Project: *Machine Learning to Predict Clinical Response to Transcranial Magnetic Stimulation: A Resting State Electroencephalography Study*
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Significance: The impact of Major Depressive Disorder (MDD) on public health cannot be overstated. MDD is the leading cause of disability worldwide [1]. Symptoms of MDD in a notable proportion of patients (~30%) do not respond to conventional treatments [2, 3], increasing the need for new treatments. One novel treatment is repetitive transcranial magnetic stimulation (rTMS, hereafter simply TMS). Cleared by the US FDA in 2008 for pharmacoresistant MDD, this new treatment offers significant promise for patients by directly targeting brain regions implicated in MDD, and is also associated with minimal side effects compared to standard pharmacotherapy [4]. Unfortunately, TMS is only effective in about two-thirds of these patients [5, 6] and is associated with significant financial and time burdens [7]. Therefore, understanding the neurobiological effects of TMS and leveraging this understanding to develop predictors of response is of great value.

The main challenges in understanding the neurobiology of psychiatric disorders and their treatments arise from the inherent complexity of the mental illness. MDD, for example, has a variable presentation, and biological and psychological data obtained from patients tend to have a high degree of freedom and notable intersubject variability. Machine learning is a model-free method which may predict individual responses to treatments when other methods do not.

I have conducted a pilot study which points to the promise of this approach. I used machine learning (Support Vector Machine trained linear classifiers and sparse (LASSO [8]) regression) to analyze patterns of brain functional connectivity based on EEG before and after a course of TMS in patients with comorbid MDD and PTSD. I successfully predicted non-response to a long and costly conventional course of TMS with 80% accuracy. This prediction relied on a limited (and thus cost-effective) EEG montage and EEG connectivity metrics in various frequency bands. The manuscript based on this study is currently under review in the journal Neuropsychopharmacology. A broadly similar approach was used elsewhere using fMRI to predict TMS treatment outcomes [9], but EEG represents a more practical alternative.

Here, I propose to build upon my pilot study (which had a sample size of 21) and recruit more participants, use a dense electrode montage (64 electrodes), and record EEG more frequently during treatment. This will allow me to research the mechanism of TMS by identifying changes and localize their sources, find the most efficient way to predict clinical outcome and move towards individually customized TMS therapy. I expect to help develop tools to better allocate the clinical infrastructure of TMS (available in over 500 U.S. clinics) to individuals most likely to benefit from this innovative treatment. Advanced training in the methods involved is integral to pursuit of this overall goal.

Aim 1. Compare functional connectivity maps (i.e., EEG coherence) in patients before and after clinical TMS. *Hypothesis1*: TMS modulates cortical networks in a predictable/reproducible way, and such network modulations can be detected by assessing functional connectivity via EEG. I will employ supervised learning algorithms (classifiers) to identify pre- and post-treatment EEG recording sessions based on functional connectivity maps at different frequency bands. I will examine the classifier to infer insights into the mechanism(s) of action of TMS.

Aim 2. Predict clinical outcomes based on pre-treatment EEG functional connectivity using a sparse regression model. *Hypothesis 2*: Baseline cortical functional connectivity can be used to predict clinical improvement in patients who undergo TMS treatment. I will use sparse regression to predict treatment outcome using EEG coherence. I will then use this data to design a clinical EEG tool that can predict treatment outcome to TMS in clinical settings.

Strategy: Patients (n = 35) will be recruited from the Providence VA's Psychiatric Neuromodulation Clinic. There is an established precedent and infrastructure to enroll the veterans in research studies from that clinic and the Providence VA. I am also a member of the Center for Neurorestoration and Neurotechnology at the Providence VA, which can provide me with research staff as well as EEG recording setting and space.

I will use this award to expand become an independent researcher using EEG acquisition and analysis, enhance my training in statistical learning and predictive analytics, and gain essential expertise in the scientific and clinical contexts of brain stimulation. To this end, I will leverage existing translational research resources at the Providence VA, combined with the infrastructure and training path at the Brown Center for Biomedical Informatics, an Advance-CTR core, and the Brown Initiative for Computation in Brain and Mind.

The knowledge gained will lay the foundation for a career development award (NIH or VA) by the end of the two-year period, which will pursue my goal to develop an independent research career in combining brain stimulation and advanced statistical analyses. Projects for the anticipated award will use data collected here to design a study that will generate individualized TMS targets (based on EEG source localization), and optimize TMS approaches for TMS non-responders.