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Title: Connectivity-guided accelerated theta burst stimulation as augmentation for inpatient treatment-resistant depression: a randomized, double-blind, sham-controlled trial

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Abstract

This study examined whether connectivity-guided accelerated intermittent theta-burst stimulation (iTBS) improves depressive symptoms beyond routine multimodal inpatient care in hospitalized patients with treatment-resistant depression (TRD).

In this randomized, double-blind, sham-controlled trial, patients with unipolar TRD received active or sham iTBS. Stimulation targeted an individualized left dorsolateral prefrontal cortex site showing most functional anticorrelation with the subgenual anterior cingulate cortex on resting-state functional MRI. Treatment was delivered as 3 daily sessions over 10 weekdays (30 sessions; 54,000 pulses) as an inpatient augmentation strategy. Primary and secondary outcomes were changes in Montgomery-Åsberg Depression Rating Scale (MADRS) and Beck Depression Inventory-II (BDI-II) scores during the 2-week stimulation phase. Exploratory endpoints included response and remission rates.

Of the 57 randomized patients, 51 completed treatment (active, *n*=27; sham, *n*=24). The cohort exhibited moderate-to-severe treatment resistance (mean Maudsley Staging Method score, 10.9) and high psychiatric comorbidity. Active iTBS was associated with significantly steeper MADRS improvement than sham (−3.54 points/week; 95% CI, −5.53 to −1.55; P_{FDR}=.02), corresponding to model-estimated reductions of 12.06 versus 4.98 points with a large effect size (*d*=−0.89). BDI-II trajectories similarly favored active treatment, though with a smaller effect (group-by-time estimate, −0.23 points/day; 95% CI, −0.41 to −0.05; P_{FDR}=.04; *d*=−0.22). MADRS response rates were higher with active iTBS (42.3% vs 13.0%), while remission rates were numerically but not significantly higher (26.9% vs 12.5%). No serious adverse events occurred.

In conclusion, connectivity-guided iTBS produced significant add-on antidepressant effects during acute inpatient treatment of TRD. Larger multicenter trials are needed to establish durability and optimize implementation.

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Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide and a major contributor to premature mortality and economic burden[1-3]. A substantial proportion of patients fail to achieve adequate symptom relief with first-line pharmacotherapy and psychotherapy, resulting in treatment-resistant depression (TRD), which is associated with prolonged suffering, greater functional impairment, and repeated health-care utilization including repeated hospitalizations compared to treatment-responsive patients[4]. In inpatient psychiatric settings, depressive episodes are often more severe and clinically urgent, making rapid and effective interventions especially important. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a safe and well-tolerated treatment option, and has shown antidepressant efficacy in TRD[5].

Yet, two central issues limit the translation of rTMS into routine inpatient care. First, the prolonged duration of standard 4-to-6-week rTMS protocols poses practical barriers in acute clinical settings, where rapid stabilization is the primary goal. Second, most sham-controlled rTMS evidence has been generated in outpatient populations[6,7]. A comprehensive meta-analysis identified only a small subset of exclusively hospitalized samples and found no superior antidepressant effect within that limited inpatient evidence base[8].In contrast, naturalistic inpatient studies suggest that rTMS may be clinically useful under routine-care inpatient conditions[9-11]. This divergence between controlled trial outcomes and observational clinical data has been widely discussed[12-14] and underscores the need for prospective, sham-controlled studies conducted in naturalistic hospital environments to determine the clinical utility of rTMS as an augmentation strategy for TRD.

To address the challenge of prolonged treatment duration and optimize efficacy for severe TRD, accelerated rTMS (a-rTMS) protocols delivering multiple sessions per day over a condensed timeframe have attracted increasing attention. This approach has gained substantial momentum following the Stanford Neuromodulation Therapy (SNT)[15-17] trials, which demonstrated high rates of rapid clinical remission utilizing a highly compressed protocol of 10 daily sessions over five days. However, translating such an intensive regimen into widely accessible standard public healthcare systems presents major logistical and economic challenges. Protocols requiring approximately 10 hours of daily clinical management are difficult to integrate into routine clinical workflows and, in inpatient settings, substantially limit patients' participation in the broader multimodal therapeutic program. Consequently, there is a need for more pragmatic and balanced a-rTMS protocols that preserve accelerated treatment benefits while remaining compatible with routine inpatient care environments.

The present randomized, double-blind, sham-controlled trial evaluated an accelerated intermittent theta-burst stimulation protocol, utilizing individualized, neuroimaging-informed targeting algorithm[18] based on dorsolateral prefrontal cortex (DLPFC) connectivity, delivered as three daily sessions over 10 weekdays, as an augmentation strategy for hospitalized patients with TRD.

Crucially, the trial was conducted under naturalistic inpatient conditions, permitting typical psychiatric comorbidities and concurrent medication adjustments within broader multimodal care, while the sham-controlled design allowed rTMS-specific effects to be distinguished from symptom improvement related to routine inpatient care. We aimed to determine whether a clinically implementable a-rTMS protocol provides added antidepressant benefit beyond ongoing inpatient treatment.

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Methods

Study design

We conducted a double-blind, randomized, sham-controlled trial. The broader trial protocol was prospectively registered at ClinicalTrials.gov (NCT04832750), and the analytical plan for the current investigation was preregistered on the Open Science Framework (doi:10.17605/OSF.IO/6EMSU) prior to analysis. Procedures complied with the Declaration of Helsinki, were approved by the Medical Ethics Committee of the University of Oldenburg [2020-144], and all participants provided written informed consent.

Participants

Based on an a priori power analysis (Supplementary Methods), we targeted 50 participants and planned to recruit 60. Participants were recruited via clinical referrals and community outreach at the Department of Psychiatry, University of Oldenburg located at the Karl-Jaspers-Klinik, Bad Zwischenahn, Germany, from May 2021 to August 2024. Inclusion criteria were a current moderate-to-severe major depressive episode confirmed using the Structured Clinical Interview for DSM-5; treatment-resistant depression, defined as failure to respond to at least one adequate antidepressant trial during the current episode; and age between 18 and 65 years. To maintain a clinically representative inpatient sample, comorbid psychiatric conditions were permitted except acute suicidality, current substance dependence, psychotic or bipolar disorder. Further exclusion criteria comprised standard neurological, MRI[19] or rTMS[20] safety contraindications.

Randomization

Participants were allocated 1:1 to active or sham rTMS by an independent researcher not involved in treatment, assessments, or patient care. Randomization initially used permuted blocks; after an emerging sex imbalance during late recruitment, sex was added as a stratification factor to improve demographic balance between treatment groups.

Intervention

Before treatment, participants underwent structural and resting-state MRI for individualized target selection following the method developed by Cash et al. [18] (Supplementary Methods). The target was defined as the DLPFC site showing maximal functional anticorrelation with the subgenual anterior cingulate cortex and was used for active and sham stimulation. Stimulation was delivered with an Apollo TMS system and 3D neuronavigation (MAG & More GmbH, Munich, Germany). Participants received accelerated high-dose intermittent theta-burst stimulation (iTBS) at 90% of resting motor threshold, with 1,800 pulses per session, and three daily sessions separated by 50-minute intersession intervals across 10 consecutive weekdays (30 sessions and 54,000 pulses in total). rTMS was administered as an add-on to routine multidisciplinary inpatient care, including pharmacotherapy and psychotherapy. Benzodiazepines and medications lowering seizure threshold were prohibited during stimulation phase[20-22].

Blinding

Participants and clinical staff were blinded to treatment allocation. An active sham coil (pCool/aCool) was used to mimic the acoustic and somatosensory properties of active stimulation, including superficial scalp sensation and facial muscle twitching, without generating a therapeutically effective cortical field. Blinding integrity was assessed using tolerability ratings and treatment guesses at follow-up (Supplementary Methods).

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Clinical outcomes

The primary outcome was change in observer-rated depression severity assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS)[23]. The secondary outcome was change in self-reported depression severity measured with the Beck Depression Inventory-II (BDI-II)[24]. For both measures, the assessment obtained immediately before the first iTBS session served as the treatment baseline (time 0) for longitudinal analyses. MADRS interviews were conducted at baseline, mid-treatment, and post-treatment, at 7-day intervals. To capture high-resolution symptom trajectories, the BDI-II was administered daily before the first iTBS session of each treatment day and again at post-treatment. Both outcomes were reassessed at 6-week follow-up via telephone interview; additional pre-treatment BDI-II assessments were obtained during the inpatient workflow (Supplementary Methods).

Baseline variables were collected prospectively for descriptive and moderator analyses and encompassed demographic factors (age, sex, employment), illness chronicity (total illness duration, duration of the current episode, chronic MDD), treatment-resistance indices (Maudsley Staging Method[25], MSM; number of antidepressant and augmentation trials, and hospitalizations), and psychological and social integration variables, including personality disorder status (SCID-5-PD[26] and medical records), childhood maltreatment (Childhood Trauma Questionnaire[27]), loneliness (UCLA Loneliness Scale[28]), relationship status, and social network size (Social Network Index[29]).

Safety and side effects

Adverse events and common rTMS-related side effects, including headache, nausea, discomfort, and fatigue, were assessed at each study visit.

Statistical analysis

Acute-treatment analyses included all participants who initiated iTBS treatment. No participant discontinued treatment after the first iTBS session. Therefore, the preregistered intention-to-treat sensitivity analysis, planned for at least 5 post-initiation dropouts, was not performed. In confirmatory analysis, *p*-values were adjusted using the Benjamini-Hochberg false discovery rate (FDR) procedure.

Confirmatory analyses

The primary outcome (MADRS) was analyzed using latent growth models (LGMs) across three time points. For the secondary outcome, BDI-II, preregistered LGMs were first estimated but showed inadequate fit for the daily data; BDI-II trajectories were therefore analyzed using random-intercept linear mixed models (LMMs), which are less strict and more parsimonious, offering benefits when working with small samples[30,31]. Models followed the preregistered sequence[32]: linear and non-parametric time functions were compared first, treatment group was then added, prespecified covariates (age, sex, chronic MDD) were examined separately, and current episode duration was tested as preregistered moderator. Final models were selected based on fit, parsimony, and information criteria. Missing data were handled under missing-at-random assumptions using robust maximum likelihood for LGMs. For LMMs, models were fitted using maximum likelihood for model comparison and restricted maximum likelihood for final parameter estimation. Additionally, standardized effect sizes were calculated (Supplementary Methods).

Exploratory analyses

The 6-week follow-up analysis required a deviation from the preregistration because extending the LGM to include the follow-up data yielded poor fit, whereas the preregistered alternative of a simple *t*-test at follow-up was considered inappropriate given baseline severity differences between groups.

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Follow-up trajectories were therefore analyzed using a piecewise LMM with a knot at Week 2, separating the acute treatment and follow-up phases.

Clinical response (≥ 50% symptom reduction) and remission (MADRS < 10[33]; BDI-II < 13[34]) rates were analyzed using Chi-square or Fisher's exact tests, with odds ratios (OR) and respective CIs. Additional non-preregistered baseline-adjusted logistic regression sensitivity analyses were conducted for MADRS outcomes to account for baseline differences. Furthermore, the moderating effects of the predefined demographic, clinical/psychological, and social integration baseline variables were explored.

All statistical procedures were performed using R Statistical Software (v.4.3.1;R Core Team 2023), utilizing the lavaan package[35] for LGMs and lme4[36] for LMMs. Additional methodological details are provided in the Supplementary Methods.

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Results

Demographics

A total of 128 patients were assessed for eligibility, of whom 57 patients were randomized (Figure 1). Fifty-one patients received and completed the intervention (sham: *n* = 24; active: *n* = 27). Six-week follow-up data were available for 44 participants. Demographic characteristics were well-balanced between groups (Table 1). The final sample represented a clinically complex inpatient TRD population with pronounced chronicity and treatment-resistance. Mean total illness duration was 12.5 years with mean current depressive episodes of 4.2 years. Participants had a history of ≥6 failed antidepressant trials on average. Corresponding MSM scores confirmed moderate-to-severe treatment resistance across the cohort (mean sham: 10.5; mean active: 11.3). Eighty-two percent of patients presented with at least one psychiatric comorbidity, and these rates did not differ significantly between groups (Supplementary Table S1).

Treatment-baseline MADRS scores were higher in the active than in the sham group (28.4 vs. 23.1); thus baseline-adjusted analyses are reported as sensitivity analyses below. Concomitant medication classes or medication adjustments did not differ significantly between groups (all $p > .05$; Supplementary Tables S2-S5). All participants had access to the same range of psychotherapeutic and other non-pharmacological inpatient treatment options throughout hospitalization. Individualized target locations are shown in Figure 2.

Individualized stimulation targets are shown for the active stimulation group (orange spheres; *n* = 27) and the sham control group (green spheres; *n* = 24). Targets were localized within the left dorsolateral prefrontal cortex (dlPFC) using individual resting-state functional MRI. Specifically, targets were defined by the maximal negative functional connectivity (anticorrelation) with the subgenual anterior cingulate cortex. To optimize spatial reliability and signal-to-noise ratio, target identification was based on anticorrelated clusters rather than single peak voxels, adhering to the methodology described by Cash et al. (2021)[18]. Details are provided in the supplement.

Primary outcome

Observed MADRS trajectories and their percentage changes across the acute treatment and follow-up phases are illustrated in Figure 3A-B. Across the full cohort, MADRS scores decreased by −4.40 points/week (95% CI, −5.53 to −3.28; p_{FDR}<.001), corresponding to a model-estimated reduction of −8.80 points over the 2-week acute treatment phase (Table 2).

Adding treatment allocation yielded a significant time-by-group interaction. MADRS scores decreased more steeply with active rTMS than with sham (β=−3.54 points/week; 95% CI, −5.53 to −1.55; p_{FDR}=.02), corresponding to a model-estimated between-group difference of −7.08 points over the acute treatment phase and a large effect ($d = -0.89$). Because baseline MADRS scores were higher in the active group, baseline severity was additionally included as a sensitivity covariate; it did not significantly influence symptom change (β=-0.121, p=.24) and the treatment effect remained significant (β=-2.921, p=.006) nor did inclusion improve the model fit.

Subsequent covariate and moderator models did not identify significant influences on symptom trajectories. However, baseline severity was significantly lower in male participants (β =−4.66; 95% CI, −8.10 to −1.21; p=.008) and higher for patients with chronic MDD (β =5.44; 95% CI, 0.04 to 10.85; p=.048). Duration of the current episode was not significantly associated with symptom change (β =-0.14; 95% CI, −2.49 to 2.20; p_{FDR}=.91) and did not significantly moderate the treatment effect (β =2.94; 95% CI, −1.87 to 7.76; p_{FDR}=.31). In the final combined model, active treatment allocation remained the only significant predictor of the longitudinal slope (β =−3.60; 95% CI, −5.60 to −1.60; p<.001; Supplementary Tables S6–S14; Supplementary Figures S1–S2).

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Secondary outcome

Observed daily BDI-II trajectories and percentage changes are shown in Figure 3C–D. Across the full cohort, BDI-II scores decreased by −0.31 points/day (95% CI, −0.40 to −0.21; $p_{FDR} < .001$), corresponding to a model-estimated reduction of −3.05 points over the acute treatment phase.

Adding treatment allocation revealed a significant time-by-group effect: BDI-II scores decreased more steeply with active rTMS than with sham (β = −0.23 points per day; 95% CI, −0.41 to −0.05; p_{FDR} = .04, $d = -0.22$), corresponding to a model-estimated between-group difference of −2.33 points over the 10-day acute treatment phase.

Subsequent covariate models showed that male participants exhibited significantly lower baseline BDI-II severity (β = −7.70; 95% CI, −13.32 to −2.08; p = .008), while neither sex nor age was significantly associated with longitudinal symptom trajectories. However, chronic MDD was associated with a steeper reduction in self-reported symptoms (β = −0.24; 95% CI, −0.42 to −0.06; p = .04). The duration of the current episode was not significantly associated with acute BDI-II change (β = −0.01; 95% CI, −0.30 to 0.28; p_{FDR} = .94) and did not significantly moderate the treatment effect (group-by-duration interaction: β = 0.42; 95% CI, −0.08 to 0.91; p_{FDR} = .31). In the final combined model, both active treatment allocation (β = −0.23; 95% CI, −0.41 to −0.05; p = .01) and chronic MDD (β = −0.24; 95% CI, −0.42 to −0.06; p = .009) remained independent, significant predictors of symptom reduction (Supplementary Tables S15–S24; Supplementary Figure S3).

Exploratory outcomes

Follow-up trajectories

Exploratory piecewise LMMs were used to characterize post-treatment trajectories from Week 2 to the 6-week follow-up (Weeks 2-8). During this phase, MADRS scores did not change significantly in the overall cohort (β = −0.11 points/week; 95% CI, −0.60 to 0.38; p = .66), whereas BDI-II scores continued to decrease modestly (β = −0.09 points/day; 95% CI, −0.13 to −0.04; $p < .001$). Post-treatment trajectories did not differ significantly between active and sham groups for either MADRS (β = 0.39 points/week; 95% CI, −0.29 to 1.07; p = .26; d = 0.19) or BDI-II (β = 0.01 points per day; 95% CI, −0.05 to 0.08; p = .72; d = 0.05; Supplementary Tables S25-S26).

Response and remission rates

Clinical response (≥ 50% symptom reduction) and remission rates (post-treatment score < 10 for MADRS and < 13 for BDI-II) were evaluated as exploratory acute-phase endpoints (Figure 4). The active rTMS group demonstrated a significantly higher MADRS response rate compared to sham (42.3% vs. 13.0%; OR = 4.73; 95% CI, 1.01 to 31.09; p = .03). However, there were no significant between-group differences for MADRS remission (26.9% vs. 12.5%; OR = 2.53; 95% CI, 0.49 to 17.36; p = .29), BDI-II response (14.8% vs. 4.5%; OR = 3.57; 95% CI, 0.32 to 188.07; p = .36), or BDI-II remission (25.9% vs. 22.7%; OR = 1.19; 95% CI, 0.27 to 5.68; p = .80).

Because treatment groups differed in baseline MADRS severity, non-preregistered baseline-adjusted logistic sensitivity analyses were conducted for MADRS outcomes. In these models, active rTMS was associated with higher odds of both MADRS response (OR = 14.45; 95% CI, 2.50 to 166.82; p = .009) and MADRS remission (OR = 9.69; 95% CI, 1.42 to 144.49; p = .04; Supplementary Tables S27-S29).

Exploratory clinical moderators

Exploratory moderator analyses did not identify any additional demographic, psychological, or social-integration variables that significantly moderated the primary MADRS treatment effect. For the secondary outcome (BDI-II), however, the active-treatment advantage was attenuated among

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patients with comorbid personality disorder (β = 0.46; 95% CI, 0.05 to 0.87; *p* = .027) and higher childhood trauma severity (β = 1.73; 95% CI, 0.22 to 3.24; *p* = .025). These effects were exploratory, self-report-specific, and not mirrored in the primary MADRS outcome (Supplementary Tables S30-S47; Supplementary Figures S4–S5).

Safety and Side effects

No serious adverse events occurred during the trial and rTMS-related side effects were comparable across the groups (all *p* > .05; Supplementary Table S48).

Blinding Integrity

Among participants who provided treatment allocation guesses ($n = 38$), guessed assignment was not significantly associated with actual assignment (*p* = .12), and confidence ratings did not differ between correct and incorrect guessers (*p* = .42). Mean session tolerability ratings did not differ between groups and did not predict guessed assignment (all *p* > .05, Supplementary Tables S49-S51; Supplementary Figures S6-S7).

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Discussion

In this randomized, double-blind, sham-controlled trial, individualized connectivity-guided accelerated, high-dose iTBS delivered as three daily sessions over 10 weekdays produced steeper acute symptom reduction than sham stimulation when added to ongoing multimodal inpatient care in hospitalized patients with TRD. During this acute stimulation phase, active iTBS resulted in a model-estimated 12.06-point reduction on the primary clinician-rated MADRS, compared with a 4.98-point reduction in the sham group, corresponding to a large between-group treatment effect. This benefit was paralleled by a significant, though smaller, treatment effect on the secondary self-reported BDI-II over the same period. Exploratory follow-up analyses did not indicate less favorable symptom courses in the active group compared to sham during follow-up.

These findings help address a major limitation of the rTMS evidence base in TRD: sham-controlled data from hospitalized patients remain sparse, and prior meta-analytic work did not identify significant antidepressant effects within the small subset of exclusively inpatient samples[8]. Naturalistic inpatient studies have nevertheless reported clinically meaningful improvement under routine-care conditions[9,11,37] and one large inpatient cohort exhibited shorter hospitalization with twice-daily compared to standard rTMS [10]. The present trial therefore adds randomized sham-controlled evidence to the limited and predominantly naturalistic inpatient literature.

The clinical relevance of this effect should be interpreted in light of the cohort's clinical complexity, reflected in protracted current depressive episodes, high treatment resistance, and high psychiatric comorbidity. The mean MSM score was 10.9 overall, with the active group reaching the severe range, and 82% of participants presented with at least one psychiatric comorbidity. This profile is clinically important as depressive and anxiety symptom severity, treatment resistance, prior treatment failures, chronicity, psychiatric admissions, and functional status have been associated with poorer antidepressant outcomes following rTMS-based treatments[38-41]. Current episode duration was therefore examined as a preregistered moderator but did not modify MADRS or BDI-II treatment trajectories in the present trial. Evidence for the impact of psychiatric comorbidity beyond anxiety remains limited and mixed: broader antidepressant-treatment data indicate poorer outcomes in MDD with psychiatric comorbidity[42], whereas TMS-specific studies suggest that patients with comorbid anxiety, trauma- and stressor-related, personality, or somatic symptom disorders can nevertheless experience meaningful improvement, with inconsistent evidence on whether these comorbidities attenuate antidepressant response[43-47]. Recent a-rTMS studies identified largely overlapping predictor profiles[48-50]. Thus, the observed treatment effect should be interpreted as evidence of added antidepressant benefit in a clinically complex inpatient TRD cohort, not as a remission benchmark for less severely affected samples or more intensive a-rTMS protocols.

Accelerated rTMS protocols address a practical limitation of conventional several-week rTMS courses by condensing treatment into shorter timeframes through multiple daily sessions. Meta-analytic evidence supports rapid symptom reduction across a-rTMS approaches, while optimal implementation in routine clinical settings remains unresolved[6,51,52]. Preclinical evidence linking accelerated iTBS to cell type-specific prefrontal circuit plasticity provides a plausible neurobiological basis for rapid effects, although clinical translation remains to be established[53]. SNT studies exemplify the most intensive end of the accelerated-treatment spectrum, delivering 50 sessions over five days, and have highlighted emergency and inpatient settings as potential applications for highly compressed protocols[16,17]. For routine multimodal inpatient care, however, feasibility depends not only on shortening the treatment course but also on integrating stimulation alongside psychotherapy, other ward-based interventions, medication management, and daily clinical care. The present protocol thus represents a pragmatic middle-ground schedule with three daily iTBS sessions over 10

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weekdays, broadly consistent with sham-controlled outpatient evidence supporting a similar 3-session/day accelerated approach in TRD[54].

While both the primary MADRS and secondary BDI-II trajectories significantly favored active stimulation, the treatment effect was substantially larger for the clinician-rated outcome. Because baseline assessments occurred after patients had entered multimodal care, these trajectories capture only the acute incremental effect of active iTBS over the stimulation window. In this compressed window, scale-specific differences matter: the MADRS was developed to detect treatment-related change, whereas the BDI-II captures broader depressive burden from the patient perspective, with inpatient factor-analytic data showing distinct MADRS and BDI symptom structures[23,24,55,56]. The smaller BDI-II effect also aligns with evidence that clinician-rated and self-reported depression scales are not interchangeable and that self-reported outcomes can yield more conservative treatment estimates[57,58]. Finally, daily BDI-II assessment may additionally have captured short-term symptom variability, contributing to the smaller net effect estimate[59,60].

The exploratory response and remission analyses provide categorical translation of the continuous symptom trajectories. During the acute rTMS window, active stimulation yielded higher MADRS response (42.3% vs 13.0%) and numerically but not statistically higher MADRS remission (26.9% vs 12.5%) than sham. Baseline-adjusted sensitivity analyses supported higher odds of both response and remission, although estimates remained imprecise as reflected by wide confidence intervals. The active-arm rates fall within the broad range reported in a recent meta-regression of accelerated protocols, which found response rates of 19.4% to 90.5% and average response and remission rates of 52.2% and 32.5%, respectively, amid substantial heterogeneity[61]. Direct comparisons, however, are limited by differences in study designs, stimulation protocols, outcome definitions, and inpatient status. By contrast, BDI-II response and remission did not differ significantly between groups. Given the smaller effect size observed for the self-reported outcome and the greater day-to-day variability captured by daily BDI-II assessments, dichotomization based on a single post-treatment threshold may have been less sensitive than the repeated continuous trajectory analyses. Exploratory moderation analyses did not identify moderators of the primary MADRS treatment effect, whereas the attenuated BDI-II treatment effects observed in patients with personality disorder and greater childhood trauma warrant further investigation.

The accelerated schedule was well tolerated, with no serious adverse events observed, comparable side-effect rates across groups, and no evidence from treatment guesses or tolerability ratings that blinding integrity had been compromised.

Several limitations should be considered. First, while continuous longitudinal modeling maximized use of available data, the single-site design and modest sample size limit the precision, particularly for categorical endpoints and moderator analyses. Second, this trial evaluated accelerated iTBS as a pragmatic augmentation within a naturalistic inpatient setting. Although the sham-control isolated the incremental benefit of active stimulation, concurrent medication adjustments or ward therapies were not explicitly modeled; thus, these findings reflect the additive clinical value of accelerated iTBS combined with ongoing routine care, rather than its efficacy under stable-medication conditions. Third, the study tested a bundled accelerated iTBS protocol and cannot determine the independent contribution of sessions per day, pulses per session, total sessions, intersession interval, or individualized connectivity-guided targeting. This is relevant because stimulation parameters may influence outcomes, while the added clinical value of individualized precision targeting over simpler localization strategies remains unresolved[51,61-63]. Lastly, the baseline MADRS imbalance raises the possibility of regression to the mean. However, baseline severity did not predict acute MADRS trajectories, improve model fit, or attenuate the primary treatment effect. Additionally, higher baseline severity is typically associated with poorer clinical outcome[38]. Furthermore, including

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MADRS baseline to response and remission analyses further increased active-group ORs, now also reaching significance of active-group advantage for remission, contradicting a regression artifact. Finally, the secondary BDI-II trajectory also significantly favored the active intervention without any baseline imbalance, further suggesting a true therapeutic effect.

In conclusion, this randomized sham-controlled trial provides evidence that an individualized connectivity-guided accelerated iTBS protocol can produce added antidepressant benefit when integrated into routine multimodal inpatient care for hospitalized patients with TRD. The effect was clearest for clinician-rated depressive symptoms and occurred in a clinically complex cohort characterized by chronicity, high treatment resistance, and substantial psychiatric comorbidity. Larger multicenter trials are needed to establish durability, clarify optimal stimulation and targeting parameters, and guide implementation in routine inpatient psychiatric care.

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Table 1. Baseline demographic and clinical characteristics of participants in the trial

Variable	**Sham rTMS** (*n* = 24)	**Active rTMS** (*n* = 27)
	n (%)	*n* (%)
Gender		
Female	13 (54%)	16 (59%)
Male	11 (46%)	10 (37%)
Diverse	0 (0%)	1 (3.7%)
Employment Status		
Not Employed	13 (54%)	15 (56%)
Employed	11 (46%)	12 (44%)
	Mean (*SD*)	Mean (*SD*)
Age (years)	40 (12)	40 (14)
Education (years)	16 (3)	15 (3)
MADRS Score (Baseline)[a]	23.1 (8.1)	28.4 (7.1)
BDI Score (Baseline) [b]	26.9 (12.1)	28.2 (10.5)
Total duration of illness (years)	12.4 (8.8)	12.7 (8.1)
Duration of current episode (months)	42.5 (61.6)	57.4 (39.2)
Maudsley Staging Method (MSM)	10.5 (2.3)	11.3 (1.9)
Number of antidepressant trials	6.4 (3.3)	7.4 (4.2)
Number of augmentation trials	3.5 (1.5)	4.8 (3.9)
Number of previous hospitalizations	2.5 (2.5)	2.7 (2.5)
Motor Threshold (% of machine output)	51.3 (8.9)	50.8 (7.6)
Treatment intensity (% of machine output)	45.4 (8.0)	45.5 (5.8)
Treatment intensity (% of motor threshold)	88.3 (3.5)	89.1 (2.8)

[a] Baseline assessed after admission and immediately before start of rTMS treatment
[b] Baseline assessed after admission and two days before start of rTMS treatment

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Table 2. Model-Estimated Longitudinal Trajectories and Treatment Effects for Clinician-Rated and Self-Reported Depression Severity

Outcome	Clinical comparison	Model term	Model-Estimated Total Change[a] (95% CI) [*d*[b]]	*P* value	Sham model-derived change[a] (95% CI)	Active model-derived change[a] (95% CI)
Primary outcome: MADRS	Overall acute symptom change (baseline to week 2)	Overall change	-8.81 (-11.05 to -6.56) [*d* = -1.11]	<.0001[c]	—	—
	Between-group difference in acute symptom change (baseline to week 2)	Group effect on change	-7.08 (-11.05 to -3.10) [*d* = -0.89]	< .001[c]	-4.98 (-7.06 to -2.91)	-12.06 (-15.46 to -8.67)
	Association of episode duration with acute symptom change (baseline to week 2)	Episode duration effect on change	-0.28 (-4.97 to 4.41)	.906[c]	—	—
	Moderation of the treatment effect by episode duration (baseline to week 2)	Group × episode duration effect on change	5.89 (-3.75 to 15.52)	.308[c]	—	—
	Between-group difference in follow-up change (week 2 to week 8)	Group effect on follow-up change	-2.31 (-6.39 to 1.76) [*d* = 0.19]	.264[d]	-0.64 (-3.58 to 2.29)	1.67 (-1.16 to 4.49)
Secondary outcome: BDI-II	Overall acute symptom change (baseline to week 2)	Overall change	-3.05 (-3.96 to -2.15) [*d* = -0.29]	<.0001[c]	—	—
	Between-group difference in acute symptom change (baseline to week 2)	Group effect on change	-2.33 (-4.14 to -0.52) [*d* = -0.22]	.023[c]	-1.79 (-3.12 to -0.47	-4.12 (-5.35 to -2.90)
	Association of episode duration with acute symptom change (baseline to week 2)	Episode duration effect on change	1.28 (-1.08 to 3.63)	.941[c]	—	—
	Moderation of the treatment effect by episode duration (baseline to week 2)	Group × episode duration effect on change	0.42 (-0.08 to 0.91)	.135[c]	—	—
	Between-group difference in follow-up change (week 2 to week 8)	Group effect on follow-up change	0.01 (-0.05 to 0.08) [*d* = 0.05]	.720[d]	-3.57 (-5.54 to -1.61)	-3.09 (-4.88 to -1.29)

Abbreviations: BDI-II, Beck Depression Inventory-II; CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale.

[a] Estimates represent the model-derived total change in respective clinical scale points over the entire respective period (acute treatment/ follow-up).

[b] Effect sizes (Cohen d) are reported for overall and group-specific mean changes, but omitted for the main effect of episode duration and the group × duration interaction, as Cohen d is mathematically designed for discrete mean differences and is not equivalently interpretable for continuous predictors (which were additionally mean-centered and log_{10}-transformed) or their interaction terms.

[c] Indicates false discovery rate (FDR)–adjusted P values for pre-registered confirmatory analyses.

[d] Indicates unadjusted P values for exploratory analyses.

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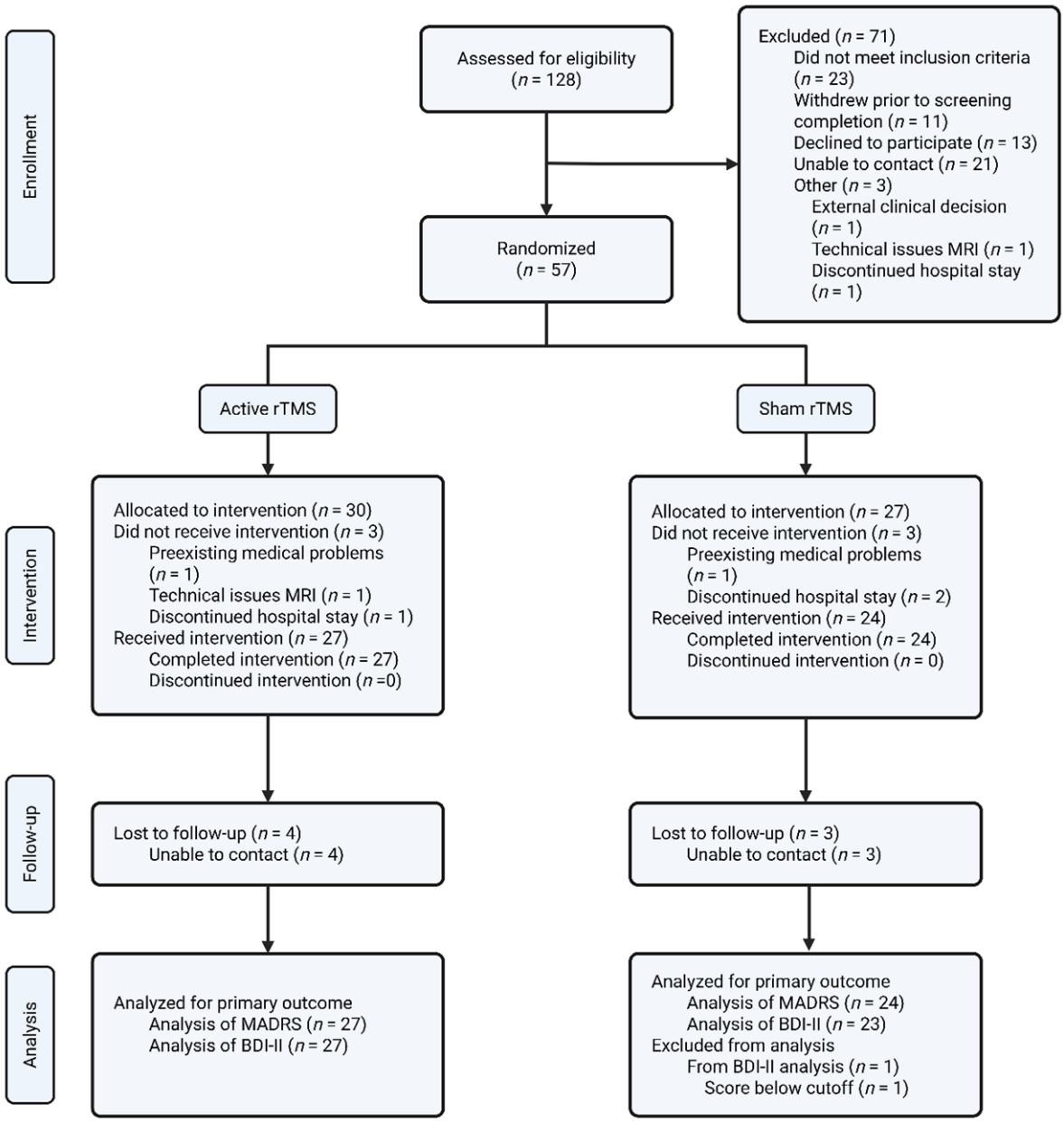

Figure 1. CONSORT diagram.

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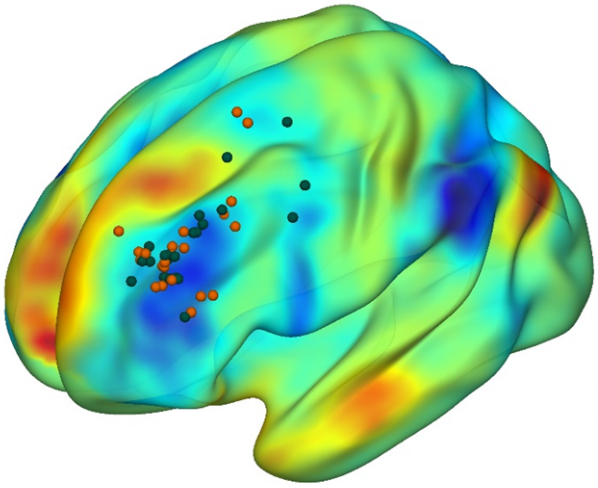

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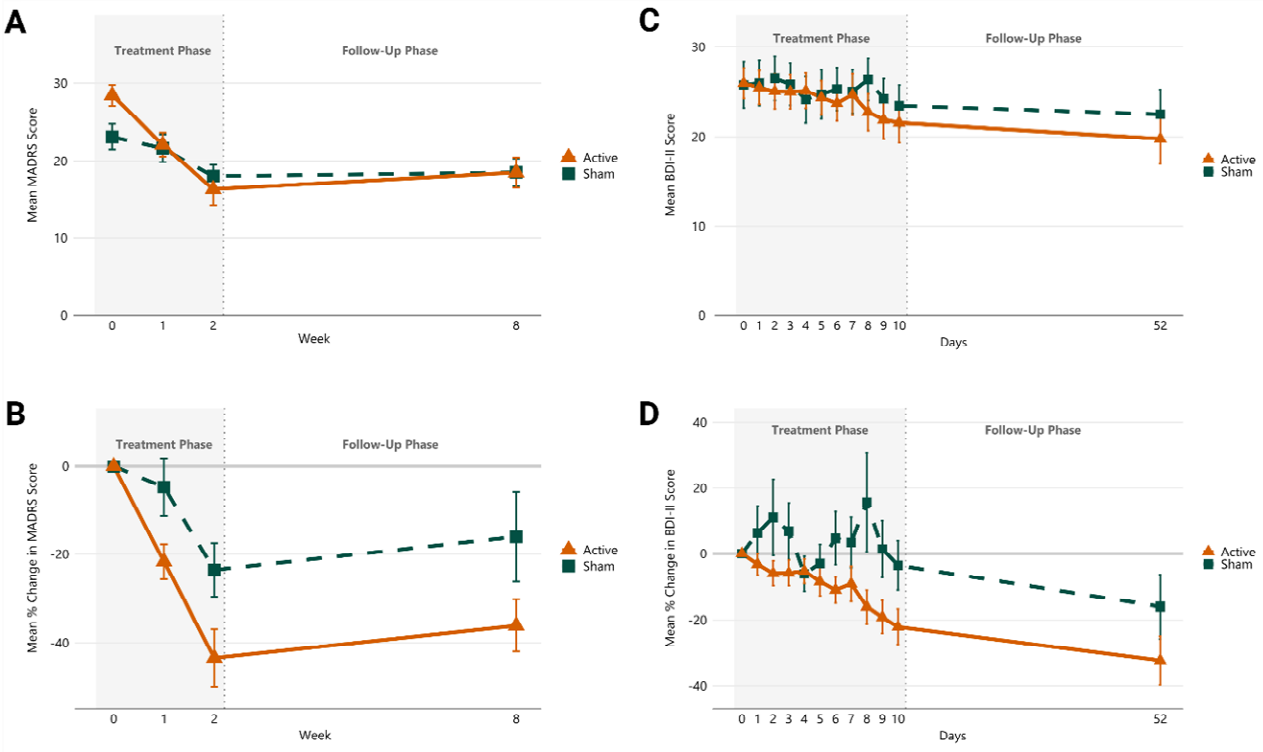

Figure 3. Longitudinal trajectories of clinician-rated and self-reported depression severity across the acute treatment and follow-up phases.

(A) Observed mean Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline (Week 0) through the 6-week follow-up (Week 8). (B) Mean percentage change from baseline in MADRS scores. (C) Observed mean Beck Depression Inventory-II (BDI-II) scores assessed daily during the acute treatment phase (Days 0–10) and at the 6-week follow-up (Day 52). (D) Mean percentage change from baseline in daily BDI-II scores. Across all panels, the gray shaded region denotes the 2-week acute inpatient treatment phase. Solid orange lines with triangles indicate the active stimulation group; dashed green lines with squares indicate the sham control group. Error bars represent standard errors.

Abbreviations: BDI-II, Beck Depression Inventory-II; iTBS, intermittent theta-burst stimulation; MADRS, Montgomery-Åsberg Depression Rating Scale.

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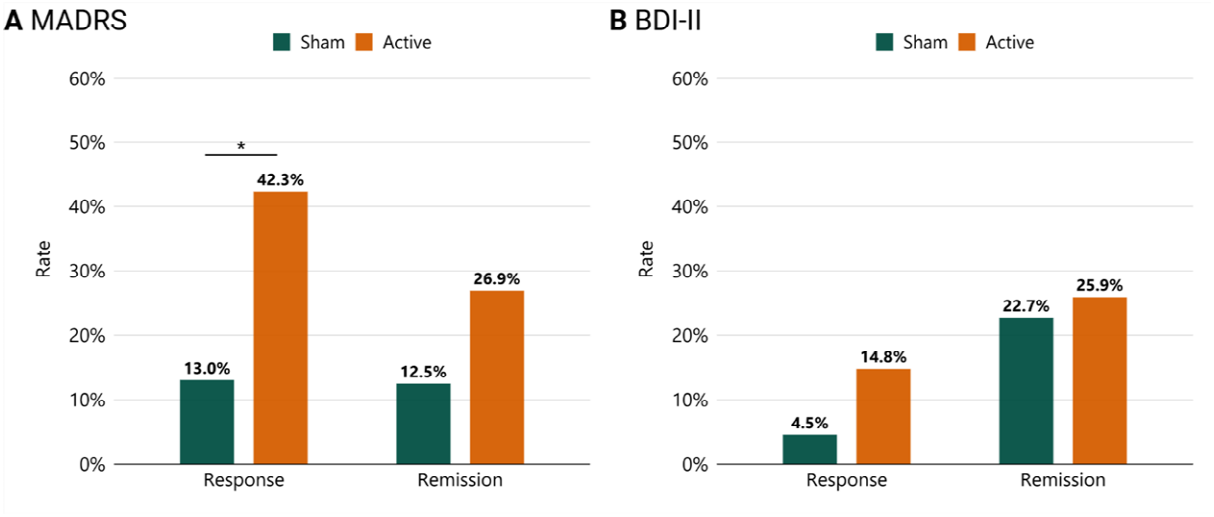

Figure 4. Categorical Rates of Clinical Response and Remission.

(A) Proportions of patients achieving clinical response and remission on the clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS). (B) Proportions of patients achieving clinical response and remission on the self-reported Beck Depression Inventory-II (BDI-II). Orange bars indicate the active stimulation group; dark green bars indicate the sham control group; asterisk indicates statistically significant group difference.

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Table 1. Baseline demographic and clinical characteristics of participants in the trial

Variable	**Sham rTMS** (*n* = 24)	**Active rTMS** (*n* = 27)
	n (%)	*n* (%)
Gender		
Female	13 (54%)	16 (59%)
Male	11 (46%)	10 (37%)
Diverse	0 (0%)	1 (3.7%)
Employment Status		
Not Employed	13 (54%)	15 (56%)
Employed	11 (46%)	12 (44%)
	Mean (*SD*)	Mean (*SD*)
Age (years)	40 (12)	40 (14)
Education (years)	16 (3)	15 (3)
MADRS Score (Baseline)[a]	23.1 (8.1)	28.4 (7.1)
BDI Score (Baseline) [b]	26.9 (12.1)	28.2 (10.5)
Total duration of illness (years)	12.4 (8.8)	12.7 (8.1)
Duration of current episode (months)	42.5 (61.6)	57.4 (39.2)
Maudsley Staging Method (MSM)	10.5 (2.3)	11.3 (1.9)
Number of antidepressant trials	6.4 (3.3)	7.4 (4.2)
Number of augmentation trials	3.5 (1.5)	4.8 (3.9)
Number of previous hospitalizations	2.5 (2.5)	2.7 (2.5)
Motor Threshold (% of machine output)	51.3 (8.9)	50.8 (7.6)
Treatment intensity (% of machine output)	45.4 (8.0)	45.5 (5.8)
Treatment intensity (% of motor threshold)	88.3 (3.5)	89.1 (2.8)

[a] Baseline assessed after admission and immediately before start of rTMS treatment
[b] Baseline assessed after admission and two days before start of rTMS treatment

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Table 2. Model-Estimated Longitudinal Trajectories and Treatment Effects for Clinician-Rated and Self-Reported Depression Severity

Outcome	Clinical comparison	Model term	Model-Estimated Total Change[a] (95% CI) [*d*[b]]	*P* value	Sham model-derived change[a] (95% CI)	Active model-derived change[a] (95% CI)
Primary outcome: MADRS	Overall acute symptom change (baseline to week 2)	Overall change	-8.81 (-11.05 to -6.56) [*d* = -1.11]	<.0001[c]	—	—
	Between-group difference in acute symptom change (baseline to week 2)	Group effect on change	-7.08 (-11.05 to -3.10) [*d* = -0.89]	< .001[c]	-4.98 (-7.06 to -2.91)	-12.06 (-15.46 to -8.67)
	Association of episode duration with acute symptom change (baseline to week 2)	Episode duration effect on change	-0.28 (-4.97 to 4.41)	.906[c]	—	—
	Moderation of the treatment effect by episode duration (baseline to week 2)	Group × episode duration effect on change	5.89 (-3.75 to 15.52)	.308[c]	—	—
	Between-group difference in follow-up change (week 2 to week 8)	Group effect on follow-up change	-2.31 (-6.39 to 1.76) [*d* = 0.19]	.264[d]	-0.64 (-3.58 to 2.29)	1.67 (-1.16 to 4.49)
Secondary outcome: BDI-II	Overall acute symptom change (baseline to week 2)	Overall change	-3.05 (-3.96 to -2.15) [*d* = -0.29]	<.0001[c]	—	—
	Between-group difference in acute symptom change (baseline to week 2)	Group effect on change	-2.33 (-4.14 to -0.52) [*d* = -0.22]	.023[c]	-1.79 (-3.12 to -0.47	-4.12 (-5.35 to -2.90)
	Association of episode duration with acute symptom change (baseline to week 2)	Episode duration effect on change	1.28 (-1.08 to 3.63)	.941[c]	—	—
	Moderation of the treatment effect by episode duration (baseline to week 2)	Group × episode duration effect on change	0.42 (-0.08 to 0.91)	.135[c]	—	—
	Between-group difference in follow-up change (week 2 to week 8)	Group effect on follow-up change	0.01 (-0.05 to 0.08) [*d* = 0.05]	.720[d]	-3.57 (-5.54 to -1.61)	-3.09 (-4.88 to -1.29)

Abbreviations: BDI-II, Beck Depression Inventory-II; CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale.

[a] Estimates represent the model-derived total change in respective clinical scale points over the entire respective period (acute treatment/ follow-up).

[b] Effect sizes (Cohen d) are reported for overall and group-specific mean changes, but omitted for the main effect of episode duration and the group × duration interaction, as Cohen d is mathematically designed for discrete mean differences and is not equivalently interpretable for continuous predictors (which were additionally mean-centered and log_{10}-transformed) or their interaction terms.

[c] Indicates false discovery rate (FDR)–adjusted P values for pre-registered confirmatory analyses.

[d] Indicates unadjusted P values for exploratory analyses.

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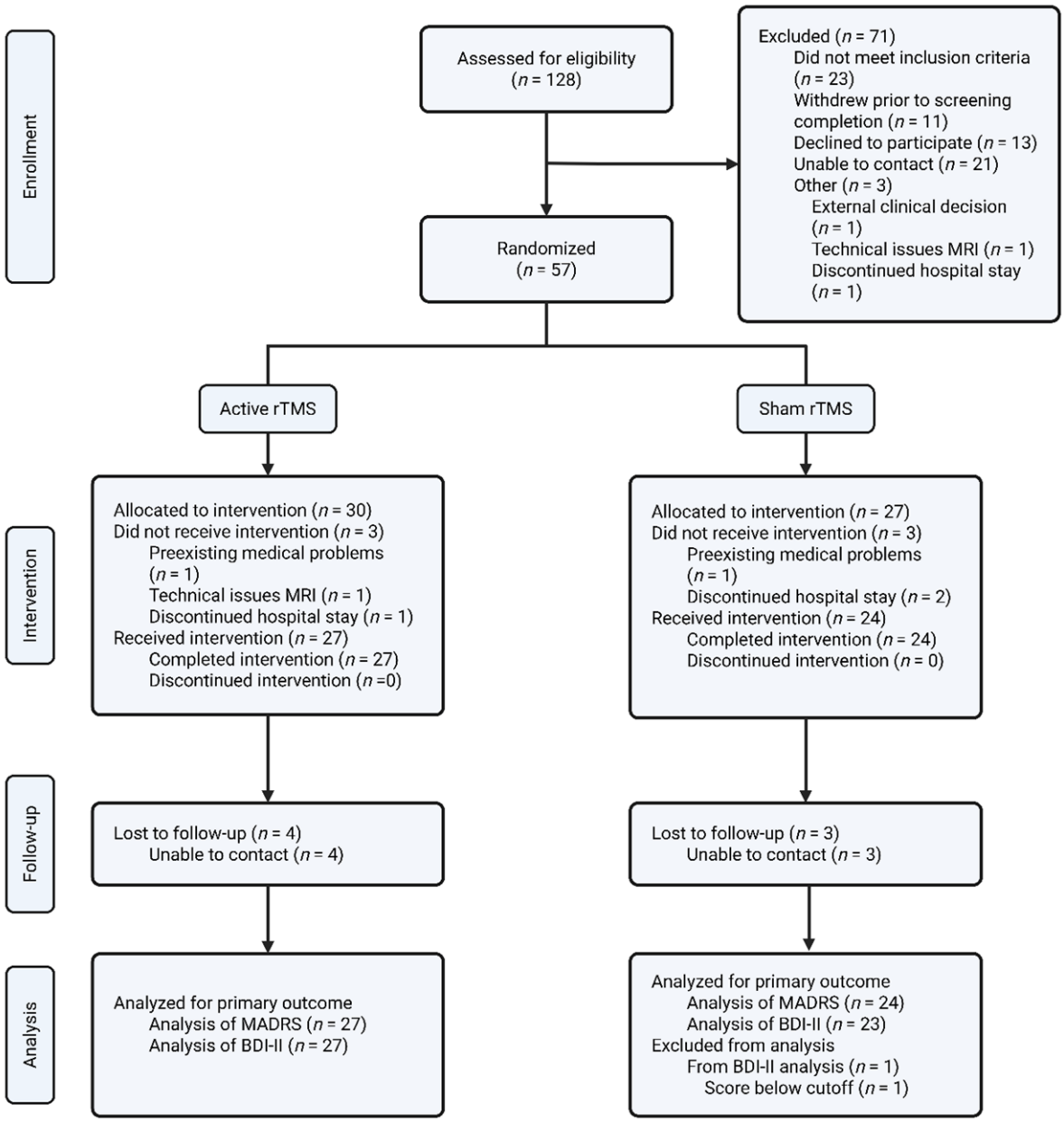

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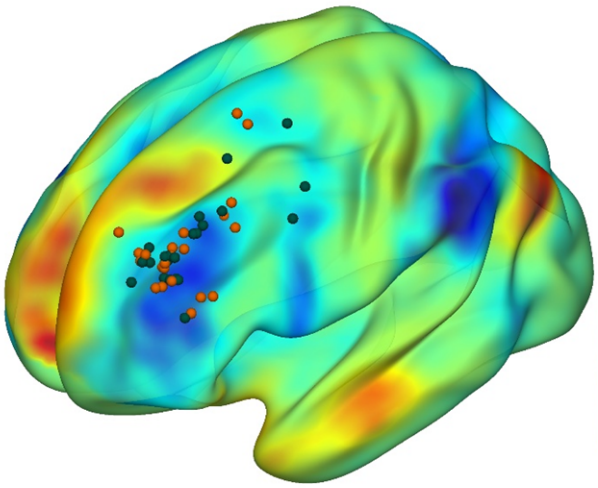

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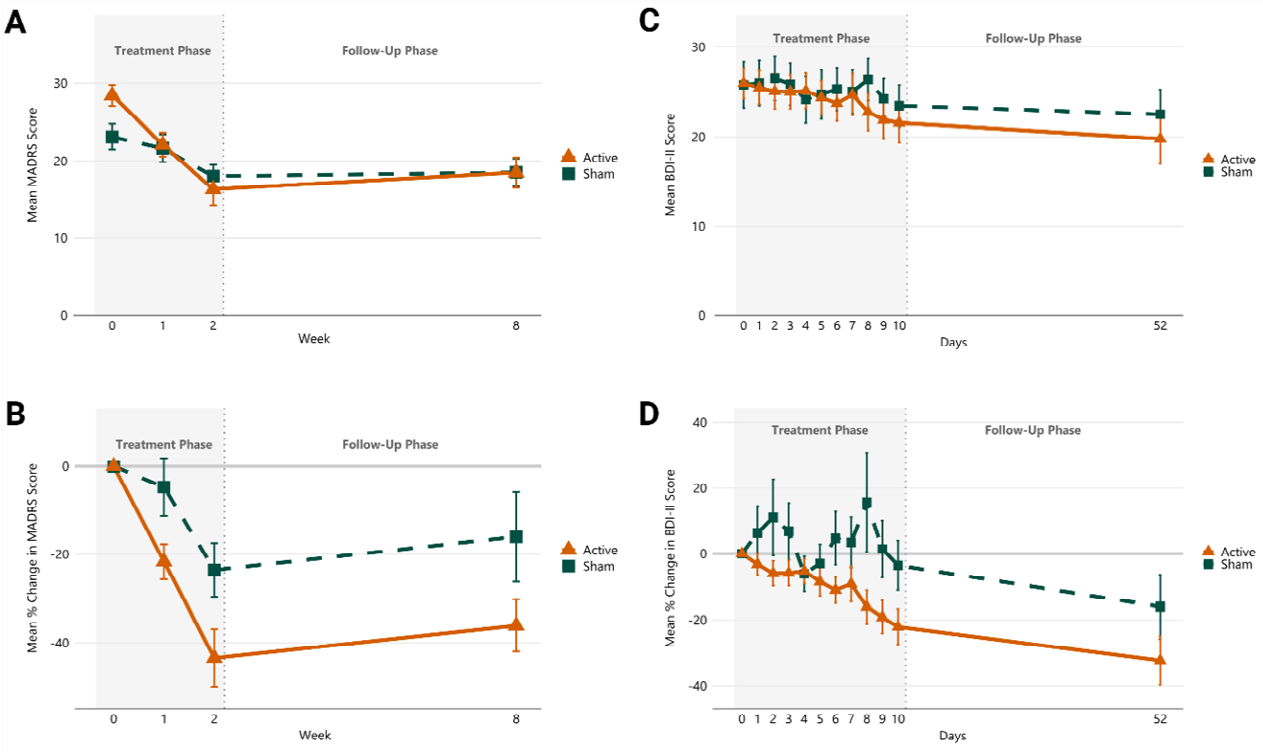

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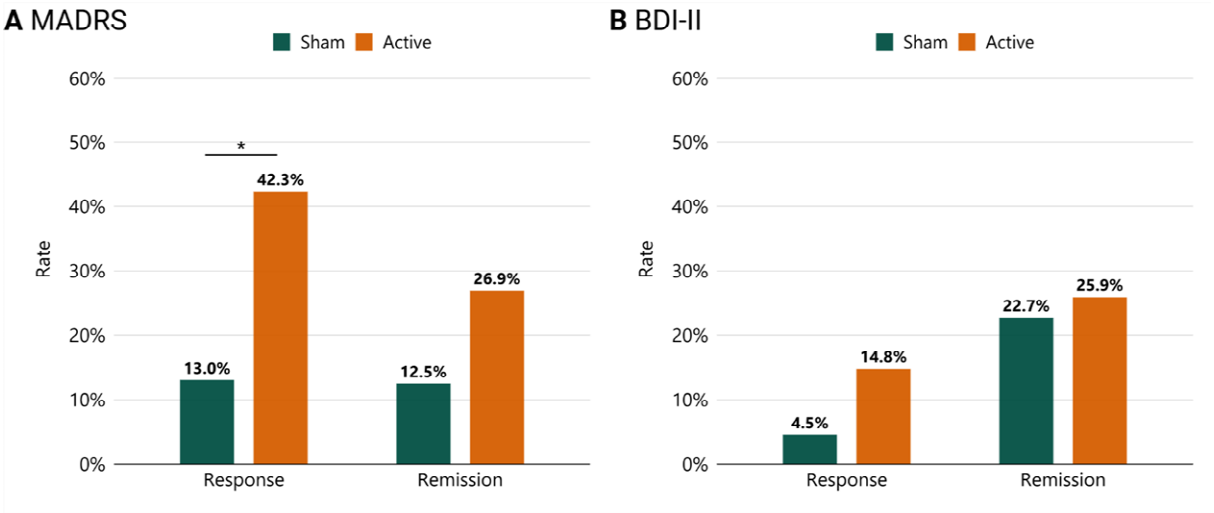

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