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Is more better? Comparing 600, 1200 and 1800 pulses/session (p/s) of intermittent theta-burst stimulation (iTBS) for the treatment of depression

Katharina Kerkel [a,*], Stefan Schoisswohl [a,c], Berthold Langguth [a], Mohamed A. Abdelnaim [a], Jost Bernet [b], Martin Schecklmann [a], Andreas Reissmann [a]

[a] Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany
[b] University Medical Center, University of Regensburg, Regensburg, Germany
[c] Institute of Psychology, Universität der Bundeswehr München, Neubiberg, Germany

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ABSTRACT

Introduction: Repetitive Transcranial magnetic stimulation (rTMS) is a non-invasive therapy for treatment-resistant disorders. Intermittent theta-burst stimulation (iTBS) has emerged as a favorite treatment protocol for the treatment of therapy resistant depression, with the tendency to administer an increasing number of pulses/session (p/s).

Methods: We retrospectively analyzed the records of 215 in- and out-patients, suffering from unipolar or bipolar depressive disorder in a German tertiary care hospital between January 2021 and September 2024. All patients received left prefrontal iTBS with either 600 ($n = 68$), 1200 ($n = 67$) or 1800 ($n = 80$) p/s over the course of 15–20 days. Depressive symptoms were assessed with the 21-item Hamilton Depression Rating Scale (HAMD-21) and the Major Depression Inventory (MDI) before and at the end of the respective treatment. Side effects were quantified by the number of patients reporting a side effect in at least one of the rTMS sessions.

Results: In all groups, the HAMD-21 and MDI scores improved significantly. There was no significant difference between the three groups (HAMD-21: $p = .198$, MDI: $p = .281$). Further, this result equally applies to men and women (all p's $> .145$). No serious side effects occurred. Patients who were treated with 600 p/s reported most side effects.

Conclusion: Our retrospective analysis suggests that an increase of p/s from 600 to 1200 or 1800 does not result in more pronounced antidepressant effects.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique for the treatment of various psychiatric and/or neurologic diseases (Lefaucher et al., 2020). rTMS over the left dorsolateral prefrontal cortex (DLPFC) has been FDA approved for the treatment of Major depressive disorder (MDD). A patterned form of rTMS, intermittent theta-burst stimulation (iTBS) that uses 50Hz triplets repeated at 200ms (theta/5Hz)-intervals, has significantly shortened the duration of one treatment session to 3 min (when treating with 600 pulses/session (p/s)) and has shown similar antidepressant effectiveness as compared to a tonic protocol (e.g. 20 Hz), where a session lasts about 25 min (Blumberger et al., 2018).

Even though rTMS is an effective treatment option for patients, who do not sufficiently respond to first-line treatment such as pharmacotherapy or psychotherapy (Brent et al., 2008; March et al., 2004), there is great heterogeneity in terms of effectiveness, with response rates ranging from 29 % to 46 % (Berlim et al., 2014). Among the reasons that may account for this variable outcome could be the variability in stimulation parameters that are used for antidepressant treatments (Guerra et al., 2020; López-Alonso et al., 2014; Polanía et al., 2018). Thus, optimization of the needed number of p/s for the treatment of depressive disorders has to be investigated in ongoing research (Caulfield and Brown, 2022; Lefaucheur et al., 2020; Chung et al., 2015).

Previous literature has investigated the influence of different numbers of p/s during stimulation of the motor cortex with theta-burst protocols. For example, Gamboa et al. (2010) found that iTBS over the motor cortex has excitatory effects when stimulating with 600 p/s, whereby doubling the number of p/s (1200) leads to a paradoxical

* Corresponding author. Department of Psychiatry and Psychotherapy, University of Regensburg, Universitätsstraße 84, 93053, Regensburg, Germany.
E-mail address: katharina.kerkel@medbo.de (K. Kerkel).

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inhibitory effect. The same reverse effect appears with continuous theta-burst stimulation (cTBS), which has normally an inhibitory effect on the motor cortex at 600 p/s, but suddenly shows excitatory effects at 1200 p/s (Gamboa et al., 2010). More recent studies have produced similar paradoxical findings that iTBS protocols and cTBS at different numbers of p/s produce differing facilitatory or inhibitory effects. For example, McCalley et al. (2021) found that 3600 p/s of cTBS produces excitatory whereas 1200 p/s of iTBS produces inhibitory effects when stimulating the motor cortex. In contrast, Tang et al. (2019) showed that effects on motor cortex excitability do not differ between 600 and 1200 p/s. Another study by Nettekoven et al. (2014) showed that three blocks of iTBS (each block consisted of 600 p/s separated by 15 min) over the primary motor cortex resulted in a significant increase of cortical excitability whereas an additive increase in motor evoked potential (MEP) amplitudes was only observed after the third (1800 p/s), but not the second (1200 p/s) block of iTBS.

Regarding the relevance of the needed number of p/s for the antidepressant effect of iTBS over the left DLPFC, the data of previous literature is inconclusive. A subgroup analysis in a recent meta-analysis found a better antidepressant effect with 1800 or more p/s (Chu et al., 2021). This finding is in accordance with the studies by Cole et al. (2020, 2022), who showed that >90 % remission rates can be achieved with 1800 p/s as part of an accelerated one-week iTBS protocol (10 stimulations per day leading to a total of 90.000 pulses). Nevertheless, another study by Richard, 2022 found that, in the context of an accelerated protocol, 1800 p/s of iTBS were not well tolerated and had low antidepressant effects (only 4 out of 27 patients responded to the treatment) (Richard, 2022). In another recent placebo-controlled study by Zhang et al. (2024), in which MDD patients received 600 p/s once or twice a day (duration of treatment was 10 days), no difference was found between the two treatment groups regarding the reduction of the 17-item Hamilton Depression Rating Scale (HAMD-17). Further, the authors found that the treatment groups did not differ from a sham group (Zhang et al., 2024). In another study by Sackeim et al. (2020), the authors showed that female patients as well as patients who were treated with a larger number of p/s (max. 5000 p/s) had superior clinical outcomes, when being treated with a tonic protocol (10Hz).

Overall, there seems to be a tendency in clinical trials towards applying more p/s for antidepressant treatment (Desforges et al., 2022; George et al., 2010). However, the higher the number of p/s in antidepressant treatment with iTBS protocols, the more human, space and energy resources are required for each treatment (Desforges et al., 2022). Accordingly, in the present retrospective analysis, we compared the effectiveness and tolerability of three different iTBS protocols with varying p/s (600, 1200 and 1800 p/s) in the treatment of MDD with iTBS. In addition, based on a study by Sackeim et al. (2020), we further investigated whether there will be an interaction between gender and the number of applied p/s.

2. Methods and materials

This study is a retrospective analysis of 1032 clinical records of in- and outpatients with either a unipolar or bipolar depression. All patients received rTMS at the Bezirksklinikum Regensburg, Germany, between January 2021 and September 2024. All patients were treated with iTBS: From January 1st, 2021 until April 16th, 2023, all patients were treated with 600 p/s (one session lasts approximately 3 min) and between April 17th, 2023 and December 31st, 2023, all patients were treated with 1200 p/s (one session lasts approximately 6 min). Those patients were treated with a treatment duration of either 3, 4 or 6 weeks. From January 1st, 2024 until September 31st, 2024, all patients were treated with 1800 p/s (one session lasts approximately 9 min) with a treatment duration of 4 weeks. Notably, this is a retrospective analysis of records of systematically assessed data from clinical routine practice. There was no sham condition and patients were not randomly assigned to one of the treatments. The analysis was approved by the local ethics committee of the University of Regensburg (22-2958-104).

All in- and out-patients referred to the TMS unit were interviewed by a psychiatrist or a clinical psychologist with experience in brain stimulation to evaluate the indication and possible contraindications of rTMS-treatment. All patients provided written informed consent for rTMS-treatment as well as for data collection and analysis. Treatments were administered by experienced psychiatric nurses or physician assistants. All patients were treated over the left DLPFC, determined via the F3 position of the 10-20-EEG-system (Herwig et al., 2003). Each treatment was performed with a MagVenture system (MagVenture A/S, Farum, Denmark) using a figure-of-8 coil aiming (default current direction) aiming for a target treatment intensity of 120 % resting motor threshold (RMT). The RMT was measured by delivering single pulses at the optimal location over the left motor cortex and was defined as the lowest stimulation intensity needed to produce electrical activity in an intended finger muscle resulting from stimulation, measured by using electromyography (EMG), allowing the recording of the response of MEPs (Barker et al., 1985). Depressive symptoms were assessed with the 21-item HAMD (HAMD-21; Hamilton, 1967) and the Major Depression Inventory (MDI; Bech et al., 2001) before the beginning and after the end of rTMS-treatment. Only patients with complete HAMD-21 and MDI questionnaires before and after treatment were included in the analyses.

In the interest of comparability, only patients with 15–20 treatment sessions were included in the analyses. Additionally, only patients who were treated for the first time with TMS, with a diagnosis of a depressive disorder (F31.3, F31.4; F31.5; F32.x or F33.x according to ICD 10), without an organic depression (F0) or adjustment disorder (F43.2) and who were treated with at least 110% RMT were included ($N = 215$).

All demographic and clinical characteristics of the enclosed patients are provided in Table 1. As it can be seen in the table, there are some significant differences in terms of medication use and TMS variables, which can be attributed to the passage of time and thus, for example, to different treatment practitioners.

2.1. Statistical analysis

Group differences (600 vs. 1200 vs. 1800 p/s) in demographic or clinical characteristics were investigated using chi-square tests of independence or one-way analyses of variance (ANOVAs). Due to the use of two depression questionnaires, the level of significance was adjusted for multiple comparisons by Bonferroni's correction ($p < .025$). For the analysis of group differences in the course of depressive symptoms, we calculated two mixed ANOVAs with time as within factor (2 levels: before and after treatment) and group as between factor (3 levels: 600, 1200 and 1800 p/s) for each of the outcome variables (HAMD-21, MDI). In case of a significant interaction, a post-hoc *t*-test was performed. As an exploratory analysis of a possible gender-related difference of the course of depressive symptoms as a function of the applied number of p/s, two further mixed ANOVAs were calculated with time as a within-factor (2 levels: before and after) and two between-subjects factors (p/s: 3 levels and gender: 2 levels). In order to evaluate potential correlations between changes in depressive symptoms and TMS parameters, the course of scores in both depression questionnaires (calculated as final score – baseline score) across all groups was correlated (Pearson's *r*) with the number of sessions, RMT (%) and the stimulation intensity (%). Side effects were quantified by the number of patients reporting a side effect in at least one of the rTMS sessions. A linear regression was calculated to determine whether treatment intensity (%) had a significant impact on the rate of reported side effects.

For effect sizes we used Cohen's *d* (Cohen, 1988), partial η^2 or the phi-coefficient (φ). By convention (Cohen, 1988), effect sizes are divided in small ($d = .2$; partial $\eta^2 = .01$; $\varphi = .1$), medium ($d = .5$; partial $\eta^2 = .06$; $\varphi = .3$), and large effects ($d = .8$; partial $\eta^2 = .14$; $\varphi = .5$). All statistical analyses were conducted with SPSS version 29.0 (IBM SPSS, Chicago, IL).

Table 1
Demographic and clinical data of the present sample.

	600 p/s (n = 68)	1200 p/s (n = 67)	1800 p/s (n = 80)	Statistics for group comparisons
General variables				
sex: m (%)	29 (42.6%)	25 (37.3%)	35 (43.8%)	χ^2 (2) = .69, p = .709; φ = .06
age: M (SD)	50.90 (17.94)	45.69 (16.33)	46.50 (15.58)	F(2,214) = 1.96, p = .143, partial η^2 = .02
age: range	18–83	20–84	20–84	
Type of Depression (ICD-10)				
Unipolar Depression (F3): *n* (%)	63 (92.6%)	65 (97.0%)	76 (95.0%)	χ^2 (2) = 1.33, p = .514; φ = .08
Comorbid psychiatric Diagnoses (ICD-10): *n* (%)				
Mental and behavioral disorders due to psychoactive substance use (F1)	4 (5.9%)	4 (6.0%)	7 (8.8%)	χ^2 (2) = .62, p = .734; φ = .05
Schizophrenia, schizotypal and delusional disorders (F2)	0	1 (1.5%)	0	χ^2 (2) = 2.22, p = .330; φ = .10
Neurotic, stress-related and somatoform disorders (F4)	19 (27.9%)	17 (25.4%)	19 (23.8%)	χ^2 (2) = .34, p = .843; φ = .04
Behavioral syndromes associated with physiological disturbances and physical factors (F5)	5 (7.4%)	4 (6.0%)	1 (1.3%)	χ^2 (2) = 3.47, p = .177; φ = .13
Disorders of adult personality and behaviour (F6)	6 (8.8%)	4 (6.0%)	3 (3.8%)	χ^2 (2) = 1.67, p = .435; φ = .09
Other psychiatric diagnoses (F8, F9)	1 (1.5%)	3 (4.5%)	5 (6.3%)	χ^2 (2) = 2.11, p = .347; φ = .10
Psychiatric medication: *n* (%)				
Benzodiazepines	9 (13.2%)	11 (16.4%)	12 (15.0%)	χ^2 (2) = .27, p = .873; φ = .04
SSRI/SNRI/SSNRI	40 (58.8%)	49 (73.1%)	58 (72.5%)	χ^2 (2) = 4.10, p = .122; φ = .14
Neuroleptics	37 (54.4%)	27 (40.3%)	54 (67.5%)	χ^2 (2) = 10.91, p = .004; φ = .23
Mood stabilizer	6 (8.8%)	9 (13.4%)	1 (1.3%)	χ^2 (2) = 8.13, p = .017; φ = .20
Other antidepressants (e. g. MAO, TeCa, TCA)	14 (20.6%)	32 (47.8%)	12 (15.0%)	χ^2 (2) = 21.32, p < .001; φ = .32
TMS variables				
No. of sessions: M (SD)	16.44 (1.90)	18.33 (1.51)	18.49 (1.21)	F(2,214) = 37.87, p < .001, partial η^2 = .263
Resting motor threshold (%): M (SD)	44.35 (9.57)	43.49 (10.20)	40.05 (8.00)	F(2,214) = 4.575, p = .011, partial η^2 = .099
Intensity of treatment[1] (%): M (SD)	50.81 (8.60)	50.06 (9.33)	47.40 (8.32)	F(2,214) = 3.16, p = .044, partial η^2 = .080

Notes. p/s: pulses/session. 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. MAO: monoamine oxidase inhibitors. [1] expressed as percentage of maximum stimulator output (%MSO).

3. Results

Neither for the course of the HAMD-21 nor for the course of the MDI there were any significant correlations with the number of treatment sessions, RMT (%) or treatment intensity (all p's > .625).

Fig. 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 ($F_{(1,212)} = 218.80$, $p < .001$, partial $\eta^2 = .508$). There was no significant group effect ($F_{(1,212)} = 2.552$, $p = .080$, partial $\eta^2 = .204$). There was no significant interaction between time and group ($F_{(2,212)} = 1.63$, $p = .198$, partial $\eta^2 = .015$). Further, a mixed ANOVA regarding the MDI data also revealed a significant effect of time ($F_{(1,212)} = 262.36$, $p < .001$, partial $\eta^2 = .553$). There was no significant group effect ($F_{(1,212)} = 2.463$, $p = .088$, partial $\eta^2 = .023$). There was also no significant interaction between time and group ($F_{(2,212)} = 1.28$, $p = .281$, partial $\eta^2 = .012$) (see Table 2 for exact mean scores).

Fig. 2 illustrates mean changes in depressive symptoms over the course of the treatment separated for men and women and treatment group. A mixed ANOVA regarding the HAMD-21 data revealed a significant effect of time ($F_{(1,209)} = 203.14$, $p < .001$, partial $\eta^2 = .493$). There were no significant group effects (p/s: $F_{(2,209)} = 2.751$, $p = .066$, partial $\eta^2 = .026$; gender: $F_{(1,\ 209)} = .020$, $p = .888$, partial $\eta^2 < .001$). There was no significant interaction between time and p/s ($F_{(2,209)} = 1.59$, $p = .207$, partial $\eta^2 = .015$), nor between time and gender ($F_{(2,209)} = 2.14$, $p = .145$, partial $\eta^2 = .010$). There was also no three-way interaction ($F_{(2,209)} = .02$, $p = .978$, partial $\eta^2 = .001$). Regarding the MDI data, a significant effect of time could be found ($F_{(1,209)} = 251.43$, $p < .001$, partial $\eta^2 = .546$). There were no significant group effects (p/s: $F_{(2,209)} = 3.003$, $p = .052$, partial $\eta^2 = .028$; gender: $F_{(1,\ 209)} = .007$, $p = .935$, partial $\eta^2 < .001$). There was no significant interaction between time and p/s ($F_{(2,209)} = 1.11$, $p = .332$, partial $\eta^2 = .010$), nor between time and gender ($F_{(2,209)} = .29$, $p < .592$, partial $\eta^2 = .001$). Also, no significant three-way interaction was found ($F_{(2,209)} = 1.05$, $p = .353$, partial $\eta^2 = .010$).

4. Tolerability

The intensity of treatment was significantly correlated with the side effect rate ($F_{(1,214)} = 4.576$, $p = .034$). The R^2 for the overall model was .021 (adjusted $R^2 = .016$), indicative for a low goodness-of-fit according to Cohen (1988). Table 3 provides the number of patients reporting a side effect in at least one of the rTMS sessions. In some cases, a patient reported more than one side effect. Results show a significant association between p/s and side effects ($\chi^2(1) = 14.52$, $p < .001$, φ = .26), with the treatment group of 600 p/s demonstrating the most side effects.

5. Discussion

The aim of the present retrospective analysis was to investigate the effectiveness and tolerability of rTMS-treatment with left prefrontal iTBS using different p/s (600 vs. 1200 vs. 1800) for patients suffering from unipolar or bipolar depressive disorder. In our analysis, we found significantly reduced scores in the used questionnaires (HAMD-21, MDI) after rTMS-treatment, independently from the number of administered p/s. Neither of the analyzed TMS variables (number of sessions, RMT and treatment intensity) showed a significant correlation with the course of the depressive symptoms.

A possible reason for the lack of superior clinical outcome when treating with more p/s may be that iTBS exert its antidepressant effect not through direct cortical activation mechanism but may result from activity changes in brain regions engaged in processing negative emotions (Chou et al., 2023). In a randomized, double-blind, sham controlled and fMRI-based study, Chou et al. (2023) showed that clinical symptoms improved significantly when being treated with bilateral stimulation (600 p/s of continuous theta-burst stimulation followed by 600 p/s of iTBS), which leaves the question open of whether simply doubling or tripling the number of p/s when treating only the left DLPFC is necessary to achieve the same antidepressant effect. Our results are in accordance with a study by Zhang et al. (2024), who treated their patients for 10 days and couldn't find a significant difference in terms of

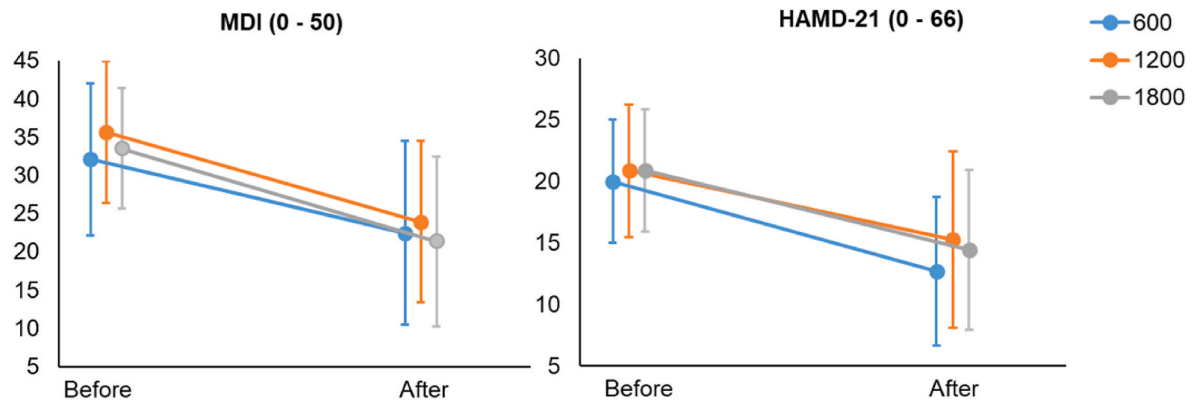

Fig. 1. Mean scores and SDs for the treatment with 600 (blue), 1200 (orange) and 1800 (grey) p/s (pulses/session) before and after treatment for (**A.**) Hamilton Depression Rating Scale and (**B.**) Major Depression Inventory. Error bars indicate standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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

	600 p/s (n = 68)	1200 p/s (n = 67)	1800 p/s (n = 80)	Statistics for group comparisons
HAMD-21				
Scores at baseline: M (SD)	19.98 (5.06)	20.87 (5.41)	20.65 (4.97)	$F_{(2,214)} = .56$, $p = .571$, partial $\eta^2 = .033$
Scores at end of treatment: M (SD)	12.55 (6.00)	15.42 (7.11)	14.27 (6.27)	$F_{(2,214)} = 3.37$, $p = .036$, partial $\eta^2 = .031$
MDI				
Scores at baseline: M (SD)	31.89 (9.86)	35.68 (7.94)	33.10 (9.36)	$F_{(2,214)} = 3.04$, $p = .050$, partial $\eta^2 = .079$
Scores at end of treatment: M (SD)	22.24 (11.97)	24.13 (11.02)	20.85 (10.45)	$F_{(2,214)} = 1.59$, $p = .206$, partial $\eta^2 = .015$

Notes. p/s: pulses/session. HAMD-21: Hamilton Depression Scale 21 items. MDI: Major Depression Inventory.

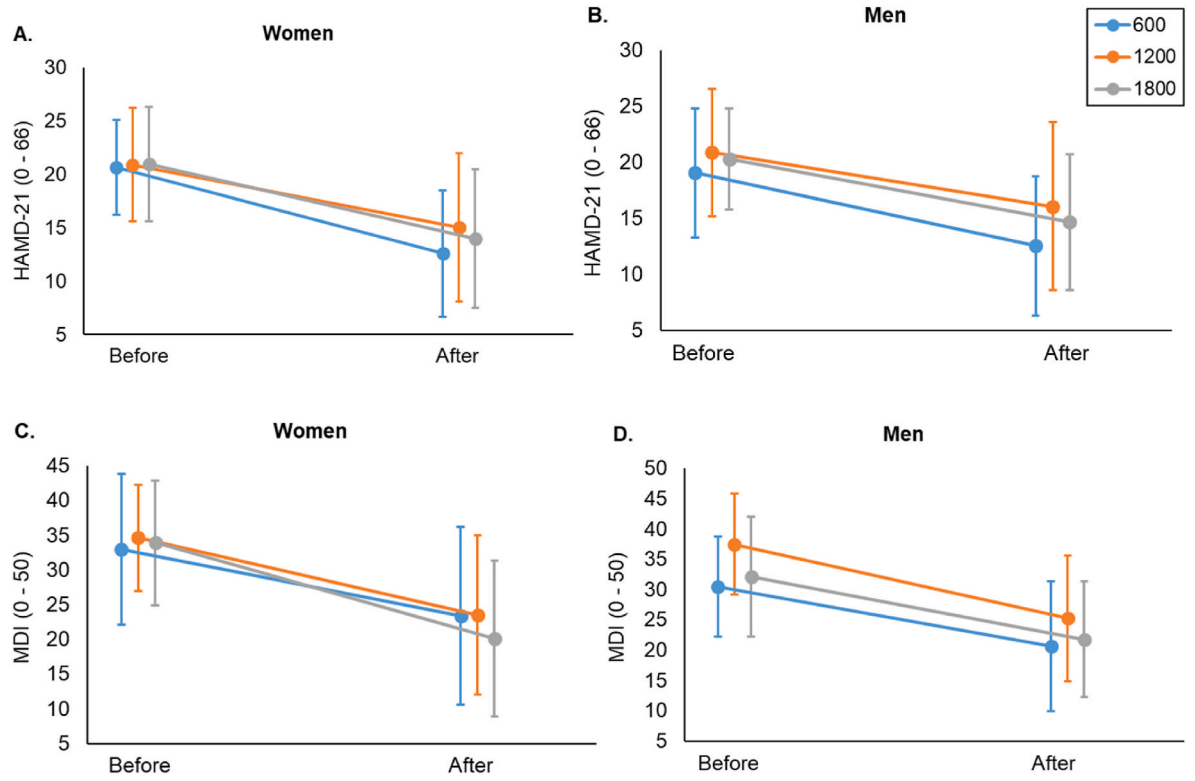

Fig. 2. Mean scores and SDs for the treatment with 600 (blue), 1200 (orange) and 1800 (grey) p/s (pulses/session) before and after treatment for the Hamilton Depression Rating Scale (**A., B.**) and the Major Depression Inventory (**C., D.**), separately shown for women and men. Error bars indicate standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Number of patients with side effects.

Side effect: *n* (%)	600 p/s (n = 68)	1200 p/s (n = 67)	1800 p/s (n = 80)
(mild) headache in at least one session	13 (19.1%)	10 (14.9%)	9 (11.3%)
treatment site was painful/less intensity used	13 (19.1%)	10 (14.9%)	1 (1.3%)
dizziness/balance disturbances	3 (4.4%)	2 (3.0%)	1 (1.3%)
fatigue	1 (1.5%)	1 (1.5%)	–
nausea	2 (2.9%)	–	1 (1.3%)
pulling in the head	1 (1.5%)	–	–
high blood pressure	1 (1.5%)	–	–
numbness in the trigeminal nerve	1 (1.5%)	–	–
toothache	–	1 (1.5%)	–
tension	–	1 (1.5%)	–
migraine	–	1 (1.5%)	–
fear/anxiety	–	–	1 (1.3%)
Total: *n* (%)	26 (38.2%)	10 (14.9%)	12 (15.0%)

Note. p/s: pulses/session. Some patients have reported more than one side effect.

changes in the HAMD-17 between once or twice daily iTBS stimulations with 600 p/s. In contrast, in a study by Sackeim et al. (2020), the authors found that patients who were treated with significantly more pulses (max. 5000 p/s) had superior clinical outcomes. These results are limited for comparison as our patients got treated with iTBS whereas Sackeim et al. (2020) compared different numbers of p/s when treating with tonic stimulation protocols (e.g. 10Hz protocols). Beyond that, Sackeim et al. (2020) administered up to 5000 p/s, whereas our analysis is limited to a maximum of 1800 p/s.

In a study by Nettekoven et al. (2014), who investigated the dose-dependent effects of iTBS on the motor system, the authors they observed a significant increase after three blocks of 600 p/s of iTBS. The dose-dependent effects were more pronounced when evoking MEPs with near-threshold intensities (90–110% RMT) compared to higher intensities (120–150% RMT). While no significant differences were observed in average, tailoring the number of applied p/s to individual patient characteristics, such as the RMT, might improve antidepressant treatment outcome. Thus, future studies treating depressive disorders should consider to investigate a potential interaction between the number of used p/s and stimulation intensity, as another study, by Chen et al. (2021) revealed in a large multicenter study that there is no significant difference between 80 % RMT and 120 % RMT when treating bilaterally with an accelerated protocol. Future studies should investigate weather more p/s automatically lead to superior clinical outcomes when treating only the left DLPFC.

In contrast to a study by Richard, 2022, who found that iTBS treatment with 1800 p/s was not well-tolerated, and somewhat counterintuitive we observed that treatment with 600 p/s was associated with a higher rate of reported side effects compared to treatment with 1200 and 1800 p/s. One potential explanation may be, that patients who were treated with 1800 p/s had the lowest resting motor threshold and correspondingly also the lowest treatment intensity. In Regensburg, treatment with iTBS was introduced in 2021, which means that potentially relevant clinician related biases cannot be ruled out, because they had been unexperienced with this kind of treatment at this point. Even if the staff was well trained and procedures were standardized, an increasing routine with treatment procedures over time might have played an important role. Thus, this might have resulted in a tendency towards lower RMT and stimulation intensities over time.

Furthermore, in an analysis by Sackeim et al. (2020), female patients had superior clinical outcomes. A reason for the discrepancy with our results may be the difference in settings, as our data was collected from everyday clinical practice and analyses were done retrospectively. Further, in our real-world data all in- and outpatients have presumably more comorbidities than e.g., in randomized controlled trials (RCTs) and it has been shown that comorbidities such as from the F4-category (ICD-10) can make rTMS-treatment less effective (Hu et al., 2021).

Limitations: Our results have to be interpreted cautiously, as they come from a retrospective analysis lacking randomized treatment assignment and a sham control group. Further, the study lacks from follow-up data. Chou et al. (2020) found in their study that the number of responders to theta-burst treatment increase even after 4 and after 20 weeks of follow-up periods. Thus, follow-up visits should also be carried out in everyday clinical practice. Further, we didn't measure the refractoriness of the three different groups. Future studies should systematically test for refractoriness, e.g. with the Maudsley staging method (= multidimensional model developed to define and stage treatment-resistance in depression disorders (Fekadu et al., 2009)), as there might have been a significant difference regarding an important predictor for response to rTMS-treatment. Even if treatment was performed according to a standard operating procedure, we cannot exclude slight variations in rTMS applications and side effects reporting over time due to different practitioners. Thus, it cannot be ruled out that time effects may have influenced the results. Here, we included patients with bipolar depression. Even though we didn't include many patients and they didn't have an impact on the overall outcome, it may have led to biased results as a recent meta-analysis by Hsu et al. (2024) showed that bipolar depression is characterized by more diffuse disruptions in cortico-striatal-limbi-subcortical connectivity leading to a possible need of disorder-specific TMS protocols (e.g. broader or deeper stimulation). Further, we cannot exclude a selection bias, as we only selected those patients for the analysis who had at least 15 but no more than 20 treatment days. Finally, 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.

Conclusions: The present retrospective analysis of a large cohort suggests that antidepressant effects of iTBS when treating the left DLPFC are independent of the number of applied p/s. This is highly relevant for everyday clinical practice as a short treatment duration is both convenient for the patient and cost-relevant for the treatment provider. Therefore, future studies should confirm our results by implementing controlled trials.

CRediT authorship contribution statement

Katharina Kerkel: Writing – original draft, Visualization, Investigation, Formal analysis. **Stefan Schoisswohl:** Writing – review & editing, Supervision. **Berthold Langguth:** Writing – review & editing, Supervision, Resources, Conceptualization. **Mohamed A. Abdelnaim:** Writing – review & editing, Investigation. **Jost Bernet:** Writing – review & editing. **Martin Schecklmann:** Writing – review & editing, Supervision, Investigation. **Andreas Reissmann:** Writing – review & editing, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships thatcould have appeared to influence the work reported in this paper. The work was supported by the dtec.bw – Digitalization and Technology Research Center of the Bundeswehr (MEXT project). dtec.bw is funded by the European Union NextGenerationEU.

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