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Research paper

The relationship of white matter microstructure with psychomotor disturbance and relapse in remitted psychotic depression

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ABSTRACT

Background: Psychomotor disturbance is common in psychotic depression and is associated with relapse. In this analysis, we examined whether white matter microstructure is associated with relapse probability in psychotic depression and, if so, whether white matter microstructure accounts for the association between psychomotor disturbance and relapse.

Methods: We used tractography to characterize diffusion-weighted MRI data in 80 participants enrolled in a randomized clinical trial that compared efficacy and tolerability of sertraline plus olanzapine with sertraline plus placebo in the continuation treatment of remitted psychotic depression. Cox proportional hazard models tested the relationships between psychomotor disturbance (processing speed and CORE score) at baseline, white matter microstructure (fractional anisotropy [FA] and mean diffusivity [MD]) in 15 selected tracts at baseline, and relapse probability.

Results: CORE was significantly associated with relapse. Higher mean MD was significantly associated with relapse in the each of the following tracts: corpus callosum, left striato-frontal, left thalamo-frontal, and right thalamo-frontal. CORE and MD were each associated with relapse in the final models.

Limitations: As a secondary analysis with a small sample size, this study was not powered for its aims, and is vulnerable to types I and II statistical errors. Further, the sample size was not sufficient to test the interaction of the independent variables and randomized treatment group with relapse probability.

Conclusions: While both psychomotor disturbance and MD were associated with psychotic depression relapse, MD did not account for the relationship between psychomotor disturbance and relapse. The mechanism by which of psychomotor disturbance increases the risk of relapse requires further investigation.

Clinical trial registration: Study of the Pharmacotherapy of Psychotic Depression II (STOP-PD II); NCT01427608. URL: https://clinicaltrials.gov/ct2/show/NCT01427608.

1. Introduction

Major depressive disorder (MDD) with psychotic features ("psychotic depression") is a severe disorder with a high risk of relapse (Rothschild, 2013). Current evidence-based treatments, either combination antidepressant and antipsychotic pharmacotherapy or electroconvulsive therapy, are not uniformly effective, are limited by adverse effects, and are associated with high relapse rates after discontinuation (Flint et al., 2019). A deeper understanding of the neurobiology of psychotic depression and its relationship with relapse may allow more precise

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management, for example by informing a predictive model of relapse risk to increase the precision of continuation pharmacotherapy to prevent relapse, and illuminate the mechanisms of relapse.

Psychomotor disturbance is common in psychotic depression, and is more severe than in non-psychotic depression, both during acute episodes and in remission (Bingham et al., 2021; Fleming et al., 2004; Parker et al., 1993). Psychomotor performance is associated with white matter microstructure in healthy subjects (Chopra et al., 2018) and in psychiatric conditions with deficits in information processing speed, including schizophrenia (Kochunov et al., 2017) and MDD (Bracht et al., 2015; Hyett et al., 2018). Slower processing speed at baseline has been linked to poorer acute treatment outcome in MDD (Groves et al., 2018), with one proposed mechanism, particularly in older adults, being structural damage to striato-frontal circuits rendering pharmacotherapy less effective (Alexopoulos et al., 1997). Disorganized white matter microstructure in frontal, subcortical, and limbic regions has been linked to poorer acute treatment outcome in MDD in all open-label clinical trials and observational studies (Alexopoulos et al., 2008, 2002; Hoogenboom et al., 2014; Korgaonkar et al., 2014; Vasavada et al., 2016), except for one (Taylor et al., 2008).

To our knowledge, there are no published data on the relationship of white matter microstructure with risk of relapse of MDD with or without psychotic features. We recently reported that psychomotor disturbance in remitted psychotic depression was associated with subsequent risk of relapse in a randomized controlled trial (RCT) that compared sertraline plus olanzapine with sertraline plus placebo in the continuation treatment of psychotic depression (Study of the Pharmacotherapy of Psychotic Depression II [STOP-PD II; NCT01427608]) (Flint et al., 2021). The association between psychomotor disturbance and relapse was found in each treatment arm (Flint et al., 2021). In this context, we explored whether white matter microstructure contributes to the relationship between psychomotor disturbance and relapse in psychotic depression. In a subgroup of STOP-PD II participants who had an MRI at randomization baseline, we examined whether i) psychomotor disturbance, and ii) white matter microstructure, were associated with probability of relapse, and, if so, whether white matter microstructure accounted for the association between psychomotor disturbance and relapse.

2. Patients and methods

2.1. Participants

This report is based on 80 participants who participated in a neuroimaging study embedded within the STOP-PD II clinical trial that examined the effect of sertraline plus olanzapine versus sertraline plus placebo on MRI measured brain structure (Voineskos et al., 2020). The design and methods of the STOP-PD II RCT and the associated neuroimaging study have been described in detail (Flint et al., 2013; Voineskos et al., 2020). The RCT was conducted at the following academic health centers: University Health Network (with imaging at the Centre for Addiction and Mental Health), Toronto; University of Massachusetts Medical School; University of Pittsburgh School of Medicine; and Weill Cornell Medicine (with imaging at the Nathan Kline Institute for Psychiatric Research). Using procedures approved by local institutional review boards, written informed consent was obtained from all participants or their substitute decision maker prior to the initiation of any research procedures.

STOP-PD II had three phases: an open acute phase lasting up to 12 weeks, an 8-week open stabilization phase, and a 36-week RCT. At the time of enrolment in the acute phase of the study, participants were aged between 18 and 85 years, met Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) (DSM-IV-TR) (First et al., 2001) for a current major depressive episode with at least one associated delusion, and had a 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960; Williams et al., 2008) total score $\geq$ 21. The study's exclusion criteria included: DSM-IV-TR (APA, 1994) criteria for lifetime bipolar disorder, any other psychotic disorder, or intellectual disability; DSM-IV-TR criteria for current body dysmorphic disorder or obsessive-compulsive disorder; DSM-IV-TR defined dementia preceding the index episode of depression or a 26-item IQCODE (Jorm, 2004) mean score $\geq$ 4 at acute phase baseline; DSM-IV-TR defined substance abuse or dependence within the preceding 3 months; type 1 diabetes mellitus; neurologic disease that might affect neuromuscular function; and unstable physical illness. Participants with standard contraindications for MRI (e.g., ferromagnetic implants) were not eligible for the neuroimaging study.

In the acute phase, participants received combination open-label sertraline (target dosage of 150–200 mg/day) plus open-label olanzapine (target dosage of 15–20 mg/day). 'As needed' lorazepam to a maximum of 3 mg/day and 'as needed' benztropine to a maximum dosage of 2 mg/day were the only other psychotropic medications allowed in the study. Participants entered the stabilization phase as soon as they met the study's criteria for remission, or near remission at week 12 of the acute phase. Remission was defined as the absence of delusions and hallucinations and a 17-item HAM-D total score of $\leq$10 for two consecutive weeks. Near-remission at week 12 of the acute phase was defined as the absence of delusions and hallucinations, a HAM-D score of 11–15 with $\geq$50 % reduction in baseline HAM-D score, and being rated as 'very much improved' or 'much improved' on the Clinical Global Impression (CGI) Scale (Guy, 1976). At the end of the 8-week stabilization phase, participants who still met remission or near-remission criteria following open-label treatment with sertraline plus olanzapine, and had a Mini-Mental State Examination (Folstein et al., 1975) (MMSE) score $\geq$ 24 (the cut-off associated with clinically significant cognitive impairment), were eligible for the RCT.

All participants continued to take open-label sertraline for the duration of the 36-week RCT. They were randomized under double-blind conditions to either continue olanzapine or switch from olanzapine to identically appearing placebo pills during a protocolized 4-week taper of olanzapine. Participants in the RCT were assessed weekly for the first 8 weeks and once every 4 weeks after that until they reached a study end point: either relapse (the primary outcome), study completion at RCT week 36, or early termination. Relapse was defined by at least one of the following: (1) sufficient SCID-rated symptoms to meet criteria for a DSM-IV major depressive episode; (2) 17-item HAM-D total score of $\geq$18; (3) SCID-rated psychosis (delusions or hallucinations); or (4) other significant clinical worsening defined as: (i) a suicide plan or suicide attempt, (ii) development of SCID-rated symptoms of mania or hypomania, or (iii) psychiatric hospitalization.

2.2. Measurement of psychomotor disturbance

Psychomotor disturbance at RCT baseline (i.e, following 8 weeks of remission or near remission) was measured in two ways: i) the CORE instrument (Parker and McCraw, 2017), which combines ratings of retardation, agitation, and non-interactiveness in a total score, and ii) the Coding task from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which measures information processing speed (Randolph, 1998). The CORE is a clinician-administered, sign-based instrument that is intended for use during a clinical interview of a depressed patient and is rated based on observation: higher total scores indicate more severe psychomotor disturbance. The CORE total score has satisfactory inter-rater reliability and construct validity as a measure of psychomotor disturbance (Parker and McCraw, 2017). The RBANS Coding subtest involves having participants match a digit to a symbol from a legend as quickly and accurately as possible. It is sensitive to impairment in information processing speed in a variety of populations, including MDD (Jaeger, 2018). Lower Coding score indicates slower processing speed. Coding scores were normed for each participant's age within 10-year strata using the population norms provided by the RBANS manual (Randolph, 1998). The CORE was

administered by trained research psychiatrists and the Coding subtest was administered by research assistants who had been trained to a level of proficiency by a neuropsychologist.

2.3. MRI data acquisition

All MRI data were acquired on 3-Tesla MRI scanners. Anatomical T1-weighted images were collected along with diffusion weighted imaging (DWI) (b = 1000 s/mm2, 60 gradient directions and 5 reference b = 0 s/mm2). Scanner models were as follows: GE Discovery MR750 (Centre for Addiction and Mental Health, Toronto), Philips Achieva (University of Massachusetts), Siemens TIM Trio (Nathan Kline Institute for Psychiatric Research and University of Pittsburgh). Prior to study start up, acquisition protocols for key parameters were harmonized across study sites.

2.4. Diffusion imaging and analysis

We fitted a tensor and reconstructed participants' white matter tracts via deterministic unscented Kalman filter (UKF) tractography (Malcolm et al., 2010) using the 'WhiteMatterAnalysis' computational algorithm available in 3D Slicer (https://github.com/SlicerDMRI). We then clustered fibers via supervised groupwise registration (O'Donnell et al., 2012), and parcelled reconstructed fibers (approximately one million per participant) into anatomical tracts in accordance with the O'Donnell Research Group (ORG) white matter atlas (F. Zhang et al., 2018), which has been validated across different scanners and protocols (Zhang et al., 2019). We performed visual quality control after initial tractography, registered tracts to the ORG atlas, and created final tracts based on macroscopic features (e.g., trajectory shape and volume). We also reviewed FA and MD values and tract-level characteristics (mean fiber count and length) for extreme outliers.

2.5. Measurement of white matter microstructure

White matter microstructure at RCT baseline was measured with fractional anisotropy (FA) and mean diffusivity (MD). To avoid extensive multiplicity in our analyses, we selected eight tracts a priori that i) either connect regions and circuits well-established as being relevant in MDD (i.e., those tracts connecting frontal-subcortial and frontal-limbic regions) (F.-F. Zhang et al., 2018); or ii) that have been associated with outcome in acute MDD studies (Alexopoulos et al., 2008, 2002; Hoogenboom et al., 2014; Korgaonkar et al., 2014; Taylor et al., 2008; Vasavada et al., 2016). Selected tracts include the arcuate fasciculus (AF), cingulum bundle (CB), corona radiata (frontal) (CR-F), corpus callosum (genu) (CC2), striato-frontal (SF), major component of the superior longitudinal fasciculus (SLF-II), thalamo-frontal (TF) and uncinate fasciculus (UF). All tracts, except the CC2, are intrahemispheric and include both left and right sides, making 15 total individual tracts.

Even with harmonization of acquisition protocols across sites, cross-sectional DWI data are sensitive to inter-site variability, including scanner manufacturing differences and differences in field strength (Fortin et al., 2017). Meta-analytic techniques are often used to adjust for these differences, but have their limitations, including bias secondary to unbalanced data in site-specific summary statistics and uncertainty in statistical inferences in studies with smaller sample sizes (Fortin et al., 2017). More recent studies suggest that the use of batch-effect correction methods, originally pioneered in genomic research, can address these limitations (Fortin et al., 2017). One such method, ComBat, a model that was designed for studies characterized by smaller sample sizes, uses an empirical Bayes framework to adjust data for batch (in this case site) effects (Johnson et al., 2007). ComBat has been validated for use in DWI studies, with the ability to remove spurious inter-site variation while conserving biological variability in data from participants in multi-site studies (Fortin et al., 2017). We, therefore, used ComBat to harmonize MD and FA values across all study sites, using site and age in the models. Harmonized values were used in all analyses.

2.6. Statistical analysis

All statistical analyses were conducted using SAS 9.4 (©SAS Institute, Cary, NC), except for ComBat (neuroCombat v. 1.0.13), which was performed in R v. 4.1.0. Prior to the multivariable analyses, we first examined the bivariate relationship between the psychomotor disturbance variables (CORE and Coding) using Pearson's r, and then constructed a correlation matrix (Spearman's r) for each tract investigating the bivariate relationships between psychomotor disturbance (CORE and Coding) and white matter microstructure (MD and FA) for each of the 15 tracts, in order to place the results of the multivariable analyses in context.

For each tract, the proportional hazards assumptions of the Cox models were confirmed by visual inspection of complementary log-log plots and tests of correlation of the Schoenfeld residual with time. Cox proportional hazards regression models were constructed to test the relationship between: (i) psychomotor disturbance (CORE total score and Coding score in two separate models) and probability of relapse, and (ii) white matter microstructure (FA and MD in two separate models) and probability of relapse, in each tract. Given the well-established relationship between age and both psychomotor disturbance and white matter microstructure (Barrick et al., 2010; Salthouse, 1996), all models included age as a covariate. For tracts in which both psychomotor disturbance and white matter microstructure contributed significantly to probability of relapse in the first two analyses, we conducted a third analysis in which we constructed two nested models to predict probability of relapse: the first included psychomotor disturbance and age as potential predictors, and the second included psychomotor disturbance, age and white matter microstructure. White matter microstructure would be conceptualized as accounting for the association between psychomotor disturbance and relapse if i) psychomotor disturbance dropped out of the model after entering white matter microstructure, and ii) the models were significantly different based on the likelihood ratio test. In order to address the potential problem of multiple comparisons, we provide both the unadjusted values and the *p*-values corrected for a false discovery rate of 20 % (using the Benjamini-Hochberg procedure) for the results of Aim 2.

The sample size was insufficient to examine the interaction of each of the independent variables and randomized treatment group with outcome.

3. Results

3.1. Quality control

Eighty-eight STOP-PD II participants were eligible for the study having received MRI scans. Two participants were excluded from all STOP-PD II neuroimaging analyses due to incidental findings on the MRI scans, five additional participants were excluded from the current analyses based on visual quality control and one other participant was excluded based on outlying tract-level characteristics. Thus, $N = 80$ participants were included in the current analyses. There was no statistically significant difference between excluded participants and the remainder of the participants on age, CORE or Coding score. Of these 80 participants, 16 individual tracts from 6 participants were excluded due to poor segmentation. The tractography of the selected tracts from an individual study participant is shown in Fig. 1.

3.2. Harmonization

Spearman's correlation coefficients examining the relationship between MD and FA and site prior to harmonization with ComBat showed moderate size site effects ($r = 0.492$ and $r = 0.324$, respectively). ComBat was effective in minimizing site effects ($r = 0.089$ for site and MD and $r = 0.022$ for site and FA).

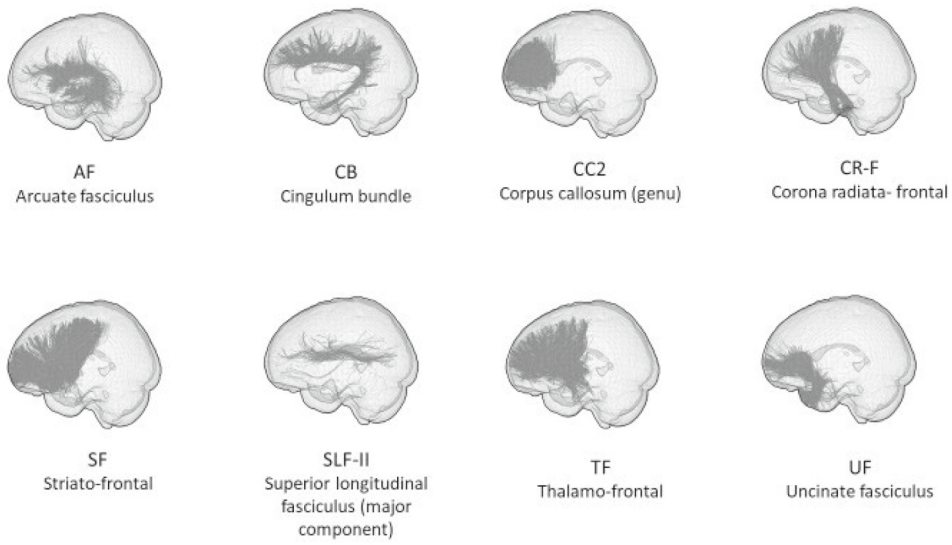

Fig. 1. Mid-sagittal plane image of the brain with superimposed tractography of one individual study participant to illustrate the eight selected tracts.

3.3. Participant characteristics

Table 1 shows the sociodemographic and clinical characteristics of the participants included in these analyses. Twenty-nine of 80 (36.3 %) participants experienced a relapse: 7/40 (17.5 %) of the sertraline plus olanzapine group and 22/40 (55 %) of the sertraline plus placebo group. Relapse events were: depression only ($n = 16$), psychosis only (n = 1), depression and psychosis ($n = 9$), suicide plan or attempt ($n = 2$), psychiatric hospitalization ($n = 11$) [Note: more than one event occurred in some cases of relapse].

Table 1
Participant characteristics ($N = 80$).

Characteristic	Value
Acute phase baseline	
Age, Mean (SD), (years)	54.9 (15.3)
Age group, N (%)	
18–59 (years)	46 (57.5)
≥60 (years)	34 (42.5)
Gender, N (%)	
Men	32 (40.0)
Women	48 (60.0)
Race, N (%)	
White	62 (78.5)
Black	12 (15.2)
Other	5 (6.3)
Hispanic ethnicity, N (%)	12 (15.0)
Education, Mean (SD), (years)	13.8 (3.5)
Inpatient status at acute phase enrollment, N (%)	55 (68.8)
≥2 lifetime depressive episodes, N (%)	60 (75.0)
Duration of current episode of depression, Median (IQR), (months)	6 (3,12)
CIRS-G total score, Median (IQR)	2.5 (1,6)
Randomization phase baseline	
Ham-D 17 total score, Mean (SD)	5.6 (3.6)
CORE total score, Median (IQR)	1 (0, 4.5)
RBANS Coding total score, Mean (SD)	5.3 (3.4)
Sertraline dosage, Median (IQR) (mg/day)	150 (150, 200)
Olanzapine dosage, Median (IQR) (mg/day)	15 (10,20)

Abbreviations: CIRS-G = Cumulative Rating Scale for Geriatrics (Miller et al., 1992); Ham-D 17 = 17-item Hamilton Depression Rating Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

3.4. Bivariate relationships between psychomotor disturbance variables, and between white matter microstructure and psychomotor disturbance

CORE and Coding were significantly and negatively correlated ($r = -0.341$; $p = 0.002$).

As shown in Table 2, MD had an absolute correlation coefficient of ≥0.3 (typically regarded as medium effect size (Cohen, 1988)) with one or both measures of psychomotor disturbance (CORE or Coding) in 10 of the 15 tracts investigated; CORE was more frequently correlated at this threshold than was Coding ($N = 9$ tracts versus $N = 3$ tracts, respectively). All correlations were in the expected direction, with less organized white matter microstructure (higher MD) being associated with more severe psychomotor disturbance (higher total CORE and lower Coding scores). In contrast, FA had a correlation of ≥0.3 with one or both measures of psychomotor disturbance in only 3 of 15 tracts, with

Table 2
Correlation coefficients (Spearman's r) between white matter microstructure (MD or FA) and psychomotor (CORE and Coding) measures in each white matter tract.

Tract	MD - CORE	MD - Coding	FA - CORE	FA - Coding
AF left	0.319[a]	−0.277[a]	−0.321[a]	0.327[a]
AF right	0.314[a]	−0.249[a]	-0.241[a]	0.181
CB left	0.305[a]	−0.189	−0.192	0.230[a]
CB right	0.337[a]	−0.253[a]	−0.246[a]	0.221
CC2	0.371[a]	−0.293[a]	−0.332[a]	0.337[a]
CR-F left	0.287[a]	−0.219	−0.0005	0.107
CR-F right	0.214	−0.254[a]	0.092	0.205
SF left	0.306[a]	−0.275[a]	−0.016	0.150
SF right	0.181	−0.245[a]	0.020	0.093
SLF-II left	0.336[a]	−0.230[a]	−0.163	0.165
SLF-II right	0.129	−0.189	−0.051	0.205
TF left	0.380[a]	−0.388[a]	−0.094	0.194
TF right	0.359[a]	−0.359[a]	−0.079	0.165
UF left	0.237[a]	−0.297[a]	−0.112	0.197
UF right	0.207	−0.347[a]	−0.157	0.300[a]

Abbreviations: AF = arcuate fasciculus; CB = cingulum bundle; CC2 = corpus callosum (genu); CR-F = corona radiata-frontal component; FA = fractional anisotropy; MD = mean diffusivity; SF = striato-frontal; SLF-II = superior longitudinal fasciculus II, TF = thalamo-frontal; UF = uncinate fasciculus.
[a] $p < 0.05$.

correlations in the expected direction (lower FA being correlated with more severe psychomotor disturbance).

3.5. Aim 1. Relationship between psychomotor disturbance and relapse

In separate multivariable Cox proportional hazards models that adjusted for age, higher CORE total score at RCT baseline was associated with greater probability of relapse (hazard ratio [HR], 1.104 [95 % CI, 1.026–1.187], $p = 0.008$), but Coding score was not associated with relapse (HR, 0.894 [95 % CI, 0.787–1.015], $p = 0.083$).

3.6. Aim 2. Relationship between white matter microstructure and relapse

Table 3 shows the relationship between MD and relapse for each tract. Controlling for age, higher MD was significantly associated with greater probability of relapse in the following tracts: CC2, left SF, left and right TF. Using the Benjamini-Hochberg procedure to correct for a potential false discovery rate of 20 %, the adjusted alpha level was $p = 0.04$ for this analysis. At this alpha level, only MD in the left SF and left TF were significantly related to outcome. FA was not associated with probability of relapse in any of the 15 tracts (data not shown).

3.7. Aim 3. Relationships among white matter microstructure, psychomotor disturbance, and relapse

Table 4 shows the nested models (i.e., CORE and age predicting probability of relapse versus CORE, age, and MD predicting probability of relapse), examining whether MD accounts for the relationship between CORE and relapse. Only white matter tracts where MD was found to have a significant relationship with relapse (Table 2) were included in this analysis. The −2 Log L column in Table 4 represents the model fit (lower values represent better fit) and the LRT is the likelihood ratio test, used to compare the fit of the nested models statistically via the −2 Log L values for each model.

For all models, adding MD to CORE and age improved the model fit, as shown by the better fit statistic and statistically significant LRT values. However, for each model, the inclusion of MD does not substantially change the relationship between CORE and probability of relapse. MD demonstrates a significant relationship with probability of relapse in each model. Taken together, these findings suggest that psychomotor disturbance predicts relapse beyond MD, and vice versa.

Given that neither Coding nor FA were related to probability of relapse, we did not examine the relationships among Coding, MD and relapse, nor did we examine the relationships among FA, psychomotor disturbance and relapse.

Table 3
Results of age-adjusted cox proportional hazards models showing relationships between mean diffusivity and probability of relapse in each white matter tract.

Tract	N	Hazard ratio	95 % Wald CL		P-value	P-value (corrected for FDR)
AF left	79	1.013	0.999	1.027	0.077	0.080
AF right	79	1.006	0.990	1.020	0.476	0.160
CB left	80	1.013	0.997	1.030	0.109	0.120
CB right	80	1.011	0.999	1.022	0.076	0.067
CC2	79	1.012	1.001	1.022	0.029[a]	0.040
CR-F left	75	1.004	0.988	1.020	0.623	0.173
CR-F right	78	1.006	0.993	1.020	0.381	0.133
SF left	80	1.012	1.002	1.023	0.023[a]	0.027[b]
SF right	80	1.011	0.998	1.023	0.087	0.107
SLF-II left	80	1.002	0.989	1.016	0.726	0.200
SLF-II right	78	1.003	0.990	1.016	0.644	0.187
TF left	80	1.019	1.005	1.033	0.009[a]	0.013[b]
TF right	80	1.015	1.001	1.028	0.029[a]	0.053
UF left	77	1.007	0.999	1.014	0.085	0.093
UF right	79	1.004	0.995	1.013	0.396	0.147

Alpha adjusted using Benjamini-Hochberg procedure for false discovery rate of 20 % = 0.04.
Abbreviations: AF = arcuate fasciculus; CB = cingulum bundle; CC2 = corpus callosum (genu); CR-F = corona radiata-frontal component; SF = striato-frontal; SLF-II = superior longitudinal fasciculus II, TF = thalamo-frontal; UF = uncinate fasciculus.
[a] $p < 0.05$.
[b] $p < 0.04$.

4. Discussion

The main finding of this study is that psychomotor disturbance and white matter microstructure were related to probability of relapse in patients with remitted psychotic depression. White matter microstructure and psychomotor disturbance were correlated, but white matter microstructure did not account for the relationship between psychomotor disturbance and relapse in multivariable statistical models. Rather, both psychomotor disturbance (as measured by the CORE) and MD in corpus callosum (genu), left striato-frontal, and left and right thalamo-frontal each significantly contributed to prediction of relapse.

This study is the first to examine the relationship between white matter microstructure and relapse in psychotic depression. Relevant brain regions that have typically been associated with acute treatment outcome of non-psychotic depression in open-label trials and observational studies include frontal-limbic and frontal-subcortical pathways. For instance, Alexopoulos and colleagues found that lower FA in frontal regions lateral to the anterior cingulate at baseline was associated with lower remission of late-life depression following open-label treatment with citalopram (Alexopoulos et al., 2002). In another study, Alexopoulos et al. found that lower FA in multiple frontal limbic brain regions was associated with lower remission rate following 12 weeks of escitalopram treatment in late-late life depression (Alexopoulos et al., 2008). Based on data from electronic health records and naturalistic follow up, Hoogenboom and colleagues reported that not attaining remission of MDD was associated with lower FA in the medial body of the fornix (Hoogenboom et al., 2014). In a logistic regression analysis of several anterior cingulate-limbic tracts, Korgaonkar et al. identified that a model containing the cingulum cingulate (higher FA) and stria terminalis (lower FA) were significant predictors of remission (Korgaonkar et al., 2014). A preliminary study in adult patients with MDD found that response to ketamine was related to FA, MD, and radial diffusivity (RD), all in expected directions in the cingulum and forceps minor (Vasavada et al., 2016). On the other hand, Taylor and colleagues found that participants with late-life depression who did not attain remission following treatment with open-label sertraline exhibited higher FA values in the superior frontal gyri and anterior cingulate cortices bilaterally compared to those who did remit. This study did not identify any differences in apparent diffusion coefficient (ADC; analogous to MD) between remitters and non-remitters. The authors postulated that the unexpected association between higher FA and remission probability may reflect population and methodological limitations or limitations inherent to diffusion tensor imaging (Taylor et al., 2008).

From a neuroanatomical perspective, the results of the current study are broadly in keeping with these findings in acute treatment studies of non-psychotic depression. In addition, our findings that MD in the thalamo-frontal tract, part of the cortico-striatal-thalamic-cortical (CSTC) loop, was most strongly related to both psychomotor performance and relapse is in keeping with convergent evidence from functional and structural neuroimaging studies involving the CSTC. The CSTC, as part of the salience network, is of relevance to multiple psychiatric and movement disorders, and links cortical and subcortical regions involved in cognition, attentional control, motivation, motor control and salience (Peters et al., 2016). In MDD, a relationship between functional connectivity among components of the CSTC and outcome has been described. Striato-frontal functional connectivity during reward processing in patients with MDD was found to be

Table 4
Comparison of nested models demonstrating the relationships among CORE, MD, and probability of relapse in each white matter tract.
Five models are shown — the base model containing CORE and age (applicable to all tracts), and one model for each individual tract containing CORE, age, and MD.

Model	Variables in model	Parameter	Hazard ratio	95 % Wald CL		−2 LOG L	LRT (df 1)[a]	*p*-Value (LRT)
Base	CORE, age	CORE	1.104	1.026	1.187	232.477	–	–
CC2	CORE, age, MD	CORE	1.111	1.028	1.201	226.741	4.876	0.027
		MD	1.012	1.001	1.022			
SF left	CORE, age, MD	CORE	1.099	1.022	1.183	228.283	4.194	0.041
		MD	1.012	1.001	1.023			
TF left	CORE, age, MD	CORE	1.091	1.016	1.171	227.300	5.177	0.023
		MD	1.019	1.003	1.034			
TF right	CORE, age, MD	CORE	1.107	1.026	1.194	228.033	4.444	0.035
		MD	1.015	1.001	1.028			

All models and parameter estimates presented in table are statistically significant at a level of $p < 0.05$.
Abbreviations: CC2 = corpus callosum (genu); MD = mean diffusivity; SF = striato-frontal; TF = thalamo-frontal.
[a] LRT (likelihood ratio test) represents the likelihood ratio test of nested the models (CORE, age vs. CORE, age and MD). df indicates one degree of freedom in the LRT as there is one additional parameter in the second model.

predictive of response to behavioral activation therapy (Walsh et al., 2019), and increased baseline activity in the anterior cingulate, as well as decreased activation in the insula and striatum, were associated with greater likelihood of response to pharmacological treatment on meta-analysis (Fu et al., 2013).

Despite our and others' findings that white matter abnormalities are associated with MDD outcome in frontal-subcortical and frontal-limbic tracts, it is possible that this relationship is generalized throughout the brain, rather than confined to specific tracts. In this study and in previous studies, potentially relevant regions were selected a priori based on their evidence in MDD. Larger studies with sample sizes allowing for testing of multiple white matter tracts with reduced risk of type II error, as well as multimodal studies (e.g., combining functional and structural imaging) would allow researchers to gain a more detailed understanding of the microstructural abnormalities associated with MDD outcomes and their functional correlates.

The clinical significance of the relationship between CORE score and relapse probability is apparent: for each point on the CORE, the probability of relapse during the observation period increased by 10 %. Higher MD is also associated with a higher probability of relapse, but the clinical meaning of a unit of MD (measured as mm^2/s) is unknown, and the size of the hazard ratios pertaining to MD and relapse cannot be interpreted clinically. For example, in the left thalamo-frontal tract, the expected hazard increased by 1.9 % for each unit increase in MD, but the clinical meaning of this finding is unknown.

Although previous studies identified a relationship between acute treatment outcome and FA, we did not find that FA was related to relapse. Instead, we found that MD was particularly relevant, both in terms of its relationship to psychomotor disturbance across multiple tracts and in terms of its relationship to relapse. DTI metrics are non-specific, representing various aspects of myelin status and axonal organization. FA represents the fraction of the magnitude of the tensor that is due to anisotropic water diffusion (indicates directionality of the voxel), while MD is non-directional and represents the magnitude of water diffusion within brain tissue (O'Donnell and Westin, 2011). Therefore, white matter could exhibit an increase in diffusion in all directions but maintain the same overall directionality. Relationships between DTI and clinical indices could vary depending on study methodology and population. For example, in examining DTI data from persons with Alzheimer's, mild cognitive impairment and controls in the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, Nir et al., found that, while there were group differences among all diffusivity measures, MD was most sensitive to the subtle cognitive differences observed in mild cognitive impairment, with FA being least sensitive to group differences (Nir et al., 2013). In our group of remitted participants, it is possible that only MD is sensitive to more subtle white matter pathology associated with risk of relapse. More sophisticated neuroimaging techniques, such as combining quantitative magnetization transfer with multi-shell diffusion weighted imaging and post-processing models to separate the myelin and axonal volume fractions of the white matter (Mohammadi and Callaghan, 2021), will hopefully allow us to probe white matter abnormalities in MDD further.

In terms of psychomotor disturbance, we identified that CORE, but not Coding, was associated with risk of relapse. This finding is not surprising; CORE is a general clinical measure of psychomotor performance, while Coding represents information processing speed only, a neurocognitive measure. Therefore, CORE may be a more sensitive measure of the construct of psychomotor disturbance in this setting, or may be measuring aspects of psychomotor performance that are predictive of relapse not measured by Coding.

Given our finding that psychomotor disturbance and white matter microstructure each contribute to relapse, the neurobiological mechanisms underlying the relationship between psychomotor disturbance and relapse remain undetermined. A variety of mechanisms could be considered in future studies, including unmeasured abnormalities in white matter microstructure, cortical thinning (Voineskos et al., 2020), abnormalities in functional connectivity (Berwian et al., 2020), or a combination of factors.

Strengths of this study include a well-characterized sample, a rigorous approach to the diagnosis of psychotic depression and the assessment of relapse, and the use of state-of-the-art tractography methods with a comprehensive white matter atlas (F. Zhang et al., 2018). Confounding medication effects were minimized as all participants were taking sertraline and olanzapine at the time of the MRI acquisition and measurement of psychomotor disturbance. Our selected tractography method allowed us to probe the relationship between variables of interest across multiple potentially relevant tracts.

This study has several limitations. First, as a secondary analysis, it was not powered to test the aims of these analyses. Second, the sample size was not sufficient to test the interaction of the independent variables and randomized treatment group with probability of relapse. In the full STOP-PD sample, CORE total score was significantly associated with relapse in each treatment group (Flint et al., 2021). However, we do not know whether this is the case for MD. Thus, analysis of the association between MD and risk of relapse may potentially have been confounded by the heterogeneity of randomized treatment. Third, because of the smaller sample size, we elected a priori to include age as the only covariate in the Cox regression models and not to include additional covariates that are not typically related to both white matter microstructure and psychomotor disturbance. Fourth, given the possibility of both a type I error (because of the number of statistical tests) and a type II error (because of small sample size), these findings must be considered preliminary and in need of replication.

In conclusion, both psychomotor disturbance and MD were associated with relapse in patients with remitted psychotic depression. MD did not account for the relationship between psychomotor disturbance and

relapse. The mechanism underpinning psychomotor disturbance and relapse in psychotic depression remains unexplained and warrants further investigation. However, our findings add to a growing body of literature suggesting that abnormalities of white matter microstructure portend to worse treatment outcome of MDD.

CRediT authorship contribution statement

Substantial contributions to the conception or design of the work and/or the acquisition, analysis, or interpretation of data for the work: All authors.

Drafting of the manuscript and/or revising it critically for important intellectual content: All authors.

Final approval of the version to be published: All authors.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.04.136.

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