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Rostral anterior cingulate cortex is a structural correlate of repetitive TMS treatment response in depression

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for medication-refractory major depression, yet the mechanisms of action for this intervention are poorly understood. Here we investigate cerebral cortex thickness as a possible biomarker of rTMS treatment response.

Methods: Longitudinal change in cortical thickness is evaluated relative to clinical outcomes across 48 participants in 2 cohorts undergoing left dorsolateral prefrontal cortex rTMS as a treatment for depression.

Results: Our results reveal changes in thickness in a region of the left rostral anterior cingulate cortex that correlate with clinical response, with this region becoming thicker in patients who respond favorably to rTMS and thinner in patients with a less favorable response. Moreover, the baseline cortical thickness in this region correlates with rTMS treatment response – those patients with thinner cortex before treatment tended to have the most clinical improvement.

Conclusions: This study is the first analysis of longitudinal cortical thickness change with rTMS as a treatment for depression with similar results across two cohorts. These results support further investigation into the use of structural MRI as a possible biomarker of rTMS treatment response.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for medication-refractory major depressive disorder [1], yet the mechanisms of action for this intervention are poorly understood. Studies have shown that rTMS treatment for depression may be associated with changes in serum markers (e.g. BDNF) as well as functional and neurochemical changes in the brain, both at the site of stimulation and in remote regions [2]. These studies aim to identify potentially clinically useful biomarkers that would provide an objective measure of treatment response, provide mechanistic insight to rTMS, and, ideally, predict which patients are most likely to benefit from rTMS. To date there are relatively few studies investigating the structural correlates of rTMS treatment response, yet if useful, structural MRI has the potential to be incorporated into clinical practice more easily than other biomarkers under evaluation (e.g. resting state functional

Abbreviations: BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; BIDMC, Beth Israel Deaconess Medical Center; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; GABA, gamma-Aminobutyric acid; HamD, Hamilton Depression Rating Scale-24 Item; MNI, Montreal Neurological Institute; PET, positron emission tomography; rACC, rostral anterior cingulate cortex; ROI, Region-of-interest; rTMS, Repetitive transcranial magnetic stimulation.

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connectivity MRI or EEG) as it uses existing, largely automated analysis software packages and routine clinical imaging hardware.

In 2007, May et al. published a first demonstration that focal 1 Hz rTMS delivered daily for five days is associated with a local increase in gray matter at the site of stimulation in the temporal lobe of healthy adults [3]. For patients receiving rTMS to the dorsolateral prefrontal cortex (DLPFC) as a treatment for depression, longitudinal studies have shown no global change in brain volume [4], a significant reduction in left hippocampus volume that was driven by the non-responders [5], and a significant increase in hippocampus volume that did not correlate with clinical response [6]. A 2016 study showed a longitudinal increase in gray matter density in several brain areas over a course of rTMS for depression and a single region, the rostral anterior cingulate cortex (rACC) extending into medial prefrontal cortex, with increased gray matter density that correlated with clinical improvement [7].

In the present study we sought to evaluate whether cerebral cortex thickness may be a potential biomarker of rTMS treatment response in depression. Specifically, we examined whether there were regional changes in cerebral cortex thickness associated with clinical improvement. We hypothesized that cortical thickness would increase in the left DLPFC based on prior research showing regional structural changes at the stimulation site [3], along with increases in cortical thickness at the anterior cingulate in correspondence with clinical improvement, which may correspond to increased gray matter density reported previously [7]. In addition we measured hippocampus volume to evaluate whether non-responders had decreased hippocampus volume with rTMS treatment, as was reported previously [5] versus hippocampal enlargement, which has been reported recently in association with rTMS treatment for depression [6] and with some consistency with electroconvulsive treatment of depression [8]. While we had specific anatomical hypotheses, our analyses included both region-of-interest (ROI) and vertex-wide analyses that were not constrained by pre-specified ROIs.

Methods and materials

48 patients with treatment-resistant major depression were evaluated and treated using rTMS at one of two sites, the Berenson Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center (BIDMC) (N = 21) or Weill Cornell Medical College (N = 27). Both datasets have been analyzed previously [9,10,31], including a voxel-based morphometry analysis of gray matter density with findings in the rostral anterior cingulate cortex as reported above [7]. Cerebral cortex thickness has not been evaluated previously in either dataset. Diagnosis was confirmed in both groups by a clinical interview performed by a psychiatrist. While major depression was the target population, three patients had prior episodes of hypomania and thus met criteria for bipolar II disorder.

TMS Treatment. Each participant had a treatment course of rTMS applied to the left DLPFC according to the following protocol: 10 Hz rTMS in 4 s trains with 26 s intertrain interval, 3000 pulses, over 37.5 min. At BIDMC TMS was delivered using a NeuroStar TMS Therapy System (Neuronetics, Inc., Malvern, Pennsylvania) or Magstim Super Rapid stimulator (Magstim Company Ltd., UK) equipped with a 70-mm figure-of-eight coil and at Cornell TMS was delivered with the NeuroStar system. DLPFC targeting was 5.5 cm anterior to the motor cortex at BIDMC and via the beam F3 method at Cornell [11]. The number of rTMS sessions was 30–36 at BIDMC and 25 at Cornell. The primary measure of treatment response was the Beck Depression Inventory (BDI) [12] at BIDMC and the Hamilton Depression Rating Scale-24 Item (HamD) [13] at Cornell.

Imaging Acquisition. An MRI was acquired within a 7-day window before and after the rTMS treatment course. At BIDMC the MRI was conducted using a GE 3T HDX scanner. High-resolution T1-weighted structural images were acquired via a 3D-turbo field echo sequence (TE = 2.9 ms, flip angle = 15°, $0.94 \times 0.94 \times 1$ mm resolution). At Cornell the MRI was acquired using a GE Signa Excite 3T scanner. High-resolution T1-weighted anatomical scans with $1 \times 1 \times 1$ mm resolution were obtained with an 8-channel phase array head coil using a three dimensional spoiled gradient echo sequence with TR/TE/FA of 9 ms/3.5 ms/13°. Other details of this sample have been reported previously [7,9,10].

FreeSurfer Processing. Structural MRI (T1\ MPRAGE sequences) data were processed using FreeSurfer, an automated software package that parcellates the brain using anatomical landmarks, including delineation of the white and pial surface to define cerebral cortex thickness across over a hundred thousand vertices [14]. The longitudinal processing stream of FreeSurfer was used to optimize detection of changes in cerebral cortex thickness in the same individual across two time points [15], before and after the course of rTMS, a timespan of 4–7 weeks. This resulted in a cortical thickness difference value from pre-to post-rTMS for each vertex in the cerebral cortex for each patient. There is a lack of consensus regarding the optimal smoothing kernel size for FreeSurfer so we report data for commonly used kernels of 10, 15 and 20 mm. 15 was used for the main analyses with other smoothing kernel data reported as supplementary material. FreeSurfer parcellation of the cerebral cortex boundaries was reviewed individually for each scan to ensure anatomical accuracy prior to performing any analyses. The data from three patients was excluded due to inadequate parcellation, likely secondary to motion artifact (2 patients, which included 1 patient with bipolar II) or marked atrophy at baseline (1 patient).

A Priori Regions of Interest. To evaluate cortical thickness changes at the stimulation site each individual from the BIDMC cohort had the stimulation site identified using neuronavigation with Brainsight frameless stereotactic equipment. Patient-specific stimulation sites were recorded in stereotactic space and projected to the nearest brain surface position perpendicular to a plane tangential to the scalp. Sites were then transformed as a 20 mm diameter spherical ROI from MNI volume space to FreeSurfer surface space. For the Cornell cohort the site was estimated using a 20 mm diameter spherical ROI at the average F3 MNI coordinate −41.5, 41, 33 [16].

Hippocampus volume was traced manually using a previously published protocol [17]. Prior to tracing for this analysis reliability was demonstrated using both inter-rater (with original study data) and intra-rater intraclass correlations, at 0.958 (95% confidence interval 0.835–0.989) and 0.974 (95% confidence interval 0.894–0.993) respectively. The FreeSurfer-derived hippocampus volume was also evaluated.

ROI analyses, other than the stimulation site and the manual segmentation of the hippocampus described above, were conducted using FreeSurfer-derived regions from their standard atlas ROIs [18,19].

Statistical Analysis. The main analysis examined the relationship between longitudinal cortical thickness changes with change in depression ratings using a general linear model in FreeSurfer's QDEC program (www.surfer.nmr.mgh.harvard.edu). In order to combine depression ratings across different rating scales we rank-ordered the percent change in HamD and BDI separately and scaled it to a 100-point scale before combining data from the two groups into a single continuous scale. A statistical threshold of $P < 0.001$ uncorrected was selected a priori for the main analysis as the effect size was expected to be small, due to minute changes in cortical thickness in adults over a period of weeks and high inter-individual variability given the heterogeneity of depression and variable

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