

Efficacy of Transcranial Magnetic Stimulation Targets for Depression Is Related to Intrinsic Functional Connectivity with the Subgenual Cingulate

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Background: Transcranial magnetic stimulation (TMS) to the left dorsolateral prefrontal cortex (DLPFC) is used clinically for the treatment of depression. However, the antidepressant mechanism remains unknown and its therapeutic efficacy remains limited. Recent data suggest that some left DLPFC targets are more effective than others; however, the reasons for this heterogeneity and how to capitalize on this information remain unclear.

Methods: Intrinsic (resting state) functional magnetic resonance imaging data from 98 normal subjects were used to compute functional connectivity with various left DLPFC TMS targets employed in the literature. Differences in functional connectivity related to differences in previously reported clinical efficacy were identified. This information was translated into a connectivity-based targeting strategy to identify optimized left DLPFC TMS coordinates. Results in normal subjects were tested for reproducibility in an independent cohort of 13 patients with depression.

Results: Differences in functional connectivity were related to previously reported differences in clinical efficacy across a distributed set of cortical and limbic regions. Dorsolateral prefrontal cortex TMS sites with better clinical efficacy were more negatively correlated (anticorrelated) with the subgenual cingulate. Optimum connectivity-based stimulation coordinates were identified in Brodmann area 46. Results were reproducible in patients with depression.

Conclusions: Reported antidepressant efficacy of different left DLPFC TMS sites is related to the anticorrelation of each site with the subgenual cingulate, potentially lending insight into the antidepressant mechanism of TMS and suggesting a role for intrinsically anticorrelated networks in depression. These results can be translated into a connectivity-based targeting strategy for focal brain stimulation that might be used to optimize clinical response.

Key Words: Depression, dorsolateral prefrontal cortex, intrinsic connectivity, MRI, resting state functional connectivity, subgenual, TMS, transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive technique that utilizes short, rapidly changing magnetic field pulses to induce electrical currents in underlying cortical tissue (for reviews, see [1–3]). By applying repeated pulses (repetitive transcranial magnetic stimulation) at low frequencies (e.g., 1 Hz), one can suppress underlying cortical activity and high-frequency stimulation (e.g., 20 Hz) can result in excitatory changes [1–3]. Further, the effects of TMS can propagate beyond the site of stimulation, impacting a distributed network of brain regions [4–10].

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One of the first clinical uses of TMS and its only Food and Drug Administration approved therapeutic indication is high-frequency stimulation to the left dorsolateral prefrontal cortex (DLPFC) for the treatment of medication-resistant depression (11–14). Depression involves a distributed network of cortical and limbic regions, including the DLPFC (especially the left), hippocampus, and subgenual cingulate among others (15,16). Of these, the subgenual region has shown some of the most reproducible abnormalities. The subgenual decreases its activity in response to multiple treatment modalities (Table 1) and is a successful target of deep brain stimulation (DBS) (16–18). Unfortunately, TMS is largely limited to the cortical surface and deeper limbic regions, including the subgenual, cannot be directly or selectively stimulated with traditional stimulation coils. Transcranial magnetic stimulation studies have, therefore, focused on the left DLPFC as one accessible node of this depression network. It has been hypothesized that left DLPFC TMS might have distributed effects on deeper limbic regions such as the subgenual (12,13,19); however, combined TMS imaging studies designed to investigate this hypothesis have produced conflicting results (20–34). It therefore remains unclear how TMS to the DLPFC exerts its antidepressant effect.

Paralleling our limited understanding of the antidepressant mechanism of TMS, its therapeutic efficacy, while statistically significant, also remains limited (11–14). One problem known to contribute to limited average clinical efficacy is difficulty identifying the appropriate stimulation target in the left DLPFC (12,35–38). The Food and Drug Administration approved Neuronetics Neurostar protocol, along with the majority of TMS depression studies, identifies the left DLPFC stimulation site by moving 5 cm anterior to the motor cortex along the curvature of the scalp (11–14,39). However, this technique frequently misses the DLPFC (37,38). Alternative approaches to DLPFC target identification have been examined, in-

Table 1. Coordinates Used to Generate A Priori Regions of Interest

| | Tx | Ty | Tz | MNIx | MNIy | MNIz | Treatment |
|--|-----|----|-----|------|------|------|-------------------|
| Subgenual Region^a | | | | | | | |
| Study | | | | | | | |
| Wu <i>et al.</i> 1999 (48) | 7 | 17 | −4 | 7 | 18 | −4 | Sleep Deprivation |
| Mayberg <i>et al.</i> 2000 (50) | 4 | 2 | −4 | 4 | 2 | −5 | SSRI |
| Drevets <i>et al.</i> 2002 (51) | 3 | 31 | −10 | 3 | 32 | −10 | SSRI |
| Mayberg <i>et al.</i> 2005 (17) | −2 | 8 | −10 | −2 | 9 | −11 | DBS |
| Mayberg <i>et al.</i> 2005 (17) | 10 | 20 | −4 | 10 | 21 | −4 | DBS |
| Kito <i>et al.</i> 2008 (23) | 17 | 16 | −14 | 17 | 17 | −16 | TMS |
| Kito <i>et al.</i> 2011 (24) | 8 | 21 | −9 | 8 | 22 | −9 | TMS |
| Nahas <i>et al.</i> 2007 (52) | 0 | 8 | −16 | 0 | 9 | −19 | VNS |
| Average | | | | 5.9 | 16.3 | −9.8 | |
| DLPFC Regions^b | | | | | | | |
| Study/Site | | | | | | | |
| Herwig <i>et al.</i> 2001 (37) 5 cm Stimulation Site | −42 | 17 | 52 | | | | |
| Herbsman <i>et al.</i> 2009 (36) 5 cm Stimulation Site | −42 | 20 | 49 | | | | |
| Herbsman <i>et al.</i> 2009 (36) 5 cm Sham Site | −39 | 17 | 47 | | | | |
| Average 5 cm Coordinates | −41 | 18 | 49 | −41 | 16 | 54 | |
| Herbsman <i>et al.</i> 2009 (36) Responders | −46 | 25 | 44 | −46 | 23 | 49 | |
| Herbsman <i>et al.</i> 2009 (36) Nonresponders | −41 | 19 | 50 | −41 | 17 | 55 | |
| Herwig <i>et al.</i> 2003 (43) EEG (F3) Site | −37 | 27 | 44 | −37 | 26 | 49 | |
| Rajkowska and Goldman-Rakic 1995 (54) BA46 Definition | −44 | 40 | 25 | −44 | 40 | 29 | |
| Rajkowska and Goldman-Rakic 1995 (54) BA9 Definition | −36 | 40 | 38 | −36 | 39 | 43 | |
| Paus <i>et al.</i> 2001 (25) TMS Target | −40 | 32 | 30 | −40 | 31 | 34 | |
| Cho and Strafella 2009 (53) TMS Target | −40 | 32 | 30 | −40 | 31 | 34 | |
| Fitzgerald <i>et al.</i> 2009 (35) TMS Target | −46 | 45 | 35 | −46 | 45 | 38 | |
| Rusjan <i>et al.</i> 2010 (41) TMS Target | −50 | 31 | 32 | −50 | 30 | 36 | |

BA, Brodmann area; DBS, deep brain stimulation; EEG, electroencephalogram; MNI, Montreal Neurological Institute; SSRI, selective serotonin reuptake inhibitors; T, Talairach; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation.

^aCoordinates of treatment-related decreases in the subgenual cingulate tied to antidepressant effect, the treatment modality used, and finally the average coordinates used to generate our a priori region of interest.

^bCoordinates of various left dorsolateral prefrontal cortex transcranial magnetic stimulation targets suggested in the literature. For all prior studies,^{a,b} we show the published coordinates in either Talairach (Tx, Ty, Tz) or Montreal Neurological Institute (MNIx, MNIy, MNIz) space along with the transformed Montreal Neurological Institute coordinates used in the present study.

cluding standardized electroencephalogram electrode positions (40), a variety of anatomical magnetic resonance imaging (MRI) coordinates focused around Brodmann areas (BA) 9 and 46 (35,36,41), and individualized hypometabolic foci (42–44) (Table 1). These alternative targeting strategies have not led to substantial clinical improvements beyond the 5 cm approach; however, data from these studies suggest that some DLPFC stimulation sites are more effective than others (12,35,36,42). Unfortunately, it remains unclear why some sites are more effective, making it difficult to capitalize on this information to optimize target selection or clinical effect.

In the current study, we hypothesized that previously reported differences in clinical efficacy of different left DLPFC stimulation sites are related to differences in the connectivity of these sites to deeper limbic regions, especially the subgenual cingulate. We tested this hypothesis using intrinsic (resting state) functional connectivity MRI, a powerful imaging technique that utilizes correlations in spontaneous fluctuations in the blood oxygen level-dependent signal to assess functional relationships between regions (45–47). We first examined a large cohort of normal subjects to detect subtle differences in connectivity between adjacent regions, then confirmed these findings in a smaller cohort of patients with major depressive disorder.

Methods and Materials

Full methodological details can be found in Supplement 1. Two datasets collected at different sites were used in the present analy-

sis. The first consisted of 98 healthy right-handed subjects (48 male subjects, ages 22 ± 3.2 years [mean \pm SD]). The second dataset consisted of 13 right-handed subjects with major depressive disorder (3 male subjects, mean age 40.2 years, mean Hamilton Depression Rating Scale [HAM-D] 23.8) and 11 healthy control subjects (5 male subject, mean age 29 years, mean HAM-D .4). These cohorts differed in age, gender ratio, and MRI scanner parameters and therefore cannot be directly compared to look for cohort differences; however, they can be used to test for reproducibility across cohorts. All subjects completed one or more resting state functional connectivity magnetic resonance imaging (fcMRI) scans. Functional connectivity magnetic resonance imaging data were processed in accordance with the strategy of Fox *et al.* 2005 (48) as implemented in Van Dijk *et al.* (47), including global signal regression. An a priori region of interest (ROI) was defined in the subgenual cingulate cortex (Figure S1 in Supplement 1) based on coordinates from prior studies showing reductions in subgenual activity tied to antidepressant response (17,23,24,49–52) (Table 1). Additionally, a priori ROIs were defined in the left DLPFC based on coordinates previously used or proposed as TMS targets for depression (Table 1) (25,35–37,41,42,53,54).

Three different analyses were used to relate functional connectivity of various left DLPFC TMS sites to previously reported clinical efficacy: 1) paired comparison of functional connectivity between two TMS sites previously shown to differ in clinical efficacy (35,36); 2) correlation between functional connectivity and clinical efficacy as predicted by a previously reported equation (36): HAM-D drop =

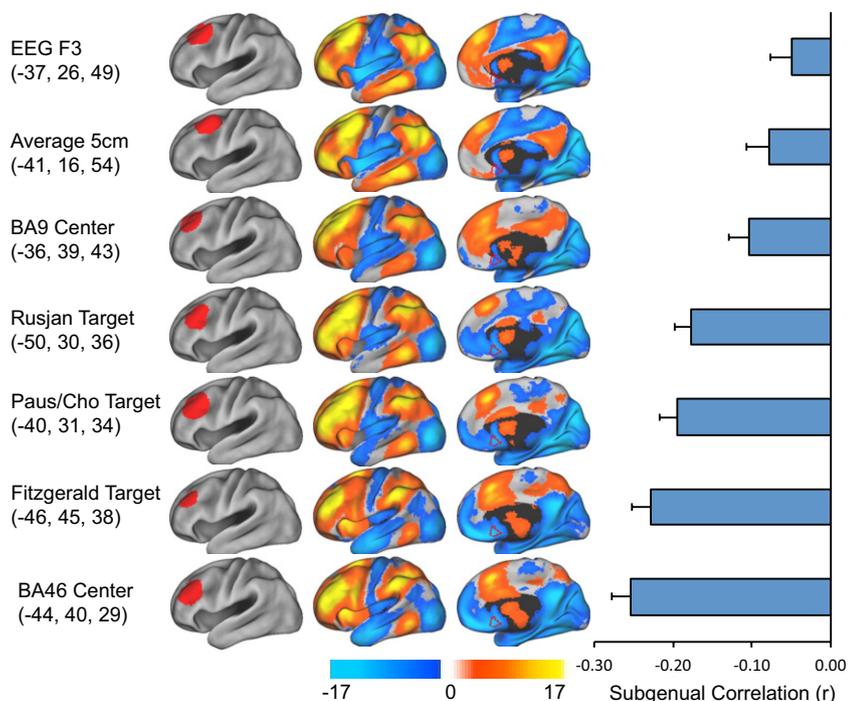


Figure 1. Different left dorsolateral prefrontal cortex (DLPFC) transcranial magnetic stimulation targets show variability in resting state functional connectivity, especially with the subgenual cingulate. The left hand column shows the coordinates and regions of interest for various left DLPFC transcranial magnetic stimulation targets employed in the literature. The middle columns show resting state functional connectivity maps for each DLPFC region of interest. The border of our a priori defined subgenual region of interest is shown for reference in red. The right hand column is the correlation coefficient between the time course from each DLPFC region of interest and that of the subgenual cingulate. BA, Brodmann area; EEG, electroencephalogram.

-.84 + (X * -.022) + (Y * .012); and 3) correlation between functional connectivity and clinical efficacy as previously reported in individual patients (42).

Motivated by the results of the above analyses, coordinates were identified in the left DLPFC that could potentially serve as optimized TMS targets by computing seed-based functional connectivity with our a priori ROI in the subgenual and our effective-ineffective map. Principal findings in normal subjects were confirmed in patients with depression.

Results

We first determined whether the different left DLPFC stimulation sites suggested in the literature showed heterogeneity in their underlying functional connectivity, both on a voxelwise basis and specifically with our a priori defined region of interest in the subgenual cingulate (Figure 1). Clear differences in functional connectivity were observed across multiple regions in the subgenual, medial prefrontal cortex, insula, and anterior cingulate. Interestingly, all DLPFC sites tested showed a significant negative correlation (anticorrelation) with the subgenual, ranging from $p < .01$ for the F3 site to $p < 10^{-26}$ for BA46. All sites except F3 remained significantly anticorrelated ($p < 10^{-3}$) after Bonferroni correction for multiple comparisons. Stimulation sites relying on external skull-based landmarks, including the 5 cm method and the electroencephalogram electrode method, showed the weakest anticorrelation with the subgenual. Sites with strong physiological data showing distributed effects of TMS in the medial prefrontal cortex (25,53) revealed a stronger anticorrelation. While both our BA9 and BA46 ROIs were anticorrelated, the stronger effect was for BA46. Finally, anatomical sites with either proven (35) or suggested (41) enhancement in clinical antidepressant response showed some of the strongest levels of anticorrelation.

Direct Comparison of Effective and Ineffective TMS Sites

Next, we directly compared the functional connectivity between pairs of coordinates from prior studies reporting that one

coordinate was clinically superior to another for producing an antidepressant effect. In the first study (Figure 2A), Herbsman *et al.* (36) recorded the stimulation coordinates from 54 subjects treated with the 5 cm method. They averaged the stimulation sites for responders (-46, 23, 49) and showed this was anterior and lateral to the average stimulation site for nonresponders (-41, 17, 55). Despite the fact that these coordinates were very close to one another, significant differences in functional connectivity were apparent (Figure 2B). The more effective stimulation site was significantly more anticorrelated with the subgenual cingulate compared with the less effective site (Figure 2C, $p < .005$). In the second study (Figure 2D), Fitzgerald *et al.* (35) targeted a specific anatomical coordinate (-46, 45, 38) based on evidence from the depression neuroimaging literature and showed (in secondary analyses) that this was superior to the standard 5 cm target (-41, 16, 54 from our analysis). The voxelwise distribution of significant differences in functional connectivity between these two targets (Figure 2E) is similar to that in Figure 2B, although more robust, given the larger separation in the DLPFC coordinates. Also similar to the comparison using the Herbsman *et al.* (36) coordinates, the more effective stimulation site was significantly more anticorrelated with the subgenual cingulate compared with the less effective site (Figure 2F, $p < .0001$).

We combined results across these two pairwise comparisons to generate a single map of voxels showing significant differences in functional connectivity between more effective versus less effective DLPFC stimulation sites (Figure S2 in Supplement 1). Peaks in this map were identified (23 positive, 29 negative) and include the subgenual cingulate in addition to several other regions implicated in depression, including the medial prefrontal cortex, orbitofrontal cortex, subgenual cingulate, insula, thalamus, hypothalamus, and hippocampus (Table S1 in Supplement 1).

Correlation Between fMRI and Equation-Based Clinical Efficacy

In addition to the above pairwise comparisons, we examined the relationship between functional connectivity and the clinical

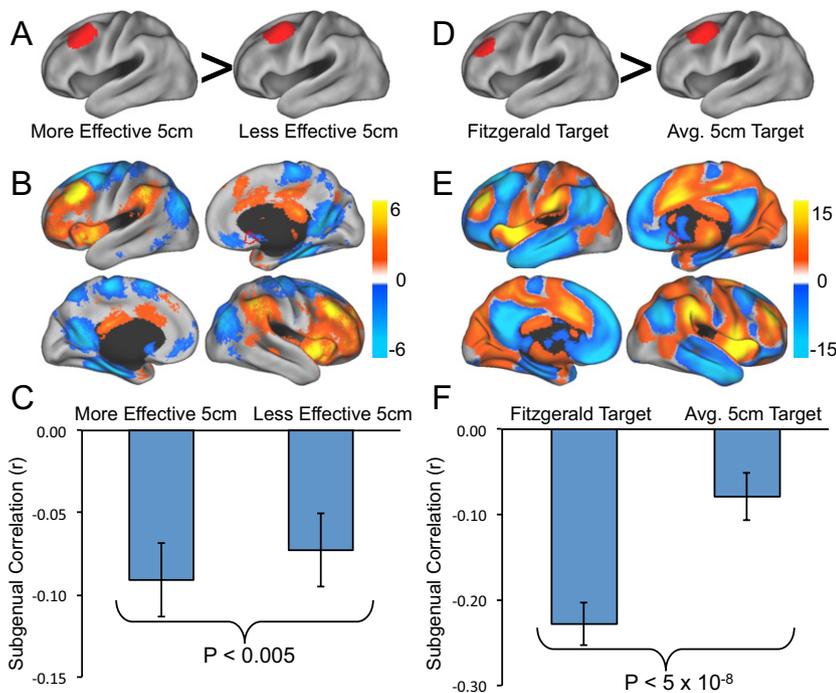


Figure 2. Differences in resting state functional connectivity between more effective versus less effective dorsolateral prefrontal cortex (DLPFC) stimulation sites. Coordinates are taken from Herbsman *et al.* (35) (A–C) and Fitzgerald *et al.* (35) (D–F). (A, D) DLPFC regions of interest compared in each study. (B, E) Significant differences in resting state functional connectivity between the two sites (more effective – less effective). The border of our a priori defined subgenual region of interest is shown for reference in red. (C, F) Bar graphs of the correlation of each DLPFC site with the subgenual cingulate. In both cases, the more effective DLPFC site is significantly more anticorrelated with the subgenual cingulate than the less effective site.

efficacy of different DLPFC stimulation sites on a continuous basis. First, we computed the average clinical efficacy expected across a group of subjects based on the coordinates of each stimulation site using an equation empirically derived by Herbsman *et al.* (36). We then plotted the predicted group-level clinical efficacy of all DLPFC stimulation sites considered in the current study (Table 1) versus the resting state correlation of each site with the subgenual cingulate (Figure S3A in Supplement 1). Similar to the paired comparisons, DLPFC sites with higher predicted clinical efficacy showed stronger anticorrelation with the subgenual ($r = -.842, p < .001$ two-tailed). In fact, anticorrelation with the subgenual cingulate accounted for over 70% of the variance in clinical efficacy as predicted by the Herbsman *et al.* (36) empirically derived equation.

Correlation Between fcMRI and Clinical Efficacy from Individual Patients

Moving beyond estimated group-level clinical efficacy using an equation, we next determined whether the above relationship held true for data from individual patients. To test this, we utilized a published table of left DLPFC stimulation coordinates and changes in the Montgomery-Åsberg Depression Rating Scale for 27 individual patients receiving therapeutic TMS for depression (42). For each patient, we plotted their antidepressant response versus the resting state correlation between their specific stimulation site and the subgenual cingulate (Figure S3B in Supplement 1). Note that resting state correlation values in this analysis are average values across our 98 normal subjects, not values from these specific patients, as no resting state functional magnetic resonance imaging data were collected in this prior study. Despite this limitation, left DLPFC sites with higher clinical efficacy in individual patients again showed stronger anticorrelation with the subgenual ($r = -.355, p < .05$, one-tailed). Interestingly, when applied to this independent cohort, there was not a significant relationship between clinical efficacy measured in individual patients and group-level clinical efficacy as predicted by the Herbsman *et al.* (36) ($r = .122, p > .25$, one-tailed; Figure S3C in Supplement 1). This suggests that anticorrelation with

the subgenual captures important variance not captured by the Herbsman *et al.* (36) equation alone.

Identification of Optimized TMS Targets

The above results are potentially of interest for understanding the antidepressant mechanism of TMS (see Discussion), but perhaps more importantly, this information can be directly translated into a method to identify connectivity-based coordinates in the left DLPFC that could serve as an optimized TMS target. For example, the above results suggest that anticorrelation with the subgenual is related to antidepressant response. We can therefore use the subgenual ROI as a seed region and identify the peak anticorrelation in the left DLPFC ($-44, 38, 34$; Figure 3A). Similarly, the above results provide a map of voxels more functionally connected to effective compared with less effective stimulation sites (Figure S2 in Supplement 1). One can use this map as a weighted seed region (minus the left DLPFC to avoid biasing results and inverted to maintain consistency with the subgenual results) to identify an optimized left DLPFC target ($-38, 44, 26$; Figure 3B). Note that despite some difference in the coordinates of the peak anticorrelation, these two maps are very similar both across all gray matter voxels (spatial $r = .630$) and specifically within the left DLPFC (spatial $r = .806$). Interestingly, there were several other nodes besides the DLPFC that were anticorrelated with the subgenual, including parietal cortex/intraparietal sulcus, anterior insula, anterior supplementary motor area, and thalamus, which could potentially serve as novel targets of focal brain stimulation for the treatment of depression (Table S1 in Supplement 1) (55,56).

Replication of Results in Depression

Since resting state functional connectivity can differ between normal subjects and patients with depression (57), we confirmed our results in an independent cohort of 13 patients with depression using both our subgenual seed region and our efficacy-based seed map. Similar to normal subjects, we found a significant anticorrelation between the subgenual and multiple left DLPFC TMS targets,

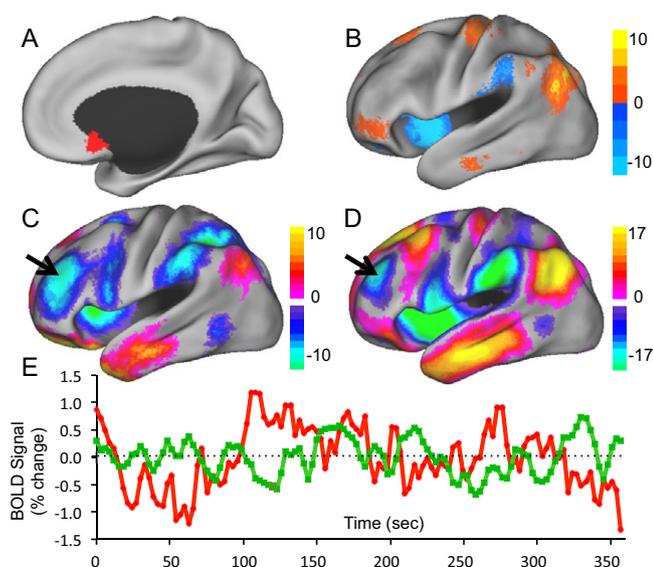


Figure 3. Identification of optimized left dorsolateral prefrontal cortex transcranial magnetic stimulation targets for depression based on functional connectivity. Regional time courses were extracted from our seed region in the subgenual cingulate (**A**) and our efficacy-based seed map (**B**) and used to generate resting state functional connectivity maps (**C**) and (**D**), respectively). Peak anticorrelations were identified in the left dorsolateral prefrontal cortex that could serve as optimized targets for focal brain stimulation. Functional magnetic resonance imaging time courses from the subgenual region of interest (red) and the anticorrelated left dorsal lateral prefrontal cortex (green) are shown for a representative subject ($r = -.23$) (**E**). BOLD, blood oxygen level-dependent.

including the optimized targets identified above ($p < .05$; Figure 4A). In paired comparisons, more effective sites showed a trend toward stronger anticorrelation with the subgenual, and the optimized left DLPFC site was significantly more anticorrelated with the subgenual than the standard 5 cm target ($p < .05$; Figure 4B). As in normal subjects, there was a robust relationship between clinical efficacy as predicted by the Herbsman *et al.* (36) equation and anticorrelation with the subgenual ($r = -.812, p < .005$; Figure 4C). Results were even more robust using our distributed efficacy-based seed map rather than the smaller and noisier subgenual ROI (Figure 4D–F). Similar to the subgenual, many DLPFC targets, including our optimized sites, showed a significant negative correlation with the seed map (Figure 4E). In paired comparisons, more effective sites were significantly more anticorrelated than less effective sites, including the Herbsman *et al.* (36) regions ($p < .05$), the Fitzgerald *et al.* (35) regions ($p < 10^{-4}$), and our new optimized site compared with the standard 5 cm target ($p < 10^{-6}$). Finally, there was a highly significant relationship between predicted clinical efficacy and correlation with our efficacy-based seed map ($r = -.875, p < .001$).

Analyses were also replicated on the 11 control subjects from the same dataset as the 13 patients with depression (Figure S4 in Supplement 1). There were no significant differences between these control subjects and patients with depression.

Discussion

In the current article, we used a novel connectivity-based approach to gain insight into why some left DLPFC TMS targets have proven more clinically effective than others. We identified robust differences in functional connectivity related to previously reported differences in clinical efficacy, particularly anticorrelation with the subgenual cingulate. We then demonstrated how one

could translate this information into a connectivity-based targeting technique to identify coordinates in the left DLPFC that could potentially be stimulated to optimize clinical response.

These results are likely relevant to understanding network models of depression, the antidepressant effect of TMS, and the functional relevance of intrinsic anticorrelations in resting state functional magnetic resonance imaging. Most importantly, the current results suggest that the clinical efficacy of focal brain stimulation might be optimized by targeting based on connectivity, a concept that remains to be tested in clinical trials but could find broad applicability across a number of diseases and stimulation techniques.

Relevance to Network Models of Depression

Depression is becoming increasingly recognized as a network disorder associated with alterations in a distributed set of regions, including DLPFC (especially left), medial prefrontal, orbitofrontal, subgenual cingulate, insula, thalamus, hypothalamus, and hippocampus (15,16). Of these regions, the left DLPFC and the subgenual cingulate have received the most attention due to the consistency of their depression-related abnormalities, their modulation with treatment across a range of therapies, and their use as targets of focal brain stimulation (58). Although depression functional imaging studies have produced heterogeneous results (16,59–61), on average, the abnormalities in these two regions have been opposite one another (58). The subgenual has been observed to be hyperactive in depression and a decrease in this hyperactivity is associated with antidepressant response (16,17,58) (Table 1). Conversely, the left DLPFC tends to be hypoactive in depression and an increase in activity is associated with antidepressant response (58,59). Consistent with this dichotomy, lesions of the ventral medial prefrontal cortex can improve depression, while lesions of the dorsal lateral prefrontal cortex can exacerbate it (62).

The current finding that the subgenual and DLPFC are intrinsically anticorrelated during the resting state mirrors this dichotomy and suggests that there is a link between the depression-related abnormalities in these two regions. There are several implications of this result. First, observed depression-related abnormalities in one region could theoretically be due solely to pathology in the opposing region. Primary hyperactivity in the subgenual might result in secondary hypoactivity of the DLPFC without anything being abnormal in the DLPFC and vice versa. Second, this anticorrelation could mediate compensatory responses. The DLPFC could increase its activity in response to subgenual hyperactivity in an attempt to suppress or normalize activity in this region, a mechanism that could explain the occasional finding of DLPFC hyperactivity in depression (15,59,60). Finally, focal inhibition/excitation of one region could be expected to, respectively, enhance/suppress activity of the other region. Indeed, DBS of the subgenual (which suppresses activity locally) results in an increase in activity in the DLPFC (17).

While the above discussion focused on the subgenual and the DLPFC, it is important to remember that the current results include several other regions previously implicated in the pathology of depression (15,61). Our results suggest two anticorrelated groups of regions. The first consists of the subgenual, medial prefrontal, superior frontal, hippocampus, posterior cingulate/precuneus, middle temporal gyrus, and cerebellar tonsils, while the second consists of the DLPFC, anterior insula, dorsal anterior cingulate/presupplementary motor area, thalamus, DLPFC, and parietal cortex.

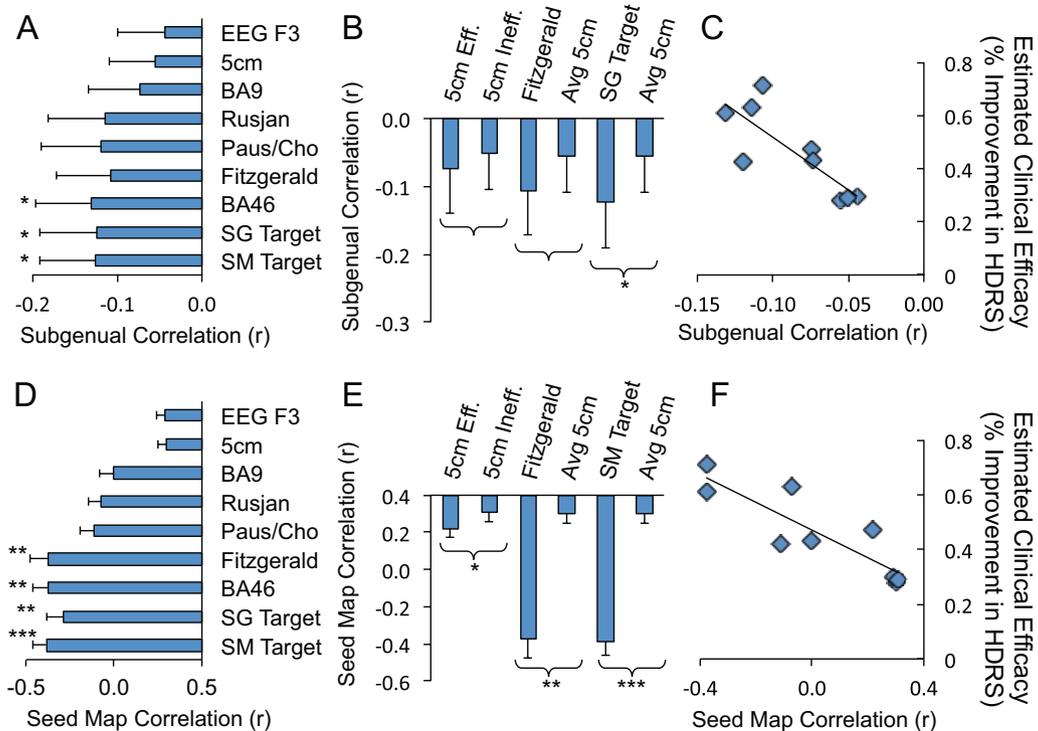


Figure 4. Replication of principal findings in patients with major depressive disorder. Time course correlations are shown between regions of interest in the dorsolateral prefrontal cortex (DLPFC) and the subgenual seed region (A–C) or the efficacy-based seed map (D–F). Similar to normal subjects, there is an anticorrelation between transcranial magnetic stimulation targets in the DLPFC and the subgenual (A). Paired comparisons of effective versus less effective DLPFC targets show the same trend as normal subjects and a significant difference between the optimized DLPFC target identified using the subgenual seed region (SG Target) and the average 5 cm target (B). Also similar to normal subjects, there is a strong relationship between estimated clinical efficacy (using the Herbsman equation) and anticorrelation with the subgenual (C) ($R^2 = .66, p < .005$). Using the efficacy-based seed map rather than the small subgenual seed region produces similar but more robust results, including examination of regional time course correlations (D), paired comparisons (E), and the correlation between functional connectivity and estimated clinical efficacy (F) ($R^2 = .76, p < .001$). Labels for DLPFC regions of interest are as in Figures 1 and 2, with the addition of optimized DLPFC targets identified in normal subjects using the subgenual seed region (SG Target) and the efficacy-based seed map (SM Target). * $p < .05$, ** $p < .001$, *** $p < 10^{-4}$. Avg, average; BA, Brodmann area; EEG, electroencephalogram; Eff., effective; HDRS, Hamilton Depression Rating Scale; Ineff., ineffective.

Understanding the Antidepressant Mechanism of TMS

There has been much research into the antidepressant mechanism of DLPFC TMS in the hopes that this knowledge would facilitate optimization of the effect and improve clinical utility. Many hypotheses have been proposed (12,63); however, one idea that has been pursued aggressively is the propagation of TMS effects through anatomical connections to deeper limbic regions (12). A number of groups have attempted to localize the remote effects of DLPFC TMS by pairing it with neuroimaging techniques both in normal subjects and patients with depression. A full review of these heterogeneous results is beyond the scope of this article; however, given the current findings, we examined the results of these studies with respect to changes in the subgenual cingulate or adjacent medial prefrontal cortex (Table S2 in Supplement 1). Although many studies found TMS-induced decreases in subgenual activity (20–24) or adjacent medial prefrontal activity (25–27), other studies found no significant changes in these regions (28,29,31–33) and one study observed increased medial prefrontal activity (29). The present findings using a novel connectivity-based approach are consistent with 8 of the above 13 studies and suggest that part of the antidepressant mechanism of DLPFC TMS may be remote suppression of activity in the subgenual cingulate and other limbic regions.

Relevance to the Debate Surrounding Anticorrelations

There has been substantial debate surrounding the appropriate interpretation of anticorrelations observed with resting state fMRI in the setting of a preprocessing step termed global signal regression (47,64–67). This processing can improve the specificity of resting state correlations and the correspondence with anatomy (65); however, there are mathematical concerns that anticorrelations could emerge as processing artifact. While the technical issues surrounding processing strategy and anticorrelations are beyond the scope of this article (see Fox *et al.* [65] for discussion), the current results add information to be considered in the ongoing debate. First, the fact that the resting state anticorrelation between the subgenual and DLPFC is recapitulated in patterns of pathological abnormalities seen in depression provides additional evidence that anticorrelations may reflect functionally meaningful relationships. Second, the focal brain stimulation interventions used in depression might serve as a causal test of the functional importance of anticorrelations. If stimulation/inhibition of one node suppresses/augments the activity of the anticorrelated node in a spatially specific manner and in proportion to the strength of the anticorrelation, this would support the biological importance of anticorrelations.

An interesting issue is determining how anticorrelations observed with resting state fMRI are mediated. In the case of the subgenual and DLPFC, the anticorrelation is unlikely to be the result

of direct inhibitory connections. Monkey track-tracing studies suggest that there are no direct anatomical connections between BA46 and BA25 (68,69). However, there are direct anatomical connections between the subgenual (BA25) and the anterior insula and mediodorsal nucleus of the thalamus, both of which are anticorrelated with the subgenual in the current analysis. Previous studies have implicated the fronto-insular cortex as a potential node mediating anticorrelations (70), and other studies have suggested the thalamus, especially the mediodorsal nucleus, as the site of integration of otherwise separate cortical-subcortical loops (71).

Targeting Focal Brain Stimulation Based on Connectivity

The idea that targets for focal brain stimulation should be selected, at least partly, based on their connectivity to other regions is not new; however, implementing this strategy in practice has been difficult and empiric evidence supporting the utility of this approach has been limited (for review, see [10]). It has been suggested that stimulation should be targeted to the portion of the DLPFC with connectivity to deeper limbic regions (12,19). Unfortunately, the connectivity between the DLPFC and various limbic regions is complicated even in monkeys (68,69), and the DLPFC is one of the areas that has expanded the most throughout evolution (54,72). It has remained unclear which part of the human DLPFC should be stimulated and which limbic regions are important, even if the human connectivity between the DLPFC and limbic regions was well established.

In the current article, we use intrinsic fMRI with the subgenual and our efficacy-based seed map to identify left DLPFC TMS coordinates designed to optimize antidepressant response. These coordinates might serve as the basis for a clinical trial; however, this connectivity-based targeting approach can be taken further. First, our results suggest the existence of other connectivity-based TMS targets for depression besides the DLPFC (Figure 3; Table S1 in Supplement 1). Of these, the cerebellum and parietal cortex have previously been suggested as potential TMS targets in depression based on mood effects in normal subjects (56). A recent trial of low-frequency parietal stimulation failed to show a significant response beyond sham (55); however, the present results suggest that high-frequency stimulation to the peak parietal node anticorrelated with the subgenual may be more effective. Second, the current study reports average group-level coordinates. Although average coordinates have previously been used in clinical trials of TMS for depression (35), an advantage of the current targeting approach is it might be applied at the single subject level. Given cross-subject heterogeneity in the location of the DLPFC (54), the full potential of connectivity-based targeting may be realized with identification of individualized TMS targets tailored to individual patients. Finally, the current targeting approach is potentially applicable across other diseases and brain stimulation techniques. Cortical correlates of deep brain stimulation sites based on fMRI could serve as important TMS targets in Parkinson's disease, dystonia, obsessive-compulsive disorder, or any other disease for which DBS provides clinical benefit (73). The converse of this approach also holds promise. Specifically, intrinsic fMRI could be used to identify optimized DBS sites in individual patients based on connectivity with distributed cortical networks known to be impacted by disease.

Limitations and Future Work

The current work was limited in several respects and these limitations suggest important avenues for future research. First, our results were generated on normal subjects then confirmed in a small cohort of patients with depression. While this makes it likely

that our findings will further generalize to a larger cohort of patients with medication-refractory depression undergoing TMS, our results remain to be confirmed in this specific population. Second, measures of clinical efficacy in the current article were based on previously published data and not obtained *de novo*. Ideally, one would measure clinical efficacy and resting state functional connectivity in the same cohort of patients. However, the fact that our connectivity results in normal subjects predicted clinical efficacy in an independent set of patients suggests that future work measuring both parameters in the same cohort should only increase the strength of the relationship. Finally, the current findings suggest that the antidepressant effect of TMS might be optimized through connectivity-based targeting; however, this remains a hypothesis. The clinical utility of this method remains to be tested in a clinical trial.

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AP-L serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Allied Mind, Neosync, and Novavision and is listed as inventor in issued patents and patent applications on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging. All other authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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