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Prefrontal rTMS for treating depression: Location and intensity results from the OPT-TMS multi-site clinical trial

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ABSTRACT

Background: Motor cortex localization and motor threshold determination often guide Transcranial Magnetic Stimulation (TMS) placement and intensity settings for non-motor brain stimulation. However, anatomic variability results in variability of placement and effective intensity.
Objective: Post-study analysis of the OPT-TMS Study reviewed both the final positioning and the effective intensity of stimulation (accounting for relative prefrontal scalp-cortex distances).
Methods: We acquired MRI scans of 185 patients in a multi-site trial of left prefrontal TMS for depression. Scans had marked motor sites (localized with TMS) and marked prefrontal sites (5 cm anterior of motor cortex by the "5 cm rule"). Based on a visual determination made before the first treatment, TMS therapy occurred either at the 5 cm location or was adjusted 1 cm forward. Stimulation intensity was 120% of resting motor threshold.
Results: The "5 cm rule" would have placed stimulation in premotor cortex for 9% of patients, which was reduced to 4% with adjustments. We did not find a statistically significant effect of positioning on remission, but no patients with premotor stimulation achieved remission (0/7). Effective stimulation ranged from 93 to 156% of motor threshold, and no seizures were induced across this range. Patients experienced remission with effective stimulation intensity ranging from 93 to 146% of motor threshold, and we did not find a significant effect of effective intensity on remission.
Conclusions: Our data indicates that individualized positioning methods are useful to reduce variability in placement. Stimulation at 120% of motor threshold, unadjusted for scalp-cortex distances, appears safe for a broad range of patients.

Introduction

Daily repetitive Transcranial Magnetic Stimulation (rTMS) of left prefrontal cortex over 4–6 weeks is now an acute therapy option for treatment-resistant depression and is being evaluated for other purposes [1,2]. The neurobiological and antidepressant effects of TMS likely depend on a variety of factors, including coil positioning [3,4], intensity of stimulation (magnitude of the magnetic field) [5], pulse duration [6], and frequency [7,8], as well as characteristics of the brain during stimulation [9–11]. In a recent multi-site sham-controlled double-blind randomized trial of TMS to treat major depressive disorder (NIH-sponsored OPT-TMS Study), we used structural MRI brain scans to review and potentially adjust coil positioning before starting treatment [12,13]. Following the primary report of the TMS trial in patients with major depressive disorder [13], this article describes the positioning adjustments

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made during the trial and retrospectively assesses positioning and scalp-to-cortex distance of stimulation (to estimate effective intensity).

As daily left prefrontal rTMS is being used clinically to treat depression, it is important to review methods for selecting the prefrontal stimulation site. The earliest studies used a "5 cm rule" for positioning TMS over prefrontal cortex for treatment of depression [14–16]. The motor cortex is functionally localized as a scalp position where TMS evokes a motor movement (and a measureable motor-evoked potential) in the contralateral hand, and the prefrontal cortex stimulation site is determined as 5 cm anterior to motor cortex in a parasagittal line. Given variability in both localizing motor cortex and in head (skull and brain) size, there are obvious limitations to this rigid approach that does not adjust for such individual variability. One study estimated that the "5 cm rule" would localize 7 of 22 (32%) patients to premotor cortex, with variable positioning for the remaining patients covering regions of premotor cortex, the frontal eye fields, and dorsolateral prefrontal cortex [17]. In this multi-site trial, we used an adjustable "5 cm" or "5 cm + 1 cm" (essentially a "6 cm rule") with the aim to increase the number of patients receiving stimulation actually in the prefrontal cortex. A primary objective of this report is to describe the positioning using this adjustable approach and also to assess whether the positioning impacted on clinical response.

Stimulation intensity of the TMS device is also a critical factor in the magnitude of brain and behavioral effects generated [5]. Stimulation of motor cortex generates an effect that is immediate and easy to observe or measure (muscle movement or motor-evoked potential) while stimulation of other brain regions, such as the prefrontal cortex, does not. Resting motor threshold is a typical measure used to set the TMS device intensity of stimulation for an individual and is defined by the minimal amount of machine power needed to generate a motor-evoked potential in a relaxed muscle of that person [18,19]. Motor threshold is an indication of the pulse intensity needed to induce an electrical current in motor cortex of sufficient magnitude to elicit a movement in the target muscle, and is used to estimate the intensity needed to stimulate other brain regions. Motor threshold is also an important component of safe TMS administration, as it is the benchmark used to limit stimulation below intensities that may lead to a seizure [19]. A variety of factors influence motor threshold, with scalp-to-cortex distance being an anatomic determinant accounting for about 50% of the between-individual variance [20,21]. As magnetic field strength decreases exponentially with increased distance away from the coil, underdosing could occur if the prefrontal scalp-to-cortex distance is significantly greater than the motor scalp-to-cortex distance [22]. Another objective of this report is to characterize scalp-to-cortex distances at the motor and the prefrontal positions in a large patient population. We also estimate the range of effective stimulation intensity based on motor and prefrontal distances and test whether anatomical location or effective intensity were related to remission of depression in the clinical trial. Optimizing factors of TMS treatment, such as positioning and intensity, may lead to better treatment outcomes [4,22].

Methods and materials

Participants

Data for this report come from a multi-site sham-controlled randomized trial of TMS as a therapy for major depression, and a previous report provides details of recruitment, enrollment, demographics, and clinical outcome [13]. Briefly, 190 antidepressant medication-free patients with unipolar nonpsychotic major depressive disorder were in the intent-to-treat sample (sample of all randomized patients who started at least 1 treatment). Of this sample, 185 participants had archived MRI scans with positioning markers. These patients had a mean age of 46.9 years (range 22–69 years; SD = 11.4 years), and 77 patients (42%) were male. Four sites (Medical University of South Carolina, Columbia University/New York State Psychiatric Institute, University of Washington, and Emory University) conducted the study and obtained MRI scans. The institutional review board at each center approved the protocol, and all the participants provided written informed consent. Handedness was assessed with the Annett Handedness Scale [23]. Remission of depressive symptoms was defined in the clinical trial as two consecutive scores less than 10 during the first sham-controlled phase or as a score of 3 or less during any phase, using the 24-item Hamilton Scale for Depression [13,24,25]. Following TMS treatment sessions, patients rated the scalp pain of TMS at the beginning, middle, and end of the session on a Visual Analog Scale (converted to a mean session pain score on a 0–100 scale).

Motor threshold determination and TMS localization of motor and prefrontal "5 cm" sites

After providing informed consent and completing initial screening, each patient completed a TMS laboratory session and a neuroimaging session prior to the first rTMS treatment session. In the laboratory session, TMS administrators functionally localized the left and right scalp positions that maximally induced a motor-evoked potential of the contralateral thumb (abductor pollicus brevis). Resting motor threshold was determined at these positions using electromyography (3 clinical sites) or visual monitoring (Emory University) to identify motor-evoked potentials. At these positions, the center of the TMS coil (Neuronetics, Malvern, Pennsylvania) marked the "left hemisphere motor cortex" and "right hemisphere motor cortex". The "5 cm rule" marked the prefrontal position, in a sagittal plane 5 cm anterior of each motor site, measured on the scalp. TMS administrators marked these four positions ("left motor cortex", "left 5 cm prefrontal cortex", "right motor cortex", and "right 5 cm prefrontal cortex") by taping small fiducials (vitamin E capsules) on a swim cap for MRI scanning. Each clinical site acquired a T1-weighted MRI scan of the head with the fiducials visible, matching the study guidelines as close as technically possible ($256 \times 256 \times 180$ dimensions; $1 \times 1 \times 1$ mm^3 resolution). A fifth fiducial by the left ear helped confirm orientation of scans from the various sites. Sites sent MRI scans to a central server for review prior to the first TMS treatment. The reason for determining right hemisphere motor location and motor threshold is that some patients, if they were non-remitters in the early phases of the trial, were candidates for a trial of right prefrontal TMS [26].

Within-study visual inspection method and "5 cm + 1 cm" prefrontal adjustment procedure

The Visual Inspection Method (VIM) was a simple, real-time method for assessing whether the "5 cm rule" actually positioned TMS over prefrontal cortex (and not premotor cortex) [12]. With transverse MRI slices oriented parallel to the plane intersecting the anterior and posterior commissures, a landmark coronal plane is positioned at the anterior tip of the temporal lobe. The VIM rater judged the "5 cm" site to be "premotor" if the fiducial was posterior to the landmark coronal plane or to be "prefrontal" if the fiducial was anterior to the landmark coronal plane. TMS treatment occurred at the "5 cm" site if VIM indicated "prefrontal" (determination of "No Adjustment") or at "5 cm + 1 cm" site if VIM indicated "premotor" (determination of "Move Forward"). Borderline calls (such as landmark plane through fiducial) always defaulted to the

1 cm move forward ("5 cm + 1 cm" site). A single rater (KAJ) evaluated all scans in this study prior to treatment. Actual real-time assessments were not logged for 35 patients, so the same rater re-did these evaluations after total study completion, blind to randomization and outcomes.

Post-study semi-automated method for positioning and distance determinations

The semi-automated method was a different post-study procedure to more precisely examine the TMS positioning. This method used various image processing tools from FSL 4.1.6 (FMRIB, Oxford, UK) and "New Segment" tissue classification with SPM8 (FIL, London, UK). First, each of the four fiducials was manually marked in the FSL image viewer. Second, the closest scalp point to each fiducial was determined. This was found as the maximum intensity from the intersection of the smoothed fiducial mark (creates spheres with decreasing intensity as radii increase) and of the scalp surface (using FSLUTILS tools and FSL BET brain extraction tool). Each scalp point was visually checked and corrected as needed (a common error was in determination of the scalp surface, due to fiducials on or near the scalp). Third, the closest cortical surface to the scalp mark was determined. This was found as the maximum intensity from the intersection of the smoothed scalp mark (using FSLUTILS tools) and the brain surface (using SPM "New Segment"). Each cortical point was visually checked and corrected as needed (common errors were dura mater or fiducials being identified as brain tissue). Fourth, the "5 cm + 1 cm" positions were estimated. A 1 cm sphere was created from the 5 cm scalp point, intersected with the scalp surface, and the most anterior point defined as the "5 cm + 1 cm" position (using FSLUTILS tools). The "5 cm + 1 cm" cortical position was found from the scalp position as described above. Fifth, scans were spatially normalized into MNI template space [27,28]. A study template was created from all scans in the study and morphed to MNI template space (using FSLUTILS tools and FSL FLIRT 12 parameter affine registration). Then individual scans were morphed into atlas space (FSL FLIRT 12 parameter affine registration) and the individual spatial transform was applied to cortical points. Finally, using the Brodmann template from MRIcron software [29], cortical points in template space were converted to Brodmann values. Scalp-to-cortex distance measurements were performed from coordinates in native space.

Results

Localization of motor cortex

We present the localization of motor cortex visually, in terms of MNI coordinates, and by Brodmann areas. The distribution of motor cortex localization is shown in Fig. 1. The mean MNI coordinates for localizing motor cortex are shown in Table 1. The mean right hemisphere motor location was 5 mm posterior to the left hemisphere motor location, and this asymmetry in the *y*-axis was statistically significant [paired-$t(182) = 5.22$, $P < .001$]. Brodmann areas (BA) of localized motor cortex are listed in Table 2. The top three BA areas were BA 6 (premotor cortex), followed by BA 4 (primary motor cortex), and then BA 3 (primary somatosensory area).

We assessed whether the localization of motor cortex or the magnitude of motor threshold differed by handedness. Of the 185 study participants, 162 were right-handed, 14 were left-handed, 7 were mixed-handed, and 2 had unavailable handedness data. Comparing right-handed and left-handed individuals, we failed to find significant differences of MNI motor coordinates or motor thresholds (independent samples *t*-tests, $P > .05$).

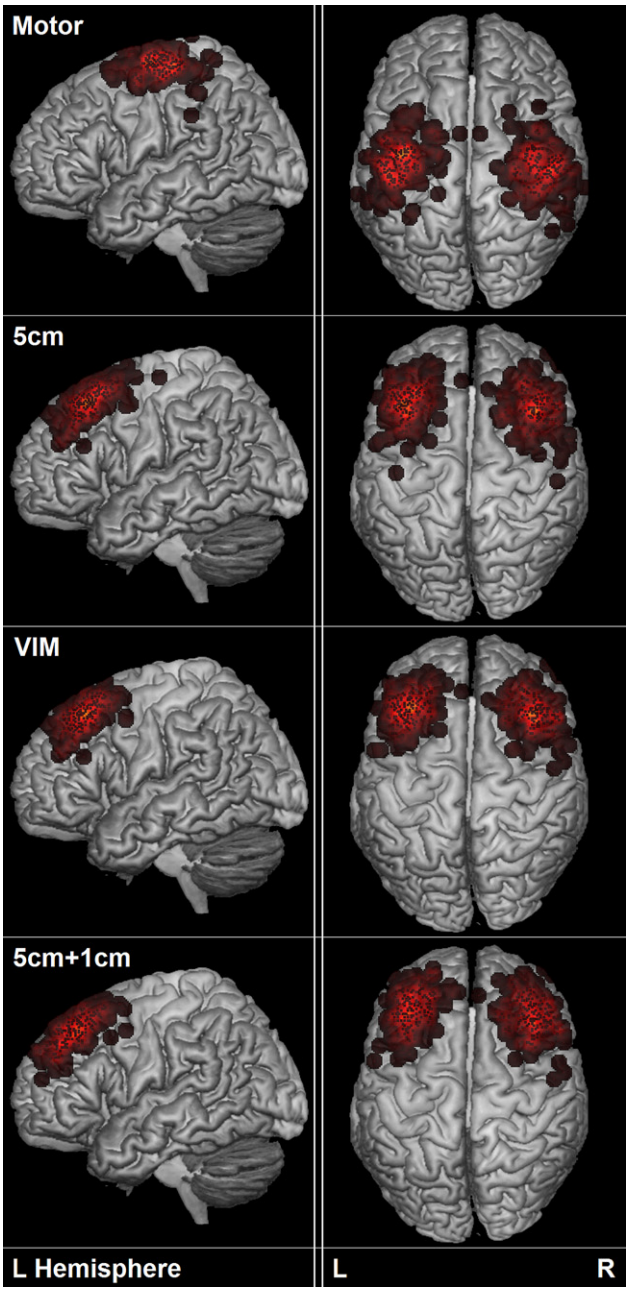

Figure 1. Brain images of motor and prefrontal localization (by the 5 cm, VIM, and 5 cm + 1 cm methods). Points of motor and prefrontal localization (by the 5 cm, VIM, and 5 cm + 1 cm methods) in MNI space are overlaid on a template brain. Points are smoothed to portray relative density of localization (dark red = few scans, bright red = many scans).

We also assessed if there was a relationship between the localization of motor cortex and the magnitude of motor threshold, as we would expect motor threshold to increase as distance increased from the optimal location in motor cortex. No significant correlations were found between left hemisphere motor thresholds and the left hemisphere motor *x*, *y*, and *z* MNI coordinates (Pearson's correlations, $P > .05$). Significant correlations were found between right hemisphere motor thresholds and the right hemisphere motor *x* MNI coordinates (left to right axis) [$r(175) = .19$, $P < .05$] and the right hemisphere motor *z* MNI coordinates (inferior to superior axis) [$r(175) = -.21$, $P < .01$]. Right hemisphere motor thresholds tended to increase as right hemisphere MNI coordinates

Table 1
MNI coordinates of motor and prefrontal localization (by the 5 cm, VIM, and 5 cm + 1 cm methods).

	Left hemisphere			Right hemisphere			Left vs. Right		
	x	y	z	x	y	z	x	y	z
Motor									
Mean	−42	−16	65	41	−21	65	ns	***	ns
SD	10	12	6	10	12	7			
5 cm rule									
Mean	−38	25	49	37	22	51	ns	***	ns
SD	8	10	9	9	12	10			
VIM									
Mean	−37	28	48	37	26	49	ns	***	ns
SD	9	9	8	9	10	10			
5 cm + 1 cm									
Mean	−35	34	45	36	30	46	ns	***	ns
SD	8	10	9	9	11	11			

$P > .05$ (ns or not significant), $P < .001$ (***).

were more lateral and inferior. No significant correlation was found between right hemisphere motor thresholds and the right hemisphere motor *y* MNI coordinates (posterior to anterior axis) (Pearson's correlation, $P > .05$).

Localization of prefrontal cortex

We present the localization of prefrontal cortex (using the "5 cm rule", the VIM adjusted method, and by a "5 cm + 1 cm" method) visually, in terms of MNI coordinates, and by Brodmann areas. The distributions of prefrontal cortex determined by the "5 cm rule", by the VIM adjustments as done in this study, and by the "5 cm + 1 cm" method are also shown in Fig. 1. The mean MNI coordinates for localizing prefrontal cortex by the "5 cm rule", by the VIM adjustments as done in this study, and by the "5 cm + 1 cm" method are listed in Table 1. The mean right hemisphere prefrontal locations are posterior to the left hemisphere locations by paired *t*-tests of *y*-axis MNI coordinates [$t_{5\ cm}(181) = 4.18$; $t_{VIM}(181) = 3.63$; $t_{5\ cm+1}(181) = 5.13$; all *P's* $< .001$]. Brodmann areas (BA) for localizing prefrontal cortex by the "5 cm rule", by the VIM adjustments as done in this study, and by the "5 cm + 1 cm" method are shown in Table 2. All methods place stimulation in BA 9 (dorsolateral prefrontal cortex) for the majority of patients. Other common areas were BA 8 (contains frontal eye fields), BA 44 (orbital inferior frontal cortex), and BA 45 (inferior frontal cortex). Localization to the BA 6 (premotor cortex) decreased progressively with the VIM and "5 cm + 1 cm" methods, while localization to BA 46 (dorsolateral prefrontal cortex) increased particularly with the "5 cm + 1 cm" method.

Table 2
Brodmann areas of motor and prefrontal localization (by the 5 cm, VIM, and 5 cm + 1 cm methods).

	BA	Left hemisphere		Right hemisphere	
		Count	%	Count	%
Motor					
	6	87	47.0	65	35.5
	4	49	26.5	57	31.1
	3	31	16.8	38	20.8
	40	5	2.7	9	4.9
	1	4	2.2	9	4.9
	8	4	2.2	0	0.0
	2	3	1.6	3	1.6
	7	1	0.5	1	0.5
	9	1	0.5	1	0.5
5 cm					
	9	105	56.8	97	53.3
	8	34	18.4	35	19.2
	6	16	8.6	25	13.7
	45	14	7.6	7	3.8
	44	10	5.4	11	6.0
	46	5	2.7	6	3.3
	4	1	0.5	0	0.0
	3	0	0.0	1	0.5
VIM					
	9	113	61.1	112	61.5
	8	36	19.5	33	18.1
	45	14	7.6	6	3.3
	44	9	4.9	14	7.7
	6	7	3.8	9	4.9
	46	6	3.2	8	4.4
5 cm + 1					
	9	114	61.6	102	56.0
	46	30	16.2	21	11.5
	8	24	13.0	31	17.0
	45	8	4.3	12	6.6
	44	4	2.2	11	6.0
	6	3	1.6	5	2.7
	32	2	1.1	0	0.0

We compared the motor-to-prefrontal distance in our population sample to a common brain template, to characterize how structural dimensions may account for variability in prefrontal localization. The native space distance from left motor site to left prefrontal site (by the "5 cm rule") was compared to the MNI space distance (to determine if a patient's motor-to-5 cm distance was increased or decreased by spatial normalization to the MNI template). The mean distance decreased by 6.5% (range of 26.6% decrease to 15.8% increase, SD = 8.9) from native space to MNI space, indicating that patients in the study had, on average, larger motor to prefrontal distances than the MNI template.

We further assessed the impact of relative motor-to-prefrontal distance, and we examined how the localization of the motor site impacted the localization of prefrontal cortex. We created three categories of scans based on whether left dorsolateral prefrontal cortex (BA 9 and 46) was reached by the "5 cm rule", or subsequently by the "5 cm + 1 cm" position, or not reached by the "5 cm + 1 cm" position. In assessing the impact of relative head size on localizing dorsolateral prefrontal cortex, we failed to find a significant effect for the motor-to-5 cm distance change from native space to MNI space between the three categories [$F(2, 182) = .75$, $P > .05$]. In assessing the impact of relative motor position on localizing dorsolateral prefrontal cortex, a significant effect was found for the *y*-axis position (posterior to anterior) between the three categories [$F(2, 182) = 5.40$, $P < .01$]. Scans that reached left dorsolateral prefrontal cortex by the "5 cm rule" had a motor site on average 1.8 mm (SD 10.7) anterior to the mean motor location, while scans that failed to reach left dorsolateral prefrontal cortex with the "5 cm + 1 cm" adjustment had a motor site on average 5.5 mm (SD 11.7) posterior to the mean motor location. This post-hoc comparison was statistically significant [$t(140) = 3.31$, $P < .001$].

We also examined the relationship of prefrontal localization to self-report ratings of scalp pain during the rTMS procedure. A subset of patients rated the pain experienced with real TMS in Phase 1 during prefrontal stimulation. Of these 55 patients, the average pain experienced with the first TMS session was significantly correlated with positioning in the *x*-axis of MNI coordinates (pain ratings tended to increase as the coil position moved toward the left side away from the midline) [$r(53) = -.31$, $P < .05$]. Pain was not correlated with positioning in the *y*-axis (posterior to anterior axis) or *z*-axis (inferior to superior axis) (Pearson's correlations, $P > .05$). Pain was significantly related to motor threshold, with increased pain ratings correlated to increased stimulation intensity [$r(53) = .54$, $P < .01$].

Visual inspection method

We characterized the VIM used during the clinical trial for prefrontal localization, including post-study comparisons to the MNI and Brodmann area brain atlases. Using the VIM, 63 of 185 (34%) left hemisphere determinations and 85 of 182 (47%) right hemisphere determinations resulted in the instruction to move the stimulation site 1 cm forward from the location set by the "5 cm rule". The distributions of "5 cm" prefrontal sites are separated according to VIM determinations of "No Adjustment" (stimulation performed at "5 cm rule" site) and of "Move Forward" (stimulation performed at "5 cm + 1 cm" site) in Fig. 2. Distributions are shown for only the MNI *y*-axis in Fig. 2, as this was the dimension used to make VIM determinations (based on relative position to the anterior tip of the temporal lobe). The BA distributions at the marked 5 cm prefrontal sites for VIM determinations of "No Adjustment" and for VIM determinations of "Move Forward" are listed in Table 3. Considering marked 5 cm sites in left premotor cortex (BA 6), 12 of 16 (75%) determinations were to move stimulation forward. Considering marked 5 cm sites in left dorsolateral prefrontal cortex (BA 9), 69 of 105 (66%) determinations were "No Adjustment".

Scalp-to-cortex distance and effective stimulation intensity

We compared the scalp-to-cortex distances at the motor and prefrontal treatment sites (VIM positions), and we also related motor scalp-to-cortex distances with motor threshold and age. The scalp-to-cortex distances for motor positions and VIM-determined prefrontal positions are shown in Table 4. We failed to find a significant difference between the distances at motor sites and at the VIM-determined sites (paired sample *t*-tests, $P > .05$) for either right or left hemispheres. The right motor distance was significantly greater than the left motor distance [$t(182) = 2.70$, $P < .01$]. We failed to find a significant difference between right and left motor thresholds (paired sample *t*-test, $P > .05$). The left motor scalp-to-cortex distance was correlated with left motor threshold (motor threshold increased as distance increased) [$r(182) = .24$, $P < .01$], and was correlated with age (distance increased as age increased) [$r(183) = .15$, $P < .05$]. The right motor scalp-to-cortex distance was not significantly correlated with right motor threshold, and also was not correlated with age (Pearson's correlations, $P > .05$).

Prefrontal stimulation intensity for treatment was set to be 120% of motor threshold unadjusted for scalp-to-cortex distances, so we then calculated stimulation intensities adjusted for scalp-to-cortex distances. Considering the exponential decay in magnetic field strength decay with increasing distance, we calculated the effective intensity of prefrontal stimulation by adjusting for relative differences of motor and frontal scalp-cortex distances: Effective Stimulation (% of motor threshold) = 120% Motor Threshold X Adjustment Factor, where the Adjustment Factor = $e^{0.036(\text{Motor Distance in mm})}/e^{0.036(\text{Prefrontal Distance in mm})}$ [22,30]. Without adjusting for prefrontal distance changes, all patients in the study had prefrontal stimulation set at 120% of motor threshold (so effective stimulation would be 120% of motor threshold if motor and frontal scalp-cortex distances were equal). The left hemisphere effective stimulation calculations ranged from 93.0% to 156.0% of motor threshold, with a mean of 120.7% (Table 4).

Positioning and intensity relationships to remission

We examined whether positioning, both in terms of MNI coordinates and by BA regions, differed between patients with and without treatment remission. In the first sham-controlled phase of this study, 12 of 88 (14%) patients who received real TMS met remission criteria. Through the open-label follow-up, 58 of 185 (31%) patients met remission criteria. Considering MNI coordinates (independent assessments of *x*, *y*, and *z* coordinates), we failed to find any significant differences between remitters and non-remitters in either the first or through the follow-up phase (independent samples *t*-tests, $P > .05$). Considering all the Brodmann areas stimulated (BA 6, 8, 9, 44, 45, and 46), BA 6 (premotor cortex) was the only stimulated area that did not result in any patients achieving remission (Table 5 and Fig. 3). For those few patients with stimulation in BA 6, the remission rate in BA 6 (0/7) was nearly statistically significantly less than the remission rate for the other frontal regions (58/178) (Fisher's Exact Test, 1-sided $P = .068$).

We examined whether absolute TMS intensity (machine setting at 120% of motor threshold) or effective TMS intensity (% motor threshold after scalp-cortex distance adjustment) differed between patients with and without remission. We failed to find any significant difference in left motor threshold (absolute TMS intensity) between remitters and non-remitters in the first sham-controlled phase or through the follow-up phase (independent samples *t*-tests, $P > .05$). Considering the effective stimulation (% of motor threshold) reaching prefrontal cortex adjusting for distance, we still failed to find any significant difference between remitters and non-remitters in either phase (independent samples *t*-tests, $P > .05$). The majority of remitters in the open-label follow-up had stimulation in

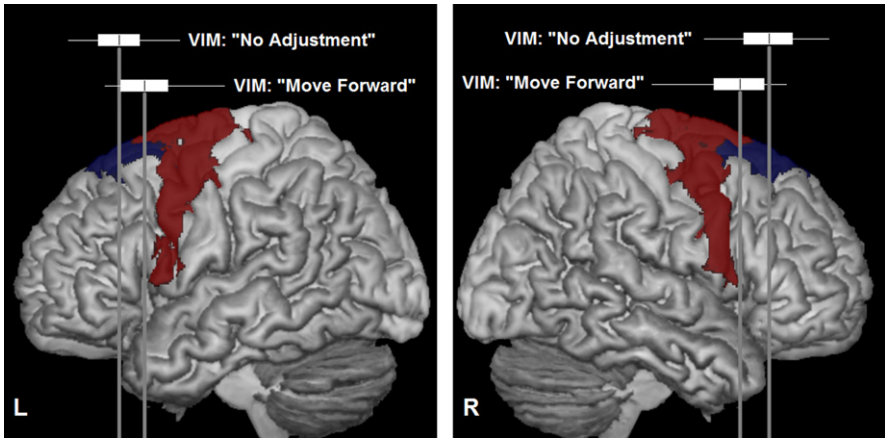

Figure 2. MNI distribution of VIM determinations of "No Adjustment" or "Move Forward". For the marked 5 cm prefrontal sites, distributions in the MNI *y*-axis are shown for either VIM determinations of "No Adjustment" or "Move Forward". Distributions indicate mean (vertical gray lines), standard deviation (white rectangles), and range (thin white horizontal line). Brodmann area 6 (red) and 8 (blue) are displayed on the template brain for reference.

Table 3
Brodmann distributions at the marked 5 cm prefrontal sites for VIM determinations of "No Adjustment" and for VIM determinations of "Move Forward".

	Left-hemisphere count	Right-hemisphere count
VIM: "No Adjustment"		
BA 3	0	0
BA 4	0	0
BA 6	4	4
BA 8	23	8
BA 9	69	62
BA 44	8	11
BA 45	14	6
BA 46	4	6
VIM: "Move Forward"		
BA 3	0	1
BA 4	1	0
BA 6	12	21
BA 8	11	27
BA 9	36	35
BA 44	2	0
BA 45	0	1
BA 46	1	0

either BA 8 ($n = 10$) or BA 9 ($n = 39$); however, we failed to find a significant difference in either left motor threshold or effective stimulation of prefrontal cortex (Fig. 3) between remitters and non-remitters in independent analysis of these two regions (independent samples t-tests, $P > .05$).

We failed to find significant differences in treatment efficacy considering the full range of effective stimulation intensity, but we did note a possible effect at the outlying ends of the distribution (see Fig. 3). Only three patients were estimated to actually receive less than 100% of motor threshold intensity adjusted for scalp-cortex distances, receiving 93.0%, 98.7%, and 99.6% of motor threshold. Interestingly, all three of these potentially under-dosed patients were remitters to TMS treatment. Furthermore, the lowest 10-percentile of effective stimulation (109% or less of motor threshold) had a remission rate of 9 of 19 (47.4%), and the highest 10-percentile of effective stimulation (135% or greater of motor threshold) had a remission rate of 5 of 19 (26.3%). However, we failed to find that these remission rates at the outlying ends of effective stimulation were significantly different [$X^2(1, N = 38) = 1.81, P = .179$].

Table 4
Scalp-to-cortex distances for motor and prefrontal sites, motor thresholds, and effective stimulation.

	Left hemisphere	Right hemisphere	Left vs. Right
Motor distance (mm)			
Mean	16.1	16.6	**
SD	2.7	2.6	
Range	9.9–22.9	10.0–27.3	
VIM PFC distance (mm)			
Mean	16.1	16.3	ns
SD	2.4	2.3	
Range	11.0–22.6	10.5–23.2	
Motor threshold (Machine Intensity)			
Mean	57.9	57.0	ns
SD	10.7	12.6	
Range	26–95	36–95	
Effective Stimulation (% of Motor Threshold)			
Mean	120.7	121.7	ns
SD	10.3	10.1	
Range	93.0–156.0	101.3–153.1	

$P > .05$ (ns or not significant), $P < .01$ (**).

Table 5
Remission by Brodmann areas.

Brain Region	Remission *(Number of Patients)*	Number of Patients *(Total in Region)*	Remission Rate *(% of Patients in Region)*
BA 6	0	7	0.0
BA 8	10	36	27.8
BA 9	39	113	34.5
BA 44	2	9	22.2
BA 45	5	14	35.7
BA 46	2	6	33.3
All Regions	58	185	31.4

Discussion

Positioning and stimulation intensity must have roles in whether a patient will respond to TMS therapy. As part of a multi-site trial of TMS for depression, we used structural MRI to adjust positioning. Here we report on prefrontal localization resulting from the adjustable approach used in the actual trial, as well as potential localization using the standard "5 cm rule" or a "6 cm rule". All patients had TMS intensity set at 120% of their resting motor threshold, and we additionally reviewed the effective intensity reaching prefrontal cortex. Within the optimized parameters of this trial, positioning and stimulation intensity do not appear to have significantly impacted on treatment remission, however potentially important information regarding location and intensity did emerge from the data. First, basing prefrontal cortex location on motor cortex location creates a wide range of potential targets across a population, with the risk that some patients will still be stimulated in premotor areas. Of note, none of the 7 patients treated over premotor cortex remitted. Second, the rule of dosing TMS based on MT threshold (120%) appears adequate to affect prefrontal cortex for this adult treatment-resistant population. Almost all patients had effective prefrontal stimulation greater than 100% of MT threshold, and the three below 100% of MT remitted.

Potential limitations of methods

This was the largest structural imaging study in the context of a TMS depression treatment. However, there were many potential sources of error and limitations with this study. Procedural error can occur in localizing motor cortex, marking a prefrontal site 5 cm anterior to motor cortex (especially given non-uniform curvature of the head), and in placement of fiducial markers for scanning (given the potential for the swim cap to be misplaced). Analytic errors could occur in manually marking fiducials, and we assumed that the closest cortical location is most critical (while angle of stimulation and stimulation of surrounding areas are likely also important). We found that fully automated analysis of this data is challenging, given that fiducials and image quality can impact tissue surface classification and normalization (similar future studies may want to acquire images with and without fiducials). Other methodological limitations occur with spatial normalization to template space. We found that slight discrepancies can lead to different Brodmann area determinations particularly around atlas edges, suggesting that continuous, probabilistic atlases may be more appropriate for group comparisons of neuroanatomical data. Despite such challenges, the rather large sample size of this study (185 patients) is a particular strength and helps to mitigate potential procedural and analysis errors.

Motor positioning

The mean MNI coordinates for motor cortex seem reasonable and consistent with other reports of localization on the "hand

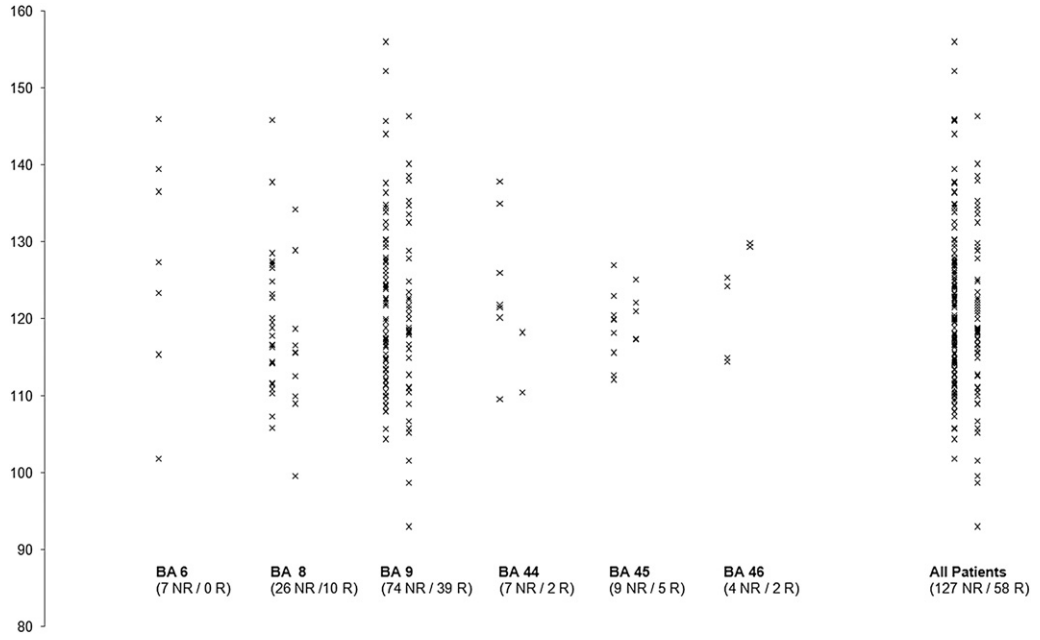

Figure 3. Effective stimulation by remission status for each Brodmann area. The *y*-axis is effective stimulation in terms of motor threshold (adjusted for scalp-cortex distance) in each Brodmann area (BA 6, 8, 9, 44, 45, 46, and all areas combined), separated into two columns for patients not achieving remission (NR) and patients achieving remission (R). The effective stimulation is displayed as an "x" and appears bolded or blurred for patients with equal or overlapping effective stimulation in a column. No patients achieved remission in BA 6, so only one column is seen for BA 6. No statistical significant differences of TMS intensity were found between patients not achieving remission and patients achieving remission (independent sample *t*-tests of BA8, BA 9, and also of all patients combined, $P > .05$).

knob" [31–33]. Some variability in localization around primary motor cortex (BA 4) may be explained by the relatively small size of this region and by imprecision in TMS localization and in spatial normalization to template space. Motor-evoked potentials from locations more anterior in premotor cortex and posterior even into parietal cortex are not explained by increased motor thresholds (no evidence that more power was used to reach a more distance motor site), raising the possibility that motor-evoked potentials can be generated through stimulation of non-primary motor cortex through mechanisms that are not entirely clear [34,35].

Hemisphere asymmetry in positioning was identified, perhaps reflecting structural asymmetry [36]. Some prior reports indicate functional asymmetry in motor localization and motor thresholds [37–39], while others do not [40]. We failed to find evidence of a functional explanation for this asymmetry, considering handedness and motor thresholds. There is some evidence in our data that right motor localization may be errant in the coronal plane for some patients, given the correlation between right motor threshold and positioning (*x* and *z* MNI coordinates), and the lack of correlation between right motor threshold and scalp-to-cortex distance. This may result from operator bias in localizing left motor cortex first, with assumptions that positioning should be symmetrical.

Prefrontal positioning

Our data indicate that the "5 cm rule" for localizing prefrontal cortex (BA 9) may not be as poor as previously reported, but is still less than optimal. Motor localization, hemispheric asymmetry, and head size contributed to variability in localizing prefrontal cortex using the "5 cm rule". For our patient population, we estimate that the "5 cm rule" would place stimulation in left premotor cortex (BA 6) for 9% of patients and would fail to reach left prefrontal cortex in 27% of patients (based on the number of BA 6 and 8 localizations by the "5 cm rule"). This compares to a previous report where 7 or 22 (32%) were clearly in BA 6 and 15 of 22 (68%) of patients are estimated to receive BA 6 or 8 stimulation using the "5 cm rule" [17]. Both brain size and motor localization may contribute to differences in targeting using the "5 cm rule". Our sample brain size was on average larger than the MNI template (6.5%), and our data indicates that variability in localizing motor cortex in this study may have an even greater impact on the "5 cm rule". Noting the hemispheric asymmetry, the "5 cm rule" may have a higher error rate for localizing right prefrontal cortex relative to left prefrontal cortex.

The VIM was intended to be a quick in-study method for ensuring that prefrontal stimulation was adequately anterior, given concerns regarding the "5 cm rule". While our adjustable VIM helped focused prefrontal localization, it was constrained by dimensionality (only adjustments in the *y*-axis), directionality (only anterior adjustments), and magnitude (only could move forward 1 cm forward, when more may be needed). The VIM performed fairly well in determining "Move Forward" for BA 6 premotor sites (75%), but also determined "Moved Forward" for some BA 9 dorsolateral prefrontal sites (34%). Overlap in the distributions of VIM determinations likely reflects variability in the morphometry of temporal lobe and prefrontal cortex, and coil position along the inferior–superior axis can impact the actual BA site of stimulation (see Fig. 2). Given limitations of the VIM, there are a variety of other individually adjusted positioning approaches that one could consider, from simple skull measurements to advanced image-guided methods [41–48].

Individually adjusted prefrontal positioning can help focus targeting of stimulation. All positioning methods ("5 cm rule", VIM, and "5 cm + 1 cm" method) of this study place stimulation in BA 9 for the majority of patients (57–62%), but result in variable distributions. The adjustable VIM reduces variability in the *y*-axis (posterior to anterior axis) by moving many forward. A "6 cm rule" would have variability similar to the "5 cm rule", but would shift the range forward. Compared to the "5 cm rule", a "6 cm rule" would reduce premotor stimulation in BA 6 (from 9% to 2% for BA 6), and it would increase the amount of anterior stimulation, especially in BA 46 (from 3% to 16%).

The tolerability of TMS is an important practical consideration for prefrontal positioning, as well as for setting stimulation intensity

[49–51]. Data from this trial on this topic is presented in separate publications [13,49]. Experientially, we find that patients report TMS to be more painful as the coil is positioned more anterior (a potential concern for a "6 cm rule"); however, we failed to find a relationship between pain and the *y*-axis in this study. This may be due to the reduced variability of positioning in the *y*-axis with VIM adjustments. Our data does show more pain more lateral versus medial stimulation, suggesting medial stimulation may be more tolerable.

Effective stimulation intensity based on scalp-to-cortex distance

We used the relative motor and prefrontal scalp-to-cortex distances to estimate the effective amount of stimulation reaching prefrontal cortex (as a percent of motor threshold). With the intensity of TMS stimulation often based on motor threshold [18,19], differences in scalp-to-cortex distance certainly raises concern regarding the effective amount of stimulation received at other brain regions [22]. While we found that the motor and prefrontal scalp-to-cortex distances were on average equal, we did find considerable individual variability. Only 3 patients were estimated to receive less than 100% of resting motor threshold, while 29 patients were estimated to receive over 130% of resting motor threshold. This range of effective stimulation may have implications for both the safety and efficacy of TMS administration.

The safety of rTMS above 130% of motor threshold has not been evaluated [19], and we failed to induce seizure or to identify other safety concerns using 120% of motor threshold, unadjusted for distance [13]. Our data raises the possibility that TMS, appropriately adjusted for distance, may be safely administered above 130% of motor threshold. However, future research should employ caution extrapolating from this finding. We did not test safety of unadjusted stimulation above 130% of motor threshold, which could generate even higher levels of effective stimulation if not properly adjusted for distance. Stimulation above unadjusted 130% of motor threshold could also have other effects that we did not assess (including effects on non-cortical tissue). We also note that the scalp discomfort of TMS increases with greater stimulation and that increased levels of effective stimulation did not produce greater levels of efficacy (discussed below).

Treatment outcome

Within this optimization study, positioning adjustments limit the scope of inferences we can make regarding positioning and treatment outcome. The "5 cm rule" would have placed 9% of patients in BA 6 (premotor cortex), but this was reduced to 4% by the VIM. We do note that of the 7 patients nonetheless stimulated in BA 6, none achieved remission (not statistically different from the remission rate of frontal cortex, but this analysis is limited by the reduced sample size). Using MNI coordinates, we failed to find any overall difference in positioning between patients achieving remission or not. One study using the "5 cm rule" suggested that better treatment responses occur more lateral and anterior [4], and our VIM did move stimulation anterior into a more focused, less variable localization. Our data indicates that a "6 cm rule" would obviously shift all sites anterior, placing 16% of patients in BA 46. As the coil placement adjustment rules were used for all patients, we cannot provide a definitive test of whether adjustment makes a difference for efficacy as has been previously reported in a study directly comparing the "5 cm rule" with a more precise neuronavigation method [52]. Future studies would be needed to examine the efficacy of other targeting methods and of stimulating other brain regions.

Overall, we failed to find a significant difference in effective intensity of stimulation between patients achieving remission or experiencing non-remission. Given the variability in effective stimulation seen in this study, these data support using 120% resting MT stimulation intensity to guarantee an adequate prefrontal stimulation intensity. Stimulation at a higher intensity will impact a larger volume of brain tissue, possibly mitigating some imprecision in anatomic positioning. One study using 100% resting MT reports improved responses with anatomic-adjusted stimulation [52]; however, another study with the unadjusted "5 cm rule" and 120% MT stimulation had response rates comparable to this study [53]. We failed to find that higher intensities yielded higher or lower remission rates across brain regions. Ultimately, resting MT may not be the best measures for determining the minimal TMS dose required to stimulate cortex. We note that only 3 patients had effective stimulation less than 100% of resting motor threshold, and yet all three of these patients achieved remission. Active MT studies demonstrate that cortical effects can be generated at intensities lower than resting MT [54], and motor cortex threshold may not be fully predictive of prefrontal intensity range needed for a therapeutic response.

Recommendations

Based on findings in this study, we recommend that TMS positioning methods should be carefully considered in future research and clinical treatments. Adjustable, individualized methods for targeting anatomical regions are more precise than fixed rules. Structural imaging can aid localization. Anchoring targeting based exclusively on functionally localized motor cortex can introduce considerable variability. Our data do not provide a clear evidence for an optimal therapeutic sub-region of prefrontal cortex; however, premotor cortex is likely a poor target region. Furthermore, left and right asymmetry should be considered when targeting right prefrontal cortex.

Based on the review of effective intensity in this study, we also recommend that the intensity of stimulation be considered in future research and clinical treatments. Stimulation at 120% of resting motor threshold appears to be sufficient to generate therapeutic effects in a subset of patients. We did not find evidence of greater treatment effects at higher effective stimulation levels, and safety and patient comfort concerns would suggest caution in using higher intensities. We also note that patients over the age of 70 years old and patients with dementia were excluded from this trial, so effective stimulation characterizations may not generalize to other groups such as elderly with depression or groups with asymmetric atrophy between motor and prefrontal cortex. While motor threshold is a simple and well-established estimate of measure based on a single-pulse TMS, other brain measures (such as EEG or NIRS) may be useful to functionally threshold individuals for stimulation of other brain regions with rTMS [55–59]. Also, cortical effects can depend on a variety of factors including relative coil and tissue orientation, cortical structure, and brain state [9,31,60,61]. Previous analysis indicates that most remitters had low antidepressant treatment resistance [13], and additional analysis will examine whether brain structure can provide clues regarding responsiveness to stimulation.

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