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Review

Personalizing Repetitive Transcranial Magnetic Stimulation Parameters for Depression Treatment Using Multimodal Neuroimaging

Deborah C.W. Klooster, Michael A. Ferguson, Paul A.J.M. Boon, and Chris Baeken

ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is a tool that can be used to administer treatment for neuropsychiatric disorders such as major depressive disorder, although the clinical efficacy is still rather modest. Overly general stimulation protocols that consider neither patient-specific depression symptomology nor individualized brain characteristics, such as anatomy or structural and functional connections, may be the cause of the high inter- and intraindividual variability in rTMS clinical responses. Multimodal neuroimaging can provide the necessary insights into individual brain characteristics and can therefore be used to personalize rTMS parameters. Optimal coil positioning should include a three-step process: 1) identify the optimal (indirect) target area based on the exact symptom pattern of the patient; 2) derive the cortical (direct) target location based on functional and/or structural connectomes derived from functional and diffusion magnetic resonance imaging data; and 3) determine the ideal coil position by computational modeling, such that the electric field distribution overlaps with the cortical target. These TMS-induced electric field simulations, derived from anatomical and diffusion magnetic resonance imaging data, can be further applied to compute optimal stimulation intensities. In addition to magnetic resonance imaging, electroencephalography can provide complementary information regarding the ongoing brain oscillations. This information can be used to determine the optimal timing and frequency of the stimuli. The heightened benefits of these personalized stimulation approaches are logically reasoned, but speculative. Randomized clinical trials will be required to compare clinical responses from standard rTMS protocols to personalized protocols. Ultimately, an optimized clinical response may result from precision protocols derived from combinations of personalized stimulation parameters.

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Major depressive disorder (MDD) is one of the earliest, most well-recognized mental disorders and is a major contributor to the overall global disease burden (1). Symptoms include mood disturbances, anhedonia, weight changes, abnormal sleep patterns, psychomotor alterations, tiredness, persistent feelings of worthlessness, loss of focus, and potential suicidal thoughts (2). Because diagnosis entails patient reports of at least five of nine symptoms, there are several hundred unique combinations of clinical symptoms. This makes depression a highly heterogeneous disorder (2). Approximately 1 of 3 patients do not respond to current available treatment options, such as psychotherapy and pharmacotherapy (2). Alternative treatment options are needed to improve the response and remission rates.

Transcranial magnetic stimulation (TMS) is a biomechanical tool that can be used to noninvasively interfere with ongoing neuronal activity in the brain (3). The duration of the effects of repetitive application of stimuli outlasts the actual period of stimulation, making repetitive TMS (rTMS) a potential treatment option for a broad variety of neurologic and psychiatric disorders (4). High-frequency rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) using a figure-of-eight or an H1-coil has level A evidence (i.e., definite efficacy) for the treatment of depression (5). Moreover, level B evidence (probable efficacy) was obtained for low-frequency rTMS of the right DLPFC and bihemispheric stimulation, combining right-sided low-frequency rTMS (or continuous theta burst stimulation) and left-sided high-frequency rTMS (or intermittent theta burst stimulation) (5). The overall clinical response rates remain rather modest, irrespective of the chosen rTMS protocol. According to a meta-analysis by Berlim *et al.* (6), 29.3% and 18.6% of subjects with depression who received rTMS responded (i.e., ≥50% reduction in Hamilton Depression Rating Scale) or remitted (i.e., Hamilton Depression Rating Scale ≤8), respectively. Heterogeneous effects across individuals are very common. This heterogeneity could potentially be attributed to the application of too general one-fits-all rTMS protocols for a broad patient population.

Owing to the large parameter space, including coil position and orientation, stimulation intensity, stimulation frequency, pulse frequency, number of pulses, number of sessions, and intersession intervals, there are innumerable ways in which rTMS can be administered. At present, stimulation protocols are derived from knowledge about the neuropathology that needs to be treated. These one-fits-all stimulation protocols do not take into account interindividual variations in brain

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characteristics that can be extracted from multimodal neuroimaging. For example, anatomical magnetic resonance imaging (MRI) can provide detailed information about individual anatomy. Furthermore, advanced MRI data can be used to derive connectivity maps between brain regions on the individual level, further referred to as individualized connectomes (7,8). For example, resting-state functional MRI (rs-fMRI) can reveal information about brain function and functional networks, and diffusion-weighted MRI (DW-MRI) can provide information about the white matter networks with high spatial resolution. Because psychiatric disorders such as MDD are being newly conceptualized as disorders of brain networks instead of single brain regions, network imaging is important for the understanding of both pathology and treatment response (9,10). In addition to MRI, electroencephalography (EEG) provides complementary information by recording electrical activity within the brain with a high temporal resolution. Previous work shows that the brain's excitability state, derived from EEG data, can be used to administer stimulation at the optimal timing (11). Furthermore, stimulation frequencies can be adapted to individual firing frequencies (12,13).

Here, we describe ways in which multimodal imaging may be used to determine patient-specific stimulation parameters. These personalized rTMS protocols could reduce variability in clinical outcomes and thereby potentially increase overall clinical efficacy (14–16). Information on the search criteria can be found in the Supplement. Recently, Modak and Fitzgerald (17) published a systematic review on the added value of personalizing TMS protocols for the treatment of depression. It was suggested that personalized protocols, derived from various neuroimaging techniques, tend to be more effective than standard TMS. The Stanford Accelerated Intelligent Neuromodulation Therapy trial is a recent example of an evidence-based indication that personalized rTMS may play a role in enhanced treatment efficacy (18). A remission rate of 86.4% was reported, which is significantly higher than open-label remission rates reported earlier.

In this paper, new developments are discussed and recommendations for future personalized rTMS protocols are offered. To do this, we focus on the stimulation parameters that can be personalized using multimodal imaging techniques: coil position, stimulation intensity, timing, and frequency.

TMS TARGETING

The brain area that is affected by TMS depends on the position of the TMS coil on the scalp. Because of physical properties, the TMS-induced electric field is strong enough in the superficial layers of the cortex to interfere with neuronal activity. Deeper brain structures can be reached, but because of the depth focality trade-off, it is impossible to directly target deep brain structures without stimulating more superficial structures that are closer to the stimulation coil (19). However, even though stimulation is commonly administered to a single brain region using a figure-of-eight coil, the effects propagate via distributed functional and/or structural networks (20–26). As such, rTMS is conceptualized as a brain circuit therapy (8).

The left DLPFC is the most used stimulation target for antidepressant treatment, although other cortical targets have been suggested (7,27,28). The 5-cm rule, which requires identification of the motor cortex and moving the coil 5 cm in the rostral direction, is still often used to position the stimulation coil over the DLPFC. However, this 5-cm rule does not consider interindividual differences, such as the head size and shape, making this method suboptimal (29,30). Together with the findings that more anterior stimulation sites led to a better clinical response, the 5.5-cm or even 6-cm rules are currently in use (31,32). Alternative methods have been proposed to localize the DLPFC based on the 10–20 EEG system (33–36) or anatomical MRI in combination with neuronavigation (37,38). None of these methods consider differences in individual brain connectivity.

In this section, we propose a pipeline for optimal coil positioning at the scalp based on neuroimaging that involves three steps. A distinction is made between the coil position at the scalp, the direct targets (also referred to as cortical targets), and the indirect targets (i.e., deeper brain regions that are likely to contribute to clinical response).

Optimal Indirect Targets for Depression Treatment

The subgenual anterior cingulate cortex (sgACC) has received much attention as an indirect target for rTMS treatment (Figure 1A) (21,32,39,40). It has been linked to depression and clinical response across diverse antidepressant treatment modalities (41). An important recent study showed further evidence that the sgACC is part of the general depression circuit (42). It was shown that the depression circuits, derived by correlating depression scores with functional connectivity maps from lesion data, and TMS and deep brain stimulation sites converge (42,43). To date, it remains unclear whether the sgACC is the only indirect target for depression treatment or if it is even the most important indirect target.

Connectome-Based Cortical Target Derivation

Functional Connectivity. Using a priori knowledge regarding the role of the sgACC in the clinical effectiveness of rTMS studies, investigations have focused on the link between clinical response and sgACC connectivity with the direct cortical target in the left DLPFC. rs-fMRI showed that the functional anticorrelation between the DLPFC and sgACC is associated with clinical outcomes of rTMS in patients with depression, suggesting that the spot with the highest functional anticorrelation may be an optimal cortical stimulation target for MDD treatment (Figure 1B) (32,44–46). It should be noted that a recent study could not replicate these findings (47). More recently, a relationship between the distance between the actual stimulation site and the individual's optimal stimulation site, defined based on sgACC anticorrelations, was shown in two independent studies using individual rs-fMRI data (16,48) (Figure 2).

Normative Versus Individualized Functional Connectome Data. It is challenging to obtain robust individualized connectomes. Limbic regions are prone to low signal-to-noise ratios given their physical proximity to artifact-generating anatomy (e.g., sinus cavities). This is unfortunate for neuropsychiatric treatment planning because functional localization within the limbic network is crucial for indirect target

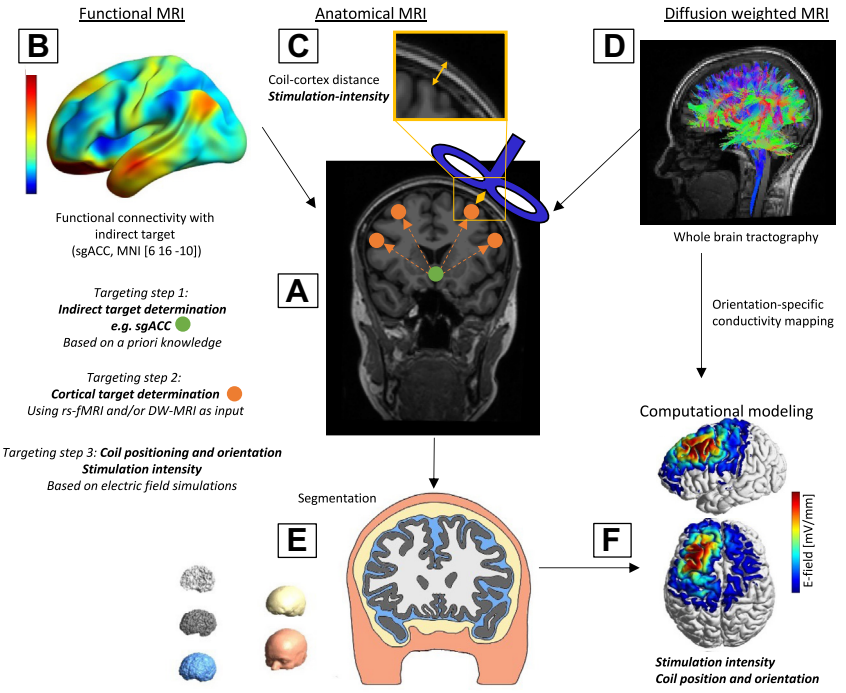

Figure 1. Contribution of various magnetic resonance neuroimaging (MRI) modalities to personalize repetitive transcranial magnetic stimulation (TMS) parameters for depression treatment. **(A, B, D)** The proposed three-step approach to determine the optimal coil position. A priori knowledge about the pathophysiology of major depressive disorder can be used, also including the subjects' symptom profile, to determine the optimal indirect stimulation target. This can be a deep brain structure, such as the subgenual anterior cingulate cortex (sgACC) **(A)**. Subsequently, functional and structural connectome information, derived from resting-state functional MRI (rs-fMRI) **(B)** and diffusion-weighted MRI (DW-MRI) **(D)**, can be used to define the cortical target. **(F)** TMS-induced electric field simulation can help to determine coil position and orientation at the scalp such that there is maximal overlap between the TMS-induced electric field and the cortical target. Instead of simulating a TMS-induced electric field based on a coil position and a head model, an inverse method can be used to derive the coil position and orientation given a cortical target area. A comparable inverse method can provide information about the stimulation intensity if the preferred electric field strength in the cortex is set a priori. **(E)** These individual computational models require anatomical MRI data for the generation of an individual head model, including segmentation. These models benefit from incorporation of DW-MRI **(D)** data because the direction-dependent conductivity values can be derived from fiber tracts. Anatomical data can furthermore be used to correct the stimulation intensity for the coil-cortex distance **(C)**. E-field, electric field; MNI, Montreal Neurological Institute.

determination and subsequent connectivity analyses. To compensate for the poor signal-to-noise ratio of individualized connectomes, relatively long scanning sessions are required that might be hard for patients to tolerate and logistically unfeasible (49–51).

Given these limitations, average connectomes (also referred to as the normative connectome) were developed (52). These publicly available normative connectomes are more robust and have also shown their potential value in a large range of clinical applications (32,44,45,53). However, these normative

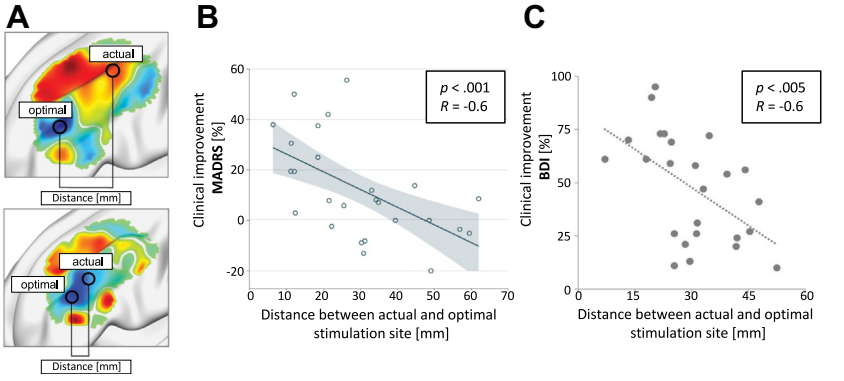

Figure 2. Relationship between the proximity to personalized stimulation sites and clinical responses to repetitive transcranial magnetic stimulation for depression treatment was shown by two independent retrospective studies [Cash *et al.* (16) and Siddiqi *et al.* (48)]. **(A)** Examples of the distance between the actual stimulation position that was used for treatment (derived from beam F3 method in Cash *et al.* and 5.5-cm rule in Siddiqi *et al.*) and the presumed optimal stimulation target, defined as the mean of the cluster with the highest anticorrelation with the subgenual anterior cingulate cortex. **(B, C)** The relationship between these distances and clinical responses. **(B)** Clinical improvement was defined as the change in Montgomery–Åsberg Depression Rating Scale (MADRS) measured after 3 weeks of repetitive transcranial magnetic stimulation with respect to baseline. For the derivation of the individualized optimal stimulation targets, 13 minutes (2 sessions of 6 min 40 s concatenated) resting-state functional magnetic resonance imaging data were used. This study included 26 subjects. **(C)** Beck Depression Inventory (BDI) was used to define clinical response after 6 weeks of repetitive transcranial magnetic stimulation treatment with respect to baseline, and 28 minutes of resting-state functional magnetic resonance imaging data were collected to define the individual's optimal stimulation site. In this study, 25 patients with depression were included. In both studies, significant ($p < .001$ and $p < .005$) and negative correlations ($R = -0.6$) were found, indicating that the clinical response increased when the stimulation was administered to a position closer to one's individual optimal stimulation site. [Reproduced from Cash *et al.* and Siddiqi *et al.* with permission from publishers.]

connectomes are, by definition, unable to represent individual differences in connectivity.

A direct comparison between the use of individual MRI data and normative connectome data was performed by Cash *et al.* (45) and Siddiqi *et al.* (54). Both studies found similar results using these types of connectomes in predicting clinical responses based on the connectivity between the stimulation site and the sgACC at the group level. However, a slight trend toward better prediction using the individual data was reported (45).

Recently, the importance of using individual data to derive TMS targets was emphasized in a follow-up study by Cash *et al.* (55). Their observations showed that the interindividual variability of TMS target sites was a factor up to 6.85 times higher than the intraindividual variability using individual MRI data. This result confirms that individual targets do not converge to group-average positions, arguing in favor of using individual rs-fMRI data. In addition, this study showed high test-retest reliability of TMS targets in contrast to previous work by Ning *et al.* (56).

A few clinical trials prospectively implemented the use of individualized connectomes to determine the cortical target based on the functional connectivity with the sgACC (18,57–59). These studies showed promising clinical efficacy, emphasizing the need for future larger trials to investigate the effect of personalized coil positioning in more detail.

Structural Connectivity. The effects of TMS also propagate throughout the brain via structural connections (22,24,60,61). A recent TMS-EEG study combined with rs-fMRI and DW-MRI showed that propagation of TMS effects prefers to follow structural rather than functional pathways (23). TMS coil positioning based on structural connections has not yet been extensively studied (Figure 1D). It is not straightforward to reproduce findings from rs-fMRI with DW-MRI data because there might be no direct structural connections with the sgACC, as shown earlier in tracer studies in primates (62). A first attempt indicated that indirect connections between the stimulation site in the left DLPFC and the caudal and posterior parts of the cingulate cortex were correlated to the clinical response to an accelerated rTMS protocol (20).

Symptom Specificity

Defining optimal indirect and related direct stimulation targets is further complicated by the possibility that these might differ between subjects with the same pathology. Weigand *et al.* (32) investigated the potential of resting-state functional connectivity between the DLPFC and the sgACC to predict the clinical response to rTMS in subgroups of patients with cognitive, affective, and somatic symptoms. sgACC connectivity was a significant predictor of improvement in subjects with cognitive and affective symptoms. Siddiqi *et al.* used the lesion network mapping technique to show that optimal cortical stimulation targets may be symptom specific (54). Here, brain networks related to specific depression symptoms were determined by clustering symptom-response maps. The proposed optimal target for dysphoric symptoms was close to the left DLPFC location with the highest anticorrelation with the subgenual cingulate cortex, whereas the target for anxiosomatic symptoms was located more medial and posterior in Brodmann area 8. Earlier, Drysdale *et al.* also showed a relationship between symptom profiles, resting-state connectivity, and clinical responses to rTMS (63). Four depression subtypes were defined, and the subtype mostly related to anhedonia showed the most clinical response to rTMS applied to the dorsomedial prefrontal cortex. However, this depression subtyping could not be replicated by Dinga *et al.* (64).

Value of Computational Models for Coil Positioning

Most often, simple projections are used between the coil position at the scalp and the assumed direct cortical stimulation region. However, subject-specific brain geometries uniquely shape the electric fields induced by TMS (65–67). Therefore, the peak of the TMS-induced electric field is not always located directly underneath the stimulation coil, and hence the projection method is not optimal to convert between the coil position and the cortical target.

Computational modeling (Figure 1E, F) of the TMS-induced electric fields can provide insights into the brain areas that are affected by the stimulation. Individual head models for such computational models can be derived from anatomical MRI data (Figure 1E). These head models are segmented in different tissue types with specific conductivity values. In addition, DW-MRI data (Figure 1D) can be used for more accurate orientation-specific conductivity mapping (68,69).

Pipelines that are based on a predetermined cortical target and subsequently derive the optimal coil position and orientation by maximizing the magnitude or a directional component of the TMS-induced electric field in this predefined target region were recently proposed (70–72). Whereas Balderston *et al.* (71) defines the coil position based on the projection from the cortical target to the scalp and iterates the coil orientation at that position, Dannhauer *et al.* (70) iterates over both coil location and orientation, using an auxiliary dipole method that allows for fast computation of TMS-induced electric fields (73). Both pipelines define the optimal coil orientation as the one that induces the maximum electric field strength in the predefined target. In addition, the pipeline by Dannhauer *et al.* (70) has the option to maximize a directional component of the electric fields.

Coil Positioning Based on Concurrent TMS-fMRI

The use of concurrent TMS-fMRI techniques could also aid in determining the coil position. The causal effects of TMS in the modulation of brain networks can provide a direct proof of target engagement, i.e., activation of the indirect target (19,74). Vink *et al.* (75) showed activation in the sgACC in 4 of 9 healthy subjects who received single TMS pulses to the DLPFC, determined by the 5-cm rule, during fMRI scanning. Recently, Oathes *et al.* (76) used resting-state guided TMS-fMRI to provide proof of downstream target engagement of the sgACC. Note that the use of concurrent TMS-fMRI techniques limits the optimal coil positioning pipeline to a two-step process.

STIMULATION INTENSITY

To date, stimulation intensity is the only stimulation parameter that is derived from subject-specific characteristics.

Stimulation intensity is most often expressed as a percentage of one's resting motor threshold (rMT), defined as the minimal stimulation intensity that induces a reliable motor evoked potential (MEP) of minimal amplitude in the targeted muscle (77). According to this gold standard, individual adjustment for stimulation intensity is purely based on the electrical responsivity of the primary motor cortex. Previous work showed variation in response to TMS in the prefrontal and motor cortices (78).

Variation between coil-cortex distance in the motor cortex and other stimulation regions could cause a deviation in effective stimulation intensity. Stokes *et al.* (79) proposed a method to derive a corrected rMT for distinct stimulation sites based on differences in the coil-cortex distance. These distances can be extracted from anatomical MRI data (Figure 1C). However, adjusting the stimulation intensity to account for individual coil-to-cortex distance did not enhance the efficacy rates in a previous trial by Blumberger *et al.* (80).

To address this issue more accurately, simultaneous TMS-fMRI or TMS-EEG might help to further optimize subject-specific stimulation intensities and to validate the correction method proposed by Stokes *et al.* (79). Dose (i.e., intensity)-response relationships can be derived by systematically varying stimulation intensity (19). Responses can be quantified by means of blood oxygen level–dependent activity or TMS-evoked potentials.

Furthermore, computational models may help to determine the optimal stimulation intensity. Caulfield *et al.* (81) recently published a personalized E-field X motor threshold method for dosing based on electric field simulations. The proposed approach combines the ability of rMT to determine cortical electric field strengths (derived from electric field simulations at the motor cortex) necessary to induce neuronal activity with the knowledge that electric field strengths scale linearly with stimulation intensity. Hence, the required intensity necessary to induce neuronal activation in the DLPFC can be derived by a linear scaling of the (random) intensity used to perform electric field simulation at the DLPFC by the ratio of the simulated and intended electric field strengths in the DLPFC.

STIMULATION TIMING AND FREQUENCY

The effects of rTMS differ not only between subjects but also within subjects and across and even within sessions (82). Even though animal studies already suggested that this variability might reflect dynamics in brain state, this phenomenon was for a long time mostly ignored in human research (83,84). In 2008, Silvanto and Pascual-Leone (85) described the potential importance of the baseline cortical activation state when applying TMS. Ongoing brain oscillations can reveal information about the brain's excitability state (Figure 3) (86). This information is currently not incorporated in brain stimulation protocols (at least not in clinical settings), which might add to the heterogeneous outcomes (87). The neuron's excitability state during the application of stimuli is an essential factor that determines the capabilities of the induction of synaptic plasticity within neuronal networks. Based on this fact, it can be hypothesized that the efficacy of rTMS can be enhanced when the stimulation is tuned to instantaneous phase or power values that reflect high excitability states (88). Real-time analysis of EEG data combined with a forward prediction model allows optimal timing of the TMS pulses at a preferred brain state. This method is further referred to as brain oscillation–synchronized rTMS (89,90).

The impact of brain oscillation–synchronized TMS applied to the motor cortex in healthy subjects was represented in different MEP sizes (11,91). The negative peak of the μ-rhythm (part of the alpha rhythm extracted from the motor region), extracted from EEG data at the motor cortex, was associated with a high excitability state, whereas the positive peak represented low excitability. Hence, motor cortex stimulation during negative peaks of the μ-rhythm resulted in significantly higher MEPs (11). As a first step toward future brain oscillation–synchronized rTMS treatment for depression, single-session alpha-synchronized rTMS applied to the left DLPFC was investigated and showed to be feasible and safe (92). Clinical trials with repeated alpha-synchronized stimulation sessions to investigate the therapeutic potential and efficacy of brain oscillation–synchronized rTMS in MDD compared with current rTMS therapies are warranted.

Combining brain oscillation–synchronized rTMS with real-time functional brain imaging can be considered an ideal method to combine optimal targeting (based on concurrent TMS-fMRI) and administering TMS pulses during predefined brain states. The feasibility of a concurrent TMS-EEG-fMRI system has been shown (93), and this setup was used to show the influence of pre-TMS alpha power on distributed effects in the motor network (94). However, combining the three techniques is challenging.

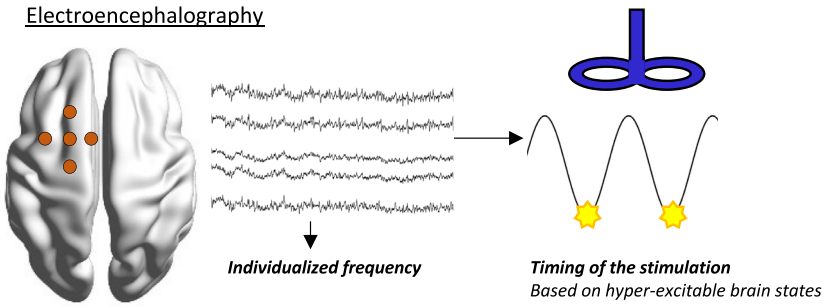

Figure 3. Contribution of electroencephalography to personalization of the timing and frequency of stimulation. Effects of stimulation are thought to be more pronounced if the pulses are administered during the brain's hyperexcitability state. Previous work used five electroencephalography electrodes to derive brain waves and used negative peaks (troughs) as the optimal timing of stimulation. Individualized stimulation frequencies, for example for theta burst stimulation, could also be extracted from electroencephalography.

EEG also reveals information about the individual firing patterns. Because every individual has different rhythmic firing patterns, it can be hypothesized that the stimulation frequency to obtain clinical effects from rTMS is also subject specific and can be personalized for rTMS treatment. Concretely, this means that standard 10-Hz rTMS treatment protocols could become more effective if the frequency is tuned to an individual frequency. Previous work showed that smaller deviations between the individual alpha frequency and the stimulation frequency (10 Hz) were related to better responses to 10-Hz rTMS in patients with depression (13,95). There are various ways to define and calculate the optimal individual stimulation frequency (12,96). In addition to a role of frequency in standard rTMS protocols, Chung *et al.* (97) highlighted the importance of the stimulation frequency in intermittent theta burst stimulation protocols by comparing 30-Hz bursts repeated at 6 Hz, 50-Hz bursts at 5 Hz, or individualized frequency in healthy volunteers. In contrast to the two standard protocols, individual intermittent theta burst stimulation significantly increased the amplitude of the TMS-evoked potentials at specific latencies.

CHALLENGES TOWARD CLINICAL IMPLEMENTATION

All methods for personalization as described in this manuscript require additional time and effort. It is therefore of paramount importance to prove the superiority (and not simply the noninferiority) of personalization before these methods can be adopted in daily clinical practice. It is not known if all parameters that can be personalized have equal added value. Standard pipelines to obtain these personalized parameters from neuroimaging data are necessary to extract these parameters in clinical settings.

Imaging Limitations

Although some previous works used normative connectome data to derive stimulation targets, the methods described in this paper might benefit from the use of individual connectome data (55). A disadvantage is that they require advanced brain imaging technologies that are not universally available. In addition, rs-fMRI time series are contaminated by many nonneuronal sources of noise, and it remains challenging to accurately reconstruct individual structural pathways (98–100). There is a significant variability between scanners and protocols, which makes it challenging to obtain and use truly quantitative measures (101,102). One potential compromise between individual and normative connectome methods might be the use of demographically specific connectomes that account for stable neurodiversity, for example, sex- and age-based connectomes or pathology-based connectomes. Initiatives to develop demographically specific connectome methods for MDD treatment are currently underway (http://banda.mit.edu/ and http://enigma.ini.usc.edu/ongoing/enigma-mdd-working-group/).

Even though electric field simulations can provide valuable information about optimal coil position and orientation at the scalp and stimulation intensity, state-of-the-art head modeling methods are only an approximation of true individual anatomy. In particular, potential segmentation errors, limited number of tissue types, and the use of standard conductivity values might lead to various sources of inaccuracies (103,104). Moreover, currently there is no consensus on the threshold that should be applied to simulated electric field distributions to select only the gray matter regions that are activated. Standard depression treatment mostly uses a stimulation intensity of 120% rMT at the left DLPFC. Some studies used a threshold of 83% to comply with the proven activation, i.e., induction of MEPs, when stimulating the motor cortex at rMT (22), and a personalized E-field X motor threshold method could also provide insight in this threshold (81). This would lead to distributions with a width of approximately 2 cm. However, unexpected focality was shown by Romero *et al.* (105), who studied the effects of single TMS pulses on the single-cell level; single neurons in an area $<$2-mm diameter in the cortex were affected. In addition, knowledge about effective electric fields and consecutive TMS signal propagation could benefit from coupling these fields with DW-MRI–derived fiber pathways (3,60,106). Furthermore, it must be stated that subthreshold effects might also play a role in the responses to TMS (26).

Alpha oscillations could be used to derive the optimal timing and personalized stimulation frequency. However, DLPFC alpha oscillations are not easy to extract because of a low signal-to-noise ratio in rest. An algorithm to automatically reject EEG power spectra that do not contain a clear alpha peak was recently published (96). Individually optimized spatial filters might improve the signal-to-noise ratio in the preferred frequency range in EEG (107). These filters could further benefit from beamforming techniques incorporating information about the individual's structural brain connections.

Randomized Controlled Trials: Investigating Superiority of Personalized Stimulation Parameters

While there is an emerging body of evidence to support the vision for personalized brain stimulation, large, potentially multicenter, prospective clinical trials in which patients with highly treatment-resistant depression are randomized to receive standard rTMS procedures (in practice usually without neuronavigation) versus personalized protocol are required (17). To prevent patients from having different placebo effects due to varying treatment duration (caused by the additional steps necessary for personalization), the pipeline to derive personalized stimulation parameters should be done for both groups. Only one group actually receives personalized stimulation. We anticipate that the added value of personalization (compared with standard rTMS) could achieve a moderate effect size (Cohen's $d \sim 0.35$). In line with Cole *et al.* (18), we believe that more patients will remit (instead of solely respond) after personalized treatment. A randomized controlled trial should include 204 subjects (102 per group) to show this potential added value of personalized protocols compared with standard protocols (power = 0.8, alpha = 0.05) (108).

CONCLUSIONS

Antidepressant treatment by rTMS has shown promising results. However, treatment efficacy is hampered owing to the diversity in depressive symptoms and neural phenotypes and the use of overall one-fits-all stimulation protocols. We propose that rTMS parameters can be personalized by using

multimodal neuroimaging techniques for delivering higher-precision interventions. These personalized stimulation protocols may reduce variability in treatment response and increase overall clinical effectiveness. We anticipate that optimal clinical effectiveness may ultimately be achieved using treatment protocols integrating these personalized stimulation parameters. Even though the focus is on treatment for patients with depression, the methods proposed here may easily be translated to the treatment of other neuropsychiatric pathologies.

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REFERENCES

1. Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, *et al.* (2016): Major depressive disorder. Nat Rev Dis Primers 2:16065.
2. Fava M, Kendler KS (2000): Major depressive disorder. Neuron 28:335–341.
3. Wagner T, Valero-Cabre A, Pascual-Leone A (2007): Noninvasive human brain stimulation. Annu Rev Biomed Eng 9:527–565.
4. Klooster DCW, de Louw AJA, Aldenkamp AP, Besseling RMH, Mestrom RMC, Carrette S, *et al.* (2016): Technical aspects of neurostimulation: Focus on equipment, electric field modeling, and stimulation protocols. Neurosci Biobehav Rev 65:113–141.
5. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, *et al.* (2020): Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018) [published correction appears in Clin Neurophysiol 2020; 131:1168–1169]. Clin Neurophysiol 131:474–528.
6. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ (2014): Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: A systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med 44:225–239.
7. Cash RFH, Weigand A, Zalesky A, Siddiqi SH, Downar J, Fitzgerald PB, Fox MD (2021): Using brain imaging to improve spatial targeting of TMS for depression. Biol Psychiatry 90:689–700.
8. Horn A, Fox MD (2020): Opportunities of connectomic neuromodulation. Neuroimage 221:117180.
9. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA (2015): Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72:603–611.
10. Fornito A, Bullmore ET, Zalesky A (2017): Opportunities and challenges for psychiatry in the connectomic era. Biol Psychiatry Cogn Neurosci Neuroimaging 2:9–19.
11. Zrenner C, Desideri D, Belardinelli P, Ziemann U (2018): Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. Brain Stimul 11:374–389.
12. Leuchter AF, Wilson AC, Vince-Cruz N, Corlier J (2021): Novel method for identification of individualized resonant frequencies for treatment of major depressive disorder (MDD) using repetitive transcranial magnetic stimulation (rTMS): A proof-of-concept study. Brain Stimul 14:1373–1383.
13. Corlier J, Carpenter LL, Wilson AC, Tirrell E, Gobin AP, Kavanaugh B, Leuchter AF (2019): The relationship between individual alpha peak frequency and clinical outcome with repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder (MDD). Brain Stimul 12:1572–1578.
14. Fitzgerald PB (2021): Targeting repetitive transcranial magnetic stimulation in depression: Do we really know what we are stimulating and how best to do it? Brain Stimul 14:730–736.
15. Vila-Rodriguez F, Frangou S (2021): Individualized functional targeting for rTMS: A powerful idea whose time has come? Hum Brain Mapp 42:4079–4080.
16. Cash RFH, Cocchi L, Lv J, Fitzgerald PB, Zalesky A (2021): Functional magnetic resonance imaging-guided personalization of transcranial magnetic stimulation treatment for depression. JAMA Psychiatry 78:337–339.
17. Modak A, Fitzgerald PB (2021): Personalising transcranial magnetic stimulation for depression using neuroimaging: A systematic review. World J Biol Psychiatry 22:647–669.
18. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, *et al.* (2020): Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. Am J Psychiatry 177:716–726.
19. Bergmann TO, Varatheeswaran R, Hanlon CA, Madsen KH, Thielscher A, Siebner HR (2021): Concurrent TMS-fMRI for causal network perturbation and proof of target engagement. Neuroimage 237:118093.
20. Klooster DCW, Vos IN, Caeyenberghs K, Leemans A, David S, Besseling RMH, *et al.* (2020): Indirect frontocingulate structural connectivity predicts clinical response to accelerated rTMS in major depressive disorder. J Psychiatry Neurosci 45:243–252.
21. Fox MD, Buckner RL, Liu H, Chakravarty MM, Lozano AM, Pascual-Leone A (2014): Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. Proc Natl Acad Sci U S A 111:E4367–E4375.
22. Momi D, Ozdemir RA, Tadayon E, Boucher P, Shafi MM, Pascual-Leone A, Santarnecchi E (2021): Network-level macroscale structural connectivity predicts propagation of transcranial magnetic stimulation. Neuroimage 229:117698.
23. Momi D, Ozdemir RA, Tadayon E, Boucher P, Di Domenico A, Fasolo M, *et al.* (2021): Perturbation of resting-state network nodes preferentially propagates to structurally rather than functionally connected regions. Sci Rep 11:12458.
24. Amico E, Bodart O, Rosanova M, Gosseries O, Heine L, van Mierlo P, *et al.* (2017): Tracking dynamic interactions between structural and

functional connectivity: A TMS/EEG-dMRI study. Brain Connect 7:84–97.
25. Tik M, Hoffmann A, Sladky R, Tomova L, Hummer A, Navarro de Lara L, *et al.* (2017): Towards understanding rTMS mechanism of action: Stimulation of the DLPFC causes network-specific increases in functional connectivity. Neuroimage 162:289–296.
26. Harita S, Momi D, Mazza F, Griffiths JD (2021): Mapping inter-individual functional connectivity variability in TMS targets for major depressive disorder. bioRxiv. https://doi.org/10.1101/2021.07.15.452518.
27. Downar J, Daskalakis ZJ (2013): New targets for rTMS in depression: A review of convergent evidence. Brain Stimul 6:231–240.
28. Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ (2008): A meta-analytic study of changes in brain activation in depression [published correction appears in Hum Brain Mapp 2008; 29:736]. Hum Brain Mapp 29:683–695.
29. Herbsman T, Avery D, Ramsey D, Holtzheimer P, Wadjik C, Hardaway F, *et al.* (2009): More lateral and anterior prefrontal coil location is associated with better repetitive transcranial magnetic stimulation antidepressant response. Biol Psychiatry 66:509–515.
30. Herwig U, Padberg F, Unger J, Spitzer M, Schönfeldt-Lecuona C (2001): Transcranial magnetic stimulation in therapy studies: Examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry 50:58–61.
31. Johnson KA, Baig M, Ramsey D, Lisanby SH, Avery D, McDonald WM, *et al.* (2013): Prefrontal rTMS for treating depression: Location and intensity results from the OPT-TMS multi-site clinical trial. Brain Stimul 6:108–117.
32. Weigand A, Horn A, Caballero R, Cooke D, Stern AP, Taylor SF, *et al.* (2018): Prospective validation that subgenual connectivity predicts antidepressant efficacy of transcranial magnetic stimulation sites. Biol Psychiatry 84:28–37.
33. Herwig U, Satrapi P, Schönfeldt-Lecuona C (2003): Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 16:95–99.
34. Mir-Moghtadaei A, Caballero R, Fried P, Fox MD, Lee K, Giacobbe P, *et al.* (2015): Concordance between BeamF3 and MRI-neuronavigated target sites for repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. Brain Stimul 8:965–973.
35. Beam W, Borckardt JJ, Reeves ST, George MS (2009): An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul 2:50–54.
36. Trapp NT, Bruss J, King Johnson M, Uitermarkt BD, Garrett L, Heinzerling A, *et al.* (2020): Reliability of targeting methods in TMS for depression: Beam F3 vs. 5.5 cm. Brain Stimul 13:578–581.
37. Peleman K, Van Schuerbeek P, Luypaert R, Stadnik T, De Raedt R, De Mey J, *et al.* (2010): Using 3D-MRI to localize the dorsolateral prefrontal cortex in TMS research. World J Biol Psychiatry 11:425–430.
38. Hebel T, Göllnitz A, Schoisswohl S, Weber FC, Abdelnaim M, Wetter TC, *et al.* (2021): A direct comparison of neuronavigated and non-neuronavigated intermittent theta burst stimulation in the treatment of depression. Brain Stimul 14:335–343.
39. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A (2012): Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry 72:595–603.
40. Oathes DJ, Zimmerman J, Duprat R, Cavdaroglu S, Scully M, Rosenberg B, *et al.* (2018): Individualized non-invasive brain stimulation engages the subgenual anterior cingulate and amygdala. bioRxiv. https://doi.org/10.1101/503441.
41. Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM (2011): The subcallosal cingulate gyrus in the context of major depression. Biol Psychiatry 69:301–308.
42. Siddiqi SH, Schaper FLWVJ, Horn A, Hsu J, Padmanabhan JL, Brodtmann A, *et al.* (2021): Brain stimulation and brain lesions converge on common causal circuits in neuropsychiatric disease. Nat Hum Behav 5:1707–1716.
43. Fox MD (2018): Mapping symptoms to brain networks with the human connectome. N Engl J Med 379:2237–2245.
44. Fox MD, Liu H, Pascual-Leone A (2013): Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. Neuroimage 66:151–160.
45. Cash RFH, Zalesky A, Thomson RH, Tian Y, Cocchi L, Fitzgerald PB (2019): Subgenual functional connectivity predicts antidepressant treatment response to transcranial magnetic stimulation: Independent validation and evaluation of personalization. Biol Psychiatry 86:e5–e7.
46. Baeken C, Marinazzo D, Wu GR, Van Schuerbeek P, De Mey J, Marchetti I, *et al.* (2014): Accelerated HF-rTMS in treatment-resistant unipolar depression: Insights from subgenual anterior cingulate functional connectivity. World J Biol Psychiatry 15:286–297.
47. Hopman HJ, Chan SMS, Chu WCW, Lu H, Tse CY, Chau SWH, *et al.* (2021): Personalized prediction of transcranial magnetic stimulation clinical response in patients with treatment-refractory depression using neuroimaging biomarkers and machine learning. J Affect Disord 290:261–271.
48. Siddiqi SH, Weigand A, Pascual-Leone A, Fox MD (2021): Identification of personalized transcranial magnetic stimulation targets based on subgenual cingulate connectivity: An independent replication. Biol Psychiatry 90:e55–e56.
49. Gordon EM, Laumann TO, Adeyemo B, Petersen SE (2017): Individual variability of the system-level organization of the human brain. Cereb Cortex 27:386–399.
50. Greene DJ, Marek S, Gordon EM, Siegel JS, Gratton C, Laumann TO, *et al.* (2020): Integrative and network-specific connectivity of the basal ganglia and Thalamus defined in individuals. Neuron 105:742–758.e6.
51. Poldrack RA, Laumann TO, Koyejo O, Gregory B, Hover A, Chen MY, *et al.* (2015): Long-term neural and physiological phenotyping of a single human. Nat Commun 6:8885.
52. Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, *et al.* (2011): The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 106:1125–1165.
53. Padmanabhan JL, Cooke D, Joutsa J, Siddiqi SH, Ferguson M, Darby RR, *et al.* (2019): A human depression circuit derived from focal brain lesions. Biol Psychiatry 86:749–758.
54. Siddiqi SH, Taylor SF, Cooke D, Pascual-Leone A, George MS, Fox MD (2020): Distinct symptom-specific treatment targets for circuit-based neuromodulation. Am J Psychiatry 177:435–446.
55. Cash RFH, Cocchi L, Lv J, Wu Y, Fitzgerald PB, Zalesky A (2021): Personalized connectivity-guided DLPFC-TMS for depression: Advancing computational feasibility, precision and reproducibility. Hum Brain Mapp 42:4155–4172.
56. Ning L, Makris N, Camprodon JA, Rathi Y (2019): Limits and reproducibility of resting-state functional MRI definition of DLPFC targets for neuromodulation. Brain Stimul 12:129–138.
57. Siddiqi SH, Trapp NT, Hacker CD, Laumann TO, Kandala S, Hong X, *et al.* (2019): Repetitive transcranial magnetic stimulation with resting-state network targeting for treatment-resistant depression in traumatic brain injury: A randomized, controlled, double-blinded pilot study. J Neurotrauma 36:1361–1374.
58. Barbour T, Lee E, Ellard K, Camprodon J (2019): Individualized TMS target selection for MDD: Clinical outcomes, mechanisms of action and predictors of response. Brain Stimul 12:P516.
59. Williams NR, Sudheimer KD, Bentzley BS, Pannu J, Stimpson KH, Duvio D, *et al.* (2018): High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression. Brain 141:e18.
60. De Geeter N, Crevecoeur G, Leemans A, Dupré L (2015): Effective electric fields along realistic DTI-based neural trajectories for modelling the stimulation mechanisms of TMS. Phys Med Biol 60:453–471.
61. Nummenmaa A, McNab JA, Savadjiev P, Okada Y, Hämäläinen MS, Wang R, *et al.* (2014): Targeting of white matter tracts with transcranial magnetic stimulation. Brain Stimul 7:80–84.

62. Pandya DN, Van Hoesen GW, Mesulam MM (1981): Efferent connections of the cingulate gyrus in the rhesus monkey. Exp Brain Res 42:319–330.
63. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, *et al.* (2017): Resting-state connectivity biomarkers define neurophysiological subtypes of depression [published correction appears in Nat Med 2017; 23:264]. Nat Med 23:28–38.
64. Dinga R, Schmaal L, Penninx BWJH, van Tol MJ, Veltman DJ, van Velzen L, *et al.* (2019): Evaluating the evidence for biotypes of depression: Methodological replication and extension of Drysdale, et al. Neuroimage Clin 22:101796.
65. Opitz A, Legon W, Rowlands A, Bickel WK, Paulus W, Tyler WJ (2013): Physiological observations validate finite element models for estimating subject-specific electric field distributions induced by transcranial magnetic stimulation of the human motor cortex. Neuroimage 81:253–264.
66. Cocchi L, Zalesky A (2018): Personalized transcranial magnetic stimulation in psychiatry. Biol Psychiatry Cogn Neurosci Neuroimaging 3:731–741.
67. Weise K, Numssen O, Thielscher A, Hartwigsen G, Knösche TR (2020): A novel approach to localize cortical TMS effects. Neuroimage 209:116486.
68. Opitz A, Windhoff M, Heidemann RM, Turner R, Thielscher A (2011): How the brain tissue shapes the electric field induced by transcranial magnetic stimulation. Neuroimage 58:849–859.
69. Thielscher A, Opitz A, Windhoff M (2011): Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation. Neuroimage 54:234–243.
70. Dannhauer M, Huang Z, Beynel L, Wood E, Bukhari-Parlakturk N, Peterchev AV (2022): TAP: Targeting and analysis pipeline for optimization and verification of coil placement in transcranial magnetic stimulation. J Neural Eng 19(2).
71. Balderston NL, Roberts C, Beydler EM, Deng Z-D, Radman T, Luber B, *et al.* (2020): A generalized workflow for conducting electric field–optimized, fMRI-guided, transcranial magnetic stimulation. Nat Protoc 15:3595–3614.
72. Balderston NL, Beer JC, Seok D, Makhoul W, Deng Z-D, Girelli T, *et al.* (2022): Proof of concept study to develop a novel connectivity-based electric-field modelling approach for individualized targeting of transcranial magnetic stimulation treatment. Neuropsychopharmacology 47:588–598.
73. Gomez LJ, Dannhauer M, Peterchev AV (2021): Fast computational optimization of TMS coil placement for individualized electric field targeting. Neuroimage 228:117696.
74. Oathes DJ, Balderston NL, Kording KP, DeLuisi JA, Perez GM, Medaglia JD, *et al.* (2021): Combining transcranial magnetic stimulation with functional magnetic resonance imaging for probing and modulating neural circuits relevant to affective disorders. Wiley Interdiscip Rev Cogn Sci 12:e1553.
75. Vink JJT, Mandija S, Petrov PI, van den Berg CAT, Sommer IEC, Neggers SFW (2018): A novel concurrent TMS-fMRI method to reveal propagation patterns of prefrontal magnetic brain stimulation. Hum Brain Mapp 39:4580–4592.
76. Oathes DJ, Zimmerman JP, Duprat R, Japp SS, Scully M, Rosenberg BM, *et al.* (2021): Resting fMRI-guided TMS results in subcortical and brain network modulation indexed by interleaved TMS/fMRI. Exp Brain Res 239:1165–1178.
77. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, *et al.* (2015): 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 126:1071–1107.
78. Kähkönen S, Komssi S, Wilenius J, Ilmoniemi RJ (2005): Prefrontal TMS produces smaller EEG responses than motor-cortex TMS: Implications for rTMS treatment in depression. Psychopharmacology (Berl) 181:16–20.
79. Stokes MG, Barker AT, Dervinis M, Verbruggen F, Maizey L, Adams RC, Chambers CD (2013): Biophysical determinants of transcranial magnetic stimulation: Effects of excitability and depth of targeted area. J Neurophysiol 109:437–444.
80. Blumberger DM, Maller JJ, Thomson L, Mulsant BH, Rajji TK, Maher M, *et al.* (2016): Unilateral and bilateral MRI-targeted repetitive transcranial magnetic stimulation for treatment-resistant depression: A randomized controlled study. J Psychiatry Neurosci 41:E58–E66.
81. Caulfield KA, Li X, George MS (2021): Four electric field modeling methods of Dosing Prefrontal Transcranial Magnetic Stimulation (TMS): Introducing APEX MT dosimetry. Brain Stimul 14:1032–1034.
82. Ziemann U, Siebner HR (2015): Inter-subject and inter-session variability of plasticity induction by non-invasive brain stimulation: Boon or bane? Brain Stimul 8:662–663.
83. Huerta PT, Lisman JE (1993): Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. Nature 364:723–725.
84. Huerta PT, Lisman JE (1995): Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron 15:1053–1063.
85. Silvanto J, Pascual-Leone A (2008): State-dependency of transcranial magnetic stimulation. Brain Topogr 21:1–10.
86. Buzsáki G, Draguhn A (2004): Neuronal oscillations in cortical networks. Science 304:1926–1929.
87. Mansouri F, Fettes P, Schulze L, Giacobbe P, Zariffa J, Downar J (2018): A real-time phase-locking system for non-invasive brain stimulation. Front Neurosci 12:877.
88. Thut G, Bergmann TO, Fröhlich F, Soekadar SR, Brittain JS, Valero-Cabré A, *et al.* (2017): Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: A position paper. Clin Neurophysiol 128:843–857.
89. Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR (2016): Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: Current approaches and future perspectives. Neuroimage 140:4–19.
90. Shirinpour S, Alekseichuk I, Mantell K, Opitz A (2020): Experimental evaluation of methods for real-time EEG phase-specific transcranial magnetic stimulation. J Neural Eng 17:046002.
91. Schaworonkow N, Triesch J, Ziemann U, Zrenner C (2019): EEG-triggered TMS reveals stronger brain state-dependent modulation of motor evoked potentials at weaker stimulation intensities. Brain Stimul 12:110–118.
92. Zrenner B, Zrenner C, Gordon PC, Belardinelli P, McDermott EJ, Soekadar SR, *et al.* (2020): Brain oscillation-synchronized stimulation of the left dorsolateral prefrontal cortex in depression using real-time EEG-triggered TMS. Brain Stimul 13:197–205.
93. Peters JC, Reithler J, Schuhmann T, de Graaf T, Uludag K, Goebel R, Sack AT (2013): On the feasibility of concurrent human TMS-EEG-fMRI measurements. J Neurophysiol 109:1214–1227.
94. Peters JC, Reithler J, de Graaf TA, Schuhmann T, Goebel R, Sack AT (2020): Concurrent human TMS-EEG-fMRI enables monitoring of oscillatory brain state-dependent gating of cortico-subcortical network activity. Commun Biol 3:40.
95. Roelofs CL, Krepel N, Corlier J, Carpenter LL, Fitzgerald PB, Daskalakis ZJ, *et al.* (2021): Individual alpha frequency proximity associated with repetitive transcranial magnetic stimulation outcome: An independent replication study from the ICON-DB consortium. Clin Neurophysiol 132:643–649.
96. Janssens SEW, Sack AT, Ten Oever S, de Graaf TA (2021): Calibrating rhythmic stimulation parameters to individual electroencephalography markers: The consistency of individual alpha frequency in practical lab settings [published online ahead of print Aug 7]. Eur J Neurosci.
97. Chung SW, Sullivan CM, Rogasch NC, Hoy KE, Bailey NW, Cash RFH, Fitzgerald PB (2019): The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: A TMS-EEG study. Hum Brain Mapp 40:608–627.
98. Murphy K, Fox MD (2017): Towards a consensus regarding global signal regression for resting state functional connectivity MRI. Neuroimage 154:169–173.

99. Maier-Hein KH, Neher PF, Houde JC, Côté MA, Garyfallidis E, Zhong J, *et al.* (2017): The challenge of mapping the human connectome based on diffusion tractography [published correction appears in Nat Commun 2019; 10:5059]. Nat Commun 8:1349.
100. Yeh CH, Jones DK, Liang X, Descoteaux M, Connelly A (2021): Mapping structural connectivity using diffusion MRI: Challenges and opportunities. J Magn Reson Imaging 53:1666–1682.
101. Ning L, Bonet-Carne E, Grussu F, Sepehrband F, Kaden E, Veraart J, *et al.* (2020): Cross-scanner and cross-protocol multi-shell diffusion MRI data harmonization: Algorithms and results. Neuroimage 221:117128.
102. Tax CM, Grussu F, Kaden E, Ning L, Rudrapatna U, Evans CJ, *et al.* (2019): Cross-scanner and cross-protocol diffusion MRI data harmonisation: A benchmark database and evaluation of algorithms. Neuroimage 195:285–299.
103. Opitz A, Falchier A, Linn GS, Milham MP, Schroeder CE (2017): Limitations of ex vivo measurements for in vivo neuroscience. Proc Natl Acad Sci U S A 114:5243–5246.
104. Puonti O, Van Leemput K, Saturnino GB, Siebner HR, Madsen KH, Thielscher A (2020): Accurate and robust whole-head segmentation from magnetic resonance images for individualized head modeling. Neuroimage 219:117044.
105. Romero MC, Davare M, Armendariz M, Janssen P (2019): Neural effects of transcranial magnetic stimulation at the single-cell level. Nat Commun 10:2642.
106. Deslauriers-Gauthier S, Lina JM, Butler R, Whittingstall K, Gilbert G, Bernier PM, *et al.* (2019): White matter information flow mapping from diffusion MRI and EEG. Neuroimage 201:116017.
107. Schaworonkow N, Caldana Gordon P, Belardinelli P, Ziemann U, Bergmann TO, Zrenner C (2018): μ-Rhythm extracted with personalized EEG filters correlates with corticospinal excitability in real-time phase-triggered EEG-TMS. Front Neurosci 12:954.
108. Faul F, Erdfelder E, Lang AG, Buchner A (2007): G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39:175–191.