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MRI-guided dmPFC-rTMS as a treatment for treatment-resistant major depressive disorder

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Abstract:	Here we outline the protocol for magnetic resonance imaging (MRI) guided repetitive transcranial magnetic stimulation (rTMS) to the dorsal medial prefrontal cortex (dmPFC) in patients with major depressive disorder (MDD). Technicians used a neuronavigation system to process patient MRIs to generate a 3-dimensional head model. The head model was subsequently used to identify patient-specific stimulatory targets. The dmPFC was stimulated daily for 20 sessions. Stimulation intensity was titrated to address scalp pain associated with rTMS. Weekly assessments were conducted on the patients using the Hamilton Rating Scale for Depression (HamD17) and Beck Depression Index II (BDI-II). Treatment-resistant MDD patients achieved significant improvements on both HAMD and BDI-II. Of note, angled-coil rTMS at 120% resting motor threshold allows for optimal stimulation of midline prefrontal regions. One major limitation of the rTMS field is the heterogeneity of treatment parameters across studies, including duty cycle, number of pulses per session and intensity. Further work

	should be done to clarify the effect of stimulation parameters on outcome. Future dmPFC-rTMS work should include sham-controlled studies to confirm its clinical efficacy in MDD.
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Question	**Response**
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Allison Diamond
Associate Editor, *Journal of Visualized Experiments*

Dear Ms. Diamond,

Please find attached our manuscript entitled "MRI-guided dmPFC-rTMS as a treatment for treatment-resistant major depressive disorder." We wish to submit this manuscript for consideration as a JoVE-produced methods article in the *Journal of Visualized Experiments*. We have not previously published any manuscript on or related to this submission.

Neurostimulation treatments are steadily gaining interest in psychiatry, not only as effective treatment options for illnesses refractory to medications and therapy, but also as anatomically targeted 'intervention-probes' that can illuminate the neurobiological mechanisms of the pathologies themselves. Given the rapid increase in the use of neurostimulation treatments, it is crucial these medical devices in the research setting are safely used. Here, we outline the protocol for repetitive transcranial magnetic stimulation (rTMS) using a novel cortical target to treat major depressive disorder. A multimedia format, therefore, allows us to better explain the detailed treatment methods than with text alone.

Our protocol also highlights four key details crucial for successful stimulation. First, an angled, double-cone coil allows for optimal stimulation of deeper structures within the medial aspect of the prefrontal cortex. Second, treatment stimulation at 120% resting motor threshold, a significantly higher intensity than conventional stimulation, was used without serious adverse events. Third, magnetic resonance imaging guidance was used for precise, individualized anatomical localization. Finally, adaptive titration of stimulation intensity was used to aid in rTMS-related discomfort adaptation.

All authors contributed to the rTMS treatment protocol design, revised the manuscript, and made final approval for submission. Authors KD, PG, and JD also drafted the manuscript, and analyzed and interpreted data included in the representative results section of the manuscript.

Two editors have assisted us with the submission process: yourself and Dr. Nandita Singh. We would like to thank both editors for their assistance.

We hope you will agree that our rTMS protocol has important implications for the treatment of major depression, and that it meets the necessary criteria for JoVE's multimedia format.

We look forward to receiving your response.

Sincerely,

Jonathan Downar, MD PhD FRCPC
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TITLE:
MRI-guided dmPFC-rTMS as a treatment for treatment-resistant major depressive disorder

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SHORT ABSTRACT:
Here we outline the procedure for MRI-guided repetitive transcranial magnetic stimulation to the dorsomedial prefrontal cortex as an experimental treatment for major depressive disorder.

LONG ABSTRACT:
Here we outline the protocol for magnetic resonance imaging (MRI) guided repetitive transcranial magnetic stimulation (rTMS) to the dorsal medial prefrontal cortex (dmPFC) in patients with major depressive disorder (MDD). Technicians used a neuronavigation system to process patient MRIs to generate a 3-dimensional head model. The head model was subsequently used to identify patient-specific stimulatory targets. The dmPFC was stimulated daily for 20 sessions. Stimulation intensity was titrated to address scalp pain associated with rTMS. Weekly assessments were conducted on the patients using the Hamilton Rating Scale for Depression ($HamD_{17}$) and Beck Depression Index II (BDI-II). Treatment-resistant MDD patients achieved significant improvements on both HAMD and BDI-II. Of note, angled, double-cone coil rTMS at 120% resting motor threshold allows for optimal stimulation of deeper midline prefrontal regions, which results in a possible therapeutic application for MDD. One major limitation of the rTMS field is the heterogeneity of treatment parameters across studies, including duty cycle, number of pulses per session and intensity. Further work should be done to clarify the effect of stimulation parameters on outcome. Future dmPFC-rTMS work should include sham-controlled studies to confirm its clinical efficacy in MDD.

INTRODUCTION:
Repetitive transcranial magnetic stimulation (rTMS) is a form of indirect focal cortical stimulation. rTMS employs brief, focal electromagnetic field pulses that penetrate the skull to stimulate target brain regions. rTMS is thought to engage the mechanisms of synaptic long-term potentiation and long-term depression, thereby increasing or decreasing the cortical excitability of the region stimulated[1]. Generally, the rTMS pulse frequency determines its effects: higher frequency stimulation tends to be excitatory, while lower frequency is inhibitory. Non-invasive stimulatory procedures are also widely used as a causal probe to induce temporary 'cortical lesions,' and establish neural-behavior relationships or functional regions by temporarily disabling the function of a desired cortical region[2–4].

Therapeutic rTMS involves multiple stimulation sessions, usually applied once daily over several weeks, to treat a variety of disorders, including major depressive disorder (MDD)[5], eating disorders[6], and obsessive-compulsive disorder[7]. rTMS for MDD is a potential option for medically refractory patients, and allows the clinician to noninvasively target and alter the excitability of a cortical region directly involved with depressive etiology or pathophysiology. The conventional cortical target for MDD-rTMS is the dorsolateral prefrontal cortex (DLPFC)[8]. However, convergent evidence from neuroimaging, lesion, and stimulation studies identifies the dorsomedial prefrontal cortex (dmPFC) as a potentially important therapeutic target for MDD[9] and a variety of other psychiatric disorders characterized by deficits in self-regulation of thoughts, behaviors, and emotional states[10]. The dmPFC is a region of consistent activation in emotional regulation[11], behavioral regulation[12,13]. The dmPFC is also associated with neurochemical[14], structural[15], and functional[16] abnormalities in MDD

Described here is the procedure for 20 sessions (4 weeks) of magnetic resonance imaging (MRI) guided rTMS to the dmPFC bilaterally, as a treatment for major depressive disorder. In addition to a conventional 10 Hz protocol applied over 30 min, an intermittent theta burst stimulation protocol (TBS) is discussed, which applies 50 Hz triplet bursts at 5 Hz over a 6-minute session[17]. Both protocols are thought to be excitatory, with the TBS protocol having the potential to achieve comparable effects using a much shorter session[18]. In both protocols, anatomical MRIs as well as clinical assessments are acquired prior to rTMS. Neuronavigation uses the anatomical scans to account for anatomical variability of dmPFC and optimize the location of rTMS. A relatively new 120º-angled fluid-cooled rTMS coil was also used in order to stimulate deeper midline cortical structures. Finally, rTMS intensity titration was used over the first week of rTMS sessions to ensure that patients could habituate to the higher pain levels associated with dmPFC stimulation as compared to conventional DLPFC stimulation.

PROTOCOL:

This study was approved by the Research Ethics Board at the University Health Network.

1) Subject Selection

1.1) Conduct an initial assessment on a prospective patient. The inclusion criteria included the presence of a current depressive episode that is resistant to at least 1 adequate trial of medication, and a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) diagnosis of MDD as established by the assessing psychiatrist. Confirm the diagnosis with a standardized Mini Mental State Examination (MINI).

1.2) Ensure that patients are on a stable medication or are washed out of their medication routine for at least 4 weeks prior to their first rTMS treatment session. Do not alter this medication regiment throughout rTMS treatment to help disambiguate the cause of any observed clinical improvement or deterioration.

1.3) Exclude patients who may have a potential contraindication to rTMS or MRI, including seizure history, cardiac arrhythmia, implanted or foreign devices/metal particulates, unstable medical conditions, or pregnancy. Patients with comorbid post-traumatic stress disorder, obsessive-compulsive disorder, other anxiety disorders, attention deficit hyperactivity disorder, bulimia nervosa or binge eating disorder, or moderate Cluster B personality features are also suitable for this treatment and need not be excluded. Patients with bipolar disorder rather than MDD may also be suitable for this treatment. Patients with psychotic disorders, active substance use, a primary diagnosis of borderline or antisocial personality disorder, or persistent depressive disorder (dysthymia) may be less suitable for treatment and may require exclusion.

2) Acquiring Magnetic Resonance Images

2.1) Acquire patients' MRIs at any time prior to treatment. Here, use a 3 Tesla scanner with an

8-channel phased-array head coil (refer to Table of Materials), or any scanner capable of created a 3D representation of a patient's brain.

2.2) Adhering to local site protocol, acquire a T1-weighted fast spoiled gradient-echo anatomical scan. Use the following parameters: TE=12 ms, TI=300 ms, flip angle=20 degrees, 116 sagittal slices, thickness=1.5 mm, no gap, 256x256 matrix, FOV 240 mm. This scan will be used for real-time rTMS neuronavigation during motor thresholding and treatment sessions.

3) Preprocessing Anatomical Scans for Real-Time Neuronavigation

3.1) Prepare for MRI guidance using a neuronavigation system.

Note: The following steps employ the Visor 2.0 neuronavigation system (refer to Table of Materials), but other navigation systems such as the Brainsight TMS Navigation, StealthStation, Aimnav, and NBS System 4 use similar procedures.

3.2) Segment anatomical MRIs into its scalp and brain components. Register the two segments into standard stereotactic space, such as Talairach and Tournoux space[19].

3.3) Place target markers by selecting the following points on the MRI: Nasion; Left and right ear, targeting the tragus; Anterior commissure; Posterior commissure; Interhemispheric point (point between the two hemispheres); the anterior most point of the brain; the posterior most point of the brain; the superior most point of the brain; and the left and right most point of the brain.

3.4) Reconstruct the surfaces of the patient's scalp and brain in standard space to create a three-dimensional surface-based head model – this image will be used to identify stereotactic scalp coordinates overlying the dmPFC (Talairach and Tournoux coordinate X0, Y+60, Z+60) for optimal coil vertex placement during treatment.

Note: This method uses population coordinates to identify the stimulation target. Other methods to identify a stimulation target, outlined in the Discussion, include single-subject anatomy or fMRI activation maps.

3.5) Register brain and scalp coordinates from stereotactic space to patient space for individualized coil placement.

4) Motor Threshold Assessment

4.1) Seat patient in the treatment chair, adjusting the camera for an unobstructed view of the patient.

4.2) Place the headband with the marker clip attached to it around the patient's head. The marker clip should sit above bridge of nose.

4.3) Preprocess the anatomical scan for the patient as described above in Step 3.

4.4) Load the preprocessed anatomical scans to the neuronavigation program and turn on the camera.

4.5) Using a neuronavigation pen, highlight each scalp target point on the patient. The movements made with the neuronavigation pen will be projected on the television screen in the form of red lines.

4.6) Assess patients' motor thresholds, the minimum intensity needed to globally excite the motor pathway, prior to rTMS treatment. For this step, begin by having the patient's lower limbs extended and supported from below, using a stool or a chair equipped with an extensible leg rest.

4.7) For motor threshold determination, under neuronavigation, target the medial primary motor cortex. Place the coil vertex over the sagittal fissure, 0.5-1.0 cm anterior to the central sulcus. Use an angled or double-cone coil for deeper pulse penetration into medial areas. Use stimulator equipped with a fluid-cooled coil, whose windings are angled at 120º to allow deeper penetration of the pulses (refer to Table of Materials).

4.8) Perform motor thresholding separately for the left and right hemispheres. Orient the coil laterally to direct rTMS-evoked current flow to the desired hemisphere[20]. For example, to stimulate the left hemisphere, orient the coil with the handle pointing rightwards and the direction of current flow toward the left hemisphere. Observe the contralateral (right) lower limb for movements during this procedure.

4.9) Determine threshold and elicited motor movement visually by the halluces longus muscle of the big toe.

Note: Unlike conventional motor threshold testing that targets the hand muscle, stimulating the medial wall of the motor cortex will target the toe muscle. Motor evoked potentials (MEPs) may also be used as a more accurate determination of motor threshold, however it is a much lengthier approach.

4.9.1) Begin by stimulating at 55% of maximum machine intensity, then adjust upwards or downwards in increments of ~5% depending on whether a response is observed. Reduce the increment size steadily to ~1% as the motor threshold is approached, as previously described[21]. Stimulate no more frequently than 0.2 Hz (once per 5 s) to avoid inhibitory or excitatory effects over time.

4.9.2) Once a motor threshold is established, move the vertex 1-2 cm anteriorly and posteriorly, in exploratory increments of 2-3 mm, to determine whether any alternative site offers a lower motor threshold. Use the lowest threshold achieved along this arc for each side.

5) rTMS Treatment & Adaptive Titration

5.1) Perform a course of neuronavigated dmPFC-rTMS, using a total of 20-30 daily sessions over 4-6 weeks. For treatments, use the 120º angled, fluid-cooled coil and the parameters listed below for dmPFC stimulation in each treatment session (refer to Table of Materials).

5.2) Seat the patient in the treatment chair, adjusting the camera for an unobstructed view of the patient.

5.3) Place a headband with a marker clip attached to it around the patient's head (placed laterally so as not to block the rTMS coil placement over the medial target site) as described above. Using a camera, the neuronavigation system, will detect the marker clip and will allow for preprocessing and neuronavigation.

5.4) Load the preprocessed anatomical scans to the neuronavigation program and turn on the camera.

5.5) Using a neuronavigation pen, highlight each scalp target point on the patient. The movements made with the neuronavigation pen will be projected on the television screen in the form of red lines.

5.6) Place the coil over the dmPFC target under MRI guidance using the neuronavigation system. For verification purposes, this point should lie close to 25% of the distance from nasion to inion. Laterally. Orient the coil laterally, with the handle pointing away from the hemisphere to be stimulated. Stimulate the left hemisphere, then re-orient the coil by 180 degrees to stimulate the right hemisphere, maintaining the vertex in the same location over the dmPFC scalp site.

5.7) Ensure that the scalp site for dmFPC remains in close contact with the coil itself throughout treatment. Ensure that the patient and operator wear earplugs or other hearing protection during treatment.

5.8) For 10 Hz stimulation, use a duty cycle of 5 seconds on, 10 seconds off for a total of 60 trains (3000 pulses) per hemisphere per session. Perform this protocol of the left then right hemisphere by orienting the coil laterally, as previously described[20].

Note: The described protocol for 10 Hz rTMS is outside international safety guidelines (ROSSI et al, 2009). There is evidence for its safety[18,22].

5.9) For TBS stimulation, use a duty cycle of 2 seconds on, 8 seconds off for a total of 600 pulses per hemisphere per session. Perform this protocol of the left then right hemisphere by orienting the coil laterally, as previously described[20].

5.10) Adaptively titrate the rTMS stimulus intensity upwards from an initial value of 20% maximum stimulator intensity, to allow the patient to habituate to the pain and scalp discomfort associated with rTMS during the initial sessions[23]. Increment the stimulation intensity by 2-5% on each train of stimulation, as tolerated.

5.10.1) To assess tolerability, have the patient rate pain on a verbal analogue scale (VAS) from 0 to 10 (0=no pain, 10=limit of tolerability without emotional distress) after each train of stimulation is delivered.

5.11) Begin with a higher stimulation intensity on each session, using a level associated with moderate tolerability (VAS 5-6) from the previous session, until the patient is starting at the target intensity of 120% of resting motor threshold on each hemisphere. Maintain a verbal analogue scale of less than 9 throughout treatments during this titration process. Titration is typically completed in 2-5 days.

5.12) Monitor the patient for other adverse effects during treatment.

Note: The most common treatment-interrupting adverse effect is a syncopal episode, arising during the first or second session of treatment in ~1% of patients. The patient may recount feeling dizzy, faint, or disoriented, and may transiently (~10 s) lose consciousness. Regular, repeated convulsive movements or post-episode confusion lasting more than a few seconds should be absent, however. In the event of a syncopal episode, lower the headrest on the chair if possible and encourage the patient to remain still until recovered. The session may proceed if the patient is recovered and willing to go on after a few minutes.

5.13) Monitor the patient for a generalized tonic-clonic seizure during treatment.

Note: These events are rare, and we have not observed a seizure in ~8000 sessions of dmPFC-rTMS across >200 individual patients to date. Regular, rhythmical, vigorous convulsive movements lasting 10-40 s, initially around 3 Hz and becoming progressively less rapid, accompanied by unresponsiveness, are suggestive of seizure rather than syncope. However, the two may be difficult to distinguish for an untrained observer.

5.13.1) Use video monitoring during all treatments so that the episode can be reviewed by a neurologist at subsequent assessment, if necessary. In the event of such an episode, apply standard seizure first aid steps, including clearing the area of objects with the potential to cause injury, placing the patient on the ground if possible or lowering the treatment chair to the horizontal position if not, laying the patient on the left side if possible, ensuring a clear airway, and ensuring that someone remains with the patient until the seizure terminates and the person regains full alertness.

5.13.2) Call emergency services if the seizure does not self-terminate after ~ 60 s.

6) Clinical Data Collection

6.1) Collect standardized self-reported questionnaires at baseline, weekly throughout treatment and at follow-up (e.g., 2, 4, 6, 12, and 26 weeks post-treatment). Collect the following self-report data: Beck Depression Inventory (BDI-II)[24], and Beck Anxiety Inventory[25] on a daily basis throughout treatment.

6.2) Collect depression severity scores via the clinician-rated 17-item Hamilton Rating Scale for Depression score[26] ($HamD_{17}$) at baseline, weekly during treatment, and at 2, 4, 6, 12 and 26 weeks post-treatment in follow-up.

REPRESENTATIVE RESULTS:

In previous work, $HamD_{17}$ was used as a measure of treatment response for 10 Hz dmPFC-rTMS. **Table 1** displays the pre- and post-treatment $HamD_{17}$ scores in a previously published case series[27]. Among all subjects, pre-treatment $HamD_{17}$ score was 21.6±6.9 that significantly decreased by 43±31% to 12.5±8.2 post-rTMS (t_{22}=6.54, $p<0.0001$)[27]. Using a remission criterion of $HamD_{17}\leq 7$, 8 of 23 subjects remitted following treatment. **Table 2** displays the pre- and post-treatment BDI-II scores in the same case series[27]. Pre-treatment BDI-II was 32.5±9.9 and significantly decreased by 34.2±31.7% to 22.0±12.8 post-rTMS (t_{22}=5.11, $p<0.001$). $HamD_{17}$ and BDI-II percent improvement was correlated to determine whether the same subjects responded on both measures (r=0.72, p=0.0001).

Adaptive titration was reported in a larger subset of 47 MDD patients undergoing 10 Hz dmPFC-rTMS[23]. In a case series that included this subset of patients, subjects achieved the target stimulus intensity in 0.9±1.8 sessions and were able to complete an entire rTMS session at the intended intensity at 4.5±3.7 sessions[23]. Adaptive titration was not correlated to treatment improvement.

A comparison of TBS to 10 Hz dmPFC stimulation was recently performed in a recent 185-subject chart review[18]. Outcomes did not differ significantly between groups. On the $HamD_{17}$, 10 Hz patients had a 50.6% response and 38.5% remission rate, while TBS patients achieved a 48.5% response and 27.9% remission rate. On the BDI-II, 10 Hz patients had a 40.6% response an 29.2% remission rate, while TBS patients achieved a 43.0% response and 31.0% remission rate[18].

Table 1: Individual subject $HamD_{17}$ improvement, using baseline and post-treatment $HamD_{17}$ scores.

Table 2: Individual subject BDI-II improvement, using baseline and post-treatment BDI-II scores.

DISCUSSION:

Here, MRI-guided dmPFC-rTMS was applied for treatment-resistant MDD. In general, rTMS at this site was well tolerated, with mild scalp discomfort and pain at the site of stimulation that was adequately managed using adaptive titration. In open-label trials and a chart review, both

10 Hz and theta burst stimulation resulted in significant improvements in depressive severity as measured by the $HamD_{17}$ and BDI-II.

There are two critical steps worth noting in the rTMS treatment procedure for optimal dmPFC stimulation. First, an angled, double-cone coil allows for optimal stimulation of deeper structures within the medial aspect of the prefrontal cortex[28]. Second, a treatment stimulation intensity of 120% resting motor threshold at this medial site is well-tolerated and without serious adverse events, despite the relatively high intensity of the applied stimulation in absolute terms when compared to the lower absolute intensities required for conventional DLPFC-rTMS. This same intensity also appears to be safe and tolerable for TBS protocols with dmPFC-rTMS, notwithstanding the significantly lower values of 80% active motor threshold more commonly used with TBS[18]. As previously mentioned, significant pain and discomfort is associated with anterior medial prefrontal stimulation at higher intensities[29]. Adaptive titration was quickly and successfully used to aide in rTMS-related discomfort adaptation. In sum, the use of an angled rTMS coil and relatively high stimulation intensity (with adaptive titration) may allow for deeper penetration of stimulation to the medial prefrontal and underlying cingulate cortices[28], without incurring higher risks of seizure of intolerable scalp pain.

Neuronavigation is often used for precise individualized anatomical landmarking for coil vertex placement. However, one problem with MRI-guided neuronavigation is that it potentially omits the functional relationships of the desired stimulation target to other brain regions in favor of anatomical specificity across subjects. Indeed, there is significant functional connectivity variability found in association cortices, including regions of prefrontal cortex, which may impede treatment efficacy[30]. For example, a recent study used resting-state functional connectivity to show that left DLPFC-rTMS treatment efficacy in MDD was dependent on left DLPFC connectivity to the subgenual cingulate cortex[31]. Patients that improved with left DLPFC-rTMS tended to have anticorrelated functional connectivity between the DLPFC and the subgenual cingulate cortex at baseline. Therefore, resting-state functional connectivity could be harnessed to further optimize target placement and identify potential biomarkers once the functional characteristics of response are identified[32].

One major limitation of rTMS as a treatment is that it is unclear how certain stimulation parameters influence its treatment efficacy. There is substantial variability in the parameters of conventional left DLPFC stimulation for MDD across studies, and there is also increasing evidence of substantial inter-individual variability in how some rTMS parameters affect cortical excitation and inhibition or treatment efficacy[33,34]. For example, the effects of 10 Hz stimulation on motor evoked potential (MEP) was recently shown to vary considerably across subjects, with some showing *decreases* rather than increases in MEP strength after stimulation[35]. Other rTMS treatment parameters that potentially require further optimization (or individualization) to maximize treatment efficacy include the number of pulses per session, the number of sessions per day, stimulation intensity and the duty cycle (how many seconds stimulation is on and off per cycle).

There are also general limitations to rTMS as a treatment. These include the logistical

requirements for patients to make multiple visits to hospital for treatment, limited access to treatment for patients in remote areas, the high cost of treatment (>$250 per session) with conventional parameters, and the low volumes of patients who can be treated per device using conventional parameters (1-2 per hour at most). Parameter optimization may help to address some of these problems in future. Other forms of non-invasive stimulation, such as transcranial direct current stimulation (tDCS), may also come to serve as a less expensive alternative to rTMS, suitable for use at home rather than in the clinic[36].

Despite its technical limitations, dmPFC-rTMS is clinically promising for treatment-resistant MDD. rTMS, and dmPFC-rTMS in particular, may also probe to be a promising option in other medication-resistant psychiatric illnesses including eating disorders[10], obsessive-compulsive disorder[37], and post-traumatic stress disorder[38]. Identifying good treatment candidates for these disorders may require additional tools other than traditional symptom-based diagnostic classification schemas – in particular, neuroimaging. Acquiring patient neuroimaging data before and after treatment allows for the identification of potential biological pre-treatment predictors and mechanisms of treatment response. Dorsomedial and subgenual cingulate resting-state functional connectivity have been identified as potential predictors to treatment response[27]. Additionally, graph theoretical measures such as betweenness centrality have been shown to differentiate dmPFC-rTMS responders and non-responders at baseline based on subscales for hedonic responses[23]. Neuroimaging also points to anterior mid-cingulate cortex and dorsomedial thalamic resting state functional connectivity change that correlates to treatment response[27]. In sum, functional neuroimaging may become a useful clinical tool as potential predictors and mechanisms of treatment response are identified.

Since current dmPFC-rTMS studies have used an open-label design, future directions should include the creation of a sham-controlled trial to assess its therapeutic efficacy in MDD versus sham and conventional stimulation. However, creating a convincing sham-control arm is technically challenging, particularly for simulating somatosensory or nociceptive sensations, as well as convincingly blinding the rTMS technician[39]. In a recent meta-analysis, over half of patients were able to correctly guess their treatment arm[39]. In another meta-analysis, placebo effects were large, but comparable to escitalopram trials[40]. Future studies involving a rTMS sham arm should consider a design that addresses all sensory aspects of rTMS for both the patient and the technician. Nonetheless, augmenting magnetic stimulation techniques through TBS[41], priming stimulation[42] or adjunctive cognitive behavioral therapy[43] or pharmacotherapy[44] may also help to optimize the therapeutic effects of rTMS. TBS in particular has the potential to achieve significant improvements in treatment duration and thus in patient volumes, access times, and treatment cost, while achieving equivalent outcomes to much longer conventional protocols[18,45].

In summary, rTMS of the dmPFC is a promising novel approach to therapeutic brain stimulation for treatment-resistant MDD. By incorporating the use of a MRI-guided neuronavigation system, a fluid-cooled, 120º angled stimulation coil, a high stimulation intensity and an adaptive titration schedule, dmPFC-rTMS can be safely and accurately delivered to deep targets in the medial prefrontal cortex. As these regions are central to the pathophysiology of many

neuropsychiatric disorders, this approach may have promising applications not only for MDD, but also for a variety of other psychiatric conditions that are resistant to standard treatments.

DISCLOSURES:

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Table 1

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Subject #	Pre-Treatment HAMD	Post-Treatment HAMD	% Improvement
11	21	1	95.24
6	18	2	88.89
4	28	4	85.71
2	12	2	83.33
9	22	4	81.82
25	19	4	78.95
12	20	5	75.00
10	20	5	75.00
14	14	4	71.43
16	26	10	61.54
7	19	8	57.89
24	17	9	47.06
3	19	11	42.11
8	21	14	33.33
5	36	24	33.33
17	23	16	30.43
15	37	27	27.03
23	12	9	25.00
19	28	21	25.00
13	29	22	24.14
1	12	10	16.67
21	13	12	7.69
18	23	22	4.35
22	21	22	-4.76
20	22	24	-9.09
Mean	21.28	11.68	46.28
Standard Dev.	6.68	8.24	31.81

Table 2

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Subject #	Pre-rTMS BDI	Post-rTMS BDI	% Improvement
11	26	3	88.46
6	21	4	80.95
4	45	9	80.00
2	17	4	76.47
16	36	13	63.89
5	35	17	51.43
3	30	15	50.00
12	26	14	46.15
14	22	12	45.45
1	33	19	42.42
10	34	20	41.18
23	32	19	40.63
9	22	15	31.82
15	57	40	29.82
19	38	28	26.32
7	25	22	12.00
18	45	41	8.89
20	45	43	4.44
17	25	24	4.00
13	44	44	0.00
22	36	37	-2.78
21	30	32	-6.67
8	24	31	-29.17
Mean	32.52	22.00	34.16
Standard Dev.	9.86	12.83	31.70
	TTEST	3.99713E-05	5.114221135

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Editor Comments

1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues. The JoVE editor will not copy-edit your manuscript and any errors in the submitted revision may be present in the published version.

We have proofread the manuscript.

2. Please revise the highlighting of the protocol for the filming. Currently you have just over 3 pages and there is a 2.75 page limit to ensure that the filming can occur in a single day.

We have altered the highlighting to the required 2.75 pages.

3. Step 1.3 can not be filmed, but is highlighted. We have made a note to the scriptwriters telling them to reference patient criteria based on the text protocol, but this is not something we can ask our scriptwriters to script and have any kind of accompanying visual.

We have un-highlighted this step.

4. Please describe how to "Perform motor thresholding separately for the left and right hemispheres." in step 4.8. Please be explicit.

By orienting the coil laterally, you can unilaterally inspect the motor threshold. We have edited this section for clarity.