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New Targets for rTMS in Depression: A Review of Convergent Evidence

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ABSTRACT

Although rTMS is moving steadily into the mainstream as a treatment for medically refractory depression, its efficacy continues to lag behind that of more invasive neuromodulation treatments such as ECT or DBS. Here we review evidence to suggest that a fruitful, but neglected, strategy for improving rTMS efficacy may be to explore alternatives to the conventional stimulation target in the dorsolateral prefrontal cortex (DLPFC). The convergent evidence of lesion, stimulation, connectivity, and correlative neuroimaging studies suggests that the DLPFC may have a relatively peripheral role in mood regulation, at least compared to several alternative areas within the prefrontal cortex. In particular, we consider the evidence base in support of four new potential targets for rTMS in depression: dorsomedial prefrontal cortex (DMPFC), frontopolar cortex (FPC), ventromedial prefrontal cortex (VMPFC), and ventrolateral prefrontal cortex (VLPFC). Each of these regions enjoys broader support, from a more diverse evidence base, than the DLPFC in terms of its role in emotion regulation in major depression. We discuss the relative merits of each of these novel targets, including potential obstacles to stimulation using currently available technologies, and potential strategies for overcoming these obstacles. It is hoped that this detailed review will spur a more vigorous exploration of new targets for rTMS in depression. The use of new targets may help to propel rTMS across the threshold of efficacy required of a first-line treatment, to assume a more widespread role in the treatment of depressed mood.

Introduction

It has been nearly 18 years since the first trials of rTMS for treatment-resistant depression showed marked improvement with high-frequency stimulation of the left dorsolateral prefrontal cortex (DLPFC) [1,2]. Since then, dozens of trials have demonstrated a statistically significant improvement in depressive symptoms with active over sham rTMS. However, until recently, the absolute proportion of patients achieving response or remission has remained modest. As recently as 2008, a meta-analysis of 24 studies in 1092 patients found overall response rates of only 25% for DLPFC rTMS, with remission rates even lower at 17% [3]. Around the same time, a large randomized controlled trial obtained nearly identical rates of ~25% response and ~16% remission [4]. Although any positive outcomes in medically refractory depression are encouraging, a treatment that offers remission in only 1 in 6 patients certainly has substantial scope for improvement, especially when compared to remission rates of 65–75% for ECT [5] or remission rates of >40% in ECT-refractory patients with DBS [6]. Thus, a key question is whether rTMS is already nearing its efficacy ceiling, or whether further optimization could generate substantial (i.e., 2- or 3-fold) improvements in outcome from the levels seen in 2008.

Over the last several years, a new generation of rTMS studies has identified significant limitations in the earlier trials, and has sought to address them [7]. This new generation of studies has steadily improved rTMS outcomes via stronger or accelerated dosing regimens [8,9], longer treatment courses [10], bilateral stimulation protocols [11,12], individually-tailored stimulation frequencies [13], new coil geometries [14], more precise neuronavigation technologies [15–17], and more accurate methods than the traditional "5 cm rule" for locating the DLPFC [18]. With such improvements, the more recent studies have consistently achieved rTMS remission and response rates of around 30–35% and 40–55%, respectively

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[9–12,19–21]. Several of these trials enrolled >100 and in some cases >200 patients, while making use of improved techniques such as bilateral stimulation or MRI-based neuronavigation. Although the use of sham controls in large trials is no longer universal given the well-established superiority of active over sham rTMS, the reported outcomes in these trials are more than 5-fold better than the ~5% remission/~10% response rates consistently seen for sham stimulation in this refractory population [3].

This near-doubling of rTMS efficacy over the last 4 years represents a significant advance towards the viability of rTMS as a first-line treatment for refractory depression. In this population, rTMS remission rates now match or exceed the 23–33% remission rates seen for an open-label second medication trial or cognitive therapy in patients failing a first medication trial in the STAR*D study [22], or the 35% response and 22% remission rates seen for patients switching to psychotherapy after failing an antidepressant medication [23]. At the same time, these advances also suggest that rTMS still has substantial scope for optimization, and that clinically meaningful improvements in rTMS efficacy may accrue with further refinements in technique.

One relatively underexplored parameter is the target of the stimulation itself. Virtually all rTMS trials to date have targeted the DLPFC for stimulation in depression. Yet the cytoarchitectonically-defined DLPFC constitutes less than 10% of the surface of the prefrontal cortex, leaving over 90% of the frontal lobes as essentially unexplored territory. The relative dearth of studies on rTMS beyond the DLPFC is striking for two reasons. First, the most potent forms of neuromodulation (i.e., ECT and DBS) are typically directed at non-DLPFC targets, some of which lie deep in the cranial vault, but others of which are readily accessible with standard rTMS equipment. Second, new coil geometries have recently enabled stimulation of areas known to be important for mood regulation, but previously considered too deep to serve as targets for conventional rTMS. In light of these developments, this may be an opportune time to re-evaluate potential alternative targets for rTMS in major depression, based on the significant advances in affective neuroscience that have been achieved since the first reports of DLPFC rTMS nearly 20 years ago.

Here we will review a variety of lines of evidence to suggest that, while the DLPFC does play a role in emotion regulation, several other prefrontal regions are not only readily accessible to rTMS, but also much more central to the pathophysiology of major depression. As stimulation targets, these regions offer the possibility of substantial and clinically meaningful improvements in rTMS efficacy within a relatively short time-frame. If this potential can be realized, the use of targets beyond the DLPFC may be the new approach that finally carries rTMS across the threshold of efficacy required of a first-line treatment.

Using convergent evidence to identify new rTMS targets in depression

Over the last 25 years, non-invasive neuroimaging has played a key role both in delineating the neuroanatomical correlates of depression and in identifying potential targets for neuromodulation. A canonical example would be the series of studies in the late 1990s and early 2000s that found a correlation between depression and hyperactivity in the subgenual cingulate cortex, eventually leading to the selection of this region as a target for DBS [24]. Another example would be the earlier generation of studies in the 1980s and early 1990s that found a correlation between depression and hypoactivity in the left DLPFC, eventually leading to the selection of this region as a target for rTMS [2,25].

Yet the mere correlation of abnormal activity in a given region to increased symptoms of depression does not by itself imply causation. However, if a given region can be linked to mood regulation not only through the correlational evidence of functional neuroimaging studies, but also through the causational evidence of lesion or stimulation studies, then the case for its involvement in depression is bolstered substantially. Likewise, if a given region shows strong anatomical and functional connectivity to emotion-regulating regions, it is again more likely to play a central rather than a peripheral role in mood regulation. Hence, the *convergent* evidence of lesion studies, stimulation studies, and connectivity studies backs correlative neuroimaging studies in identifying the most central nodes of the brain's emotion-regulating networks.

These four lines of convergent evidence were not available for the emotional functions of the frontal lobes 20 years ago, but they are all available today. If rTMS for depression had been devised using the evidence base of 2012, rather than 1994, would the DLPFC still be the target of choice for stimulation? The emerging literature of affective neuroscience suggests that targets beyond the DLPFC may in fact enjoy better support as therapeutic targets in depression. Here we will consider the currently available convergent evidence in support of the DLPFC as compared to four alternative prefrontal targets for rTMS in major depression: dorsomedial prefrontal cortex (DMPFC), frontopolar cortex (FPC), ventromedial prefrontal cortex (VMPFC), and ventrolateral prefrontal cortex (VLPFC). Although non-prefrontal targets such as the precuneus or middle temporal gyrus also participate in emotion-regulation networks and could be argued to represent potential rTMS targets, this paper will focus on the much larger body of evidence available for regions of the prefrontal cortex.

Nodes and networks for emotion regulation in depression

Although each prefrontal region is considered separately here, it is important to bear in mind that these regions do not function in isolation, but rather as nodes in larger networks involved in depression-related functions: cognitive control, rumination and self-reflection, and the generation of visceral states sometimes known as *somatic markers* [26]. For example, fluorodeoxyglucose positron emission tomography (FDG-PET) studies of resting brain function in depression reveal net hypoactivity in a widespread network that includes all of the areas listed above, bilaterally, along with hypoactivity in partner regions in the precuneus, lateral parietal lobes and middle temporal gyri and increased activity of amygdala, hippocampus, and brainstem raphe nuclei [21,27]. Within this network, the overall trend involves a shift from cortical to subcortical activity within the nodes of emotion-regulating regions of the resting brain, at least over the 30–60 min exposure times used for FDG-PET acquisitions.

Underlying this overall shift, the increased temporal resolution of fMRI reveals more subtle shifts in functional connectivity and relative dominance among a set of ~20 cortical networks that can be consistently identified in resting-state fMRI studies of human brain function [28]. In the non-depressed brain, these networks include a *cognitive control network*, centered on the DLPFC and lateral parietal cortex, a ruminating/self-reflecting *default mode network*, centered on the precuneus and medial FPC, and a visceral-state-generating affective or *somatic marker network* centered on the VMPFC. In depression, these normally distinct networks all show increased connectivity to one another via a *dorsal nexus* in the DMPFC [29], suggesting an untrammelled and pathological pattern of information flow among regions responsible for cognition, self-reflection, rumination, and visceral sensation. This pattern may represent a neuroanatomical substrate for the link between thoughts, emotions, and sensations often described in CBT models of depression [30]. The normal patterns of connectivity among these regions can reverse itself in depressed individuals: for example,

VLPFC regions normally suppressing amygdalar responses to emotional stimuli can instead serve to increase such responses [31]. Conversely, antidepressant medications and therapy can both effect changes in the connectivity between emotion-regulation nodes such as the DMPFC, insula, amygdala, and hippocampus [32,33].

The key point here is that although each of the rTMS targets below can be considered as a node with a distinct contribution to emotion regulation (Fig. 1), these nodes also participate in larger networks that draw together the closely-related functions of cognitive control, rumination and self-reflection, stimulus evaluation, and the generation of visceral and motivational states [34]. Applying rTMS to any given node within these networks is also likely to also modulate the activity of the other nodes via their shared anatomical connections [35]. With this potential for overlap in mind, let us now proceed to consider the evidence for each of the prefrontal nodes in turn, beginning with the conventional rTMS target in the DLPFC.

Dorsolateral prefrontal cortex (DLPFC)

In the late 1980s and early 1990s, a series of PET neuroimaging studies first identified DLPFC hypoactivity in major depression [36–38]. Although hypoactivity in the left DLPFC was emphasized in the interpretation of these studies, the results themselves showed essentially symmetrical bilateral reductions in DLPFC activity in depression – a finding that has remained consistent across a large number of studies conducted over the ensuing two decades [21,24,39–44]. Likewise, recovery from depression is accompanied by symmetric changes in DLPFC activity, across a wide variety of treatment modalities [40,43–45]. However, as neuroimaging provides only correlative evidence, casual studies involving stimulation or lesions may be more illuminating regarding the role of the DLPFC in mood regulation.

Stimulation studies provide some of the strongest support for DLPFC involvement in depression. With rTMS, the DLPFC has served as the stimulation target in the vast majority of successful randomized controlled trials [3,4,46]. Although high-frequency stimulation of the left DLPFC enjoys the largest base of support, low-frequency right DLPFC stimulation shows similar efficacy [47,48]. It should also be noted that low-frequency stimulation of the left DLPFC has also shown efficacy in several studies [13,49,50] – a finding consistent with modern observations of symmetrical changes in DLPFC activity in depression. Accurate neuronavigation appears critical to the success of DLPFC-rTMS; inadvertent stimulation of the premotor cortex or frontal eye fields yields little or no antidepressant effect [51].

The DLPFC has also proved to be a successful target for epidural cortical stimulation (EpCS) in refractory MDD [52,53]. With both

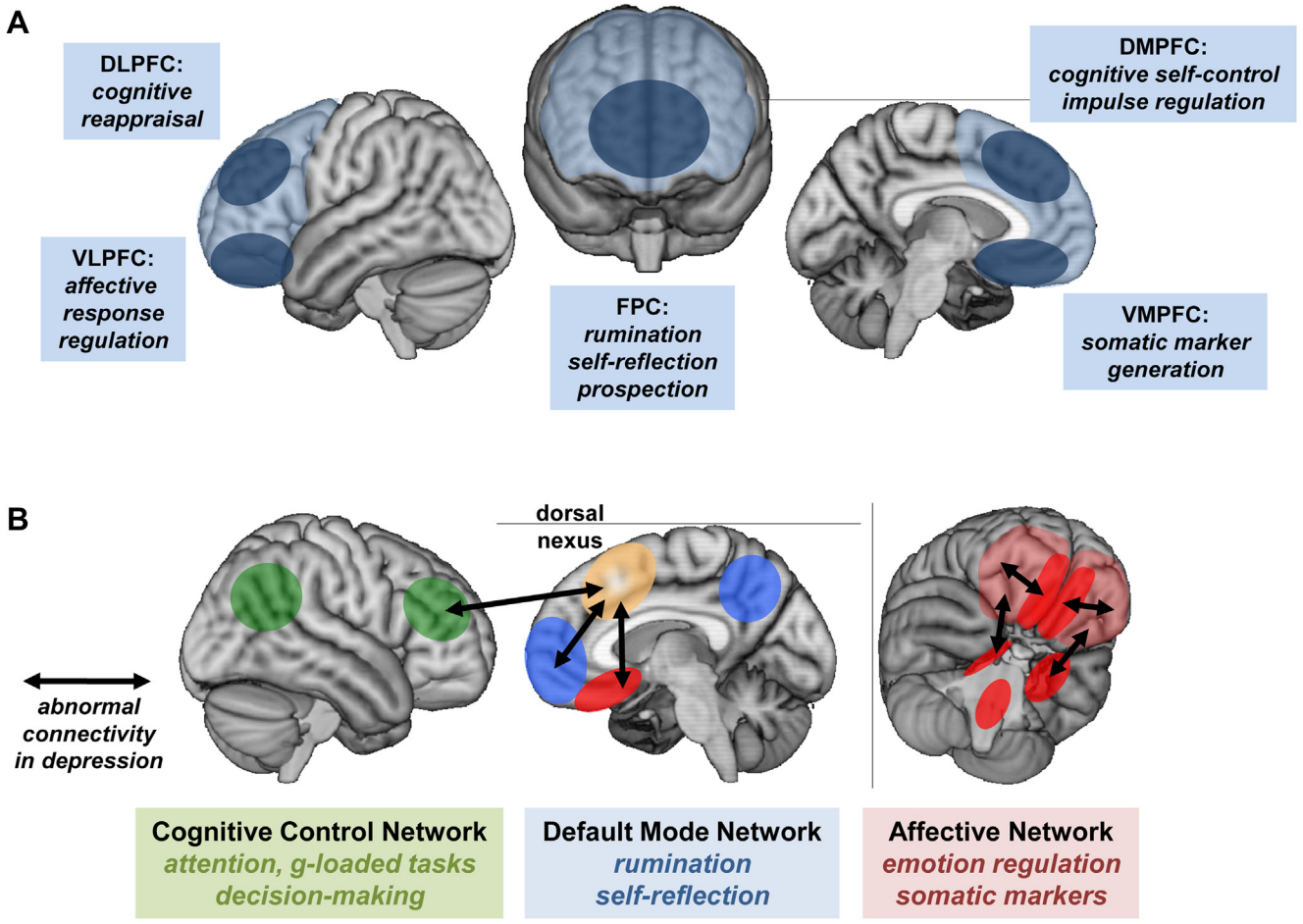

Figure 1. Cortical nodes and networks involved in the pathophysiology of depression. (A) In patients with depression, 20 years of FDG-PET studies have revealed a network of prefrontal regions whose resting metabolic activity shows a general reduction over the ~1 h timescales required for scan acquisition using this technique. The prefrontal nodes of this network include DLPFC, DMPFC, VLPFC, VMPFC, and FPC. DLPFC, dorsolateral prefrontal cortex. The proposed contributions of each region to emotion regulation in depression are shown in the panel. (B) Abnormal network activity in depression. Resting-state functional MRI in depression reveals a "dorsal nexus" in the DMPFC linking networks for cognitive control (DLPFC), default-mode reflection (FPC), and somatic marker generation (VMPFC). VLPFC also shows abnormal connectivity to VMPFC in depression. DMPFC, dorsomedial prefrontal cortex. VLPFC, ventrolateral prefrontal cortex. VMPFC, ventromedial prefrontal cortex. FPC, frontopolar cortex.

EpCS and rTMS, more anterior and more lateral placement of the stimulator appears to be more efficacious, underscoring the need for accuracy in targeting this region [18,53,54]. With ECT, changes in global functional connectivity to the left DLPFC have recently been observed in conjunction with treatment, with the caveats that subjects were performing a visuomotor task during imaging and the changes were not specifically correlated to ECT response [55].

Lesion studies are more equivocal in terms of the role of the DLPFC in depression. Studies of stroke patients in the 1970s suggested the risk of depression increased with left prefrontal lesions and decreased with right prefrontal lesions [56]. By 2000, however, a meta-analysis of 48 lesion studies, published in *Lancet*, found that the risk of depression after stroke was no higher for left or right prefrontal cortex, or any other region studied, either acutely or chronically [57]. This result has since been confirmed in several other meta-analyses [58,59]. Stroke lesions often span large areas of cortex; however, a notable recent study of focal lesions of the DLPFC, in veterans with head wounds, confirmed that neither left *nor* right DLPFC lesions conferred any greater risk of depression than lesions outside the prefrontal cortex, although *g*-loaded intellectual functions were reduced in both groups (Fig. 2) [60].

Looking forward, several recent studies have begun to explore transcranial direct current stimulation (tDCS) of the DLPFC as a treatment for depression. The typical approach has been to apply excitatory, anodal stimulation over left DLPFC and inhibitory, cathodal stimulation over right DLPFC. While some studies have shown efficacy with this approach [61], others have shown no advantage over sham stimulation [62]. In light of the convergent evidence above, it may be worth considering whether efficacy could be improved with symmetrical DLPFC stimulation, or with stimulation of the alternative targets below.

Dorsomedial prefrontal cortex (DMPFC)

The DMPFC is perhaps the most promising alternative target for rTMS, based on a broad base of convergent evidence, particularly from lesion studies. In contrast to the neutral effects of DLPFC lesions, DMPFC lesions confer a very high risk (~80%) of severe depression, when compared to lesions outside the prefrontal cortex or to a control groups without brain injury [63] (Fig. 2).

Likewise, in a recent meta-analysis of voxel-based morphometry (VBM) studies in ~1000 depressed patients versus a similar number of healthy controls, only minimal changes were seen in the DLPFC, and only on the right side. Instead, the most consistent and extensive region of abnormality encompassed the DMPFC and adjacent anterior cingulate cortex (ACC) [64] (Fig. 3). The region of abnormality was almost identical in location and extent to region identified in a PET study comparing baseline metabolic activity in

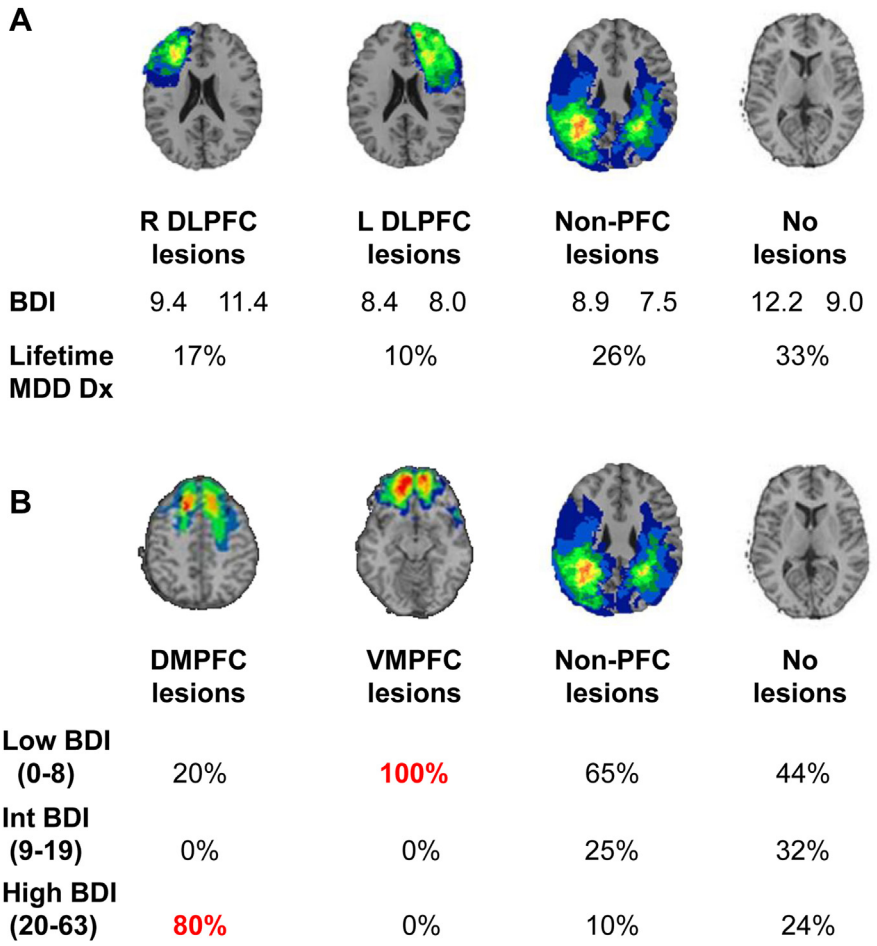

Figure 2. Lesion evidence for a more central role of DMPFC and VMPFC over DLPFC in the pathophysiology of depressed mood. (A) In veterans with focal brain injury, neither left nor right DLPFC lesions produce significant increases in depressive symptomatology, or in the lifetime prevalence of major depressive disorder, when compared to non-prefrontal lesions or to a control group with no lesions. (B) In veterans with focal brain injury, DMPFC lesions confer a strong risk of severe depressive symptomatology, while VMPFC lesions have the opposite effect, when compared against control groups with non-prefrontal lesions or no lesions. DLPFC, dorsolateral prefrontal cortex. DMPFC, dorsomedial prefrontal cortex. PFC, prefrontal cortex. BDI, Beck Depression Inventory. Adapted from refs. [60,63].

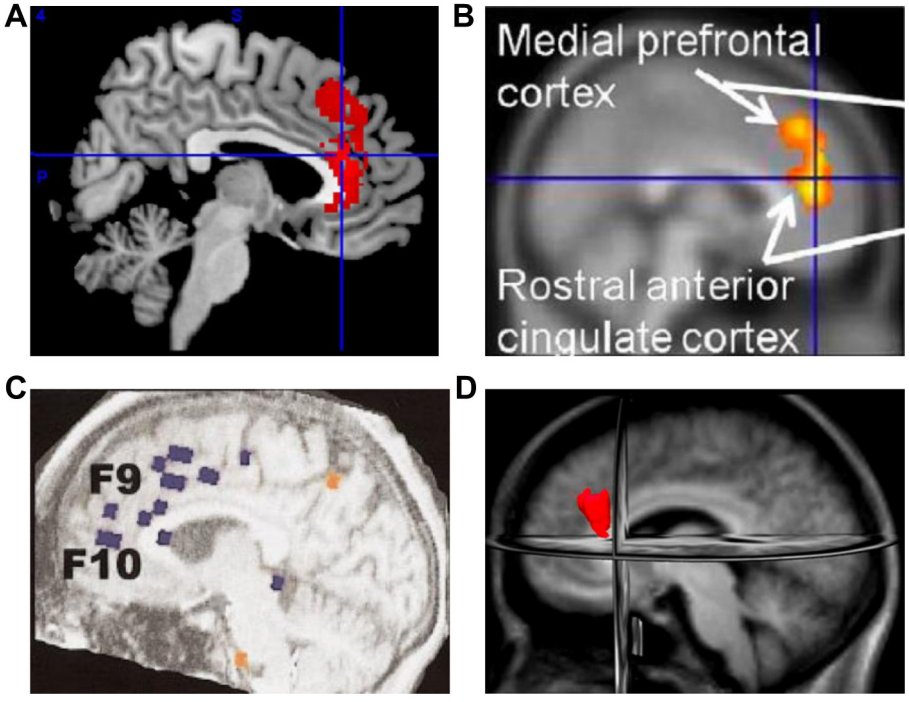

Figure 3. Convergent evidence from stimulation, volumetric, connectivity, and lesion studies in support of the DMPFC as a target for excitatory rTMS in depression. (A) Ref. [64]. A large ($n \sim 2000$) meta-analysis of VBM studies in MDD reveals the most extensive changes in DMPFC and neighbouring ACC, with only minor changes in DLPFC. (B) Ref. [21]. The region identified in A is virtually identical in position and extent to a region identified in a PET study as showing lower metabolism in non-responders vs. responders to rTMS of the DLPFC. (C) Ref. [65]. DBS-induced inhibition of this DMPFC region (shown in blue) produced an intense, near-instantaneous dysphoric response in a patient with remitted major depression, which resolved with the termination of stimulation. (D) Ref. [29]. The DMPFC was the only brain region identified as a "nexus" of abnormally increased functional connectivity across a conjunction of resting-state networks for self-reflection, affect regulation, and cognitive control in an fMRI study of MDD patients vs. healthy controls.

responders vs. non-responders to DLPFC-rTMS for depression [21] (Fig. 3). As noted above, the DMPFC was also recently identified as a 'dorsal nexus' in depression: a unique brain region where cortical networks for cognitive control, affect regulation, and self-reflection converge in depressed patients but not in healthy controls [29] (Fig. 3).

Stimulation studies of the DMPFC are rare, but one case study is instructive. Here, a patient with a history of remitted depression was undergoing DBS implantation in the subthalamic nucleus for refractory Parkinsonism. On one side, the electrode was inadvertently malpositioned during surgery. On activation of this electrode, the patient immediately developed a severe dysphoric reaction, and reported an instantaneous subjective reproduction of her depressed emotional state. Functional MRI revealed that the malpositioned electrode was inhibiting activity in the DMPFC, instead of the intended projection site in the slightly more posterior motor areas of the medial wall [65] (Fig. 3). Repositioning of the electrode eliminated the dysphoric effect.

Neuroimaging studies in healthy controls have begun to suggest why the DMPFC might be especially important in depression. For example, while both the DLPFC and DMPFC are active bilaterally during cognitive reappraisal of emotional stimuli, the *success* of the reappraisal correlates not with DLPFC activity but with DMPFC activity [66]. The DMPFC (but not the DLPFC) also develops increased functional connectivity to the amygdala in studies where individuals use fMRI-based 'neurofeedback' to learn to regulate their own mood, by recalling positive memories [67]. The DMPFC (but not the DLPFC) also modulates amygdala activation to produce the so-called 'framing effect' in which individuals reverse their choice behavior depending on whether the options are presented in terms of losses or gains [68].

The DMPFC may also be particularly important in self-regulation of cognition, emotion, and action. For example, a VBM study in healthy controls identified the DMPFC as the brain region most closely correlated to individuals' tendency to "keep calm and carry on", or suppress emotional reactions [69]. The DMPFC also activates during self-inhibition of loss-chasing in pathological gamblers [70], and of cigarette cravings in smokers [71]. Enhancement of emotional self-regulation and impulse control via excitatory rTMS could prove to be a promising approach to alleviating the symptoms of depression. In keeping with this proposal, recent case reports have found DMPFC stimulation to be effective in achieving remission from refractory alcohol cravings in refractory alcohol dependence [72], and remission from purging behaviors in refractory bulimia nervosa, in addition to remission from depression [73].

Frontopolar cortex/Brodmann area 10 (FPC/BA 10)

Another promising target for inhibitory forms of rTMS is the frontopolar cortex (FPC), cytoarchitectonically defined as Brodmann Area 10. Uniquely among frontal lobe regions, BA10 has no direct inputs from sensory cortex. This leaves BA10 well-positioned to consider events beyond the present moment: self-reflection, long-term goals, past or future events, or hypothetical scenarios [74–76]. Pathological patterns of rumination and self-reflection are important features of depression, and a recent neuroimaging meta-analysis revealed increased resting-state activity in BA10 as a consistent finding in patients with depression [77]. Correcting the excessive activity in BA10 could serve as a plausible new strategy for rTMS in refractory depression.

Reducing BA10 activity does appear to be an important factor in the success of other neuromodulation techniques, such as ECT and DBS. For example, while ECT produces widespread changes in neural activity throughout the brain, it is the degree of decrease in frontopolar activation that correlates most closely with improvements in depressive symptoms (Fig. 4) [78,79]. A reduction in FPC

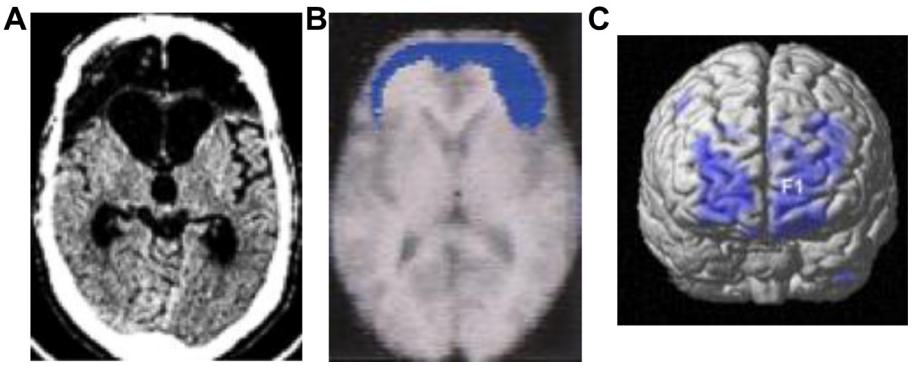

Figure 4. Convergent evidence from lesion, correlation, and stimulation studies in support of the FPC as a target for inhibitory rTMS in depression. (A) Ref. [63]. Following an attempt at suicide by gunshot, this patient suffered severe damage to frontopolar cortex, and experienced near-total remission of her symptoms, with "no signs of depression whatsoever since the accident" according to her partner and treatment team. (B) Ref. [79]. Although ECT produces widespread changes in brain activity, it is the degree of reduction in frontopolar cortical activity that correlates best with symptom improvement. (C) Ref. [80]. DBS electrodes implanted in the nucleus accumbens have been used successfully to treat MDD. DBS in this region produces inhibition in the frontopolar cortex, rather than the DMPFC as in the case shown in Fig. 3c.

activity also arises from DBS of the nucleus accumbens, which has been used with some success to treat severe, refractory depression [80]. Reductions in BA10 activity also correlate with the success of cognitive behavioral therapy (CBT) [81], and with performing mindfulness meditation — a core component of another effective treatment for depression, mindfulness-based cognitive therapy (MBCT) [82].

Lesion studies of the FPC are relatively rare. However, one meta-analysis in post-stroke depression found that the proximity of the lesion to the frontal pole correlated with a greater severity of depression [83]. More notably, in one case report, a woman with a longstanding history of depression attempted suicide by gunshot to the head. She survived, but sustained extensive damage to the ventral frontopolar cortex. Strikingly, her symptoms of depression remitted after this injury. 11 years later, she remained free of the cognitive and affective symptoms of depression, both by her own report and by the collateral reports of her partner, neuropsychologist, and neurosurgeon [63]. Inhibitory rTMS of this region could potentially provide a much less drastic pathway to remission in refractory depression.

Ventromedial prefrontal cortex (VMPFC)

The link between the VMPFC and emotion regulation extends back to the famous 19th-century case of Phineas Gage, whose temperament changed drastically after he sustained a lesion to the VMPFC (as well as the DMPFC — a point that is often overlooked) [84]. In a more recent case of a 'reverse Phineas Gage', a 33-year-old man with a history of pathologically aggressive and violent behavior sustained a similar penetrating injury to the VMPFC following an attempt at suicide by crossbow. Following the injury he became uncharacteristically docile, indifferent to his injury, and inappropriately jovial [85]. Similarly, in studies of veterans with head wounds, focal lesions of the ventromedial prefrontal cortex (VMPFC) are strongly protective against depressed mood, when compared to lesions outside the prefrontal cortex or to a control group of veterans without brain injury [63]. In this respect, the effects of VMPFC lesions appear to be opposite to those of DMPFC lesions.

Stimulation studies largely confirm this relationship. Inadvertent DBS-induced inhibition of the DMPFC produced intense dysphoria in the patient described above. Conversely, DBS-induced inhibition of the subgenual cingulate cortex and adjacent VMPFC (within the general region of the VMPFC) relieves depression in patients otherwise refractory to treatment [42,44].

As noted above, the original choice of the subgenual cingulate cortex as a DBS target rested on a body of neuroimaging evidence indicating that this region is consistently overactive in depression. Correction of this overactivity is a common factor in the successful treatment of depression by pharmacotherapy, psychotherapy, somatic therapy, or even placebo treatment (reviewed in [24]). Connectivity studies using DTI demonstrate a close relationship between the VMPFC and the centromedial amygdala, which has played a key role in regulating brainstem and autonomic activity [86]. The subgenual cingulate cortex also projects to a variety of cortical and subcortical regions with abnormal activity in depression, including the hypothalamus, nucleus accumbens, and dorsal brainstem [87,88]. These widespread limbic and autonomic connections may account for the potent effects of VMPFC stimulation in alleviating the symptoms of depression.

Ventrolateral prefrontal cortex (VLPFC)

The VLPFC is a key region for evaluating the emotional significance of external stimuli, and also serves as an important substrate for cognitive influences on emotional states. In terms of connectivity, it draws input from visceral as well as external sensory modalities, while projecting to the basolateral amygdala, hypothalamus, ventral striatum, and other subcortical limbic structures [86,89]. Its activity mediates the success of emotional reappraisal in healthy volunteers, by modulating activity in the amygdala and nucleus accumbens [66].

VLPFC activity normally dampens the responses of the amygdala and sympathetic nervous system to negative stimuli; however, in depression this pattern reverses, and greater VLPFC activity actually correlates with *higher* amygdala activity and stronger sympathetic responses [31]. Thus, depression may involve a counterproductive recruitment of the VLPFC in the face of external stressors. Consistently with this, many neuroimaging studies have found VLPFC metabolic activity to be increased in patients with depression [90]. These observations suggest that inhibitory VLPFC stimulation may be helpful in at least some cases of depression.

VLPFC abnormalities may also underlie depression in the setting of bipolar illness. VBM meta-analyses have found consistent reductions in VLPFC grey matter volume in patients with bipolar disorder, alongside the similar reductions in DMPFC and subgenual cingulate cortex discussed above [91]. fMRI meta-analyses have also found reductions in VLPFC activity during emotion regulation, specifically in patients with bipolar disorder rather than unipolar depression, and particularly during mania [92,93].

Neuroimaging studies of responders vs. non-responders to rTMS at the DLPFC have recently found reductions in both metabolic activity and grey matter volume in the VLPFC in rTMS non-responders, relative to responders [94]. In keeping with this, during excitatory rTMS of the DLPFC for depression, placement of the coil at more lateral and more anterior sites (i.e., closer to the VLPFC) led to better antidepressant response [18]. Hence, the VLPFC already shows some hints of promise as a target for rTMS in depression.

Individualized rTMS: optimizing the site, side, and stimulation parameters

As we have seen, at least four prefrontal regions beyond the DLFPC show theoretical promise as targets for rTMS in depression. However, the optimal type of stimulation may turn out to be different at each site. At the DMPFC, excitatory stimulation may be beneficial, while inhibitory stimulation may actually be harmful, as in the DBS case presented earlier. Conversely, at the FPC and VMPFC, inhibitory stimulation would likely be required to reproduce the beneficial effects of DBS and ECT; excitatory stimulation would presumably be harmful, although this would require empirical confirmation. At the VLPFC, some studies imply overactivity in depression, while others imply underactivity. Thus, it remains unclear whether the greatest benefit would derive from excitatory or inhibitory stimulation, or whether different patients will require different stimulation parameters (as may be the case for the DLPFC as well [13]).

For both inhibitory and excitatory rTMS, multiple stimulation protocols are now available: for example, low-frequency (~1 Hz) and continuous theta burst stimulation (cTBS) for inhibition, and high-frequency (~20 Hz) and intermittent theta burst stimulation (iTBS) for excitation [95]. Multiplying just these 4 options by the 5 stimulation sites discussed here gives no less than 20 different available protocols for stimulation – and this ignores the additional option of multiple-site stimulation, which increases the number of possibilities exponentially.

If new rTMS targets do prove their worth, it will become important to develop methods for optimizing the stimulation protocol (target, laterality, and parameters) for each individual patient presenting for treatment. For the moment, such methods are mostly speculative, and a full review will be deferred pending the emergence of a wider literature on this subject. However, neuroimaging may offer one approach to predicting outcomes with different forms of rTMS. Indeed, there is already an incipient literature suggesting that pre-treatment neuroimaging can not only distinguish rTMS responders from nonresponders, but can also predict response to excitatory versus inhibitory rTMS at a given cortical target [13,96]. Clinical symptom scales may also prove useful as response predictors. For example, in one recent study, patients with high apathy scores were less likely to respond to DLPFC-rTMS [97]. Conversely, individual case reports suggest patients with high impulsivity (for example, those with comorbid bulimia or substance abuse) might respond well to DMPFC-rTMS [72,73].

In the longer term, it may be possible to replace expensive and laborious MRI-based predictors with non-invasive behavioral predictors of response. Behavioral markers, such as eye gaze bias during the viewing of emotional pictures, or the degree of recall for emotional words, have shown promise both as biomarkers of depression and as predictors of response to medication [98]. Studies extending these findings from pharmacotherapy to rTMS would be straightforward to execute, and will likely be reported in the near future. If the results are similar, then behavioral biomarkers may also turn out to be useful in guiding site selection during the initial sessions of a course of rTMS.

Overcoming obstacles to the use of non-DLPFC targets

Strength of evidence aside, some practical issues complicate the use of non-DLPFC targets for rTMS. For example, the VMPFC region lies as much as 7 cm deep to the closest point on the scalp. Conventional, flat figure-8 rTMS coils are unable to reach this depth. However, newer coils with non-conventional geometries, such as the 'H-coil' [20], C-shaped coils with ferromagnetic cores, crown-shaped coils [99], and 'bat-wing'-shaped coils [100], are now being constructed to stimulate deeper structures within the brain. Coils with such geometries may be suitable for stimulation of the VMPFC. The effectiveness of this approach should become clearer shortly, with several studies either planned or already underway.

The VLPFC also presents a challenging target for conventional rTMS, as much of it lies deep within the frontal operculum, or along the orbital surface of the prefrontal cortex. However, even for superficial VLPFC regions, tolerability remains a problematic issue, due to the proximity of the extraocular and temporalis muscles. There are several alleviating measures that may be effective in improving the tolerability of stimulation at this region, as reviewed in detail below. With appropriate measures to alleviate discomfort, conventional figure-8 coils may be suitable for stimulating some VLPFC regions, and newer coil designs should be able to address the depth-of-target issue in future. Hence, the VLPFC could also serve as a practical target in future studies of rTMS for depression, with appropriate refinements to technique.

The DMPFC and FPC are comparatively much more accessible. The DMPFC lies at a depth of just 3–5 cm on standard templates, while the polar and lateral regions of the FPC are less than 2 cm deep to scalp. Conventional figure-8 coils, particularly those with the windings angled obliquely (i.e. 120–150°) are capable of reaching these depths. Coil placement is also simpler at these sites, as they are both at midline and close to the nasion. Hence, consistent accuracy of placement can be achieved even without MRI guidance, and consistent coil orientation with respect to the sagittal plane is also straightforward. Thus, DMPFC and FPC targets may offer the best prospects for widespread use in community settings where the availability of non-conventional coils or high-resolution neuroimaging is limited.

Even when technical limitations are overcome, tolerability remains a significant obstacle at some scalp sites. Compared to the DLPFC, coil placements over medial, lateral, or polar targets are more prone to producing uncomfortable contractions of the frontalis, temporalis, or extraocular muscles, as well as painful stimulation of the trigeminal nerve branches. However, several strategies could help to mitigate these effects. For example, some newer coil designs route the windings orthogonally to scalp for part of their circuit, reducing the area of scalp that is exposed to uncomfortable field strengths [14]. With more conventional coils, lidocaine injections or intervening foam sheets can reduce pain intensity and unpleasantness [101]; certain patients may also obtain relief with topical lidocaine [102]. rTMS pain also appears to diminish markedly over the course of treatment [102,103]. Titrating stimulus intensity gradually upwards to target, while tracking pain on a visual analog scale or equivalent, may be helpful in patients for whom pain is problematic.

One additional strategy that may increase both tolerability and efficacy may be to employ shorter protocols, such as theta-burst stimulation. These protocols achieve lasting excitatory or inhibitory effects with as little as 40 s of stimulation per session [104], as opposed to nearly 40 min in many conventional protocols (e.g., [4,46]). In addition, the typical stimulation strengths for theta burst protocols tend to be around 80% of resting motor threshold, as opposed to up to 120% with standard 10 Hz protocols. Some preliminary studies targeting the DLPFC have found theta burst

protocols to be effective for treating depression [105,106]. Hence, these shorter protocols, at lower intensities, could help to increase tolerability substantially while preserving efficacy.

Conclusions

At a time when the efficacy of antidepressant medications has remained essentially unchanged for over 50 years, rTMS is one of the few emerging treatment modalities that offers the potential for widespread adoption and a measurable impact on public health. While stimulation of the DLPFC has been the dominant approach until now, convergent evidence suggests that the most promising targets may in fact lie elsewhere. With the new coil geometries and new stimulation protocols now available, the time has never been better to begin a systematic exploration of prefrontal regions beyond the DLPFC as targets for rTMS in depression. We hope that this review will help to stimulate a more vigorous investigation of these promising alternative sites in the near future. It should be reiterated that targeting regions *correlated* with depression may or may not prove effective in *causing* an antidepressant response in clinical trials. However, if these sites do turn out to offer significantly better outcomes, then rTMS may be poised to cross a critical threshold of efficacy, at last achieving response and remission rates high enough to warrant its adoption as a first-line treatment for the millions of individuals who suffer from refractory depression.

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