Prediction of Non-Remission to Anti-Depressant Therapy Using Diffusion Tensor Imaging

Running Title: Predicting Depression Nonremission with DTI

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ABSTRACT

Objective: Over 50% of outpatients with nonpsychotic major depressive disorder (MDD) do not achieve remission with any single antidepressant medication (ADM). There are currently no clinically useful pre-treatment measures that inform the decision to prescribe or select ADMs. This report examines whether a biomarker based on diffusion tensor imaging (DTI) measures of brain connectivity can identify a subset of non-remitting patients with a sufficiently high degree of specificity that they could avoid a medication that is likely to fail.

Method: MDD outpatients recruited from community and primary-care setting underwent pretreatment magnetic resonance imaging as part of the international Study to Predict Optimized Treatment for Depression (iSPOT-D; conducted Dec 2008 – June 2014). DSM-IV criteria and a 17-item Hamilton Rating Scale for Depression (HRSD17) score ≥ 16 confirmed the primary diagnosis of non-psychotic MDD. Data from the first cohort of MDD patients (n = 74) were used to calculate fractional anisotropy measures of the stria terminalis and cingulate portion of the cingulate bundle (CgC). Based on our previous data, we hypothesized that non-remission might be predicted using a ratio of these two values. Remission was defined as an HRSD17 of ≤ 7 following 8 weeks of open-label treatment with escitalopram, sertraline, or venlafaxine-extended release, randomized across participants. The second study cohort (n = 83) was used for replication.

Results: 35% of all participants achieved remission. A value > 1.0 for the ratio of the fractional anisotropy of the stria terminalis over the CgC identified 38% of the non-remitting participants with an accuracy of 88% (test cohort; odds ratio [OR], 9.6; 95%CI, 2.0-45.9); 24% with an accuracy of 83% (replication cohort; OR, 1.8; 95%CI, 0.5-6.9) and 29% with an
accuracy of 86% (pooled data; OR, 4.0; 95%CI, 1.5-11.1). Treatment moderation analysis showed greater specificity for escitalopram and sertraline ($\chi^2=8.07; p=0.003$).

**Conclusions:** To our knowledge, this simple DTI-derived metric represents the first brain biomarker to reliably identify non-remitting patients in MDD. The test identifies a meaningful proportion of non-remitters, has high specificity and may assist in managing the antidepressant treatment of depression.

**Clinical Trials Registration**

**Trial Registration:** International Study to Predict Optimized Treatment - in Depression (iSPOT-D)

**Registry Name:** ClinicalTrials.gov

**URL:** http://www.clinicaltrials.gov/ct2/show/NCT00693849?term=iSPOT-D&rank=1

**Registration Number:** NCT00693849

**Keywords:** major depressive disorder, antidepressant treatments, imaging, biomarker, DTI, iSPOT-D
INTRODUCTION
Depressive disorders, which are often chronic or recurrent, are common, disabling and life shortening\(^1\). While a range of antidepressant treatments is available, there are currently no clinically useful pre-treatment measures that inform the selection among these treatment options\(^2\). Since symptom remission, the goal of treatment, occurs in less than 50% of depressed outpatients treated with an initial antidepressant medication (ADM)\(^3-6\), one way to enhance the effectiveness of our available treatments would be to identify a meaningful proportion of depressed outpatients who are highly unlikely to remit acutely with medication. The result of such a test would be to limit the use of ineffective medication for those patients who are unlikely to remit, without the need to undertake a trial of the medication itself. This would enable earlier initiation of alternative treatments such as cognitive behavioral therapy, repetitive transcranial magnetic stimulation, deep brain stimulation, electroconvulsive therapy or a combination of medications or treatment regimes, which in turn should improve the speed of effective treatment and reduce effort, cost and patient burden. However, the prediction of non-remission must be accurate enough (i.e., certainty in excess of 80%) for the clinician to take action— in this case, to not give the treatment\(^7,8\).

Functional activity of the amygdala-hippocampal complex and the anterior cingulate region (specifically the subgenual anterior cingulate cortex: sgACC) are central to current theories of clinical depression and the action of ADMs\(^9-11\). Diffusion tensor imaging (DTI) measures the connectivity in brain circuitry and can identify white matter tracts that are relevant to depression\(^12-14\). In a previous report, we demonstrated that aberrant connectivity is present in two white matter tracts associated with these regions i.e. the cingulate portion of the cingulum bundle (CgC) and the stria terminalis and that the disruptions to white matter connectivity in these tracts relate to antidepressant outcomes\(^15\). These data suggested that
these two tracts may together form part of an anatomical circuit that underpins response/remission in depression. Critically, the effect appeared to be interactive with opposing directionality of altered white matter microstructure between the two tracts i.e. remission to ADM was associated with higher fractional anisotropy [FA] in the CgC and lower FA in the stria terminalis. While these and previous functional findings have been encouraging, a biomarker with high level of reproducibility and for prediction at a clinically useful level of accuracy applicable to an individual participant still remains to be established\textsuperscript{16}. This report builds on our initial findings in an effort to identify a single such DTI biomarker that could predict a proportion of depressed patients who are rather certain to not remit to one of three commonly used ADMs.

We reasoned that, based on these findings, non-remission from depression would be associated with higher stria terminalis FA, and lower FA of the cingulate portion of the cingulate gyrus, and hence a higher ratio of stria terminalis:CgC. We required that the threshold chosen had to be associated with at least an 80% certainty of a poor outcome, in keeping with the fact that a prediction of non-remission would need a high degree of certainty to justify any deviation from usual care. This level of certainty assumed the availability of alternative treatments that have a greater than 1 in 5 chance of producing remission. In this instance, possible treatments could range from medication combinations to electroconvulsive therapy (ECT). To be clinically useful, this actionable threshold would also have to identify a meaningful number of all the non-remitters. This report evaluates the performance of DTI as a measure of altered microstructure in these two white matter tracts as an indicator of treatment non-remission in depression for three commonly prescribed ADMs.

**METHODS**
**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 (Registration Number: NCT00693849)\(^{17,18}\). The Mini-International Neuropsychiatric Interview\(^{19}\), using DSM-IV criteria\(^{20}\), and a 17-item Hamilton Rating Scale for Depression\(^{21}\) (HRSD\(_{17}\)) score ≥ 16 confirmed the primary diagnosis of non-psychotic MDD. Participants were not currently suffering or had a history of bipolar disorders, schizophrenia, schizoaffective, psychosis not otherwise specified, anorexia, bulimia, obsessive compulsive disorders, primary post-traumatic stress disorder or substance abuse disorders. Participants did not have substance dependence including alcohol intake of equaling 29 standard alcoholic drinks per week for males (or greater than 15 for females) in the past six months. 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 excluded if they had used a non-protocol antidepressant or CNS drug (antipsychotic, anticonvulsant, anxiolytic, clonidine) that could not be washed out prior to participation. Participants did not have contra-indication for escitalopram, sertraline or venlafaxine-extended release (venlafaxine-XR), or previous treatment failure at the highest recommended dose. They were also not taking escitalopram, sertraline or venlafaxine-XR in the current episode of MDD. Participants were randomized to receive escitalopram, sertraline or venlafaxine-XR. Investigators and participants were not blinded to treatment. ADMs were prescribed and doses adjusted by the participants’ treating clinicians according to routine clinical practice. An HRSD\(_{17}\) of ≤ 7 at week 8 was used to ascribe remission.
None of the MDD participants underwent psychotherapy or other alternative treatment for MDD during the participation of the study. Any treatment for concurrent general medical conditions were allowed and recorded. Comorbid general medical conditions were recorded under the categories (with examples) of cardiovascular (hypertension), digestive (IBS), endocrine (diabetes), hemic/lymphatic (gout), metabolic/nutritional (high cholesterol), musculoskeletal (tendonitis), respiratory (asthma), urogenital (kidney stone), skin (eczema) and special senses (astigmatism) disorders. Approximately 50% of the sample reported no comorbid general medical condition in these categories, 23% reported one condition and 27% one or more conditions. Psychotropic medication was discontinued prior to randomization except for occasional (i.e., ≤1 dose/week) use of anxiolytics; sleep aids and medications to manage antidepressant-induced side-effects (e.g., nausea) as they reflect common practice. Of the total sample 4.9% of patients were taking a concomitant psychotropic medication and these (by generic name) included the anxiolytic Alprazolam and the sedative/hypnotics, Zolpidem, Zopiclone, Eszopiclone and Triazolam.

As per the analysis plan, the first 50% of the MDD participants who completed the iSPOT-D study imaging protocol were used as the test cohort and the second 50% of the MDD participants were used as the replication cohort. The CONSORT diagram for the study is shown in Figure 1. 80 MDD participants from the test cohort returned for their week 8 follow-up visit, 74 of whom had DTI data. For the replication cohort, DTI data from 83 participants were available for analysis. This study was approved by the Western Sydney Ethics Committee, participants provided written informed consent.

FIGURE 1
**MRI acquisition and analysis**

The details of the DTI protocol, processing and analytic methods have previously been described and also provided in the supplementary section\textsuperscript{15}.

**Statistical Analyses**

A combined measure of the stria terminalis and CgC was created by calculating the ratio of the FA values for each participant ($R_{ST-CB}$=[FA for stria terminalis]/[FA for CgC]). A threshold value of $R_{ST-CB}$=1.0 was then applied to the data. This threshold was chosen for simplicity, and is approximately a Z-score of +1, i.e., one standard deviation above the expected ratio in normal participants ($R_{ST-CB}$ from control participants, $n=34$: mean=0.93; standard deviation=0.05). The rationale for the ratio was that the combination of an abnormally high FA for stria terminalis and low FA for the CgC would characterize non-remission in a single metric. The accuracy of this measure for the identification of non-remitters was then calculated. The replication cohort was tested using the same threshold. Chi-square statistics were calculated to test significance of distributions and odds ratio (OR) calculated. The proportion of non-remitters in the replication cohort was much higher than that observed in the test cohort and previously published prevalence rate for ADM use (Table 1). To remove this bias in testing the validity of the biomarker, an additional cross-validation procedure was performed using 1000 iterations of 100 MDD participants randomly chosen across both cohorts (supplementary section). To characterize the non-remitter sample identified using the $R_{ST-CB}$ metric, the demographic and clinical characteristics of the selected non-remitters (S-NR) were compared to the non-remitters not selected (N-NR) and also to the entire non-selected group (i.e. all remitters+N-NR) using independent t-tests or chi-squared
tests. To examine for treatment moderation effects, we analyzed the data using a 3-way chi-square analysis. For this analysis, the pooled sample was used to maximize power.

**TABLE 1**

**RESULTS**

*Participant Characteristics*

Table 1 shows the clinical and demographic characteristics of the test (n=74) and the replication (n=83) cohorts as a group, and by remission status. The average daily dose (mg/d) (±S.D.) at week 8 for the treatment arms were: escitalopram = 13±5; sertraline = 61±27; and venlafaxine-XR = 100±35. A small difference existed between escitalopram dose between cohorts (test = 11±4 vs. replication = 14±6mg/d; p=0.018). No difference existed for the other two treatment arms. The remission rates were lower in the replication cohort (χ²=8.02; p=0.005): 46% for the test cohort vs. 24% for the replication cohort. Remission rates within each cohort were similar across treatment arms depending on the cohort: test cohort (χ²=0.58; p=0.75): escitalopram = 42% (10/24); sertraline = 52% (13/25); and venlafaxine-XR = 44% (11/25); replication cohort (χ²=0.09; p=0.96): escitalopram = 23% (7/31); sertraline = 24% (6/25); and venlafaxine-XR = 26% (7/27). Remitters were younger and had shorter disease duration in the test cohort (Table 1); no significant difference in these parameters existed in the replication cohort. There was a significant difference in average ADM dose between remitters and non-remitters for venlafaxine-XR only – where non-remitters were prescribed a higher average dose (non-remitters 108±38 mg/day vs remitters: 83±24 mg/day; p=0.015). No difference in ADM dose was present for sertraline or escitalopram. Significant differences existed for baseline and week 8 symptom severity (HRSD₁₇ Baseline, HRSD₁₇ Week 8):
replication cohort>test cohort; p<0.05), however, improvement in symptoms (HRSD_{17} % change), age of onset and duration of illness was similar for both cohorts.

**Prediction of non-remission**

**Test cohort**

Figure 2A shows the distribution of $R_{ST-CB}$ for both the remitting and non-remitting participants in the test cohort. Both groups do not significantly deviate from a normal distribution (Shapiro-Wilk=0.98, p>0.5). The remitting population is skewed to the left (0.160), while the non-remitting population has a distribution skewed to the right (-0.116). $R_{ST-CB}$ was lower for remitters compared to non-remitters (0.933±0.047 versus 0.968±0.067, p<0.011). Using a threshold of $R_{ST-CB}>1.0$ to select non-remitters, 38% (15/40) of the overall non-remitters and 6% (2/34) of overall remitters were selected ($\chi^2=10.4; p=0.001$), which corresponds to an accuracy of 88% (OR=9.6; 95%CI=2.0-45.9). The accuracy and fraction of S-NRs versus N-NRs for each treatment type were: 100% for escitalopram (S-NR/N-NR=5/9), 100% for sertraline (S-NR/N-NR=4/8), and 75% for venlafaxine-XR (S-NR/N-NR=6/8).

**FIGURE 2**

**Replication cohort**

The distributions of $R_{ST-CB}$ for both the remitting and non-remitting participants in the replication cohort are shown in Figure 2B. Both groups do not significantly deviate from a normal distribution (Shapiro-Wilk=0.97, p>0.5). In contrast to the test cohort, no significant difference in $R_{ST-CB}$ was observed between remitters and non-remitters in the replication cohort (0.940±0.056 versus 0.948±0.061, p=0.61). However, applying the same threshold of
R_{ST-CB}>1.0, 23.8% (15/63) of the overall non-remitters and 15% (3/20) of the overall remitters were selected ($\chi^2=0.69; p=0.41$) resulting in an accuracy of 83.3% (OR=1.8; 95%CI=0.5-6.9). The accuracy for each treatment arm was: 83.3% for escitalopram (S-NR/N-NR=5/19); 100% for sertraline (S-NR/N-NR=4/15), and 75% for venlafaxine-XR (S-NR/N-NR=6/14).

For the pooled cohort, the accuracy in identifying non-remitters was 85.7% (30/35) with an overall selection of 29.1% of non-remitters and 9.3% of remitters using the same threshold ($R_{ST-CB}>1.0$) ($\chi^2=8.07; p=0.004; OR=4.0; 95\% CI=1.5-11.1$).

Treatment-type analysis on pooled test and replication cohorts

Sample size did not permit the testing of sub-groups by treatment for test and replication cohorts separately. The pooled data showed a significant difference between treatment arms with the $R_{ST-CB}$ ratio accurately predicting non-remission in a high proportion of participants prescribed with the two selective serotonin reuptake inhibitors (SSRIs) used in the study (3-way chi square: overall: $\chi^2=8.07; p=0.003$, escitalopram: $\chi^2=3.07; p=0.077$, sertraline: $\chi^2=5.84; p=0.015$, venlafaxine-XR, $\chi^2=0.94; p=0.259$). The non-remission predictive accuracy for the three treatment arms were: 90.9% for escitalopram (S-NR/N-NR=10/28); 100% for sertraline (S-NR/N-NR=8/23), and 75% for venlafaxine-XR (S-NR/N-NR=12/22). When the data from the two SSRI medications were pooled, the accuracy was 94.7% ($\chi^2=8.67; p=0.002$) (S-NR/N-NR=18/51).

Characteristics of the non-remitter groups

The baseline clinical and demographic characteristics of the S-NR group were compared to the N-NR group and also for the entire non-selected group (i.e., all remitters+N-NR) for both
the test and replication cohorts (Table 2). For the test cohort, the only significant difference was in age between the S-NR and N-NR groups (S-NR<N-NR, p=0.015). No significant difference in the age at diagnosis, disease duration, gender, or baseline severity was present. There were no significant differences between S-NR and N-NR groups, or between the S-NR and the entire non-selected group for the replication cohort.

**TABLE 2**

**DISCUSSION**

This study has identified a DTI biomarker, the ratio of FA of the stria terminalis to the FA of the CgC, which reliably identifies with a high degree of certainty (83-88%) a meaningful subgroup of those depressed patients (>20%) who will not remit acutely with at least one of the three most common ADMs used in clinical practice. MDD participants with $R_{ST-CB}>1.0$ were 4 times more likely to not achieve remission (overall OR=4.0; 95%CI=1.5-11.1). Our results raise the possibility that using brain connectivity methods such as DTI to sub-type participants with MDD may prove to be more clinically useful than traditional clinical measures.

We used the first 50% of MDD participants who completed week 8 of ADM treatment to form a test cohort (n=74) to define this DTI biomarker. The threshold ratio was *a priori* chosen as 1.0 since this is approximately one standard deviation above the measured ratio in controls. Using this threshold identified 38% non-remitting participants at a specificity of 88%. The high degree of specificity of this biomarker was again demonstrated in the independent replication cohort (83%). To our knowledge, these data represent the first DTI biomarker to reliably identify non-remitting patients in MDD.
Treatment of patients with ADMs is a trial-and-error process, requiring substantial investments of patient and clinician time to ultimately identify an effective treatment for an individual patient. It is generally accepted that the first 2-4 weeks are required to assess an initial response to the prescribed ADM and in the case of a zero or partial response, is typically followed by an increased dose for another 2-4 weeks before switching to a different ADM \(^{22,23}\). Therefore, identifying patients who will not remit on 3 different standard medications would potentially take many months. The early and reliable identification of individuals who are very likely to not remit with multiple treatments would be a clinically valuable tool, if it could avoid prolonged yet ultimately unsuccessful treatment trials. The simple metric we used appears to have the potential for identifying such patients, and thus improving the targeting or personalization of treatment.

The non-remitting participants who were selected using this ratio were not clinically different from the not selected non-remitters, except that they were younger. When controlled for age, the performance of the test remained diagnostic (93% specificity with S-NR/N-NR=14/26, p<0.05). This age difference was not present in the replication cohort, suggesting that the biomarker is not a proxy for an age-related effect. This ratio therefore reflects a connectivity pattern that is strongly associated with non-remission in a sub-set of individuals and which appears to be independent of many indices that are normally used to sub-type depressive patients.

Our baseline analyses of DTI data show that compared to controls, MDD participants have significant alterations in the CgC and the fornix, but not the stria terminalis\(^{15}\). Functional MRI data comparing controls and MDD participants also highlight abnormal activation
patterns in the amygdala\textsuperscript{24} and sgACC\textsuperscript{10,11,25}. Our previous data highlighted these two tracts for the prediction of remission. Results indicate that while both the CgC and stria terminalis are abnormal in depression, the patterns of these differences and how they interact with ADM treatment are quite dissimilar. The CgC collects projections from the rostral prefrontal/anterior cingulate cortices to the posterior cingulate, while the fornix and stria terminalis are comprised of axonal projections from the hippocampus and the amygdala, respectively, and connect to the hypothalamus and the rest of the limbic system\textsuperscript{26}. Lower FA of the cingulate tract in non-remitters would be consistent with the known abnormalities of the sgACC in MDD\textsuperscript{27} and the existing associations of this region with treatment outcome\textsuperscript{28}. Similarly, greater FA in the stria terminalis with non-remission would be consistent with the increased reactivity of the amygdala in MDD patients with current depression and its normalization with remission\textsuperscript{29,30}. A barrier for translating an imaging-based biomarker is degree of variation of the measurement - one of the key advantages of using a ratio of FA for the two tracts (instead of the actual FA value) as a decision-defining measure is that much of the site-to-site or longitudinal variation should be accounted for.

We also found a partial association of treatment arms, with the relationship of the R\textsubscript{ST-CB} ratio and prediction of non-remission to be significantly present with the two selective serotonin reuptake inhibitor treatment types used in the study (and not for the serotonin–norepinephrine reuptake inhibitor, venlafaxine-XR). However, given the sample size, we were able to test this only for the pooled cohort. Further investigation is needed to confirm this effect in a separate cohort.

This study has some limitations. First, it is likely that more sophisticated and anatomically detailed diffusion tractography methods may capture more completely the abnormal tracts
that drive this result. However, our decision to focus on the use of a simple hypothesis-driven ratio using TBSS data was a deliberate one, made with an eye toward ease of routine clinical use. The use of TBSS to quantify FA values is practically important since this method is well established, robust, easily automated and does not require extensive computation time, all of which favor the potential translation of this measure for routine use in a clinical setting.

Second, one could argue with our a priori “actionable threshold” being set at 80%. This threshold is, in part, practical; new methods must substantially outperform existing clinical decision algorithms. The validity of an 80% criteria also rests on the existence of an the availability of alternative treatments that have a greater than 1 in 5 chance of resulting in remission, something we recognize that the study has not addressed, although, in theory, ECT should result in at least a 50% remission rate for patients with several medication failures. The power of our analysis (the largest single cohort DTI analysis of a MDD population published to date) is an important factor supporting our finding. Our study tested the predictive power of our test using a second cohort, and although this analysis that did not reach significance using a chi-squared test, the low number of false negatives is supportive evidence, given the transparent nature of our study design and the maintenance of the significance levels in the pooled group. This was also supported by a high accuracy in the cross-validation analysis. The replication cohort had a lower remission rate than the test cohort. The higher pre-treatment severity and higher frequency of “near miss” remissions in the replication cohort (23% versus 15% in the test cohort) are possible mediating factors for this observation. A recent study failed to detect baseline differences using FA in a pooled group of three MDD cohorts (total n=134) compared to controls, and identified the potential for false positives using small samples, results the authors say may be attributable to the heterogeneity of MDD. Our current result, however, is not inconsistent with these data, as we identify—with a high degree of accuracy—a baseline difference in a select cohort of
MDD participants that predicts treatment outcome. Indeed, our result further serves to emphasise the heterogeneous nature of MDD. Finally, our findings are limited to the three commonly prescribed ADMs used in the study, the generalizability of these findings to other classes of ADMs currently available needs further work.

In conclusion, approximately 30% of depressed outpatients with a high risk for non-remission were identified with a high level of specificity using a DTI biomarker that reflects connectivity in two tracts (CgC and stria terminalis) that are central to the development or maintenance of a depressed state. In these two tracts, the direction of the effect is consistent with the known dysfunction of the amygdala (stria terminalis: numerator, relating to amygdala overactivity) and the fronto-limbic system (CgC: relating to poorer fronto-limbic function). That the DTI ratio effectively identified patients who did not remit with one of the three offered ADMs suggests that it may identify at least a subset of the patients who are expected to not remit after completing more than one medication treatment.

Clinical Points

- There are currently no clinically useful predictors of outcome to guide treatment decisions in Major Depressive Disorder.
- A Diffusion Tensor Imaging biomarker can identify patients who are unlikely to remit to anti-depressant medication, this may streamline the identification for patients for whom alternative therapy may be more beneficial.
REFERENCES


eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited. 2014.

Korgaonkar MS, Grieve SM, Etkin A, Koslow SH, Williams LM. Using Standardized fMRI Protocols to Identify Patterns of Prefrontal Circuit Dysregulation that are Common and specific to Cognitive and Emotional Tasks in Major Depressive Disorder: First wave Results from the iSPOT-D study. Neuropsychopharmacology 2012.


Sheline YI. Depression and the hippocampus: cause or effect? Biological psychiatry 2011 Aug 15;70(4):308-309.


TABLE LEGENDS

**Table 1:** Demographics and clinical measures summary.

*Abbreviations:* HRSD17, 17-item Hamilton Rating Scale for Depression; SD, Standard deviation.

**Table 2:** Characteristics of selected non-remitting participants compared to non-selected subject group.

*Abbreviations:* E, escitalopram; FIBSER; Frequency, Intensity and Burden of Side Effects Rating; HRSD17, 17-item Hamilton Rating Scale for Depression; NR, Non-remitters; NS, Not significant; Rx, Medication; SD, Standard deviation; S, sertraline; V, venlafaxine-extended releaseps.
FIGURE LEGENDS

Figure 1: CONSORT diagram for the iSPOT-D imaging study.

*Abbreviations:* ADHD, Attention deficit hyperactivity disorder; ADM, Antidepressant medication; DTI, Diffusion tensor imaging; iSPOT-D, international Study to Predict Optimized Treatment in Depression; MDD, Major depressive disorder; MRI, Magnetic resonance imaging; XR, Extended release

Figure 2: Distribution of participants stratified by remission status and the ratio of the FA of the stria terminalis tract divided by the FA of the cingulate portion of the cingulate bundle (RST-CB). Remitters are depicted as green columns (positive direction), non-remitters as red columns (negative direction). (A) The test cohort (n=74). (B) The replication cohort (n=83). (C) The combined group (n=157).

*Abbreviations:* FA, Fractional anisotropy
Participants were recruited from physician referrals at Sydney site or responded to advertisements (including individuals who had already presented to a physician plus those who had not).

Phone screen completed by site staff to assess eligibility (n=1,302)

Baseline Visit – Assessed for eligibility (n=380)

Provided baseline MRI assessments (204 MDD participants)

Test Cohort (n=102) (First 50% of MDD participants with baseline MRI data)

MDD participants randomized

Allocation to Escitalopram (n=34)

Allocation to Sertraline (n=34)

Allocation to Venlafaxine-XR (n=34)

Completed Week 8 visit (n=80)

Analyzed Completers (n=74) Escitalopram (n=24); Sertraline (n=25); Venlafaxine-XR (n=25)

Replication Cohort (n=102) (Second 50% of MDD participants with baseline MRI data)

MDD participants randomized

Allocation to Escitalopram (n=34)

Allocation to Sertraline (n=34)

Allocation to Venlafaxine-XR (n=34)

Completed Week 8 visit (n=87)

Analyzed Completers (n=83) Escitalopram (n=31); Sertraline (n=25); Venlafaxine-XR (n=27)

n=922 Excluded for:
Practical reasons (n=79): Travel or Schedule difficulties, Cost of doctor visit, or Staff difficulties
Uninterested after being informed about randomized medical arms and study design
Not meeting eligibility criteria (n=716): Or Treatment n=223, Previous Contraindication ADM n=91, Sub-Clinical MDD n=89, Bipolar Episodes n=74, Primary Anxiety Disorder n=38, Alcohol & Drug Dependence Receiving Therapy n=23, Age n=22, Medic Neurological n=20, Psychosis n=13, ADHD treatment n=5, language skills n=5, Personality n=3, Eating Disorder n=1, participation in study n=1.

21 did not meet the inclusion criteria at baseline visit & 155 were not included in this MRI sample

No DTI data at baseline (n=6)