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Author/s:

Cash, RFH;Weigand, A;Zalesky, A;Siddiqi, SH;Downar, J;Fitzgerald, PB;Fox, MD

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Using Brain Imaging to Improve Spatial Targeting of Transcranial Magnetic Stimulation for Depression

Robin F.H. Cash, Anne Weigand, Andrew Zalesky, Shan H. Siddiqi, Jonathan Downar, Paul B. Fitzgerald, and Michael D. Fox

ABSTRACT

Transcranial magnetic stimulation (TMS) is an effective treatment for depression but is limited in that the optimal therapeutic target remains unknown. Early TMS trials lacked a focal target and thus positioned the TMS coil over the prefrontal cortex using scalp measurements. Over time, it became clear that this method leads to variation in the stimulation site and that this could contribute to heterogeneity in antidepressant response. Newer methods allow for precise positioning of the TMS coil over a specific brain location, but leveraging these precise methods requires a more precise therapeutic target. We review how neuroimaging is being used to identify a more focal therapeutic target for depression. We highlight recent studies showing that more effective TMS targets in the frontal cortex are functionally connected to deep limbic regions such as the subgenual cingulate cortex. We review how connectivity might be used to identify an optimal TMS target for use in all patients and potentially even a personalized target for each individual patient. We address the clinical implications of this emerging field and highlight critical questions for future research.

Keywords: Depression, Functional connectivity, Magnetic resonance imaging, Subgenual cingulate cortex, Target, Transcranial magnetic stimulation

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THERAPEUTIC BRAIN STIMULATION FOR DEPRESSION

Major depressive disorder affects approximately 1 in 5 individuals and 350 million people worldwide and is the leading cause of years lived with disability (1). As few as 30% of patients achieve remission with first-line therapies (2). Individuals who fail multiple treatments are classified as having treatment-resistant depression, and these patients are unlikely to respond to further medication trials (2). Repetitive transcranial magnetic stimulation (rTMS) is an established, safe, and efficacious treatment approved by the U.S. Food and Drug Administration that can alleviate symptoms in patients with treatment-resistant depression (3). It involves focal magnetic stimulation applied externally to the scalp, typically at the dorsolateral prefrontal cortex (DLPFC), which induces electrical stimulation in underlying cortical tissue. The most commonly used clinical TMS coils are figure eight coils, which have a relatively focal stimulation field and will be the focus of this review. However, less focal TMS coils exist, an important topic that is addressed in the [Supplement](#).

While rTMS is effective for some individuals, many others with similar clinical profiles receive little benefit. Typical response rates, defined as >50% reduction in depression score, and remission rates, defined as a post-TMS depression score below the level that qualifies for depression, are typically

between 29% and 46% (response) and 18% and 31% (remission) (3,4). Although therapeutic response is clinically meaningful, particularly in a treatment-refractory population, remission should be considered the ultimate goal. Research efforts over the past 2 decades have aimed to improve the efficacy and consistency of treatment effects across individuals. While optimal stimulation parameters and dosing are important, one major source of interindividual heterogeneity in treatment outcomes arises from variation in the stimulated site across the spatial extent of the DLPFC (5–17).

Therapeutic targets for the treatment of depression using rTMS have been informed and guided by neuroimaging since its clinical inception in the mid-1990s (Figure 1). Early studies of patients with stroke and tumors suggested that the risk of depression increased with left prefrontal lesions [for further discussion see (10,18,19)]. Functional neuroimaging studies in primary depression reported hypometabolism in the left prefrontal cortex that improved with successful antidepressant treatment (19). As such, early rTMS studies targeted the left DLPFC commensurate with our neuroanatomical knowledge of depression (20,21).

Over time, it became clear that the left DLPFC is highly heterogeneous, and response rates may depend on exactly where in the DLPFC one administers rTMS (5–7,13,22). Lesion and metabolic neuroimaging studies failed to replicate the

simple association between the left DLPFC and depression (18,23). More importantly, psychiatric disorders began to be conceptualized as disorders of brain networks, not individual brain regions (24–28). Similarly, rTMS began to be conceptualized as a network therapy—although stimulation is commonly applied to a single brain region, its effects are mediated via distributed networks (29–32). Advances in mapping brain networks and brain connectivity now allow us to identify these networks and potentially refine our therapeutic targets for depression (4–7,10,33,34). This review describes the evolution of therapeutic targeting strategies in depression and new developments in this area.

TARGETING TMS USING SCALP MEASUREMENTS

The first clinical investigations of rTMS for depression identified the DLPFC target site as being 5 cm anterior to the motor cortical hotspot (20,21), overlying Brodmann area (BA) 46 and BA 9 in the Talairach atlas (20,21). This 5-cm method was subsequently used in larger clinical trials that led to Food and Drug Administration approval (35–37). However, this approach does not account for differences in head dimensions or anatomy, leading to stimulation of the premotor cortex or frontal eye fields in a large percentage of patients (13,15,17,38). Many clinical centers therefore adopted 5.5 or 6 cm to move the average stimulation site more anterior and lateral (7,13,39,40). Recent work estimates that the intersection of BA 9 and BA 46 is actually 6.9 cm anterior to the motor hotspot, but this has not been adopted clinically (17). It is also perhaps worth noting that the areal delineation of BA 9 and BA 46 has been redefined several times (41–43) since originally parcellated by Brodmann in 1909 (44) and is highly variable across individuals (45). The 5- to 6-cm approach has been the most commonly

employed targeting method, accounting for 84% of randomized clinical trials as of 2016 (5 cm: 75%; 6 cm: 9%) [computed from supplemental information in (40)].

A newer targeting approach based on the 10-20 electroencephalography system has been proposed to account for variation in individual skull dimensions. Coregistration of electroencephalography electrode positions with anatomical magnetic resonance imaging (MRI) suggests that the electrode position 1 cm anterolateral to F3 (46), between F3 and F5 (47), or between AF3 and F3 would reliably target the DLPFC (Figure 2) (48). Software has since been developed to estimate the F3 electrode position based on only a few scalp measurements (Beam F3) (49,50). This approach has seen widespread clinical implementation, is located with high reliability (51), and is endorsed by the Clinical TMS Society (52). However, this targeting approach has not yet been validated in double-blinded randomized trials as the 5- to 6-cm method has. Further, although this technique ensures that the DLPFC is more consistently targeted (46,48,50), and the more anterolateral sites of the DLPFC selected by this approach are understood to be more effective (Figure S2) (13), clear gains in antidepressant efficacy remain to be demonstrated [e.g., (3,5)]. Another point of interest is the only marginal extent of spatial overlap between targets derived from the 5.5-cm and Beam F3 targeting methods (Figure 2). Given this spatial difference, future work should directly compare these targeting methods to determine if there are differences in antidepressant response or side effects.

TARGETING TMS BASED ON BRAIN STRUCTURE, FUNCTION, AND METABOLISM

Targeting TMS based on scalp-based measures is reasonable if the target is rather broadly defined as the left DLPFC.

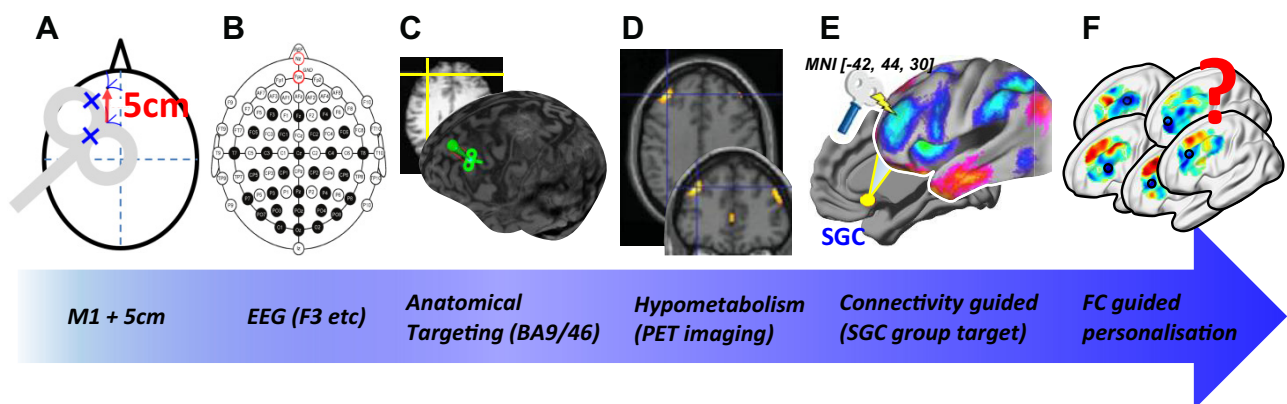


Figure 1. Evolution of transcranial magnetic stimulation (TMS) targeting approaches for the treatment of depression. This timeline is intended to be conceptual, as research efforts into different targeting approaches have overlapped considerably. Scalp-based measures identified the dorsolateral prefrontal cortex stimulation site as 5–6 cm anterior to the motor cortical hotspot (A) or based on the electroencephalography (EEG) 10-20 system to account for interindividual differences in skull dimensions (B). Neuronavigated approaches were implemented to target an anatomical coordinate in the dorsolateral prefrontal cortex implicated in depression based on prior functional neuroimaging studies (C) or based on positron emission tomography (PET) imaging in individual patients (D). Recent studies suggest that repetitive TMS (rTMS) treatment response is related to resting-state functional connectivity (FC) between the dorsolateral prefrontal cortex stimulation site and subgenual cingulate cortex (SGC), leading to a connectivity-based rTMS target (E). Future research toward precision psychiatry may include connectivity-based rTMS targets that are individualized based on symptoms or patient-specific connectivity (F). BA, Brodmann area; MNI, Montreal Neurological Institute. [Panels (D) and (E) adapted from Weigand *et al.* (7), Paillere Martinot *et al.* (54), and Fox *et al.* (84).]

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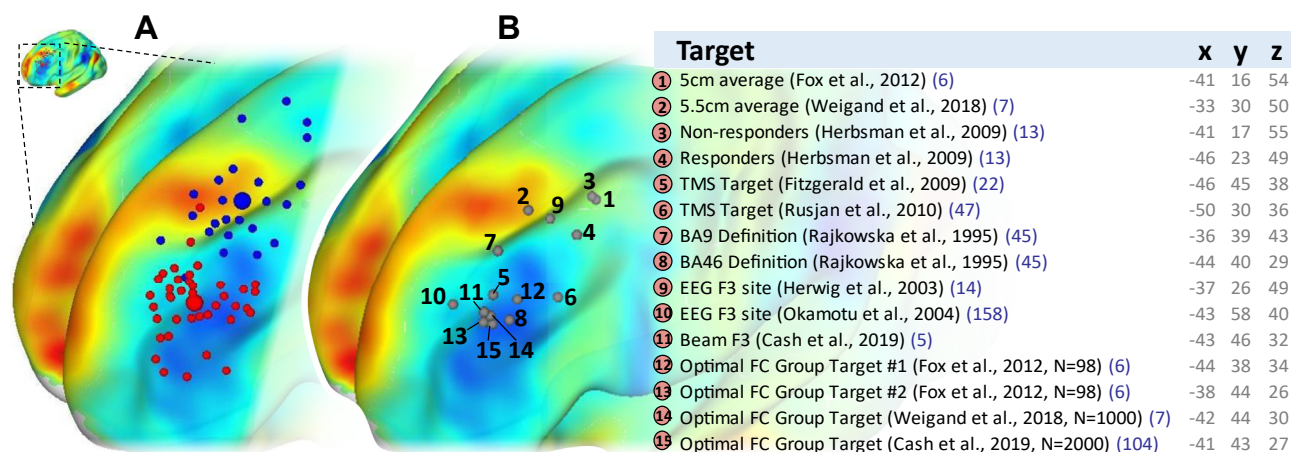


Figure 2. Heterogeneity in transcranial magnetic stimulation (TMS) sites for depression. **(A)** The distributions of cortical targets derived from the 5.5-cm (Boston cohort; blue) and Beam F3 targeting approaches (Melbourne cohort; red) are depicted. Sites are shown overlaid on a map of resting-state functional connectivity (FC) with the subgenual cingulate cortex. There is relatively little spatial overlap between the sites derived from these 2 targeting methods. Average group coordinates are depicted as larger spheres. The Boston and Melbourne data are derived from open-label studies (5,7). **(B)** Various cortical repetitive TMS targets proposed or used for the treatment of depression are depicted. Note the divergence between the electroencephalography (EEG) F3 coordinates across different studies [compare sites 9–11 (6,46,158)]. Recent studies have proposed coordinates that converge on a more anterolateral site defined by functional connectivity with the subgenual cingulate cortex [sites 12–15 (6,7,96)]. TMS e-fields (detailed in Supplement) are larger than the depicted spheres, which are intended only to indicate the relative spatial positioning of stimulation sites across studies. BA, Brodmann area.

However, as our knowledge regarding the neuroanatomy of depression increases, more accurate targeting of TMS is warranted. In one of the first examples of this approach, Fitzgerald *et al.* (53) conducted a meta-analysis of functional imaging studies of depression to identify a precise coordinate in the left DLPFC that was most consistently abnormal. The authors then used neuronavigated TMS to target this coordinate in patients with depression. Neuronavigation enables the TMS coil to be positioned to target specific anatomical sites based on an individual subject's structural brain images. Both the neuronavigated and the conventional 5-cm approaches yielded reductions in depression severity; however, there was no significant interaction between targeting approach and clinical trajectory across the two cohorts, nor was there clear decrease in response variability across individuals (22). Nonetheless, the neuronavigated approach appeared to be more effective at a trend level, resulting in an overall reduction in symptom severity of approximately 49% compared with the 27% observed with the 5-cm approach [recomputed from the absolute values of clinical scores presented in (22)]. Other studies targeting this anatomical location found it to be better than sham conditions (54) [although see (55)], but likewise failed to demonstrate superiority relative to conventional scalp-based targeting (56,57). Interestingly, adjusting stimulus intensity to account for individual scalp-to-cortex distance did not enhance the effects of anatomical targeting (57). This might be because while TMS effects are often dependent on intensity, cortical thresholds or reactivity may differ or even be unrelated across brain regions (58–60), presenting a potential caveat for current clinical practice. In any case, these studies do not provide clear support for the superiority of TMS targeting this anatomical location for depression, possibly because these

studies were underpowered, the optimal anatomical target differs from that employed above (61), or anatomical targeting does not address individual variation in DLPFC functional organization (45,62–64).

Other groups have tried to improve TMS for depression by targeting individual differences in metabolism [for review of metabolic abnormalities see (14,19,65)]. In one such study, the site of maximum hypometabolism in the DLPFC was first localized using a positron emission tomography scan for each individual and then targeted using high-frequency rTMS. However, neither this study (54) nor other similar studies (14,66) were able to demonstrate superiority of this approach relative to conventional targeting approaches. Possible reasons for the failure of this approach include poor spatial resolution of positron emission tomography imaging (67), unknown reproducibility of the targets, or the fact that individual foci of prefrontal hypometabolism are not the best antidepressant target. Interestingly, the hypometabolic maximum was located in the right DLPFC in 33% (54) to 73% (14) of individuals, which challenges the traditional valence hypotheses of mood lateralization in depression, in line with other recent studies (10,23,68–71).

Finally, at least 1 trial of TMS for depression has targeted individualized sites of functional MRI (fMRI) activation. This trial used an n-back working memory task to identify individualized TMS targets for each patient, but failed to show a difference in antidepressant response or imaging biomarkers relative to sham (72).

BRAIN STIMULATION IN THE CONNECTOMICS ERA

Localization of psychiatric symptoms, including depression, has gradually shifted from a focus on individual brain regions,

such as the DLPFC, to a focus on distributed brain networks (10,25,27,73–75). For example, lesion locations associated with depression are not solely located in the left DLPFC, but instead map to a distributed brain network that is centered on the left DLPFC (18). Similarly, recent network models of depression include a variety of cortical and subcortical brain regions (27). In parallel, it has become clear that the effects of rTMS are not restricted to the stimulated region, but propagate to affect the network of regions connected to the stimulation site (5–7,10,28–31,33,34).

One valuable neuroimaging technique for visualizing brain networks is resting-state functional connectivity (FC) MRI (76,77). Brain regions are interconnected to form intrinsic networks, characterized by shared temporal fluctuations in spontaneous brain activity. These distributed networks can be delineated, even in the absence of external stimuli, and are therefore termed resting-state networks. One advantage of recording these networks at rest is that there is a reduced need for patient compliance and avoidance of confounds related to task performance or instructions (78). Resting-state networks may also exhibit higher reproducibility compared with conventional task-based imaging (79). The FC within and between these networks is often altered in psychiatric and neurological conditions (25,27,80), while partial normalization may occur following successful treatment (27,28), including brain

stimulation (29–31,81). It is now clear that different regions across the spatial extent of the DLPFC map on to different distributed brain networks (82), potentially explaining a portion of the response variability associated with conventional TMS targeting techniques (Figure S1).

The shift in focus from brain regions to brain networks has motivated various new approaches to improve TMS for depression. These include the use of TMS to modify connectivity, with the goal of correcting network abnormalities in depression (29–31,81,83,84). Another is the use of brain connectivity to predict which patients will respond to TMS treatment (28,85–87). Finally, brain connectivity has been used to identify rTMS targets for depression based on the connectivity of the stimulated target to other brain regions (5–7,34,88).

TARGETING TMS BASED ON CONNECTIVITY TO THE SUBGENUAL CINGULATE CORTEX

An example of the latter approach relates to the observation that antidepressant outcomes were better when stimulation was serendipitously delivered at sites of the DLPFC that displayed stronger negative (anticorrelated) FC with the subgenual cingulate cortex (SGC) (Figure 3) (6). The SGC is a region positioned at the anterior-inferior end of the cingulum bundle with extensive connections across prefrontal and limbic

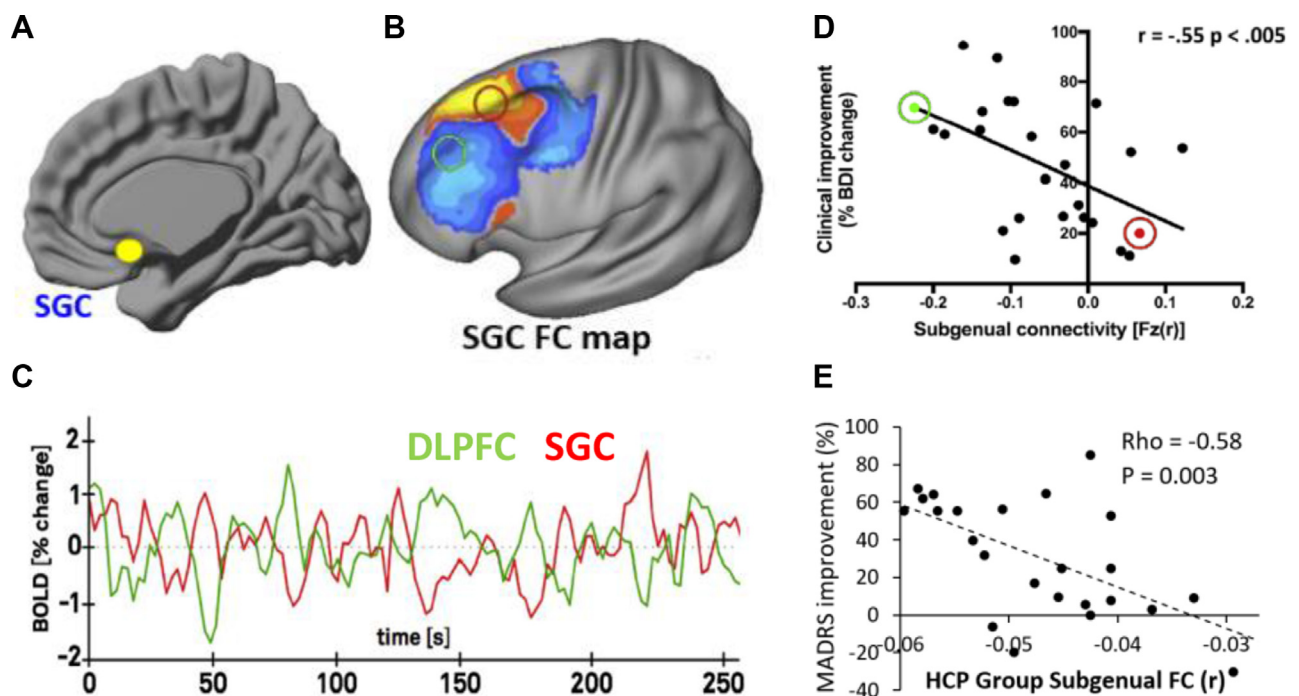


Figure 3. Antidepressant response to repetitive transcranial magnetic stimulation is associated with functional connectivity (FC) between the stimulation site and the subgenual cingulate cortex (SGC) across different international cohorts. The intrinsic spontaneous activity of the SGC (A) can be compared with that of other regions of the brain to identify regions of strong positively or negatively correlated FC. The dorsolateral prefrontal cortex (DLPFC) (B) includes regions of positive (red) and negative (blue) FC with the SGC. Stronger negative FC with the SGC occurs at more anterolateral sites. (C) Illustration of negative (anticorrelated) time course between the DLPFC (green) and SGC (red). (D, E) Greater treatment outcome (% change in clinical score) was associated with more negative SGC FC at the individual DLPFC stimulation site across the Boston (D) and Melbourne (E) cohorts. For the Boston cohort, the green and red circles in panel (D) highlight individual participants with good and poor clinical outcomes, corresponding to circled cortical sites of negative and positive SGC FC, respectively, displayed in panel (B). BDI, Beck Depression Inventory; BOLD, blood oxygen–level dependent; HCP, Human Connectome Project; MADRS, Montgomery–Åsberg Depression Rating Scale.

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structures that have been implicated in depression (74). It is associated with abnormal emotional regulation and processing and has been linked to depression and clinical response across diverse antidepressant treatment modalities (89–91).

The association between DLPFC-SGC FC at the stimulation site and treatment response has additionally been replicated across 3 geographically distinct clinical cohorts, with findings robust across different populations, methodologies, scanners, stimulators, and DLPFC targeting approaches (5.5-cm, cognitive activation, Beam F3) (5,7). More specifically, a 60% to 70% reduction in depressive symptoms occurred when individuals were stimulated near the DLPFC site of maximal FC anticorrelation with SGC, while those stimulated farther away showed no response or worsening of depressive symptoms [c.f. Figure 1C in (5)]. The association between SGC FC and treatment response is also unique to individuals receiving active and not sham stimulation (7).

Based on these associations, it has been suggested that the DLPFC site most anticorrelated with the SGC could represent an optimal TMS target for depression (5–7). The DLPFC coordinates of maximal SGC-FC anticorrelation are at Montreal Neurological Institute coordinates $x = -42$, $y = 44$, $z = 30$ (5–7). In line with this reasoning, a recent large randomized trial of TMS used neuronavigation to target this coordinate with the goal of optimizing antidepressant response (61). However, the goal of this trial was to compare two different forms of active rTMS, not to validate this target. Whether neuronavigated TMS to this target results in stronger or more consistent antidepressant response compared with conventional scalp-based targeting remains to be tested in a dedicated clinical trial. It also remains unclear whether connectivity to the SGC is the only or the most important connection for defining an optimal TMS target. Connectivity of the TMS target to other brain regions implicated in depression may also be important (10,86,88).

TARGETING TMS BASED ON INDIVIDUALIZED CONNECTIVITY

The above TMS target based on SGC connectivity may not be optimal for all patients owing to individual differences in brain connectivity. The above target was based on group connectivity, averaged across 1000 healthy individuals. This averaging allows for robust maps that help counteract the low signal-to-noise ratio of the SGC region (6); however, it ignores potentially important individual differences in connectivity.

Many have suggested that rTMS might be improved by personalizing the stimulation site based on individual differences in connectivity (5,6,9,11,12,16,92–96). Recent work demonstrates that SGC FC shows considerable interindividual variation across the spatial extent of the DLPFC (5,92,96). Indeed, prefrontal regions show some of the highest levels of interindividual variation in terms of cytoarchitecture, structural morphology, neural function, and connectivity (45,62–64,97–99). However, these individual differences are likely to prove useful as TMS targets only if one can overcome signal-to-noise limitations of single-subject fMRI data (92).

The past decade has seen substantial advances in fMRI acquisition, preprocessing, and noise-reduction strategies (100) as well as in our capacity to model the relationship between stimulation site, network engagement, and treatment

response (described further in the Supplement). With sufficient data, clear individual differences in functional network architecture are evident (Figure S1) (62,63,101–103); however, several of these studies used many hours of MRI scanning, which is not practical for clinical patients. Further, limbic areas such as the SGC are particularly prone to signal-to-noise problems, limiting our ability to identify robust TMS targets (92). In fact, recent work indicated that single-subject TMS targets derived from individual connectivity to a small region of interest in the SGC are not reproducible enough to provide an advantage over group-based connectivity (92,95). This signal-to-noise hurdle may be overcome through creative strategies to obtain reproducible individualized targets. In one such strategy, connectivity to a network of limbic regions, rather than just the subgenual alone, resulted in robust individualized targets (92), findings that have since been replicated and extended (96,104).

A number of small clinical trials have begun using SGC-FC TMS targets derived from individualized connectivity (Table 1). Some of these trials have reported very high response and remission rates (8,9,11,105), but whether personalization exceeds the efficacy of conventional targeting methods remains to be established in a dedicated clinical trial. It is important to note that these studies have been performed in small cohorts and typically without a comparison target or sham group. It is also possible that the placebo effect of rTMS is greater when additional technologies such as MRI scanning and neuronavigation are used. Future research with larger trials and comparator groups is warranted. These trials would further benefit from validation of the accuracy and reproducibility of the individualized targeting method [e.g., as per (104)].

TARGETING TMS BASED ON SYMPTOM-SPECIFIC BRAIN NETWORKS

The TMS target based on SGC connectivity may not be the best target for all depression symptoms (Figure 4A). Emerging evidence suggests that separate symptom clusters might respond to stimulation of different brain circuits (10,86,88,106). Anterolateral DLPFC sites with anticorrelated FC to the SGC may be more effective in moderating dysphoric symptoms such as sadness, decreased interest, and suicidality, whereas posterior DLPFC and medial prefrontal targets appear more effective for ameliorating anxiosomatic symptoms such as insomnia, decreased libido, and irritability (Figure 4B) (88). Different depression symptoms may therefore benefit from different TMS targets.

TMS SITES OUTSIDE THE LEFT DLPFC

Thus far, our review has focused on high-frequency rTMS to the left DLPFC; however, other TMS sites and parameters have been selected for depression. The most common alternative is low-frequency TMS to the right DLPFC, which has produced comparable clinical outcomes to high-frequency left DLPFC TMS in randomized trials (4,107–109). Traditionally, high- and low-frequency rTMS paradigms have been delivered with the aim of increasing or decreasing cortical activity and potentially normalizing metabolic abnormalities in depression. However, whether 1-Hz rTMS reduces cortical activity (when measured in terms of regional cerebral blood flow, etc.) remains uncertain

Table 1. Clinical Outcomes of rTMS for Depression Using Conventional or Connectivity-Based Targeting

Study	Sample and Size	Control Condition	Treatment Paradigm	Response Rate (%)	Remission Rate (%)
Conventional Targeting					
Berlim <i>et al.</i> , 2014 (4)	Meta-analysis of 29 RCTs, double-blinded sham-controlled ($N = 1371$)	Various sham control conditions	HF rTMS (≥ 10 sessions)	Active: 29% Sham: 10%	Active: 19% Sham: 5%
Fitzgerald <i>et al.</i> , 2016 (3)	Internal review of 11 RCTs, mostly open-label with active-comparator ($N = 1132$)		Various	Active: 46%	Active: 31%
Group SGC FC Target					
Blumberger <i>et al.</i> , 2018 (61)	MDD ($N = 414$)	All conditions active; rTMS ($n = 205$) vs. TBS ($n = 209$)	Target was SGC FC group coordinate [MNI $x = -38$, $y = 44$, $z = 26$]. rTMS (10 Hz, 120% RMT, 3000 pulses/session); iTBS (120% RMT, 600 pulses/session). Once-daily, Monday–Friday, 4 weeks	rTMS: 47% iTBS: 49%	rTMS: 27% iTBS: 32%
Personalized SGC FC Target					
Cole <i>et al.</i> , 2020 (105)	MDD ($n = 31$)	Active condition only	Accelerated TBS. 10 sessions of iTBS per day for 5 consecutive days (90,000 total pulses). 90% RMT	90%	90% (all responders were remitters)
Siddiqi <i>et al.</i> , 2019 (11)	TBI with treatment-resistant depression ($N = 14$)	Active ($n = 9$) and sham ($n = 5$)	Bilateral standard rTMS. 20 daily sessions of bilateral rTMS (10-Hz left DLPFC, 4000 pulses followed by 1 train of 1-Hz rTMS, 1000 pulses; 120% RMT)	Active: 77% Sham: 0%	Active: 44% Sham: 0%
Williams <i>et al.</i> , 2018 (8)	Highly refractive TRD that previously failed standard or deep rTMS ($N = 6$)	Active condition only	Accelerated TBS with personalized target. As for Cole <i>et al.</i> , 2018 (above)	83%	66%

DLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; HF, high-frequency; iTBS, intermittent theta burst stimulation; MDD, major depressive disorder; MNI, Montreal Neurological Institute; RCT, randomized controlled trial; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SGC, subgenual cingulate cortex; TBI, traumatic brain injury; TRD, treatment-resistant depression.

(65,110–115) and may depend on stimulation intensity, flipping from inhibitory to excitatory at higher intensities (4,116–119) [for a discussion of the physiological mechanisms mediating this phenomenon see (120)]. A similar phenomenon has been described with continuous theta burst stimulation, which elicits excitatory, rather than inhibitory, effects at higher stimulus intensities (121), as typically employed clinically (40). Consistent with this observation, studies comparing the effects of low- and high-frequency rTMS to the left DLPFC have often reported similar antidepressant efficacy (122–127), with high-frequency stimulation generally delivering more robust effects (40,124). In sum, the assumption that rTMS normalizes an imbalance in cortical activity between the left and right DLPFC may be too simplistic. Connectivity-based studies of TMS sites in the right DLPFC, similar to those reported here for the left DLPFC, may shed light on whether the same connections mediate rTMS response in the two hemispheres. It is worth noting that high- and low-frequency rTMS do not implicitly evoke opposite changes in FC; indeed, the effects on connectivity explicitly depend on stimulation site and frequency and are difficult to anticipate prior to experimentation (29–33,128,129).

Other targets include dorsomedial PFC (DMPFC) and orbitofrontal cortex (OFC) (10,106,130). The DMPFC target was identified from convergent evidence of lesion, stimulation, and connectivity studies in depression (10), and TMS to this target was found to impact impulsivity in healthy control subjects (131,132). In depression, case series suggest comparable remission rates to DLPFC rTMS (133) and a bimodal outcome distribution (85,134). Congruently, more recent work identified 4 biotypes of patients with major depressive disorder based on whole-brain FC (86), with markedly higher DMPFC rTMS response rates in certain biotypes.

The lateral OFC is proposed as a nonreward pathway complementary to classic medial reward projections from ventral striatum; the nonreward attractor theory of depression proposes that lateral OFC-striatal nonreward circuits may enter a feedback loop in major depressive disorder (135). A recent study using implanted cortical electrodes in patients with depression and epilepsy found that 100-Hz lateral OFC stimulation specifically attenuated negative thought content (136). Case series of 1-Hz right OFC rTMS suggest antidepressant effects (24% remission) in a subset of patients failing previous DMPFC rTMS (130). Notably, in one study (86), one of the

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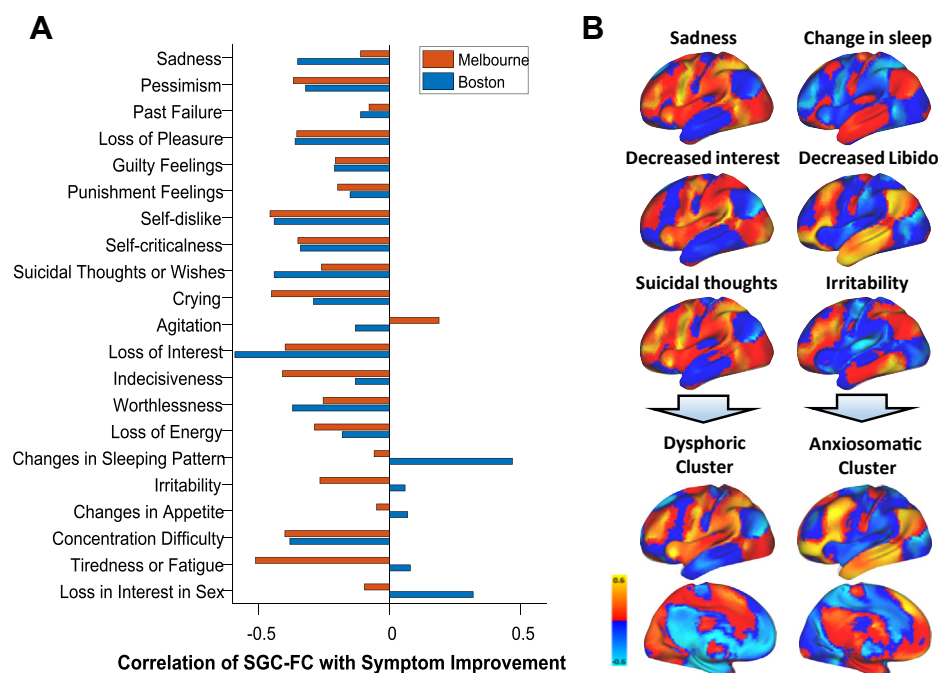


Figure 4. Symptom specificity. **(A)** Many, but not all, symptoms improve as the transcranial magnetic stimulation (TMS) target site approaches the site of most negative subgenual cingulate cortex (SGC) functional connectivity (FC). The relationship between SGC FC at the stimulation site and symptom improvement appears to be relatively consistent across the Boston and Melbourne cohorts. The symptoms that appeared less consistently related to SGC FC were agitation, sleeping pattern, irritability, appetite, fatigue, and interest in sex. These might be better treated at an alternative stimulation site. The Boston and Melbourne data are derived from open-label studies (5,7). **(B)** Therapeutic response to anatomically targeted TMS (5- to 5.5-cm approach) was used to identify symptom-specific spatial TMS targets (88). Together these maps were found to delineate 2 distinct spatial profiles corresponding to amelioration of a cluster of either dysphoric symptoms (sadness, decreased interest, and suicidal thoughts) or anxiousomatic symptoms (changes in sleep, decreased libido, and worry/irritability) following TMS therapy (88). Accordingly, it might

be possible to spatially target TMS to ameliorate specific symptom clusters on a personalized basis. The color bar represents the spatial correlation between symptom improvement and FC to the stimulation site. These therapeutic response profiles were delineated retrospectively following treatment and as such remain preliminary until they can be confirmed prospectively.

biotypes featured a large nexus of abnormal connectivity in the right OFC. Prospective studies of biotype-targeted rTMS of OFC, DMFPC, and DLPFC are under way. It will also be important to test whether TMS to these different targets impacts different symptoms of depression as predicted by recent work (88).

RELATIONSHIP TO OTHER DISORDERS AND STIMULATION MODALITIES IN THIS FIELD

Although TMS and deep brain stimulation have traditionally been considered separate therapies with distinct neuroanatomical treatment targets, they may target different nodes of the same brain network (34). Indeed, connectomics is lending major insight into deep brain stimulation just as it has lent insight into TMS (74,137). For example, while early trials of SGC deep brain stimulation failed to exceed antidepressant efficacy relative to sham stimulation (sham: electrodes inserted but not active), more refined targeting strategies have demonstrated stepwise gains in efficacy by selecting a single anatomical site defined based on treatment response in a previous cohort (41% response at 6 months) (138) and, more recently, individualized connectomics-based targeting (73% response rate at 6 months) (74). Connectomics is also increasingly being used to inform rTMS targeting for cognitive applications (31,139,140) and to guide the modulation of corticostriathalamic loops in obsessive-compulsive disorder (141,142). Connectivity-guided targeted brain stimulation therefore offers a manifold of opportunities for improving clinical outcomes across treatment-resistant psychiatric disorders (34).

MOVING BEYOND “WHERE” TO “HOW” TO ADMINISTER TMS

Answering the question of where to administer TMS may be easy compared with questions of how to administer TMS. Trials directly comparing different forms of TMS, such as 10-Hz versus intermittent theta burst stimulation, are starting to emerge (61), but there are an almost endless number of ways in which TMS might be administered. For example, 20-Hz rTMS is rarely employed in the clinic but may elicit more reliable changes in brain activity (29,116,117,143) compared with 10-Hz or theta burst stimulation (144,145). Standard protocols could potentially be substantially shortened, with recent work indicating that rTMS is equally effective when the intertrain interval is reduced from 32 to 4 seconds, enabling a course of 20-Hz rTMS to be delivered in as little as 3 minutes (143,146) with equivalent clinical effects (146–148). Personalized temporal tuning according to individual patterns of cortical inhibition (149) or endogenous brain rhythms (150) also appears promising. Similarly, TMS may be more effective when delivered during specific phases of oscillatory brain activity, a phenomenon we first described as phase-dependent plasticity (151). Innovative closed-loop systems have now been developed that enable this phenomenon to be harnessed and personalized by triggering stimulus bursts during specific phases of brain activity determined using electroencephalography (152–155). This approach is now being trialed in individuals with depression (155). Finally, rTMS might be improved if administered during a behavioral task designed to activate affective or emotional regulatory pathways (156,157).

The parameter space for how to administer TMS is much larger than the parameter space for where to administer TMS. We hope that advances in where to target TMS for depression will help guide or complement ongoing research into how to administer TMS, and together these advances will improve antidepressant outcomes.

FUTURE DIRECTIONS

Mounting evidence suggests that connectivity-based TMS targets may lead to clinical improvements, but much of this evidence is based on retrospective analyses or observational trials. A central focus for future work will be to prospectively test connectivity-based TMS targeting in large, blinded, comparator-controlled clinical trials to evaluate and quantify their superiority relative to conventional scalp-based targeting methodologies. Control conditions will also help to disambiguate TMS-specific effects relative to behavioral activation associated with regular attendance for daily treatment. This line of research may also yield new targets for different symptoms (10,86,88,105), subgroups of patients (10), or treatment personalization (96). Emerging research is also delineating a depression circuit (18) and may help define additional or refine existing stimulation targets. The DMPFC and OFC are promising alternative cortical targets, which might target different neural networks, depression biotypes, or symptom clusters and benefit individuals who previously did not respond to rTMS at alternative stimulation sites (10,106,130).

CONCLUSIONS

The integration of brain imaging in basic and clinical TMS research has played a fundamental role in defining stimulation targets and continues to provide new insights into the mechanisms underpinning depression and treatment response. The cost of an MRI scan is small relative to the cost of a full course of TMS for depression (52), but whether the expense of routine neuroimaging is justified for clinical TMS remains uncertain. Future work is needed to determine whether different depression symptoms require different TMS targets, whether individualized connectivity maps improve our ability to target TMS, and whether connectivity-based approaches can improve TMS efficacy in prospective randomized controlled trials. Finally, advances in spatial targeting of TMS should be combined with parallel advances in how to administer TMS, which together may improve clinical outcomes.

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ARTICLE INFORMATION

From the Melbourne Neuropsychiatry Centre (RFHC, AZ) and Department of Biomedical Engineering (RFHC, AZ), University of Melbourne, Parkville; Epworth Centre for Innovation and Mental Health (PBF), Epworth Healthcare and Monash University Central Clinical School, Camberwell, Victoria, Australia; Berenson-Allen Center for Noninvasive Brain Stimulation (AW, SHS, MDF), Department of Neurology, Harvard Medical School and Beth Israel Deaconess Medical Center; Department of Psychiatry (SHS), Harvard Medical School; Departments of Neurology and Radiology (MDF), Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston; Departments of Neurology, Psychiatry, and Radiology (MDF), Center for Brain Circuit Therapeutics, Brigham and Women's Hospital, Boston; Division of Neurotherapeutics (SHS), McLean Hospital, Belmont, Massachusetts; Berlin School of Mind and Brain (AW), Humboldt-Universität zu Berlin, Berlin, Germany; and Institute of Medical Science (JD) and Department of Psychiatry (JD), Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.

Address correspondence to Robin F.H. Cash, Ph.D., Melbourne Neuropsychiatry Centre, The University of Melbourne, Victoria 3010, Australia; E-mail: robin.cash@unimelb.edu.au; or Michael D. Fox, M.D., Ph.D., Center for Brain Circuit Therapeutics, Brigham and Women's Hospital, 70 Fenwood Rd, Hale Building 7002P, Boston, MA 02215; E-mail: foxmdp@dphd@gmail.com.

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REFERENCES

1. Kessler RC (2012): The costs of depression. *Psychiatr Clin North Am* 35:1–14.
2. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. (2006): Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am J Psychiatry* 163:1905–1917.
3. Fitzgerald PB, Hoy KE, Anderson RJ, Daskalakis ZJ (2016): A study of the pattern of response to rTMS treatment in depression. *Depress Anxiety* 33:746–753.
4. Berlin 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.
5. 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.

Improving Spatial Targeting of TMS for Depression

6. 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.
7. 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.
8. 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.
9. 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* 12:516.
10. Downar J, Daskalakis ZJ (2013): New targets for rTMS in depression: A review of convergent evidence. *Brain Stimul* 6:231–240.
11. 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.
12. Siddiqi SH, Trapp NT, Shahim P, Hacker CD, Laumann TO, Kandala S, *et al.* (2019): Individualized connectome-targeted transcranial magnetic stimulation for neuropsychiatric sequelae of repetitive traumatic brain injury in a retired NFL player. *J Neuropsychiatry Clin Neurosci* 31:254–263.
13. 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.
14. Herwig U, Lampe Y, Juengling FD, Wunderlich A, Walter H, Spitzer M, *et al.* (2003): Add-on rTMS for treatment of depression: A pilot study using stereotaxic coil-navigation according to PET data. *J Psychiatr Res* 37:267–275.
15. Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C (2001): Transcranial magnetic stimulation in therapy studies: Examination of the reliability of “standard” coil positioning by neuro-navigation. *Biol Psychiatry* 50:58–61.
16. Singh A, Erwin-Grabner T, Sutcliffe G, Antal A, Paulus W, Goya-Maldonado R (2019): Personalized repetitive transcranial magnetic stimulation temporarily alters default mode network in healthy subjects. *Sci Rep* 9:5631.
17. Ahdab R, Ayache SS, Brugieres P, Goujon C, Lefaucheur JP (2010): Comparison of “standard” and “navigated” procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. *Neurophysiol Clin* 40:27–36.
18. Padmanabhan JL, Cooke D, Joutsma J, Siddiqi SH, Ferguson M, Darby RR, *et al.* (2019): A human depression circuit derived from focal brain lesions. *Biol Psychiatry* 86:749–758.
19. George MS, Ketter TA, Post RM (1994): Prefrontal cortex dysfunction in clinical depression. *Depression* 2:59–72.
20. George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, *et al.* (1995): Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport* 6:1853–1856.
21. Pascual-Leone A, Rubio B, Pallardo F, Catala MD (1996): Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 348:233–237.
22. Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, *et al.* (2009): A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. *Neuropsychopharmacology* 34:1255–1262.
23. Starkstein SE, Robinson RG, Honig MA, Parikh RM, Joselyn J, Price TR (1989): Mood changes after right-hemisphere lesions. *Br J Psychiatry* 155:79–85.
24. Shafi MM, Westover MB, Fox MD, Pascual-Leone A (2012): Exploration and modulation of brain network interactions with noninvasive brain stimulation in combination with neuroimaging. *Eur J Neurosci* 35:805–825.
25. Fornito A, Bullmore ET, Zalesky A (2017): Opportunities and challenges for psychiatry in the connectomic era. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2:9–19.
26. Hamilton JP, Farmer M, Fogelman P, Gotlib IH (2015): Depressive rumination, the default-mode network, and the dark matter of clinical neuroscience. *Biol Psychiatry* 78:224–230.
27. 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.
28. Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, *et al.* (2014): Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry* 76:517–526.
29. Eldaief MC, Halko MA, Buckner RL, Pascual-Leone A (2011): Transcranial magnetic stimulation modulates the brain’s intrinsic activity in a frequency-dependent manner. *Proc Natl Acad Sci U S A* 108:21229–21234.
30. Halko MA, Farzan F, Eldaief MC, Schmahmann JD, Pascual-Leone A (2014): Intermittent theta-burst stimulation of the lateral cerebellum increases functional connectivity of the default network. *J Neurosci* 34:12049–12056.
31. Rastogi A, Cash R, Dunlop K, Vesia M, Kucyi A, Ghahremani A, *et al.* (2017): Modulation of cognitive cerebello-cerebral functional connectivity by lateral cerebellar continuous theta burst stimulation. *Neuroimage* 158:48–57.
32. Castrillon G, Sollmann N, Kurcys K, Razi A, Krieg SM, Riedl V (2020): The physiological effects of noninvasive brain stimulation fundamentally differ across the human cortex. *Sci Adv* 6:eaay2739.
33. Hawco C, Voineskos AN, Steeves JKE, Dickie EW, Viviano JD, Downar J, *et al.* (2018): Spread of activity following TMS is related to intrinsic resting connectivity to the salience network: A concurrent TMS-fMRI study. *Cortex* 108:160–172.
34. 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:E4367–4375.
35. George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, *et al.* (1997): Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: A placebo-controlled crossover trial. *Am J Psychiatry* 154:1752–1756.
36. O’Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, *et al.* (2007): Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial. *Biol Psychiatry* 62:1208–1216.
37. Herwig U, Fallgatter AJ, Hoppner J, Eschweiler GW, Kron M, Hajak G, *et al.* (2007): Antidepressant effects of augmentative transcranial magnetic stimulation: Randomised multicentre trial. *Br J Psychiatry* 191:441–448.
38. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, *et al.* (2010): Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: A sham-controlled randomized trial. *Arch Gen Psychiatry* 67:507–516.
39. Fitzgerald PB, Daskalakis ZJ (2013): Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders: A Practical Guide. Berlin: Springer.
40. Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, *et al.* (2017): Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: A systematic review with network meta-analysis. *JAMA Psychiatry* 74:143–152.
41. Sarkissov S, Filimonoff I, Kononowa E, Preobraschenskaja I, Kukuev L (1955): Atlas of the Cytoarchitectonics of the Human Cerebral Cortex. Moscow: Medgiz.
42. Rajkowska G, Goldman-Rakic PS (1995): Cytoarchitectonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. *Cereb Cortex* 5:307–322.
43. von Economo CF, Koskinas GN (1925): Die Cytoarchitektonik der Hirnrinde des Erwachsenen Menschen. J. Springer.

44. Brodmann K (1909): Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Barth.
45. Rajkowska G, Goldman-Rakic PS (1995): Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach Coordinate System. *Cereb Cortex* 5:323–337.
46. 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.
47. Rusjan PM, Barr MS, Farzan F, Arenovich T, Maller JJ, Fitzgerald PB, *et al.* (2010): Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. *Hum Brain Mapp* 31:1643–1652.
48. Fitzgerald PB, Maller JJ, Hoy KE, Thomson R, Daskalakis ZJ (2009): Exploring the optimal site for the localization of dorsolateral prefrontal cortex in brain stimulation experiments. *Brain Stimul* 2:234–237.
49. 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.
50. 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.
51. Trapp NT, Bruss J, Johnson MK, 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.
52. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, *et al.* (2018): Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *J Clin Psychiatry* 79:16cs10905.
53. Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ (2008): A meta-analytic study of changes in brain activation in depression. *Hum Brain Mapp* 29:683–695.
54. Paillere Martinot ML, Galinowski A, Ringuenet D, Gallarda T, Lefaucheur JP, Bellivier F, *et al.* (2010): Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: A [(18)F]-fluorodeoxyglucose PET and MRI study. *Int J Neuropsychopharmacol* 13:45–59.
55. Duprat R, Desmyter S, Rudi de R, van Heeringen K, Van den Abbeele D, Tandt H, *et al.* (2016): Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: A fast road to remission? *J Affect Disord* 200:6–14.
56. Li CT, Cheng CM, Chen MH, Juan CH, Tu PC, Bai YM, *et al.* (2020): Antidepressant efficacy of prolonged intermittent theta burst stimulation monotherapy for recurrent depression and comparison of methods for coil positioning: A randomized, double-blind, sham-controlled study. *Biol Psychiatry* 87:443–450.
57. 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.
58. Stewart L, Walsh V, Rothwell J (2001): Motor and phosphene thresholds: A transcranial magnetic stimulation correlation study. *Neuropsychologia* 39:415–419.
59. Gerwig M, Kastrop O, Meyer BU, Niehaus L (2003): Evaluation of cortical excitability by motor and phosphene thresholds in transcranial magnetic stimulation. *J Neurol Sci* 215:75–78.
60. Lioumis P, Kicic D, Savolainen P, Makela JP, Kahkonen S (2009): Reproducibility of TMS-evoked EEG responses. *Hum Brain Mapp* 30:1387–1396.
61. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, *et al.* (2018): Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): A randomised non-inferiority trial. *Lancet* 391:1683–1692.
62. Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, *et al.* (2015): Functional connectome fingerprinting: Identifying individuals using patterns of brain connectivity. *Nat Neurosci* 18:1664–1671.
63. Fischl B, Rajendran N, Busa E, Augustinack J, Hinds O, Yeo BT, *et al.* (2008): Cortical folding patterns and predicting cytoarchitecture. *Cereb Cortex* 18:1973–1980.
64. Mueller S, Wang D, Fox MD, Yeo BT, Sepulcre J, Sabuncu MR, *et al.* (2013): Individual variability in functional connectivity architecture of the human brain. *Neuron* 77:586–595.
65. Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, *et al.* (1999): Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biol Psychiatry* 46:1603–1613.
66. Garcia-Toro M, Salva J, Daumal J, Andres J, Romera M, Lafau O, *et al.* (2006): High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjunct treatment in medication-resistant depression. *Psychiatry Res* 146:53–57.
67. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, *et al.* (2007): Resting-state functional connectivity in major depression: Abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biol Psychiatry* 62:429–437.
68. van der Vinne N, Vollebregt MA, van Putten M, Arns M (2017): Frontal alpha asymmetry as a diagnostic marker in depression: Fact or fiction? A meta-analysis. *Neuroimage Clin* 16:79–87.
69. Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, de Castella A, Bradshaw JL, *et al.* (2004): Motor cortical excitability and clinical response to rTMS in depression. *J Affect Disord* 82:71–76.
70. Carson AJ, MacHale S, Allen K, Lawrie SM, Dennis M, House A, *et al.* (2000): Depression after stroke and lesion location: A systematic review. *Lancet* 356:122–126.
71. Schiffer F, Teicher MH, Anderson C, Tomoda A, Polcari A, Navalta CP, *et al.* (2007): Determination of hemispheric emotional valence in individual subjects: A new approach with research and therapeutic implications. *Behav Brain Funct* 3:13.
72. Taylor SF, Ho SS, Abagis T, Angstadt M, Maixner DF, Welsh RC, *et al.* (2018): Changes in brain connectivity during a sham-controlled, transcranial magnetic stimulation trial for depression. *J Affect Disord* 232:143–151.
73. Fox MD (2018): Mapping symptoms to brain networks with the human connectome. *N Engl J Med* 379:2237–2245.
74. Riva-Posse P, Choi KS, Holtzheimer PE, Crowell AL, Garlow SJ, Rajendra JK, *et al.* (2018): A connectomic approach for subcallosal cingulate deep brain stimulation surgery: Prospective targeting in treatment-resistant depression. *Mol Psychiatry* 23:843–849.
75. Anderson RJ, Hoy KE, Daskalakis ZJ, Fitzgerald PB (2016): Repetitive transcranial magnetic stimulation for treatment resistant depression: Re-establishing connections. *Clin Neurophysiol* 127:3394–3405.
76. Zalesky A, Fornito A, Cocchi L, Gollo LL, Breakspear M (2014): Time-resolved resting-state brain networks. *Proc Natl Acad Sci U S A* 111:10341–10346.
77. Fox MD, Raichle ME (2007): Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8:700–711.
78. Fox MD, Greicius M (2010): Clinical applications of resting state functional connectivity. *Front Syst Neurosci* 4:19.
79. Elliott ML, Knodt AR, Ireland D, Morris ML, Poulton R, Ramrakha S, *et al.* (2019): What is the test-retest reliability of common task-fMRI measures? New empirical evidence and a meta-analysis. <https://doi.org/10.1101/681700>.
80. Fornito A, Zalesky A, Breakspear M (2015): The connectomics of brain disorders. *Nat Rev Neurosci* 16:159–172.
81. 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 increase in functional connectivity. *Neuroimage* 162:289–296.
82. Opitz A, Fox MD, Craddock RC, Colcombe S, Milham MP (2016): An integrated framework for targeting functional networks via transcranial magnetic stimulation. *Neuroimage* 127:86–96.

Improving Spatial Targeting of TMS for Depression

83. Chen AC, Oathes DJ, Chang C, Bradley T, Zhou ZW, Williams LM, *et al.* (2013): Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proc Natl Acad Sci U S A* 110:19944–19949.
84. Fox MD, Halko MA, Eldaief MC, Pascual-Leone A (2012): Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). *Neuroimage* 62:2232–2243.
85. Cash RFH, Cocchi L, Anderson R, Rogachov A, Kucyi A, Barnett AJ, *et al.* (2019): A multivariate neuroimaging biomarker of individual outcome to transcranial magnetic stimulation in depression. *Hum Brain Mapp* 40:4618–4629.
86. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, *et al.* (2017): Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med* 23:28–38.
87. Salomons TV, Dunlop K, Kennedy SH, Flint A, Geraci J, Giacobbe P, *et al.* (2014): Resting-state cortico-thalamic-striatal connectivity predicts response to dorsomedial prefrontal rTMS in major depressive disorder. *Neuropsychopharmacology* 39:488–498.
88. Siddiqi SH, Taylor S, 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.
89. Siegle GJ, Thompson WK, Collier A, Berman SR, Feldmiller J, Thase ME, *et al.* (2012): Toward clinically useful neuroimaging in depression treatment: Prognostic utility of subgenual cingulate activity for determining depression outcome in cognitive therapy across studies, scanners, and patient characteristics. *Arch Gen Psychiatry* 69:913–924.
90. Drevets WC, Savitz J, Trimble M (2008): The subgenual anterior cingulate cortex in mood disorders. *CNS Spectr* 13:663–681.
91. 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.
92. 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.
93. Cocchi L, Zalesky A (2018): Personalized transcranial magnetic stimulation in psychiatry. *Biol Psychiatry Cogn Neurosci Neuroimaging* 3:731–741.
94. Sack AT, Cohen Kadosh R, Schuhmann T, Moerel M, Walsh V, Goebel R (2009): Optimizing functional accuracy of TMS in cognitive studies: A comparison of methods. *J Cogn Neurosci* 21:207–221.
95. 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.
96. Cash R, Cocchi L, Fitzgerald P, Zalesky A (2019): Precision psychiatry: Development of methodology for personalized therapeutic brain stimulation. Program No. 684.09. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience. Online.
97. Miranda-Dominguez O, Mills BD, Carpenter SD, Grant KA, Kroenke CD, Nigg JT, *et al.* (2014): Connectotyping: Model based fingerprinting of the functional connectome. *PLoS One* 9: e111048.
98. Doucet GE, Lee WH, Frangou S (2019): Evaluation of the spatial variability in the major resting-state networks across human brain functional atlases. *Hum Brain Mapp* 40:4577–4587.
99. 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.
100. Parkes L, Fulcher B, Yucel M, Fornito A (2018): An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. *Neuroimage* 171:415–436.
101. Gratton C, Laumann TO, Nielsen AN, Greene DJ, Gordon EM, Gilmore AW, *et al.* (2018): Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation. *Neuron* 98:439–452.e435.
102. Braga RM, Buckner RL (2017): Parallel interdigitated distributed networks within the individual estimated by intrinsic functional connectivity. *Neuron* 95:457–471.e455.
103. Horien C, Shen X, Scheinost D, Constable RT (2019): The individual functional connectome is unique and stable over months to years. *Neuroimage* 189:676–687.
104. Cash R, Cocchi L, Lv J, Fitzgerald P, Zalesky A (2020): Toward state-of-the-art connectivity-guided TMS: Personalization, precision & clinical response. Program No. 0047. Proceedings of the Organization for Human Brain Mapping, June 23–July 3.
105. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, *et al.* (2020): Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression [published online ahead of print Apr 7]. *Am J Psychiatry*.
106. Downar J (2019): Orbitofrontal cortex: A “non-rewarding” new treatment target in depression? *Curr Biol* 29:R59–R62.
107. Fitzgerald PB, Hoy K, Daskalakis ZJ, Kulkarni J (2009): A randomized trial of the anti-depressant effects of low- and high-frequency transcranial magnetic stimulation in treatment-resistant depression. *Depress Anxiety* 26:229–234.
108. Isenberg K, Downs D, Pierce K, Svarakic D, Garcia K, Jarvis M, *et al.* (2005): Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients. *Ann Clin Psychiatry* 17:153–159.
109. Stern WM, Tormos JM, Press DZ, Pearlman C, Pascual-Leone A (2007): Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: A double-blind, randomized, placebo-controlled trial. *J Neuropsychiatry Clin Neurosci* 19:179–186.
110. Li X, Nahas Z, Kozel FA, Anderson B, Bohning DE, George MS (2004): Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. *Biol Psychiatry* 55:882–890.
111. Loo CK, Sachdev PS, Haindl W, Wen W, Mitchell PB, Croker VM, *et al.* (2003): High (15 Hz) and low (1 Hz) frequency transcranial magnetic stimulation have different acute effects on regional cerebral blood flow in depressed patients. *Psychol Med* 33:997–1006.
112. Speer AM, Benson BE, Kimbrell TK, Wassermann EM, Willis MW, Herscovitch P, *et al.* (2009): Opposite effects of high and low frequency rTMS on mood in depressed patients: relationship to baseline cerebral activity on PET. *J Affect Disord* 115:386–394.
113. Speer AM, Kimbrell TA, Wassermann EM, D Repella J, Willis MW, Herscovitch P, *et al.* (2000): Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biol Psychiatry* 48:1133–1141.
114. Nahas Z, Teneback CC, Kozel A, Speer AM, DeBrux C, Molloy M, *et al.* (2001): Brain effects of TMS delivered over prefrontal cortex in depressed adults: Role of stimulation frequency and coil-cortex distance. *J Neuropsychiatry Clin Neurosci* 13:459–470.
115. Fitzgerald PB, Sriharan A, Daskalakis ZJ, de Castella AR, Kulkarni J, Egan G (2007): A functional magnetic resonance imaging study of the effects of low frequency right prefrontal transcranial magnetic stimulation in depression. *J Clin Psychopharmacol* 27:488–492.
116. Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A (2000): Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. *Exp Brain Res* 133:425–430.
117. Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A (2000): Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clin Neurophysiol* 111:800–805.
118. Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, *et al.* (1997): Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 48:1398–1403.
119. Berger U, Korngreen A, Bar-Gad I, Friedman A, Wolfus S, Yeshurun Y, *et al.* (2011): Magnetic stimulation intensity modulates motor inhibition. *Neurosci Lett* 504:93–97.
120. Cash RF, Jegatheeswaran G, Ni Z, Chen R (2017): Modulation of the direction and magnitude of hebbian plasticity in human motor cortex by stimulus intensity and concurrent inhibition. *Brain Stimul* 10:83–90.
121. Doeltgen SH, Ridding MC (2011): Low-intensity, short-interval theta burst stimulation modulates excitatory but not inhibitory motor networks. *Clin Neurophysiol* 122:1411–1416.

122. Rosenberg PB, Mehndiratta RB, Mehndiratta YP, Wamer A, Rosse RB, Balish M (2002): Repetitive transcranial magnetic stimulation treatment of comorbid posttraumatic stress disorder and major depression. *J Neuropsychiatry Clin Neurosci* 14:270–276.
123. Padberg F, Zwanzger P, Thoma H, Kathmann N, Haag C, Greenberg BD, *et al.* (1999): Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: Comparative study of fast, slow and sham rTMS. *Psychiatry Res* 88:163–171.
124. Miniussi C, Bonato C, Bignotti S, Gazzoli A, Gennarelli M, Pasqualetti P, *et al.* (2005): Repetitive transcranial magnetic stimulation (rTMS) at high and low frequency: An efficacious therapy for major drug-resistant depression? *Clin Neurophysiol* 116:1062–1071.
125. Speer AM, Wassermann EM, Benson BE, Herscovitch P, Post RM (2014): Antidepressant efficacy of high and low frequency rTMS at 110% of motor threshold versus sham stimulation over left prefrontal cortex. *Brain Stimul* 7:36–41.
126. Dell'Osso B, Oldani L, Camuri G, Dobrea C, Cremaschi L, Benatti B, *et al.* (2015): Augmentative repetitive transcranial magnetic stimulation (rTMS) in the acute treatment of poor responder depressed patients: A comparison study between high and low frequency stimulation. *Eur Psychiatry* 30:271–276.
127. Liu Q, Shen Y, Cao X, Li Y, Chen Y, Yang W, *et al.* (2017): Either at left or right, both high and low frequency rTMS of dorsolateral prefrontal cortex decreases cue induced craving for methamphetamine. *Am J Addict* 26:776–779.
128. Cocchi L, Sale MV, L Gollo L, Bell PT, Nguyen VT, Zalesky A, *et al.* (2016): A hierarchy of timescales explains distinct effects of local in wdb 390 inhibition of primary visual cortex and frontal eye fields. *Elife* 5:e15252.
129. Beynel L, Powers JP, Appelbaum LG (2020): Effects of repetitive transcranial magnetic stimulation on resting-state connectivity: A systematic review. *Neuroimage* 211:116596.
130. Feffer K, Fettes P, Giacobbe P, Daskalakis ZJ, Blumberger DM, Downar J (2018): 1Hz rTMS of the right orbitofrontal cortex for major depression: Safety, tolerability and clinical outcomes. *Eur Neuropsychopharmacol* 28:109–117.
131. Cho SS, Koshimori Y, Aminian K, Obeso I, Rusjan P, Lang AE, *et al.* (2015): Investing in the future: Stimulation of the medial prefrontal cortex reduces discounting of delayed rewards. *Neuropsychopharmacology* 40:546–553.
132. Cho SS, Ko JH, Pellicchia G, Van Eimeren T, Cilia R, Strafella AP (2010): Continuous theta burst stimulation of right dorsolateral prefrontal cortex induces changes in impulsivity level. *Brain Stimul* 3:170–176.
133. Bakker N, Shahab S, Giacobbe P, Blumberger DM, Daskalakis ZJ, Kennedy SH, *et al.* (2015): rTMS of the dorsomedial prefrontal cortex for major depression: Safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. *Brain Stimul* 8:208–215.
134. Downar J, Geraci J, Salomons TV, Dunlop K, Wheeler S, McAndrews MP, *et al.* (2014): Anhedonia and reward-circuit connectivity distinguish nonresponders from responders to dorsomedial prefrontal repetitive transcranial magnetic stimulation in major depression. *Biol Psychiatry* 76:176–185.
135. Rolls ET (2016): A non-reward attractor theory of depression. *Neurosci Biobehav Rev* 68:47–58.
136. Rao VR, Sellers KK, Wallace DL, Lee MB, Bijanzadeh M, Sani OG, *et al.* (2018): Direct electrical stimulation of lateral orbitofrontal cortex acutely improves mood in individuals with symptoms of depression. *Curr Biol* 28:3893–3902.e3894.
137. Horn A (2019): The impact of modern-day neuroimaging on the field of deep brain stimulation. *Curr Opin Neurol* 32:511–520.
138. Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, *et al.* (2012): Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry* 69:150–158.
139. Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, *et al.* (2014): Targeted enhancement of cortical-hippocampal brain networks and associative memory. *Science* 345:1054–1057.
140. Koch G, Bonni S, Pellicciari MC, Casula EP, Mancini M, Esposito R, *et al.* (2018): Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease. *Neuroimage* 169:302–311.
141. Cocchi L, Zalesky A, Nott Z, Whybird G, Fitzgerald PB, Breakspear M (2018): Transcranial magnetic stimulation in obsessive-compulsive disorder: A focus on network mechanisms and state dependence. *Neuroimage Clin* 19:661–674.
142. Dunlop K, Woodside B, Olmsted M, Colton P, Giacobbe P, Downar J (2016): Reductions in cortico-striatal hyperconnectivity accompany successful treatment of obsessive-compulsive disorder with dorsomedial prefrontal rTMS. *Neuropsychopharmacology* 41:1395–1403.
143. Cash RFH, Dar A, Hui J, De Ruiter L, Baarbé J, Fettes P, *et al.* (2017): Influence of inter-train interval on the plastic effects of rTMS. *Brain Stimul* 10:630–636.
144. Hamada M, Murase N, Hasan A, Balaratnam M, Rothwell JC (2013): The role of interneuron networks in driving human motor cortical plasticity. *Cereb Cortex* 23:1593–1605.
145. Jannati A, Block G, Oberman LM, Rotenberg A, Pascual-Leone A (2017): Interindividual variability in response to continuous theta-burst stimulation in healthy adults. *Clin Neurophysiol* 128:2268–2278.
146. Miron JP, Feffer K, Cash RFH, Derakhshan D, Kim JMS, Fettes P, *et al.* (2019): Safety, tolerability and effectiveness of a novel 20 Hz rTMS protocol targeting dorsomedial prefrontal cortex in major depression: An open-label case series. *Brain Stimul* 12:1319–1321.
147. Xie J, Chen J, Wei Q (2013): Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: A meta-analysis of stimulus parameter effects. *Neurol Res* 35:1084–1091.
148. Ke J, Zou X, Huang M, Huang Q, Li H, Zhou X (2020): High-frequency rTMS with two different inter-train intervals improves upper limb motor function at the early stage of stroke. *J Int Med Res* 48(6): 0300060520928737.
149. Cash RF, Murakami T, Chen R, Thickbroom GW, Ziemann U (2016): Augmenting plasticity induction in human motor cortex by disinhibition stimulation. *Cereb Cortex* 26:58–69.
150. Chung SW, Sullivan CM, Rogasch NC, Hoy KE, Bailey NW, Cash RF, *et al.* (2018): The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: A TMS-EEG study. *Hum Brain Mapp* 40:608–627.
151. Cash RF, Mastaglia FL, Thickbroom GW (2013): Evidence for high-fidelity timing-dependent synaptic plasticity of human motor cortex. *J Neurophysiol* 109:106–112.
152. Stefanou MI, Baur D, Belardinelli P, Bergmann TO, Blum C, Gordon PC, *et al.* (2019): Brain state-dependent brain stimulation with real-time electroencephalography-triggered transcranial magnetic stimulation. *J Vis Exp* (150):10.3791/59711.
153. Bergmann TO, Molle M, Schmidt MA, Lindner C, Marshall L, Born J, *et al.* (2012): EEG-guided transcranial magnetic stimulation reveals rapid shifts in motor cortical excitability during the human sleep slow oscillation. *J Neurosci* 32:243–253.
154. 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.
155. 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.
156. Donse L, Padberg F, Sack AT, Rush AJ, Arns M (2018): Simultaneous rTMS and psychotherapy in major depressive disorder: Clinical outcomes and predictors from a large naturalistic study. *Brain Stimul* 11:337–345.
157. Neacsu AD, Luber BM, Davis SW, Bernhardt E, Strauman TJ, Lisanby SH (2018): On the concurrent use of self-system therapy and functional magnetic resonance imaging-guided transcranial magnetic stimulation as treatment for depression. *J ECT* 34:266–273.
158. Okamoto M, Dan H, Sakamoto K, Takeo K, Shimizu K, Kohno S, *et al.* (2004): Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping. *Neuroimage* 21:99–111.