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Original Article

# Magnetic Resonance Imaging Measures of Brain Structure to Predict Antidepressant Treatment Outcome in Major Depressive Disorder

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ABSTRACT

*Background:* Less than 50% of patients with Major Depressive Disorder (MDD) reach symptomatic remission with their initial antidepressant medication (ADM). There are currently no objective measures with which to reliably predict which individuals will achieve remission to ADMs.
*Methods:* 157 participants with MDD from the International Study to Predict Optimized Treatment in Depression (iSPOT-D) underwent baseline MRIs and completed eight weeks of treatment with escitalopram, sertraline or venlafaxine-ER. A score at week 8 of 7 or less on the 17 item Hamilton Rating Scale for Depression defined remission. Receiver Operator Characteristics (ROC) analysis using the first 50% participants was performed to define decision trees of baseline MRI volumetric and connectivity (fractional anisotropy) measures that differentiated non-remitters from remitters with maximal sensitivity and specificity. These decision trees were tested for replication in the remaining participants.
*Findings:* Overall, 35% of all participants achieved remission. ROC analyses identified two decision trees that predicted a high probability of non-remission and that were replicated: 1. Left middle frontal volume < 14 · 8 mL & right angular gyrus volume > 6 · 3 mL identified 55% of non-remitters with 85% accuracy; and 2. Fractional anisotropy values in the left cingulum bundle < 0 · 63, right superior fronto-occipital fasciculus < 0 · 54 and right superior longitudinal fasciculus < 0 · 50 identified 15% of the non-remitters with 84% accuracy. All participants who met criteria for both decision trees were correctly identified as non-remitters.
*Interpretation:* Pretreatment MRI measures seem to reliably identify a subset of patients who do not remit with a first step medication that includes one of these commonly used medications. Findings are consistent with a neuroanatomical basis for non-remission in depressed patients.
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## 1. Introduction

Major depressive disorder (MDD) is a chronic disease with a relapsing and remitting course. Antidepressant medications (ADMs) form the front-line treatment for MDD and less than 50% of patients respond or remit to their first treatment (Gartlehner et al., 2012; Hansen et al., 2008). There are currently no objective measures to guide the treatment decisions in MDD, and the clinical standard is to use a "watch and wait" strategy relying on trial and error (Rush et al., 2008). The time taken to conduct iterative trials of different medications represents an enormous source of direct healthcare costs, indirect economic losses and an increase of the total healthcare burden associated with MDD.

Prompted by this context, there has been a recent focus on the development of neurobiological markers ("biomarkers") including techniques that are able to capture disruptions to the underlying brain

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circuitry (Insel et al., 2010; Leuchter et al., 2010). These biomarkers are yet to be validated for sufficient clinical utility (Fu et al., 2013; Labermaier et al., 2013). Neuroimaging provides a means to noninvasively capture the spatiotemporal circuitry relationships in the brain that may reflect the functional abnormalities present in depression — hence approaches that use imaging measures of brain abnormalities represent excellent candidates for tests of treatment prediction. Evidence of structural and functional abnormalities in MDD comes from molecular imaging (McGrath et al., 2013), and from multiple MR imaging modalities including diffusion tensor imaging (DTI) (Korgaonkar et al., 2011, 2012, 2014a), gray matter (GM) volume from T1 weighted MRI scans (Grieve et al., 2013a), as well as task-based and resting-state functional MRI (Korgaonkar et al., 2013; Greicius et al., 2007). Most studies have concentrated on key circuits thought to be central to the development and maintenance of MDD (e.g., limbic structures including the cingulate cortex and the dorsolateral prefrontal medial orbitofrontal cortices). This approach, however, may limit the power of imaging to capture whole brain patterns of dysfunction.

Also, different imaging measures may capture different aspects of malfunctioning circuits in MDD, and may therefore contribute to treatment prediction in a unique, and likely an independent (and potentially additive) manner. Integrating data across different imaging measures can therefore provide a powerful approach to isolate groups of patients with similar pre-treatment impairments. These groups of patients with common patterns of brain alterations may therefore respond in a similar way to treatments tailored to their underlying circuitry abnormalities. Signal detection analyses employing receiver operator curve (ROC) analysis procedures are well suited to developing dichotomous outcomes from multiple measures (Kraemer, 1992). This analysis assesses different variables at all possible cut points identify an optimal trade-off between sensitivity and specificity.

This report addresses the question of whether pre-treatment brain measures from T1 weighted (volume) and DTI (structural connectivity) MR Imaging sequences can identify individuals who will, or will not, remit during acute phase ADM treatment. Both these imaging sequences are routinely prescribed in clinical neurological assessments and offer an easy translation of findings to a clinical setting. We use signal detection ROC analyses with structural imaging measurements of both GM volume and connectivity across the entire brain, to identify the best possible combination of pre-treatment imaging measures and cut-points to prospectively predict remission status following acute treatment with ADMs. Our aim was to identify general predictors of which patients remit and which patients do not, with the goal of developing a practical algorithm to help inform clinical decision making about ADMs. We tested this aim using data drawn from the imaging sub-study of the International Study to Predict Optimized Treatment in Depression (iSPOT-D). Following the planned design of iSPOT-D, we first evaluated our aims in the test cohort, the first subsample of patients, and then tested for replication in the second validation subsample.

## 2. Methods

### 2.1. Participant Characteristics and Study Protocol

Data was gathered from participants in the International Study to Predict Optimized Treatment in Depression (iSPOT-D), for which the study protocol, clinical assessments, inclusion/exclusion criteria and diagnosis procedures have been previously described (Williams et al., 2011; Grieve et al., 2013b). In short, the Mini-International Neuropsychiatric Interview, using DSM-IV criteria, and a 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) score $\geq 16$ confirmed the primary diagnosis of MDD. Participants were not currently suffering or had a history of bipolar disorders, schizophrenia, schizoaffective, psychosis not otherwise specified, anorexia, bulimia, obsessive compulsive disorders or primary post-traumatic stress disorder. All MDD participants were either ADM-naïve or had undergone a wash-out period of at least 5 half-lives of a previously prescribed ADM. Participants were randomized to receive flexibly-dosed, open-label escitalopram, sertraline or venlafaxine-extended release (venlafaxine-ER) for eight weeks. Our study recruited from primary care, community and academic psychiatry settings with the goal of representing a broad sample of antidepressant treatment seekers. Medications were prescribed and doses adjusted by treating clinicians according to routine clinical practice, but following the recommended dose ranges. An $HRSD_{17}$ of $\leq 7$ was used to ascribe remission. In addition to the $HRSD_{17}$ score, participant age, gender, age of onset of depression, depression duration, number of previous depression episodes, previous treatment, melancholia, and score of the 42 item depression-anxiety-stress scale were recorded at baseline.

As per the analysis plan, the first 50% of the MDD participants who completed imaging at baseline visit were used as the test cohort ($n = 102$) and the second 50% of the MDD participants as the validation cohort ($n = 102$) (Grieve et al., 2013b). Fig. 1 provides the CONSORT diagram. 80 and 87 participants completed their 8-week course of assigned ADM in the test and validation cohorts respectively. Of the 80 participants from the test cohort, six participants did not complete the DTI scan while four participants did not complete the T1 structural scan resulting in 74 and 76 participants for each analysis. For the validation cohort, DTI and T1 data from 83 participants who completed the clinical follow-up at week 8 were available for analysis. These sample sizes represent the biggest cohort to be used to identify imaging prognostic markers for ADM treatment. Based on effect sizes from previous work in the field, we anticipated these sample sizes to provide sufficient power for analysis. The Western Sydney Ethics Committee approved this study and all participants provided written informed consent.

### 2.2. Image Acquisition and Analysis

DTI and T1-weighted sagittal 3D SPGR MRI data were acquired using a 3 Tesla GE Signa HDx scanner (GE Healthcare, Milwaukee, Wisconsin) as previously described (Grieve et al., 2013b). Volumetric analysis was performed using voxel-based morphometry (VBM8), and 116 cortical and subcortical brain regions were generated using the Automated Anatomical Labeling (AAL) atlas (Grieve et al., 2013a; Tzourio-Mazoyer et al., 2002). DTI data analyzed using Tract-Based Spatial Statistical analysis (TBSS) to generate fractional anisotropy (FA) measurements for 46 major white matter tracts in the brain using the Johns Hopkins University International Consortium for Brain Mapping (JHU ICBM)-DTI-81 white matter labels atlas (Korgaonkar et al., 2011; Mori et al., 2008). Details for the MRI sequences and volume and DTI analyses are provided in the supplementary section.

### 2.3. Statistical Analyses

ROC analyses, based on signal detection methods (Kraemer, 1992) were used to identify which MRI measures (GM region/white matter tract), and at what level (volume or FA), optimally discriminate non-remitters and remitters. This analysis is non-parametric and operates via a recursive partitioning procedure. This approach is designed to handle multiple variables and as compared to traditional regression analysis methods can analyze all possible interactions, rather than only those specified a priori and can analyze interactions even when the main effects are not included in the model. More specifically, for each measured potential predictor, cutoff points are generated at all values observed in the variable. The quality of a cutoff point is based on its ability to divide the sample into 2 subsamples maximally distinct in discriminating non-remitters and remitters. A kappa statistic is calculated for each cut-point, and the largest kappa coefficients correspond to cut-points with maximum sensitivity and specificity (Kraemer, 1992) (QROC available at mirecc.stanford.edu).

The cutoff point that yields the best prediction is identified across all values of all variables. That cutoff point is then used to divide the total