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

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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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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 yet 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.
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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 (29–31,83,84). 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 (anti-correlated) 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 4E) (86). 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
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 whole-brain FC (85,134) and TMS to this target proposes that lateral OFC-striatal nonreward circuits may enter a feedback loop in major depressive disorder (135). A recent case series suggests that 1-Hz right OFC rTMS may attenuate negative thought content (136).

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(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 anxiosomatic 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.

**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 or theta burst stimulation (144,145) with equivalent clinical effects (146) or endogenous brain rhythms (150) also appears promising. Similarly, TMS may be more effective when delivered at 20-Hz rTMS to be delivered in as little as 3 minutes (143,146) compared with intermittent theta burst stimulation, are starting to emerge (61), but there are an almost endless number of ways to administer TMS. Trials directly comparing different forms of TMS, such as 10-Hz or theta burst stimulation, are starting to emerge (61), but there are an almost endless number of ways to administer TMS. 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) (137) and, more recently, individualized connectomics-based targeting (73% response rate at 6 months) (74). Connectomics is also increasingly being used to inform rTMS for cognitive applications (31,139,140) and to guide the modulation of corticostriatothalamic 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).

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) (137) and, more recently, individualized connectomics-based targeting (73% response rate at 6 months) (74). Connectomics is also increasingly being used to inform rTMS for cognitive applications (31,139,140) and to guide the modulation of corticostriatothalamic 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).
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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