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Research paper

The antidepressant effectiveness of transcranial magnetic stimulation is not impacted by comorbid neurotic, stress-related or somatoform disorders

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ABSTRACT

Introduction: Depression is frequently accompanied by neurotic, stress-related and somatoform disorders (F4 diagnoses, ICD-10), which are linked to greater severity and poorer treatment outcomes. Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique used for treatment-resistant depression. We investigated whether comorbid F4 diagnoses affect the antidepressant efficacy of different TMS protocols under real-world conditions.

Methods: We retrospectively analyzed data from 416 in- and outpatients with unipolar or bipolar depression at a German tertiary hospital between 2019 and 2024, of whom 107 had an F4 comorbidity. All patients received left prefrontal TMS: intermittent theta-burst stimulation (iTBS) with 600 ($n = 138$), 1200 ($n = 98$), or 1800 pulses per session ($n = 104$), or tonic repetitive TMS (rTMS) at 20 Hz with 2000 pulses ($n = 76$). Depressive symptoms were assessed before and after treatment using the HAMD-21 and MDI.

Results: Depression scores improved significantly in both groups, with no significant difference between patients with or without F4-comorbidity. Remission rates were lower in patients with comorbid F4-diagnoses. No significant differences were observed between TMS protocols in patients with F4-comorbidity. Network analyses revealed similar symptom profiles in both groups.

Conclusion: Comorbid F4-diagnoses do not affect the antidepressant efficacy of TMS. iTBS is as effective as other protocols, but shorter and more cost-efficient, making it preferable for patients and providers.

1. Introduction

1.1. Major Depressive Disorder (MDD) and comorbid F4-diagnoses (ICD-10)

According to the World Health Organization, Major Depressive Disorder (MDD) affects approximately 332 million people globally (https://www.who.int/news-room/fact-sheets/detail/depression, access: 2025-09-03). MDD severely impacts psychosocial functioning and can cause substantial impairments across several aspects of daily life, including personal, occupational and educational domains (Malhi and Mann, 2018). MDD represents one of the most burdensome diseases worldwide and is frequently accompanied by anxiety disorders (Coombes Coombes et al., 2023). A study by Steffen et al. (2020) showed that neurotic, stress-related and somatoform disorders (ICD-10: F4-categories), which mainly comprise anxiety disorders, were by far the most prevalent comorbidities in depression (52–65%), irrespective of depression severity. Importantly, ICD-10 subsumes a number of diagnostically distinct conditions—beyond anxiety disorders—within the F4 category, including trauma- and stressor-related disorders, obsessive–compulsive disorder, and somatoform disorders. While these conditions have been reported as F4 comorbidities in major depressive disorder (MDD), ICD-11 differentiates them into separate diagnostic categories (Reed et al., 2019). Accordingly, the symptom profile and course of illness in MDD can vary depending on the specific pattern of the F4-comorbidity, with differences in symptom severity and potentially distinct treatment responses (Hernandez, 2020; Oriuwa et al., 2022; Tendler et al., 2021). It has been demonstrated that MDD patients who suffer from a comorbid anxiety disorder not only have a higher suicide risk or higher depressive symptom severity, but are often associated with greater illness severity, chronicity and poorer response to standard pharmacological and/or psychotherapeutic treatments (Dold,

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2017; Clarke et al., 2019; Fava et al., 2008; Coombes Coombes et al., 2023). Accordingly, there is a high need for effective therapeutic options for patients suffering from MDD and a comorbid disorder from the F4-category of the ICD-10. Current treatment strategies primarily include pharmacotherapy, psychotherapy and their combination, yet patients with comorbid anxiety often show reduced response and may require complex, individualized treatment plans (Fava et al., 2008; Coombes Coombes et al., 2023). Furthermore, while it remains largely unclear whether comorbid F4 diagnoses generally influence the efficacy of antidepressant transcranial magnetic stimulation (TMS) in treatment-resistant depression (non-response to at least one prior antidepressant trial of adequate dose and duration), the efficacy of rTMS in MDD comorbid with specific F4 subcategories has been extensively investigated. Recent examples include e.g., Tendler et al. (2021), who demonstrated that deep rTMS using an H7 coil improved both major depressive disorder (MDD) and comorbid obsessive-compulsive disorder (OCD) symptoms. Similarly, Ng et al. (2025) reported that patients with comorbid post-traumatic stress disorder (PTSD) symptoms, including those related to childhood adversities, should not be excluded from antidepressant rTMS, as they can also benefit from the intervention. Additionally, Caussat et al. (2025) found that unilateral antidepressant TMS positively affected comorbid anxiety symptoms. Collectively, these findings suggest that specific comorbid F4 conditions do not prevent patients from benefiting from antidepressant TMS and that such symptoms may improve alongside depressive symptoms.

1.2. TMS as an established antidepressant treatment

High-frequency repetitive transcranial magnetic stimulation (HF-rTMS; 10–20 Hz) applied over the left dorsolateral prefrontal cortex (DLPFC) constitutes a non-invasive neuromodulatory technique with established antidepressant efficacy (Lefaucheur et al., 2020). HF-rTMS has been shown to be effective for patients suffering from treatment-resistant MDD (patients who did not respond to two treatments with antidepressants), with response rates significantly higher than sham stimulation (Vida et al., 2023).

A newer protocol, the intermittent theta-burst stimulation (iTBS), a patterned TMS protocol delivering bursts of three 50 Hz pulses repeated at a frequency of 5 Hz, has demonstrated antidepressant efficacy comparable to conventional HF-rTMS, while substantially reducing treatment duration (approximately 3 min versus 25 min) (Blumberger et al., 2018). A retrospective analysis, that we did ourselves, revealed that there is no significant difference in antidepressant outcome when MDD patients are treated with 600, 1200, or 1800 pulses per session (p/s), while the treatment duration of a session with 600 p/s is even the most time- and cost-efficient, lasting only 3 min (Kerkel et al., 2025). Both HF-rTMS and iTBS are now recognized as evidence-based, non-invasive brain stimulation treatments for depression. Their therapeutic use is FDA-approved and endorsed in the current German S3 guideline for the treatment of unipolar depression (Cheng et al., 2021; Härter and Prien, 2023; https://register.awmf.org/assets/guidelines/nvl-005l_S3 Unipolare-Depression_2023-07.pdf, access: 2025-10-30).

1.3. The role of comorbid anxiety symptoms on TMS treatment response

Several studies have investigated whether comorbid anxiety symptoms in patients suffering from MDD affect the antidepressant response to TMS. Durmaz et al. (2017) reported that somatic anxiety symptoms (measured with the Hamilton Anxiety Rating Scale, HAM-A) were associated with greater response to left-sided HF-rTMS (20 Hz), whereas Kazemi et al. (2025) found that somatic anxiety symptoms (measured with the Beck Anxiety Inventory, BAI) predicted lower response and psychological anxiety predicted better outcomes across different rTMS protocols. These findings indicate that the qualitative characteristics of anxiety symptoms, rather than their simple occurrence, may influence treatment outcomes.

1.4. Effects of different TMS protocols on anxiety symptoms

Several studies have investigated whether different TMS protocols differ in their effects on anxiety symptoms in depression. For example, Chen et al. (2019) found no significant differences in anxiety reduction between left-sided high-frequency rTMS (10 Hz), right-sided low-frequency rTMS (1 Hz), and sequential bilateral rTMS. Similarly, Trevizol et al. (2021) reported comparable reductions in anxiety symptoms following 10 Hz rTMS and intermittent theta-burst stimulation (iTBS).

1.5. TMS in MDD with comorbid F4-diagnoses (ICD-10)

Although comorbid F4-diagnoses are highly prevalent and clinically relevant in MDD patients, evidence on the efficacy of TMS treatment in this subgroup remains limited. To the best of our knowledge, only one study, done by Clarke et al. (2019), has specifically examined patients with MDD and a comorbid F4-disorder (diagnosed with the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998)). In their study, the authors showed that both patients with and without a comorbid diagnosis from the F4-spectrum (ICD-10) had significant improvement in depressive symptoms following rTMS treatment. Among those with a comorbid F4-diagnosis, 23.3% achieved remission and 39.5% met response criteria, with no significant differences compared to patients without comorbidity (Clarke et al., 2019).

Despite the comparable improvements in depressive symptoms reported by Clarke et al. (2019) for patients with and without a comorbid F4 diagnosis, underlying symptom patterns may differ depending on the specific F4 subtype. Comorbid anxiety disorders can intensify rumination and avoidance behaviors, obsessive-compulsive disorder may amplify intrusive thoughts and compulsions, trauma-related disorders such as PTSD often heighten hyperarousal and stress reactivity and somatic symptom disorders primarily increase bodily distress and physical symptom perception (WHO, 1992). At the same time, these disorders share overlapping symptom dimensions that contribute to overall distress in depression. Network analyses have identified “bridge symptoms” that link disorder-specific clusters, while a subset of predominantly physical symptoms often drives comorbidity across F4 subtypes (Kaiser et al., 2021). Taken together, these findings suggest that patients with MDD and comorbid F4 diagnoses may exhibit both unique and shared symptom constellations, which could influence treatment outcomes, including the response to antidepressant TMS.

1.6. Aim of the present study

To the best of our knowledge, the above-mentioned studies are the only ones focusing on the efficacy of TMS on anxiety symptoms of depressive patients or on depressive patients with a comorbid F4-diagnosis, respectively. While rTMS has been shown by Clarke et al. (2019) to yield similar antidepressant outcomes in patients with MDD regardless of a comorbid F4-diagnosis, the efficacy of iTBS in this population remains to be systematically investigated. Further, no study has yet investigated whether rTMS and iTBS differ in their efficacy for depressive patients with a comorbid F4-diagnosis.

Hence, we analyzed data taken from a naturalistic sample of depressed patients with or without a comorbid F4-diagnosis treated with different stimulation protocols (iTBS 600, 1200 or 1800 p/s or 20 Hz rTMS) in everyday clinical practice of a tertiary care hospital. The following three research questions were investigated:

1 Does the response to TMS treatment (irrespective of the stimulation protocol) differ between MDD patients with and without a comorbid F4-diagnosis?
   1.1 Are there differences in overall TMS treatment outcomes between MDD patients with and without a comorbid F4-diagnosis?

1.2 Do item-level symptom changes during TMS treatment differ between MDD patients with and without a comorbid F4-diagnosis?

2 Is there a difference in overall treatment response in patients suffering from depression **and** a comorbid F4-diagnosis between iTBS with 600, 1200 or 1800 p/s and rTMS with 20 Hz?

3 As an additional exploratory analysis, we attempted to identify whether there were significant differences in symptom severity between the two groups (depressed patients with and without a comorbid F4-diagnosis) at the symptom level, as these differences could indicate different neurobiological correlates, which could explain a possible different response to TMS. Therefore, we compared MDI baseline scores between MDD patients with and without a comorbid F4-diagnosis and conducted a network analysis to investigate whether MDD patients with a comorbid F4-diagnosis exhibit a different symptom profile compared to MDD-only patients.

2. Methods and materials

This retrospective study analyzed 416 clinical records of in-and outpatients treated with TMS at the Center for Neuromodulation of the Psychiatric University hospital Regensburg, Germany between 2019 and 2023. Treatment resistant patients diagnosed with either unipolar or bipolar depression (ICD-10: F31.x, F32.x, F33.x, F34.x) were included. The sample was not stratified by depression subtype and thus potential differences in rTMS efficacy between bipolar and unipolar patients were not assessed. A comorbid F4-diagnosis was present in 107 patients (25.7%). In our sample, the most common comorbid F4-diagnosis was post-traumatic stress disorder (ICD-10: F43.1; 43%), followed by chronic pain disorder (ICD-10: F45.41; 16.8%) and social phobia (ICD-10: F40.1; 12.1%). Multiple diagnoses within the F4 spectrum were possible ($n = 18$). In this retrospective study, it is possible that patients may have had other comorbidities in addition to comorbid F4 diagnoses, but these have been disregarded in this analysis. Please see Table 1 for detailed information.

The present analysis was approved by the local ethics committee of the University of Regensburg, Germany (22-2958-104). Notably, this is a retrospective data analysis of systematically collected records derived from routine clinical practice. Thus, there was no sham condition, and patients were not randomly assigned to the different protocols. Fig. 1 depicts an overview of the different protocols. All patients received TMS treatment over the left DLPFC. From January 7th 2019 to September 7th 2020, all patients were treated with a 20 Hz rTMS protocol using 2000 pulses/session (one session lasting approximately 25 min) with a treatment duration of either 3 (15 treatment sessions) or 6 weeks (30 treatment sessions). Between January 3rd 2022 and April 3rd 2023, all patients were treated with iTBS using 600 p/s (one session lasting approximately 3 min) with a treatment duration of either 3 (15 treatment sessions) or 6 weeks (30 treatment sessions). From April 17th 2023 until December 18th 2023, all patients were treated with iTBS using 1200 p/s (one session lasting approximately 6 min) with a treatment duration of either 1 (25 treatent sessions) or 4 weeks (20 treatment sessions). Between December 28th 2023 and December 16th 2024, all patients were treated with iTBS using 1800 p/s (one session lasting approximately 9 min) with a treatment duration of either 1 (25 treatment sessions) or 4 weeks (20 treatment sessions). In order to create groups of similar sizes with regard to the protocols used, no patients treated in 2021 were included in the analysis, as in 2021 all patients were treated with iTBS using 600 p/s and inclusion of these patients would have inflated this group.

A psychiatrist or a clinical psychologist with experience in non-invasive brain stimulation evaluated the indication and possible contraindications of rTMS-treatment and performed the ratings. All patients provided written informed consent for TMS-treatment as well as for data collection and analysis. Treatments were administered by experienced psychiatric nurses or medical assistants.

Each treatment was performed with a MagVenture system (MagVenture A/S, Farum, Denmark) using a figure-of-8 coil (default current direction) aiming for a target treatment intensity of 120% resting motor threshold (RMT, see below). Because of local discomfort, stimulation intensity had to be lowered for some patients in some sessions to the highest intensity which could be tolerated. All patients were treated over the left DLPFC, determined via the F3 position of the 10–20-EEG-system (Herwig et al., 2003). For determination of the RMT, the individual motor hotspot was detected by administering single pulses at different positions over the left primary motor cortex. Using electromyography (EMG), the subject's motor hotspot was defined as the point where single TMS pulses evoked stable motor-evoked potentials (MEPs) with the highest amplitude. Once the subject's motor hotspot was identified, the treatment-coil was fixated and the subject's RMT was then measured by stimulating the individual hotspot while simultaneously recording the MEPs from the thenar muscles of the right hand using EMG (Barker et al., 1985). The RMT was determined using the Rossini-Rothwell method, which defines it as the lowest stimulation intensity necessary to elicit MEPs of at least 50 μV in 50% of the applied pulses (Rossini et al., 1994).

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 TMS-treatment. Only patients who were TMS-naive, with available HAMD-21 and MDI questionnaires before and after treatment and who were treated with a stimulation intensity of at least 110% RMT were included in the analyses ($N = 416$). Demographic and clinical characteristics of the enclosed patients, split for depressed patients with and without a comorbid F4-diagnosis, are provided in Table 2.

Table 1
Distribution of comorbid F4-Diagnoses (ICD-10) by absolute case numbers.

ICD-10 code	Diagnosis	*n*
F40.01	Agoraphobia	5
F40.1	Social phobia	13
F40.2	Specific (isolated) phobia	3
F41.0	Panic disorder	7
F41.1	Generalized anxiety disorder	9
F41.3	Other mixed anxiety disorder	2
F42.0	Obsessive-compulsive disorder with predominantly obsessive thoughts	7
F42.1	Obsessive-compulsive disorder with predominantly compulsive actions	4
F42.2	Obsessive-compulsive disorder with mixed obsessive thoughts and compulsive behaviors	2
F42.8	Other obsessive-compulsive disorder	1
F43.1	Posttraumatic stress disorder (PTSD)	46
F43.2	Adaption disorder	1
F43.8	Other reactions to severe stress	1
F44.0	Dissociative amnesia	1
F45.0	somatization disorder	5
F45.1	Undifferentiated somatization disorder	3
F45.2	Hypochondriacal disorder	1
F45.3	Somatoform autonomic dysfunction	1
F45.41	Chronic pain disorder with somatic and psychological factors	18
F48.1	Depersonalization and derealization syndrome	1

Notes. Some patients had more than one comorbid F4-diagnosis. ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

3. Statistical analysis

Group differences between MDD patients with or without a comorbid F4-diagnosis in demographic or clinical characteristics were investigated using chi-square tests of independence or independent samples *t*-tests. Due to the use of two depression scales as primary outcome, level of significance was adjusted for multiple comparisons by Bonferroni's correction ($p = .025$). Secondary treatment outcomes were response and

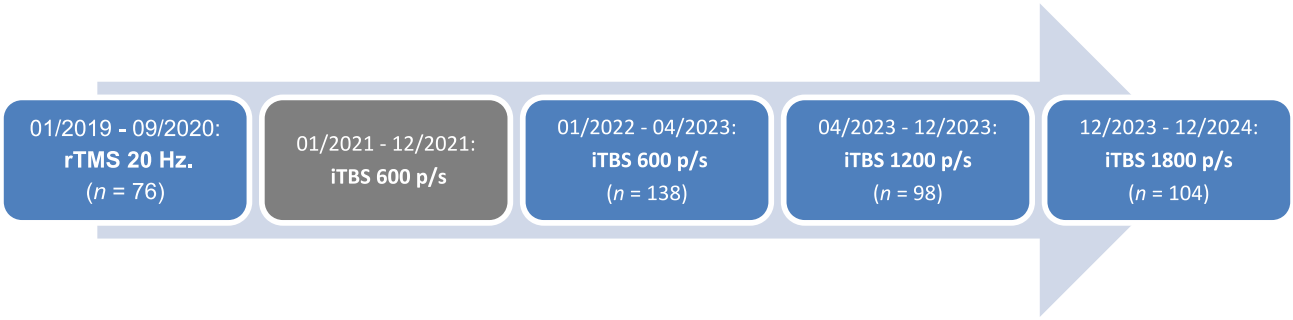

Fig. 1. Course of the used protocols (2019–2024) for antidepressant TMS-treatment. This graph illustrates which protocol was used over time in clinical practice at the Center for Neuromodulation Regensburg, Germany. Blue boxes: Patient data included into analyses. Grey box: Patient data excluded from analyses. n: number of included patients into the analyses. rTMS: repetitive transcranial magnetic stimulation using a 20 Hz protocol; p/s: pulses per session; iTBS: intermittent Theta-burst stimulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

remission rates. Treatment response was defined as ≥50% reduction in the mean score on the MDI and/or HAMD-21 from pre- to post-treatment. Remission rates were defined as a total value of ≤20 points in the MDI and/or ≤ 10 points in the HAMD-21 at end of treatment (Hebel, 2021). Group differences with regard to response and remission rates were investigated using chi-square tests of independence.

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 = 0.2; partial $\eta^2 = 0.01$; φ = 0.1), medium (d = 0.5; partial $\eta^2 = 0.06$; φ = 0.3), and large effects (d = 0.8; partial $\eta^2 = 0.14$; φ = 0.5).

First research question:

1.1 In order to evaluate potential differences between the change of overall depressive symptoms for patients with or without a comorbid F4-diagnosis, two mixed analyses of variance (ANOVA) were calculated, one for each depression scale (HAMD-21 and MDI), with time as within factor (2 levels: pre- and post-treatment) and group as between factor (2 levels: with or without a comorbid F4-diagnosis). In case of a significant interaction, a post-hoc *t*-test was performed.

1.2 Further, in order to evaluate the change of depression scores on item-level, further mixed ANOVAs were calculated, one for each item for each depression scale (HAMD-21 and MDI), with time as within factor (2 levels: pre- and post-treatment and group as between factor (2 levels: with or without a comorbid F4-diagnosis). In case of a significant interaction, post-hoc *t*-tests were performed.

Second research question: To investigate potential differences between different protocols for depressed patients with a comorbid F4-diagnosis, we calculated two mixed ANOVAs with time as within factor (2 levels: before and after treatment) and group as between factor (4 levels: iTBS with 600, 1200, 1800 p/s and 20 Hz rTMS with 2000 p/s) for the HAMD-21 and the MDI. In case of a significant interaction, a post-hoc t-test was performed.

All statistical analyses for the first and second research questions were conducted with SPSS version 29.0 (IBM SPSS, Chicago, IL).

Third research question (exploratory): We compared the baseline scores of the MDI for depressed patients with or without a comorbid F4-diagnosis by using independent samples t-tests. Furthermore, based on pre-treatment MDI data, we estimated symptom networks separately for both groups. In line with the findings of Feiten et al. (2021) that showed that self-reported data can provide more detailed information about symptom interrelationships than clinician-rated data (e.g. HAMD-21), we opted to use the MDI in this study. The networks were computed using the R package bootnet (Epskamp and Fried, 2018) applying a Gaussian graphical model with the EBICglasso estimation method and cor_auto to compute the correlation matrix appropriate for ordinal data. Group differences between the networks of participants with depression only and those with comorbid F4 diagnoses were examined using a permutation-based Network Comparison Test implemented in the NCT function from the NetworkComparisonTest R package (van Borkulo et al., 2022). This method employs resampling to generate a null distribution, as regularization violates the assumption of normality. The test consists of three components: The invariant network structure test performs an omnibus comparison of all edges under the null hypothesis that the networks are identical. If this hypothesis is rejected, an invariant edge strength test assesses differences in the strength of individual edges. Finally, the invariant global strength test evaluates differences in overall network connectivity, calculated as the sum of absolute edge weights.

4. Results

4.1. First research question: does a comorbid F4-diagnosis have an impact on antidepressant TMS treatment?

4.1.1. Overall treatment response

Fig. 2 illustrates mean changes in depressive symptoms from pre- to post-treatment, separated for depressed patients with or without a comorbid F4-diagnosis (see Table 4 for exact score).

A mixed ANOVA regarding the HAMD-21 data revealed a significant effect of time ($F_{(1,414)} = 379.55$, $p < .001$, partial η2 = 0.478) as well as a significant group effect ($F_{(1,414)} = 24.10$, $p < .001$, partial η2 = 0.055). No significant interaction between time and group was found ($F_{(1,414)} = 0.09$, $p = .768$, partial η2 < 0.001).

Further, a mixed ANOVA regarding the MDI data also revealed a significant effect of time ($F_{(1,414)} = 362.79$, $p < .001$, partial η2 = 0.467) as well as a significant group effect ($F_{(1,414)} = 8.33$, $p = .004$, partial η2 = 0.020). The interaction between time and group did not reach the level of significance ($F_{(1,414)} = 3.92$, $p = .049$, partial η2 = 0.009).

Response rates for patients with a comorbid F4-diagnosis were 24% (HAMD-21) and 26% (MDI). Response rates for patients without a comorbid F4-diagnosis were 33% (HAMD-21) and 36% (MDI), respectively. These differences did not reach significance. Remission rates for patients with a comorbid F4-diagnosis were 24% (HAMD-21) and 38% (MDI), whereas for patients without a comorbid F4-diagnosis 41% (HAMD-21) and 53% (MDI), respectively. These differences reached significance with a small effect size (see Table 3 for details).

4.1.2. Treatment response on Item-level

Mixed ANOVAs regarding the course of HAMD-21 data on Item-level revealed **only** for **Item 15** (hypochondriasis) a significant interaction between time and group ($F_{(1,414)} = 5.016$, $p = .026$, partial η2 = 0.012). Further, significant effects of time ($F_{(1,414} = 17.877$, $p < .001$, partial η2 = 0.043) and group ($F_{(1,414)} = 0.5747$, $p = .017$, partial η2 = 0.014)

Table 2
Demographic and clinical data of depressed patients **with** and **without** a comorbid F4-diagnosis (ICD-10).

	With a comorbid F4-diagnosis (ICD-10) (n = 107)	Without a comorbid F4-diagnosis (ICD-10) (n = 309)	Statistics for group comparisons
Gender: m/f	37/70	142/167	χ^2 (1) = 4.195, p = .041, φ = −0.10
Age: M (SD)	42.45 (14.74)	48.38 (15.25)	t(414) = 3.494, p < .001, d = 0.39
Age: Range	19–83	19–85	
In-/Outpatient: n	84/23	233/76	χ^2 (1) = 0.421, p = .516, φ = 0.03
TMS variables			
No. of treatment sessions: M (SD)	19.15 (4.78)	18.80 (5.23)	t(414) = −0.604, p = .546, d = −0.07
RMT (%): M (SD)	43.60 (10.87)	43.37 (9.72)	t(414) = −0.204, p = .839, d = −0.02
Treatment intensity: M (SD)	49.00 (9.53)	49.33 (8.96)	t(414) = 0.326, p = .745, d = 0.04
Psych. Medication: yes/no			
SSRI	28/79	76/233	χ^2 (1) = 0.105, p = .746, φ = 0.02
S(*S*)NRI	44/63	136/173	χ^2 (1) = 0.271, p = .603, φ = −0.03
Tricyclics	13/94	29/280	χ^2 (1) = 0.669, p = .413, φ = 0.04
Tetracyclics	15/92	36/273	χ^2 (1) = 0.414, p = .520, φ = 0.03
MAO Inhibitors	1/106	2/307	χ^2 (1) = 092, p = .762, φ = 0.02
Other antidepressants	16/91	38/271	χ^2 (1) = 0.496, p = .481, φ = 0.04
Benzodiazepines	14/93	39/270	χ^2 (1) = 0.015, p = .902, φ = 0.01
Z-Drugs	1/106	3/306	χ^2 (1) = 0.001, p = .974, φ < −0.01
Neuroleptics: First and Second Generation Antipsychotics	46/61	153/156	χ^2 (1) = 1.356, p = .244, φ = −0.06
Mood stabilizer (e.g. lithium)	6/101	39/270	χ^2 (1) = 4.053, p = .044, φ = −0.10
Other psych. medication	19/88	50/259	χ^2 (1) = 0.143, p = .706, φ = 0.02
No medication	17/90	60/249	χ^2 (1) = 0.656, p = .418, φ = −0.04

Notes. RMT: resting motor threshold (%); HAMD-21: Hamilton Depression Rating Scale, 21 Items; MDI: Major Depression Inventory; iTBS: intermittent Theta-burst stimulation; 20 Hz rTMS: repetitive transcranial magnetic stimulation using a 20 Hz protocol; SSRI: selective serotonin reuptake inhibitors; S(*S*)NRI: selective serotonin/noradrenalin reuptake inhibitors; MAO: Monoaminooxydase inhibitors; .Z-drugs: Zopiclon, Zolpidem.

were found. Depressed patients with a comorbid F4-diagnosis (M = −0.23, SD = 0.75) dropped in hypochondriac symptoms more than depressed patients without a comorbid F4-diagnosis (M = −0.07, SD = 0.57). Anxiety symptoms, as measured by **Item 10** and **11** dropped significantly from pre- to post-treatment (effects of time; Item 10: $F_{(1,414}$ = 59.641, p < .001, partial η2 = 0.126; Item 11: $F_{(1,414}$ = 94.445, p < .001, partial η2 = 0.186), independent of the presence of a comorbid F4-diagnosis (for either Item, that measures anxiety symptoms, no significant interaction was found: ps > 0.473). A further analysis of **Item 3** (suicidality) showed no significant interaction between time and group ($F_{(1,414)}$ = 1.420, p = .234, partial η2 = 0.003).

Mixed ANOVAs regarding the course of MDI data on item-level revealed only for **Item 8b** (passivity) a significant interaction between time and group ($F_{(1,414)}$ = 5.666, p = .018, partial η2 = 0.014). Further, a significant effect of time ($F_{(1,414}$ = 212.998, p < .001, partial η2 = 0.349) was found. There was no significant group effect ($F_{(1,414)}$ = 1.389, p = .238, partial η2 = 0.003) found. Patients without a comorbid F4-diagnosis had a significantly higher reduction of passivity symptoms (M = −1.62, SD = 1.70) than patients with a comorbid F4-diagnosis (M = −1.16, SD = 1.58).

4.2. Second research question: is there a difference in treatment response in patients suffering from depression and a comorbid F4-diagnosis between iTBS with 600, 1200 or 1800 pulses/session, and rTMS with 20 Hz?

Table 4 provides an overview of the distribution of patients with and without a comorbid anxiety disorder across the various TMS protocols. The proportion of individuals with a comorbid anxiety diagnosis was comparable within the respective treatment groups.

Fig. 3 shows mean changes in depressive symptoms (HAMD-21 and MDI) for patients with a comorbid F4-diagnosis over the course of the treatment separated for the four different protocols (see Table 5 for exact scores). A mixed ANOVA regarding the HAMD-21 data revealed a significant effect of time ($F_{(1,103)}$ = 119.68, p < .001, partial η2 = 0.537) as well as a significant group effect ($F_{(3,103)}$ = 3.71, p = .014, partial η2 = 0.097). There was no significant interaction between time and group ($F_{(3,103)}$ = 0.80, p = .497, partial η2 = 0.023).

Regarding the MDI data, a significant effect of time could be found ($F_{(1,103)}$ = 108.97, p < .001, partial η2 = 0.514). There was no significant group effect ($F_{(3,\ 103)}$ = 1.37, p = .256, partial η2 = 0.038). There was again no significant interaction between time and protocols ($F_{(3,103)}$ = 2.11, p = .104, partial η2 = 0.058).

Among the four different protocols, response rates varied between 15% and 38% (HAMD-21) and between 18% and 47% (MDI). Remission varied between 12% and 48% (HAMD-21) and between 26 and 43% (MDI). On a descriptive level, patients with a comorbid F4-diagnosis appeared to benefit most from the 20 Hz protocol, showing higher response and remission rates on both the HAMD-21 and MDI. However, these differences did not reach the level of significance with small to medium effect sizes (see Table 6 for details).

4.3. Third, exploratory, research question: network analysis for depressed patients with/without a comorbid F4-diagnosis

On a descriptive level MDI pre-treatment mean scores were slightly higher in the group with comorbid F4-diagnosis, but this difference did not reach statistical significance (group with comorbid F 4 diagnosis: 34.86 (SD: 9.43); group without comorbid F4-diagnosis: 33.22 (8.76); t(414) = −1.641, p = .102, d = −0.18). The **network invariance test** (NCT) did not indicate a statistically significant difference between the two groups (M = 0.27, p = .36). Similarly, the **global strength invariance test** showed no significant difference in overall connectivity (S = 1.12, p = .24), although the global strength was numerically higher in the comorbid group (5.92) compared to the depression-only group (4.80) (see Fig. 4).

5. Discussion

The aim of the present study was to investigate whether patients that suffer from a unipolar or bipolar depressive disorder and a comorbid F4-diagnosis (ICD-10) would have a different outcome after an antidepressant TMS-treatment then depressed patients without this comorbidity (**first research question**). Further, we analyzed different TMS protocols (rTMS with 20 Hz and 2000 p/s, iTBS with 600, 1200 or 1800

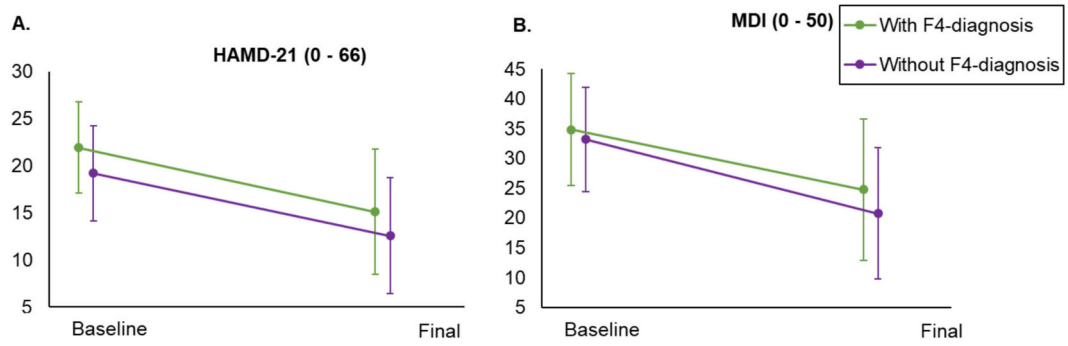

Fig. 2. Course of depressive symptoms. This graph shows the course of the HAMD-21 (A.) and MDI (B.) scores from pre- to post-treatment, split for depressed patients with (green) and without (purple) a comorbid F4-diagnosis (ICD-10). Error bars indicate SDs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Response and remission rates of depressed patients with and without comorbid anxiety disorder after TMS treatment.

	with comorbid F4-diagnosis (ICD-10) (n = 107)	without comorbid F4-diagnosis (ICD-10) (n = 309)	Statistics for group comparisons
HAMD-21			
Pre-treatment: M (SD)	21.90 (4.84)	19.18 (5.07)	
Post-treatment: M (SD)	15.10 (6.65)	12.57 (6.13)	
Response: yes/no Response rate	26/81 24.3%	103/206 33.3%	χ^2 (1) = 3.032, p = .082; φ = − 0.09
Remission: yes/no Remission rate	26/81 24.3%	126/183 40.8%	χ^2 (1) = 9.306, p = .002; φ = −0.15
MDI			
Pre-treatment: M (SD)	34.86 (9.43)	33.22 (8.76)	
Post-treatment: M (SD)	24.48 (11.88)	20.79 (11.04)	
Response: yes/no Response rate	28/79 26.2%	112/197 36.2%	χ^2 (1) = 3.615, p = .057; φ = −0.09
Remission: yes/no Remission rate	41/66 38.3%	163/146 52.8%	χ^2 (1) = 6.625, p = .010; φ = −0.13

Notes. HAMD-21: Hamilton Depression Rating Scale, 21 Items; MDI: Major Depression Inventory.

p/s) for depressed patients with a comorbid F4-diagnosis to investigate whether one protocol provided greater benefit than another (**second research question**). In a last exploratory step, we conducted a network analysis (based on the pre-treatment values from the MDI) for depressed patients with or without a comorbid F4-diagnios and compared those to see, whether the symptom networks are comparable between those patient cohorts (**third research question**).

Regarding the **first research question**, we found no significant difference in the antidepressant outcome after TMS treatment between depressed patients with and without a comorbid F4-diagnosis (lack of a significant interaction in the respective ANOVA). This result is in line with the findings by Clarke et al. (2019). Neurobiologically, depressive disorders and certain F4 diagnoses share overlapping neural circuits that are targeted by TMS, as summarized in van den Heuvel and Oberman (2024). While only a subset of patients in our sample had anxiety disorders (30% of F4 diagnoses), this overlap may provide a partial explanation for why TMS can simultaneously improve depressive and

Table 4
Distribution of comorbid F4-diagnoses for the different applied TMS protocols by absolute case numbers.

	iTBS			20 Hz rTMS	
	600 p/s (n = 138)	1200 p/s (n = 98)	1800 p/s (n = 104)	2000 p/s (n = 76)	Statistics for group comparisons
Comorbid F4-diagnosis (ICD-10): yes/no	33/105	27/71	26/78	21/55	χ^2 (3) = 0.409, p = .938, φ = 0.031

Notes. iTBS: intermittent Theta-burst stimulation; p/s: pulses per session; 20 Hz rTMS: repetitive transcranial magnetic stimulation using a 20 Hz protocol.

certain comorbid symptoms. Consistent with this, our analysis of symptom profiles (**third research question**) revealed that the overall structure and connectivity of MDI symptom networks (pre-treatment) are largely comparable between patients with depression alone and those with any comorbid F4 diagnosis. Kaiser et al. (2021) similarly found no significant differences in overall symptom structure between depression alone and depression with comorbid anxiety, although specific bridge symptoms, such as psychomotor agitation and concentration difficulties, linked depressive and anxiety symptom clusters. These findings suggest that shared symptom dimensions, rather than overlapping neurocircuitry alone, may contribute to comparable responses to TMS across groups. Improvements in depressive symptoms were often accompanied by reductions in comorbid symptoms during TMS (Hernandez, 2020). While TMS has also been applied in primary anxiety disorders with beneficial outcomes, the evidence remains heterogeneous, highlighting variability across protocols and patient populations (Cirillo et al., 2019; Parikh et al., 2022).

At Item-level, only two significant differences in symptom improvement were found: hypochondriac symptoms (HAMD-21, Item 15) improved better in depressed patients with a comorbid anxiety disorder than in those without after treatment with TMS. This finding aligns with the study by Durmaz et al. (2017), which revealed a correlation between somatic anxiety symptoms and a better response to left-sided HF-rTMS. Furthermore, depressive patients without a comorbid F4-diagnosis were found to show a significantly greater reduction in passivity (MDI, Item 8b) than patients with a comorbid F4-diagnosis. This may reflect the additional symptom overlap present in most F4 disorders, such as avoidance behaviors, intrusive thoughts, or heightened stress reactivity, which can sustain passivity even as core depressive symptoms improve. Such overlapping symptoms may slow the translation of clinical improvements into active behaviors (Miethe et al., 2023). Consistent with Trevizol et al. (2021), who reported improvements in anxiety symptoms across TMS protocols, we found that the score of the anxiety-related HAMD-21 items (psychic anxiety (Item 10)

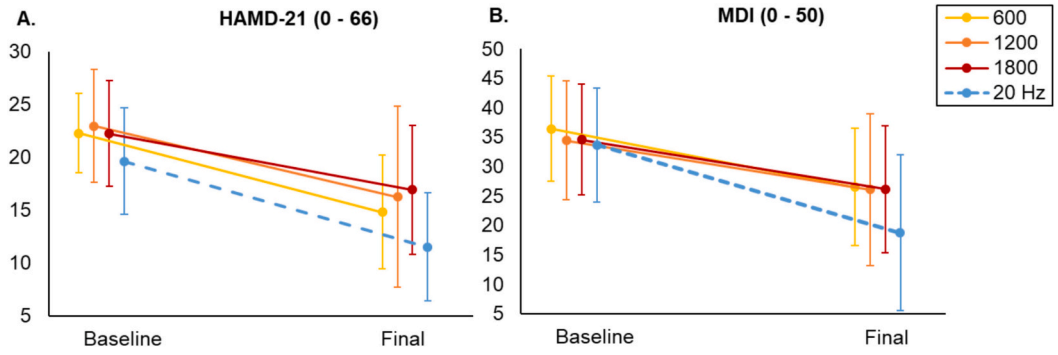

Fig. 3. Course of depressive symptoms. This graph shows the course of the HAMD-21 (A.) and MDI (B.) scores for depressed patients with a comorbid anxiety disorder (ICD-10: F4), split for the 20 Hz. rTMS protocol (blue) and iTBS 600 pulses per session (yellow), 1200 pulses per session (orange) and 1800 pulses per session (red). Error bars indicate SDs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
M and SD values for pre- and post-treatment scores (HAMD-21, MDI) for patients with a comorbid F4-diagnosis (ICD-10).

	iTBS			20 Hz rTMS
	600 p/s (n = 33)	1200 p/s (n = 27)	1800 p/s (n = 26)	2000 p/s (n = 21)
HAMD-21				
Pre-treatment scores: M (SD)	22.21 (3.76)	22.98 (5.36)	22.25 (5.00)	19.62 (5.03)
Post-treatment: M (SD)	14.98 (5.38)	16.25 (8.58)	16.93 (6.12)	11.53 (5.08)
MDI				
Pre-treatment scores: M (SD)	36.22 (9.03)	34.41 (10.10)	34.58 (9.38)	33.67 (9.66)
Post-treatment: M (SD)	26.42 (10.10)	26.11 (12.89)	26.15 (10.80)	18.76 (11.88)

Notes. HAMD-21: Hamilton Depression Rating Scale, 21 Items; MDI: Major Depression Inventory; iTBS: intermittent Theta-burst stimulation; p/s: pulses per session; 20 Hz rTMS: repetitive transcranial magnetic stimulation using a 20 Hz protocol.

Table 6
Response and remission rates for depressed patients and comorbid F4d-diagnosis (ICD-10) depending on the TMS protocol used.

	iTBS			20 Hz rTMS	
	600 p/s (n = 33)	1200 p/s (n = 27)	1800 p/s (n = 26)	2000 p/s (n = 21)	Statistics for group comparisons
HAMD-21					
Response: yes/no Response rate	5/28 15.2%	9/18 33.3%	4/22 15.4%	8/13 38.1%	χ^2 (3) = 5.995, p = .112, φ = 0.24
Remission: yes/no Remission rate	6/27 18.2%	7/20 25.9%	3/23 11.5%	10/11 47.6%	χ^2 (3) = 9.220, p = .027, φ = 0.29
MDI					
Response: yes/no Response rate	7/26 21.2%	5/22 18.5%	6/20 23.1%	10/11 47.6%	χ^2 (3) = 6.367, p = .095, φ = 0.24
Remission: yes/no Remission rate	11/22 33.3%	7/20 25.9%	11/15 42.3%	9/12 42.8%	χ^2 (3) = 5.425, p = .143, φ = 0.23

Notes. HAMD-21: Hamilton Depression Rating Scale, 21 Items; MDI: Major Depression Inventory; iTBS: intermittent Theta-burst stimulation; 20 Hz rTMS: repetitive transcranial magnetic stimulation using a 20 Hz protocol.

and somatic anxiety (Item 11) did not differ significantly between patients with depression alone and those with comorbid F4 diagnoses. This suggests that, as in Trevizol et al., TMS led to comparable improvements in anxiety symptoms across treatment protocols irrespective of the presence of comorbid anxiety-related disorders. Further analyses of Item 3 of the HAMD-21 (suicidality) showed that its course over treatment did not differ between the two groups.

Further, we found significant higher remission rates for depressed patients without a comorbid F4-diagnosis. This result is in contrary to a study done by Clarke et al. (2019). Nevertheless, in our sample, patients with a comorbid F4-diagnosis had significantly higher pre-treatment HAMD-21 scores. Given that elevated baseline symptom severity can be associated with a reduced likelihood of remission, this difference may partly explain the observed variation in remission rates between the two groups. Another possible explanation for this difference could be that Clarke et al. (2019) only treated outpatients, whereas we mainly treated inpatients. In an inpatient setting, depressed patients typically receive additional intensive antidepressant treatment, e.g. in the form of regular individual or group psychotherapy and occupational therapy. Therefore, it may be possible that a remission of depressive symptoms is achieved faster, provided no additional psychiatric disorders are present. For patients suffering from depression with a comorbid F4-diagnosis, it may be necessary to undergo additional therapy focused on the respective F4-diagnosis in order to achieve full remission (Dold, 2017; Coombes et al., 2023). In line with the study by Clarke et al. (2019), the response rates of the two groups do not differ from each other. Taken together, this shows that individuals with and without a comorbid F4-diagnosis experience a comparable improvement in depression symptoms after TMS treatment.

Regarding the **second research question**, we found no difference between various TMS protocols for depressed patients who suffer from a comorbid F4-diagnosis with respect to antidepressant outcome. For MDD patients, this result is in accordance with studies by Blumberger et al. (2018) and Bulteau et al. (2022), both showing that iTBS with 600 p/s is non-inferior to HF-rTMS (10 Hz) in depressed populations. Further, those results align with a study done by Noda et al. (2025), who showed no difference between iTBS protocols with either 600 p/s or 1200 p/s regarding antidepressive outcome. These results imply that depressive patients with F4 comorbidity behave like depressive patients without comorbid F4-diagnoses. This also means that our data do not

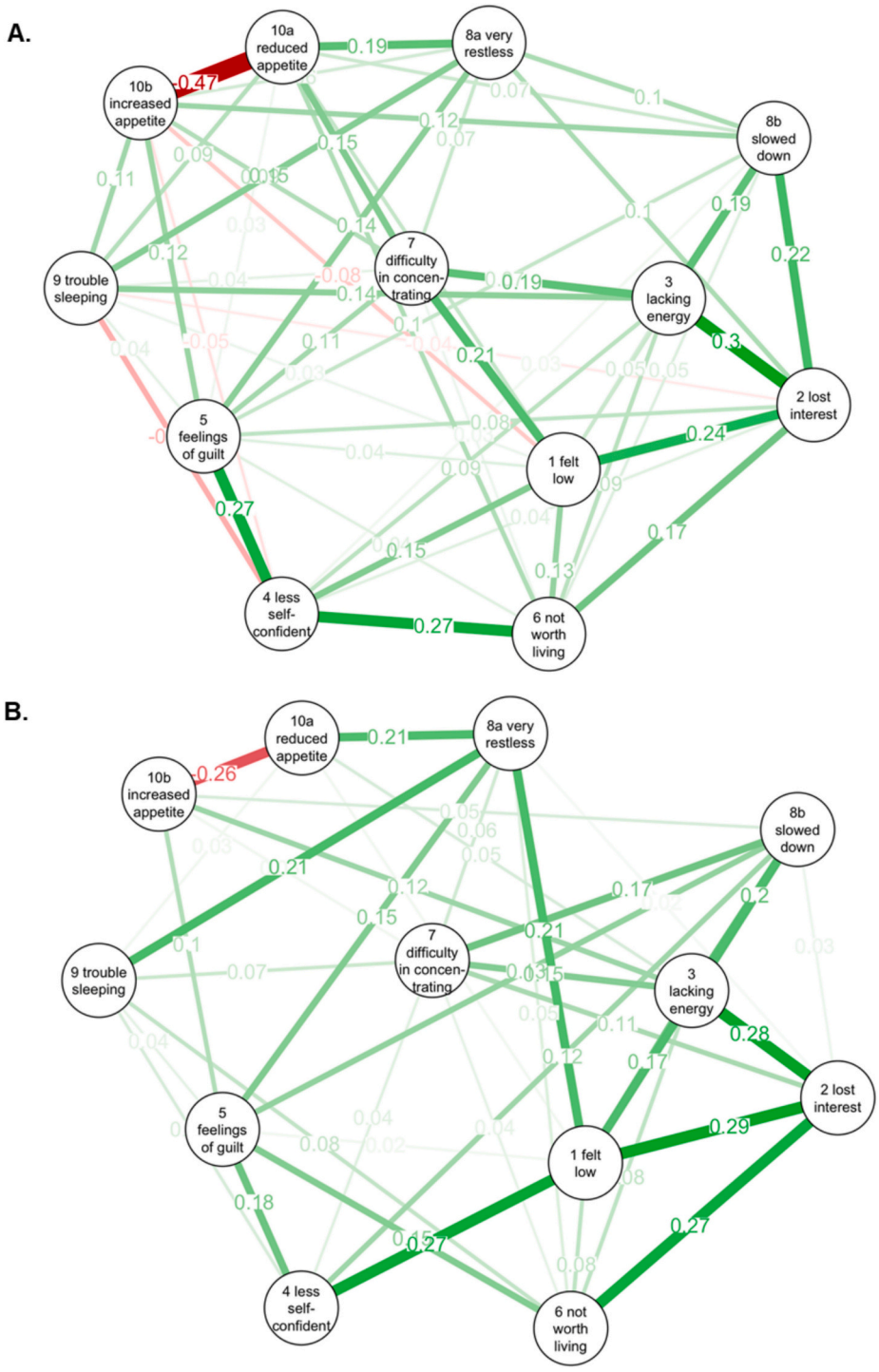

Fig. 4. Network analyses for depressed patients without (A.) and with (B.) a comorbid F4-diagnosis (ICD-10). This graph shows the partial correlations between MDI items (numbering of the original items 1–10 with a brief description in each circle; pre-treatment data was used for the networks), separated for depressive patients with and without a comorbid F4-diagnosis. The thicker the line, the greater the partial correlation. Green lines indicate a positive association, red lines indicate a negative association. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

provide a hint that for depressive patients with F4 comorbidity a specific protocol might be particularly effective. Nevertheless, on a descriptive level, our findings suggest that patients with a comorbid F4-diagnosis appeared to benefit most from the 20 Hz protocol, exhibiting higher response and remission rates on both the HAMD-21 and MDI. These observations warrant further investigation in future randomized studies, ideally applying all four TMS protocols within the same trial.

Importantly, for the first and second research question, overall, number of responders and remitters was high. Considering the high number of remitters when compared to responders, there might have been a kind of "bottom effect", as in Hebel (2021), where some patients' initial baseline scores were sufficiently low to allow them to reach remission. This should be considered, when interpreting treatment outcomes.

5.1. Limitations

The results should be interpreted with caution, as these analyses are retrospective. Treatment allocation was not randomized to specific TMS protocols or a sham control condition. Moreover, the group of depressive patients with comorbid F4 diagnoses was heterogeneous regarding the specific type of comorbidity within the F4 category. It should be noted that using a broad F4 category may have limited the generalizability of the findings. The F4 category in ICD-10 includes a heterogeneous group of disorders, such as anxiety disorders (F40–F41), obsessive-compulsive disorder (F42), trauma- and stressor-related disorders like PTSD (F43.1), and somatoform disorders (F45) (WHO, 1992). Each of these subtypes can differ in symptom patterns, severity and response to treatment. By combining them into a single category, the results may not fully reflect the specific effects of each disorder, which could reduce the general applicability of the present findings.

Another limitation is that symptom improvement in patients with comorbid F4 diagnoses was assessed exclusively with depression-specific questionnaires. Therefore, we cannot exclude the possibility that different TMS protocols may have exerted distinct effects on the comorbid anxiety or somatoform disorders that were not captured by these measures. Further, potential cohort and time effects, as well as inter-rater variability, were not controlled for and may have influenced the observed outcomes. The treatment setting (inpatient vs. outpatient), which may involve additional therapeutic interventions, was also not systematically accounted for. Other comorbidities within the ICD-10 spectrum were not considered in the analyses. Finally, there was no balanced sampling across the years of data collection: patients treated with 600 pulses per session of iTBS were included only from selected years, while data from 2021 were excluded, which may have introduced a sampling bias. The analysis did not control for the presence of potential substance use disorders (ICD-10 category F1) or comorbid medical conditions. As substance use disorders and medical comorbidities can affect cognitive, behavioral and clinical outcomes, this may have introduced uncontrolled confounding and influenced the observed associations.

6. Conclusions

The present retrospective analysis of a large cohort suggests that TMS is equally effective in depressive patients with or without a comorbid F4-diagnosis (ICD-10). In the group with a comorbid F4-diagnosis the investigated TMS protocols (rTMS 20 Hz, iTBS with 600, 1200 or 1800 pulses/session) had similar effects. From a clinical perspective our results suggest, that in depressive patients the F4 comorbidity does not play a relevant role for the decision about TMS treatment and the selection of the treatment protocol. Additionally, investigating whether comorbid F4 diagnoses influence treatment response differently in bipolar versus unipolar depression help clarify potential differential effects of comorbidity on TMS outcomes across depression subtypes.

CRediT authorship contribution statement

Katharina Kerkel: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Stefan Schoisswohl:** Writing – review & editing, Validation, Supervision, Conceptualization. **Lea Steinecker:** Writing – review & editing, Data curation, Conceptualization. **Milena Engelke:** Writing – review & editing, Formal analysis. **Mohamed A. Abdelnaim:** Writing – review & editing, Investigation. **Berthold Langguth:** Writing – review & editing, Supervision, Resources, Conceptualization. **Andreas Reissmann:** Writing – review & editing, Investigation.

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Declaration of competing interest

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