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Total number of authors:
13

Published in:
NeuroImage

Link to article, DOI:
10.1016/j.neuroimage.2024.120596

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

NeuroImage 291 (2024) 120596

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Neural response during prefrontal theta burst stimulation: Interleaved TMS-fMRI of full iTBS protocols

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ARTICLE INFO

Keywords:
Functional MRI (fMRI)
Transcranial magnetic stimulation (TMS)
Concurrent TMS-fMRI
Interleaved iTBS-fMRI
Non-invasive brain stimulation
Neuromodulation

ABSTRACT

Background: Left prefrontal intermittent theta-burst stimulation (iTBS) has emerged as a safe and effective transcranial magnetic stimulation (TMS) treatment protocol in depression. Though network effects after iTBS have been widely studied, the deeper mechanistic understanding of target engagement is still at its beginning. Here, we investigate the feasibility of a novel integrated TMS-fMRI setup and accelerated echo planar imaging protocol to directly observe the immediate effects of full iTBS treatment sessions.
Objective/hypothesis: In our effort to explore interleaved iTBS-fMRI feasibility, we hypothesize that TMS will induce acute BOLD signal changes in both the stimulated area and interconnected neural regions.
Methods: Concurrent TMS-fMRI with full sessions of neuronavigated iTBS (i.e. 600 pulses) of the left dorsolateral prefrontal cortex (DLPFC) was investigated in 18 healthy participants. In addition, we conducted four TMS-fMRI sessions in a single patient on long-term maintenance iTBS for bipolar depression to test the transfer to clinical cases.
Results: Concurrent TMS-fMRI was feasible for iTBS sequences with 600 pulses. During interleaved iTBS-fMRI, an increase of the BOLD signal was observed in a network including bilateral DLPFC regions. In the clinical case, a reduced BOLD response was found in the left DLPFC and the subgenual anterior cingulate cortex, with high variability across individual sessions.
Conclusions: Full iTBS sessions as applied for the treatment of depressive disorders can be established in the interleaved iTBS-fMRI paradigm. In the future, this experimental approach could be valuable in clinical samples, for demonstrating target engagement by iTBS protocols and investigating their mechanisms of therapeutic action.

1. Introduction

In the field of non-invasive brain stimulation (NIBS) techniques, repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) has been developed into an effective treatment for depressive disorders (Brunoni et al., 2017; Kan et al., 2023). Intermittent theta-burst stimulation (iTBS) is a variant of rTMS and was originally introduced for motor cortex stimulation based on its capacity for inducing long-term potentiation-like plasticity effects through a coupling between gamma (circa 50 Hz) and theta rhythms (circa 5 Hz). More recently, iTBS has been applied over prefrontal cortex regions and established as therapeutic intervention for people with depressive

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https://doi.org/10.1016/j.neuroimage.2024.120596
Received 13 November 2023; Received in revised form 25 March 2024; Accepted 28 March 2024
Available online 29 March 2024

disorders (Grossheinrich et al., ; Huang et al., 2005; Suppa et al., 2016). Besides its potential superiority in inducing plasticity effects (Hermiller et al., 2020), iTBS has the clear advantage of shorter treatment duration, i.e. 3 min and 20 s as compared to 37.5 min for the standard 10 Hz protocol (Blumberger et al., 2018), and can easily be repeated in accelerated iTBS protocols (Cole et al., 2020).

Previous rTMS studies have shown changes in functional MRI connectivity within and between brain networks in MDD, and symptom reduction has been associated with individual connectivity patterns, e.g. with functional connectivity between subgenual anterior cingulate cortex (sgACC) and prefrontal cortex regions (Salomons et al., 2014; Liston et al., 2014; Baeken et al., 2014; Baeken et al., 2017; Tik et al., 2017; Vink et al., 2018; Weigand et al., 2018; Ge et al., 2020; Tura and Goya-Maldonado, 2023). However, disentangling mechanistic effects of rTMS protocols at the cortex level from non-specific network modulation due to auditory and somatosensory artefacts as well as intra-individual changes of brain states is challenging and demonstration of causality and target engagement difficult to achieve (Siebner et al., 2022). To fill this knowledge gap, researchers have combined magnetic resonance imaging (MRI) with TMS to investigate the immediate blood-oxygen-level-dependent (BOLD) response caused by TMS, a technique commonly known as combined or concurrent TMS-fMRI (Bohning et al., 1998; Bergmann et al., 2021; Mizutani-Tiebel et al., 2022). The first publication on combined TMS-fMRI was more than 20 years ago, but the field has shown relatively slow growth since (Bohning et al., 1998; Bohning et al., 1999), which may have been due to technical constraints. Early concurrent TMS-fMRI setups showed low signal-to-noise-ratio (SNR) and TMS-induced artifacts during fMRI acquisition (Bergmann et al., 2021; Mizutani-Tiebel et al., 2022; Riddle et al., 2022). As a result, only a few prior studies have explored the effects of rTMS on the left DLPFC (Vink et al., 2018; Hanlon et al., 2013; Li et al., 2004; Hawco et al., 2017; Oathes et al., 2021; Tik et al., 2023a,b; Nahas et al., 2001). Importantly, previous concurrent TMS-fMRI studies have investigated short rTMS sequences, but not full iTBS protocols (e.g. 600 pulses) as originally reported (Huang et al., 2005).

Given that iTBS protocols are used for clinical treatment of depressive disorders and other psychiatric conditions (Kan et al., 2023), there is a strong research interest in the acute effects of such protocols in health and disease. Thus, the main focus of the current study was the feasibility of interleaved iTBS-fMRI within an integrated TMS-fMRI setup and accelerated echo planar imaging (EPI) protocol. Our hypothesis was that iTBS leads to acute changes of BOLD signal in the iTBS target area as well as in interconnected regions. In order to investigate feasibility in a clinical context, we additionally applied our approach in a patient with bipolar depression during long-term iTBS maintenance treatment at four different time points.

2. Methods & materials

2.1. Samples

2.1.1. Healthy participants

We recruited 27 healthy right-handed adult participants who met the usual MRI and TMS inclusion criteria (incl. no history of psychiatric or neurological conditions). Six subjects dropped out after the baseline session due to high resting motor thresholds (rMT), DLPFC stimulation intolerance (after TMS test pulses), or incidental findings in the brain. Additionally, 2 subjects dropped out during the interleaved TMS-fMRI sessions due to either personal reasons and or the implantation of a new medical device. Finally, 19 participants completed all four sessions of the experiment (8 females, 11 males; ages 21–36 years, average age = 26.4 years, standard deviation = 3.2 years). All participants signed written informed consent approved by the LMU ethical committee in accordance with the Declaration of Helsinki.

2.1.2. Patient with bipolar depression

We recruited a 59-year-old male patient who has been undergoing long-term maintenance treatment at our department for recurrent major depressive episodes in bipolar disorder. The patient was first admitted to a psychiatric ward at the age of 24 (1986), and over the next 20 years, 5 further inpatient stays followed. He was finally diagnosed with bipolar disorder with predominantly depressive episodes. In 2009, after most available treatment options had failed, TMS treatment was offered to the patient, within a series of the first clinical iTBS applications in patients with depressive episodes (Holzer and Padberg, 2010). Following the start of iTBS, in addition to the continuation of the patient's medication and regular outpatient visits, the severity of symptoms decreased and no further inpatient treatment has been required since. However, minor to medium, rarely severe, depressive and occasionally hypomanic symptoms have occurred over the years, so that the maintenance iTBS treatment could not be phased out fully and was maintained at a varying frequency of 1–3 times per week, adapted to patient condition. To date, the patient has received almost 1500 rTMS sessions. He participated in 4 interleaved iTBS-fMRI treatment sessions, conceived as an initial exploration into the topic of test-retest reliability in a single-subject. The patient met the criteria for the TMS and MRI safety check and also participated in a baseline session before undergoing the concurrent TMS-fMRI. During the concurrent TMS-fMRI, the patient received 80% rMT stimulation of the DLPFC.

2.2. Experimental setup

For this study, all participants were requested to complete at least two experimental sessions. These sessions included a baseline assessment and an interleaved iTBS-fMRI 80% rMT DLPFC session, with a minimum of one week between each session. During the baseline session, participants were required to provide written informed consent and subsequently underwent structural and functional MRI scans for neuronavigation, rMT measurement inside the MR scanner, and test stimulation over the left DLPFC with 80% rMT intensity to assess their ability to tolerate discomfort caused by TMS. The second session involved a concurrent TMS-fMRI session. Photos illustrating an example of our TMS-fMRI setup are available in Mizutani-Tiebel et al. (2022) and Fig. 1C.

2.2.1. Magnetic resonance imaging

In the baseline session, we collected structural MRI and resting-state functional MRI (rsfMRI) using a 3T Siemens PRISMA scanner (Siemens, Erlangen, Germany) with a standard 64-channel head/neck coil. Structural images were acquired using a T1-weighted MPRAGE (Magnetization-Prepared Rapid Acquisition with Gradient Echo) sequence (TR = 2300 ms; TE = 2.26 ms; TI = 900 ms; flip angle = 8°; voxel size 1 × 1 × 1 mm; 256 mm FOV; number of slices = 192; scan duration 5 min 21 s), and a T2-weighted SPACE (Sampling Perfection with Application-optimized Contrasts) sequence (TR = 5000 ms; TE = 383 ms; TI =1800 ms; voxel size 1 × 1 × 1 mm; 256 mm FOV; number of slices = 176; scan duration 4 min 57 s).

2.2.2. Concurrent TMS-fMRI

For concurrent TMS-fMRI, an integrated system with two 7-channel surface RF coils (Navarro de Lara et al., 2015) and an MR-compatible TMS set-up (MagVenture A/S, Farum, Denmark). One RF coil was mounted with the TMS coil, while the other was placed over the contralateral hemisphere to ensure complete brain coverage. An MP2RAGE sequence (TR = 4000 ms, TE = 2.98 ms, TI1/TI2 = 700/2500 ms, flip angle 1/flip angle 2 = 4° / 5°, 160 slices, 1 mm slice thickness), was used to perform a structural scan in the concurrent TMS-fMRI sessions (Marques et al., 2010).

Interleaved iTBS-fMRI was performed continuously for 3 min and 32 s (12 s dummy scan included), using a multiband EPI sequence with an MB-factor of 4, TR = 2000 ms, TE = 30 ms, 40 slices, and voxel size of

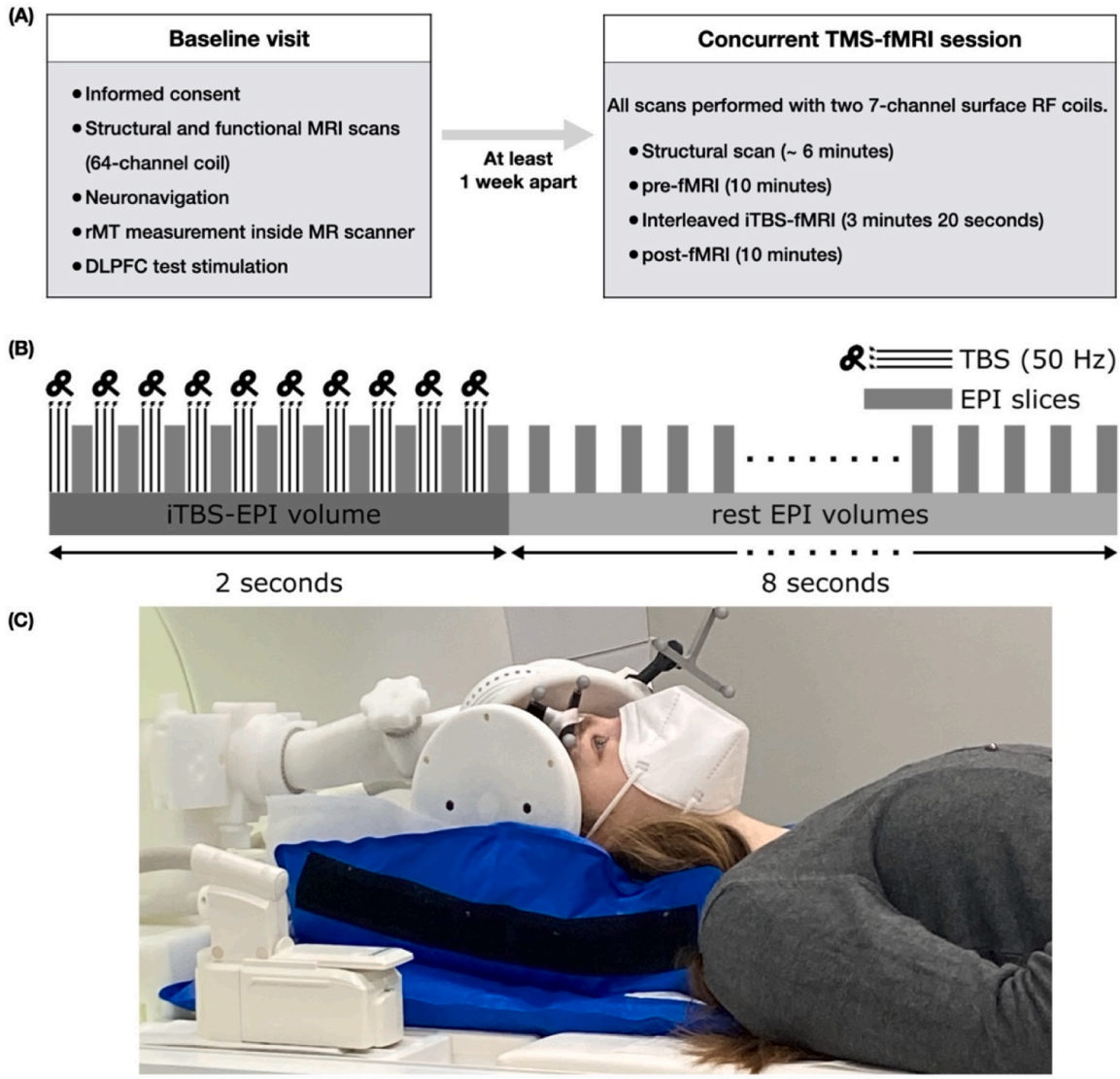

Fig. 1. (A)The experiment protocol on the baseline visit and concurrent TMS-fMRI session. (B)The interleaved iTBS-fMRI sequence. The standard clinical iTBS consisted of 50 Hz triplets repeated 10 times at 5 Hz over 2 s, followed by 8 s of rest. The train was repeated 20 times. EPIs were acquired continuously throughout the stimulation paradigm. (C)Concurrent TMS-fMRI set-up with two 7-channel surface RF coils positioned over the left and right anterior hemisphere. The MR-compatible TMS coil was mounted on top of the left RF coil and positioned over the stimulation target (left DLPFC). The mask was exclusively worn during the photo session.

3.3 × 3.3 × 3 mm. This protocol matches standard clinical iTBS protocols and consists of 50 Hz triplets repeated 10 times (at 5 Hz) within 2 s (Huang et al., 2005; Suppa et al., 2016), followed by 8 s inter train interval.

2.2.3. Neuronavigation

T1-weighted images from the baseline session (see above) were used for MR-compatible neuronavigation (Localite GmbH, Bonn, Germany) with a Polaris Vega camera (NDI, Waterloo, Canada) to target the left DLPFC. The left DLPFC target was determined using MNI (x,y,z) coordinates of −38, 44, 26 with the coil rotated at a 45° angle to midline. This targeting approach has been demonstrated to be clinically effective, safe, and as well-tolerated in iTBS as standard 10 Hz rTMS treatment of patients with treatment-resistant depression (Blumberger et al., 2018). To replicate the typical clinical setting, the clinical case utilized an EEG cap with 5 cm rules to locate the left DLPFC position (George et al., 1995), and stimulation location was recorded with neuronavigation.

2.2.4. TMS

All TMS was performed inside the MRI scanner room using an MRi-B91 MR-compatible TMS coil and MagProX100 stimulator (MagVenture A/S, Farum, Denmark). Biphasic pulses were used with a duration of approximately 290 μs. Maximum machine output is 180 A/μs (di/dt).

A 7-channel surface RF coil (Navarro de Lara et al., 2015) was mounted to the TMS coil throughout our concurrent TMS-fMRI sessions and motor threshold determination, which increased the distance between the TMS coil and skull, resulting in higher thresholds than usual. For motor threshold determination, participants were positioned lying down, and their hands relaxed on the MR scanner bed, using an MR-compatible electromyography (EMG) recorder (Brain Product, Gilching, Germany). EMG electrodes were attached over the right abductor pollicis brevis (APB), and a ground electrode was placed over the right ankle. Suprathreshold motor-evoked potentials (MEP) were defined as responses with amplitudes greater than 50 μV within 15 and 35 ms after each TMS pulse. The TMS intensity was reduced in steps of 2% of the stimulator output until such MEP responses were absent in 5 out of 10 trials.

2.2.5. MRI data preprocessing

Preprocessing was performed as described in Tik et al. (2023a) using Matlab, SPM12, AFNI and ANTS transformation of EPIs into MNI space (cat12) and spatial smoothing with a 6 mm FWHM Gaussian kernel (SPM12).

2.2.6. Statistical analyses

Both single-subject and group-level analyses were performed using SPM12. One subject was excluded due to showing excessive motion (more than 3 mm). For single-subject (first-level) analysis linear regression was performed on each voxel using generalized least squares with a global approximate AR (Brunoni et al., 2017) autocorrelation model and high-pass filter with a cutoff of 128 s. The regressors were 2-second blocks of theta burst volleys. The beta (β) map from first-level (theta burst block) generalized linear model (GLM) analyses were used for the group analysis in SPM12, performed with linear regression on each voxel and one-sample *t*-tests. Resulting single-subject beta map estimates of BOLD responses were used for group analyses. Linear regression was performed at each voxel, using generalized least squares with a global repeated measures correlation model.

2.2.7. E-field simulation

We utilized SimNIBS 4.0 (https://simnibs.github.io/simnibs/build/html/index.html), a free software package designed for electric field modeling in NIBS such as TMS. Prior to conducting the E-field simulation, it was necessary to generate a volume conductor model of each subject's head. This was accomplished using "charm", which uses anatomical MRI images (T1-weighted & T2-weighted) acquired from the baseline session. For the simulation of DLPFC TMS, we specified the MRi-B91 TMS coil file and set the stimulation intensity to the di/dt value recorded from the TMS stimulator during the iTBS protocol at 80% rMT for each subject. The first TMS marker saved during neuronavigation provided the location and orientation of the TMS coil.

The group-level analysis of peak electric field magnitude and focality included a total of 16 subjects from the MRI data analysis, because two subjects did not have TMS markers recorded during neuronavigation.

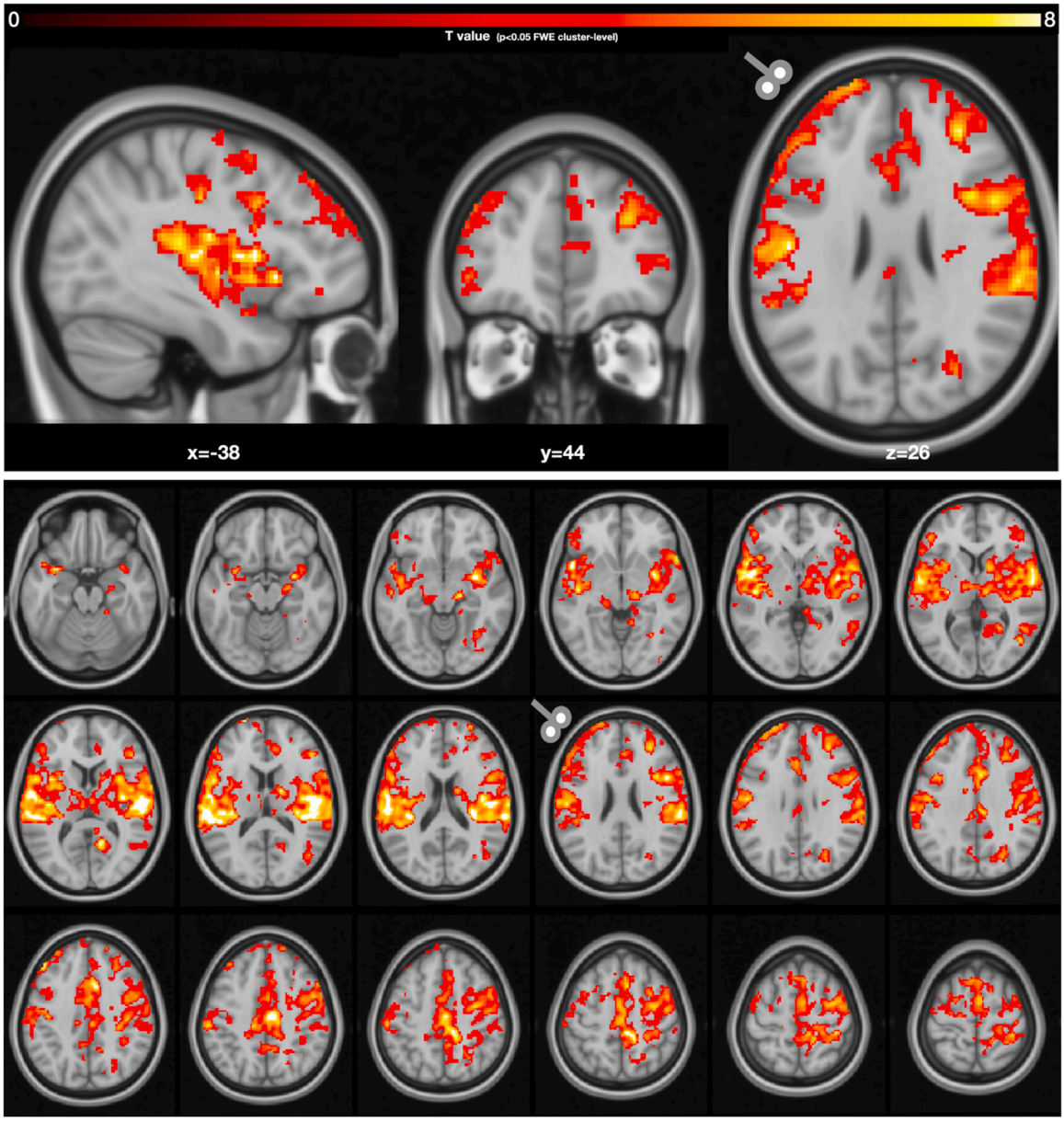

Fig. 2. Acute BOLD changes during interleaved iTBS-fMRI in healthy subjects. A full iTBS protocol (i.e. 600 pulses) resulted in increased brain activation, bilaterally in the DLPFC and auditory cortex regions as well as the right superior frontal gyrus.

We visualized the group results by transforming the individual simulation results from native space to MNI space in order to present the group peak electric field (Saturnino et al., 2019).

3. Results

3.1. Healthy controls

Mean rMT was 83% (sd = 12%) of maximum stimulator output, corresponding to the recorded dI/dt of 120 A/μs (sd = 19.1 A/μs). Note that the effective stimulation intensity is lower in the TMS-fMRI set-up compared to standard TMS settings because of several factors: (a) the cable length, (b) the hardware for suppressing leakages, and (c) an increased coil-to-brain distance due to the RF coil, where the TMS coil is mounted on.

Subjects were asked to self-report their pain levels during and after the TMS sessions (see Supplementary Fig. S1). This result suggests that the interleaved iTBS-fMRI procedure was generally tolerable, as the reported pain levels were tolerable, with a reasonable degree of variability among the participants.

3.1.1. Immediate BOLD changes during interleaved iTBS-fMRI in healthy subjects

As shown in Fig. 2 and Table 1, iTBS resulted in increased brain activation in the bilateral DLPFC (left DLPFC peak at −20, 68, 14 mm MNI, t = 10.3; right DLPFC peak at 32, 42, 26 mm MNI, t = 7.74), bilateral auditory cortex consistent with perception of the sound of TMS (left temporal region peak at −56, −8, 8 mm MNI, t = 12.3; right temporal region peak at 48, −12, 14 mm MNI, t = 12.3), and right superior frontal gyrus (28, 62, 18 mm MNI, t = 6.87).

3.1.2. Group results of SimNIBS based e-field models

We compared the patterns of BOLD response to interleaved iTBS-fMRI with the intensity and distribution of the iTBS induced electric field (e-field) (Fig. 3). Although the e-field was distributed around the primary target region, i.e. the left DLPFC, there was significant variability in positioning, attributable to variation in individual anatomy. Note that this simulation only models the acute effect of TMS on tissue and not any spreading across synapses to other brain areas.

3.2. Clinical case

3.2.1. Clinical information

During study participation, the patient continued his long-term medication (i.e. 20 (mornings) / 0 (evenings) mg citalopram, 25 / 250 mg quetiapine IR, 0 / 200 mg quetiapine XR, 300 / 300 mg pregabalin, and 100 / 200 mg lamotrigine daily, with additional 25 mg of quetiapine and 0,25 mg lorazepam to be taken as needed, on average twice per week). The interleaved iTBS-fMRI sessions were consistently conducted in the early afternoon, ensuring a consistent time gap between MRI scans and medication administration. Depression questionnaires (Hamilton rating scale for depression, Montgomery–Åsberg Depression Rating Scale) are being collected as part of the standard care of the patient and suggested mild depressive symptoms during study participation (HAMD 9–12, MADRS 9–10). While the clinical symptoms remained stable at less severe levels throughout our investigations, the patient underwent subtle mood changes from his bipolar disorder which resulted in dosage adaptations by the patient himself (i.e. citalopram increased at visit 4, lorazepam discontinued after visit 2). The patient was able to participate in the TMS-fMRI experiment without any adverse events.

Table 1
Peak BOLD activation results during interleaved iTBS-fMRI.

Peak activation during interleaved iTBS-fMRI						
Area	peak MNI (mm)			cluster size	t-value	Z
Left dorsolateral prefrontal region	−20	68	14	34,033	10.03	5.66
Left temporal region	−56	−8	8		12.3	6.17
Right temporal region	48	−12	14		14.52	6.52
Right dorsolateral prefrontal region	32	42	26	1036	7.74	5.00
Right superior frontal region	28	62	18		6.87	4.69

3.2.2. Interleaved iTBS-fMRI: results of a clinical case study

MRI quality control (see Supplementary Fig. S3) and visual inspection were performed before data analysis, and we had to exclude the results from the third session due to strong ghosting artifacts. We found considerable variance in activation pattern over the three sessions: During the first session, we found a statistically significant reduction of BOLD response in the left DLPFC region (peak at −24, 44, 38 mm MNI, t = −6.5) located at the stimulation site. In the second session, a significant BOLD reduction was observed in the sgACC region (peak at 6, 16, −14 mm MNI, t = −13.08). In the fourth session, we did not observe any statistically significant BOLD changes in the left DLPFC or sgACC regions.

4. Discussion

4.1. Feasibility of interleaved TMS-fMRI with full clinical iTBS protocols

This study shows that interleaved TMS-fMRI can be applied with 600 pulses of iTBS (Huang et al., 2005) as originally reported by Huang et al. (Huang et al., 2005) and clinically used for the treatment of depressive disorders (Holzer and Padberg, 2010; Blumberger et al., 2018). In addition, test-retest TMS-fMRI sessions were conducted in a single patient with a bipolar depression in order to test the transfer of this paradigm in a clinical case.

Previous concurrent TMS-fMRI studies have only used much shorter sequences of rTMS, e.g. TBS with 30 pulses in 2 s (Hermiller et al., 2020), but not full rTMS treatment protocols, due to restrictions from coil capacity and cooling in TMS-fMRI setting (see reviews by (Bergmann et al., 2021; Mizutani-Tiebel et al., 2022)). However, concurrent TMS-fMRI represents a promising approach in specialized settings for investigating effects of iTBS and other protocols, and allows studying acute and short-term effects of iTBS on regional BOLD activation and connectivity. None of the participants reported any adverse effects during or after the experiment, indicating a generally safe and well-tolerated procedure.

4.2. Neural response to iTBS in healthy individuals

In healthy subjects, we observed an increase in BOLD signals during iTBS (600 pulses) of the left DLPFC in several regions, including the bilateral DLPFC, bilateral auditory cortex, and contralateral frontal areas beyond DLPFC regions (Fig. 2). In contrast, the majority of previous concurrent TMS-fMRI studies has primarily used low-frequency (e.g., 1 Hz) rTMS, or single TMS pulses, or only applied high frequency protocols with a low number of pulses delivered (Nahas et al., 2001; Li et al., 2004; Dowdle et al., 2018; Eshel et al., 2020; M Tik et al., 2023; M Tik et al., 2023). Furthermore, most of these studies used suprathreshold intensity during TMS, and it has generally been observed that higher TMS intensity result in greater BOLD activation underneath the coil compared to subthreshold intensities (Bohning et al., 1999; M Tik et al., 2023; Nahas et al., 2001; Navarro de Lara et al., 2017). Despite utilizing an iTBS protocol at 80% rMT intensity, i.e. a protocol very close to the original iTBS protocol by Huang et al. (Huang et al., 2005), our study still yielded significant BOLD activations in both directly stimulated and remote areas. However, it is important to note that we observed changes in BOLD activation only in cortical, but not in subcortical regions. This finding differs from those of other TMS-fMRI studies targeting the left DLPFC, which also observed BOLD changes in subcortical regions, e.g.

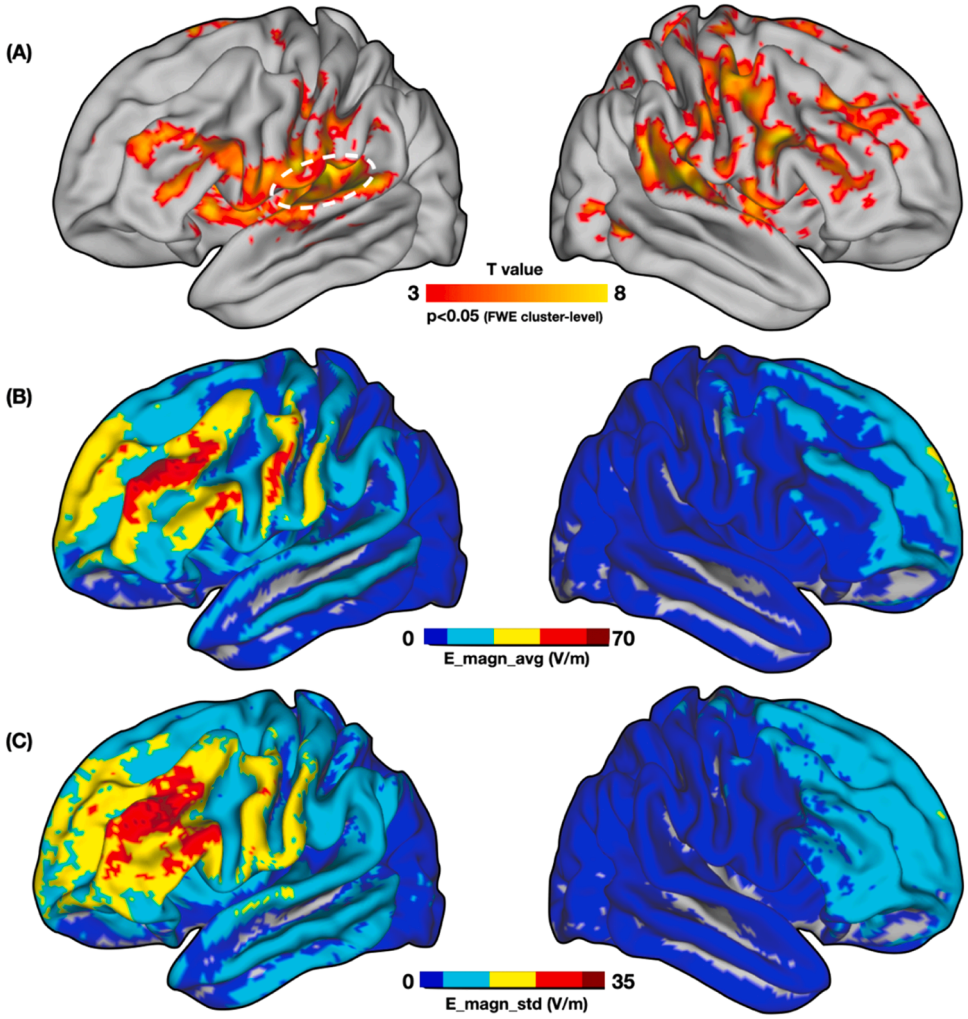

Fig. 3. (A) Acute BOLD changes during iTBS (i.e. 600 pulses) in the healthy control group. Auditory cortex activation is represented by the marked white dashed line. (B) E-field simulation group average peak electric field magnitude and focality in 16 subjects. (C) E-field simulation group standard deviation in magnitude value in 16 subjects.

sgACC (Vink et al., 2018; Hanlon et al., 2013; Oathes et al., 2021); however, Vink et al. (2018) noted that only half of their sample showed this activation pattern. This heterogeneity in findings may be attributed to several factors, such as different TMS and fMRI protocols, and the two RF coils used in this study, which were attached at the left and right frontal regions. This configuration may have resulted in limited tSNR in the subcortical and occipital regions (Supplementary Fig. S4). We believe that incorporating a third RF coil, particularly to cover the occipital region, could potentially enhance the tSNR across the whole brain.

Moreover, it is important to highlight that changes in BOLD activation in healthy subjects were not confined to the iTBS target region (i.e. the left DLPFC), but rather spread to other prefrontal areas. This distribution may be compared with our e-field modeling results, which also indicated non-focal DLPFC stimulation, which may be influenced by variability in DLPFC targeting. To analyze the change of BOLD activation over the course of an iTBS session, we conducted an investigation wherein the complete 20 iTBS trains were divided into four blocks, each consisting of 5 trains of iTBS (equivalent to 150 stimuli). Interestingly, in the initial block, the left stimulated DLPFC did not exhibit strong BOLD activation at the stimulated location, as the number of iTBS stimuli increased, we observed a cumulative effect, resulting in stronger BOLD activation in the left prefrontal region (see Supplementary Fig. S5). Given that this is the first complete iTBS protocol conducted inside MRI, our primary aim was to present the most straightforward and comprehensible analyses. We therefore provide fMRI results with minimal data preprocessing. However, it is important to mention that previous research has suggested the necessity of including independent component analysis (ICA) denoising in the preprocessing pipeline for concurrent TMS-fMRI data. The rationale behind this recommendation is that the TMS coil can induce vibrations and leakage currents, and these effects can persist for up to 8 s after TMS (Riddle et al., 2022). ICA analysis may be better at eliminating these and other artifacts, but at the cost that ICA may also eliminate biologically relevant information.

4.3. Neural response across three TMS-fMRI sessions in a single patient with bipolar depression

In a further step, we applied the concurrent TMS-fMRI protocol with full 600 pulse iTBS sessions in a patient who has undergone long-term iTBS treatment for bipolar depression. In a clinical setting, this approach allows monitoring the effects of iTBS on a patient during maintenance treatment. Despite the patient's prior experience with TMS, remaining inside the MRI for over thirty minutes posed a challenge and resulted in increased motion compared to healthy controls. We initially conducted quality control measures on motion, temporal signal to noise ratio (tSNR) calculation, and visual inspection (see supplementary materials). We noted that the third session showed strong

ghosting artifacts, and this dataset was consequently excluded from further analysis. Across the remaining three sessions, we observed a high degree of inter-session variability in BOLD effects. For example, we found reduced neural activity in the stimulated area, the left DLPFC (Fig. 4), during the first session. There are several possible reasons for this variability, e.g. intra-individual variation of brain states or differences in coil position/orientation in relation to target regions, i.e. DLPFC and interconnected sgACC areas (Fox et al., 2012; Fox et al., 2013; Dunlop et al., 2017; Weigand et al., 2018; Cash et al., 2019). Importantly, the distance between the TMS coil and the cortex was variable across sessions, which could have been due to differences in coil positioning; i.e. the coil-to-cortex distance was larger in the first (37 mm) and second (38 mm) sessions, while it was reduced in the third (25 mm) and fourth (28 mm) sessions. Taken together, we acknowledge that there are (at least) four of sources of variability in the measurement of target engagement with TMS-fMRI which are essential for future studies to investigate: (Brunoni et al., 2017) fluctuations in the tSNR; (Kan et al., 2023) variations in the coil position and hence distance between TMS coil and cortex; (Grossheinrich et al.,) intrinsic spontaneous fluctuation in resting functional connectivity between sessions; and (Huang et al., 2005) the subject's psychopathological status (i.e. healthy volunteers or patient population).

4.4. Limitations

While piloting this approach, our study does not allow the interpretation of BOLD signal changes as being specific to iTBS of the DLPFC, as auditory and somatosensory effects were not controlled for in our experiment, and could significantly contribute to large scale network activation (Siebner et al., 2019), for example through activating auditory cortex. Additionally, our experiment lacks sham iTBS or other active sites for comparison. Including a sham or other active site

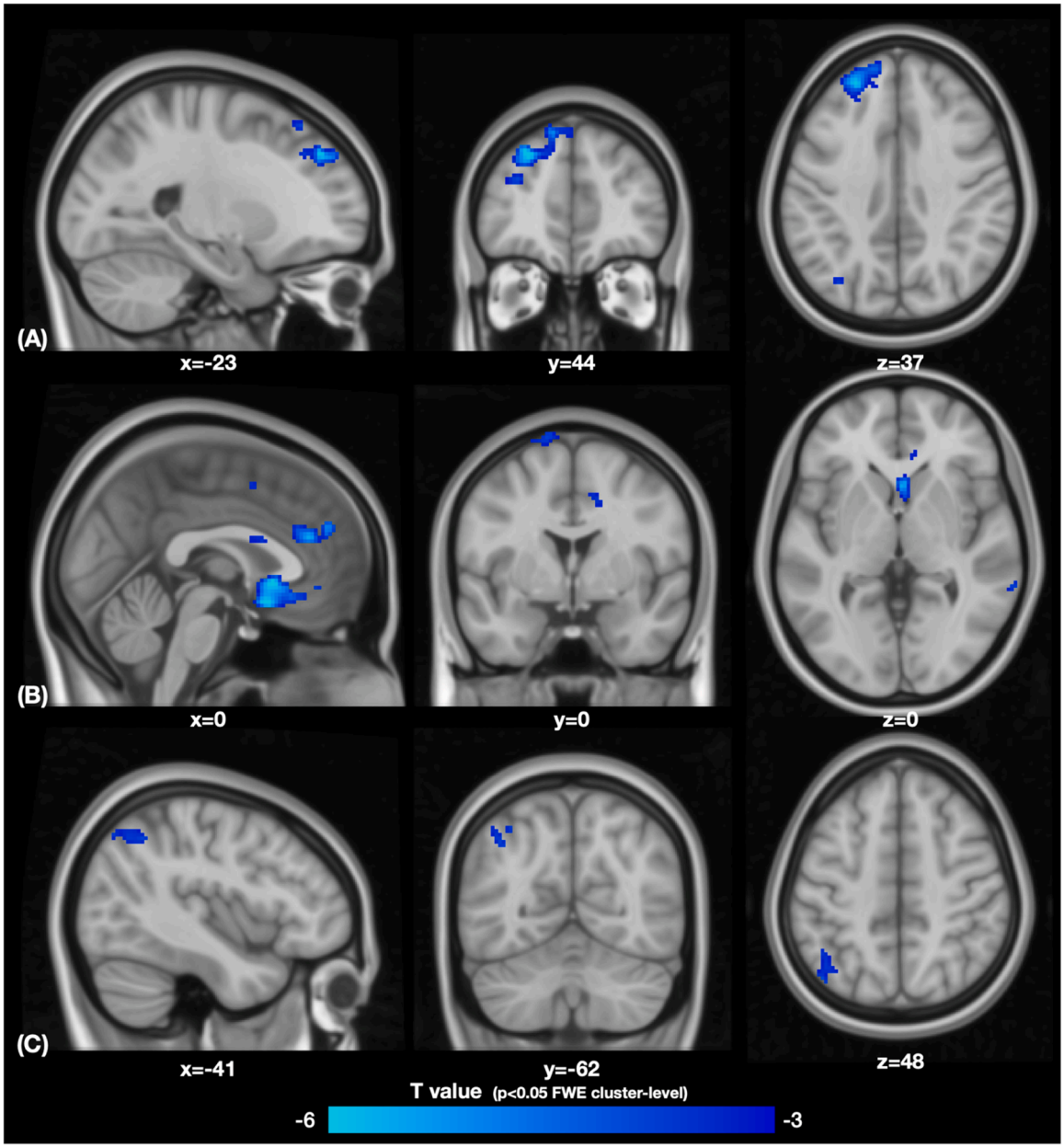

Fig. 4. Acute BOLD changes in a patient with bipolar depression. (A) First session: Negative BOLD response in the left DLPFC during iTBS. (B) Second session: Negative BOLD response in the sgACC during iTBS (C) Fourth session: No statistically significant BOLD changes in the DLPFC or sgACC. The third session was not included in the analysis due to strong ghosting artifacts.

condition is crucial for disentangling the effects of cortex stimulation from peripheral sensory or auditory effects of TMS and other non-specific sources (e.g., parameters of the experimental setting) (Siebner et al., 2022). It is essential to note that implementing a sham control in concurrent TMS-fMRI studies poses inherent challenges. Although future should always consider sham conditions as controls, TMS sham controls are far from ideal (Duecker and Sack, 2015), particularly in the concurrent TMS-fMRI field. To address this limitation, we performed e-field simulations to simulate the potential TMS effect over the left DLPFC, resulting in a similar pattern of the BOLD activation. Thirdly, while our design notably deviates from the Food and Drug Administration approved iTBS treatment protocol at 120% rMT (Blumberger et al., 2018), several other trials suggest that iTBS at the 80% rMT poses an effective strategy for treating MDD (Bulteau et al., 2022). Due to increased pain levels at higher stimulation intensities, we decided to apply the lower intensity in this feasibility study. Fourthly, MR imaging coils used for concurrent TMS-fMRI studies have fewer channels (i.e. two 7-channel coils) than standard MR head coils (i.e. 64-channel coils), which may affect the accuracy and reliability of TMS-fMRI BOLD signal measurements, especially in the deep subcortical regions. Additionally, while facing challenges such as a complicated technical setup, a large amount of experimental time, and personnel requirements, the sample size of our TMS-fMRI study is small, and we included only one clinical case. Finally, while we were able to show the feasibility of this approach in one participant from the clinical population, the generalizability of these findings to larger healthy and clinical cohorts needs further investigation in future studies. In particular, this patient is older than the young healthy control group and may differ from the clinical population included in many TMS clinical trials, having had previous TMS experience and having major depressive episodes with high chronicity levels based on the diagnosis of bipolar disorder. The patient has received pharmacological and rTMS treatment for many years, thus potentially affecting neuronal responses to the acute interventions applied in our study. Thus, future work is necessary to investigate whether the high intraindividual variability of BOLD effects we observed is representative of individuals with major depressive episodes.

5. Conclusions

In conclusion, we were able to establish a full iTBS treatment protocol in the concurrent TMS-fMRI setting and could disentangle several sources of variability relevant for this approach. We propose that this experimental paradigm could reveal acute effects of clinical iTBS treatment at the single session level, and may not only be used to demonstrate the immediate target engagement, but could also provide deeper insights into putative mechanisms of action.

Funding information

PT's work is funded by the DFG (TA 857/3-2). The procurement of the Prisma 3T MRI scanner was supported by the Deutsche Forschungsgemeinschaft (DFG, INST 409/193-1 FUGG). LB's work is part of the funding program of the Medical Faculty of LMU (FöFöLe Plus, Munich Clinician Scientist Program). The project was funded by the Federal Ministry of Education and Research within the ERA-NET NEURON program (FKZ: 01EW1903: DiSCoVeR Project) and the German Center for Mental Health (Deutsches Zentrum für Psychische Gesundheit, DZPG, grant: 01EE2303, project MUC6).

CRediT authorship contribution statement

Kai-Yen Chang: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Martin Tik:** Investigation, Formal analysis, Conceptualization, Methodology, Software, Supervision, Validation, Writing – review & editing. **Yuki Mizutani-Tiebel:** Conceptualization, Data curation, Methodology, Investigation, Project administration. **Anna-Lisa Schuler:** Writing – review & editing. **Paul Taylor:** Writing – review & editing. **Mattia Campana:** Methodology. **Ulrike Vogelmann:** Methodology, Data curation. **Barbara Huber:** Writing – review & editing. **Esther Dechantsreiter:** Resources, Project administration, Funding acquisition. **Axel Thielscher:** Writing – review & editing, Validation, Software. **Lucia Bulubas:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Frank Padberg:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization, Funding acquisition, Investigation. **Daniel Keeser:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

This work is a part of K-YC's Ph.D. program at Munich Medical Research School. YM-T received remuneration from neuroCare Group AG as a part-time office worker. FP is a member of the European Scientific Advisory Board of Brainsway Inc., Jerusalem, Israel, and the International Scientific Advisory Board of Sooma, Helsinki, Finland. He has received speaker's honoraria from Mag&More GmbH, the neuroCare Group, Munich, Germany, and Brainsway Inc. His-lab has received support with equipment from neuroConn GmbH, Ilmenau, Germany, Mag&More GmbH and Brainsway Inc. MT, A-LS, PT, MC, UV, BH, ED, AT, LB, & DK reported no potential conflicts of interest.

Data availability

Data will be made available on request.

Acknowledgments

We want to thank Linda Schuster, Zane Wilkinson, and Cuici Voon for assisting TMS-fMRI data collection and Larissa Behnke for E-field simulation data preprocessing. We would like to thank Christian Windischberger (Center for Medical Physics and Biomedical Engineering at the Medical University of Vienna, Austria) for providing his comprehensive expertise in concurrent TMS-MRI, as well as Patrik Kunz (Localite GmbH, Bonn, Germany) and Matthias Kienle (MagVenture A/S, Farum, Denmark) for their kind support with the technical setup.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2024.120596.

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