Effects of continuation versus discontinuation of antipsychotic treatment on white matter microstructure in first episode psychosis

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Abstract

Background: Diffusion tensor imaging (DTI) studies have reported decreased white matter (WM) integrity in first-episode psychosis (FEP) patients. However, the impact of long-term exposure and discontinuation of antipsychotic medications on WM in FEP patients is unclear.

Methods: Fifty-four FEP patients three to six months in remission underwent DTI scanning at baseline and 31 patients were re-scanned after 12 months, during which patients either continued or discontinued antipsychotic medication. Voxel-wise between-group (continue/discontinue) comparisons of fractional anisotropy (FA) values were performed at baseline and follow-up. Additionally, linear mixed models were performed to assess the interaction between time (baseline/follow-up) and continuation versus discontinuation on FA values of WM tracts.

Results: Voxel-wise between group comparisons demonstrated no significant differences in FA at baseline or follow-up. However, longitudinal analyses indicated increased FA in the left ($t = 2.53$, $p = 0.0181$) and right ($t = 2.38$, $p = 0.0251$) corticospinal tract after antipsychotic discontinuation, although the results did not survive multiple comparisons correction. Further, a trend toward a relationship between the decrease in antipsychotic dosage and increased FA in the right cingulum ($t = 2.029$, $p = 0.0597$) was observed.

Conclusions: The current study provided tentative evidence that discontinuation of antipsychotics after achieving remission from FEP is associated with increased FA in the bilateral corticospinal tract. Future studies should investigate whether the changes in FA observed in this study reflect reversal of a pathological process, as this can provide important insight into the potential risks and/or benefits of antipsychotic maintenance treatment after FEP.

Layman's summary

Psychosis is a serious mental disorder that affects how people think, feel, and behave. People experiencing psychosis often lose contact with reality, for example, they see or hear things that others do not. It's a symptom of a group of mental disorders called schizophrenia spectrum- or related disorders. These disorders are often treated with drugs called antipsychotics, which work well in reducing psychotic symptoms. It is believed these psychotic symptoms are partly caused by problems in the connections between different parts of the brain. These connections are formed by a substance called white matter. White matter transmits information from one part of the brain to another, comparable to highways connecting different cities. Previous studies have photographed the white matter of the brain using a specific method called diffusion tensor imaging (DTI). DTI allows researchers to investigate the amount and quality of white matter between different parts of the brain. Previous studies that used this technique have shown that people with psychosis have less white matter in brain regions responsible for emotion processing and regulation. However, it is not clear if using antipsychotics for several months influences the amount and quality of the white matter. Also, it is unclear what happens to the amount and quality of the white matter when people who previously used antipsychotics stop using them.

This study aimed to investigate what happens to the connections of the brain when patients who experienced a first episode of psychosis use antipsychotic medications for an entire year or stop using them. The study used brain scans to measure the white matter in 54 patients that recovered from a first psychosis three to six months ago and measured white matter again after 12 months in 31 patients. During this time, some of the patients continued taking their antipsychotic medication while others stopped taking it. The study found that when patients stopped taking antipsychotic medication, connections in areas of the brain responsible for movement and emotion regulation improved over time. However, it is important to note that the study had some limitations. First, the brain scan was not repeated after 12 months in almost half of the participants, which was partly due to the COVID-19 pandemic. Second, there was no control group present, which is a group of patients that does not receive the treatment. Therefore, the current study is not able to compare if the changes in the white matter are related to the antipsychotic treatment. At this moment, doctors recommend patients use their medication for at least a year after they recover from a psychosis, but this recommendation may change if further research supports the current findings.

1. Introduction

Psychosis is the defining feature of a group of mental disorders classified as schizophrenia spectrum- or related disorders (American Psychiatric Association, 2013) and is characterized by positive symptoms (e.g. hallucinations, delusions, disorganized thought and behavior), negative symptoms (e.g. avolition, alogia, emotional numbing), and cognitive dysfunction (e.g. impairments in sustained attention, diminished working memory) (Arciniegas, 2015). Disrupted functional and structural connectivity across neuronal networks have been argued to be part of the pathophysiological mechanism that underlies psychotic disorders (Friston, 2002; Stephan et al., 2009). In line with this hypothesis, studies using various brain imaging techniques have found widespread alterations in white matter (WM) microstructure in patients with schizophrenia and related disorders, which is indicative of reduced structural connectivity (Bora et al., 2011; Ellison-Wright & Bullmore, 2009; Kelly et al., 2018; Mighdoll et al., 2015).

WM can be studied in-vivo using diffusion tensor imaging (DTI), a non-invasive magnetic resonance imaging (MRI) technique that measures water diffusion in the brain, which reflects the organizational integrity of WM microstructure and fiber organization (Assaf & Pasternak, 2008; Basser et al., 1994; le Bihan et al., 2001). DTI provides several quantitative measurements, of which fractional anisotropy (FA) is the most frequently employed. FA assesses the degree of anisotropic diffusion, which is high in regions with high fiber density such as WM bundles. Hence, decreased FA can be interpreted as a degradation of myelin sheet and/or a reduction in axon density (Bartzokis, 2004; Sullivan & Pfefferbaum, 2006).

DTI studies have consistently reported reduced FA in patients with psychotic disorders, specifically in the frontal-limbic-striatal circuit which correlated with illness chronicity (Bora et al., 2011; Ellison-Wright & Bullmore, 2009; Yao et al., 2013). The largest cross-sectional DTI study and meta-analysis to date by Kelly et al. (2018) reported significantly lower FA values in schizophrenia patients (n = 1963) across 29 studies compared to healthy controls (n = 2359) throughout the whole brain, with specific reductions in the corpus callosum and anterior corona radiata. These reductions were associated with positive and negative symptom severity scores (Kelly et al., 2018). Previous research also linked integrity of WM to the severity of cognitive impairment (Knöchel et al., 2012; Rosenberger et al., 2012; Whitford et al., 2010). Studies of patients with first-episode psychosis (FEP) have yielded mixed results, with some studies finding WM abnormalities (Bora et al., 2011; Faria et al., 2019; Kraguljac et al., 2021) and others not (Kong et al., 2011; Peters et al., 2010). However, factors such as illness course, symptom severity, and exposure to antipsychotic medication may affect the degree of WM abnormalities (Bora et al., 2011).

Antipsychotics exert their therapeutic properties by (partially) blocking the dopamine D2 receptor in ventral striatal regions (Kaar et al., 2020), while preclinical studies have shown that dopamine D2 receptor blockage is associated with a reduction in myelin structural proteins,

oligodendrocytes, and astrocytes in the brain (Dorph-Petersen et al., 2005; Feng, 2008; Konopaske et al., 2008; Niu et al., 2010). Clinical studies examining the effect of antipsychotic treatment on WM microstructure using DTI in drug naïve FEP patients have reported conflicting results. Wang et al. (2013) observed that after six weeks of antipsychotic treatment, FEP patients (n = 35) showed significant decreases in FA in several WM tracts. Szeszko et al. (2014) found decreased FA in the parietal and occipital lobes in FEP patients treated with aripiprazole or risperidone for 12 weeks. Correspondingly, Meng et al. (2019) reported widespread decreases in FA after six weeks of treatment with second-generation antipsychotics in 35 FEP patients. In contrast, Reis Marques et al. (2014) found a positive association between increased FA and antipsychotic exposure in 63 FEP patients after 12 weeks of treatment. Ebdrup et al. (2016) showed that FA increased after six weeks of treatment with amisulpride in 28 FEP patients. Furthermore, Serpa et al. (2017) reported increased FA in several WM tracts once patients achieved remission from FEP with successful antipsychotic treatment. However, two other studies observed no effect of eight weeks of antipsychotic treatment on FA in FEP patients (Zeng et al., 2016; Zong et al., 2019). To date, no DTI study has yet investigated the impact of prolonged exposure to antipsychotic medication on WM microstructure in FEP patients. This knowledge gap is clinically relevant as current treatment guidelines recommend the continuation of antipsychotic medication for at least one year following remission of FEP to reduce the risk of relapse (Leucht et al., 2017; Leucht et al., 2012; van Alphen et al., 2012).

To evaluate the impact of antipsychotic medication on WM microstructure, we conducted a longitudinal one-year follow-up DTI study in 54 remitted FEP patients. Since previous research on the effect of antipsychotic exposure on WM tracts has given inconsistent results in terms of direction and location of WM changes, we chose an exploratory approach without selecting specific regions of interest. Additionally, as previous studies investigating the effect of antipsychotics on WM microstructure have primarily been conducted in patients with acute psychosis, the presence of psychotic symptoms may have affected the results. To eliminate this possibility, we assessed FEP patients who were 3-6 months in remission, after which half of them discontinued medication and others continued medication. We hypothesized that discontinuation of antipsychotic medication would be associated with increased FA in FEP patients compared to antipsychotic maintenance treatment. Additionally, we hypothesized that reducing the dosage of antipsychotics would be associated with an increase in FA values at follow-up compared to baseline.

2. Methods

2.1 Participants

Fifty-four patients of the ongoing Handling Antipsychotic Medication Long-term Evaluation of Targeted Treatment (HAMLETT) study underwent MRI scans at baseline (3-6 months in remission from FEP), and at follow-up after 12 months (Begemann et al., 2020). Ethical approval for the

HAMLETT study was obtained from the Medical Ethics Committee of the University Medical Center Groningen, the Netherlands (protocol number: NL 62202.042.17, trial registration EudraCT number: 2017-002406-12). Recruitment, in-, and exclusion criteria and study procedures of the HAMLETT study are described by Begemann et al., (2020). Briefly, patients aged between 16 and 60 years who were 3-6 months in remission of FEP, and used antipsychotic medication were included in the study. Additional exclusion criteria for participation in the MRI study included MRI contraindications (e.g., claustrophobia, metal implants) and pregnancy. Written informed consent was obtained before study participation.

2.2 Study design

Participants underwent two MRI sessions with a 12-month interval, during which they either continued or discontinued antipsychotic medication. Patients who continued medication were allowed to adjust their dosage if clinically indicated. The baseline assessment was conducted when participants were three to six months in remission of FEP and were all using antipsychotic medication. Diagnosis and illness duration were measured with the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). During the 12-month interval (serious) adverse events were recorded, including psychotic relapse and hospitalization due to psychotic symptoms. Furthermore, as part of the HAMLETT study, the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess psychotic symptom severity and the Global Assessment of Functioning (GAF) to evaluate psychosocial functioning (Jones et al., 1995).

Data on dispensed antipsychotic medication were obtained from the Dutch Foundation for Pharmaceutical Statistics (in Dutch: Stichting Farmaceutische Kengetallen, SFK), an independent organization that collects dispensation data from 98% of the community pharmacies in the Netherlands (SFK, 2021). An anonymous matching procedure was used to obtain information with regards to the type and dosage of antipsychotic drug that was dispensed. For participants where SFK data was not available (n = 7), self-reported questionnaires on medication use were used to obtain information on the type, dosage, start and stop date of antipsychotic medication. Due to the naturalistic study design, patients used different types of medication. Therefore, antipsychotic dosages used at baseline and follow-up were converted to olanzapine equivalents using the method described by Leucht et al. (2016). Type of antipsychotic medication was grouped into three categories: aripiprazole, olanzapine, and other (haloperidol, risperidone, amisulpride, and quetiapine) as sample sizes did not permit separate analyses.

2.3 Data acquisition

MR images were obtained at the Radiology department of the University Medical Center Groningen using a Siemens MAGNETOM Prisma 3T MRI scanner with a 64-channel head coil. Diffusion data were acquired using an echo-planar imaging sequence with the following parameters: voxel resolution = 2 mm isotropic, repetition time/echo time = 550/85.0ms, field of view = 210 mm x 210 mm, slice

thickness = 2.0 mm, EPI factor = 104, phase encoding (PE) = anterior > posterior. Diffusion weighted images were acquired along 64 directions, of which 64 volumes with a b-value of 1000 s/mm2 and 64 volumes with a b-value of 2500 s/mm2. Additionally, two unweighted reference images (b = 0 s/mm2) with reversed PE directions (anterior/posterior) were acquired, which resulted in a total acquisition time of 13:07 min. The same scan sequence and parameters were used for both DTI scan sessions.

2.4 Data (pre)processing

Diffusion MRI processing was performed with MRtrix3 version 3.0.3 (Tournier et al., 2019) and FSL version 6.0.5.1 using the FMRIB's software library (Jenkinson et al., 2012; Smith et al., 2004). The following steps of processing were used: (i) a principal component analysis-based algorithm (dwidenoise package*;* Tournier et al., 2019; Veraart et al., 2016) was used to concatenate and denoise the images; (ii) data was corrected for susceptibility-induced distortions (topup package; Andersson et al., 2003), (iii) eddy current correction (eddy_openmp*;* Andersson & Sotiropoulos, 2016) was performed to correct for gradient-coil distortions and head motion; (iv), non-brain tissue was removed from the data (dwi2mask; Tournier et al., 2019); (iv) dtifit (Andersson et al., 2003; Andersson & Sotiropoulos, 2016) was used for local diffusion tensor fitting at each voxel. This yielded voxel-wise participant-specific maps of FA values. After pre-processing, FA maps were skeletonized using the TBSS pipeline (Smith et al., 2006). First, FA images were nonlinearly transformed into a $1 \times 1 \times 1$ mm3 MNI152 template using affine registration. Then, all participant's FA maps were averaged to create a mean FA image and narrowed to generate a mean FA skeleton (threshold at FA = 0.2) after which values of every participant's FA map were projected onto the mean skeleton. Whole brain and regional mean FA values were extracted using the Johns Hopkins University (JHU) White-Matter Tractography Atlas (Wakana et al., 2004).

2.5 Statistical analysis

Statistical analysis was performed using the R software package, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Differences in demographic and clinical characteristics between patients who continued versus discontinued medication, and between baseline and follow-up were analyzed using independent t-tests for continuous variables, chi-square (χ^2) for categorical variables, and paired t-tests to compare changes in clinical characteristics over time. Participants that did not complete both assessments were compared to those who did with the same set of statistical tests.

To evaluate differences in skeletonized FA data between FEP patients who continued versus discontinued medication, voxel-wise analyses based on a general linear model were performed at baseline and follow-up using FSL's randomize tool. Non-parametric permutation-based tests with 5000 permutations and threshold-free cluster enhancement to control for familywise error (FWE) rate were applied in the final statistical models. Clusters were identified as significant when the corrected voxel-wise *p*-vales were < .05.

We explored the changes in FA over time of specific WM tracts identified with the JHU white matter tractography atlas using linear mixed-effect models (Kuznetsova et al., 2017). For each region of interest (ROI), we investigated the interaction between time (baseline/follow-up) and group (continue/discontinue) with time-by-group and age modeled as fixed effect and subject as random effect. Post hoc testing was performed with models showing a significant main- and/or interaction effect. Due to the significant difference in the duration of untreated psychosis and symptom severity score measured with the PANSS at baseline between groups, these variables were included as covariates in the final model.

In addition, for each ROI, we examined how antipsychotic dosage and type of antipsychotic medication affected fractional anisotropy over time using a linear mixed model. The model included time, dosage of antipsychotics, and type of antipsychotic medication as fixed factors, and subject as a random factor. We chose to use a linear mixed model as it can handle missing data under the assumption that the data are missing completely at random. This allowed us to include participants who only completed the baseline (n = 29) or follow-up (n = 3) assessment. We ensured no violation of the multivariate normal distribution assumption by visual inspection of residuals and quantile-quantile plots. Variables that showed non-normal distributions were normalized using logarithmic transformations. Dosage of antipsychotics in olanzapine equivalents was successfully normalized using a logarithmic transformation. Statistical significance was determined using a threshold of $p \leq .05$, and multiple testing was corrected using the false discovery rate procedure (FDR; Benjamini & Hochberg, 1995) with $p = .05$. As these analyses are explorative in nature, the raw and FDR-adjusted *p*-values were reported.

3. Results

Demographic and clinical characteristics

Patient demographic and clinical characteristics are reported in Table 1. The duration of untreated psychosis ($p = .047$) and severity of negative psychotic symptoms at baseline ($p = .009$) of patients who discontinued antipsychotic medication was significantly lower compared to patients who continued medication. Between baseline and follow-up, eight patients had a psychotic relapse (five in the continue group, three in the discontinue group). The number of relapses did not differ significantly between the two groups ($t = 0.82$, $p = .422$). No significant changes in PANSS and GAF scores were observed in the continue and discontinue groups between baseline and 12 months follow-up ($p > 0.05$, Supplementary Table 1). Due to the COVID-19 pandemic, several participants were not able to complete the baseline or follow-up assessment (n = 26) and for some participants, the scan interval was longer than 12 months. The scanning interval did not differ between the continue and discontinue groups ($p > 0.05$). In total, we included 51 scans at baseline and 31 scans at follow-up. Participants who completed both assessments did not significantly differ from those who did not on age, sex, handedness, education, duration of untreated psychosis, age of onset psychosis, antipsychotic dosage, and PANSS and GAF scores (Supplementary Table 2).

Table 1. Baseline demographic and clinical characteristics

	Baseline characteristics participants				
	All (n =54)	Continue (n = 14)	Discontinue (n = 14)	Statistic	*p*-value
Age (mean ± SD)	27.20 ± 7.91	27.43 ± 8.10	24.43 ± 4.80	t = 1.19	.247
Sex (male | female)	37 | 17	7 | 7	9 | 5	$\chi^2 = 0.15$	.703
Years of education (mean ± SD)	14.37 ± 1.95	14.43 ± 2.14	14.07 ± 2.34	t = 0.42	.677
Handedness (right | left)	44 | 10	11 | 3	11 | 3	*F*	1.00
Age of onset psychosis (mean ± SD)	26.26 ± 8.05	26.07 ± 8.15	23.43 ± 5.39	t = 1.01	.322
Duration of untreated psychosis in days (mean ± SD)	102.96 ± 104.96	104.14 ± 122.11	30.64 ± 34.77	t = 2.17	.047*
Days between scans (mean ± SD)	442.65 ± 139.14	410.86 ± 85.40	474.43 ± 192.87	t = -1.13	.274
PANSS total	43.41 ± 9.16	43.64 ± 7.06	38.79 ± 7.47	t = 1.89	.070
PANSS positive	9.35 ± 2.93	9.21 ± 2.72	8.07 ± 1.98	t =1.27	.216
PANSS negative	10.90 ± 3.57	11.64 ± 2.92	8.86 ± 2.18	t = 2.86	.009**
PANSS general	23.17 ± 4.86	22.79 ± 5.13	21.57 ± 4.75	t = 0.65	.522
GAF-score	66.90 ± 12.51	63.50 ± 11.12	71.86 ± 13.31	t = -1.80	.083
Days of antipsychotic exposure before baseline assessment	197.36 ± 81.83	191.07 ± 91.86	203.64 ± 73.39	t =-0.46	.652
Antipsychotic dosage	7.55 ± 5.51	10.33 ± 6.19	7.28 ± 5.76	t = 1.35	.188
Type of antipsychotic					
Olanzapine	19 (35.2 %)	3 (21.4 %)	4 (28.6 %)		
Aripiprazole	17 (31.5 %)	6 (42.9 %)	6 (42.9 %)		
Haloperidol	6 (11.1 %)	1 (7.14 %)	1 (7.14 %)		
Risperidone	4 (7.41 %)	2 (14.3 %)	-		
Amisulpride	2 (3.70 %)	1 (7.14 %)	1 (7.14 %)		
Quetiapine	5 (9.26%)	1 (7.14 %)	2 (14.3 %)		
Clozapine	1 (1.85 %)	-	-		

SD = standard deviation; PANSS = Positive and Negative Syndrome Scale; GAF = Global Assessment of Functioning; F = Fisher's exact; Continue = group participants who use antipsychotic medication at baseline and follow-up; Discontinue = group of participants who stopped using antipsychotics at time of follow-up. The statistics and *p*-values are the results of comparisons between the continue and discontinue group at baseline. Antipsychotic dosage is reported in olanzapine equivalents, calculated as described by Leucht et al. (2016). *Significant at the $p < .05$ level. ** Significant at the $p < .01$.

Voxel wise whole brain analyses at baseline and follow-up

At baseline, voxel-wise between-group comparisons of the patients who continued versus discontinued antipsychotic medication of skeletonized WM maps yielded no significant differences ($p < 0.05$; FWE-corrected). The voxel-wise between-group comparisons at follow-up showed no significant differences between patients who continued medication compared to patients who discontinued in skeletonized WM maps ($p > 0.05$; FWE-corrected).

Longitudinal analysis of white matter tracts

The results of the linear mixed models performed to investigate the effects of continuation versus discontinuation of antipsychotic medication on FA of WM tracts over time are displayed in Table 2. There was a significant interaction between time and group in the left ($t = 2.53$, $p = 0.0181$) and right ($t = 2.38$, $p = 0.0251$) corticospinal tract indicating changes in FA over time differed between the two groups (Table 2). Post-hoc comparisons revealed that patients who discontinued antipsychotic medication showed a greater FA increase over the course of 12 months in the left ($t = 3.22$, $p = 0.0033$) and right ($t = 3.257$, $p = 0.030$) corticospinal tract compared to patients who continued antipsychotic medication (left: $t = 0.136$, $p = 0.8928$; right: $t = 0.31$, $p = 0.756$; Figure 1a). Furthermore, the interaction between time and group showed a trend towards significance in the right inferior longitudinal fasciculus ($t = 1.979$, $p = 0.0589$). Post-hoc comparisons showed that patients who discontinued antipsychotic medication had a greater FA increase in the right inferior longitudinal fasciculus ($t = 2.93$, $p = 0.0068$), compared to patients that continued medication ($t = 0.14$, $p = 0.8887$). None of the other subfields showed a significant interaction between time and group ($p > 0.05$, Table 2). Further, the left uncinate fasciculus indicated a significant main effect of time ($t = 2.270$, $p = 0.0317$; Supplementary Table 3). Post hoc testing showed a significant increase of FA in the left uncinate fasciculus in patients who continued medication ($t = 2.270$; $p = 0.0317$), but not in patients who discontinued medication ($t = 0.574$, $p = 0.5709$; Figure 1b). The above-mentioned results did not change after controlling for negative symptom severity scores at baseline or the duration of untreated psychosis. However, after FDR correction for multiple testing, the observed effects were non-significant (Table 2).

Table 2. Linear mixed-effect models to test the effect of continuation versus discontinuation of antipsychotics over 12 months in first episode psychosis patients on fractional anisotropy (FA)

White matter tract	Region	Group	Time by group interaction				Main effect of time		
			Contrast 10^{-3}	*df*	*t*-value	*p*-value	*df*	*t*-value	*p*-value
Anterior thalamic radiation	Left	Continue	2.46	26.47	0.77	.451	26.35	0.93	.335
		Discontinue	5.17						
	Right	Continue	2.18	26.24	0.97	.342	26.14	0.92	.364
		Discontinue	5.41						
Corticospinal tract	**Left**	**Continue**	**-1.23**	**25.74**	**2.53**	**.012***	25.54	-0.31	.757
		Discontinue	**12.8**			(.251)			
	Right	**Continue**	**-0.62**	**26.28**	**2.36**	**.023***	26.03	-0.14	.892
		Discontinue	**14.5**			(.251)			
Cingulum (cingulate gyrus)	Left	Continue	0.83	26.54	1.37	.181	26.45	0.21	.837
		Discontinue	8.52						
	Right	Continue	0.05	26.16	0.92	.365	26.10	-0.01	.989
		Discontinue	4.30						
Cingulum (hippocampus)	Left	Continue	2.42	26.36	0.53	.601	26.27	0.46	.651
		Discontinue	6.34						
	Right	Continue	0.72	26.28	0.37	.716	26.19	0.14	.888
		Discontinue	3.33						
Forceps	Major	Continue	-1.08	26.55	1.63	.116	26.46	-0.41	.683
		Discontinue	4.93						
	Minor	Continue	2.40	26.15	-1.16	.255	26.11	1.36	.185
		Discontinue	-0.50						
Inferior fronto-occipital	Left	Continue	2.37	26.20	0.40	.693	26.15	1.05	.306
		Discontinue	3.64						
fasciculus	Right	Continue	0.07	26.23	0.79	.439	26.17	0.03	.979
		Discontinue	3.07						
Inferior longitudinal	Left	Continue	1.83	26.63	0.86	.396	26.52	0.61	.550
		Discontinue	5.51						
fasciculus	Right	Continue	0.43	26.23	1.98	.059	26.14	0.14	.887
		Discontinue	8.94						
Superior longitudinal	Left	Continue	1.70	26.26	0.66	.518	26.21	0.71	.487
		Discontinue	3.93						
fasciculus	Right	Continue	0.81	26.18	0.86	.401	26.14	0.36	.723
		Discontinue	3.55						
Uncinate fasciculus	**Left**	**Continue**	7.84	26.21	-1.20	.241	**26.17**	**2.27**	**.032***
		Discontinue	1.98						(.640)
	Right	Continue	-3.25	26.41	0.90	.378	26.34	-0.81	.428
		Discontinue	1.87						
Superior longitudinal	Left	Continue	0.20	26.14	0.71	.482	26.08	0.06	.952
		Discontinue	3.53						
fasciculus (temporal)	Right	Continue	-0.86	26.15	-0.53	.602	26.10	-0.20	.602
		Discontinue	-4.31						

Contrast = follow-up minus baseline based on estimated marginal means from the linear mixed model; *t*-value = *t*-statistic of the interaction term and main effect; *df* = estimated degrees of freedom using the Satterthwait's approximation; *p*-value = non-corrected, FDR corrected *p*-value between in brackets. *Significant at the $p < .05$ level.

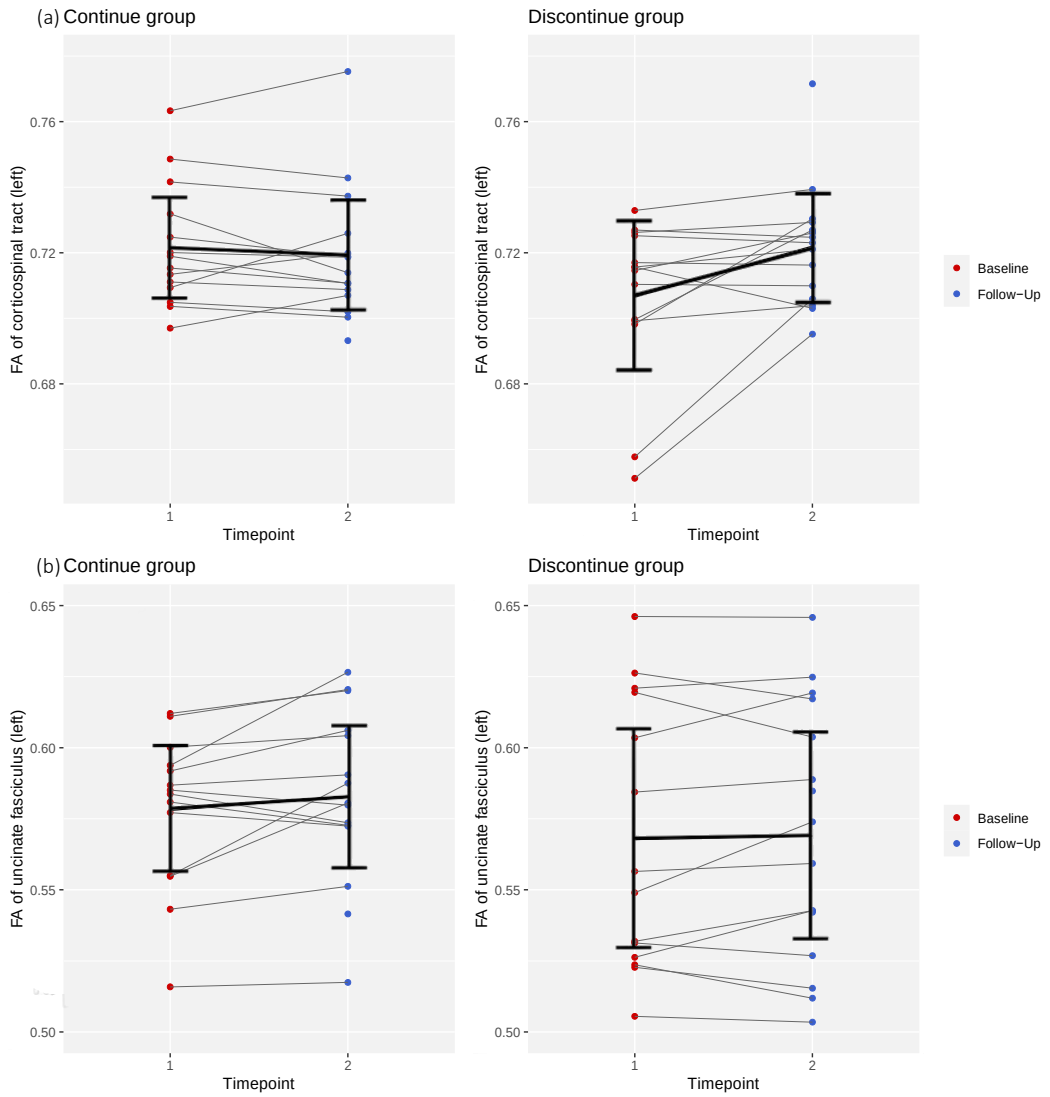

Figure 1. Fractional anisotropy (FA) of the left corticospinal tract (a) and left uncinate fasciculus (b) at the baseline (red) and 12 months follow-up (blue) of patients who continued or discontinued antipsychotic medication. Each line represents an individual participant.

To assess the effect of antipsychotic dosage on FA of WM tracts over time, linear mixed models were performed with antipsychotic dosage over time modeled as fixed factor, and subject as random factor. A significant effect of antipsychotic dosage over time on FA values was observed in the right inferior longitudinal fasciculus (t = -2.156, df = 34.76, p = 0.038) and left cingulate gyrus (t = -2.062, df = 32.17, p = 0.047). When controlling for type of antipsychotic medication, the effect of antipsychotic dosage on FA values of the right inferior longitudinal fasciculus and left cingulate gyrus disappeared (p > 0.05). However, while correcting for the type of antipsychotic medication, a trend toward significance was observed for the effect of antipsychotic dosage in the right cingulum (t = 2.029, df = 15.78, p = 0.0597) which indicates that a decrease in antipsychotic dosage was associated with an increase in FA (Figure 2; Supplementary Table 3).

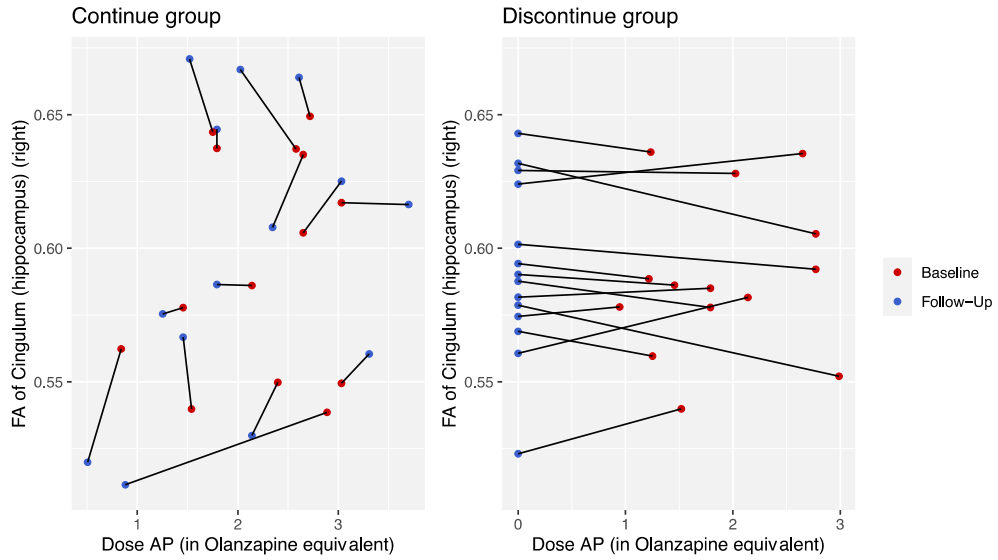

Figure 2. The relationship between antipsychotic dose (AP) (in olanzapine equivalents) and fractional anisotropy (FA) in the right cingulum (hippocampus) at baseline (red) and 12 months follow-up (blue). Each line represents an individual participant. In the continue group, no clear relationship is observed between AP dose and FA values, whereas most of the participants who discontinued medication show an increase in FA values in the right cingulum.

An effect of type of antipsychotic medication in the left (t = -2.53, p = 0.0178) and right cingulum (t = -3.01, p =0.00694) was observed (Supplementary Table 3). Post-hoc comparisons revealed that patients who used aripiprazole had significantly higher FA in the left (M = 0.59, SD = 0.04; Figure 3) and right (M = 0.61, SD = 0.04) cingulum compared to patients using other types (M = 0.56, SD = 0.04; right: M = 0.58, SD = 0.05) at baseline, although this effect did not remain significant after multiple comparisons correction. At baseline, there were no differences in FA values in the left (M = 0.59, SD = 0.05) or right (M = 0.60, SD = 0.04) cingulum of patients who used olanzapine compared to patients who aripiprazole or other. At follow-up, no effect of type of antipsychotic medication on FA values was observed.

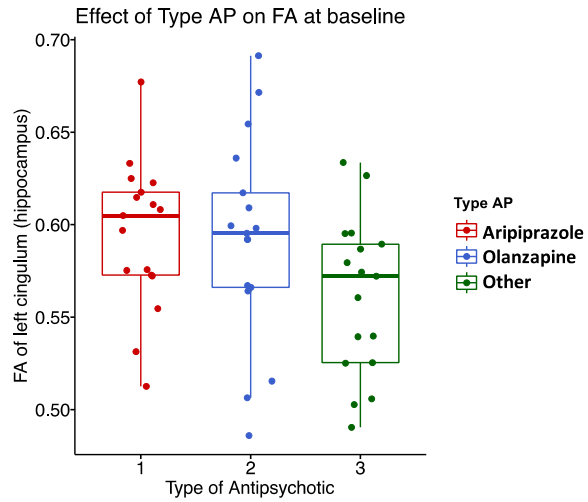

Figure 3. The effect of type of antipsychotic (AP) on fractional anisotropy (FA) of the left cingulum (hippocampus) at the baseline assessment.

4. Discussion

This study examined the long-term effects of continuation versus discontinuation of antipsychotics on WM microstructure in 54 remitted FEP patients, of whom 31 completed the 12-month follow-up. Whole brain voxel-wise analyses revealed no significant differences in FA, a proxy for microstructural WM organization, in patients who discontinued medication compared to those who continued medication at the 12-month follow-up. However, findings from the longitudinal mixed effects analyses indicate a trend towards higher FA in the right inferior longitudinal fasciculus and significantly increased FA in the bilateral corticospinal tract after antipsychotic discontinuation at follow-up compared to antipsychotic maintenance. This increase did not remain statistically significant after adjusting for multiple testing. Moreover, a trend towards higher FA in the right cingulum was observed among patients who received lower doses of antipsychotics at follow-up.

Our results give tentative evidence that discontinuation of antipsychotic medication is associated with increased FA compared to antipsychotic maintenance treatment at 12 months follow-up. As studies consistently reported lower FA in FEP patients compared to healthy controls (Sagarwala & Nasrallah, 2021), these results suggest that discontinuation of antipsychotics in stable and remitted FEP patients might be beneficial for the integrity of WM. Our observations are similar to those reported by Boonstra et al. (2011), who studied the effects of discontinuation of antipsychotics on WM volume in 14 remitted FEP patients. They observed an increase in WM volume in medicated and unmedicated patients at 12 months follow-up compared to healthy controls. However, Boonstra et al. (2011) used T1-imaging to assess WM volume, which is less sensitive to WM microstructural changes compared to DTI (le Bihan et al., 2001), and might explain why no significant differences were observed between the two patient groups. DTI studies that have investigated the effects of antipsychotics on WM microstructure in FEP patients have been inconclusive, reporting increases, decreases, or no changes in FA after short-term exposure to antipsychotics (Ebdrup et al., 2016; Meng et al., 2019; Reis Marques et al., 2014; Serpa et al., 2017; Szeszko et al., 2014; Wang et al., 2013; Zeng et al., 2016; Zong et al., 2019). However, variability in antipsychotic type, scanning interval, and prior exposure to antipsychotic medication hinder uniform comparison of previous studies.

We observed that patients who discontinued antipsychotics showed increased FA in the bilateral corticospinal tract compared to patients who continued treatment for 12 months, which contradicts previous findings by Edrup et al. (2014) who observed a positive correlation between amisulpride dosage and increased FA after six weeks of exposure to antipsychotics. However, as hypothesized by Tishler et al. (2018), antipsychotic exposure might affect WM integrity following an inverted U-shape relationship, which explains the contradictory results of previous DTI studies. Accordingly, short-term exposure to antipsychotics improves WM integrity, while exposure exceeding 12 months negatively impacts WM (Tishler et al., 2018). Although speculative, short-term antipsychotic exposure may counteract the adverse impact of untreated psychosis on WM (Kraguljac et al., 2021). This is supported

by Serpa et al. (2017) who found increased FA after several weeks of antipsychotic treatment, which was associated with improved psychotic symptoms but not antipsychotic exposure. On the other hand, long-term exposure to antipsychotics can lead to a state of dopamine supersensitivity (Chouinard et al., 2017; Yin et al., 2017). Dopamine supersensitivity increases the risk of relapse and can result in tardive dyskinesia which in turn, is associated with decreased FA in patients with schizophrenia (Bai et al., 2009). Although we did not observe significant decreases in FA after 12 months of antipsychotic maintenance treatment, our results do suggest that discontinuation of antipsychotics results in increased WM integrity compared to continuation of antipsychotics over 12 months. Future studies are needed to confirm these hypotheses and to determine whether changes in FA after short- and long-term exposure to antipsychotics reflect (reversal of) a pathological process by examining these changes in relation to improvement in functional outcomes.

Although the molecular pathology by which antipsychotic medications may impact WM microstructure after long-term exposure remains uncertain, several lines of research suggest that long-term blockage of postsynaptic dopamine D2/3 receptors has adverse effects on the brain. Specifically, blocking D2/3 receptors results in increased dopamine turnover (Samaha et al., 2007). Increased dopamine turnover is associated with elevated production of hydrogen peroxide, which in turn results in oxidative stress (Spina & Cohen, 1989; Wang et al., 2013). Studies have shown that white matter is highly vulnerable to damage by oxidative stress (Brockmann et al., 2002). Thus, long-term exposure to antipsychotics might result in oxidative stress which influences WM causing changes in anisotropy. As aripiprazole is a partial agonist for the dopamine D2/3 receptors (Kaar et al., 2020), it is hypothesized to cause less dopamine turnover and therefore results in less oxidative stress (Rosin et al., 2005). This could explain why at baseline, patients using aripiprazole had significantly higher FA in the bilateral cingulum compared to patients using haloperidol, risperidone, amisulpride, or quetiapine. Nonetheless, as we were unable to replicate these findings at follow-up with 14 FEP patients in the continue group, future studies on this matter are needed.

Contrary to our hypotheses, we observed that patients who continued antipsychotic medication showed significantly increased FA in the left uncinate fasciculus after 12 months, while no significant increases were observed in patients who discontinued antipsychotics. The uncinate fasciculus is the largest of three white matter tracts that connect the inferior frontal and anterior thalamic lobes (Hasan et al., 2009; Price et al., 2008). Previous research has shown that decreased FA in the left uncinate fasciculus is associated with the severity of negative symptoms (Kitis et al., 2012; Sigmundsson et al., 2001; Szeszko et al., 2008). Although we corrected for the severity of negative symptoms at baseline, the increase in FA may reflect improvements in negative symptoms, as a trend towards improvement of negative symptoms over time was observed for patients who continued antipsychotics ($p = 0.087$) but not in patients who discontinued antipsychotics ($p = 0.234$). This is consistent with other studies reporting improvements in negative symptoms during the first year after achieving remission from FEP (Austin et al., 2015; Gee et al., 2016).

The current study has several limitations that warrant consideration. First, due to the COVID-19 pandemic, 48% of the participants were unable to complete both assessments. Second, the current study lacks a control group consisting of antipsychotic treatment naive FEP patients and healthy controls, which makes it difficult to determine if the changes in FA are due to disease progression, exposure to antipsychotics, or general systematic scanning errors. However, a previous study utilizing a DTI scanning procedure reported no changes in WM microstructure during a one-year follow-up period in a healthy control group (n = 30) with the same age, sex ratio, and education level as the current sample (Sidaros et al., 2008). This suggests that the changes observed in this study are unlikely to be due to general systematic errors between scans. Third, the mean dose of antipsychotics in the current study was lower compared to other studies examining FEP patients, and patients who continued antipsychotic medication were allowed to taper off medication which might have affected our results. Fourth, it should be noted that our sample consisted primarily of high-functioning FEP patients as those included were in remission of FEP and were able to undergo extensive testing and neuroimaging as part of a randomized controlled trial. This may limit the generalizability of our findings to other psychotic patient samples, which is a common limitation in MRI studies aimed to investigate psychosis.

In conclusion, discontinuation of antipsychotic medication was found to be associated with a significant increase in FA in the bilateral corticospinal tract and a trend towards increased FA in the right inferior longitudinal fasciculus. Additionally, a trend toward an association between decreased antipsychotic dosage and increased FA in the right cingulum was observed. Future research is needed to determine whether changes in FA have a beneficial or pathological impact on functional outcomes, for example by investigating the relationship between changes in WM microstructure and long-term clinical outcomes. Given that FEP patients are typically recommended to use antipsychotic medication for at least one year after achieving symptomatic remission, these findings may provide important insights for the ongoing debate on the potential risks and benefits of antipsychotic maintenance treatment after FEP.

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Supplementary Material

Supplementary Table 1. Results of paired *t*-tests investigating the changes of clinical characteristics between baseline and follow-up for both groups.

	Continue group				Discontinue group			
	Baseline (n = 14)	Follow-up (n = 14)	*t*-value	*p*-value	Baseline (n = 14)	Follow-up (n = 14)	*t*-value	*p*-value
PANSS T	43.64 ± 7.06	42.07 ± 6.72	0.71	.490	38.79 ± 7.47	36.57 ± 9.14	0.99	.341
PANSS P	9.21 ± 2.72	9.71 ± 2.76	-0.58	.575	8.36 ± 2.10	8.43 ± 2.87	-0.11	.916
PANSS N	11.64 ± 2.92	10.07 ± 2.02	1.84	.087	8.93 ± 2.23	8.07 ±1.73	1.25	.234
PANSS G	22.78 ± 5.13	22.29 ± 3.38	0.37	.719	21.50 ± 4.74	20.07 ± 4.92	1.18	.258
GAF	63.50 ± 11.12	65.71 ± 10.39	-0.58	.575	71.86 ± 13.31	79.00 ± 15.37	-1.57	.142

Values are mean ± standard deviation unless stated otherwise. Continue = group participants who use antipsychotic medication at baseline and follow-up; Discontinue = group of participants who stopped using antipsychotics at time of follow-up. PANSS = Positive and Negative Syndrome Scale; T = total; P = Positive; N = Negative; G = General; GAF = Global Assessment of Functioning; *t-value* = *t*-score of paired t-tests; *p*-value is non-corrected.

Supplementary Table 2. Demographic characteristics of participants who completed both assessments compared to participants who did not complete both.

	Completed both (n = 28)	Completed one (n = 26)	Statistic	*p*-value
Age (mean ± SD)	25.93 ± 6.71	28.58 ± 8.95	t = -1.22	.228
Sex (male | female)	17 | 11	20 | 6	χ^2=2.48	.115
Years of education (mean ± SD)	14.25 ± 2.20	14.50 ± 1.66	t =0.47	.638
Handedness (right | left)	22 | 6	22 | 4	*F*	.381
Age of onset psychosis (mean ± SD)	24.75 ± 6.91	27.88 ± 8.96	t = 1.43	.159
Duration of untreated psychosis in days (mean ± SD)	67.39 ± 95.72	148.23 ± 243.7	t = 1.47	.154
PANSS total	41.21 ± 7.55	45.39 ± 10.27	t = 1.62	.112
PANSS positive	8.79 ± 2.42	9.96 ± 3.25	t = 1.43	.161
PANSS negative	10.29 ± 2.90	11.49 ± 4.44	t = 1.11	.275
PANSS general	22.14 ± 4.88	23.95 ± 4.86	t = 1.32	.192
GAF-score	67.93 ± 12.72	65.91 ± 12.96	t = -0.55	.584
Antipsychotic dosage	8.80 ± 6.07	6.19 ± 4.56	t = -1.80	.079

Values are mean ± standard deviation unless stated otherwise. SD = standard deviation; PANSS = Positive and Negative Syndrome Scale; GAF = Global Assessment of Functioning. Antipsychotic dosage is reported in olanzapine equivalents, calculated as described by Leucht et al. (2016).

Supplementary Table 3. Linear mixed-effect models investigating the effect of type and dosage of antipsychotics over 12 months in first episode psychosis patients on fractional anisotropy (FA).

		Effect of Type of AP			Effect of AP dosage		
White matter tract	Region	*df*	*t*-value	*p*-value	*df*	*t*-value	*p*-value
Anterior thalamic radiation	Left	37.40	0.66	.514	27.62	-0.73	.470
	Right	37.55	0.57	.573	27.17	-0.63	.536
Corticospinal tract	Left	18.00	1.13	.275	14.52	1.03	.321
	Right	22.48	0.95	.351	17.04	1.48	.158
Cingulum (cingulate gyrus)	Left	20.97	-0.98	.340	16.36	-1.20	.247
	Right	20.16	-0.34	.737	15.74	-0.70	.493
Cingulum (hippocampus)	Left	25.47	-2.53	.018* (.180)	19.16	0.52	.610
	Right	20.05	-3.01	.007* (.140)	15.78	2.03	.060
Forceps	Major	17.02	0.36	.726	14.17	1.54	.145
	Minor	13.96	-0.36	.721	11.76	0.29	.774
Inferior fronto-occipital fasciculus	Left	18.26	-1.04	.311	14.87	-0.50	.625
	Right	18.76	-0.23	.818	15.24	-0.94	.362
Inferior longitudinal fasciculus	Left	23.50	-1.12	.275	18.25	-0.45	.660
	Right	23.48	-0.86	.401	18.12	-0.92	.369
Superior longitudinal fasciculus	Left	17.03	-0.50	.621	13.77	0.46	.652
	Right	11.54	-0.76	.461	10.33	1.26	.234
Uncinate fasciculus	Left	21.66	0.91	.373	16.26	-0.69	.498
	Right	31.90	-0.92	.365	23.35	-0.70	.494
Superior longitudinal fasciculus	Left	18.27	-0.45	.660	14.91	1.43	.174
(temporal)	Right	22.36	-0.04	.970	17.21	-0.54	.594

AP = antipsychotic; *t*-value = *t*-statistic of the linear mixed model; *df* = estimated degrees of freedom using the Satterthwait's approximation; *p*-value = non-corrected, FDR corrected *p*-value between in brackets. *Significant at the $p < .05$ level.