Brain Stimulation 14 (2021) 335–343

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

A direct comparison of neuronavigated and non-neuronavigated intermittent theta burst stimulation in the treatment of depression

Tobias Hebel [a, *], Alina Göllnitz [b], Stefan Schoisswohl [a], Franziska C. Weber [a], Mohamed Abdelnaim [a], Thomas C. Wetter [a], Rainer Rupprecht [a], Berthold Langguth [a], Martin Schecklmann [a]

[a] Department of Psychiatry and Psychotherapy, University of Regensburg, Germany
[b] Faculty of Medicine, University of Regensburg, Germany

ARTICLE INFO

Article history:
Received 10 June 2020
Received in revised form
7 January 2021
Accepted 14 January 2021
Available online 22 January 2021

Keywords:
Neuronavigation
Intermittent theta burst stimulation
iTBS
Depression

ABSTRACT

Objective: To investigate whether a four-week course of neuronavigated intermittent theta burst stimulation (iTBS) of the left dorsolateral prefrontal cortex is superior to the non-neuronavigated F3-EEG method of positioning.

Methods: We conducted a single-center, two-arm, randomized and double-blinded study (clinicaltrials.gov NCT03953521). 37 inpatients with an at least moderate depressive episode were randomized to receive either neuronavigated or 10-20-EEG-system based F3 guided iTBS. Both groups received twenty week daily sessions of iTBS while continuing to receive standard-of-care treatment by their ward physicians. For navigated iTBS, we used magnetic resonance imaging to target the border between the anterior and middle third of the middle frontal gyrus considered to represent the left dorsolateral prefrontal cortex (lDLPFC).

Differences in the treatment arms were blinded by completely mimicking the procedures of the respective other treatment group. Rating physicians were not involved in the treatment procedure.

Primary outcome was defined as the change of the 21-item version of the Hamilton Depression Score (HAMD) from baseline to end of treatment at week 4. Secondary outcomes included HAMD score during the treatment, Patient Health Questionnaire-9, WHO Quality of Life-BREF and Clinical Global Impression. For primary outcome, we used a planned group comparison for the absolute change in the HAMD. For secondary outcome measures we calculated analyses of variance (ANOVAs) with the within-subjects factor time (primary: baseline vs. week 4; secondary: all visits) and the between-subjects factor group (navigated vs. F3 guided group). We also did planned contrasts between both groups for all variables and all treatment and follow-up visits with the aim not to oversee any group differences. For group contrasts we used Student T-tests for metric and chi-square tests for categorial variables. Significance threshold was set to 5% uncorrected for multiple comparisons.

Results: Enrolment of 80 patients with interim analysis was planned. Interim analysis was performed after 37 patients (intention to treat). 6 patients dropped out, leaving 31 for analysis. With respect to primary outcome criteria, absolute change in the HAMD did not differ significantly between groups. In accordance, relative change and number of responders and remitters were not significantly different. Overall number of responders was 53% and of remitters was 60%. On a descriptive level, the results favor the clinical effects of the F3 group for the absolute and relative change in the HAMD and the number of responders. Number of remitters were exactly the same for both groups. Therefore, we decided to stop the trial due to the added burden of magnetic resonance imaging and neuronavigated treatment in relation to the effect. Secondary outcomes did also not differ significantly between groups. Patients did not differ in their baseline characteristics nor with respect to intake of medication during the trial period and all had access to the same therapeutic interventions.

Conclusion: We noticed a high antidepressive effect of add-on iTBS treatment to standard inpatient treatment but failed to demonstrate a clinical superiority of neuronavigated localization. The non-navigated, F3 guided iTBS treatment used as a control group may be sophisticated enough to dilute

* Corresponding author. Department of Psychiatry and Psychotherapy, University of Regensburg, Universitätsstraße 84, 93053, Regensburg, Germany.
E-mail address: tobias.hebel@medbo.de (T. Hebel).

https://doi.org/10.1016/j.brs.2021.01.013

potential added benefits, and the difference between the localization approaches is either negligible or too small to justify the additional efforts of navigation. The effects of concomitant treatment may mask effects, but our patient population reflects clinical reality in an inpatient setting. Further prospective studies are warranted to compare neuronavigated with surface-based approaches.

Introduction

Widely known as one of the most common and debilitating psychiatric disorders, depression is projected to rank first as the main cause of burden of disease worldwide within the next ten years [1]. Despite an extensive array of pharmacological, psychotherapeutic and complimentary interventions, this disorder still runs a chronic and disabling course in many of the affected patients [2], highlighting the need for further innovations in treatment.

Non-invasive brain stimulation by repetitie transcranial magnetic stimulation (rTMS) is now widely accepted as a safe treatment option for a number of neurological and psychiatric disorders, albeit with variable efficacy [3]. While the debate on the optimal treatment protocol for depression is still ongoing, high-frequency stimulation of the lDLPFC has emerged as one of the main protocols and has shown convincing evidence of its efficacy in large sham-controlled clinical trials [3–5].

Non-invasive identification of a cortical target like the lDLPFC without the usage of neuroimaging presents a challenge. Traditionally, the approach has been to use the "5 cm-method", assuming the lDLPFC to sit 5 cm rostrally from the hand areal of the ipsilateral motor cortex [6,7]. An alternative approach has been to use the international 10–20 EEG system and assuming the F3 position to represent the lDLPFC [8–10]. Beam and colleagues have proposed a pragmatic and time-sparing modification of the F3 method [11]. Recently, it could be demonstrated that EEG cap based methods produce results similar to the Beam method [12].

While easy to use in everyday clinical practice, there has been some evidence that all skull surface-based approaches lack precision in identifying the location of the lDLPFC and do not fully account for inter-individual differences in human anatomy. This has been demonstrated (to varying degrees) using MRI - based neuronavigation systems [13–17]. Inter-individual differences may be related to age, sex, handedness or pathological volume abnormalities [18].

Naturally, this imprecision in targeting the lDLPFC has been suggested as one possible explanation for lowering the effect sizes in some trials regarding the efficacy of rTMS [3,19]. However, while sensible from a theoretical standpoint, there is still only limited evidence that neuronavigated treatment is clinically superior and that the higher anatomical precision translates into actual benefit for the patients.

Fitzgerald et al. conducted a two-arm study enrolling 51 patients with Major Depressive Disorder (MDD), randomizing them to receive 10 Hz-rTMS with localization by either the standard 5 cm technique or a neuro-navigational approach [19]. Patients were required to have failed two adequate courses of antidepressant medication. In the neuronavigated group, a target between the center of Brodmann areal (BA) 9 and the border of BA 9 and 46 was chosen, based on the cytoarchitectural definitions of these areas [20]. Patients treated with neuro-navigated localization technique did show significantly greater reduction in the Montgomery-Asberg Depression Rating Scale (MADRS). However, methodological limitations were discussed, as only patients with initial treatment response to a three-week course were allowed to receive the full four-week treatment.

In another study, Li et al. reported no benefit of MRI navigation when compared to the 5 cm rule in treating depressed patients with rTMS or prolonged intermittent theta burst stimulation (piTBS) [21]. Navigation was not the primary topic of this study and was treated as additional analysis.

Except for these papers, a PubMed search using the terms (rTMS or TMS or transcranial magnetic stimulation) AND (navigated OR navigation OR neuro-navigated OR neuronavigation) AND (depression OR depressed) on March 31, 2020 identified no further studies comparing navigated with surface based localization with respect to clinical outcomes.

Most publications using anatomical neuronavigation did not take into account the interference of individual brain anatomy with the induced electric field (e-field). In addition to simple anatomic-guided neuronavigation, e-field guided neuronavigation means that the position of the coil is guided by the estimated electric field which depends on the individual brain gyrification [22]. Conventional neuronavigation assumes the hot spot of the induced electric field linear under the geometric mean of the coil which is not necessarily correct [22].

Apart from the best localization method, there has been research on improving the manner of TMS pulse application. There is increasing interest in a markedly shortened protocol of "facilitating" rTMS, so called intermittent theta burst stimulation (iTBS [23]). In a landmark study, the application of iTBS was not inferior to HF-rTMS of the lDLPFC in depression [24]. Due to its much shorter duration, iTBS would allow to treat a greater number of patients in a given time.

Our aim in this study was to directly compare neuronavigated iTBS of the lDLPFC in depression with an EEG cap based localization method for F3. Navigated treatment is regarded as superior with respect to accuracy and validity and also intra- and inter-session reliability of placement. Based on these technical advantages of navigated TMS and preliminary data we hypothesized that the navigated treatment would be clinically superior to the F3-based approach.

Methods

We planned to treat 80 patients with an interim analysis after 40 patients. Sample size calculation was based on the preliminary data of Fitzgerald et al. [19]. The authors did not use the primary outcome of our study (Hamilton Depression Rating Scale, HAMD) but reported several other measures which showed an average effect size of 0.58. An assumed statistical power of 80% and a significance threshold of 5% resulted in necessary sample size of 76 (one-sided). Under consideration of possible drop-outs and a sample size of 51 in the preliminary work we assumed a sample size of 80 as sufficient. The work of Li et al. was published after study start and thus could not be taken into account for sample size calculation [21].

Patients with an at least moderate depressive episode (diagnosed by experienced psychiatrists according to ICD-10 (International Statistical Classification of Diseases and Related Health Problems) criteria) were recruited from the Department of Psychiatry and Psychotherapy at the University of Regensburg. All

patients gave written informed consent to the study. The study, patient information and consent forms were approved by the local ethics committee of the University of Regensburg (18-1231-101). The study trial was registered at the U.S. National Institutes of Health Database (www.clinicaltrials.gov) accessible with the identifier code NCT03953521.

We conducted a single-center, two-arm, randomized and double-blinded (patients and raters) study. Patients were randomized to receive either neuronavigated or EEG-cap based F3 guided iTBS. Both groups received four weeks of iTBS (triplet 50 Hz bursts at a rate of 5 Hz for 2s with 8s breaks, 600 pulses per session/day). Subjects were treated every weekday from Monday to Friday with no treatment on weekends, amounting to 20 sessions [24]. Treatment of the single patient was always done at the same time of the day.

Stimulation intensity was 120% of resting motor threshold (RMT). In some patients, in whom this intensity was not tolerated initially, we reduced and then gradually increased stimulator output aiming for target intensity, a procedure called “ramping”.

Before treatment period, RMT was determined using electromyography of the abductor pollicis brevis, the first dorsal interosseous, and the abductor digiti minimi muscle. The muscle with the best response was used for motor threshold estimation using the threshold hunting procedure [25] utilizing default options of the on-board software of the TMS stimulator. For motor threshold and stimulation we used the Nexstim NBT 2.1 system (Nexstim Plc., Finland) and the onboard figure-of-eight coils.

Groups differed with respect to guidance of the TMS coil. For the conventional localization, we used the F3 position of the standard 10–20 EEG system. For this procedure, a blank head cap was positioned in a tight-fitting fashion. Subsequently, a head cap with the marked position F3 (EasyCap GmbH, Germany) was slipped over and supported marking this position. After removing the EEG cap, a line with an angle of 45° to the midline was drawn on the blank and the onset of the coil was marked on this line. Reliable cap position was ensured by positioning the cap based on the distance between nasion and onset of the cap. We called this study arm F3 guided iTBS.

For navigated iTBS, we used the procedure described by Mylius et al. which is implemented in the Nexstim system. In brief, based on individual MRI the border between the anterior and middle third of the middle frontal gyrus is defined and is considered to represent the treatment target lDLPFC [18,19].

To evaluate the true stimulation location in the brain and the induced e-field, we extracted information on the distance between the true cortical stimulation location and the position according to the Mylius method for both groups. We also extracted the e-field at the Mylius position and the maximum induced e-field (independent of position) for both groups.

Differences in the treatment arms were blinded by mimicking the procedures of the respective other treatment group. Both patient groups received an MRI scan and the lDLPFC was marked on their MR image in accordance with the described method. Both patient groups wore head caps during each treatment and F3 position was marked by pen for each patient. In the navigated group, rTMS operators had to aim the coil at the marked target, which involved approximately up to 5 min of coil “adjustment movements” behind and next to the patients’ head. Patients in the non-navigated group still received a “sham-adjustment” procedure of comparable length although the operator ended up lining up the coil with F3 mark ignoring the MR image. The computer screen was out of patients’ sight, making the treatment modality unintelligible to them. The rating physicians were not involved in the direct treatment of the patients and therefore considered to be blind to the treatment modality. Before the first treatment session, clinical investigators marked the lDLPFC on every patient’s MR image without knowing if it would be needed for treatment.

Inclusion criteria were an age between 18 and 75 years, all sexes, unipolar or bipolar depressive episode according to ICD-10 codes F31, F32 and F33, at least moderate depression according to the HAMD or ICD-10, residence in Germany and mother tongue German, and ability to give written informed consent.

Exclusion criteria were presence of contraindications for TMS and MRI (electric devices or metal implants in the body, e.g. cardiac pace maker, insulin pump), severe neurological comorbidities (e.g. history of cerebrovascular events, neurodegenerative disorder, epilepsy, brain malformation, severe head trauma), addictive disorder with consumption in the last two years, regular intake of benzodiazepines, participation in another study parallel to the trial, pregnancy or lactation, and psychiatric confinement.

Patients continued to receive standard-of-care treatment by their ward physicians for the duration of the trial.

The severity of depression was assessed by the 21-item version of the HAMD [26]. A reduction of the HAMD sum score of 50% or more was defined as treatment response, HAMD score below 11 points was defined as remission. Additional assessment instruments for depression included the Major Depression Inventory (MDI) [27] and the PHQ-9 [28]. Further outcome measures were the WHOQOL-BREF [29] as a measure of quality of life of four different domains and the Clinical Global Impression scale (CGI [30]) for overall symptom severity and treatment response (reference). We also recorded adverse events and the intake of medication as measured by the use of specific substance groups (Table 1).

Seven visits were planned during the trial, i.e., screening (the week before treatment start), baseline (allowed to be combined with screening for the clinical ratings), first day of treatment, after each week (at Friday) of the four week’s treatment (week 1, week 2, week 3, and week 3), and 12 weeks after treatment (follow-up in week 16).

The absolute change of the HAMD sum score from baseline to the end of treatment (week 4) between both groups was defined as primary outcome. Secondary outcome measures were changes in the HAMD over the course of the trial, responder and remitter rates at week 4, as well as changes in the MDI, PHQ-9 and WHOQOL-BREF domains and values of the CGI over the course of the trial. Drop-out participants were excluded from analysis. 5 out of 6 patients dropped out after a maximum of 6 days of treatment. We consider this number of treatment days as not sufficient regarding an indicated duration of 20 treatment days. Also the number of visits is much lower for the drop-out patients. Thus, we conducted a per-protocol analysis.

For primary outcome, we used a planned group comparison for the absolute change in the HAMD. For secondary outcome measures we calculated analyses of variance (ANOVAs) with the within-subjects factor time (primary: baseline vs. week 4; secondary: all visits) and the between-subjects factor group (navigated vs. F3 guided group). We also did planned contrasts between both groups for all variables and all treatment and follow-up visits with the aim not to oversee any group differences. For group contrasts we used Student T-tests for metric and chi-square tests for categorial variables. Significance threshold was set to 5% uncorrected for multiple comparisons. Effect size and power analyses were done with G-Power 3.1 [31].

Results

Sample characteristics and patient flow

Patients were recruited between June 2019 and February 2020. An overview of the patient flow is given in Fig. 1. 176 patients with

Table 1
Intake of psychotropic medication.

	navigated iTBS (n = 16)	F3-guided iTBS (n = 15)	statistics
selective serontonine reuptake inhibitors (no/yes)	12/4	7/8	$\chi^2 = 2.620$; df = 1; p = 0.106
selective serotonine and norepinephrine reuptake inhibitors (no/yes)	4/12	6/9	$\chi^2 = 0.797$; df = 1; p = 0.372
tricyclic antidepressants (no/yes)	14/2	12/3	$\chi^2 = 0.322$; df = 1; p = 0.570
lithium (no/yes)	12/4	12/3	$\chi^2 = 0.111$; df = 1; p = 0.739
other antidepressants (no/yes)	8/8	8/7	$\chi^2 = 0.034$; df = 1; p = 0.853
anticonvulsants (no/yes)	14/2	14/1	$\chi^2 = 0.301$; df = 1; p = 0.583
antipsychotics (no/yes)	4/12	4/11	$\chi^2 = 0.011$; df = 1; p = 0.916
benzodiazepines (no/yes)	12/4	12/3	$\chi^2 = 0.111$; df = 1; p = 0.739
Z-drugs (no/yes)	16/0	14/1	$\chi^2 = 1.102$; df = 1; p = 0.294

depression presented in the Center for Neuromodulation seeking for treatment with rTMS. Most of the screening failures did not meet the inclusion criteria or fulfilled at least one exclusion criterion. One subject treated in the study was an out-patient. We excluded this single patient for reasons of homogeneity from the trial and rated this subject as screening failure. Randomization was done for in- and out-patients separately thus we have no bias due to randomization procedures by excluding this single out-patient.

Until interruption of all rTMS treatments and studies in the hospital due to the Covid-19 pandemic crisis, we included 37 in-patients in the study and decided to prepone the interim analysis which was planned after 40 patients. Interim analysis resulted in the decision to stop the trial due to no differences between study arms with respect to primary and secondary outcomes. With a proportion of 18/19 the groups had similar size presenting an equal randomization into both groups.

The navigated group had two drop-outs with one of them showing a clear association of side-effects as reason for drop-out (Table 2). The F3 guided group showed four drop-outs with two clear associations of the drop-out with side-effects of the treatment, one questionable association (severe adverse event due to suicidality and involuntary detention) and one clear drop-out that was not-associated to treatment. For details see Table 2.

Side effects were mild with the most prevalent side effects being headache and discomfort due to the magnetic pulses on the head. Based on drop-outs and adverse events there is no systematic difference present between both groups. The number of patients we lost to follow-up were very high (8 out of 16 in the navigated and 10 out of 15 in the F3 guided group) as all of our patients were in-patients and were not available for the follow-up visit (even via phone call) after hospital discharge. For this reason we decided not to include the follow-up visit in the analyses of secondary outcomes. Missing values for the outcome measures for the visits screening, baseline, week 1–4 were low (below 2%) thus we decided not to control for missing values.

Patient characteristics of both groups are given in Table 3. Both groups did not differ with respect to demographic (age, sex, education) and clinical data (severity and type of depression, comorbidity) at beginning of treatment (equals time point of randomization) and rTMS parameters (number of sessions, resting motor threshold, stimulation intensity, target intensity). Groups did not differ with respect to the fact if the patients reached the target intensity at all or the days on which they reached the target intensity. Mean stimulation intensity was also comparable (see Table 3). Intake of medication as indicated as intake of substance class did not differ between groups (Table 1).

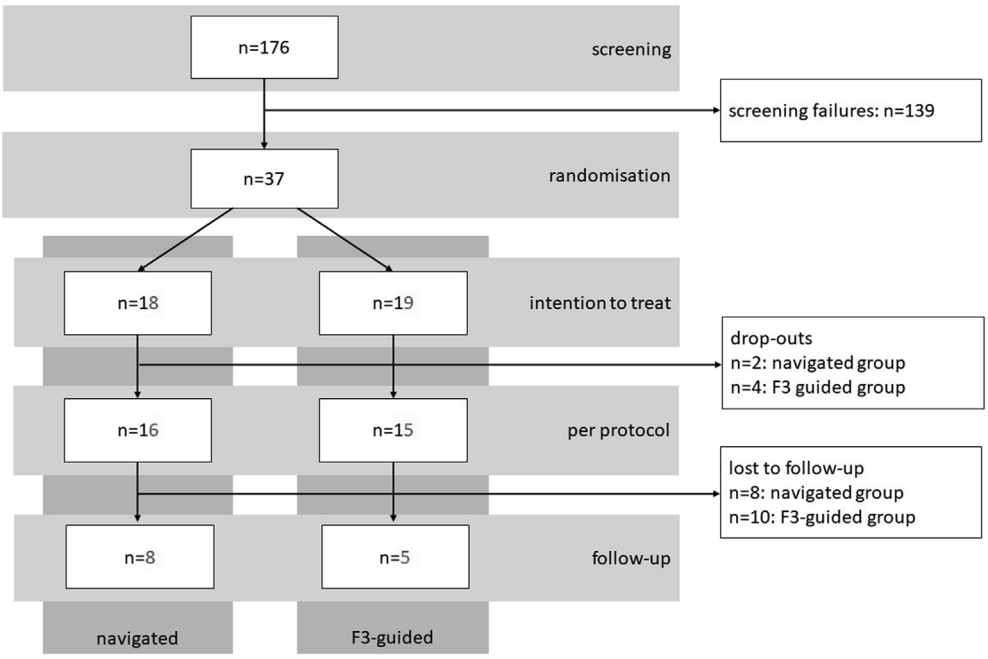

Fig. 1. Patient flow chart.

Table 2
Adverse events and drop-out reasons.

adverse events	navigated (n = 16)	F3-guided (n = 15)
Headaches	n = 5	n = 4
treatment painful/discomfortable	n = 6	n = 3
Fatigue	n = 2	
hand tremor	n = 1	
twitching of jaw or eyelid	n = 1	
memory problems		n = 2
drop-out reasons	**navigated (n = 2)**	**F3-guided (n = 4)**
panic attack during treatment, painful treatment, twitching of the jaw		n = 1 (drop-out at day 1)
inpatient discharge	n = 1 (drop-out at day 3)	n = 1 (drop-out at day 5)
worsening of depression, dizziness, restlessness, hypertension		n = 1 (drop-out at day 6)
excessive demands due to treatment, dizziness	n = 1 (drop-out at day 1)	
intoxication and suicidality		n = 1 (drop-out at day 17)

With respect to blinding, patients were not able to rate the treatment correctly (hit rate of 57%) (Table 3). Most of the patients (77%) guessed that they received the navigated treatment. The raters had a hit rate of 67%.

Outcome analysis

Interim analysis included 31 patients and showed no significant differences between the treatment groups. With respect to our defined primary outcome, absolute change in the HAMD sum score from screening/baseline to end of treatment was not significant between groups (Table 3). In accordance, relative change and number of responders and remitters were not significantly different (Table 3). Overall number (summed for both groups) of responders was 53% and of remitters was 60%. On a descriptive level, the results favor the clinical effects of the F3 group for the absolute and relative change in the HAMD and the number of responders but not for the number of remitters. Number of remitters were exactly the same for both groups. Based on these findings, we decided to stop the trial.

For secondary outcomes (Fig. 2), HAMD sum score did not show differences between groups independent from time point of assessment (main effect group: $F = 0.082$; $df = 1,28$; $p = 0.777$) and over time (interaction effect group by time: $F = 0.811$; $df = 4112$; $p = 0.521$). Main effect of time was significant showing amelioration over the course of the trial ($F = 21.673$; $df = 4112$; $p < 0.001$). The other secondary outcome measures (MDI, PHQ-9, four domains of the WHOQOL-BREF) showed similar findings with significant main effects of time for most variables (all F-values$\geq$6.390; df = 4112|2,54|2,50; all p-values$\leq$0.003; WHOQOL domain 3 (social) and 4 (environment): all F-values $\leq$ 2.888; df = 2,54; all p-values $\geq$ 0.065), not significant main effects of groups (all F-values $\leq$ 0.210; df = 1,25|27|28; all p-values $\geq$ 0.650) and not significant interaction effects group by time (all F-values $\leq$ 2.059; df = 4112|2,54|2,50; all p-values $\geq$ 0.138).

On a descriptive level, for depression scales the navigated group showed superior benefit, for quality of life scales the F3 group showed superior benefit. CGI (symptoms and treatment response) was measured only during the treatment visits and not at baseline, thus main effect of group is of interest for this analysis as it highlights differences in treatment groups. Again, main effects of time were significant (both F-values $\geq$ 3.640; df = 3,75; both p-values $\leq$ 0.016) with non-significant main effects of group (both F-values $\leq$ 0.326; df = 1,25; both p-values $\geq$ 0.573) and non-significant interaction effects group by time (both F-values $\leq$ 0.819; df = 3,75; both p-values $\geq$ 0.488).

As the goal of the study was to investigate differences between coil position methods, we also calculated planned contrasts between both study arms for all outcome variables for the baseline, treatment and follow-up visits. All contrasts were not significant (all T-values $\leq$ 1.893; all p-values $\geq$ 0.095).

Analysis of stimulation localization and e-field

Due to technical reasons, only 60% of the treatment days of the F3-guided group (100% in the navigated group) could be analysed with respect to coil localization and e-field information.

Table 3
Sample characteristics.

	navigated iTBS (n = 16)	F3-guided iTBS (n = 15)	statistics
age (years)	45.9 ± 12.2	42.5 ± 15.1	$T = 0.693$; $df = 29$; $p = 0.494$
sex (female/male)	8/8	9/6	$\chi^2 = 0.313$ $df = 1$; $p = 0.576$
education (A-levels/not A-levels)	9/7	7/8	$\chi^2 = 0.285$; $df = 1$; $p = 0.594$
HAMD at screening/baseline	17.1 ± 4.0	18.7 ± 4.8	$T = 1.012$; $df = 29$; $p = 0.320$
type of depression (ICD-10) (bipolar/unipolar/recurrent)	1/7/8	2/4/9	$\chi^2 = 1.179$; $df = 2$; $p = 0.555$
severity of depression (ICD-10) (moderate/severe/psychotic)	1/15/0	1/12/1	$\chi^2 = 1.205$; $df = 2$; $p = 0.547$
comorbidities (yes/no)	5/11	4/11	$\chi^2 = 0.079$; $df = 1$; $p = 0.779$
number of treatment sessions/days	18.8 ± 1.3	18.3 ± 1.4	$T = 0.863$; $df = 29$; $p = 0.395$
resting motor threshold (% stimulator output)	33.7 ± 8.4	33.9 ± 8.5	$T = 0.059$; $df = 29$; $p = 0.953$
mean intensity of stimulation (% stimulator output)	37.5 ± 7.0	38.1 ± 7.3	$T = 0.261$; $df = 29$; $p = 0.796$
target intensity reached (no/yes)	3/13	2/13	$\chi^2 = 0.168$; $df = 1$; $p = 0.682$
days/sessions until target intensity	1.2 ± 3.0	2.6 ± 5.4	$T = 0.812$; $df = 24$; $p = 0.425$
received treatment estimated by patients (navigated/F3)	13/3	10/4	$\chi^2 = 0.403$; $df = 1$; $p = 0.526$
received treatment estimated by raters (navigated/F3)	11/5	6/9	$\chi^2 = 2.584$; $df = 1$; $p = 0.108$
absolute change in HAMD sum score (primary outcome)	6.9 ± 6.4	9.8 ± 6.5	$T = 1.220$; $df = 28$; $p = 0.233$
relative change in HAMD sum score (%)	42.9 ± 35.3	51.3 ± 29.1	$T = 0.709$; $df = 28$; $p = 0.484$
number of responders (no/yes)	8/7	6/9	$\chi^2 = 0.536$; $df = 1$; $p = 0.464$
number of remitters (no/yes)	6/9	6/9	n.a. due to corresponding frequencies

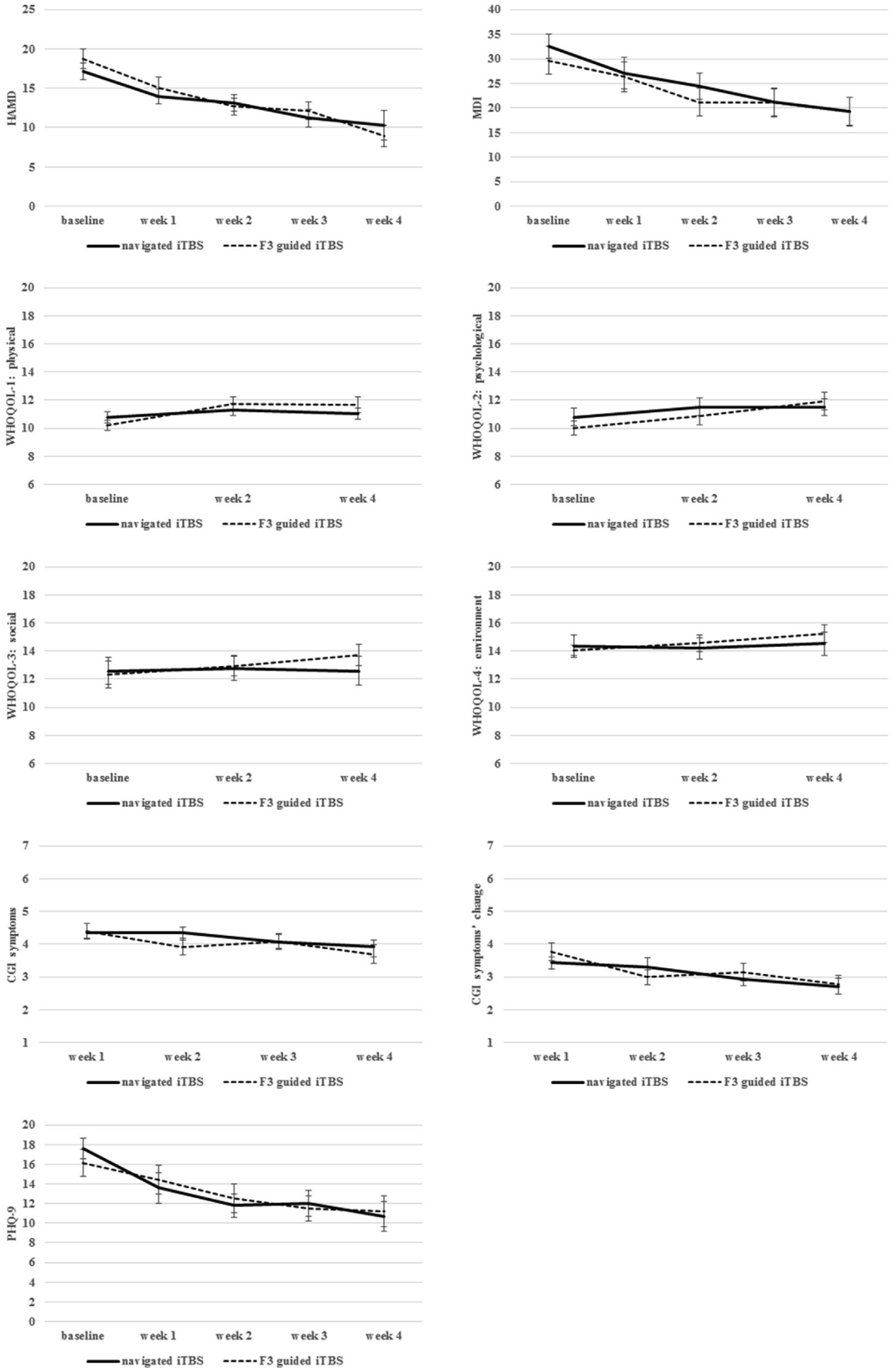

Fig. 2. Outcome analysis.

Mean distance between the Mylius location and the stimulated cortical area was 2.2 ± 0.7 mm for the navigated and 15.8 ± 5.9 mm for the F3-guided group with significant difference ($T = 9.150$; $df = 29$; $p < 0.001$). Descriptively, the stimulation positions of the F3-guided group were mostly posterior to the Mylius location.

The difference in the e-field at the Mylius position was only nearing significance between both groups (navigated: 57.1 ± 12.3; F3-guided: 50.7 ± 7.6 V/m; $T = 1.729$; $df = 29$; $p = 0.094$).

The maximum induced e-field was not different between the navigated (58.1 ± 12.4 V/m) and the F3-guided (62.7 ± 12.3 V/m) group ($T = 1.032$; $df = 29$; $p = 0.311$).

Discussion

The study failed to meet our hypothesis of clinical superiority of the navigated treatment, which we had proposed based on theoretical considerations (see introduction).

The number of side effects and drop outs showed no significant differences between the groups. On a descriptive level, patients in the navigated group reached their target treatment intensity faster, but again this effect failed to demonstrate statistical significance. Groups were comparable in all demographic, clinical and treatment parameters making a sample bias highly unlikely.

Our procedures guaranteed that the raters were blind to the treatment modality as access to case report forms and the treatment room during treatment was restricted. Statistical analysis showed the blinding to have been successful.

Overall, number of responders and remitters was high. We consider it possible that the existing "standard" rTMS protocol with surface-based positioning, which has been developed, refined and tested in large trials, might be sufficiently effective to make any further incremental improvements by navigated treatment clinically negligible, even if they might exist in principle. Considering the high number of remitters when compared to responders, there might also have been a kind of "bottom effect" where some patients' initial HAMD score was sufficiently low to allow them to reach remission.

In the same line of course, we might consider a "ceiling effect" of rTMS treatment, due to standard hospital care which means that patients got medication, counseling and the environmental effects of inpatient setting. This standard treatment may have led to overall good response and remission and the add-on effects of rTMS might then be difficult to identify resulting in ceiling effects of the treatment.

A related explanation, which at the same time presents an important limitation of our study, is the effect of concomitant inpatient treatment. We chose not to require medication to be kept stable during the trial. Therefore, patients received antidepressive pharmacotherapy by their ward physician's responsibility. The antidepressant effect of other interventions, combined with an active rTMS treatment in both groups, might further mask very small benefits of neuronavigated treatment. While this is a limitation when trying to examine "pure" rTMS effects, it also reflects clinical reality. As rTMS is typically applied add-on to pharmacological and psychotherapeutic treatment, we chose this design. Patients did not differ with respect to intake of medication classes during the trial period (see Table 1), and all had access to the same therapeutic interventions.

Including both uni- and bipolar patients in the trial might present another limitation as the conditions might differ with regards to their neurobiological underpinnings.

As a further limitation, sample size was moderate. However, sample size calculations based on the data from the interim analysis showed that an unreasonably high number of patients would need to be included to demonstrate a significant difference between the two treatment arms. Since applying navigated treatment is markedly more cost- and time-intensive than the standard F3 position, we feel we can conclude that an extension of the study would not have been reasonable and justified.

Another possibility would be that the lDLPFC is not the right, or not the best anatomical target in all depressed patients and therefore, ever more precise identification of this region cannot translate into clinical benefit so easily. It seems plausible that the clinical effects of rTMS do not strictly respect the boundaries of cytoarchitectonic or gross anatomical structure. Herbsman et al. used a "reverse approach" in which they used the 5 cm rule, but marked the actual treatment position with vitamin capsules for identification on MRI [32]. After performing a post-hoc analysis of the data, they reported better outcome on HDRS response in a linear fashion when the coil was placed further anterior and lateral.

Recent literature has suggested that the "Herbsman equation" can even predict antidepressant response to rTMS in a prospective fashion [33]. In addition, Fox et al. have suggested that even stronger evidence exists for using an approach guided not by location, but by connectivity [33,34]. They reported prediction of clinical response by subgenual connectivity and by anticorrelation between the cortical target site and the subgenual cingulate and considered these predictors to be even superior to the anatomical "Herbsman" method. Relying on the "classical" gross anatomical approach with a fixed target for navigating our treatment instead of linear topographical or connectivity navigation might be another reason why we failed to demonstrate superiority for neuronavigation and provides valuable insights for future research.

If we assume however that the optimal position for stimulation is indeed the location according to Mylius we see that the neuronavigated group was stimulated at this spot with an accuracy of 2.2 mm, which presents adequate accuracy. The F3-guidance resulted in stimulation about 16 mm distant from, and in most cases posterior of, the Mylius point. The difference to the neuronavigation site was highly significant, indicating that using the F3 approach does in fact yield a different anatomical result.

Inspecting this together with the induced electric fields we see comparable electric fields for both groups which may explain the missing group difference in efficacy. This is, at the moment, a mere hypothesis. Guiding treatment by the induced electric field has not yet been systematically studied, and it is unknown whether clinical efficacy does indeed depend on it. One small study with 26 depressed patients treated with F3-guided rTMS of the lDLPFC found no correlation between the e-field strength and clinical outcomes [35].

If we do indeed assume that clinical effects might be dependent on the actual electric field at the Mylius position, then our findings make sense insofar that the variation in anatomical location failed to produce a meaningful difference in electric fields.

Using navigated treatment to produce an adequate electric field at a given spot may not only be an alternative localization method to the "anatomical" method, but may also be related to more comfort of the treatment if we stimulate with the minimum necessary stimulator output to reach a predefined electric field strength.

We must stress that our study only compared one type of surface-based (i.e., the EEG-cap based F3 method) with one type of neuronavigation (i.e., using the Nexstim navigation system targeting the "Mylius coordinates"). In principal, it is possible that a comparison of other methods will yield differing results. The present study can therefore not make any claims on the overall usefulness of neuronavigated rTMS treatment in depression. However, the results might still encourage investigation of e-field- or functional connectivity-based approaches as avenues of navigation research in addition to the purely anatomical approach.

Conclusion

In summary, we saw a high antidepressive effect of a four week course of add-on iTBS treatment to standard in-patient treatment but failed to demonstrate a clinical superiority of neuronavigated over F3-guided application. Overall, we saw satisfying clinical effects of both treatment forms and decided to stop the trial due to lack of meaningful difference between the groups and added strain and cost of neuronavigated treatment. For our patient population, we feel that a clinically meaningful difference between the localization approaches is either negligible or so small, that a vast number of patients would need to be treated to see it. The effects of concomitant non-iTBS treatment may mask effects, but our patient population reflects clinical reality in an inpatient setting. Future research may more strictly control concomitant treatment, try to recruit many more patients, compare other modalities of navigated and surface-based targeting or shift the focus to e-field- or functional connectivity-based approaches.

CRediT authorship contribution statement

Tobias Hebel: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Alina Göllnitz:** Software, Investigation, Writing - review & editing. **Stefan Schoisswohl:** Conceptualization, Software, Formal analysis, Writing - review & editing. **Franziska C. Weber:** Investigation, Writing - review & editing. **Mohamed Abdelnaim:** Investigation, Writing - review & editing. **Thomas C. Wetter:** Investigation, Resources, Writing - review & editing. **Rainer Rupprecht:** Resources, Writing - review & editing, Supervision, Project administration. **Berthold Langguth:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration. **Martin Schecklmann:** Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Project administration.

Declaration of competing interest

All other authors have no competing interests or disclaimers to declare.

Acknowledgements

We want to thank Nexstim Plc. for providing the electric-field guided neuronavigation rTMS system, enabling to treat patients with the neuronavigated approach and performing this trial.

TH has had travel expenses paid for by Nexstim plc. BL receives royalties from Springer for edited books, received research grants from the company Neuromod as well as from national (DFG, BMBF) and European institutions (EU), received speaker's honoraria and advisory panel payments from Neuromod, Desyncra, Decibel Tx and Servier. SS received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant [agreement number 722046].

References

[1] Malhi GS, Mann JJ. Depression. Lancet 2018;392(10161):2299–312.
[2] Verduijn J, Verhoeven JE, Milaneschi Y, Schoevers RA, van Hemert AM, Beekman ATF, et al. Reconsidering the prognosis of major depressive disorder across diagnostic boundaries: full recovery is the exception rather than the rule. BMC Med 2017;15(1):215.
[3] Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). Clin Neurophysiol 2020;131(2):474–528.
[4] O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatr 2007;62(11):1208–16.
[5] George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatr 2010;67(5):507–16.
[6] George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 1995;6(14):1853–6.
[7] Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348(9022):233–7.
[8] Gerloff C, Corwell B, Chen R, Hallett M, Cohen LG. Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. Brain 1997;120(Pt 9):1587–602.
[9] Rossi S, Cappa SF, Babiloni C, Pasqualetti P, Miniussi C, Carducci F, et al. Prefrontal [correction of Prefontal] cortex in long-term memory: an "interference" approach using magnetic stimulation. Nat Neurosci 2001;4(9):948–52.
[10] Herwig U, Satrapi P, Schonfeldt-Lecuona C. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 2003;16(2):95–9.
[11] Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul 2009;2(1):50–4.
[12] Nikolin S, D'Souza O, Vulovic V, Alonzo A, Chand N, Dong V, et al. Comparison of site localization techniques for brain stimulation. J ECT 2019;35(2):127–32.
[13] Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatr 2001;50(1):58–61.
[14] Rusjan PM, Barr MS, Farzan F, Arenovich T, Maller JJ, Fitzgerald PB, et al. Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. Hum Brain Mapp 2010;31(11):1643–52.
[15] Ahdab R, Ayache SS, Brugieres P, Goujon C, Lefaucheur JP. Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. Neurophysiol Clin 2010;40(1):27–36.
[16] Nauczyciel C, Hellier P, Morandi X, Blestel S, Drapier D, Ferre JC, et al. Assessment of standard coil positioning in transcranial magnetic stimulation in depression. Psychiatr Res 2011;186(2–3):232–8.
[17] Mir-Moghtadaei A, Caballero R, Fried P, Fox MD, Lee K, Giacobbe P, et al. Concordance between BeamF3 and MRI-neuronavigated target sites for repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. Brain Stimul 2015;8(5):965–73.
[18] Mylius V, Ayache SS, Ahdab R, Farhat WH, Zouari HG, Belke M, et al. Definition of DLPFC and M1 according to anatomical landmarks for navigated brain stimulation: inter-rater reliability, accuracy, and influence of gender and age. Neuroimage 2013;78:224–32.
[19] Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology 2009;34(5):1255–62.
[20] Rajkowska G, Goldman-Rakic PS. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach Coordinate System. Cerebr Cortex 1995;5(4):323–37.
[21] Li CT, Cheng CM, Chen MH, Juan CH, Tu PC, Bai YM, et al. Antidepressant efficacy of prolonged intermittent theta burst stimulation monotherapy for recurrent depression and comparison of methods for coil positioning: a randomized, double-blind, sham-controlled study. Biol Psychiatr 2020;87(5):443–50.
[22] Opitz A, Windhoff M, Heidemann RM, Turner R, Thielscher A. How the brain tissue shapes the electric field induced by transcranial magnetic stimulation. Neuroimage 2011;58(3):849–59.
[23] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45(2):201–6.
[24] Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 2018;391(10131):1683–92.
[25] Awiszus F. TMS and threshold hunting. Suppl Clin neurophysiol 2003;56:13–23.
[26] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
[27] Bech PWL. Applicability and validity of the major depression inventory in patients with Parkinson's disease. Nord J Psychiatr 1998;52:305–9.
[28] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606–13.
[29] Development of the world Health organization WHOQOL-BREF quality of life assessment. The WHOQOL group. Psychol Med 1998;28(3):551–8.

[30] Guy W. ECDEU assessment manual for psychopharmacology. US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.
[31] Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009;41(4):1149–60.
[32] Herbsman T, Avery D, Ramsey D, Holtzheimer P, Wadjik C, Hardaway F, et al. More lateral and anterior prefrontal coil location is associated with better repetitive transcranial magnetic stimulation antidepressant response. Biol Psychiatr 2009;66(5):509–15.
[33] Weigand A, Horn A, Caballero R, Cooke D, Stern AP, Taylor SF, et al. Prospective validation that subgenual connectivity predicts antidepressant efficacy of transcranial magnetic stimulation sites. Biol Psychiatr 2018;84(1):28–37.
[34] Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatr 2012;72(7):595–603.
[35] Deng Z-D, Liston C, Gunning FM, Dubin MJ, Fridgeirsson EA, Lilien J, et al. Electric field modeling for transcranial magnetic stimulation and electroconvulsive therapy. In: Makarov S, Horner M, Noetscher G, editors. Brain and human body modeling: computational human modeling at EMBC 2018. Cham: Springer International Publishing; 2019. p. 75–84.