Neuromodulation in Depression and Stress, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Sheline, Makhoul, Batzdorf, Nitchie, Balderston); Department of Psychiatry, University of Pennsylvania, Philadelphia (Lynch); Department of Biomedical Engineering and Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia (Cash).

Corresponding Author: Yvette I. Sheline, MD, MS, Center for Neuromodulation in Depression and Stress, University of Pennsylvania Perelman School of Medicine, Richards Biomedical Building D307, 3700 Hamilton Walk, Philadelphia, PA 19104 (sheline@pennmedicine.upenn.edu).

JAMA Psychiatry. 2024;81(9):936-941. doi:10.1001/jamapsychiatry.2024.1787
Published online July 10, 2024. Corrected on July 31, 2024.

Bipolar disorder (BD) is prevalent, severe, and often excluded from clinical trials. The depressive phase accounts for the majority of time with illness—72% in BD I and 81% in BD II.[1] Many patients fail to respond adequately to pharmacotherapy or cannot tolerate adverse effects. One therapeutic option, intermittent theta-burst stimulation (iTBS), was developed as a more efficient form of repetitive transcranial magnetic stimulation (rTMS); 3 minutes of iTBS to the left dorsolateral prefrontal cortex (dlPFC) was noninferior in efficacy and safety to the traditional 10-Hz rTMS protocol (38 minutes), leading to its approval for treatment of major depressive disorder (MDD) by the Food and Drug Administration.[2] To date, the best evidence for iTBS efficacy, especially with accelerated delivery (aiTBS), has been in treatment-resistant MDD, for which patients receiving aiTBS have been shown to have a large, rapid, and sustained treatment response. Ten sessions per day for 5 days achieved 79% remission in a sham-controlled randomized clinical trial[2]—substantially better than remission rates of 20% to 30% with standard iTBS.[3]

Few sham-controlled studies have examined iTBS in BD treatment, and these studies have often not demonstrated improved outcomes with active treatment compared with sham treatment.[4] To our knowledge, no studies have reported using aiTBS for BD. We conducted a double-blind, sham-controlled randomized clinical trial using neuronavigated aiTBS applied over the left dlPFC in patients with treatment-resistant BD.

Key Points

Question Is accelerated intermittent theta-burst stimulation (aiTBS) clinically effective for treatment-refractory bipolar depression?

Findings In this randomized clinical trial of 24 patients with treatment-resistant bipolar disorder, aiTBS-treated participants had significantly lower depression scores after treatment than did those in the sham group.

Meaning The findings suggest that aiTBS in carefully selected patients offers a new treatment option for this difficult-to-treat illness.

Table. Participant Demographic Characteristics

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)
Race		
African American or Black	1 (8)	2 (17)
Asian	2 (17)	1 (8)
White	9 (75)	9 (75)
Educational attainment, mean (SD), y	15.2 (2.7)	15.8 (2.8)
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)
Medical comorbidities		
High blood pressure	1 (8)	1 (8)
Hashimoto thyroiditis	0	1 (8)
Sleep apnea	1 (8)	0
Migraine	1 (8)	0
Diabetes	0	1 (8)
GERD	0	1 (8)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; GERD, gastroesophageal reflux disease; PTSD, posttraumatic stress disorder; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

[a] Data are presented as number (%) of participants unless otherwise indicated.

Methods

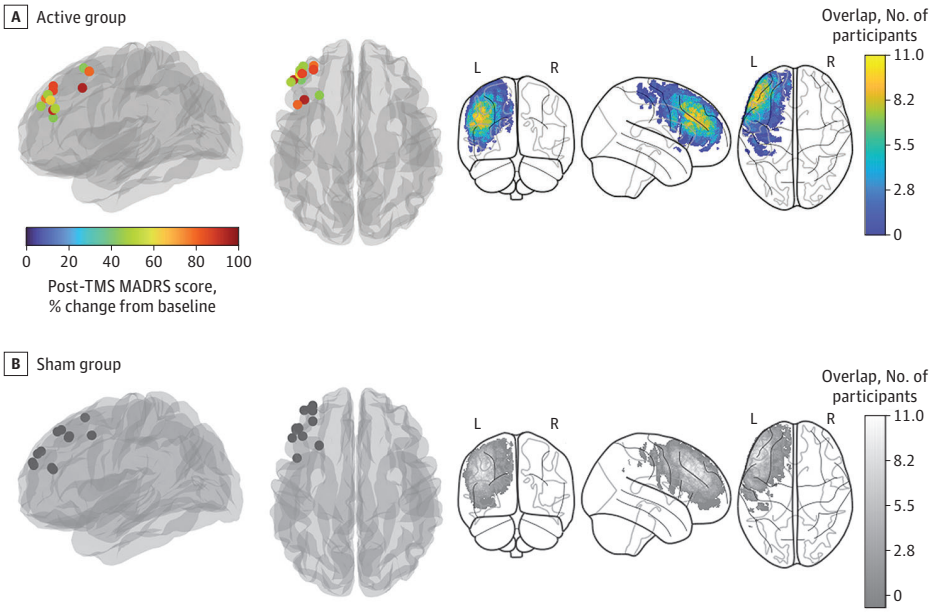
Study Design

This double-blind randomized clinical trial (NCT05228457) using a 1:1 ratio and parallel design was approved by the University of Pennsylvania institutional review board. All participants provided written informed consent. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The trial protocol is given in Supplement 1.

Participants

Participants were recruited from March 2022 through February 2024. Inclusion criteria included a primary diagnosis of BD depressed phase, an MADRS score of 20 or higher,[5] age 22 to 70 years, receipt of 2 or more failed treatments by Antidepressant Treatment History Form criteria,[6] and initiation of a stable mood stabilizer regimen 4 or more weeks prior to aiTBS. Exclusion criteria were a primary psychiatric diagnosis other than BD and rapid cycling of BD with more than 4 episodes per year. Race was ascertained through self-report but was not included in the analysis due to the small numbers of racial and ethnic minority participants and the fact that the groups did not differ in racial composition. Categories included African American, Asian, and White.

Figure 1. Accelerated Intermittent Theta-Burst Stimulation (aiTBS) Target Locations and e-Field Conjunction Maps



Images on the left represent individualized functional magnetic resonance imaging–guided target locations for aiTBS for the active and sham groups. Images on the right represent the overlap in e-field (top 1% of voxels) across the participants in the active and sham groups. Note there were no voxels where all 12 participants overlapped. MADRS indicates Montgomery-Åsberg Depression Rating Scale; TMS, transcranial magnetic stimulation.

Clinical Assessments

The primary outcome was MADRS scores[5] before and 1 day after aiTBS or sham treatment. Assessments were performed at baseline, days 1 to 5 of aiTBS administration, 1 day after aiTBS, and at 4-week follow-up. Secondary clinical outcome measures included repeated MADRS scores at all study visits, 17-item Hamilton Depression Rating Scale score, Beck Depression Inventory score (eMethods 1 and eResults in Supplement 2). Current and previous medication trials were coded by Antidepressant Treatment History Form criteria,[6] and medical diagnoses were determined by *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes.

Protocol

The intervention included 5 days with 10 sessions per day (active vs sham aiTBS) at 1 session per hour with 18 000 pulses per day at 90% resting motor threshold using a MagVenture MagPro X100 system and a double-sided Cool-B65 A/P coil (active and sham sides were labeled *A* or *B*). Sham treatment included a simultaneous electric pulse to mimic aiTBS sensation. Brainsight was used for TMS coil positioning.

Blinding Procedures

Participants were randomized 1:1 to active or sham aiTBS by a statistician (K.L.) using permuted blocks allocation. Clinical assessors (Y.S.) and treatment practitioners (W.M.) were separate individuals for all primary outcome measures. Participants, clinical assessors, and treatment practitioners were blinded (eMethods 2 in Supplement 2).

Imaging

Imaging was performed using Siemens 3T Magnetom Prisma Fit (64-channel head coil) scanners. We used previously reported sequences optimized for Siemens Prisma scanners,[7] including 23 minutes of blood oxygen level–dependent resting-state functional magnetic resonance imaging (rsfMRI) data per session (eMethods 2 in Supplement 2).

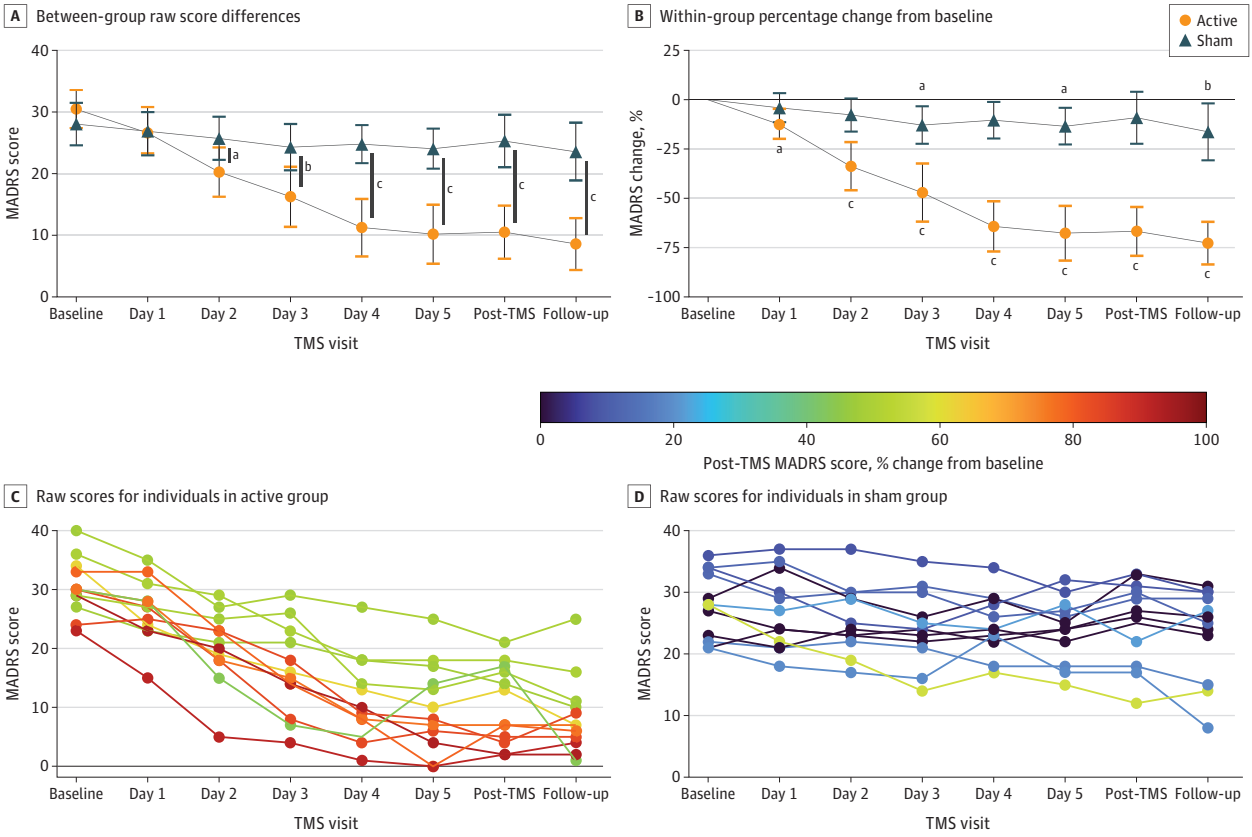
fMRI Analysis for Target Generation

Images were preprocessed according to standard methods[7]; individualized targets at left dlPFC from rsfMRI data were determined using the Cash cluster method[8] (eMethods 2 in Supplement 2). Targeting was further optimized using e-field modeling[9] (eMethods 2 and eFigure 4 in Supplement 2).

Statistical Analysis

The primary outcome was MADRS scores before and 1 day after aiTBS. A linear mixed-effects model (LME) was used to assess effects of time, treatment group, and their interaction, with a random intercept for participants, on MADRS scores before vs 1 day after aiTBS treatment. As a secondary outcome, an LME was used to assess repeated MADRS scores at all study visits. χ^2 Tests compared response (≥50% reduction) and remission (MADRS score ≤10) rates.[10] R, version 4.3.2 (R Foundation for Statistical Computing) was used for analysis. Two-sided $P < .05$ was considered significant (eMethods 2 in Supplement 2).

Figure 2. Clinical Outcomes



Montgomery-Åsberg Depression Rating Scale (MADRS) scores before and after accelerated intermittent theta-burst stimulation in participants with treatment-resistant bipolar depression. Error bars represent 95% CIs. TMS indicates transcranial magnetic stimulation.

[a]$P < .05$.
[b]$P < .01$.
[c]$P < .001$.

Results

Of 34 recruited participants, 8 did not meet inclusion or exclusion criteria and 2 withdrew; 24 participants were randomized to active (n = 12) or sham (n = 12) aiTBS (eFigure 1 in Supplement 2). Of the 24 participants, 12 (50%) were female and 12 (50%) were male; mean (SD) age was 43.3 (16.9) years. A total of 3 (12%) were African American or Black, 3 (12%) were Asian, and 18 (75%) were White. All participants completed all visits. Treatment allocation guesses did not differ across active and sham groups (eMethods 2 in Supplement 2). The **Table** gives demographic characteristics, diagnoses, comorbidities, pharmacotherapy, and prior failed antidepressant trials. Target locations are given in **Figure 1**; eFigure 4 in Supplement 2 gives each participant's e-field.

Primary Outcome

The mean (SD) MADRS score in the active group was 30.4 (4.8) at baseline and 10.5 (6.7) immediately after treatment. In the sham group, the mean (SD) MADRS score was 28.0 (5.4) at baseline and 25.3 (6.7) immediately after treatment. The LME revealed an interaction between treatment group and time ($F_{1,22} = 64.72$; $P < .001$) on MADRS scores (**Figure 2**). There was a significantly greater decrease in MADRS scores in the active group than in the sham group (estimated difference, 17.17; 95% CI, 12.74-21.59; $P < .001$; Cohen *d*, 3.28); in the active group, MADRS scores were significantly lower after treatment than at baseline (estimated difference, -19.92; 95% CI, -23.05 to -16.79; $P < .001$; Cohen *d*, -4.00), but sham group MADRS scores were not (estimated difference, -2.75; 95% CI, -5.88 to 0.38; $P = .08$; Cohen *d*, -0.50). In the active group, MADRS scores were lower than those in the sham group after treatment (estimated difference, -14.75; 95% CI, -19.73 to -9.77; $P < .001$; Cohen *d*, -2.19).

Secondary Outcomes

After 5 days of treatment, 6 participants (50%) in the active aiTBS group experienced remission compared with none in the sham group. The eResults and eFigure 3 in Supplement 2 give response and remission rates, Beck Depression Inventory and 17-item Hamilton Depression Rating Scale results, and adverse events. The eTable in Supplement 2 gives MADRS, Beck Depression Inventory, and 17-item Hamilton Depression Rating Scale results, and eFigure 2 in Supplement 2 graphically displays individual results.

Discussion

This randomized clinical trial, which was, to our knowledge, the first aiTBS trial in BD, found a large antidepressant effect of active aiTBS, an accelerated, high-dose, patterned, rsfMRI-guided iTBS protocol, for treatment-resistant BD in a current depressive episode. After 5 days of treatment, 50% of participants in the active aiTBS group experienced remission compared with none in the sham group. This finding indicated clinical efficacy and a short time to achieve improvement in this difficult-to-treat condition. The effect was seen even though the participant sample had high depression severity and treatment resistance, both associated with poor response.[11,12] The large effect size of aiTBS may be attributable to several factors, including e-field–optimized neurocircuit-based targeting, accelerated time course, and high pulse number.[2,8,9,11,13,14] Intermittent TBS targeting was designed to optimally modulate person-specific neural circuitry connectivity between the dlPFC and subgenual anterior cingulate cortex[8,9,13] and to incorporate e-field modeling, which has been shown in recent work[15] to improve treatment outcomes. Second, the accelerated pace of 10 sessions per day may enhance neuroplasticity; iTBS sessions repeated at short intervals in human participants have been shown to increase excitability and cortical activity in stimulated regions.[14] A third factor is the higher pulse number, shown to have a positive correlation with treatment outcome[11]—90 000 pulses with aiTBS vs 18 000 pulses in standard iTBS protocols. However, the individual components of our aiTBS protocol responsible for improvements in efficacy compared with conventional iTBS remain to be isolated. Future studies should investigate the relative contributions of rsfMRI-guided targeting, total pulse number, and treatment intersession interval. The short duration and high antidepressant efficacy of aiTBS present an opportunity to treat patients in acute settings where a compressed time course is necessary. This provides a new treatment option for people with BD who are often excluded from clinical trials generally and neuromodulation trials specifically.

Strengths and Limitations

Study strengths include the double-blind, sham-controlled design; careful blinding; and medication status of participants (all were receiving mood stabilizers, optional antidepressants, and no antiseizure medication). A limitation is the small sample size; replication in larger samples is required. Nonetheless, the sample size is comparable to those in recent reports of aiTBS for MDD.[2]

Conclusions

In this randomized clinical trial, aiTBS was more effective than sham stimulation for depressive symptom reduction in patients with treatment-resistant BD. Further trials are needed to determine aiTBS durability and compare with other treatments.

ARTICLE INFORMATION

Accepted for Publication: May 1, 2024.

Published Online: July 10, 2024. doi:10.1001/jamapsychiatry.2024.1787

Correction: This article was corrected on July 31, 2024, to update the Funding/Support.

Author Contributions: Dr Sheline had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Sheline, Cash, Balderston.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Sheline, Makhoul, Batzdorf, Nitchie, Lynch, Balderston.
Critical review of the manuscript for important intellectual content: Sheline, Batzdorf, Lynch, Cash, Balderston.
Statistical analysis: Makhoul, Batzdorf, Nitchie, Lynch, Balderston.
Obtained funding: Sheline.
Administrative, technical, or material support: Sheline, Makhoul, Batzdorf, Cash, Balderston.
Supervision: Sheline, Balderston.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was supported by a grant from the Baszucki Brain Research Fund (Dr Sheline).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: Maria Prociuk, BA (Center for Neuromodulation in Depression and Stress, Department of Psychiatry, University of Pennsylvania), assisted with manuscript preparation; Claudia Baldassano, MD (Outpatient Bipolar Clinic, University of Pennsylvania), assisted in referring patients with bipolar disorder; Michael Thase, MD (University of Pennsylvania), served as clinical monitor. These individuals did not receive compensation. We thank all participants for their help in making this project a success.

REFERENCES

1. Forte A, Baldessarini RJ, Tondo L, Vázquez GH, Pompili M, Girardi P. Long-term morbidity in bipolar-I, bipolar-II, and unipolar major depressive disorders. *J Affect Disord*. 2015;178:71-78. doi:10.1016/j.jad.2015.02.011

2. Cole EJ, Phillips AL, Bentzley BS, et al. Stanford neuromodulation therapy (SNT): a double-blind randomized controlled trial. *Am J Psychiatry*. 2022;179(2):132-141. doi:10.1176/appi.ajp.2021.20101429

3. Hsu JH, Downar J, Vila-Rodriguez F, Daskalakis ZJ, Blumberger DM. Impact of prior treatment on remission with intermittent theta burst versus high-frequency repetitive transcranial magnetic stimulation in treatment resistant depression. *Brain Stimul*. 2019;12(6):1553-1555. doi:10.1016/j.brs.2019.07.011

4. McGirr A, Vila-Rodriguez F, Cole J, et al. Efficacy of active vs sham intermittent theta burst transcranial magnetic stimulation for patients with bipolar depression: a randomized clinical trial. *JAMA Netw Open*. 2021;4(3):e210963. doi:10.1001/jamanetworkopen.2021.0963

5. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389. doi:10.1192/bjp.134.4.382

6. Sackeim HA, Aaronson ST, Bunker MT, et al. The assessment of resistance to antidepressant treatment: Rationale for the Antidepressant Treatment History Form: Short Form (ATHF-SF). *J Psychiatr Res*. 2019;113:125-136. doi:10.1016/j.jpsychires.2019.03.021

7. Seok D, Smyk N, Jaskir M, et al. Dimensional connectomics of anxious misery, a human connectome study related to human disease: overview of protocol and data quality. *Neuroimage Clin*. 2020;28:102489. doi:10.1016/j.nicl.2020.102489

8. Cash RFH, Cocchi L, Lv J, Wu Y, Fitzgerald PB, Zalesky A. Personalized connectivity-guided DLPFC-TMS for depression: advancing computational feasibility, precision and reproducibility. *Hum Brain Mapp*. 2021;42(13):4155-4172. doi:10.1002/hbm.25330

9. Balderston NL, Beer JC, Seok D, et al. Proof of concept study to develop a novel connectivity-based electric-field modelling approach for individualized targeting of transcranial magnetic stimulation treatment. *Neuropharmacology*. In Press.

10. Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the

Montgomery-Asberg Depression Rating Scale corresponding to the definition of remission on the Hamilton rating scale for depression. *J Psychiatr Res*. 2004;38(6):577-582. doi:10.1016/j.jpsychires.2004.03.007

11. Fitzgerald PB, Hoy KE, Anderson RJ, Daskalakis ZJ. A study of the pattern of response to rtms treatment in depression. *Depress Anxiety*. 2016;33(8):746-753. doi:10.1002/da.22503

12. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009;34(2):522-534. doi:10.1038/npp.2008.118

13. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biol Psychiatry*. 2012;72(7):595-603. doi:10.1016/j.biopsych.2012.04.028

14. Nettekoven C, Volz LJ, Kutscha M, et al. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. *J Neurosci*. 2014;34(20):6849-6859. doi:10.1523/JNEUROSCI.4993-13.2014

15. Elbau IG, Lynch CJ, Downar J, et al. Functional connectivity mapping for rTMS target selection in depression. *Am J Psychiatry*. 2023;180(3):230-240. doi:10.1176/appi.ajp.20220306