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Individualized theta-burst stimulation modulates hippocampal activity and connectivity in patients with major depressive disorder

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ABSTRACT

Background: While intermittent theta-burst stimulation (iTBS) has been shown to improve symptoms of major depressive disorder (MDD), research has been largely limited to targeting the dorsolateral prefrontal cortex (DLPFC). New approaches utilize patients' individual resting state fMRI data in order to identify superficial cortical stimulation targets functionally connected to deeper brain regions, thus enabling the modulation of previously inaccessible targets for antidepressant therapy.
Objective: To improve iTBS treatment of MDD by inducing plasticity in the hippocampus through stimulation of an individually mapped, functionally interconnected site in the parietal cortex.
Methods: Fifty-three MDD patients were randomized to three treatment groups and underwent 15 sessions of iTBS to the left DLPFC. This was augmented by adding a second daily session of (i) stimulation over individualized parietal targets functionally connected to the hippocampus, (ii) left DLPFC stimulation, or (iii) sham stimulation. To evaluate the improvement of treatment, we assessed depression severity, neuropsychological performance, functional connectivity and neural activation during an associative memory paradigm pre- vs. post-treatment.
Results: Augmentation of left DLPFC stimulation by parieto-hippocampal stimulation increased functional connectivity between hippocampus and DLPFC as well as encoding-related hippocampal activation; the latter was associated with better performance during a spatial planning task dependent on prefrontal and hippocampal contributions. Depressive symptoms improved in all groups after treatment, with best clinical outcomes following twice-daily left DLPFC stimulation.
Conclusion: Functional connectivity-guided stimulation of the hippocampus may serve as an adjunct to iTBS in order to target the cognitive symptoms of MDD.

1. Introduction

Intermittent theta burst stimulation (iTBS) [1] is a well-established repetitive transcranial magnetic stimulation (rTMS) protocol effective for the treatment of major depressive disorder (MDD) [2,3]. Many iTBS studies have focused on antidepressant effects of left dorsolateral prefrontal cortex (DLPFC) stimulation [3–5], whereas the curative potential of targets outside the DLPFC has received less attention [6]. Target selection has, traditionally, been constrained to regions near the surface of the brain due to the limited TMS pulses range (2–3 cm from the scalp [7]). Recent approaches utilize—in line with the emerging field of personalized psychiatry—patients' individual fMRI data to

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Table 1
Demographic data.

	DLPFC-iLPC (n = 18)	DLPFC-DLPFC (n = 17)	DLPFC-SHAM (n = 18)	*p*
Sex (M/F)	10/8	6/11	9/9	0.481
Age (years)	40.28 (12.65)	43.59 (11.45)	42.28 (12.99)	0.754
Education (years)	16.69 (7.59)	14.06 (3.06)	16.58 (4.43)	0.278
Duration of current depressive episode (years)	4.01 (5.39)	3.09 (3.29)	6.46 (9.22)	0.289
Number of depressive episodes [a]	3.57 (3.40)	3.28 (2.52)	2.72 (2.60)	0.701

Values are given as mean (SD). The *p*-values report the significance levels reached for analysis of variance or Fisher's exact tests comparing groups. The significance threshold was set at $p < .05$. [a] Data missing for six patients (DLPFC-DLPFC: n = 16, DLPFC-iLPC: n = 15, DLPFC-SHAM: n = 16).

identify superficial cortical stimulation targets functionally connected to brain structures that are too deep to be targeted directly, thus enabling a top-down-propagation of stimulation effects [8–10].

This functional network-guided approach allows for the modulation of new potential targets for antidepressant treatment, such as the hippocampus, which is considered a crucial node of the neuroanatomic circuitry underlying MDD [11] and therefore a promising target for modulation. Hippocampal volume reduction is a consistently reported abnormality in MDD [12] and is associated with longer illness duration [13] as well as reduced treatment responsiveness [14]. Conversely, electroconvulsive therapy (ECT) increases hippocampal volume, although it remains disputed whether or not this effect is causally related to clinical improvement [15,16]. Hippocampal functional connectivity to the limbic system [17,18] and to the default mode network [19] are aberrant in MDD patients; functional connectivity has been found to predict response to antidepressant treatment, including pharmacotherapy [20] and ECT [21]. Lastly, animal studies have further emphasized the importance of hippocampal neurogenesis [22] and synaptic plasticity [23] for the mechanism of action of serotonergic antidepressants. Functionally, the hippocampus has indisputably been linked to cognitive function and, specifically, memory [24] which is commonly impaired in MDD [25]. Unsurprisingly, hippocampal volume reduction in MDD patients is associated with decreased memory performance [26], but both improve after antidepressant treatment [27].

Previous studies in healthy individuals have utilized fMRI data to determine individualized parietal rTMS targets functionally connected to the hippocampus in order to modulate hippocampal functional connectivity [10,28], memory-associated hippocampal network activity [29,30] and performance in various memory domains [10,28–32]. However, no study to date has investigated the therapeutic potential of this functional connectivity-based approach in MDD patients. Here, we tested for potentially synergistic effects of stimulation of individualized targets in the lateral parietal cortex (iLPC) functionally connected to the hippocampus as an add-on to iTBS of the left DLPFC with regard to depressive symptom severity, cognition and hippocampal plasticity. The latter was addressed by measuring hippocampal responses and connectivity during an associative memory task. Parieto-hippocampal stimulation was compared to sham stimulation as an add-on to active DLPFC stimulation and twice-daily DLPFC stimulation. We hypothesized that the former would improve cognitive performance and modulate both hippocampal functional connectivity and memory-related functional hippocampus activity and increase the therapeutic effect of iTBS on depressive symptoms. A second daily DLPFC stimulation session served as a second control condition, which we hypothesized would enhance improvement of depressive symptoms compared to the sham condition without influencing cognitive performance or hippocampus activity and connectivity.

2. Methods and materials

2.1. Subjects

After giving written informed consent, 53 patients (28 female, age 42.02 ± 12.94 years) with unipolar MDD participated in this study between June 2016 and April 2018. Diagnosis was verified using the Mini-International Neuropsychiatric Interview (MINI; [33]) according to DSM-IV criteria. All participants were in-patients at the Department of Psychiatry, University of Bonn, Germany, and received concomitant multimodal treatment including pharmacotherapy (see Supplementary Material, Table S1), group psychotherapy and daily cognitive training [34]. Demographic and clinical data for all study patients can be found in Table 1. The study was approved by the institutional review board of the Medical Faculty of the University of Bonn and was conducted in accordance with the Declaration of Helsinki.

2.2. Study design

We conducted a randomized, double-blind, sham-controlled, registered clinical study (https://clinicaltrials.gov/show/NCT04081519) in which patients received three weeks of iTBS treatment and underwent clinical and neuropsychological assessment as well as MRI scanning prior and subsequent to the treatment course (cf. Fig. 1). Upon study inclusion patients were randomly assigned to either the DLPFC-iLPC (n = 18; 8 female), DLPFC-DLPFC (n = 17; 11 female) or DLPFC-SHAM group (n = 18; 9 female). Patients and raters were blinded regarding group assignment.

Patients underwent 15 days of stimulation with one session in the morning (S1) and one in the afternoon (S2) each day (median inter-session interval = 2.7 h, range = 1.5 to 6.5 h). While all patients received active stimulation of the left DLPFC at S1, stimulation modalities differed between groups at S2. The DLPFC-iLPC group received active stimulation over individualized targets in both the left and right LPC. The sequence of bilateral iLPC stimulation targets was counter-balanced across subjects and kept constant over the treatment course. The DLPFC-DLPFC group received a second active stimulation session of the left DLPFC (identical to S1). Patients in the DLPFC-SHAM group were randomized to receive sham stimulation of either the left DLPFC (n = 9) or over iLPC targets (n = 9) at S2. Sham data were collapsed across both sites, as there was no influence of site as revealed in subgroup comparisons.

2.3. Stimulation protocol

rTMS was applied using a Magstim Rapid2 Plus1 magnetic stimulator (Magstim Company Limited, Wales, UK) with a figure-of-eight coil (air film double 70 mm coil). Sham treatment was implemented using a magnetically shielded placebo coil that provides sensory stimulation and discharge noise without stimulating cortical tissue. Each session consisted of two 3.2 min runs of iTBS [1,35]. During each run, 20 stimulation trains were applied with an 8-second inter-train interval, each train consisting of 10 consecutive 50 Hz pulse triplets applied at a 5 Hz frequency. Hence, a total number of 600 pulses were applied per run. There was a 5-minute pause between both runs. Patients who received active or sham stimulation over iLPC at S2 obtained two iTBS runs each over both the left and right iLPC target, thus receiving a total of 2400 pulses at S2 as compared to 1200 pulses administered to patients who were stimulated exclusively over DLPFC. Stimulation intensity was set at 80% of the individual resting motor threshold, which was assessed for

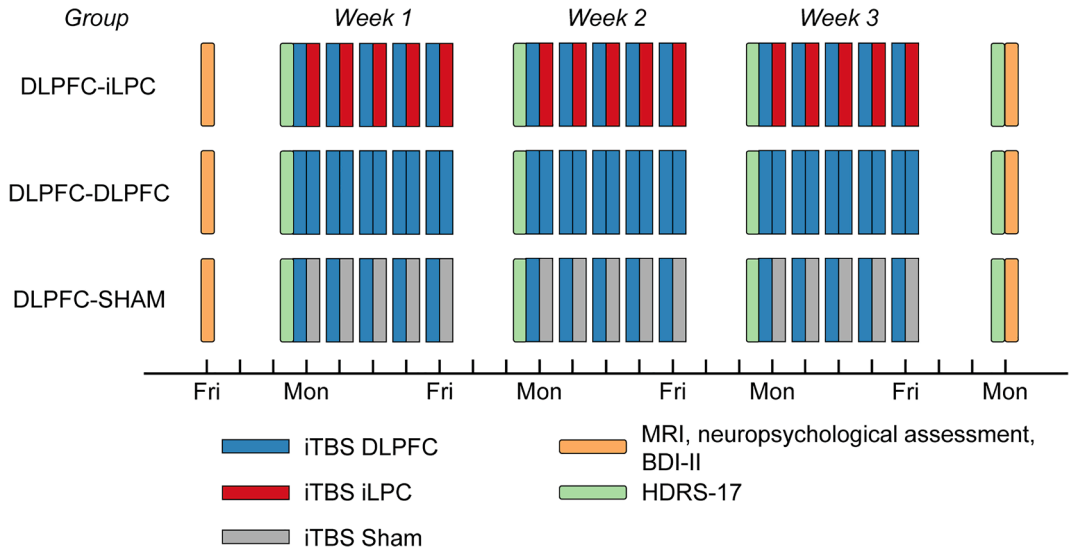

Fig. 1. Study design. Patients received two daily stimulation sessions, one over the left dorsolateral prefrontal cortex (DLPFC), the other depending on group affiliation. Follow-up Beck Depression Inventory (BDI-II) scores were acquired 4, 8 and 12 weeks after the treatment phase (not depicted). HRDS-17, Hamilton Depression Rating Scale; iLPC, individualized lateral parietal cortex target.

each patient before the first stimulation session. A frameless stereotactic neuronavigational system (Localite TMS Navigator, Localite GmbH, St. Augustin, Germany) was used to ensure precise coil positioning. After each stimulation session patients completed a short questionnaire concerning potential side effects.

2.4. Statistical analysis

To investigate group differences, analyses of covariance (ANCOVA) with group as between-subject factor, pre-treatment values as covariate and post-treatment values as dependent variable was performed for all measures [36]. Change across groups was assessed using repeated-measures analysis of variance (rmANOVA) with time (pre-treatment, post-treatment) as within-subject factor. Fisher's exact test (χ^2) was used to compare categorical data. The threshold for significance was set to $p < .05$, and p-values were Bonferroni-adjusted if appropriate. fMRI whole-brain analyses were adjusted for multiple comparisons using family-wise error (FWE). Further information regarding group comparisons at baseline and additional analyses of change across groups is provided in the Supplementary Material. Statistical analysis was performed in IBM SPSS Statistic 24 (IBM, New York, NY, USA).

2.5. Clinical and neuropsychological assessment

To quantify clinical improvement, trained raters assessed depressive symptom severity using the 17-item Hamilton Depression Rating Scale (HDRS-17) [37] prior to the first stimulation session of each week and again three days after the final stimulation session. As a measure of self-assessed depression severity, the Beck Depression Inventory (BDI-II) [38] was administered before the first and after the final stimulation session and 4, 8 and 12 weeks after the treatment course.

Neuropsychological assessment was conducted to examine visual memory, spatial planning, visual sustained attention and working memory [25]. For that purpose, patients performed the Delayed Matching to Sample (DMS, percentage of correct answers), One Touch Stockings of Cambridge (OTS, mean choices to correct answer), Rapid Visual Information Processing (RVP, target sensitivity) and Spatial Working Memory (SWM, number of errors) computerized tests as implemented in the CANTABeclipse 6 battery (Cambridge Cognition Limited, Cambridge, UK).

2.6. Resting-state fMRI data analysis

Imaging data were acquired using a 1.5 T Siemens Avanto MRI system (Siemens, Erlangen, Germany) three days before and after the treatment course. Resting-state data were preprocessed (see Supplementary Material) and analyzed employing the CONN toolbox for SPM [39]. For each subject and session, BOLD signal time courses were extracted and averaged from the following a priori defined stimulation-related regions of interest (ROIs): left and right hippocampus (3-mm spheres at MNI coordinates [−24 −20 −16] and [+22 −18 −18] based on encoding-related functional activation data from a pre-study; more information is given in the Supplementary Material), left DLPFC (5-mm sphere at [−38 +44 +26], stimulation target); and left and right iLPC stimulation targets (5-mm spheres at individualized coordinates). For the seed-to-seed analysis, BOLD signal time courses from all ROIs were correlated with one another and the resulting correlation coefficients were extracted for subsequent statistical analysis.

Additionally, we performed an exploratory whole-brain seed-to-voxel analysis. Time courses from each seed region were correlated with every voxel in the brain resulting in subject-specific correlational maps containing Fisher's z scores. These maps were then entered into a general linear model (GLM) with group as between-subject factor and time as within-subject factor. An F-test was used to detect clusters displaying differences between groups regarding change in functional connectivity (post-treatment > pre-treatment). Significance for seed-to-voxel analysis was set at a voxel height threshold of $p_{\text{uncorrected}} < 0.05$ and a cluster threshold of $p_{\text{FWE}} < 0.05$.

2.7. Stimulation target selection

The DLPFC target was defined as MNI coordinate [−38 +44 +26] previously identified as an optimal target for antidepressant rTMS treatment [40]. Bilateral iLPC targets were determined based on individual resting-state fMRI data. For each hemisphere, seed-to-voxel connectivity was calculated between the hippocampus ROIs and each voxel within a mask of the ipsilateral LPC. Subsequently, the voxel with the greatest positive correlation coefficient was selected as stimulation target. For additional information, see Supplementary Material.

2.8. Task-based fMRI experimental paradigm

An adapted version of an established associative memory paradigm that reliably elicits functional activation in the hippocampus [41,42] was employed to examine the effects of parieto-hippocampal stimulation. Patients underwent two encoding runs and one retrieval run. Before the fMRI session, patients were asked to familiarize themselves with two pairs of faces and written professions. During scanning, these two familiar pairs and 16 novel pairs were displayed for 4.6 s each. While novel stimuli were presented only once per run, familiar pairs were displayed repeatedly. Patients were tasked with memorizing these pairs and, to reinforce associative learning, had to indicate whether they thought the face fit the profession. During retrieval, previously presented novel faces were displayed again with the instruction to recall the associated profession and indicate their category (i.e. academic or artistic). For further information, see Supplementary Material.

2.9. Task-based fMRI data analysis

Data were preprocessed (see Supplementary Material) and analyzed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm)) running in MATLAB R2010b (The MathWorks, Natick, MA).

For the encoding task, conditions based on combinations of stimulus (novel, familiar, control), run (run 1, run 2) and time (pre-treatment, post-treatment) were entered into a GLM for each subject together with a constant term and six realignment parameters per run and session to account for subject motion. We then employed a data-driven leave-one-subject-out approach (LOSO) [43] to define subject-independent ROIs in the left and right hippocampus based on the main task effect, i.e. the contrast [novel > familiar] across both runs and sessions. Parameter estimate images from all but one patient were entered into a flexible factorial model and whole-brain analysis was conducted with a height threshold of $p_{FWE} < 0.05$. Subsequently, we selected the supra-threshold cluster nearest to our hippocampal target voxels ([−24 −20 −16], [+22 −18 −18]) separately for each hemisphere. For the one patient who was left out, parameter estimates were extracted for all conditions using these subject-independent ROIs and averaged across voxels. To investigate group effects, the contrast [novel > familiar] was averaged across both runs for each session.

Analysis of the retrieval task was performed correspondingly using conditions based on combinations of stimulus (novel, control) and time (pre-treatment, post-treatment). The same LOSO approach was used to extract, average and subsequently contrast ([novel > control]) parameter estimates from subject-independent ROIs across voxels. Parameter estimate contrasts were used as a measure of functional activation and further analyzed in SPSS.

3. Results

3.1. Clinical and neuropsychological results

HDRS-17 scores (pre-treatment 17.21 ± 5.59, post-treatment 10.19 ± 5.79, $F_{(1,52)} = 91.06$, $p < .001$, $\eta_p^2 = 0.64$) and BDI-II scores (pre-treatment 33.45 ± 8.83, post-treatment 18.87 ± 11.11, $F_{(1,52)} = 87.05$, $p < .001$, $\eta_p^2 = 0.63$) improved across groups after treatment. A significant group effect ($F_{(2,49)} = 3.60$, $p = .035$, $\eta_p^2 = 0.13$) revealed better post-treatment HDRS-17 scores in the DLPFC-DLPFC group (adjusted mean = 7.62, SE = 1.15) compared to the DLPFC-iLPC (adjusted mean = 11.33, SE = 1.10, $t_{(33)} = 2.30$, $p = .026$, $d = 0.80$)) and DLPFC-SHAM groups (adjusted mean = 11.47, SE = 1.09, $t_{(33)} = 2.41$, $p = .020$, $d = 0.84$); Fig. 2A) when controlling for pre-treatment scores. No group differences were found for BDI-II at the end of the treatment course ($F_{(2,49)} = 0.46$, $p = .632$; Fig. 2B) or at any of the follow-up measurements (all p's > 0.701), which was completed by 46 patients (DLPFC-iLPC: n = 17, DLPFC-DLPFC: n = 14, DLPFC-SHAM: n = 15). There were no group differences in the occurrence of stimulation-related side effects (see Supplementary Material, Table S2).

Across groups patients improved in the DMS ($F_{(1,52)} = 9.24$, $p = .004$, $\eta_p^2 = 0.15$), RVP ($F_{(1,52)} = 19.97$, $p < .001$, $\eta_p^2 = 0.28$) and SWM ($F_{(1,52)} = 4.21$, $p = .045$, $\eta_p^2 = 0.08$) tests but not in the OTS test ($F_{(1,52)} = 1.84$, $p = .181$). No group differences were found (DMS: $F_{(2,49)} = 0.42$, $p = .660$; OTS: $F_{(2,49)} = 1.74$, $p = .186$; RVP: $F_{(2,49)} = 0.83$, $p = .443$; SWM: $F_{(2,49)} = 1.33$, $p = .275$).

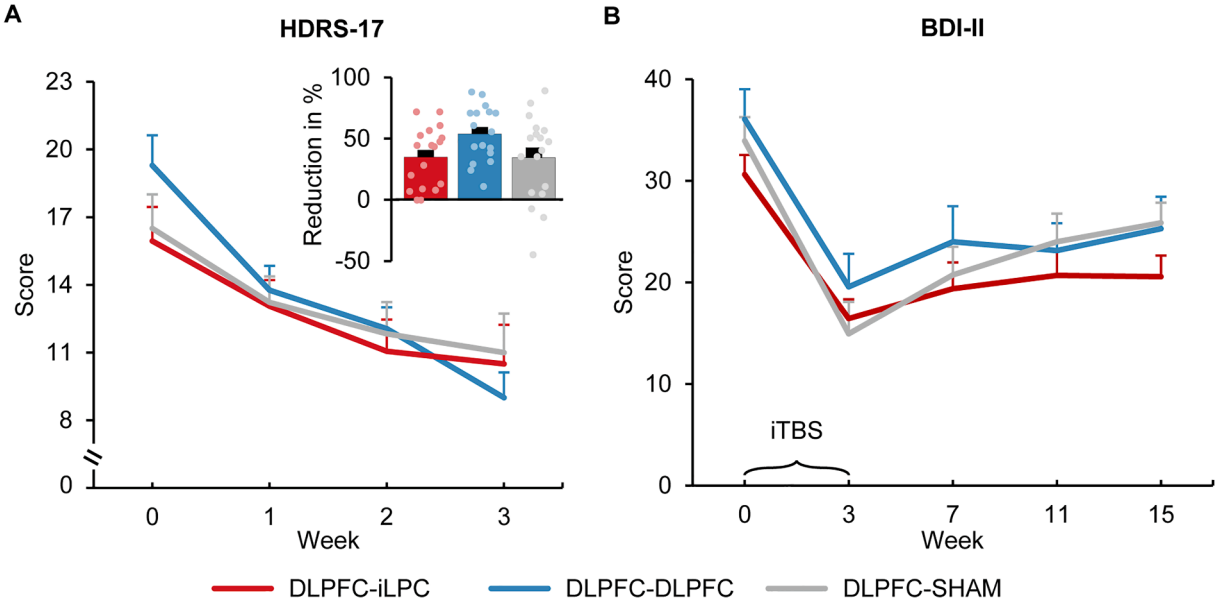

Fig. 2. Change in depression symptom severity over time. (A) Patients in the DLPFC-DLPFC group showed better outcomes in the Hamilton Depression Rating Scale (HDRS-17) than patients in the other groups when controlling for baseline scores. (B) No group differences were found for Beck Depression Inventory (BDI-II) scores at the end of treatment or at any of the follow-up measurements (data is displayed only for patients that completed follow-up; DLPFC-iLPC: n = 17, DLPFC-DLPFC: n = 14, DLPFC-SHAM: n = 15). Error bars depict standard error of the mean.

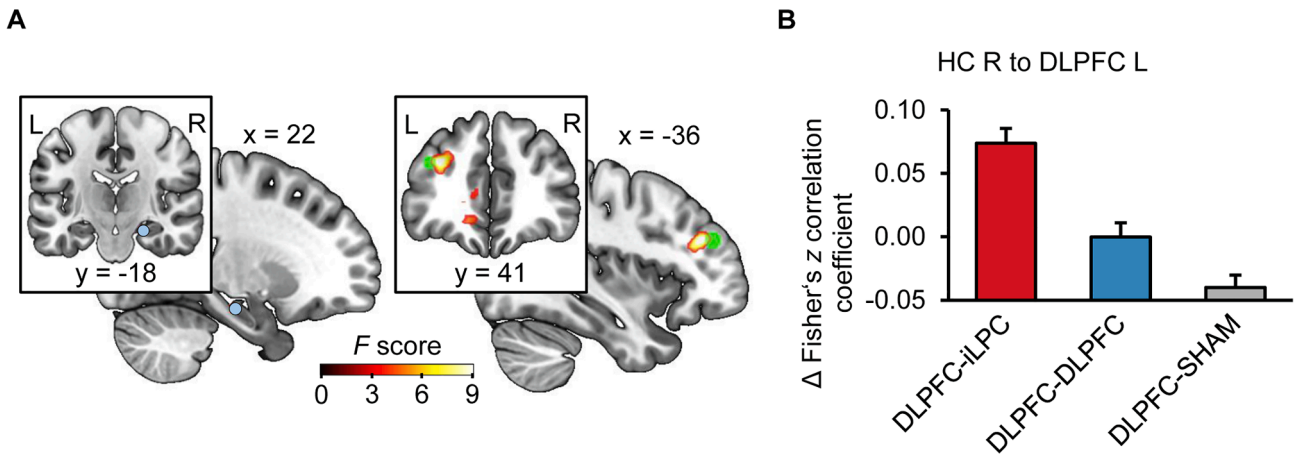

Fig. 3. Whole-brain resting-state functional connectivity of right hippocampus (HC). (A) Exploratory seed-to-voxel analysis revealed a significant group effect on change of functional connectivity between the right hippocampus seed (3-mm sphere; blue) and a prefrontal cluster topographically close to the dorsolateral prefrontal cortex (DLPFC) stimulation target (5-mm sphere; green). (B) Visual representation of change in functional connectivity. Error bars depict standard error of the mean. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Resting-state functional connectivity

We employed exploratory whole-brain functional connectivity analysis to investigate group-specific changes after treatment. Intriguingly, for the right hippocampus seed we found a significant cluster in the left DLPFC (peak at [−34 +38 +26]; cluster size 745 voxels, $p_{FWE} = 0.041$, Fig. 3A). Post-hoc tests revealed a stronger increase in connectivity in the DLPFC-iLPC group than in the DLPFC-

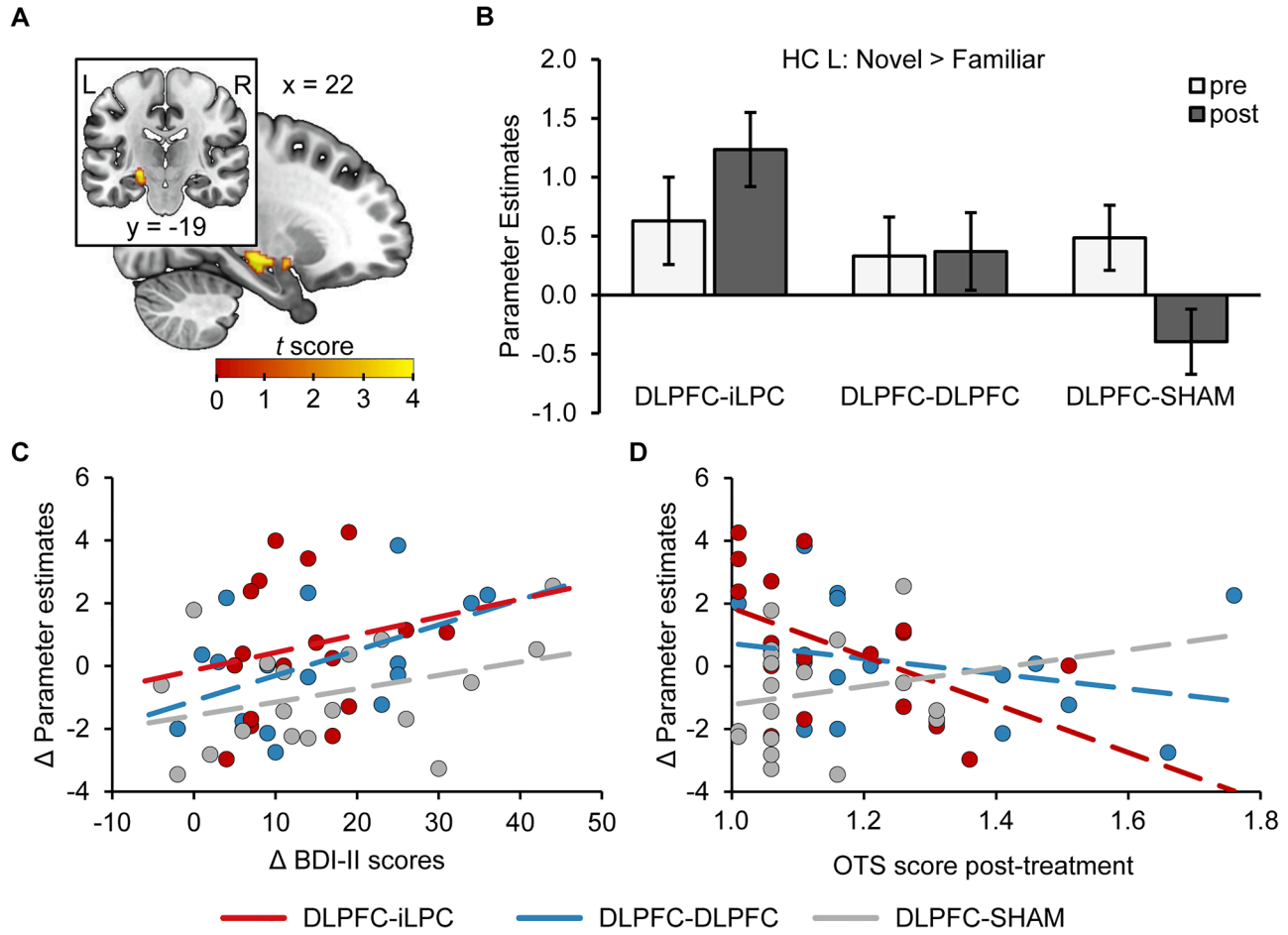

Fig. 4. fMRI results from the encoding task. (A) A leave-one-subject-out approach was used to define subject-independent regions of interest (ROIs) in the hippocampus (HC) (displayed is an exemplary ROI). (B) After treatment, patients in the DLPFC-iLPC group showed a greater increase in hippocampal response during encoding compared to patients in the other groups. (C) This increase in activation significantly correlated with improvement in Beck Depression Inventory (BDI-II) scores across groups. (D) In contrast, activation increase correlated with better (=lower) post-treatment One Touch Stockings of Cambridge task (OTS) scores in the DLPFC-iLPC group, but not in the other groups. Error bars depict standard error of the mean.

DLPFC ($t_{(33)} = 4.57, p < .001, d = 1.59$) and DLPFC-SHAM group ($t_{(34)} = 7.46, p < .001, d = 2.56$; Fig. 3B). This cluster was topographically located close to the DLPFC stimulation target (7.21 mm Euclidean distance between correlation cluster peak and stimulation target coordinate). Whole-brain analysis of other seeds did not reveal significant results.

Seed-to-seed analyses revealed no significant group effects between ROIs in the left and right hippocampus, left and right iLPC and left DLPFC (all p's > 0.372). Analysis across groups, however, revealed a significant decrease of functional connectivity between iLPC and ipsilateral hippocampus both in the left ($F_{(1,52)} = 68.12, p < .001, \eta_p^2 = 0.57$) and right hemisphere ($F_{(1,52)} = 142.22, p < .001, \eta_p^2 = 0.73$). Since hippocampal seeds and iLPC stimulation target voxels were maximally correlated at baseline by design, this finding may result from stimulation-independent regression to the mean.

3.3. fMRI associative memory paradigm

Due to technical problems during MRI acquisition, one subject (DLPFC-iLPC group) was eliminated from task-based fMRI analyses. As predicted, in the encoding task, we found a significant group effect on activation in the left hippocampus ($F_{(2,48)} = 11.80, p = .002, \eta_p^2 = 0.23$; Fig. 4A; right hippocampus: $F_{(2,48)} = 1.63, p = .207$) after treatment. Planned contrasts revealed higher activation in the DLPFC-iLPC group (1.23 ± 1.30) than in the other groups (DLPFC-DLPFC: $0.37 \pm 1.36, p = .049$; DLPFC-SHAM: $-0.39 \pm 1.17, p < .001$; Fig. 4B). No group differences were present in the retrieval task (p's > 0.107) and groups did not differ regarding their memory performance, assessed as the number of correct answers during the retrieval task ($F_{(2,48)} = 0.25, p = .777$).

To test brain-behavior relationships, we conducted post-hoc correlational analysis. Increased activation in the left hippocampus during encoding positively correlated with absolute improvement in BDI-II scores after the treatment course across all groups ($r_{(52)} = 0.29, p = .041$; Fig. 4C). Also, we found a significant correlation between post-treatment OTS scores and the increase in activation in the left hippocampus during encoding in the DLPFC-iLPC group ($r_{(17)} = -0.50, p = .040$), but not in the other groups (DLPFC-DLPFC: $r_{(17)} = -0.27, p = .295$; DLPFC-SHAM: $r_{(18)} = 0.17, p = .494$; Fig. 4D).

4. Discussion

The rationale of the present study was to optimize iTBS of MDD using a precision medicine approach by augmenting daily stimulation over the left DLPFC with an additional daily session of stimulation over individualized parietal targets. These targets were determined based on their functional connectivity to the hippocampus, a crucial node of the neuroanatomic circuitry underlying depression. This connectivity-based approach utilizes patients' individual fMRI data to identify superficial cortical stimulation targets that are connected to deeper regions of the brain, thus enabling the modulation of otherwise inaccessible targets. Our findings indicate that parieto-hippocampal stimulation combined with standard DLPFC stimulation led to increased functional connectivity between hippocampus and DLPFC, increased hippocampus response during encoding and a stronger correlation between encoding-related hippocampus response and performance in a spatial planning task. Although there was no additional benefit of parieto-hippocampal stimulation regarding depressive symptom severity compared to sham stimulation, our findings suggest that the administered stimulation protocol is effective in modulating hippocampal-prefrontal pathways and performance in tasks associated with these areas.

Firstly, exploratory functional connectivity analyses revealed that stimulation of both the individualized parietal target and the DLPFC augmented functional connectivity between the right hippocampus and DLPFC. These connectivity-enhancing effects produced by co-activation of hippocampus and DLPFC are reminiscent of studies on paired associative stimulation (PAS) over multiple cortical targets and cortico-cortical connectivity [44–47]. However, the effects of PAS are thought to reflect spike-timing dependent plasticity, which depends on either simultaneous administration of bifocal stimulation or interstimulus intervals in the range of milliseconds [44,48]. Effects on connectivity are usually measured within minutes after a single stimulation session. In contrast, we administered 15 days of stimulation, employed an inter-session interval of 2–3 h, and acquired fMRI data three days after the final stimulation session. In addition, we aimed for indirect modulation of the hippocampus, which, to our knowledge, has not been reported previously in the context of PAS. While PAS and our approach share the same premise of increased connectivity after bifocal stimulation, they differ in terms of the underlying mechanism of action. Our findings presumably rely on a more long-term and less timing-specific kind of plasticity and suggest that connectivity can be modulated by bifocal stimulation protocols even when stimulation is applied indirectly. However, since all patients received DLPFC stimulation, we cannot be certain that it is required for the observed effect. Possibly the same effect could be achieved with parieto-hippocampal stimulation alone. But, intriguingly, the connectivity cluster was located topographically right next to the DLPFC stimulation target, supporting the interpretation that this finding is indeed related to bifocal stimulation. While this effect was not accompanied by improvement of clinical symptoms, this approach might be used in future studies to achieve a targeted increase in connectivity in patients with conditions which are associated with prefrontal-hippocampal dysconnectivity, such as schizophrenia [49], memory disorders [50] and other disorders [51]. Sham-controlled studies are necessary to confirm and further explore this preliminary finding.

Secondly, parietal-hippocampal stimulation enhanced encoding-related activity near the left hippocampal stimulation site. This supports our hypothesis that our approach was successful on the neurophysiological level and is consistent with prior reports showing increased task-based hippocampus activation after parieto-hippocampal stimulation in healthy individuals [29,30].

Thirdly, correlational analysis revealed that only in patients who received parieto-hippocampal iTBS the observed increase in hippocampal response during encoding was associated with better performance in the OTS task, which is based on the extensively studied Tower of London paradigm [52,53] and reflects spatial planning. This task is usually associated with prefrontal activity [54], but there is evidence for hippocampal engagement as a function of task difficulty [55], which might reflect additional demand for spatial memory capacities. A previous study has shown that spatial cognition mediates the negative impact of MDD on psychosocial functioning [56] indicating that patients with cognitive deficits might benefit from our stimulation approach. Across groups, increases in hippocampal activation were correlated with clinical improvement as measured by BDI-II scores, implicating an involvement of the hippocampus in antidepressant response.

We found that symptom severity decreased in all three groups, with better outcomes after twice-daily active DLPFC stimulation compared to additional parieto-hippocampal or sham iTBS. This finding contributes to the ongoing discussion regarding the optimal number and frequency of sessions [57–59] by demonstrating the superiority of twice-daily DLPFC stimulation in a sham-controlled design.

Unlike previous studies that employed comparable approaches [10,28,29,31,32], we found no improvement in memory performance or other neuropsychological parameters after parieto-hippocampal stimulation. These previous studies were conducted in healthy individuals as opposed to MDD patients who commonly suffer from cognitive impairment and might therefore be less responsive to subtle stimulation effects. Differences can also be found regarding stimulation protocols: whereas most of the aforementioned studies used 20 Hz high-frequency (HF) rTMS [10,28,29], two recently published studies found effects on associative memory after a single session of continuous [32] but not intermittent TBS [31], indicating that our chosen stimulation protocol might not have been ideal for this purpose.

While employing an innovative stimulation approach, the present study is limited by a small sample size and the number of analyses. Heterogeneity regarding concomitant pharmacotherapy and the tolerance of certain comorbidities such as anxiety disorders might have introduced variance that could have concealed further stimulation-dependent effects.

In conclusion, our findings suggest that stimulation of individualized parieto-hippocampal connectivity modulates hippocampal plasticity in MDD patients. An increase in hippocampus activation after parieto-hippocampal stimulation was associated with better performance in a spatial planning task that relies on both prefrontal and hippocampal contributions and, thus, may have therapeutic potential for depressed patients with cognitive deficits. Our findings are compatible with an increase in hippocampal-prefrontal connectivity through bifocal stimulation of DLPFC and a site functionally connected to the hippocampus. Future studies should evaluate whether this approach might be used to achieve a targeted increase in connectivity in patients or healthy controls.

CRediT authorship contribution statement

Clemens Mielacher: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft. **Johannes Schultz:** Conceptualization, Methodology, Software, Writing - review & editing. **Maximilian Kiebs:** Investigation, Writing - review & editing. **Torge Dellert:** Investigation, Writing - review & editing. **Anna Metzner:** Investigation. **Larissa Graute:** Investigation. **Hanna Högenauer:** Investigation, Writing - review & editing. **Wolfgang Maier:** Resources, Writing - review & editing. **Claus Lamm:** Methodology, Writing - review & editing, Supervision. **René Hurlemann:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmip.2020.100066.

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