



Theta burst stimulation with 80 and 120% resting motor threshold do not differ in their antidepressant efficacy: a retrospective analysis

Mohamed A. Abdelnaim¹ · Andreas Reissmann¹ · Katharina Kerkel¹ · Mohamed Aamer² · Johannes Huebner¹ · Timm B. Poepl^{1,4} · Stefan Schoisswohl^{1,3} · Berthold Langguth¹

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Abstract

Background rTMS, particularly intermittent theta burst stimulation (iTBS), is an effective treatment for treatment-resistant depression; however, the optimal stimulation intensity remains uncertain. Clinical protocols typically use intensities between 80 and 120% of resting motor threshold (RMT), but direct comparative evidence is limited.

Methods We conducted a retrospective analysis of 215 patients with unipolar or bipolar depression who received iTBS at either 120% RMT ($n=108$) or 80% RMT ($n=107$). Depression severity was assessed using the Hamilton Depression Rating Scale (HAMD-21) and Major Depression Inventory (MDI) before and after treatment. Response ($\geq 50\%$ symptom reduction) and remission (HAMD-21 ≤ 7 ; MDI ≤ 14) rates were compared between groups using mixed ANOVAs, with Bonferroni correction for multiple comparisons ($p < .025$). In addition, non-inferiority analyses were performed.

Results Both groups showed large, significant symptom reductions (HAMD-21: $F(1,213)=250.98$, $p < .001$, partial $\eta^2 = 0.541$; MDI: $F(1,213)=247.45$, $p < .001$, partial $\eta^2 = 0.537$). No significant group effects or group $\times$ time interactions emerged for either scale. In a formal non-inferiority analysis (ANCOVA adjusting for baseline severity), 80% RMT was non-inferior to 120% RMT on the HAMD-21 (adjusted difference -0.90 , 95% CI $[-2.61, 0.82]$; margin 2.25 points), a result robust across sensitivity analyses. Response rates ranged from 30.84 to 38.32% and remission rates from 23.36 to 31.48%, with no significant differences between intensity groups. Side effects occurred in 20.56% (80% RMT) versus 27.77% (120% RMT) of patients. Notably, treatment-site pain necessitating intensity reduction occurred exclusively in the 120% RMT group ($n=5$, 4.6%).

Conclusion iTBS at 80% RMT produced antidepressant outcomes non-inferior to iTBS at 120% RMT on the HAMD-21, with supportive MDI findings and better tolerability. These findings suggest a broader intensity range for antidepressant effects of iTBS and support the systematic investigation of lower-intensity protocols.

Keywords Major depressive disorder (MDD) · Repetitive transcranial magnetic stimulation (rTMS) · Intermittent theta burst stimulation (iTBS) · Resting motor threshold (RMT) · Intensity

✉ Mohamed A. Abdelnaim
mohamed.abdelnaim@medbo.de;
drmohamed.abdelnaim@gmail.com

¹ Department of Psychiatry and Psychotherapy, University of Regensburg, Universitaetsstr. 84, 93053 Regensburg, Germany

² University Medical Center, University of Regensburg, Regensburg, Germany

³ Department of Psychology, University of the Bundeswehr Munich, Neubiberg, Germany

⁴ Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, RWTH Aachen University, Aachen, Germany

Introduction

Major depressive disorder (MDD) is among the most prevalent and disabling psychiatric conditions worldwide [1]. According to the World Health Organization (WHO), depression affects an estimated 332 million people, corresponding to about 4% of the population and 5.7% of adults [2], with 12-month prevalence in European populations estimated at around 6–7% [3, 4].

The evidence-based first-line treatments for MDD include pharmacotherapy with antidepressants, as well as psychotherapy, particularly cognitive-behavioural therapy (CBT) [5–7]. Despite this, evidence from large trials and

meta-analyses indicates that only less than half of patients achieve full remission following an initial adequate antidepressant trial [8, 9] and approximately 30% continue to experience treatment-resistant depression (TRD) despite multiple therapeutic interventions [10–12].

Neuromodulation therapies, like repetitive transcranial magnetic stimulation (rTMS), are important treatment options for this population [13]. A considerable body of evidence supports the efficacy of rTMS in MDD, with multiple randomized controlled trials and meta-analyses [14–17] demonstrating superiority over sham stimulation. Reported response rates range from approximately 40–55%, with remission rates of around 30–40% in TRD [18, 19]. Depressive episodes in bipolar disorder share substantial symptom overlap with unipolar depression and are similarly treated with rTMS in clinical practice, though the evidence base is smaller [20–22]. rTMS uses pulsed magnetic fields to induce cortical depolarization, producing lasting modulation of cortical excitability consistent with Hebbian mechanisms of synaptic plasticity [23–25].

Intermittent theta burst stimulation (iTBS) is a special form of TMS, which delivers bursts of three pulses at 50 Hz repeated at 5 Hz in a 2-second on/8-second off pattern, producing 600 pulses in just over three minutes [26]. The THREE-D randomised non-inferiority trial confirmed that iTBS over the left DLPFC was non-inferior to standard 10 Hz rTMS for TRD [27]. Following FDA clearance in 2018 [28], iTBS has emerged as the predominant protocol in many clinical settings due to its time efficiency. iTBS, similar to high-frequency rTMS, is thought to induce LTP-like neuroplastic changes, though the two protocols likely act through partially distinct mechanisms [29–32].

The resting motor threshold (RMT) is defined as the minimum stimulator output required to elicit motor evoked potentials (MEP) of a minimal amplitude (typically ≥ 50 μ V) in a target muscle at rest in approximately 50% of trials [33]. It provides an individualised index of cortical excitability and is commonly used to standardise stimulation intensity in TMS protocols. The international safety guidelines for TBS indicate that stimulation parameters are relatively standardized across research and clinical settings, with intensities typically ranging from 80 to 100% of RMT [34]. In clinical practice, stimulation intensities between 80 and 120% RMT are applied in the treatment of MDD [35], ensuring suprathreshold stimulation while accounting for interindividual variability [36, 37]. While meta-analytic evidence has demonstrated no clear dose-response relationship between stimulation intensity and clinical outcomes in theta burst protocols [38], the optimal intensity for iTBS in MDD remains uncertain.

TMS intensity does not directly determine cortical depolarisation; rather, the induced electric field (E-field) at the

cortical surface depends on both stimulator output and scalp-to-cortex distance [39]. Experimental data suggest that increasing this distance is associated with a proportional increase in the required stimulator output, often approximated at around 2.5–3% per millimetre, although this relationship varies across individuals [40, 41]. Because the dorsolateral prefrontal cortex (DLPFC) is typically located at a greater depth than the motor cortex, and because prefrontal scalp-to-cortex distance varies substantially between individuals, the effective stimulation dose at the DLPFC based on motor threshold calibration may differ considerably from the intended nominal dose [42].

In the TMS research field, the direct empirical evidence specifically comparing intensity levels on TMS antidepressant outcomes is limited. In their controlled study, Padberg et al. [43] observed more pronounced antidepressant effects with an intensity of 100% MT compared to 90% subthreshold stimulation. Similarly, a large pooled analysis of conventional rTMS trials reported higher response rates at 110–120% than at 100% RMT, though without further gain between 110 and 120% [44]. On the other hand, the OPT-TMS study [45] found that effective DLPFC stimulation, accounting for individual scalp-to-cortex distances, ranged from 93 to 156% MT across patients all nominally treated at 120% RMT; remission occurred across a broad intensity range (93–146%), with no significant relationship between intensity and outcome. A retrospective analysis in 149 patients found that neither RMT, %MT, nor treatment intensity significantly predicted clinical outcomes on standardised depression scales [46]. Also, the Stanford accelerated iTBS protocol (SAINT), which reported high remission rates, employed stimulation at approximately 90% RMT with adjustment for cortical depth, suggesting that high efficacy may be achievable below standard nominal intensity thresholds when other parameters are optimised [47].

Regarding tolerability, iTBS shows an excellent safety profile, with very few reported adverse events when delivered within established parameters [34], although higher stimulation intensities are associated with pain at the stimulation site or increased scalp discomfort [37]. In the THREE-D trial, patients receiving iTBS with 120% intensity reported slightly greater discomfort compared to those receiving conventional 10 Hz rTMS, although both protocols were overall well tolerated [27]. From a safety perspective, consensus guidelines suggest that sub-threshold intensities (80% RMT) may offer an optimal risk-benefit profile, as they minimize patient discomfort while maintaining therapeutic efficacy [34].

Both neurobiological concepts and experimental studies question a linear relationship between stimulation parameters and stimulation effects. Evidence suggests an inverse U-shaped intensity–response relationship [48], potentially

related to homeostatic metaplasticity mechanisms [49, 50], with experimental and clinical findings indicating that sub-threshold stimulation may be as effective as, or superior to, higher intensities [48, 51].

In the present study, we specifically aimed to investigate the impact of stimulation intensity on the antidepressant effects of iTBS. To answer this question, we compared treatment results obtained with intensities of 80 and 120% RMT with respect to effectiveness and tolerability. In detail, we hypothesized, that iTBS at 80% RMT has a similar antidepressant efficacy as iTBS at 120% RMT, but a more favorable side effect profile.

Methods and materials

Participants

This retrospective study examined clinical records from 215 inpatients and outpatients diagnosed with unipolar or bipolar depression (ICD-10: F31-F33). Ethical approval was obtained from the University of Regensburg ethics committee (approval number: 22–2958–104).

Treatment protocol

All patients underwent rTMS treatment at the Department of Psychiatry and Psychotherapy at the University of Regensburg, Germany, during the period from April 2019 to November 2025. Treatment was delivered using iTBS protocols that evolved across several phases: Initially, from April 29, 2019, through November 28, 2022, patients received 600 pulses per session (p/s). Subsequently, between April 24, 2023, and November 27, 2023, the pulse count was increased to 1200 p/s, with treatment courses lasting 3, 4, or 6 weeks. From January 8, 2024, to November 11, 2024, the protocol was further intensified to 1800 p/s, delivered over either 1 week (accelerated protocol with 5 daily sessions) or 4 weeks. Finally, from January 10, 2025, through November 3, 2025, the protocol returned to 600 p/s, administered over either 1 or 4 weeks. A critical protocol modification occurred in 2025: whereas all treatments from 2019 to 2024 were delivered at 120% of individual RMT, treatments from 2025 onward were administered at 80% RMT, based on accumulating evidence suggesting that lower stimulation intensities may produce comparable clinical outcomes [52]. Allocation to 80% versus 120% RMT was therefore determined by treatment era rather than by randomisation, and the two intensity groups were not treated concurrently. Patients referred to the TMS unit underwent evaluation by a psychiatrist or clinical psychologist with brain stimulation expertise to assess treatment indications and screen

for contraindications. Patients were diagnosed with unipolar or bipolar depression according to ICD-10 criteria (F31–F33). The term MDD is used throughout to refer to depressive episodes in both diagnostic categories. Patients were referred for rTMS after insufficient response to prior treatment; however, formal staging of treatment resistance was not systematically documented. Bipolar and unipolar depression were treated with the same iTBS protocol. Written informed consent was obtained from all participants for both treatment and data collection. Treatments were administered by trained psychiatric nurses or physician assistants. Stimulation targeted the left DLPFC, localized using the F3 position according to the 10–20 EEG system [53]. All sessions utilized a MagVenture system (MagVenture A/S, Farum, Denmark) with a figure-of-8 coil in default current direction, calibrated to deliver either 80% or 120% RMT depending on the treatment period.

Clinical assessment and outcome measures

RMT was determined by applying single-pulse stimulation over the left motor cortex to identify the minimum intensity capable of eliciting measurable electrical activity in a target finger muscle. This response, termed as MEP, was recorded via electromyography (EMG) [54]. Depressive symptom severity was evaluated using two instruments: the 21-item Hamilton Depression Rating Scale (HAMD-21) [55] and the Major Depression Inventory (MDI) [56], both administered at baseline and treatment completion. For HAMD-21, response was defined as a score reduction of $\geq 50\%$ compared to baseline, while remission was defined as a HAMD-21 score ≤ 7 at the end of TMS treatment [57]; For MDI, response was defined as a score reduction of $\geq 50\%$ compared to baseline, while remission was defined as a MDI score ≤ 14 at the end of TMS treatment [58].

The final analytical sample included only those patients with complete pre- and post-treatment assessments on both measures. All demographic and clinical characteristics of the enclosed patients are provided in Table 1.

Statistical analysis

Group differences (80 vs. 120% RMT) in demographic or clinical characteristics were investigated using independent samples *t*-tests or chi-square tests of independence, as appropriate. Due to the use of two depression scales, level of significance for baseline comparisons of depression severity was adjusted for multiple comparisons using Bonferroni correction ($p=.025$).

For the analysis of group differences in the course of depressive symptoms, we calculated two mixed ANOVAs, one for each outcome variable (HAMD, MDI). Time was

Table 1 Demographic and clinical data of the present sample

	80% RMT (<i>n</i> = 107)	120% RMT (<i>n</i> = 108)	Statistics for group comparisons
General variables			
sex: m/f	59/48	51/57	$\chi^2(1) = 1.349, p = .246; \phi = .08$
age: M (SD)	47.56 (14.83)	45.32 (15.10)	$t(213) = -1.096, p = .274, d = -.15$
age: range	19–85	19–81	*
Depression diagnosis	100	93	$\chi^2(1) = 3.158, p = .076; \phi = .12$
Unipolar: <i>n</i> (%)	(93.5%)	(86.1%)	
Bipolar: <i>n</i> (%)	7 (6.5%)	15 (13.9%)	
HAMD-21 baseline: M (SD)	21.12 (5.51)	19.78 (5.57)	$t(213) = -1.775, p = .077, d = -.24$
Psychiatric medication: yes/no (<i>n</i>)			
Benzodiazepines	18/89	16/92	$\chi^2(1) = .163, p = .687; \phi = .03$
Z-drugs	1/106	3/105	$\chi^2(1) = 1.000, p = .317; \phi = -.07$
SSRI	24/83	42/66	$\chi^2(1) = 6.844, p = .009; \phi = -.18$
SNRI/SSNRI	44/63	47/61	$\chi^2(1) = .127, p = .722; \phi = -.02$
Neuroleptics	55/52	60/48	$\chi^2(1) = .373, p = .542; \phi = -.04$
Mood stabilizer	9/98	19/89	$\chi^2(1) = 4.000, p = .045; \phi = -.14$
TCA	4/103	10/98	$\chi^2(1) = 2.691, p = .101; \phi = -.11$
TeCa	11/96	13/95	$\chi^2(1) = .167, p = .683; \phi = -.03$
MAO inhibitors	0/107	0/108	*
Other antidepressants (e.g. Bupropion)	14/93	18/90	$\chi^2(1) = .545, p = .461; \phi = -.05$
Other psychiatric medication (e.g. methylphenidate)	24/83	19/89	$\chi^2(1) = .786, p = .375; \phi = .06$
No medication	22/85	15/93	$\chi^2(1) = 1.679, p = .195; \phi = .09$
TMS variables			
no. of sessions: M (SD)	19.48 (3.22)	20.56 (5.48)	$t(213) = 1.757, p = .080, d = .24$
no. of pulses/session: M (SD)	600 (na)	900 (460.39)	$t(213) = 6.740, p < .001, d = .92$
RMT (%): M (SD)	44.57 (9.57)	41.22 (9.10)	$t(213) = -2.629, p = .009, d = -.36$
Intensity of treatment ¹ (%): M (SD)	35.78 (7.66)	47.57 (9.20)	$t(213) = 10.211, p < .001, d = 1.93$
Protocol: iTBS/aiTBS	85/22	103/5	$\chi^2(1) = 12.423, p < .001; \phi = .24$

*No statistical comparison possible. Psychiatric medication: In the event that a patient's medication could no longer be traced retrospectively, non-admission was coded. It is possible for a patient to have taken several medications per category. SSRI: selective serotonin reuptake inhibitor. S(S)NRI: selective (serotonin)/-noradrenalin reuptake inhibitor. TCA: tricyclic antidepressants. TeCa: tetracyclic antidepressants.¹ expressed as percentage of maximum stimulator output (%MSO). na: not applicable, since all patients treated with an intensity of 80% RMT received iTBS protocols with 600 pulses (hence SD = 0). aiTBS – accelerated iTBS protocol involving 5 sessions per day for 5 consecutive days.

entered as within-subject factor with two levels, before and after treatment, and group was entered as between-subject factor with two levels, 80% RMT and 120% RMT. In case of a significant time $\times$ group interaction, post-hoc t-tests were performed. Additionally, side effects were quantified as the number of patients reporting a side effect in at least one TMS session and compared between intensity groups using a chi-square test of independence.

Non-inferiority formally was assessed for the HAMD-21 endpoint using an ANCOVA model with final HAMD-21 score as the dependent variable, treatment group as fixed factor, and baseline HAMD-21 score as covariate. The adjusted between-group difference was defined as 80% RMT minus 120% RMT. Since higher HAMD-21 scores indicate greater symptom severity, non-inferiority of 80% RMT relative to 120% RMT was concluded if the upper

Table 2 Mean questionnaire scores (baseline and end of treatment)

	80% RMT (n = 107)	120% RMT (n = 108)	Statistics for group comparisons
HAMD-21			
Scores at baseline: M (SD)	21.12 (5.51)	19.78 (5.57)	$t(213) = -1.775, p = .077, d = -0.24$
Scores at end of treatment: M (SD)	13.14 (6.69)	13.25 (7.48)	$t(213) = 0.116, p = .908, d = 0.02$
Response: yes/no	41/66	34/74	$\chi^2(1) = 1.106, p = .293;$
Response rate	38.32%	31.48%	$\phi = 0.072$
Remission: yes/no	26/81	28/80	$\chi^2(1) = 0.076, p = .783;$
Remission rate	24.29%	25.93%	$\phi = -0.019$
MDI			
Scores at baseline: M (SD)	34.45 (8.49)	33.21 (8.99)	$t(213) = -1.045, p = .297, d = -0.14$
Scores at end of treatment: M (SD)	23.50 (11.38)	20.57 (10.96)	$t(213) = -1.927, p = .055, d = -0.26$
Response: yes/no	33/74	39/69	$\chi^2(1) = 0.670, p = .413;$
Response rate	30.84%	36.11%	$\phi = -0.056$
Remission: yes/no	25/82	34/74	$\chi^2(1) = 1.779, p = .182;$
Remission rate	23.36%	31.48%	$\phi = -0.091$

HAMD-21 hamilton depression scale 21 items, *MDI* major depression inventory

bound of the 95% confidence interval was below the pre-defined non-inferiority margin of 2.25 points. This margin was chosen in accordance with the THREE-D trial [27], which used the same margin to assess non-inferiority of iTBS relative to standard 10-Hz rTMS. In addition, a one-sided non-inferiority p-value was calculated by testing the adjusted group difference against this margin.

To examine the robustness of the non-inferiority findings, sensitivity analyses were conducted, accounting for a priori differences between groups regarding medication (SSRI, mood stabilizer), RMT and pulse number (see Table 1). First, the ANCOVA-based non-inferiority model was repeated after additionally adjusting for medication, number

of received treatment sessions and RMT. Second, because the number of pulses per session varied in the 120% RMT group, the analysis was repeated in the subsample of participants who received 600 pulses per session.

Because no established MDI-specific non-inferiority margin was available, MDI scores were analyzed as a supportive secondary outcome using an analogous ANCOVA model, but without a formal non-inferiority claim.

For effect sizes we used Cohen's d [59], partial η^2 or the phi-coefficient (ϕ). By convention [59], effect sizes are divided in small ($d = 0.2$; partial $\eta^2 = 0.01$; $\phi = 0.1$), medium ($d = 0.5$; partial $\eta^2 = 0.06$; $\phi = 0.3$), and large effects ($d = 0.8$; partial $\eta^2 = 0.14$; $\phi = 0.5$). Mixed ANOVAs and conventional group comparisons were conducted with SPSS version 29.0 (IBM SPSS, Chicago, IL). ANCOVA-based non-inferiority and supportive analyses were conducted in R version 4.3.2 using RStudio version 2023.12.1.

Results

The two intensity groups did not differ significantly at baseline on HAMD-21 scores or MDI scores, confirming adequate baseline comparability (see Table 2). However, groups differed with respect to RMT and the number of pulses per session (see Table 1), which were therefore considered in sensitivity analyses.

Figure 1 provides mean changes in depressive symptoms from pre to post treatment. A mixed ANOVA regarding the HAMD-21 data revealed a significant effect of time ($F_{(1,213)} = 250.98, p < .001$, partial $\eta^2 = 0.541$). There was no significant group effect ($F_{(1,213)} = 0.69, p = .406$, partial $\eta^2 = 0.003$) nor a significant interaction between time and group ($F_{(1,213)} = 2.52, p = .114$, partial $\eta^2 = 0.012$).

Further, a mixed ANOVA regarding the MDI data also revealed a significant effect of time ($F_{(1,213)} = 247.45, p < .001$, partial $\eta^2 = 0.537$). There was no significant group effect ($F_{(1,213)} = 3.34, p = .07$, partial $\eta^2 = 0.015$). There was

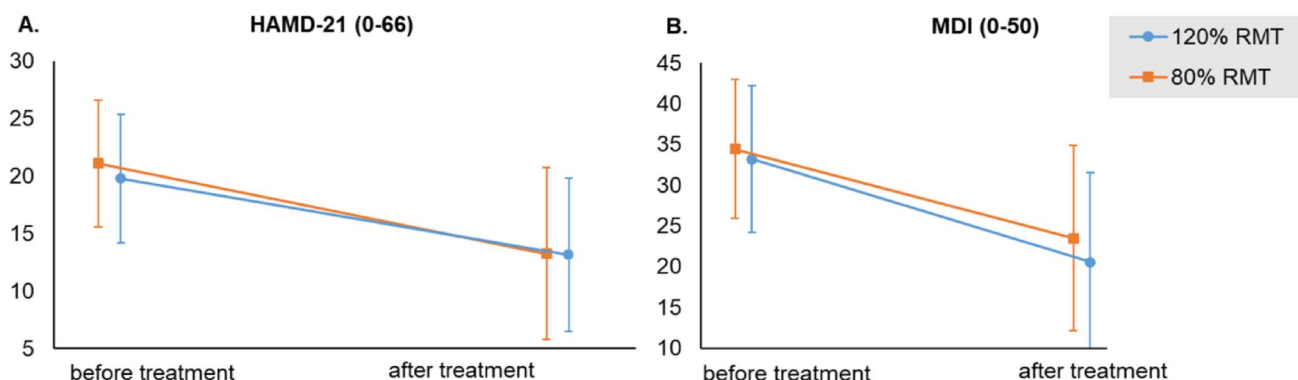


Fig. 1 Mean scores and SDs for the treatment with 80% RMT (orange) or 120% RMT (blue) before and after treatment for the HAMD-21 (A) and the MDI (B). Error bars indicate standard deviation

Table 3 Summary of ANCOVA-based non-inferiority and sensitivity analyses for the HAMD-21 endpoint

HAMD-21 ANCOVA model	Adjusted difference	95% CI	One-sided NI <i>p</i>	Conclusion
Primary model	−0.90	[−2.61, 0.82]	<0.001	NI demonstrated
+ No. of sessions	−0.78	[−2.50, 0.95]	<0.001	NI demonstrated
+ RMT	−0.87	[−2.61, 0.88]	<0.001	NI demonstrated
+ SSRI use and mood stabilizer use	−0.73	[−2.46, 1.01]	<0.001	NI demonstrated
+ RMT, SSRI use, and mood stabilizer use	−0.77	[−2.53, 0.99]	<0.001	NI demonstrated
600-pulse-only subsample	−0.20	[−2.16, 1.76]	0.007	NI demonstrated

NI Non-inferiority; adjusted differences are defined as 80% RMT minus 120% RMT. Higher HAMD-21 scores indicate greater symptom severity. Non-inferiority was concluded if the upper bound of the 95% CI was below the predefined margin of 2.25 points

also no significant interaction between time and group ($F_{(1,213)} = 1.27$, $p = .261$, partial $\eta^2 = 0.006$) (see Table 2 for exact mean scores).

To formally assess non-inferiority, we additionally conducted an ANCOVA-based non-inferiority analysis, modeling final HAMD-21 scores as a function of treatment group while adjusting for baseline HAMD-21 scores. The adjusted mean final HAMD-21 score was 13.6 in the 120% RMT group and 12.7 in the 80% RMT group. The adjusted between-group difference, defined as experimental minus reference group, was −0.90 points, with a 95% CI of [−2.61, 0.82]. The upper bound of the confidence interval was below the predefined non-inferiority margin of 2.25 points. Thus, non-inferiority of 80% RMT relative to 120% RMT was demonstrated for the HAMD-21 endpoint, one-sided $p < .001$. The conventional two-sided test of the adjusted group difference was not significant, $p = .303$.

Across all sensitivity analyses (see Table 3 for details), the adjusted HAMD-21 difference remained below the predefined non-inferiority margin. The upper bounds of the 95% confidence intervals ranged from 0.88 to 1.76 and thus consistently remained below the margin of 2.25 points, supporting the robustness of the non-inferiority finding. Notably, this held when additionally adjusting for the baseline group differences in medication (SSRI, mood-stabiliser), RMT, number of treatment sessions, and pulse number (see Table 3).

Because no established MDI-specific non-inferiority margin was available, MDI scores were analyzed as a supportive secondary outcome using the same ANCOVA framework, but without a formal non-inferiority claim. The

Table 4 Number of patients with side effects

	80% RMT (<i>n</i> = 107)	120% RMT (<i>n</i> = 108)	
(mild) headache in at least one session	18	16	
Treatment site was painful/less intensity used	0	5	
Eye pain	1	0	
Dizziness	4	4	
Fear/anxiety	1	2	
Nausea	1	1	
Fatigue	3	2	
Total*	22 (20.56%)	30 (27.77%)	χ^2 (1) = 1.527, $p = .217$; $\phi = 0.08$

*Number of patients reporting at least one side effect (some patients have reported more than one side effect)

adjusted mean final MDI score was 20.9 in the reference group and 23.2 in the experimental group. The adjusted between-group difference, defined as experimental minus reference group, was 2.28 points, with a 95% CI of [−0.47, 5.03]. The conventional two-sided test of the adjusted MDI group difference was not significant, $p = .104$.

As can be seen from Table 2, response rates for both scales ranged between 30.84 and 38.32%, with no significant differences between the two intensity groups for the HAMD-21 ($p = .293$) or the MDI ($p = .413$). The remission rates for both scales ranged between 23.36 and 31.48%, again with no significant differences between intensity groups for the HAMD-21 ($p = .783$) or the MDI ($p = .182$).

Tolerability

Table 4 provides the number of patients reporting a side effect in at least one of the TMS sessions. In some cases, a patient reported more than one side effect.

While the overall side effect frequency did not differ significantly between groups (χ^2 (1) = 1.527, $p = .217$), treatment-site pain requiring intensity reduction occurred exclusively in the 120% RMT group ($n = 5$, 4.6% of that group), suggesting a potential tolerability advantage for the lower intensity protocol.

Discussion

The primary aim of this study was to investigate whether stimulation intensity—120% versus 80% of the RMT—significantly affects the antidepressant efficacy of iTBS in patients with MDD in routine clinical practice. Our results demonstrate that both groups showed large, highly

significant reductions in depressive symptoms (partial $\eta^2 \approx 0.54$ on both scales), while no significant group effect or group $\times$ time interaction was found on either the HAMD-21 or MDI. Additional analyses demonstrated non-inferiority of 80% RMT intensity as compared to 120% RMT intensity on the HAMD-21, with supportive findings on the MDI. Response and remission rates were statistically comparable across both intensity conditions, and any numerical differences were of negligible effect size. These findings suggest that stimulation at 80% RMT is as effective as 120% RMT for iTBS in this clinical context—a conclusion consistent with, and extending prior work in the literature.

For instance, Chu et al. [52] found through subgroup analyses that subthreshold TBS intensity (approximately 80% RMT) correlated with higher antidepressant response rates, particularly in protocols delivering higher pulse counts (≥ 1800 pulses per session) over shorter treatment periods (≤ 2 weeks). However, these findings were based on indirect comparisons and should be interpreted cautiously, as evidence regarding the relationship between pulse number and antidepressant efficacy remains inconsistent across studies [60]. Another study by Chen et al. [61] provided a direct comparison in a three-arm randomized controlled trial, reporting no significant differences in response rates between 80% RMT bilateral TBS and 120% RMT bilateral TBS. Nevertheless, tolerability differed between groups; four participants (3.9%) in the 120% RMT arm withdrew due to difficulty tolerating the stimulation, while no such withdrawals were reported in the 80% RMT group. Although both intensities were considered safe and well tolerated, the findings suggest that subthreshold stimulation may offer advantages in tolerability. A recent network meta-analysis of 23 randomized controlled trials ($n=960$) conducted meta-regression analyses to examine potential moderators of treatment response, including stimulation intensity (expressed as percentage of motor threshold). No significant associations were identified between the examined moderators and treatment effect size for response [38].

The most mechanistically plausible rationale for the lack of an intensity-dependent result relates to the complex and non-linear relationship between stimulator output and effective cortical E-field at the DLPFC. As the magnetic field strength declines with distance, the difference in effective cortical dose between 80 and 120% nominal RMT is attenuated by the additional scalp-to-cortex distance at the DLPFC relative to the motor cortex where RMT is calibrated [40, 41]. Previous studies demonstrated that patients treated at a nominal 120% RMT experienced effective DLPFC stimulation ranging from 93% to 156% of MT depending on individual anatomy, yet remission was achieved across this entire range without a significant intensity-outcome relationship [45]. This suggests that stimulation intensity may

not be a critical determinant of clinical outcome when both 80 and 120% nominal RMT fall within a therapeutically relevant window, consistent with the comparable outcomes observed in the present study.

Another explanation involves metaplasticity and homeostatic regulation. The Bienenstock-Cooper-Munro (BCM) theory describes how neurons dynamically adjust their plasticity thresholds based on prior activity. In depressed patients, who show left DLPFC hypoactivity and impaired frontal-limbic connectivity [62, 63], the baseline state of reduced LTP-like plasticity [64] may lower the threshold for inducing therapeutic synaptic changes, such that even subthreshold stimulation may be sufficient to produce LTP-like effects [50, 51]. Conversely, excessively high intensity stimulation may activate homeostatic counter-mechanisms that dampen the therapeutic effects. In the present study, we did not observe inferiority of 120% RMT, which might have been predicted by a strong homeostatic ceiling effect. Rather, the comparable efficacy of both intensities is consistent with a more moderate interpretation: that both 80 and 120% RMT fall within a range where homeostatic mechanisms do not yet produce meaningful attenuation, supporting the concept of a broad therapeutic window for iTBS intensity [49, 65]. These mechanistic accounts remain hypothetical, as the present study included only clinical outcomes and no physiological measures of plasticity.

A third relevant consideration involves the stimulation pattern itself. iTBS uses a temporal pattern that mimics natural theta oscillations in the brain. These oscillations play a key role in synaptic plasticity, particularly in hippocampal long-term potentiation [66]. Pharmacological evidence demonstrates that iTBS-induced plasticity is dependent on NMDA receptor activation [29], suggesting that the specific temporal structure of theta-burst patterning may be critical for engaging synaptic plasticity. In the present study, the two intensity groups received the same stimulation patterns at the same cortical target, so that the important factor inducing plasticity (theta-patterned NMDA receptor activation) was constant across conditions and intensity may have been a modulatory rather than a determinative factor in the therapeutically relevant range. While this reasoning is consistent with our findings, it remains inferential in the absence of direct neurophysiological measurements in the present cohort.

It is also worth noting that pulse-number per session varied within the 120% RMT group (600, 1200, and 1800 p/s across successive protocol phases), whereas all patients in the 80% RMT group received a uniform 600 p/s. In this retrospective design, intensity effects therefore cannot be evaluated independently of cumulative dose and treatment schedule. The cumulative total dose across a course of treatment may be a more important efficacy determinant than

per-session intensity, particularly for building the sustained network-level connectivity changes thought to underlie antidepressant response [67]. Future studies should prospectively manipulate intensity while holding pulse number and schedule constant, or vice versa, to isolate each parameter's contribution.

Beyond efficacy considerations, treatment tolerability also warrants examination, as it directly impacts adherence and clinical feasibility in real-world settings. In our sample, although the overall difference in side-effect frequency did not reach significance (20.56% vs. 27.77%, $p = .217$), treatment-site pain necessitating intensity reduction occurred exclusively in the 120% RMT group ($n = 5$). This finding is consistent with the broader literature linking higher TMS intensity to greater scalp discomfort [27, 46] and suggests a real, if small, tolerability advantage for 80% RMT in clinical practice.

The present findings add to a growing body of evidence suggesting that the relationship between TMS intensity and clinical benefit is not as straightforward as a simple dose-response model would predict. The BRIGHtMIND trial showed that iTBS and conventional high-frequency rTMS are similarly effective in TRD, with clinical improvements sustained for 26 weeks despite variations in stimulation parameters. Neuroimaging data from that trial suggest that therapeutic effects may relate to normalising impaired connectivity between the central executive network and the default mode network, rather than to the intensity of local cortical stimulation [68, 69].

This also raises the possibility that personalized intensity selection based on individual MRI-derived E-field modelling [70]—based on each patient's brain anatomy rather than relying on fixed percentages of a motor threshold measured at a completely different cortical site—could ultimately be a more successful approach to optimizing TMS dosing, though such methods remain to be validated in prospective clinical trials. Future studies incorporating such individualized approaches could help to differentiate nominal from effective DLPFC dose, while biomarker-enriched designs using baseline TMS-EEG measures of DLPFC neuroplasticity [71] and resting-state functional connectivity could identify patient subgroups for whom intensity may be a more critical determinant of outcome.

Our findings have direct clinical relevance: it may support consideration of lower starting intensities, such as 80% RMT, with intensity escalation reserved for non-responders. This approach could improve treatment adherence and reduce dropout rates, particularly in patients sensitive to stimulation discomfort. The comparable efficacy at lower intensity also has potential healthcare system benefits, including improved patient acceptance and sustained engagement with neuromodulation therapies.

Limitations

Several limitations of this study must be acknowledged. First, this is a retrospective, non-randomised analysis. Because intensity was changed at one point in time, the two groups also differ in treatment period, pulse number per session, and treatment schedule (including the availability of accelerated protocols in the 120% RMT era). Consequently, the effect of stimulation intensity cannot be fully separated from temporal factors, evolving clinical practices, or concurrent protocol changes. Additionally, formal staging of treatment resistance (e.g., number of adequate antidepressant trials) was not systematically documented, limiting comparability with studies that apply standardised TRD criteria. The 600-pulse sensitivity analysis reduces the pulse-number confound but not the temporal one. This heterogeneity in the sample may have masked intensity-related effects or introduced differential total-dose confounds between groups. Second, the study lacks a sham control condition, preventing estimation of the non-specific treatment component. Third, the absence of MRI-based anatomical data or E-field modelling means that the actual effective DLPFC dose for each patient is unknown, limiting mechanistic inference. Fourth, due to the fact that the sample consists of real-world patients, most of them received rTMS in the context of a multimodal treatment plan with a potential influence of other therapies, such as medication or inpatient psychotherapy. Moreover, as a single-centre study, generalisability to other clinical settings may be limited. Finally, the study lacks follow-up data. Therefore, our observations from this retrospective analysis of naturalistic data should be confirmed by randomized controlled trials before final conclusions are drawn.

Conclusion

Our analysis demonstrates that iTBS at 80% RMT produced antidepressant outcomes statistically non-inferior to 120% RMT on the HAM-D-21, with supportive findings of comparable treatment effects on the MDI, and with similar response and remission rates and a marginally better tolerability profile. These findings, consistent with broader TMS literature, suggest that iTBS may remain therapeutically effective across a wider range of stimulation intensities than current guideline thresholds imply. The results further support the safety and effectiveness of lower-intensity iTBS protocols in routine clinical practice and underscore the need for prospective, controlled intensity-comparison trials, ideally with individual neuroimaging-based dose characterisation.

Author contributions K.K. and S.S. conceptualized the study. T.B.P., K.K., J.H. and A.R. developed the methodology. M.A.A., M.A., K.K.

and A.R. conducted the investigation. K.K. and A.R. performed the formal analysis. M.A.A., B.L., K.K. and A.R. wrote the main manuscript text. B.L. supervised the project. All authors reviewed the manuscript.

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Data availability The clinical data analysed in this study are not publicly available due to patient privacy and data protection regulations (EU General Data Protection Regulation). The data are, however, available from the corresponding author (mohamed.abdelnaim@medbo.de) upon reasonable request and with approval of the Ethics Committee of the University of Regensburg.

Declarations

Conflict of interest The authors declare no competing interests.

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