Prediction of Nonremission to Antidepressant Therapy Using Diffusion Tensor Imaging

Stuart M. Grieve, MBBS, DPhil[a,b,c,*]; Mayuresh S. Korgaonkar, PhD[a,d]; Evian Gordon, MD, PhD[a,e]; Leanne M. Williams, PhD[a,d,f]; and A. John Rush, MD[g]

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 pretreatment 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 nonremitting patients with a sufficiently high degree of specificity that use of a medication that is likely to fail could be avoided.

Methods: MDD outpatients recruited from community and primary-care settings underwent pretreatment magnetic resonance imaging as part of the international Study to Predict Optimized Treatment in Depression (conducted December 2008–June 2014). *DSM-IV* criteria and a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) score ≥ 16 confirmed the primary diagnosis of nonpsychotic 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). On the basis of our previous data, we hypothesized that nonremission might be predicted using a ratio of these 2 values. Remission was defined as an $HDRS_{17}$ score 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: Thirty-four percent 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 nonremitting 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 ($\chi^2 = 8.07$; $P = .003$).

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

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[a]The Brain Dynamics Centre, Sydney Medical School—Westmead and Westmead Millennium Institute, Sydney, Australia
[b]Sydney Translational Imaging Laboratory, Charles Perkins Centre & Sydney Medical School, University of Sydney, Camperdown, Australia
[c]Department of Radiology, Royal Prince Alfred Hospital, Camperdown, Australia
[d]Discipline of Psychiatry, University of Sydney Medical School: Western, Westmead Hospital, Sydney, Australia
[e]Brain Resource, Ultimo, Sydney, Australia, and San Francisco, California
[f]Department of Psychiatry and Behavioral Sciences, Stanford University, California
[g]Academic Medicine Research Institute and Office of Clinical Sciences, Duke-National University of Singapore, Singapore
**Corresponding author:* Prof Stuart M. Grieve, MBBS, DPhil, The Brain Dynamics Center, Westmead Millennium Institute for Medical Research, 176 Hawkesbury Rd, Westmead, Sydney, NSW 2145, Australia (stuart.grieve@sydney.edu.au).

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 pretreatment 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 regimens, which in turn should improve the speed of effective treatment and reduce effort, cost, and patient burden. However, the prediction of nonremission must be accurate enough (ie, 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,[15] we demonstrated that aberrant connectivity is present in 2 white matter tracts associated with these regions—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. These data suggested that these 2 tracts may together form part of an anatomic circuit that underpins response/remission in depression. Critically, the effect appeared to be interactive with opposing directionality of altered white matter microstructure between the 2 tracts; that is, remission to ADM

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 antidepressant medication, and this may streamline the identification for patients for whom alternative therapy may be more beneficial.

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 a high level of reproducibility and for prediction at a clinically useful level of accuracy applicable to an individual participant still remains to be established.[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 3 commonly used ADMs.

We reasoned that, on the basis of these findings, nonremission 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 nonremission 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 nonremitters. This report evaluates the performance of DTI as a measure of altered microstructure in these 2 white matter tracts as an indicator of treatment nonremission in depression for 3 commonly prescribed ADMs.

METHODS

Participant Characteristics and Study Protocol

Data were gathered from participants in the international Study to Predict Optimized Treatment in Depression (iSPOT-D; conducted December 2008–June 2014), for which the study protocol, clinical assessments, inclusion/exclusion criteria, and diagnosis procedures have been previously described (ClinicalTrials.gov identifier: NCT00693849).[17,18] The Mini-International Neuropsychiatric Interview,[19] using *DSM-IV* criteria,[20] and a 17-item Hamilton Depression Rating Scale[21] ($HDRS_{17}$) score ≥ 16 confirmed the primary diagnosis of nonpsychotic major depressive disorder (MDD). Participants were not currently suffering from and did not have a history of bipolar disorders, schizophrenia, schizoaffective, psychosis not otherwise specified, anorexia, bulimia, obsessive-compulsive disorders, primary posttraumatic stress disorder, or substance abuse disorders. Participants did not have substance dependence including alcohol intake greater than 29 standard alcoholic drinks per week for men (or greater than 15 for women) in the past 6 months. All MDD participants were either ADM-naive or had undergone a washout period of at least 5 half-lives of a previously prescribed ADM. Participants were excluded if they had used a nonprotocol antidepressant or CNS drug (antipsychotic, anticonvulsant, anxiolytic, clonidine) that could not be washed out prior to participation. Participants did not have contraindication 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 randomly assigned 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 $HDRS_{17}$ score ≤ 7 at week 8 was used to ascribe remission.

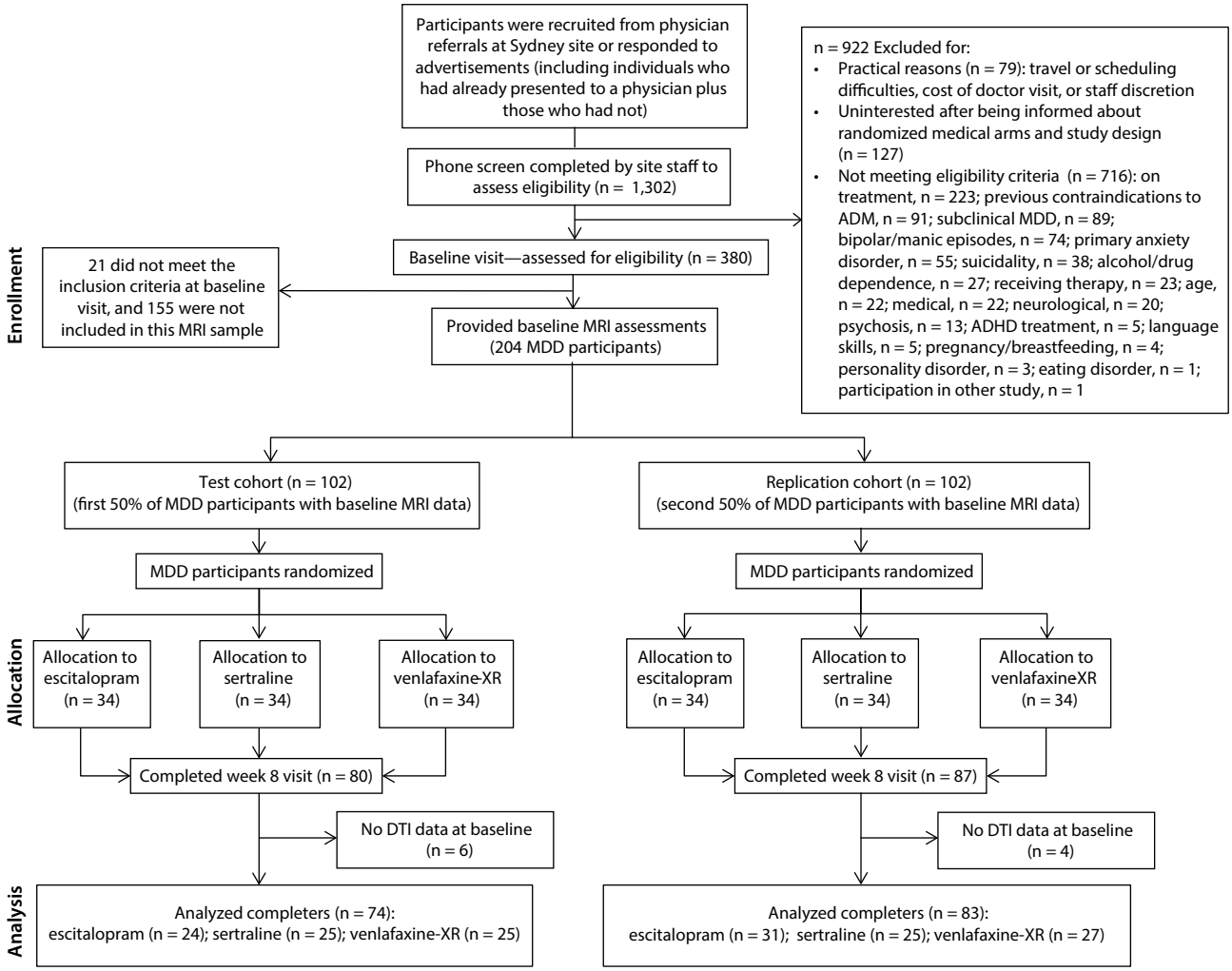
None of the MDD participants underwent psychotherapy or other alternative treatment for MDD during the participation of the study. Any treatment for concurrent general medical conditions was allowed and recorded. Comorbid general medical conditions were recorded under the categories (with examples) of cardiovascular (hypertension), digestive (irritable bowel syndrome), 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 1 condition, and 27% reported 1 or more conditions. Psychotropic medication was discontinued prior to randomization except for occasional (≤ 1 dose/wk) use of anxiolytics, sleep aids, and medications to manage antidepressant-induced side effects (eg, nausea), as they reflect common practice. Of the total sample, 4.9% of patients were taking a concomitant psychotropic medication, and these 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 imaging protocol were used as the test cohort, and the second 50% of the MDD participants were used as the replication cohort.[18] The CONSORT diagram for the study is shown in Figure 1. Eighty 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, and participants provided written informed consent.

Magnetic Resonance Imaging Acquisition and Analysis

The details of the DTI protocol, processing, and analytic methods have previously been described[15] and are also provided in the supplementary materials.

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.

Statistical Analyses

A combined measure of the stria terminalis and CgC was created by calculating the ratio of the FA values for each participant ($R_{ST\text{-}CB}$ = [FA for stria terminalis]/[FA for CgC]). A threshold value of $R_{ST\text{-}CB} = 1.0$ was then applied to the data. This threshold was chosen for simplicity and is approximately a *Z*-score of +1, ie, 1 standard deviation above the expected ratio in normal participants ($R_{ST\text{-}CB}$ from control participants, n = 34: mean = 0.93, SD = 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 nonremission in a single metric. The accuracy of this measure for the identification of nonremitters 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 nonremitters 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 1,000 iterations of 100 MDD participants randomly chosen across both cohorts (supplementary materials). To characterize the nonremitter sample identified using the $R_{ST\text{-}CB}$ metric, the demographic and clinical characteristics of the selected nonremitters (S-NR) were compared to the nonremitters not selected (N-NR) and also to the entire nonselected group (ie, all remitters + N-NR) using independent *t* tests or χ^2 tests. To examine for treatment moderation effects, we analyzed the data using a 3-way χ^2 analysis. For this analysis, the pooled sample was used to maximize power.

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 mean (± SD) doses (mg/d) at week 8 for the treatment arms were escitalopram = 13 ± 5,

Table 1. Demographics and Clinical Measures Summary

	Test Cohort						Replication Cohort					
			Remission						Remission			
	All		Yes		No		All		Yes		No	
Characteristic	n	%	n	%	n	%	n	%	n	%	n	%
Total sample	74	100	34	46	40	54	83	100	20	24	63	75
Females	37	50	16	47	21	53	42	51	11	55	31	49
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, y[a]	33.0	12.7	28.2	7.4	37.1	14.8	35.5	11.2	33.2	10.5	36.3	11.4
$HDRS_{17}$ baseline[c]	20.7	3.6	21.2	3.8	20.3	3.4	22.3	3.4	21.2	3.3	22.7	3.4
$HDRS_{17}$ week 8[a–c]	9.0	5.0	4.6	1.9	12.8	3.5	11.3	4.8	5.2	1.3	13.2	3.8
$HDRS_{17}$ % change[a,b]	55.1	27.2	78.2	9.4	35.6	21.2	49.2	21.0	75.2	6.2	41.0	16.8
Age at onset, y	20.2	11.1	18.9	7.7	21.4	13.4	22.4	8.5	20.6	9.2	23.0	8.3
Disease duration, y[a]	12.2	12.0	8.8	6.5	15.2	14.7	12.6	11.0	12.1	12.1	12.8	10.8

[a]Difference between remitters and nonremitters at $P < .05$ for test cohort.
[b]Difference between remitters and nonremitters at $P < .05$ for replication cohort.
[c]Difference between the test and replication cohorts at $P < .05$.
Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, SD = standard deviation.

sertraline = 61 ± 27, and venlafaxine-XR = 100 ± 35. A small difference existed between escitalopram dose between cohorts (test = 11 ± 4 vs replication = 14 ± 6 mg/d; $P = .018$). No difference existed for the other 2 treatment arms. The remission rates were lower in the replication cohort ($\chi^2 = 8.02$; $P = .005$): 46% for the test cohort versus 24% for the replication cohort. Remission rates within each cohort were similar across treatment arms depending on the cohort: test cohort ($\chi^2 = 0.58$; $P = .75$): escitalopram = 42% (10/24), sertraline = 52% (13/25), and venlafaxine-XR = 44% (11/25); replication cohort ($\chi^2 = 0.09$; $P = .96$): 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 mean ADM dose between remitters and nonremitters for venlafaxine-XR only: nonremitters were prescribed a higher average dose (nonremitters: 108 ± 38 mg/d vs remitters: 83 ± 24 mg/d; $P = .015$). No difference in ADM dose was present for sertraline or escitalopram. Significant differences existed for baseline and week 8 symptom severity ($HDRS_{17}$ baseline, $HDRS_{17}$ week 8: replication cohort > test cohort; $P < .05$); however, improvement in symptoms ($HDRS_{17}$ % change), age at onset, and duration of illness were similar for both cohorts.

Prediction of Nonremission

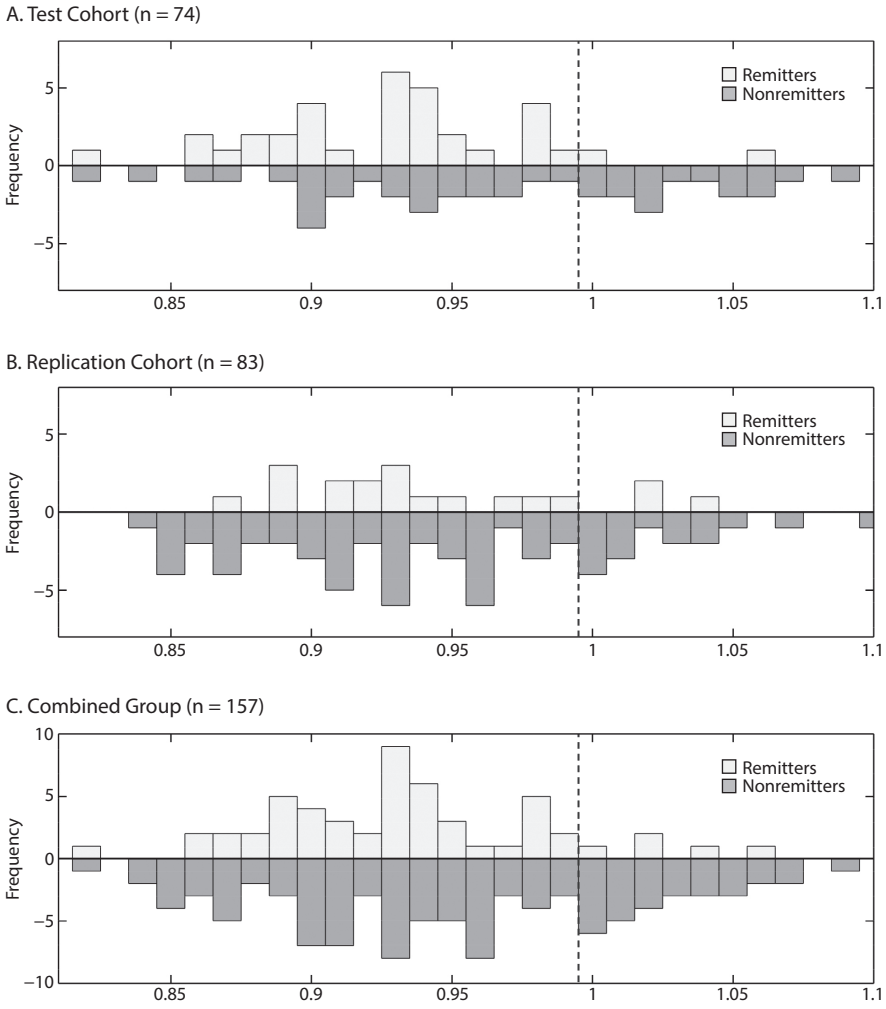
Test cohort. Figure 2A shows the distribution of $R_{ST\text{-}CB}$ for both the remitting and nonremitting participants in the test cohort. Neither group significantly deviated from a normal distribution (Shapiro-Wilk = 0.98, $P > .5$). The remitting population is skewed to the left (0.160), while the nonremitting population has a distribution skewed to the right (−0.116). $R_{ST\text{-}CB}$ was lower for remitters compared to nonremitters (0.933 ± 0.047 vs 0.968 ± 0.067, $P < .011$). Using a threshold of $R_{ST\text{-}CB} > 1.0$ to select nonremitters, 38% (15/40) of the overall nonremitters and 6% (2/34) of overall remitters were selected ($\chi^2 = 10.4$; $P = .001$), 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).

Replication cohort. The distributions of $R_{ST\text{-}CB}$ for both the remitting and nonremitting participants in the replication cohort are shown in Figure 2B. Both groups do not significantly deviate from a normal distribution (Shapiro-Wilk = 0.97, $P > .5$). In contrast to the test cohort, no significant difference in $R_{ST\text{-}CB}$ was observed between remitters and nonremitters in the replication cohort (0.940 ± 0.056 vs 0.948 ± 0.061, $P = .61$). However, applying the same threshold of $R_{ST\text{-}CB} > 1.0$, 23.8% (15/63) of the overall nonremitters and 15.0% (3/20) of the overall remitters were selected ($\chi^2 = 0.69$; $P = .41$), resulting in an accuracy of 83.3% (OR = 1.8; 95% CI, 0.5–6.9). The accuracy for each treatment arm was 83% 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 nonremitters was 85.7% (30/35) with an overall selection of 29.1% of nonremitters and 9.3% of remitters using the same threshold ($R_{ST\text{-}CB} > 1.0$) ($\chi^2 = 8.07$; $P = .004$; 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 subgroups by treatment for test and replication cohorts separately. The pooled data showed a significant difference between treatment arms with the $R_{ST\text{-}CB}$ ratio accurately predicting nonremission in a high proportion of participants prescribed the 2 selective serotonin reuptake inhibitors (SSRIs) used in the study (3-way χ^2: overall: $\chi^2 = 8.07$, $P = .003$; escitalopram: $\chi^2 = 3.07$, $P = .077$; sertraline: $\chi^2 = 5.84$, $P = .015$; venlafaxine-XR, $\chi^2 = 0.94$, $P = .259$). The nonremission predictive accuracy for the 3 treatment arms was 91% 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 2 SSRI medications were pooled, the accuracy was 94.7% ($\chi^2 = 8.67$; $P = .002$) (S-NR/N-NR = 18/51).

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 ($R_{ST\text{-}CB}$)



Abbreviation: FA = fractional anisotropy.

Characteristics of the nonremitter groups. The baseline clinical and demographic characteristics of the S-NR group were compared to those of the N-NR group and also the entire nonselected group (ie, 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, $P = .015$). No significant difference in the age at diagnosis, disease duration, gender, or baseline severity was present. There were no significant differences between the S-NR and N-NR groups or between the S-NR and the entire nonselected group for the replication cohort.

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 1 of the 3 most common ADMs used in clinical practice. MDD participants with $R_{ST\text{-}CB} > 1.0$ 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 subtype 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 1 standard deviation above the measured ratio in controls. Using this threshold identified 38% nonremitting 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 nonremitting patients in MDD.

Treatment of patients with ADMs is a trial-and-error process, requiring substantial investments of patient and

Table 2. Characteristics of Selected Nonremitting Participants Compared to Nonselected Subject Groups

	Test Cohort								Replication Cohort							
	Selected Nonremitters (n = 15)		Nonselected Nonremitters (n = 25)			Rest of Group (n = 59)			Selected Nonremitters (n = 15)		Nonselected Nonremitters (n = 48)			Rest of Group (n = 68)		
Characteristic	n	%	n	%	*P*	n	%	*P*	n	%	n	%	*P*	n	%	*P*
Patients in medication arm (escitalopram/sertraline/venlafaxine extended-release)	5/4/6		9/8/8		NS	19/21/19		NS	5/4/6		19/15/14		NS	26/21/21		NS
Females	10	66.7	11	44.0	NS	27	45.8	NS	7	46.7	24	50.0	NS	35	51.5	NS
Melancholic	3	20.0	11	44.0	NS	20	33.9	NS	0	0.0	3	6.25	NS	6	8.8	NS
	Mean	SD	Mean	SD		Mean	SD		Mean	SD	Mean	SD		Mean	SD	
Age, y	30.5	10.2	41.0	15.9	.015	33.7	13.3	NS	36.5	12.3	36.2	11.3	NS	35.3	11.1	NS
$HDRS_{17}$ baseline	20.5	3.5	20.2	3.5	NS	20.8	3.7	NS	21.9	3.3	22.9	3.4	NS	22.4	3.5	NS
$HDRS_{17}$ week 8	11.3	3.8	13.6	3.1	.048	8.4	5.1	.020	11.6	2.5	13.7	4.0	NS	11.2	5.2	NS
$HDRS_{17}$ % change	42.8	24.2	31.2	18.4	NS	58.3	27.2	.048	45.8	15.2	39.4	17.1	NS	50.0	22.0	NS
Age at onset, y	18.1	7.2	23.3	15.8	NS	20.8	11.9	NS	22.0	7.0	23.3	8.7	NS	22.5	8.9	NS
Disease duration, y	11.8	11.9	17.2	16.0	NS	12.4	12.2	NS	14.0	10.4	12.4	11.0	NS	12.3	11.2	NS
$HDRS_{17}$ anxiety	6.6	2.3	6.8	2.0	NS	6.8	1.8	NS	7.6	1.8	7.3	2.1	NS	7.2	2.1	NS
$HDRS_{17}$ non-anxiety	13.9	2.3	13.4	3.0	NS	14.0	3.1	NS	14.3	2.0	15.6	2.3	NS	15.2	2.4	NS
FIBSER (intensity)	0.80	0.56	1.04	0.74	NS	0.76	0.70	NS	1.47	1.30	1.56	1.24	NS	1.28	1.22	NS

Abbreviations: FIBSER = Frequency, Intensity and Burden of Side Effects Rating, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, NS = nonsignificant, SD = standard deviation.

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 nonremitting participants who *were* selected using this ratio were not clinically different from the nonselected nonremitters, 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, $P < .05$). 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 nonremission in a subset of individuals and that appears to be independent of many indices that are normally used to subtype 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 magnetic resonance imaging data comparing controls and MDD participants also highlight abnormal activation patterns in the amygdala[24] and sgACC.[10,11,25] Our previous data highlighted these 2 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 composed of axonal projections from the hippocampus and the amygdala, respectively, and connect to the hypothalamus and the rest of the limbic system.[26] Lower FA of the cingulate tract in nonremitters would be consistent with the known abnormalities of the sgACC in MDD[27] and the existing associations of this region with treatment outcome.[28] Similarly, greater FA in the stria terminalis with nonremission would be consistent with the increased reactivity of the amygdala in MDD patients with current depression and its normalization with remission.[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 2 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 $R_{ST\text{-}CB}$ ratio and prediction of nonremission to be significantly present with the 2 SSRI 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 tract-based spatial statistics (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,[31] robust, and 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% criterion 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.[32] 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 did not reach significance using a χ^2 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 pretreatment severity and higher frequency of "near miss" remissions in the replication cohort (23% vs 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 3 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.[33] 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 emphasize the heterogeneous nature of MDD. Finally, our findings are limited to the 3 commonly prescribed ADMs used in the study, and 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 nonremission were identified with a high level of specificity using a DTI biomarker that reflects connectivity in 2 tracts (CgC and stria terminalis) that are central to the development or maintenance of a depressed state. In these 2 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 3 offered ADMs suggests that it may identify at least a subset of the patients who are expected to not remit after completing more than 1 medication treatment.

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Drug names: alprazolam (Xanax, Niravam, and others), clonidine (Catapres and others), escitalopram (Lexapro and others), eszopiclone (Lunesta), sertraline (Zoloft and others), triazolam (Halcion and others), venlafaxine (Effexor and others), zolpidem (Ambien, Edluar, and others).

Author contributions: Drs Grieve, Korgaonkar, Gordon, and Rush conceived the concept. Drs Grieve, Korgaonkar, and Rush performed the literature search, imaging data analyses, and statistical analysis and wrote the first draft of the manuscript. Drs Grieve and Williams oversaw the structural imaging design for iSPOT-D. All authors provided major edits and advice in the drafting of the manuscript. Dr Grieve had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Potential conflicts of interest: **Dr Grieve** has received fees as a consultant for Brain Resource Ltd. **Dr Gordon** is the CEO of and has significant equity and stock options in Brain Resource Ltd. **Dr Williams** has received fees as a consultant for Brain Resource Ltd and held stock in Brain Resource Ltd. **Dr Rush** has received consulting fees from Brain Resource Ltd, H. Lundbeck A/S, National Institute on Drug Abuse, Eli Lilly, Takeda, Santium, and Medavante; royalties from Guilford Publications; a travel grant from CINP; research support from Duke-National University of Singapore; and honoraria from Hershey Penn State Medical Center, University of California San Diego, New York State Psychiatric Institute, and American Society of Clinical Psychopharmacology. **Dr Korgaonkar** has no disclosures.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Prediction of Nonremission to Antidepressant Therapy Using Diffusion Tensor Imaging

Author(s): Stuart M. Grieve, MBBS, DPhil; Mayuresh S. Korgaonkar, PhD; Evian Gordon, MD, PhD; Leanne M. Williams, PhD; and A. John Rush, MD

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List of Supplementary Material for the article

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Section

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

Running Title: Predicting Depression Nonremission with DTI

Stuart M. Grieve, MBBS, DPhil[*a,b,c], Mayuresh S. Korgaonkar, PhD[a,d] Evian Gordon, MD, PhD[a,f], Leanne M. Williams, PhD[a,d,e] A. John Rush, MD[g]

[a] The Brain Dynamics Centre, Sydney Medical School - Westmead and Westmead Millennium Institute, Sydney, NSW 2145, Australia.

[b] Sydney Translational Imaging Laboratory, Charles Perkins Centre & Sydney Medical School, University of Sydney, Camperdown NSW 2050, Australia.

[c] Department of Radiology, Royal Prince Alfred Hospital, Camperdown NSW 2050, Australia.

[d] Discipline of Psychiatry, University of Sydney Medical School: Western, Westmead Hospital, Sydney NSW 2145, Australia.

[e] Department of Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Road, Stanford, CA 94305.

[f] Brain Resource, Level 12, 235 Jones Street, Ultimo, Sydney, NSW 2007, Australia; and Suite 200, 1000 Sansome Street, San Francisco 94111, USA.

[g] Academic Medicine Research Institute and Office of Clinical Sciences, Duke-National University of Singapore, Singapore

Methods - MRI acquisition and analysis details

Image acquisition

MRI acquisition was performed at the Westmead Hospital, Sydney, Australia and utilized a 3.0T GE Signa HDx scanner with an 8-channel head coil (GE Healthcare, Milwaukee, Wisconsin). DTI parameters: 70 axial contiguous 2.5mm slices; 1.72mmx1.72mm resolution; 128x128 matrix; TR=17000ms; TE=95ms; Frequency direction=R/L; 42 diffusion orientations; b-value=1250.

Tract-based spatial statistical analysis of DTI data

DTI data was preprocessed and analyzed using the Oxford Centre for Functional MRI of the Brain (FMRIB) Diffusion Toolbox and Tract-Based Spatial Statistical analysis (TBSS) software tools as part of the FMRIB Software Library release 4.1.3 (http://www.fmrib.ox.ac.uk/fsl)[1-4].

The raw DTI data for each participant were first corrected for head movement and eddy current distortions. A binary brain mask was generated using the baseline non-diffusion weighted (b=0) image. Diffusion tensor models were then fitted independently for each voxel within the brain mask and images of fractional anisotropy (FA) were generated for each participant.

FA images from each participant were then aligned to the FMRIB58_FA template and transformed into Montreal Neurological Institute 152 $1mm^3$ standard space using the nonlinear registration tool FNIRT. Next, an average FA image was generated and thinned to

create a white matter skeleton representing the centers of all white matter tracts common to all participants. This FA skeleton was then thresholded to FA ≥0.2 to include the major white matter pathways but avoid peripheral tracts that are more vulnerable to interparticipant variability and/or partial volume effects with grey matter. Each participant's aligned FA image was then projected onto the mean FA skeleton by assigning each skeleton voxel by the maximum FA value found in a direction perpendicular to the tract. This accounts for any residual registration misalignments and variability in exact tract location between participants. The JHU ICBM-DTI-81 white matter labels atlas was used to identify parts of the tract skeleton corresponding to the cingulate portion of the cingulum bundle and the stria terminalis[5]. The mean FA for each tract was used for creating the biomarker.

Results - Cross validation analysis for the pooled (test and replication) MDD cohort:

One thousand random samples were run to provide a distribution and confidence interval of replication accuracy. The remission rates were lower in the replication cohort ($\chi 2$= 8.02; p=0.005): 46% (34/74) of the MDD participants from the test cohort achieved remission, while 24% (20/83) of the MDD participants from the replication cohort achieved remission. To remove any bias of this high proportion of non-remitters in the replication cohort on the predictive value accuracy in this cohort, this cross-validation procedure on MDD participants pooled across the test and replication cohorts was performed. One thousand random groups with 100 MDD participants randomly chosen from the pooled cohorts each time in each group were analyzed for predictive value using the threshold value of $R_{ST\text{-}CB}$ = 1.0. This provided a distribution and confidence interval of the replication accuracy.

The mean specificity from this analysis was 86.9 ± 7.7% (10% centile: 75.0%; 90% centile: 95.2%) and was found to match that obtained from the entire pooled cohort. The actual

accuracy in identifying non-remitters for the pooled groups was 85.7% (30/35) against an overall remission rate of 34.4% (54/157) with an overall selection of 29.1% of non-remitters and 9.3% of remitters selected using the threshold of RST-CB >1.0 ($\chi 2$= 8.07; p=0.004; odds ratio, 4.0; 95%CI, 1.5-11.1).

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