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Effects of bilateral sequential theta-burst stimulation on functional connectivity in treatment-resistant depression: First results

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ABSTRACT

Background: Previous studies suggest that transcranial magnetic stimulation exerts antidepressant effects by altering functional connectivity (FC). However, knowledge about this mechanism is still limited. Here, we aimed to investigate the effect of bilateral sequential theta-burst stimulation (TBS) on FC in treatment-resistant depression (TRD) in a sham-controlled longitudinal study.

Methods: TRD patients ($n = 20$) underwent a three-week treatment of intermittent TBS of the left and continuous TBS of the right dorsolateral prefrontal cortex (DLPFC). Upon this trial's premature termination, 15 patients had received active TBS and five patients sham stimulation. Resting-state functional magnetic resonance imaging was performed at baseline and after treatment. FC (left and right DLPFC) was estimated for each participant, followed by group statistics (*t*-tests). Furthermore, depression scores were analyzed (linear mixed models analysis) and tested for correlation with FC.

Results: Both groups exhibited reductions of depression scores, however, there was no significant main effect of group, or group and time. Anticorrelations between DLPFC and the subgenual cingulate cortex (sgACC) were observed for baseline FC, corresponding to changes in depression severity. Treatment did not significantly change DLPFC-sgACC connectivity, but significantly reduced FC between the left stimulation target and bilateral anterior insula.

Conclusions: Our data is compatible with previous reports on the relevance of anticorrelation between DLPFC and sgACC for treatment success. Furthermore, FC changes between left DLPFC and bilateral anterior insula highlight the effect of TBS on the salience network.

Limitations: Due to the limited sample size, results should be interpreted with caution and are of exploratory nature.

1. Introduction

Bihemispheric prefrontal theta-burst stimulation (TBS) involving excitatory, intermittent TBS (iTBS) of the left, and inhibitory, continuous TBS (cTBS) of the right dorsolateral prefrontal cortex (DLPFC) is a promising treatment approach for major depressive disorder (MDD) (Lefaucheur et al., 2020). Bilateral TBS, a type of transcranial magnetic stimulation (TMS), has shown a superior patient outcome when compared to unilateral therapy (Li et al., 2014). Similarly, repeated TMS (rTMS) including left high-frequency (HF) and right low-frequency (LF) stimulation was shown to be superior to unilateral left HF rTMS (Blumberger et al., 2016), see also (Brunoni et al., 2017) for a review.

Abbreviations: AI, anterior insula; DLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; MDD, major depressive disorder; sgACC, subgenual anterior cingulate cortex; TBS, theta-burst stimulation; TMS, transcranial magnetic stimulation; TRD, treatment resistant depression.

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MDD may be better addressed by modulating both rather than only one hemisphere, as several neuropsychological and imaging studies, e.g., (Maeda et al., 2000; Hecht, 2010; Martinot et al., 1990; Walsh et al., 2010), support a prefrontal asymmetry hypothesis of MDD, which poses a hypoactivity of the left, and a hyperactivity of the right DLPFC (Grimm et al., 2008).

Previous research has looked into TMS-related effects on neural activity using functional magnetic resonance imaging (fMRI). Here, estimates of functional connectivity (FC) are used to determine the communication between brain areas (Hahn et al., 2019). Notably, studies provided convincing evidence that a negative FC (i.e., anti-correlation) between the stimulation target at the left DLPFC and the subgenual anterior cingulate cortex (sgACC) is relevant for treatment success (Fox et al., 2012; Weigand et al., 2018; Cash et al., 2020; Cash et al., 2019; Rosen et al., 2021; Fox et al., 2013). It was further indicated that treatment response to a variety of antidepressant treatments including TMS is associated with distinct FC changes in cortical and subcortical regions (Dichter et al., 2015).

Especially non-invasive brain stimulation including TMS is seen as crucial to normalize cognitive control networks that are believed to be altered in MDD, such as the salience network (SN) and central executive network, which encompass areas such as the DLPFC, cingulate cortex and anterior insula (AI) (Disner et al., 2011; Dunlop et al., 2017). Evidence for such an enhancement comes for example from a study on healthy subjects, showing that HF rTMS of the left DLPFC selectively increases ACC connectivity towards a meso-corticolimbic network (Tik et al., 2017). However, inhibition of the left DLPFC using cTBS was also shown to increase connectivity between ACC, bilateral AI and the stimulated region in healthy controls (Gratton et al., 2013). Similarly, in depressed patients receiving iTBS to the dorsomedial prefrontal cortex (DMPFC), left DLPFC connectivity to the right insula was reduced (Struckmann et al., 2022). Other studies did not observe changes in cognitive control networks upon HF rTMS of the left DLPFC in MDD (Liston et al., 2014). Instead, stimulation reduced FC between sgACC and regions of interest in the default mode network (DMN) albeit these changes were not related to antidepressant treatment response (Liston et al., 2014). In another study, accelerated iTBS of the left DLPFC (5 daily sessions spread over 4 days) increased sgACC FC to the medial orbitofrontal cortex in responders compared to non-responders, but this effect was seemingly independent from the stimulation itself (Baeken et al., 2017). Similarly, the same authors showed that HF rTMS to the left DLPFC in MDD affects FC only in responders but not in non-responders (Baeken et al., 2014), while others corroborated FC changes in responders, irrespective of whether active or sham stimulation was applied (Taylor et al., 2018). Together, these results indicate that connectivity changes are related to clinical improvement rather than the mechanism of action of the stimulation itself.

Due to the heterogeneous responses to TMS treatment reported, in the current study we aimed to further elucidate FC changes upon brain stimulation with bilateral sequential TBS in pharmacologically treatment-resistant depression (TRD). We hypothesized characteristic FC changes compared to baseline for the treatment group after 3 weeks of bilateral TBS treatment, in networks altered in mood disorders, while investigating predictors for treatment response at baseline.

2. Materials and methods

2.1. Participants

A total of 20 (12 female, 8 male) right-handed patients with TRD, who took part in a more comprehensive, multimodal neuroimaging clinical trial (ClinicalTrials.gov Identifier: NCT02810717), were included. TRD was defined as failure to respond to two adequate medication trials of at least 4 weeks each in sufficient dosage for the current depressive episode as indicated in literature (Bartova et al., 2019). Patients were eligible for inclusion if they met DSM 4 criteria for single or recurrent MDD and had a Clinical Global Impression Scale score of $\geq$4 and a Hamilton depression rating scale (HAMD-17) total score of $\geq$18. Patients had to be on stable psychopharmacological treatment within four weeks prior to inclusion and were required to maintain their original medication regimen throughout the study. Exclusion criteria were a medical history of a major systemic illness (dating back not more than five years), neurological diseases, a history of a seizure, or any contraindications to MRI or TMS as screened by safety screening questionnaires (Rossi et al., 2011). Further exclusion criteria were substance abuse or dependence within the last three months prior to inclusion, a body weight of over 115 kg, pregnancy, active suicidal intent, or intake of benzodiazepines other than Lorazepam >2 mg/d or any dose of an anticonvulsant.

The study was approved by the Ethics Committee of the Medical University of Vienna (EK 1761/2015) and performed following the Declaration of Helsinki.

2.2. Study design and treatment protocol

The study was designed as a longitudinal, patient- and assessor-blinded, sham-controlled mono-center study. After inclusion, participants underwent a baseline MRI scan and clinical assessment. They were then randomly assigned to receive daily (Monday to Friday) active sequential bilateral TBS or sham stimulation for three weeks. Participants underwent a second MRI scan and clinical assessment within one week after the last TBS session. Follow-up assessments were performed two and four weeks after the final TBS session, respectively. After completion, participants were unblinded and the sham group was offered TBS treatment.

Daily treatments consisted of two TBS sessions, separated by 1 h, a stimulation pattern that has also been reported to have larger therapeutic effects than unilateral stimulation alone (Li et al., 2014). During each session, iTBS and cTBS were administered, with iTBS targeted to the left and cTBS targeted to the right DLPFC, respectively. The stimulation sequence, i.e. order of hemispheres treated, was reversed for every consecutive session. TBS was administered using a MagPro X100 magnetic stimulator (MagVenture, Tonica Elektronik A/S, Denmark) and a figure-of-eight shaped, liquid-cooled coil (Cool-B70), with a focality of $S_{1/2} \approx 13.9\ cm^2$ ($r_{1/2} = 2.1$ cm) and a stimulation (i.e. half-value) depth of $d_{1/2} \approx 1.35$ cm (Wessel et al., 2019; Drakaki et al., 2022). We followed the original TBS protocol described by Huang et al., comprising 3-pulse 50-Hz bursts, applied at 5 Hz (Huang et al., 2005). iTBS consisted of a 2-s train of theta-bursts and an inter-train-interval of 8 s with 20 repeated trains, whereas cTBS consisted of a continuous train of bursts, amounting to a total number of 600 pulses for each hemisphere and a total number of 1200 pulses per session. Stimulation was delivered at an intensity of 120 % of the individual resting motor threshold (RMT), determined before the first treatment using visual inspection as done previously (Ge et al., 2017). Stimulation intensity exceeding the RMT was used to address the potential problem of previously inadequate dosing and allow for comparison with the FDA-approved rTMS protocol from 2008.

Stimulation targets were identified using neuro-navigation (LOCALITE® TMS Navigator Germany) at the initial appointment and marked on personalized head-caps for later reference. The left DLPFC target was defined at Montreal Neurological Institute (MNI) coordinate [−38, +44, +26] as done previously (Fox et al., 2012), whereas the right DLPFC target was defined contralaterally at MNI coordinate [+38, +44, +26] on the patients' normalized anatomical scan in MNI space. Sham stimulation was performed with the coil angled 90° away from the skull as previously described (Blumberger et al., 2016). This produced some scalp sensation and a sound intensity comparable to active stimulation. Throughout the study, all participants, as well as clinical and research personnel handling participants were blinded (excluding the TMS operator). Possible side effects such as headache, nausea or dizziness were assessed after each stimulation.

2.3. Clinical assessment

The primary clinical endpoint was the change in HAMD-17 score at the follow-up assessment, two weeks after the last of 15 treatment days. Secondary endpoints included changing scores of the Beck Depression Inventory (BDI-II) and the Inventory of Depressive Symptomatology (IDS-C).

Following the last TBS session and prior to unblinding, patients and raters were further asked to report their suspicion on treatment allocation.

2.4. Image acquisition

MRI scans were acquired on a 3 Tesla Siemens Magnetom Prisma system (Siemens Medical, Erlangen, Germany) with a 64-channel head-neck coil. Anatomical scans were attained with a T1-weighted sequence (TE/TR = 2.91/2000 ms, 192 slices, matrix size 240 × 256 × 192, voxel size 1.00 × 1.00 × 1.00 mm^3). Resting-state parameters were: 2D single-shot gradient-recalled EPI, TE/TR = 30/2050 ms, interleaved slice order, matrix size 100 × 100 × 35, Series Length: 176 frames (6 min, 0.8 s), Voxel Dimensions (X, Y, Z): 2.1 × 2.1 × 2.8 (+25 % gap) mm^3.

2.5. Image data processing and analysis

Functional images were processed in MATLAB R2018b (The MathWorks Inc., Natick, Massachusetts) using SPM12 v6225, custom scripts and toolboxes mentioned below. fMRI scans were corrected for interleaved, ascending acquisition ("slice time") and motion, with one subject being excluded whose scans exhibited a frame-wise displacement (FD) ≥ 0.5 in ≥10 % of consecutive time frames. Then, brain images were spatially normalized to the MNI template, masked using MNI tissue probabilities (sum of gray matter (p_{GM}), white matter (p_{WM}) and cerebrospinal fluid (p_{CSF}) probabilities ≥0.5), temporally despiked using the BrainWavelet Toolbox v2.0, (Patel et al., 2014; Patel and Bullmore, 2016), threshold = 20, chsearch = 'harsh'), and spatially smoothed (FWHM = 8 mm, Gaussian kernel, implicit mask: $p_{GM} \geq 0.3$). Time series were further regressed with global (Fox et al., 2012; Cash et al., 2020; Fox et al., 2013; Fox et al., 2009; Murphy and Fox, 2017; Cash et al., 2021) and tissue specific signals (principal components derived from mean WM and CSF signals), realignment parameters including lag (difference of one frame) and their squares (Friston-24) and were temporally filtered (0.01–0.1 Hz).

DLPFC stimulation regions of interest (ROIs) were defined as spheres (r = 5 mm) in MNI space. Their respective centers were individually placed in the cortex, at 1.5 times the coil's stimulation depth below the scalp, additionally accounting for coil orientation as recorded by the neuro-navigation system prior to initial TMS administration, thus accounting for any involuntary deviations during coil placement. This approach ensured that ROIs were both within the cortex, and magnetic field strength was comparable between different subjects at the volumes of interest. sgACC time courses were derived by weighting whole brain signals with their connectivity towards the sgACC ("seedmap approach"), resulting in less noise than if extracted directly from a small ROI, as previously done (Fox et al., 2013; Cash et al., 2021). That is, a normative FC map of the sgACC derived from a large cohort (Human Connectome Project) was used to estimate the sgACC time course from whole brain data, excluding the DLPFC.

ROI mean time courses were extracted using MarsBaR (version 0.44) (Brett et al., 2010) and correlated with the whole brain on the voxel level. The resulting connectivity maps (r-scores) of the brains were Fisher-z-transformed.

Functionally defined DLPFC targets were located by anatomically masking the DLPFC, thresholding sgACC FC maps at the lowest 10 %, and taking the centroid of the most anticorrelated cluster (Cash et al., 2020).

2.6. Statistical analysis

The primary clinical endpoint was a HAMD-17 score after 15 treatment days, analyzed using a linear mixed effects model incorporating treatment group, time, group by time interaction, and patient as a random effect. Categorical treatment response was defined as any reduction from baseline HAMD-17 > 50 %, and remission was additionally defined as a HAMD-17 score < 7. Alpha was set to 0.05 and analyses were conducted in SPSS (IBM SPSS Statistics, Version 27.0. Armonk, NY: IBM Corp).

Group-level statistics (one-sample, one-sided t-tests) on imaging data were calculated using SPM12, testing for significant connectivity on the cluster level ($p_{uncorr} < 0.001$, $p_{FWE,\ Cluster} < 0.05$) in baseline and post-treatment scans, as well as their changes (M2-M1). Furthermore, we looked for correlations between depression scores and their changes, with DLPFC-sgACC FC throughout the course of the study, although these data were not fully available for each subject. Thus, we applied tests for the subset of subjects with complete data, as well as for all subjects with missing values at two weeks post-treatment replaced by those of four weeks post-treatment (next observation carried backwards, NOCB).

All analyses were run on an exploratory basis and were not corrected for the number of seeds, contrast directions and correlations.

3. Results

3.1. Study termination and clinical outcome

The study was terminated prematurely (December 2019) due to irreparable damage of the PET imaging equipment (PET results are reported elsewhere (Murgaš et al., 2022)). By then, 20 patients, aged 38.2 ± 12.2 years, with a full set of MRI scans matching the previously described criteria were available, including 15 patients receiving active stimulation and 5 patients allocated to the sham stimulation group. Demographic and clinical information of participants are depicted in Table 1.

Overall improvement in terms of a reduction of HAMD-17 compared to baseline was observed over both groups (main effect of time with $F = 21.583$, $p < 0.001$, linear mixed models analysis) There was no significant main effect of treatment group ($F = 0.307$, $p = 0.582$) and no significant interaction between group and time ($F = 1.787$, $p = 0.188$); for mean values, see Table 1. Separate analysis of the active TBS group yielded significant effects of time with larger effect size ($F = 37.422$ $p < 0.001$). One participant in the sham group reported an increase in depressive symptoms. In the treatment group, 8 participants (53 %) and in the sham group, two participants (40 %) were classified as responders. 3 participants, exclusively having received active stimulation, were classified as remitters after treatment. Raters' and patients' believes on treatment allocation confirmed successful blinding (see Table 1).

3.2. Baseline functional connectivity

To determine whether individual stimulation targets at left and right DLPFC were anticorrelated with the sgACC in the entire sample, we conducted a whole-brain voxel-wise analysis for the weighted ("Seed-map Approach") sgACC time courses (Cash et al., 2020). Results showed that both stimulation regions aimed for (MNI coordinates [±38, +44, +26]) coincided with clusters of voxels that are significantly anti-correlated with the sgACC on group level for all 20 subjects at a significance level of $p_{FWE,Cluster} = 0.05$. On the voxel level ($p_{FWE,Peak} < 0.05$) the left DLPFC cluster was found to be slightly inferior to the stimulation site (see Fig. 1). In line with above observations, 90 % of the recorded, individual stimulation sites were anticorrelated in the patients' respective sgACC connectivity maps.

Results further showed that the centroid of the individual most

Table 1
Demographics and clinical characteristics of study participants. Post-treatment scores were collected two and four weeks after the last TBS session, i.e. five (seven) weeks after the initial TBS treatment. The medication intake was stable prior to inclusion, and during the study, here displayed in four groups: namely drug-free (DF), intake of a selective serotonin reuptake inhibitor only (SSRI: incl. escitalopram, paroxetine), or intake of another antidepressant drug only (ATD: incl. amitryptiline, mirtazapine, melitracen, bupropione, mirtazapine, lithium, levothyroxine, opipramole), as well of combinations of substance groups (comb.), containing further substance groups, namely serotonin-noradrenaline reuptake inhibitors (SNRI: incl. venlafaxine, duloxetine, milnacipran), antipsychotic drugs (APD: incl. prothipendyl, quetiapine, flupentixole), benzodiazepines (BZD: incl. lorazepam), channel blockers (CB: incl. pregabaline, lamotrigine) or positive allosteric modulators (PAM: incl. zolpidem).
For mean values and standard deviations, missing values at two weeks were replaced by the next observation (next observation carried backwards, NOCB).

		Total	Treatment	Sham
Age		38.2 ± 12.2	36.1 ± 11.6	44.4 ± 13.2
Sex	F/M	12/8	8/7	4/1
Medication	DF/SSRI/ ATD/comb.	4/3/1/ 12	3/3/1/8	1/0/0/ 4
Comb.:	SSRI	4	4	0
	SNRI	6	3	3
	APD	6	4	2
	BZD	2	0	2
	CB	5	3	2
	PAM	1	0	1
	ATD	9	6	3
Baseline	HAMD-17	21.7 ± 3.9	20.5 ± 3.0	25.2 ± 4.7
	IDS-C	37.5 ± 8.4	35.4 ± 5.8	43.6 ± 12.3
	BDI-II	33.1 ± 8.2	31.9 ± 7.2	36.6 ± 10.9
Post-treatment (2 weeks, NOCB)	HAMD-17	12.5 ± 7.2	10.2 ± 5.6	19.2 ± 7.9
	IDS-C	25.0 ± 13.8	22.1 ± 13.0	33.8 ± 13.5
	BDI-II	24.1 ± 13.8	21.4 ± 12.4	32.0 ± 16.2
	Responders	10 (50 %)	8 (53 %)	2 (40 %)
	Remitters	3 (15 %)	3 (20 %)	0 (0 %)
	Worsened	1 (5 %)	0 (0 %)	1 (20 %)
Blinding correct/incorrect or inconclusive/missing	Self-assessment	6/10/4	5/8/4	1/2/0
	Rater assessment	8/11/1	6/10/1	2/1/0

anticorrelated cluster in the DLPFC (i.e., the "ideal", functionally defined stimulation location, (Cash et al., 2020)) was within a Euclidean distance of 13 mm of both actual stimulation targets (left: 11.9 ± 5 mm; right: 12.3 ± 5.9 mm (Mean ± SD)). When using stimulation targets as seed to determine voxel-wise functional connectivity to the whole-brain, we observed a significant positive correlation between left and right DLPFC seeds and clusters in bilateral AI, anterior cingulate, supplementary motor area, as well as other frontal and parietal regions (see Fig. 2 and Supplementary Table 1). Significant negative correlations were observed for several temporal clusters as well as frontal and occipital regions. There was no correlation between any of the stimulation target connectivities and symptom scores at baseline ($p \geq 0.05$).

To validate the hypothesis that sgACC-DLPFC connectivity predicts antidepressant treatment efficacy of stimulation targets (Fox et al., 2012; Weigand et al., 2018; Cash et al., 2020; Cash et al., 2019; Fox et al., 2013), we next determined whether baseline anticorrelation strength between individual stimulation targets and sgACC could predict antidepressant response in the active stimulation group. This analysis revealed no significant findings ($p \geq 0.05$). However, shorter Euclidean distances between the left stimulation target and the functionally defined "ideal" target (in terms of highest anticorrelation with the sgACC) for all subjects were significantly correlated with relative symptom improvement (% reduction in HAMD-17 score; $R_{Pearson} = 0.4664$; $p = 0.0382$, next observation carried backwards (NOCB) for missing values at two weeks post treatment). For post-treatment depression scores in the active stimulation group, we found correlations with left DLPFC-sgACC FC: $R_{Pearson} = 0.5603$; $p = 0.0581$ ($n = 12$ available at two weeks post treatment) and $R_{Pearson} = 0.6148$; $p = 0.0147$ ($n = 15$, NOCB).

Moreover, we observed a significant correlation ($R_{Pearson} = 0.6148$; $p = 0.0147$) between the absolute individual HAMD-17 reduction and the anticorrelation between sgACC and left individual stimulation targets when connectivity values were extracted from a normative connectivity map taken from (Cash et al., 2020), which is based on 2000 twenty-eight–minute resting-state scans from 1000 participants of the Human Connectome Project, (see Fig. 3).

3.3. Functional connectivity change over time

We first probed functional connectivity changes in the stimulation group. When placing the seed in the left and right stimulation target, respectively, there was no significant change for stimulation-target-to-sgACC connectivity. However, we observed a significant reduction in functional connectivity between the left stimulation target and bilateral AI (see Figs. 2 and 4 and Supplementary Material). No significant connectivity changes were observed for the right stimulation target. For the sham stimulation group, no significant connectivity changes were observed. Moreover, there was no significant correlation between connectivity changes and a change in any clinical symptom scale.

3.4. Functional connectivity after treatment

When determining if post-treatment connectivities (see Supplementary Material) correlate with post-treatment symptom scores, we observed a significant positive correlation (see Fig. 5), between left stimulation target-sgACC connectivity and residual HAMD-17 scores ($R_{Pearson} = 0.587$, $p = 0.045$) as well as IDS-C ($R_{Pearson} = 0.675$, $p = 0.016$) and a trend towards significance for BDI-II ($R_{Pearson} = 0.558$, $p = 0.060$). That is, the higher residual symptom load, the less anticorrelated was the left stimulation target with the sgACC.

4. Discussion

This study assessed the effects of a three-week bilateral sequential theta-burst stimulation, comprising left iTBS and right cTBS, on functional connectivity in treatment-resistant depression. The results were based on data from 20 patients of a prematurely closed multimodal trial and showed clinical improvement of TRD over both groups (active and sham) but no significant interaction effect of group, or group and time. The effect in the active TBS group was larger though, than in the combined analysis. In the active treatment group ($n = 15$), 53 % (8) of the patients responded (including remitters) and 20 % (3) remitted, while in the sham treatment group ($n = 5$), 40 % (2) responded and 0 % (0) remitted. The acquired resting-state fMRI data showed that the stimulation targets were anticorrelated with the sgACC in all patients, and that this association was important for treatment response. Shorter distances between actual stimulation targets, and ideal ones defined by anticorrelation with the sgACC according to (Cash et al., 2020) improved treatment response. Following active TBS treatment, no changes in stimulation target-to-sgACC connectivity, but a reduction of FC between the left DLPFC and anterior insula was found, in line with recent reports by Struckmann et al. (Struckmann et al., 2022).

Regarding the efficacy of the stimulation protocol in the unique TRD patient collective, our data show improvement of depression in both the active and sham TBS group. While there is considerable evidence for the efficacy of various rTMS protocols in major depression, data on new and

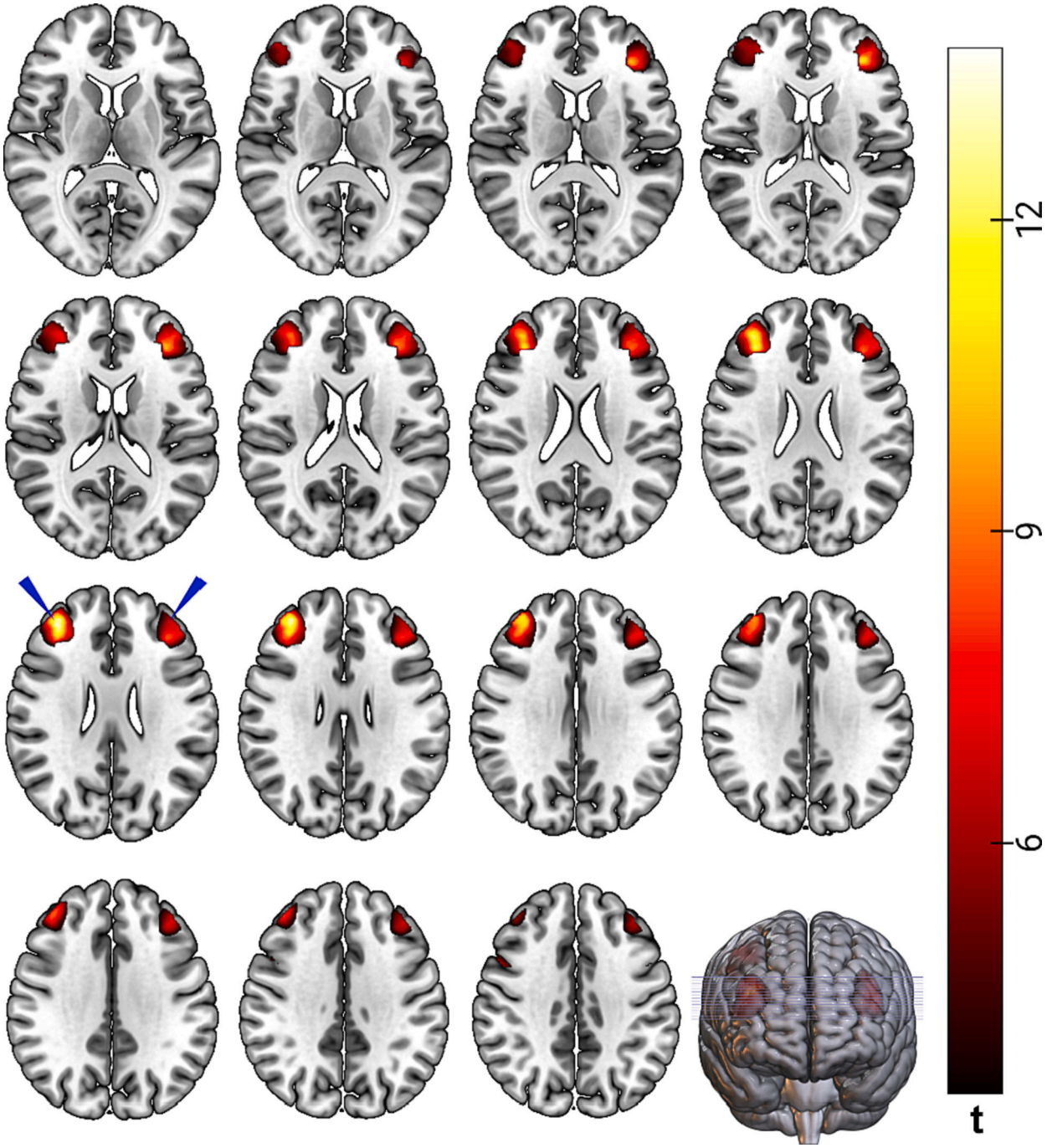

Fig. 1. Significantly anticorrelated clusters in both left and right dorsolateral prefrontal cortex were observed at group level (n = 20) corresponding to the anticipated stimulation sites in MNI space (indicated by blue arrows). $p_{uncorr} < 0.001$, height threshold $T = 3.58$; Color bar: T = [3.58, 13.66]; Left is right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

time efficient TBS protocols is only now being increasingly published, e.g. (Cole et al., 2022; Cole et al., 2020; Blumberger et al., 2022), which is also why there are no firm recommendations yet (Lefaucheur et al., 2020). Accordingly, the herein applied cTBS right and iTBS left protocol has been rated to have a probable but not yet fully proven antidepressant effect (Lefaucheur et al., 2020). A recent study in older adults with TRD, though, has established its noninferiority to the standard bilateral rTMS protocol and documented its good overall tolerability (Blumberger et al., 2022).

While most rTMS studies suggest treatment durations of 4–6 weeks, novel accelerated protocols using TBS reduce this overall time duration, increasing the stimulation density and taking advantage of spaced stimulation patterns. However, one important variable is the cumulative dose. Here, the three-week treatment course with two sessions per day lies in the upper field (with 36.000 TBS pulses), as compared to earlier protocols that applied a total of 12.000 pulses within four weeks (Blumberger et al., 2018). In contrast, the comparably recent SAINT/SNT protocol applies 90.000 pulses over 5 days, thus constituting the protocol with the highest cumulative dose in the shortest duration available to date, resulting in exceptional response rates (Cole et al., 2022; Cole et al., 2020).

While our response rate of 53 % is roughly comparable to previous well-powered trials investigating unilateral iTBS of the left DLPFC (Blumberger et al., 2016; Bakker et al., 2015), we could not find a similarly

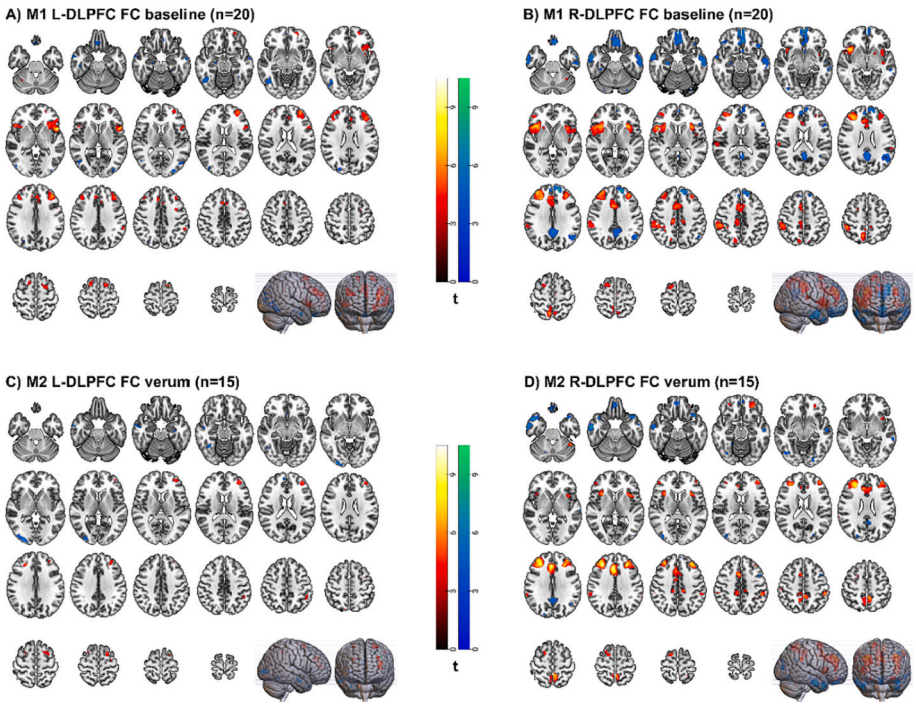

Fig. 2. Left (A, C) and right (B, D) DLPFC seeds' FC at baseline (M1) and after 3 weeks of bilateral TBS (M2). Positive correlation is shown in warm colors, anti-correlation in cold colors. Note the diminished FC in the verum group after receiving treatment. Only voxels with $p_{uncorr} > 0.001$ are shown.

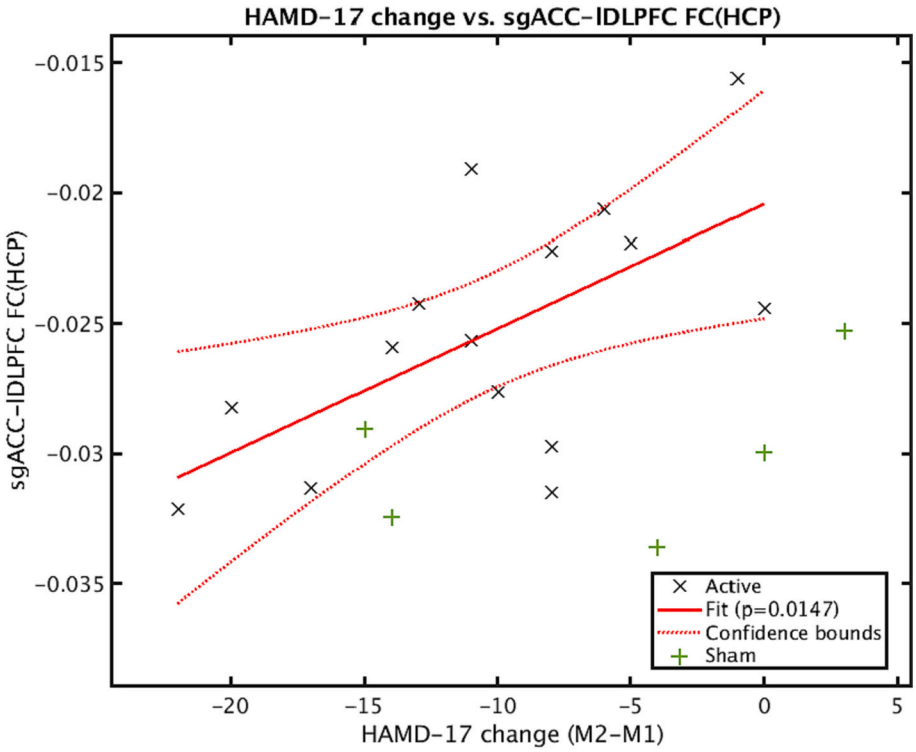

Fig. 3. There was a significant correlation between reduction in depressive symptoms in the verum group, as monitored with HAMD-17 scores, and functional connectivity towards the sgACC of the stimulation site, extracted from a FC map derived from the Human Connectome Project data.

high response rate for bilateral TBS as for example Li et al., who observed almost 67 % (Li et al., 2014). Our study would therefore rather suggest an efficacy comparable to unilateral iTBS. However, Cole et al. suggest, that left iTBS can result in a response rate of 84,6 % if administered with high doses and an optimized application pattern (Cole et al., 2022).

In line with our high response rate to sham stimulation (40 %), Li et al. also observed a considerable sham effect, especially for a subgroup with a low level of refractoriness (Li et al., 2014), a trait not assessed in our sample. It is conceivable, that other factors, such as regular social interaction to health-care personnel or having three-week daily routine

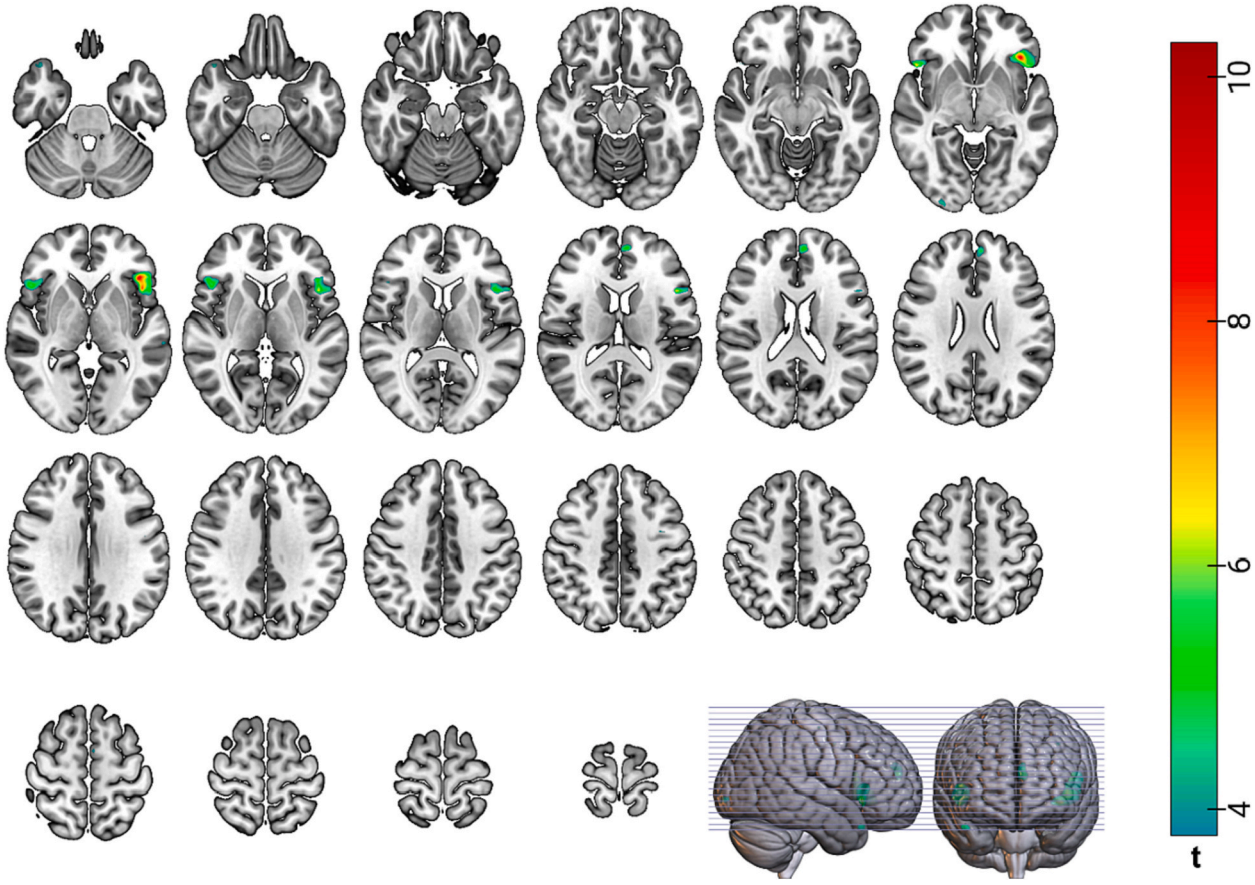

Fig. 4. In the bilateral anterior insula regions we observed significant ($p_{uncorr} < 0.001$, $p_{FWE\ Cluster} < 0.05$) functional connectivity (FC) reductions following three weeks of active theta-burst stimulation-treatment. FC-reduction in the superior frontal gyrus was significant only at $p_{uncorr} < 0.001$.
Height threshold $T = 3.79$ ($p_{uncorr} < 0.001$); Color bar: T = [3.79, 10.28]; Left is right.

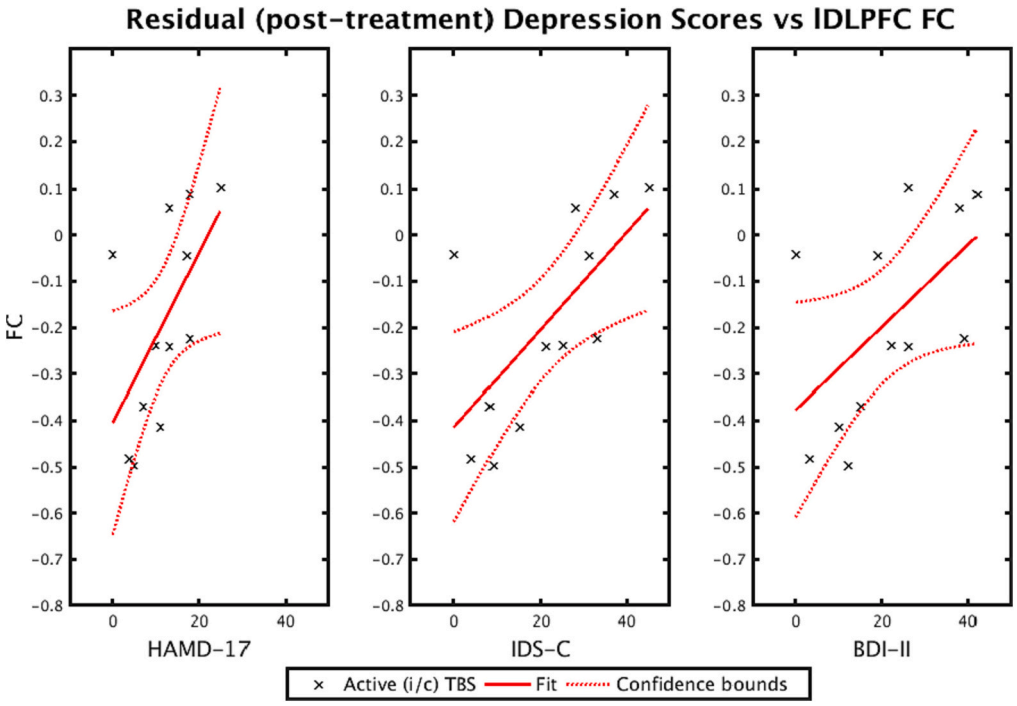

Fig. 5. Depression scores after three weeks of active theta-burst stimulation were correlated with post-treatment functional connectivity of the left dorsolateral prefrontal cortex stimulation site: HAMD-17: $R_{Pearson} = 0.587$, $p = 0.045$; IDS-C: $R_{Pearson} = 0.675$, $p = 0.016$; BDI-II: $R_{Pearson} = 0.558$, $p = 0.060$;
Please note, that due to incomplete data collection, depression scores two weeks post treatment were not fully available for each of the 15 treated subjects, thus $n = 12$.

may have contributed to the antidepressant effect. However, it should be kept in mind that due to the premature termination of our trial, our sham group is particularly small ($n = 5$), thus limiting transferability and the informative value of our results. Moreover, the response rate observed in both groups could also reflect the heterogeneity of the unique TRD patient population, where individual aspects ranging from biological, psychological, and sociocultural factors are likely to contribute to treatment-resistance (Dodd et al., 2021). Nonetheless, it should be noted that the remission rate of the comparable TRD patient collective in the third treatment step of the important STAR*D study was only 13.7 % (Rush et al., 2006). Therefore, our remission rate of 20 % following TBS, as well as the larger effect size in the active treatment group may be an argument in favor for the antidepressant effect of bilateral theta-burst stimulation. Likewise, the reductions of depression scores were markedly higher in the verum group as in the sham group. However, the direct comparison cannot be made with certainty, due to the skewed groups along with limited size of the sham group in our study.

We would next like turn to the neuroimaging data acquired in this study, that may contribute to the biological understanding of TRD, and the role bilateral TBS could have in its modulation. Most importantly, our study provided further evidence of the importance of an anticorrelation between stimulation targets primarily in the left DLPFC for antidepressant treatment success. First, stimulation targets in the left and right DLPFC were located within clusters that showed significant anticorrelation with the sgACC. Second, the distance of the left target to the largest baseline DLPFC-to-sgACC anticorrelation showed a significantly positive correlation with treatment response. This result partly confirms previous reports (Cash et al., 2020). Third, there was a significant correlation between treatment response and the FC between sgACC and left individual stimulation targets when connectivity values were extracted from a normative connectivity map taken from data of the Human Connectome Project. Fourth, after treatment, residual symptom load was significantly correlated with individual left stimulation target-to-sgACC connectivity. The higher residual symptom load, the less anticorrelated the left stimulation target was with the sgACC.

Our study indicates clinical relevance of sgACC-DLPFC connectivity primarily for the left but not right hemisphere. Interestingly, an early PET study using $_{15}$O-water demonstrated a link between mood changes and reciprocal changes in regional blood flow of sgACC and the right DLPFC. That is, with increasing scores for sadness, blood flow increases in sgACC were accompanied with blood flow decreases in right DLPFC, whereas depression recovery was associated with the reverse pattern of blood flow changes (Mayberg et al., 1999). This is in contradiction to the notion that stimulation of the right DLPFC should be inhibitory in order to counteract its presumed hyperactivity in MDD. Indeed, left HF rTMS and right LF rTMS have contrasting effects on metabolic activity in connected brain areas (Kito et al., 2011; Kito et al., 2008a; Kito et al., 2008b). Despite discrepant findings, our study does not preclude a role of right DLPFC in the antidepressant effect of therapeutic brain stimulation. More studies are needed to reveal the mechanism of action of bilateral sequential DLPFC stimulation involving left excitatory and right inhibitory stimulation.

According to the cognitive theory of depression posing prefrontal control over limbic hyper-activation, one would also expect a change in target-to-sgACC functional connectivity. Specifically, an increase in anticorrelation could be assumed and that such an increase correlates with treatment response. However, we did not observe such effect in our data, corroborating a previous study with a similar sample size, which also does not support this hypothesis (Liston et al., 2014). Studies showing an association between sgACC-to-DLPFC connectivity on the individual or group level tend to have twice our sample size (Weigand et al., 2018; Cash et al., 2019), thus the absence of such a relationship is most likely related to the insufficient sample size. Considering these aspects, rTMS may therefore not affect cognitive control networks directly, but rather modulate other networks including the DMN, as observed previously (Liston et al., 2014).

A central finding in our study is that bilateral TBS leads to a reduction in FC between the left stimulation target and bilateral AI, compatible with another recent publication (Struckmann et al., 2022). The AI is part of the SN, the main target network for rTMS in depression and addiction (Dunlop et al., 2017) and structural abnormities therein have been shown to be a common neural substrate of psychiatric disorders (Goodkind et al., 2015). A previous study in healthy participants observed an increased target-AI FC when stimulating the left DLPFC with cTBS (Gratton et al., 2013). Our results showing a reduction of FC upon iTBS to the left (and cTBS to the right) DLPFC are therefore compatible with this observation. Treatment-induced FC reduction as observed in our study may be interpreted as a decoupling of left DLPFC with the AI, which would contradict the notion of a strengthened SN upon brain stimulation. In any case, interpretations need to be done with caution, given that we observed no direct correlation with symptom improvement in our data.

With the emergence of MRI-compatible TMS-systems, in addition to baseline FC, acute FC changes have also more recently gained interest as predictors of treatment response. Among other regions, acute response in the insular cortices has been reported to robustly predict clinical improvements (Ge et al., 2022), additionally supporting involvement in TBS' mode of action.

Prefrontal and cognitive models of depression posit an insufficient top-down control of the prefrontal cortex over limbic hyperactivity in MDD (Disner et al., 2011; Mayberg, 1997) and non-invasive brain stimulation including rTMS supposedly counteracts this deficit (Plewnia et al., 2015). Our study contributes to these theories by demonstrating modulations within the SN upon bilateral sequential TBS.

4.1. Limitations

Our study has several limitations that compromise the interpretation of its results: First, due to the premature termination, the unintended small sample size, especially in the control group, suggests that interpretations should be made with caution. We also did not correct for multiplicity of whole-brain models and correlations, rendering our study exploratory. Second, accumulating evidence points to the importance of adequate dosing and specifically spaced stimulation patterns (Cole et al., 2022; Cole et al., 2020). It is conceivable that given the parameters used in our protocol, dosing and stimulation pattern were insufficient to achieve similarly pronounced antidepressant effects as, for example, the SAINT protocol (Cole et al., 2022; Cole et al., 2020). Third, positive psychological effects of the daily interaction with health-care personnel cannot be ruled out and could also explain improved symptoms without active TBS. Fourth, although patients were resistant to pharmacological treatment and on stable medication, effects and interactions with TBS cannot be ruled out. Finally, although unlikely, a subtle effect of the magnetic field in the sham orientation of the coil may also play a role in the response rates to the sham stimulation.

5. Conclusions

Our study investigated the influence of bilateral sequential theta-burst stimulation on functional connectivity in treatment-resistant depression. Imaging results are compatible with previous findings, highlighting the clinical importance of the connection between the dorsolateral prefrontal and the subgenual cingulate cortex. We further show changes within the salience network, a network thought to be crucial for the therapeutic effect of repetitive transcranial magnetic stimulation. Our study thus contributes to the growing body of literature on the effects of transcranial magnetic stimulation on functional connectivity in depression, yet inferences from our limited data about the efficacy of the protocol should be drawn with caution.

CRediT authorship contribution statement

Peter Stöhrmann: Methodology, Data Curation, Processing & Analysis, Writing-Original Draft, Writing-Review & Editing, Visualization; Godber M Godbersen: Investigation, Data Acquisition & Curation, Writing-Review & Editing; Murray B Reed: Resources, Investigation, Methodology, Data Acquisition & Curation, Writing-Review & Editing; Jakob Unterholzner: Investigation, Data Acquisition, Writing-Review & Editing; Manfred Klöbl: Methodology, Resources, Investigation, Data Acquisition & Curation, Writing-Review & Editing; Pia Baldinger-Melich: Investigation, Data Acquisition, Writing-Review & Editing; Thomas Vanicek: Investigation, Data Acquisition, Writing-Review & Editing; Andreas Hahn: Conceptualization, Methodology, Investigation, Data Acquisition & Curation, Writing-Review & Editing; Rupert Lanzenberger: Funding, Conceptualization, Methodology, Resources, Writing-Review & Editing, Supervision, Project administration; Siegfried Kasper: Funding, Supervision, Conceptualization, Resources, Project administration, Writing-Review & Editing; Georg S. Kranz: Conceptualization, Methodology, Writing-Original Draft, Writing-Review & Editing, Supervision, Project administration.

Conflict of interest

In the past 3 years S. Kasper has received grant/research support from Lundbeck; he has served as a consultant or on advisory boards for Angelini, Biogen, Esai, Janssen, IQVIA, Lundbeck, Mylan, Recordati, Sage and Schwabe; and he has served on speaker bureaus for Abbott, Angelini, Aspen Farmaceutica S.A., Biogen, Janssen, Lundbeck, Recordati, Sage, Sanofi, Schwabe, Servier, Sun Pharma and Vifor. R. Lanzenberger received investigator-initiated research funding from Siemens Healthcare regarding clinical research using PET/MR. He is a shareholder of the start-up company BM Health GmbH since 2019. G.S. Kranz declares that he received conference speaker honorarium from Roche, AOP Orphan and Pfizer. T. Vanicek has served on speaker bureaus for Jansen. The other authors do not report any conflict of interest.

Data availability

Due to data protection laws, processed, anonymized data is only available from the authors upon reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.12.088.

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