Using imaging to target the prefrontal cortex for transcranial magnetic stimulation studies in treatment-resistant depression

Structural imaging studies of the brains of patients with treatment-resistant depression (TRD) have found several abnormalities, including smaller hippocampus, orbitofrontal cortex, or prefrontal cortex. Transcranial magnetic stimulation (TMS) is a noninvasive means of modulating brain activity, and has shown antidepressant treatment efficacy.¹

The initial methods used for targeting the prefrontal cortex are most likely insufficient. Herwig et al found that a common rule-based approach (the 5-cm rule) resulted in approximately one third of subjects receiving stimulation over the premotor, and not the prefrontal, cortex.²

The work of Kozel et al,³ replicated by Mosimann et al,⁴ showed that increasing prefrontal cortical atrophy was correlated with TMS nonresponse. These studies have raised the question of whether there might be prefrontal location methods that result in higher TMS antidepressant efficacy.

Measurement of distance from skull to cortex (ds-c) provides information about both normal and pathological cortical atrophy. It has been proposed that ds-c can be used to adjust the dosage of TMS. The ds-c can be measured manually after a scan or with automated software.

We are currently involved in a four-site NIMH-sponsored trial (Optimization of TMS in Depression - OPT-TMS), testing whether daily prefrontal repetitive TMS (rTMS) has antidepressant efficacy. All subjects receive a baseline MRI scan with fiducials marking the motor and putative prefrontal cortex. We report the results concerning atrophy (intensity) and location in the first 20 subjects in this trial (estimated final sample: 240).

**Methods**

Structural brain scans were acquired at study baseline from subjects at all four sites. Prior to obtaining the magnetic resonance image (MRI), the TMS motor location and motor threshold was determined. Using the 5-cm rule, a putative prefrontal location was also determined. Subjects wore swim caps, and Vitamin E capsules were taped to the cap over these two locations. MRI scans were then stored at a central site and analyzed for distance (atrophy) and location.

**Manual method of determining distance (MEDX)**

The image is oriented using standard AC-PC alignment. In a coronal view, measurement is made from scalp to closest cortical surface. Multiple measurements are taken and averaged from the several coronal slices containing the fiducial. The appropriate power needed to stimulate the prefrontal cortex (PFC) with the same intensity as the motor cortex (taking distance into account) is given by:

\[
PFC \text{ power needed} = 100 \times (\exp((0.036) \times (DPFC-DMotor)))
\]
Figures 1 and 2 illustrate how the distance to cortex is measured manually over the motor and prefrontal cortex.

**Determined whether the prefrontal cortex is in the appropriate position**

In standard AC-PC alignment, if no temporal lobe is seen in a coronal slice, the fiducial is considered to be appropriately over PFC (Figure 2, left panel). If a small amount of temporal lobe is seen, the image is examined from other views. If it is still uncertain whether the fiducial is over the PFC, the PFC spot is moved 6 cm forward from the motor spot. If a large amount of temporal lobe is seen in the coronal slice, the PFC is automatically moved forward.

This method is limited due to variability in PFC anatomy and is dependent upon the rater’s skill.

**Prefrontal distance**

*Figure 4* shows the results.

- **Prefrontal location**

Using the anatomic landmark method, the “5-cm rule” resulted in 8/20 (40%) subjects with stimulation that would have occurred over the premotor cortex, and that needed to be moved 1 cm forward. We are still testing the automated method.

**Conclusions and future directions**

- A prefrontal stimulation intensity of 120% motor threshold would overcome all prefrontal atrophy in these subjects, and cause prefrontal stimulation sufficient to cause neuronal depolarization (assuming prefrontal cortex and motor cortex had similar thresholds).
- Confirming Herwig et al, the 5-cm rule for placement results in premotor cortex stimulation (and not prefrontal cortex) in a large percentage of subjects. We hypothesize that this may have negatively affected TMS antidepressant efficacy in prior studies.
- We are in the process of comparing the manual method of PFC determination with the automated method.
- At the conclusion of this study, after unblinding, we will test whether specific anatomic location or intensity correlates with overall response to TMS.
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FIGURE 3. Automated method for determining PFC position. PFC, prefrontal cortex.