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Brain oscillation-synchronized stimulation of the left dorsolateral prefrontal cortex in depression using real-time EEG-triggered TMS

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) is an effective treatment for major depressive disorder (MDD), but response rates are low and effect sizes small. Synchronizing TMS pulses with instantaneous brain oscillations can reduce variability and increase efficacy of TMS-induced plasticity.
Objective: To study whether brain oscillation-synchronized rTMS is feasible, safe and has neuromodulatory effects when targeting the DLPFC of patients with MDD.
Methods: Using real-time EEG-triggered TMS we conducted a pseudo-randomized controlled single-session crossover trial of brain oscillation-synchronized rTMS of left DLPFC in 17 adult patients with antidepressant-resistant MDD. Stimulation conditions in separate sessions were: (1) rTMS triggered at the negative EEG peak of instantaneous alpha oscillations (alpha-synchronized rTMS), (2) a variation of intermittent theta-burst stimulation (modified iTBS), and (3) a random alpha phase control condition.
Results: Triggering TMS at the negative peak of instantaneous alpha oscillations by real-time analysis of the electrode F5 EEG signal was successful in 15 subjects. Two subjects reported mild transient discomfort at the site of stimulation during stimulation; no serious adverse events were reported. Alpha-synchronized rTMS, but not modified iTBS or the random alpha phase control condition, reduced resting-state alpha activity in left DLPFC and increased TMS-induced beta oscillations over frontocentral channels.
Conclusions: Alpha-synchronized rTMS of left DLPFC is feasible, safe and has specific single-session neuromodulatory effects in patients with antidepressant-resistant MDD. Future studies need to further elucidate the mechanisms, optimize the parameters and investigate the therapeutic potential and efficacy of brain oscillation-synchronized rTMS in MDD.

Introduction

Major depressive disorder (MDD) is a severe mental disorder and one of the leading causes of disability worldwide [1]. Although antidepressant drugs and psychotherapeutic treatments such as cognitive behavioral therapy (CBT) are efficacious and evidence-based [2,3], at least one third of MDD patients do not respond satisfactorily to an initial antidepressant treatment [4–6], with up

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to 15% of patients being refractory to multiple pharmacological and psychotherapeutic approaches [4]. MDD therefore remains a significant mental health problem and major contributor to the overall global burden of disease [1].

High-frequency repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) was shown to be beneficial in the treatment of MDD [7,8], and was approved by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of patients who have not responded to at least one adequate prior pharmacological antidepressant treatment trial. However, despite definite antidepressant effects at the group level, high-frequency rTMS of the left DLPFC in MDD is rather limited by low response rates and small effect sizes reflecting only moderate clinical improvement [9–13].

At the level of single neurons, high-frequency (10 Hz) repetitive magnetic stimulation was shown to induce structural and functional plasticity of both excitatory [14] and inhibitory [15] postsynapses, corroborating its therapeutic potential to remodel aberrant connectivity in dysfunctional brain networks in MDD [16]. Yet, in vitro experiments in rat hippocampus suggest that the phase of the ongoing oscillatory network activity determines the sign and magnitude of stimulus-induced synaptic plasticity [17,18]. In line with this notion, it was recently shown that synchronizing TMS pulses with ongoing μ-oscillations in the electroencephalography (EEG) alpha-band (8–12 Hz) in human sensorimotor cortex results in a differential modulation of corticospinal excitability [19]: while repeated stimulation at the negative peak of the μ-alpha-rhythm, i.e., during a high excitability state of the sensorimotor cortex, resulted in long-lasting and consistent increases in motor-evoked potentials (MEPs), triggering TMS at the positive peak, i.e., during a low excitability state, or at random phase did not affect MEP amplitudes [19]. These findings suggest that it requires a synchronization of each stimulus with the individual's instantaneous brain state (i.e., oscillatory brain activity) to realize the full potential of TMS to effectively modulate brain networks.

Brain oscillations play a major role in the pathophysiology of MDD [20] and modulation of synchronized electrical activity in neuronal networks seems to be a common effect of antidepressant treatments [21]. Specifically, alpha oscillations are increased in power in MDD [20], left frontal alpha power positively correlates with depressive symptomatology [22], and a favorable response to antidepressant treatment was found to be associated with a decrease in alpha power [23]. In addition, other studies have provided evidence for a left frontal hypoexcitability/-activity in MDD [24,25]. Based on these findings we hypothesized that triggering TMS synchronized with the negative peak of endogenous alpha oscillations in left DLPFC would more effectively increase cortical excitability (as measured with TMS-evoked potentials), and decrease resting-state alpha power, respectively, than a non-alpha-synchronized stimulation protocol. TMS-induced oscillations and performance in a delayed working memory task with emotional distraction, which has been linked to left DLPFC activity [26], served as exploratory outcome measures. The study was designed as a single-session pseudo-randomized controlled crossover trial of alpha-synchronized rTMS of left DLPFC in patients with antidepressant-resistant MDD, defined as a failure of at least one adequate pharmacological treatment trial of one major class of antidepressants in the current or a previous depressive episode [27]. Using real-time EEG-triggered TMS [19] patients received either rTMS synchronized with the negative peak of instantaneous alpha oscillations in left DLPFC (alpha-synchronized rTMS), or a variation of intermittent theta-burst stimulation (modified iTBS), an increasingly used patterned rTMS protocol [28], which is non-inferior in reducing depressive symptoms compared to conventional 10 Hz high-frequency rTMS [29]. As a control condition TMS pulses were applied independent of instantaneous alpha oscillations in left DLPFC. The aim of our study was to investigate feasibility, safety and neuromodulatory effects of a single session of alpha-synchronized rTMS of left DLPFC in patients with antidepressant-resistant MDD in comparison with non-alpha-synchronized rTMS protocols, i.e., modified iTBS and Replay.

Material and methods

Subjects

The study protocol was approved by the local Ethics Review Committee of the Medical Faculty of Eberhard Karls University Tübingen (Project number: 293/2016BO2). The study was pre-registered at ClinicalTrials.gov (NCT02920840) and conducted in accordance with the latest version of the Declaration of Helsinki and present consensus guidelines on the safety, ethical considerations and application of TMS in clinical practice and research [30].

After giving written informed consent, 22 right-handed subjects (mean Edinburgh Handedness Inventory laterality score [31] of 79.4 ± 17.1, range: 50–100) meeting the clinical criteria for a single or recurrent episode of MDD as defined in the Diagnostic and Statistical Manual of Mental Illnesses Fourth Edition (DSM-IV) were screened to identify 17 subjects (7 females, 10 males; mean age ± s.d., 51.4 ± 11.8 yrs, range: 27–65 yrs; mean 17-item Hamilton Rating Scale for Depression [$HRSD_{17}$] score of 20.5 ± 2.1, range: 18–24) that fulfilled all pre-established inclusion criteria of the study. Inclusion criteria were: (i) Age between 18 and 65 years. (ii) 18 points or more on the $HRSD_{17}$ during the current depressive episode. (iii) Failure of at least one adequate pharmacological treatment trial of one major class of antidepressants in the current or a previous depressive episode [27]. (iv) Resting motor threshold (RMT, see supplementary material) of the right abductor pollicis brevis (APB) muscle <70% of maximum stimulator output (MSO). The RMT threshold criterion was applied to increase the probability of TMS-induced plasticity [32] and to ensure that the TMS stimulator would be capable of generating the rTMS protocol at the required intensity of 70% RMT (highest intensity of the stimulator at 100 Hz was 48% MSO). Two subjects failed on the RMT criterion and were thus not included in the study. One subject was excluded from the study due to intake of amitriptyline as a pro-convulsive drug [33] and two other subjects were excluded due to an acute crisis with suicidal ideation (see supplementary material for exclusion criteria).

Real-time alpha-synchronized DLPFC stimulation

For brain oscillation-synchronized stimulation of the left DLPFC [34] a EEG-TMS set-up was used, with the capability of analyzing EEG signals in real-time and triggering TMS pulses depending on the instantaneous oscillatory phase of the recorded EEG signal [19]. EEG was recorded using a 24-bit 80-channel biosignal amplifier (NeurOne Tesla with Digital Out Option, Bittium Biosignals Ltd., Finland). TMS pulses were delivered through an air-cooled TMS coil (Magstim 70 mm Double Air Film Coil, Magstim Ltd., UK) using a Magstim Super Rapid Plus magnetic stimulator (Magstim Ltd., UK) (see supplementary material for details). To extract alpha oscillations in left DLPFC at sensor-level a Hjorth-style Laplacian spatial filter [35] was computed by the real-time system (implemented in Simulink Real-Time [R2015a, MathWorks Inc., USA]), centered on the EEG electrode F5 with the average of four surrounding EEG electrodes (Fp1, F1, FCC5h, FFT9h) serving as reference. The electrode F5, as opposed to the frequently used left DLPFC sensor F3, was selected as the central electrode because the stimulation target chosen for this study is relatively lateral and located directly

underneath F5 [34]. The Laplacian montage used in our study is especially sensitive to scalp-normal oriented cortical dipoles at the crown of the cortical gyrus underlying the central electrode of the montage, in our case F5. The resulting Hjorth-F5 signal was used for subsequent estimation of power [36] and phase [37] in the alpha (8–12 Hz) frequency band (for details of real-time digital biosignal processing, see Ref. [19]). Estimated power and phase were updated every 100 ms and 2 ms, respectively. The real-time system was configured to generate an output signal to the magnetic stimulator to trigger TMS triple pulses at 100 Hz either i) in a pre-determined sequence (modified iTBS, Replay; see below), or ii) by a combined criterion of alpha phase and power of the Hjorth-F5 signal (alpha-synchronized rTMS). In the alpha-synchronized rTMS condition the phase condition was set to always trigger the first pulse of the TMS triplets at the Hjorth-F5 negative peak of the alpha oscillation. Here, "negative peak" refers to the EEG signal after application of the surface Laplacian to yield a reference-free estimate, where a negative value corresponds to an inward flow of radial currents at the scalp generated predominantly by excitatory postsynaptic potentials in scalp-normally oriented pyramidal cells in the underlying cortex [38]. Because the accuracy of the phase estimation algorithm depends on the alpha power (increased during high alpha power, not reliable during low alpha power), an alpha power threshold was used to ensure reliable phase detection. This threshold affected the average inter-triple pulse interval and was set manually before the beginning of the stimulation and, if necessary, adjusted during the intervention such that a median interval between TMS triplets of approximately 2 s was attained. However, inter-triple pulse intervals varied substantially due to the automated EEG artifact detection and trigger conditions (i.e., alpha phase and power) of the real-time algorithm. Phase trigger accuracy was determined from resting-state EEG data collected before the rTMS intervention by comparing the actual "true" phase (calculated post-hoc using a band-pass filter and Hilbert transform) at the time points where the real-time algorithm detected a negative alpha oscillation peak (without actually triggering a stimulus as the stimulus artifact would have prevented accurate post-hoc phase determination). The parameters and execution of the real-time system were asynchronously controlled from a standard PC running Microsoft Windows and MATLAB (R2015a, MathWorks Inc.).

Study design

At the beginning of each session 5 min of resting-state EEG with eyes open were obtained. Subjects were instructed to relax and fixate a cross at eye level 1 m in front of them. Next, 160 TMS pulses at 120% RMT were applied over left DLPFC [34] during simultaneous EEG recording (eyes open condition), with an inter-stimulus interval of 3 s ± 0.75 s to limit anticipation of the next trial. Thereafter, subjects conducted a non-verbal delayed response working memory task with emotional distraction, taken from a previous report [26] and implemented with slight adaptations in MATLAB (R2015a, MathWorks Inc.) using Psychtoolbox (see supplementary material).

After BASELINE measurements subjects underwent one of three rTMS interventions (600 pulses) in a pseudo-randomized controlled crossover design: 1) Alpha-synchronized rTMS, i.e., 200 TMS triple pulses at 100 Hz applied at the negative alpha peak of the Hjorth-F5 signal, 2) modified iTBS according to a previous report [28] with the adaptation of 100 Hz bursts (3 pulses at 100 Hz) instead of 50 Hz bursts to match the alpha-synchronized rTMS and modified iTBS condition, or 3) a random alpha phase control stimulation (Replay), in which the time sequence of stimuli in a given subject in the alpha-synchronized rTMS intervention was replayed in a subsequent session, i.e., TMS pulses were given independent of the phase of endogenous alpha activity. All rTMS interventions were applied with the subjects having their eyes open and fixating the cross in front of them to suppress occipital alpha activity. Stimulus intensity was set at 70% RMT, stimulation site was (−50, 30, 36) in MNI coordinates according to a previous report [34]. The position of the TMS coil in 3D-space relative to the participant's head was maintained within and across experimental sessions using an individually magnetic resonance imaging guided stereoscopic neuronavigation system (TMS Navigator, Localite GmbH, Sankt Augustin, Germany). Experimental sessions 1 (alpha-synchronized rTMS) and 2 (modified iTBS) were randomized across subjects, with session 3 (Replay) always following session 1, i.e., session orders were 1-2-3, 1-3-2 or 2-1-3. The inter-session interval was at least one week to avoid carry-over effects. Experimental sessions in a given participant were conducted always on the same time of day to avoid diurnal fluctuations in TMS-induced plasticity [39].

Immediately after the rTMS intervention measurement of resting-state EEG, TMS-evoked EEG responses and the working memory task were repeated (POST measurements) to test for rTMS-induced neurophysiological and behavioral changes.

Data and statistical analyses

Analyses were performed in MATLAB (R2017b, MathWorks Inc.) using the FieldTrip toolbox [40] and custom code. Electrophysiological data were processed as described in detail previously [41] (see supplementary material) and analyzed using cluster-based statistics [42]. Resting-state EEG data were analyzed permuting the frequency and channel domains (i.e., not analyzing predefined frequency bands or regions of interest), comparing the difference in spectral power between BASELINE and POST measurements separately in each stimulation condition (i.e., alpha-synchronized rTMS, modified iTBS, Replay). TMS-evoked potentials were analyzed permuting the time and channel domains, comparing the difference in signal amplitude between BASELINE and POST measurements in each stimulation condition, covering a latency of 30 ms–300 ms after the TMS pulse. TMS-induced oscillations were analyzed permuting the frequency and channel domains, comparing the difference in z-transformed spectral power between BASELINE and POST measurements in each stimulation condition, covering a latency of 30 ms–750 ms after the TMS pulse. The frequency domain was divided into five different frequency bands: 4–8 Hz (theta), 8–13 Hz (alpha), 13–20 Hz (low beta), 20–30 Hz (high beta) and 30–48 Hz (gamma). The number of permutations for the Monte Carlo method in the cluster-based statistics was 1000 for analysis of resting-state EEG and TMS-evoked potentials (TEPs), and 2000 for analysis of TMS-induced oscillations.

Statistical analyses of the behavioral data were performed using MATLAB (R2017b, MathWorks Inc.) and SPSS® Statistics (IBM®, v.24). To determine the effects of TIME, INTERVENTION and VALENCE on working memory performance (i.e., response accuracy) a $2 \times 3 \times 2$ three-way repeated measures analysis of variance (rmANOVA) with the within-subject factors TIME (2 levels: BASELINE, POST), INTERVENTION (3 levels: alpha-synchronized rTMS, modified iTBS, Replay) and VALENCE (2 levels: neutral, emotional) was conducted. Mauchly's Test was used to test for sphericity, and the Greenhouse-Geisser correction was applied whenever sphericity was violated. *Post-hoc* paired two-tailed t-tests and *follow-up* one- and two-way rmANOVAs were applied in case of a significant main effect or interaction.

Data are given as mean ± 1 standard deviation, if not otherwise indicated. The level of significance was set to $p < 0.05$.

Results

All 17 subjects completed all aspects of the study protocol without serious adverse events. Two subjects reported mild transient discomfort at the site of stimulation during all rTMS interventions and one subject reported mild headache lasting until the next day after iTBS. These side effects did not affect the subjects' capability to fully comply with all requirements of the study. No other side effects were reported.

Demographic and clinical subject data

Mean $HRSD_{17}$ scores were 22.1 ± 4.1 in session 1 (range: 18–31), 21.8 ± 3.7 (range: 17–29) in session 2, and 21.4 ± 3.6 (range: 17–28) in session 3, with no statistically significant difference between sessions ($p > 0.1$ for all comparisons). Mean RMT was 61.0 ± 6.9% MSO (range: 42–69% MSO). Nine of the 17 patients (52.9%) were on concomitant antidepressant pharmacotherapy, seven (41.2%) received psychotherapy, and four (23.5%) received both. No patient had undergone electroconvulsive therapy prior to study inclusion.

Alpha-synchronized left DLPFC stimulation

Triggering TMS by real-time analysis and phase prediction of instantaneous alpha oscillations in the Hjorth-F5 EEG signal was successful in 15 of the 17 subjects (88.2%). One subject showed no alpha frequency peak in the power spectrum, in another subject contamination of large occipital alpha oscillations prevented detection of frontal alpha activity using the Hjorth-F5 signal. In the remaining 15 subjects, however, TMS triple pulses could be reliably triggered based on both power and phase of local alpha activity in left DLPFC with a phase angle error distribution for alpha-synchronized rTMS targeting the negative alpha peak (phase angle, 0°) of −1.26° ± 61.9° (mean ± standard deviation) and a median inter-triple pulse interval of 1.80 s (inter-quartile range from 1.20 s to 3.15 s; note that the inter-triple pulse interval distribution is asymmetric with a long-tail due to occasional pauses when the real-time system did not trigger a stimulus due to EEG artifacts, and is better described by quartiles than mean and standard deviation [which was 2.67 s ± 2.51 s]) (Fig. 1). The median duration of alpha-synchronized rTMS was 7 min 54 s (mean 8 min 16 s ± 3 min 2 s std).

Resting-state EEG

Cluster-based statistical analysis of resting-state EEG (eyes open) revealed a significant difference between BASELINE and POST measurements in the signal's power spectrum within the frequency range of 11–14 Hz in the alpha-synchronized rTMS condition (Fig. 2). No difference in power spectra between BASELINE and POST measurements were found in the iTBS and Replay conditions (data not shown).

TMS-evoked EEG potentials

Single-pulse TMS of left DLPFC resulted in a series of deflections of the EEG signal (TEPs) with typical polarities and latencies including N40, P60, N120 and P200 potentials, in line with previous studies [43] (data not shown). Cluster-based statistical analysis showed significant differences in TEPs between BASELINE and POST measurements in the modified iTBS and Replay conditions (Fig. 3). No difference in TEPs between BASELINE and POST measurements was found in the alpha-synchronized rTMS condition.

TMS-induced oscillations

Left DLPFC TMS-induced oscillations were significantly different between BASELINE and POST measurements in all stimulation conditions, with specific patterns of significant channel clusters and changes in time-frequency responses (Fig. 4). Alpha-synchronized rTMS, but not modified iTBS or Replay, increased TMS-induced beta oscillations over mesial frontocentral channels ($p = 0.013$).

Working memory task

Performance in the working memory task was 84.0 ± 7.8% response accuracy and 1.24 ± 0.20 s latency for correct responses at BASELINE, averaged across rTMS interventions (alpha-synchronized rTMS, modified iTBS, Replay) and valence categories (neutral, emotional). There was no significant difference in response accuracy or latency for correct responses between BASELINE and POST measurements for any of the three stimulation conditions. For response accuracy, a $2 \times 3 \times 2$ three-way rmANOVA with the within-subject factors TIME, INTERVENTION and VALENCE showed no significant main effects (all $p > 0.05$), but a significant three-way interaction between TIME, INTERVENTION and VALENCE ($F_{2,28} = 5.26$, $p = 0.011$) (Fig. 5). Follow-up two-way rmANOVAs revealed no significant simple two-way interaction between TIME and INTERVENTION for neutral distractor trials ($F_{2,28} = 1.39$, $p = 0.265$), but a significant simple two-way interaction between TIME and INTERVENTION for emotional distractor trials ($F_{2,58} = 3.24$, $p = 0.046$), which was explained by a significantly higher response accuracy after vs. before modified iTBS ($F_{1,29} = 5.65$, $p = 0.024$). No changes in response accuracy between POST vs. BASELINE measurements were found in the alpha-synchronized rTMS ($F_{1,29} = 0.56$, $p = 0.46$) and Replay ($F_{1,29} = 1.54$, $p = 0.225$) conditions.

Discussion

Here we report feasibility, safety and immediate neuromodulatory effects of real-time EEG-triggered alpha-synchronized rTMS of left DLPFC in patients with antidepressant-resistant MDD. To synchronize the TMS pulses with the instantaneous oscillatory alpha activity in left DLPFC, we extracted alpha oscillations at the sensor level using a Hjorth Laplacian spatial filter centered on the electrode F5, which was the closest electrode to our targeted stimulation site [34], using Fp1, F1, FCC5h and FFT9h as adjacent electrodes. Applying an autoregressive forward prediction method [37] on the Hjorth-F5 signal led to an accurate prediction of the phase of instantaneous alpha oscillations, sufficient to trigger the 100 Hz TMS triple pulses at the predefined target phase (i.e., negative alpha peak) in 15 of the 17 patients (cf. Fig. 1). The variability of the phase angle is explained by the contamination of the signal with other oscillations, and the trade-off between filter efficacy and length of the signal delay thereby introduced, as discussed in Ref. [19]. In addition, the Hjorth-F5 signal was significantly contaminated with periocular and frontal scalp muscle activity, which could not be removed in our real-time procedure (but only post-hoc using ICA). Despite these limitations the filter settings and alpha power threshold chosen for this study worked satisfactorily for all but two patients: in one patient contamination of large occipital alpha oscillations prevented detection of frontal alpha activity using the Hjorth-F5 signal and another subject showed no alpha frequency peak at all in the power spectrum. We expect that individually optimized spatial filters computed by spatial-spectral decomposition [44] increase the signal-to-noise ratio of the EEG signal, thereby increasing accuracy and reducing

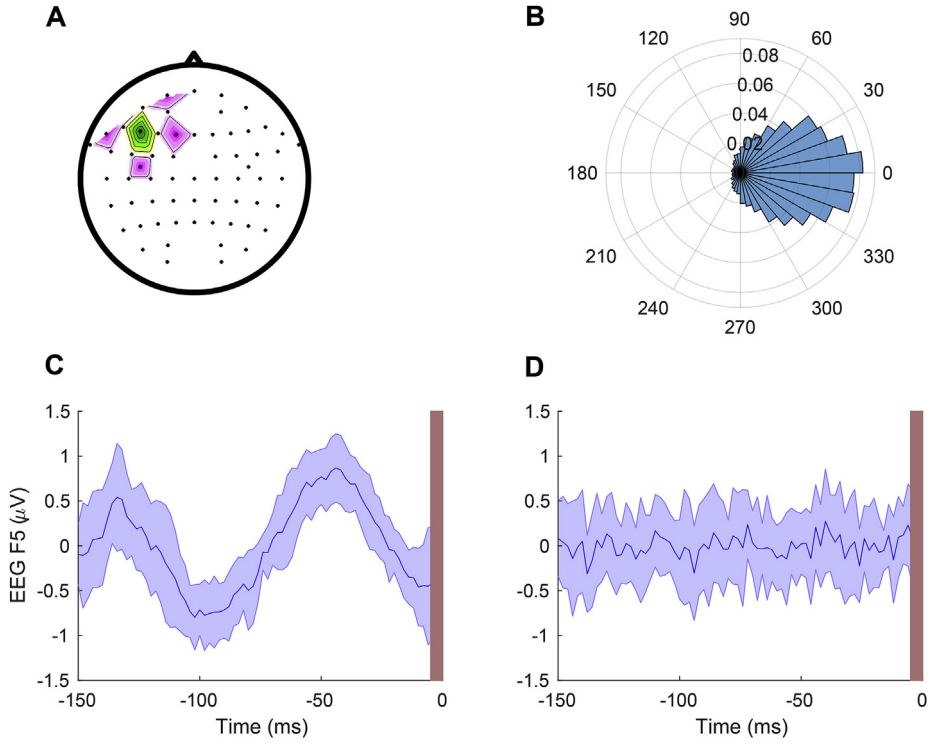

Fig. 1. Real-time EEG-triggered alpha-synchronized stimulation of the left DLPFC. (A) EEG montage using a Hjorth Laplacian filter (centered on electrode F5) to extract the EEG signal from left DLPFC. (B) Group average phase accuracy of alpha-synchronized rTMS, targeting the negative peak ('trough') of instantaneous alpha oscillations (phase angle, 0°) by real-time EEG analysis of the F5-Hjorth signal. The resting-state EEG before the experiment was used for post-hoc calibration. Phase angles are binned (width, 10°) and normalized probabilities are indicated as sector radii. (C) Group average of the pre-stimulus F5-Hjorth signal in the alpha-synchronized rTMS condition. Shade, standard deviation of the signal, the stimulus artifact is indicated by the bar at time zero. (D) Same data as in (C) for the Replay condition. Data in this and all following figures are from the n=15 subjects with successful alpha-synchronized rTMS (for details, see text).

variability of targeting a predefined phase of instantaneous brain oscillations in left DLPFC.

Alpha-synchronized rTMS, but not a predetermined static rTMS sequence (modified iTBS) or random alpha phase control stimulation (Replay), reduced left frontal resting-state alpha power and increased TMS-induced beta oscillations over mesial frontocentral channels. The phase-dependency of these neuromodulatory effects is in line with previous results from human primary motor cortex (M1) demonstrating the critical role of the phase of the sensorimotor μ-alpha-rhythm for induction of corticospinal plasticity [19]. Our findings extend these prior results by demonstrating that brain oscillation-synchronized rTMS as opposed to rTMS not synchronized with instantaneous brain oscillations differentially alters brain network dynamics in non-motor brain areas (i.e., left DLPFC) and in a disease state (i.e., MDD). Of note, left frontal and right parietal resting-state alpha power was reduced after 600 alpha-synchronized TMS pulses only (cf. Fig. 2). In contrast, no changes in resting-state EEG power spectra were seen after a single

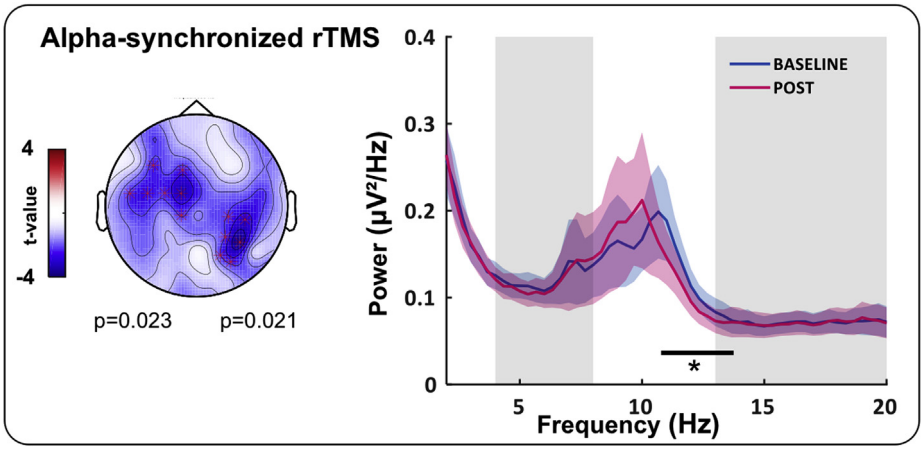

Fig. 2. Modulation of resting-state EEG spectral power by alpha-synchronized rTMS. Left: Topographical plot of the cluster statistical difference in spectral power between BASELINE and POST measurements in the alpha-synchronized rTMS condition, within the frequency range of 11-14 Hz. Asterisks correspond to channels pertaining to the statistically significant clusters. Right: Power spectrum of the signal from the channels comprising the statistically significant clusters. Black bar and asterisk mark the frequency range where the statistical difference was found. Grey and white areas delineate frequency bands: 4–8 Hz (theta), 8–13 Hz (alpha) and 13–20 Hz (low beta).

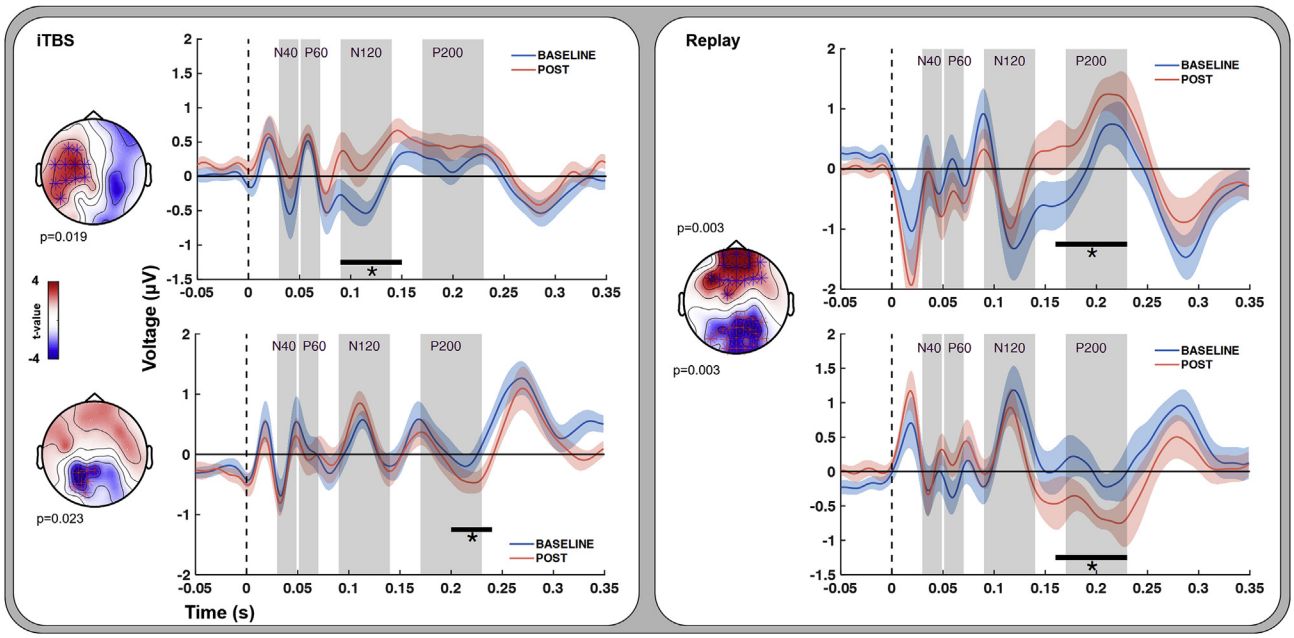

Fig. 3. Modulation of TMS-evoked potentials. Topographical plots of the statistical difference in TMS-evoked potential (TEP) amplitude between BASELINE and POST measurements in the iTBS (left top: positive cluster at 90-150 ms latency; left bottom: negative cluster at 200-240 ms latency) and Replay condition (right; positive and negative clusters at 160-230 ms latency). (*) corresponds to channels pertaining to the statistically significant clusters. TEPs were computed from channels comprising statistically significant clusters. Black bars and asterisks mark the time periods where the statistical difference was found.

session of left DLPFC transcranial direct current stimulation (tDCS) with current stimulation parameters used in tDCS protocols for depression [41]. Together, these findings suggest that real-time EEG-triggered brain oscillation-synchronized rTMS is capable of modulating fronto-parietal oscillatory network activity. In line with this notion recent studies have shown that adaptive deep brain stimulation (DBS), which uses the power or phase of oscillatory beta activity in the subthalamic nucleus (STN) to trigger DBS, is highly effective in suppressing pathological beta bursts in the STN in patients with Parkinson's disease [45–48]. As increased alpha power in left prefrontal cortex has been reported in MDD [49–51], although some studies have failed to replicate these findings (for review, see Ref. [52]), and a clinical improvement to antidepressant treatments was found to be associated with a decrease in alpha activity [23], our findings suggest that alpha-synchronized rTMS might have therapeutic potential to also alleviate depressive symptomatology in MDD. Clinical trials with multiple treatment sessions are now needed to test the therapeutic potential and efficacy of alpha-synchronized rTMS in MDD.

Several reports suggest that oscillatory brain activity in other frequency bands also plays an important role in the pathophysiology of depression (for review, see Ref. [20]). For instance, delta and beta band activity is closely correlated with functional connectivity in the default mode network [53] showing aberrant functional connectivity in MDD [54], and increased theta activity in frontal and anterior cingulate cortex has been reported in patients with MDD [55]. Although findings on oscillatory EEG biomarkers as endophenotypes of MDD are not unequivocal (for review, see

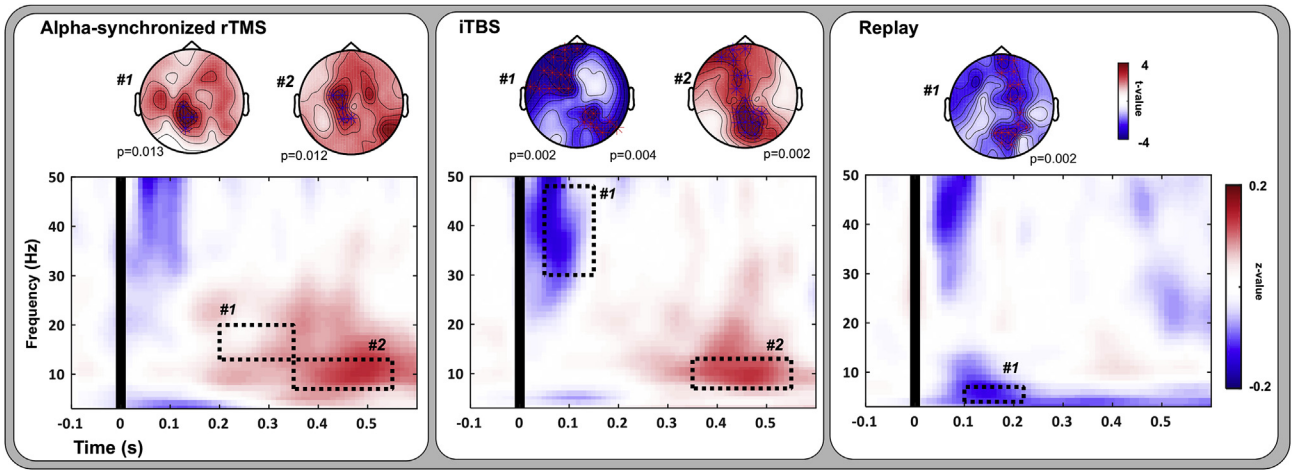

Fig. 4. Modulation of TMS-induced oscillations. Top: topographical plots of the cluster-based statistical difference in TMS-induced oscillations between BASELINE and POST measurements in the three stimulation conditions. (*) corresponds to channels pertaining to statistically significant clusters. Bottom: for each stimulation condition significantly different time-frequency responses (TFRs) are delineated by dotted-squares with designated numbers (#). TFRs correspond to the average of all channels.

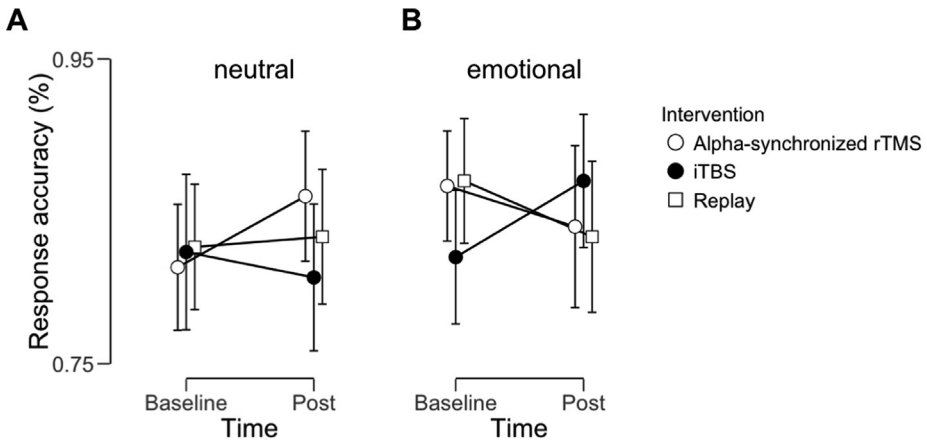

Fig. 5. Modulation of working memory performance. Response accuracy (% correct responses) in neutral (A) and emotional (B) distractor trials. Modulation of response accuracy showed a significant three-way interaction between TIME, INTERVENTION and VALENCE ($F_{2,28} = 5.26$, $p = 0.011$), which was explained by an increase in response accuracy after vs. before iTBS in emotional distractor trials ($F_{1,29} = 5.65$, $p = 0.024$). Data show mean ± 95% confidence interval.

Ref. [56]), it is intriguing to speculate in this context that brain oscillation-synchronized rTMS offers a unique tool to interfere with and modulate dysfunctional microcircuits and brain networks in MDD. Future studies on brain oscillation-synchronized rTMS in MDD should also address the question whether the resting-state is the optimal state for interference with dysfunctional brain networks, or whether task-dependent activation of these networks [57] might open a window to induce context-specific plasticity in these networks by brain oscillation-synchronized rTMS.

Modified iTBS and Replay, but not alpha-synchronized rTMS, modulated late TEPs (cf. Fig. 3). Although the physiological mechanisms of TEPs are currently not well understood, for TEPs elicited by M1 stimulation the N100 potential has been associated with GABA-B receptor activation [58] and the P180 potential may be linked to axonal excitability, as the voltage-gated sodium channel blocker lamotrigine reduces the P180 amplitude [59]. These findings suggest that modified iTBS and Replay had effects on cortical inhibition and excitation in our patients that were different from those of alpha-synchronized rTMS.

In addition to decreasing left frontal and right parietal resting-state alpha power, alpha-synchronized rTMS, but not modified iTBS or Replay, increased TMS-induced beta oscillations at 200–350 ms over mesial frontocentral channels (cf. Fig. 4). In M1, TMS typically leads to a strong beta-desynchronization at 200–400 ms in the stimulated and contralateral sensorimotor cortex [60]. It is likely that this late beta-desynchronization is linked to GABAergic inhibition, as alprazolam and diazepam (positive modulators at the GABA-A receptor) as well as baclofen (a specific GABA-B receptor agonist) enhanced this late TMS-induced beta-desynchronization [60]. Although TMS-induced perturbations of endogenous oscillatory brain activity are site-specific, i.e., show different patterns in the time-frequency response in different brain areas such as M1 and DLPFC [61], the increase in TMS-induced beta oscillations in the alpha-synchronized rTMS condition may be interpreted as a transient reduction in GABAergic neurotransmission. In line with this notion, both animal [15] and human studies [62] have suggested modulation of inhibitory neurotransmission as a possible mechanism of action of repetitive magnetic stimulation. Importantly, disinhibition may prime cortical networks for the subsequent expression of input-specific (i.e. context-dependent) associative synaptic plasticity, constituting a circuit mechanism of behavioral learning [63]. Future studies, including pharmacological studies in patients with MDD, need to test this further.

On a behavioral level, modified iTBS, but not alpha-synchronized rTMS or Replay, increased response accuracy in emotional (but not neutral) distractor trials (cf. Fig. 5). These findings are in line with one recent study, which reported an increase in performance in this delayed working memory task in emotional, but not neutral distractor trials after a single session of anodal tDCS of the left DLPFC in patients with MDD [64]. The reasons for the lack of an effect of alpha-synchronized rTMS on response accuracy in the current study remain unknown, but could involve differences in the cortical microcircuits and networks activated following stimulation of alpha-synchronized rTMS vs. modified iTBS. A deeper mechanistic understanding of alpha-synchronized rTMS vs. non-synchronized rTMS protocols, including their effects on resting-state functional connectivity in brain networks, will likely provide important insights into how rTMS therapy can be further optimized in the context of connectivity-based MDD subtypes [65].

Limitations of the study

For the purpose of comparing the effect of alpha-synchronized rTMS vs. (modified) iTBS we adapted the original iTBS protocol as described by Huang and colleagues [28] by applying 100 Hz TMS triple pulses instead of 50 Hz triple pulses. This ensured that the TMS bursts covered the same period of the alpha cycle in both stimulation conditions and allowed us to exclude that any difference in the effect of alpha-synchronized rTMS vs. modified iTBS could be attributed to the temporal structure of the TMS bursts in the two conditions. In reverse, we cannot exclude the possibility that the 100 Hz TMS triple pulses in our modified iTBS condition had different effects on the stimulated neuronal circuits as compared to 50 Hz TMS triple pulses used in the original iTBS protocol, as suggested by prior work using quadripulse stimulation in M1 [66].

Due to the constraints of our real-time phase estimation and stimulus trigger algorithm (see Material and Methods) inter-triple pulse intervals, and thus intervention durations, differed significantly across subjects in the alpha-synchronized rTMS condition (median intervention duration 7 min 54 s, mean 8 min 16 s ± 3 min 2 s), and were significantly longer than the duration of modified iTBS (3 min 10 s, fixed). Although inherent to our personalized stimulation approach, these differences in the stimulation duration may have contributed to the differences in the observed

neurophysiological and behavioral effects between alpha-synchronized rTMS and modified iTBS.

We used a comparatively low stimulation intensity of 70% RMT in our TMS intervention, given that current clinical rTMS protocols in MDD use intensities of up to 120% RMT [29]. In our pilot experiments of alpha-synchronized rTMS of the left DLPFC in healthy subjects, however, a stimulation intensity of 80% RMT, which we initially selected based on our own work in the motor system [19], was not well tolerated by some subjects due to discomfort. The reasons for this are likely (i) the use of high-frequency 100 Hz TMS triple pulses during alpha-synchronized rTMS/modified iTBS in our study as opposed to 50 Hz TMS triple pulses in the original iTBS protocol [28]; (ii) stimulation at a more lateral position in left DLPFC [67] as compared to previous work [29], which increases co-activation of scalp/facial muscles [68,69]; and (3) non-employment of a ramping-up protocol, which is often used in clinical rTMS therapy to adapt patients to the sensation of higher stimulation intensities. The 70% RMT intensity which we used in our main study was generally well tolerated by our subjects (see Results) and exceeds the intensity of 80% AMT applied in the original iTBS protocol [28] (based on studies comparing RMT and AMT for biphasic TMS [70,71]). Nevertheless, future studies investigating the clinical potential and efficacy of brain oscillation-synchronized rTMS may need to incorporate a ramping-up algorithm to test higher intensity stimulation and/or stimulation at different cortical targets.

Conclusions

Alpha-synchronized rTMS of the left DLPFC is feasible, safe and has specific single-session neuromodulatory effects in patients with antidepressant-resistant MDD. With regard to future studies, physiological investigations are necessary to better understand which frontal brain areas and which brain oscillations (in terms of both target frequency and target phase) may serve as a suitable target for the directional modulation of frontal brain networks relevant in MDD, as well as clinical trials with repeated stimulation sessions to investigate the therapeutic potential and efficacy of brain oscillation-synchronized rTMS in MDD as compared to current TMS therapies.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.10.007.

References

[1] Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390(10100):1211–59.
[2] Huhn M, Tardy M, Spineli LM, Kissling W, Forstl H, Pitschel-Walz G, et al. Efficacy of pharmacotherapy and psychotherapy for adult psychiatric disorders: a systematic overview of meta-analyses. JAMA Psychiatr 2014;71(6):706–15.
[3] Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018;391(10128):1357–66.
[4] Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. Can J Psychiatr 2007;52(1):46–54.
[5] Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008;358(3):252–60.
[6] Cuijpers P, Smit F, Bohlmeijer E, Hollon SD, Andersson G. Efficacy of cognitive-behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. Br J Psychiatry 2010;196(3):173–8.
[7] O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007;62(11):1208–16.
[8] Avery DH, Holtzheimer 3rd PE, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry 2006;59(2):187–94.
[9] Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125(11):2150–206.
[10] Lepping P, Schonfeldt-Lecuona C, Sambhi RS, Lanka SV, Lane S, Whittington R, et al. A systematic review of the clinical relevance of repetitive transcranial magnetic stimulation. Acta Psychiatr Scand 2014;130(5):326–41.
[11] Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a systematic review and meta-analysis of randomised sham-controlled trials. Neurosci Biobehav Rev 2018;92:291–303.
[12] Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS. The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. Brain Stimul 2016;9(3):336–46.
[13] Herwig U, Fallgatter AJ, Hoppner J, Eschweiler GW, Kron M, Hajak G, et al. Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. Br J Psychiatry 2007;191:441–8.
[14] Vlachos A, Müller-Dahlhaus F, Rosskopp J, Lenz M, Ziemann U, Deller T. Repetitive magnetic stimulation induces functional and structural plasticity of excitatory postsynapses in mouse organotypic hippocampal slice cultures. J Neurosci 2012;32(48):17514–23.
[15] Lenz M, Galanis C, Müller-Dahlhaus F, Opitz A, Wierenga CJ, Szabo G, et al. Repetitive magnetic stimulation induces plasticity of inhibitory synapses. Nat Commun 2016;7. 10020.
[16] Anderson RJ, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for treatment resistant depression: Re-establishing connections. Clin Neurophysiol 2016;127(11):3394–405.
[17] Huerta PT, Lisman JE. Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron 1995;15(5):1053–63.

[18] Huerta PT, Lisman JE. Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. Nature 1993;364(6439):723–5.
[19] Zrenner C, Desideri D, Belardinelli P, Ziemann U. Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. Brain Stimul 2018;11(2):374–89.
[20] Fingelkurts AA, Fingelkurts AA. Altered structure of dynamic electroencephalogram oscillatory pattern in major depression. Biol Psychiatry 2015;77(12):1050–60.
[21] Leuchter AF, Hunter AM, Krantz DE, Cook IA. Rhythms and blues: modulation of oscillatory synchrony and the mechanism of action of antidepressant treatments. Ann N Y Acad Sci 2015;1344:78–91.
[22] Diego MA, Field T, Hernandez-Reif M. CES-D depression scores are correlated with frontal EEG alpha asymmetry. Depress Anxiety 2001;13(1):32–7.
[23] Ulrich G, Renfordt E, Zeller G, Frick K. Interrelation between changes in the EEG and psychopathology under pharmacotherapy for endogenous depression. A contribution to the predictor question. Pharmacopsychiatry 1984;17(6):178–83.
[24] Levinson AJ, Fitzgerald PB, Favalli G, Blumberger DM, Daigle M, Daskalakis ZJ. Evidence of cortical inhibitory deficits in major depressive disorder. Biol Psychiatry 2010;67(5):458–64.
[25] Baxter Jr LR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatr 1989;46(3):243–50.
[26] Faehling F, Plewnia C. Controlling the emotional bias: performance, late positive potentials, and the effect of anodal transcranial direct current stimulation (tDCS). Front Cell Neurosci 2016;10:159.
[27] Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. J Clin Psychiatry 1997;58(Suppl 13):23–9.
[28] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45(2):201–6.
[29] Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 2018;391(10131):1683–92.
[30] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015;126(6):1071–107.
[31] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9(1):97–113.
[32] Müller-Dahlhaus JF, Orekhov Y, Liu Y, Ziemann U. Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. Exp Brain Res 2008;187(3):467–75.
[33] Krijzer F, Snelder M, Bradford D. Comparison of the (pro)convulsive properties of fluvoxamine and clovoxamine with eight other antidepressants in an animal model. Neuropsychobiology 1984;12(4):249–54.
[34] Rusjan PM, Barr MS, Farzan F, Arenovich T, Maller JJ, Fitzgerald PB, et al. Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. Hum Brain Mapp 2010;31(11):1643–52.
[35] Hjorth B. An on-line transformation of EEG scalp potentials into orthogonal source derivations. Electroencephalogr Clin Neurophysiol 1975;39(5):526–30.
[36] McFarland DJ, Wolpaw JR. Sensorimotor rhythm-based brain-computer interface (BCI): model order selection for autoregressive spectral analysis. J Neural Eng 2008;5(2):155–62.
[37] Chen LL, Madhavan R, Rapoport BI, Anderson WS. Real-time brain oscillation detection and phase-locked stimulation using autoregressive spectral estimation and time-series forward prediction. IEEE Trans Biomed Eng 2013;60(3):753–62.
[38] Kayser J, Tenke CE. On the benefits of using surface Laplacian (current source density) methodology in electrophysiology. Int J Psychophysiol 2015;97(3):171–3.
[39] Sale MV, Ridding MC, Nordstrom MA. Cortisol inhibits neuroplasticity induction in human motor cortex. J Neurosci 2008;28(33):8285–93.
[40] Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011. 156869.
[41] Gordon PC, Zrenner C, Desideri D, Belardinelli P, Zrenner B, Brunoni AR, et al. Modulation of cortical responses by transcranial direct current stimulation of dorsolateral prefrontal cortex: a resting-state EEG and TMS-EEG study. Brain Stimul 2018;11(5):1024–32.
[42] Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data. J Neurosci Methods 2007;164(1):177–90.
[43] Chung SW, Lewis BP, Rogasch NC, Saeki T, Thomson RH, Hoy KE, et al. Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: a TMS-EEG study. Clin Neurophysiol 2017;128(7):1117–26.
[44] Schaworonkow N, Caldana Gordon P, Belardinelli P, Ziemann U, Bergmann TO, Zrenner C. Mu-rhythm extracted with personalized EEG filters correlates with corticospinal excitability in real-time phase-triggered EEG-TMS. Front Neurosci 2018;12:954.
[45] Tinkhauser G, Pogosyan A, Little S, Beudel M, Herz DM, Tan H, et al. The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson's disease. Brain 2017;140(4):1053–67.
[46] Pina-Fuentes D, Little S, Oterdoom M, Neal S, Pogosyan A, Tijssen MAJ, et al. Adaptive DBS in a Parkinson's patient with chronically implanted DBS: a proof of principle. Mov Disord 2017;32(8):1253–4.
[47] Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, et al. Adaptive deep brain stimulation in advanced Parkinson disease. Ann Neurol 2013;74(3):449–57.
[48] Holt AB, Kormann E, Gulberti A, Potter-Nerger M, McNamara CG, Cagnan H, et al. Phase-dependent suppression of beta oscillations in Parkinson's disease patients. J Neurosci 2019;39(6):1119–34.
[49] Jaworska N, Blier P, Fusee W, Knott V. Alpha Power, alpha asymmetry and anterior cingulate cortex activity in depressed males and females. J Psychiatr Res 2012;46(11):1483–91.
[50] Henriques JB, Davidson RJ. Left frontal hypoactivation in depression. J Abnorm Psychol 1991;100(4):535–45.
[51] Schaffer CE, Davidson RJ, Saron C. Frontal and parietal electroencephalogram asymmetry in depressed and nondepressed subjects. Biol Psychiatry 1983;18(7):753–62.
[52] Olbrich S, Arns M. EEG biomarkers in major depressive disorder: discriminative power and prediction of treatment response. Int Rev Psychiatry 2013;25(5):604–18.
[53] Hlinka J, Alexakis C, Diukova A, Liddle PF, Auer DP. Slow EEG pattern predicts reduced intrinsic functional connectivity in the default mode network: an inter-subject analysis. Neuroimage 2010;53(1):239–46.
[54] Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatr 2015;72(6):603–11.
[55] Arns M, Etkin A, Hegerl U, Williams LM, DeBattista C, Palmer DM, et al. Frontal and rostral anterior cingulate (rACC) theta EEG in depression: implications for treatment outcome? Eur Neuropsychopharmacol 2015;25(8):1190–200.
[56] Olbrich S, van Dinteren R, Arns M. Personalized medicine: review and perspectives of promising baseline EEG biomarkers in major depressive disorder and attention deficit hyperactivity disorder. Neuropsychobiology 2015;72(3–4):229–40.
[57] Li CT, Hsieh JC, Huang HH, Chen MH, Juan CH, Tu PC, et al. Cognition-modulated frontal activity in prediction and augmentation of antidepressant efficacy: a randomized controlled pilot study. Cerebr Cortex 2016;26(1):202–10.
[58] Premoli I, Castellanos N, Rivolta D, Belardinelli P, Bajo R, Zipser C, et al. TMS-EEG signatures of GABAergic neurotransmission in the human cortex. J Neurosci 2014;34(16):5603–12.
[59] Premoli I, Costantini A, Rivolta D, Biondi A, Richardson MP. The effect of lamotrigine and levetiracetam on TMS-evoked EEG responses depends on stimulation intensity. Front Neurosci 2017;11:585.
[60] Premoli I, Bergmann TO, Fecchio M, Rosanova M, Biondi A, Belardinelli P, et al. The impact of GABAergic drugs on TMS-induced brain oscillations in human motor cortex. Neuroimage 2017;163:1–12.
[61] Ferrarelli F, Sarasso S, Guller Y, Riedner BA, Peterson MJ, Bellesi M, et al. Reduced natural oscillatory frequency of frontal thalamocortical circuits in schizophrenia. Arch Gen Psychiatr 2012;69(8):766–74.
[62] Daskalakis ZJ, Moller B, Christensen BK, Fitzgerald PB, Gunraj C, Chen R. The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects. Exp Brain Res 2006;174(3):403–12.
[63] Letzkus JJ, Wolff SB, Luthi A. Disinhibition, a circuit mechanism for associative learning and memory. Neuron 2015;88(2):264–76.
[64] Wolkenstein L, Plewnia C. Amelioration of cognitive control in depression by transcranial direct current stimulation. Biol Psychiatry 2013;73(7):646–51.
[65] Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 2017;23(1):28–38.
[66] Hamada M, Terao Y, Hanajima R, Shirota Y, Nakatani-Enomoto S, Furubayashi T, et al. Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. J Physiol 2008;586(16):3927–47.
[67] Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry 2012;72(7):595–603.
[68] Rogasch NC, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Short-latency artifacts associated with concurrent TMS-EEG. Brain Stimul. 2013;6(6):868–76.
[69] Mutanen T, Maki H, Ilmoniemi RJ. The effect of stimulus parameters on TMS-EEG muscle artifacts. Brain Stimul. 2013;6(3):371–6.
[70] Sommer M, Alfaro A, Rummel M, Speck S, Lang N, Tings T, et al. Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. Clin Neurophysiol 2006;117(4):838–44.
[71] Arai N, Okabe S, Furubayashi T, Mochizuki H, Iwata NK, Hanajima R, et al. Differences in after-effect between monophasic and biphasic high-frequency rTMS of the human motor cortex. Clin Neurophysiol 2007;118(10):2227–33.