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Assessing regional intracortical myelination in schizophrenia spectrum and bipolar disorders using the optimized T1w/T2w-ratio

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Abstract

Background. Dysmyelination could be part of the pathophysiology of schizophrenia spectrum (SCZ) and bipolar disorders (BPD), yet few studies have examined myelination of the cerebral cortex. The ratio of T1- and T2-weighted magnetic resonance images (MRI) correlates with intracortical myelin. We investigated the T1w/T2w-ratio and its age trajectories in patients and healthy controls (CTR) and explored associations with antipsychotic medication use and psychotic symptoms.

Methods. Patients with SCZ ($n = 64$; mean age = 30.4 years, S.D. = 9.8), BPD ($n = 91$; mean age 31.0 years, S.D. = 10.2), and CTR ($n = 155$; mean age = 31.9 years, S.D. = 9.1) who participated in the TOP study (NORMENT, University of Oslo, Norway) were clinically assessed and scanned using a General Electric 3 T MRI system. T1w/T2w-ratio images were computed using an optimized pipeline with intensity normalization and field inhomogeneity correction. Vertex-wise regression models were used to compare groups and examine group × age interactions. In regions showing significant differences, we explored associations with antipsychotic medication use and psychotic symptoms.

Results. No main effect of diagnosis was found. However, age slopes of the T1w/T2w-ratio differed significantly between SCZ and CTR, predominantly in frontal and temporal lobe regions: Lower T1w/T2w-ratio values with higher age were found in CTR, but not in SCZ. Follow-up analyses revealed a more positive age slope in patients who were using antipsychotics and patients using higher chlorpromazine-equivalent doses.

Conclusions. While we found no evidence of reduced intracortical myelin in SCZ or BPD relative to CTR, different regional age trajectories in SCZ may suggest a promyelinating effect of antipsychotic medication.

Introduction

Schizophrenia spectrum and bipolar disorders (BPD) are severe mental disorders that affect more than 1% of the population (Perälä et al., 2007). These disorders are proposed to exist along a psychosis continuum (Pearlson, 2015; Tamminga et al., 2014). Psychotic symptoms are also common in BPD, with an estimated lifetime prevalence above 60% in bipolar I disorder and above 20% in bipolar II disorder (Aminoff et al., 2022; van Bergen et al., 2019). Current evidence favors the view that both disorders reflect dysconnectivity within and across several brain circuitries rather than having focal origin (Friston, Brown, Siemerkus, & Stephan, 2016; Friston & Frith, 1995; Kelly et al., 2018; Xia et al., 2019). Dysmyelination has been proposed as one possible mechanism (Bartzokis, 2002; Whitford, Ford, Mathalon, Kubicki, & Shenton, 2012). This hypothesis is supported by genetic (Goudriaan et al., 2014; Hakak et al., 2001) and post-mortem studies (Kolomeets & Uranova, 2018; Uranova, Vikhreva, Rachmanova, & Orlovskaya, 2011; Vikhreva, Rakhmanova, Orlovskaya, & Uranova, 2016)

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indicating lower myelin content as well as lower density and altered morphology of myelinating oligodendrocytes in the prefrontal cortex (Kolomeets & Uranova, 2018; Uranova et al., 2011; Vikhreva et al., 2016). Notably, the maturation of myelin in association fiber tracts and frontal regions of the cerebral cortex, regions known to be involved in psychotic disorders, extends into early adulthood, which is a period of heightened incidence of psychosis (Paus, Keshavan, & Giedd, 2008; Whitford et al., 2012).

Magnetic resonance imaging (MRI) studies on dysmyelination in psychotic disorders have mainly examined white matter, whereas few have examined intracortical myelination (Ganzetti, Wenderoth, & Mantini, 2015; Iwatani et al., 2015; Wei et al., 2022; Wei et al., 2020). In a previous study, we examined the cortical gray–white matter contrast (GWC), i.e. the contrast between T1-weighted (T1w) intensities in gray matter and adjacent superficial white matter, which is inversely correlated with intracortical myelin. We found higher GWC values in sensory and motor regions in patients with schizophrenia spectrum disorders and, to a lesser extent, in BPD compared to healthy controls (Jørgensen et al., 2016). More recently, Makowski et al. (2019) used structural covariance and principal component analysis on the GWC in patients with first-episode psychosis. They reported a similar trend-level difference in a GWC component representing sensory and motor regions in patients relative to healthy controls. However, the GWC is based on T1w intensities in both gray and superficial white matter, and it is consequently not possible to determine if it is the signal intensity in gray matter that drives the observed group differences. Other measures of intracortical myelin are therefore needed to validate these findings.

In bipolar I disorder, Sehmbi et al. (2018) found positive associations between a T1w intensity-based measure of intracortical myelin and verbal memory. They also reported an inverted U-shaped relationship with age in healthy controls but not in patients with bipolar I disorder (Sehmbi et al., 2019). In this study, three images were acquired to create cortical maps, a standard T1w anatomic reference image, used for registration, another T1w image, optimized for intracortical contrast, and a proton-density weighted image used to normalize intensity inhomogeneities (Bock et al., 2013). This approach improves the intracortical contrast but relies on developmental sequences and may be influenced by cortical thickness. Furthermore, residual intensity inhomogeneities, e.g. those related to the B1 + field, are not eliminated. Quantitative MRI pulse sequences can compensate for field inhomogeneities and have been used to show higher T1 relaxation times in BPD (Rangel-Guerra, Perez-Payan, Minkoff, & Todd, 1983), including the somatosensory and temporal cortices (Necus et al., 2021). However, they require advanced and often time-consuming MRI pulse sequences, preventing widespread adoption.

Myelin may also be involved in the therapeutic action of antipsychotic medications (Bartzokis, 2012; Kroken et al., 2014). In animal studies, a lipogenic effect of antipsychotic agents has been demonstrated (Ersland, Skrede, Stansberg, & Steen, 2017; Ferno et al., 2011), and in clinical studies an association between serum lipid levels and treatment response was reported (Gjerde et al., 2018a; Kim, Barr, Fredrikson, Honer, & Procyshyn, 2019; Procyshyn et al., 2007). Notably, Tishler et al. (2018) investigated a measure of frontal lobe intracortical myelin volume and found a significant association within the first year of antipsychotic medication exposure that declined with prolonged exposure. In a previous study, users of second-generation antipsychotics had a higher intracortical myelin volume compared with users of first-generation antipsychotics (Bartzokis et al., 2007). In these studies, they acquired a proton-density image, which is less sensitive to myelin, and an inversion recovery image, which is sensitive to myelin. By calculating the volumetric differences based on these images they estimated the superficial myelinated volume of the cerebral cortex. While these findings are based on an indirect measure, they provide *in vivo* evidence suggestive of a promyelinating effect of antipsychotic medication in the frontal lobe of the cerebral cortex.

The T1w/T2w-ratio has been proposed as a measure of intracortical myelin (Glasser et al., 2016; Glasser & Van Essen, 2011). This interpretation is based on observations that the T1- and T2-weighted (T2w) MRI signals have positive and negative correlations with myelin content, respectively, such that the contrast due to myelin is enhanced in the ratio (Koenig, 1991; Koenig, Brown, Spiller, & Lundbom, 1990). Furthermore, shared field inhomogeneities in the T1w and T2w images are attenuated (Glasser & Van Essen, 2011). The T1w/T2w-ratio has been studied in neurological disorders such as multiple sclerosis (Beer et al., 2016), Huntington's disease (Rowley et al., 2018), and Alzheimer's disease (Pelkmans et al., 2019). In patients with schizophrenia spectrum disorders, Iwatani et al. (2015) reported lower global T1w/T2w-ratio means both in gray and white matter compared to healthy controls, but no voxel-wise group differences in the cerebral cortex. Ganzetti et al. (2015) used non-brain intensities to calibrate the T1w/T2w-ratio and found lower regional gray matter values in patients with schizophrenia spectrum disorders, particularly in the temporal lobe, frontal lobe, and the insula. However, two recent studies have indicated a more complex layer-dependent pattern of changes in first-episode psychosis (Wei et al., 2022; Wei et al., 2020). In BPD, Ishida et al. (2017) reported lower T1w/T2w-ratio values in white matter regions relative to healthy controls, but no significant differences in gray matter.

Between-subject comparisons of the T1w/T2w-ratio are challenging due to the use of weighted, rather than quantitative, MRI pulse sequences. Quantitative MRI measures have a more direct biophysical interpretation with between-subject generalizability whereas weighted signal intensities, and their ratios, are influenced by non-biological factors that affect between-subject commensurability. In a previous study, we evaluated the measurement properties of 33 T1w/T2w-ratio processing pipelines (Nerland et al., 2021). Correction for field inhomogeneities improved the agreement with the expected myeloarchitecture (i.e. the expected distribution of myelin across cortical areas). Furthermore, intensity normalization ensured acceptable test–retest reliability, which is of particular importance for between-subject comparisons.

In the present study, we investigated cortical T1w/T2w-ratio values in patients with schizophrenia spectrum and BPD relative to healthy controls. An optimized intensity normalized pipeline was used for computing the T1w/T2w-ratio maps with corrections for partial volume effects, surface outliers, and field inhomogeneities (Nerland et al., 2021). We examined if T1w/T2w-ratio values or age trajectories differed between each patient group and healthy controls with the following two hypotheses: First, that T1w/T2w-ratio values would be lower in primary sensory and motor regions in both patient groups. Second, that use of antipsychotic medication would, particularly in frontal regions of the cerebral cortex, be positively associated with the T1w/T2w-ratio. In exploratory analyses, we examined associations with psychotic symptoms.

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Methods

Study design

Participants were recruited from hospitals in the greater Oslo region to the Thematically Organized Psychosis (TOP) study conducted by the Norwegian Centre for Mental Disorders Research (NORMENT). Patients who met the criteria for a DSM-IV schizophrenia spectrum disorder (SCZ), including schizophrenia, schizophreniform disorder and schizo-affective disorder, or BPD, including bipolar I disorder, bipolar II disorder and BPD not otherwise specified, were included in the current study. Healthy controls were randomly drawn from the national population registry in the same geographical region and asked to participate. The study complied with the Helsinki Declaration and was approved by the Regional Committee for Medical Research Ethics (REC South-East Norway) and the Norwegian Data Inspectorate. All participants gave informed consent.

The inclusion criteria for the TOP study include age between 18–65 years, no mental disability (defined as IQ < 70), no history of head trauma with loss of consciousness, and no neurological disorder or other organic disorder thought to affect brain function.

Healthy controls were screened using the PRIME-MD (Spitzer et al., 1994). The absence of a mental disorder, substance use disorder, and history of severe mental disorders among first-degree relatives were criteria for inclusion. Healthy controls were selected from a larger pool ($n = 278$) based on age- and sex-matching to the patient sample (SCZ and BPD). Matching was performed with the MatchIt package in R (version 4.2.3; R Core Team, 2023; Ho, Imai, King, and Stuart, 2011). One-to-one matching was performed with the nearest neighbor method and quantile–quantile (Q–Q) plots were inspected to ensure adequate matching.

Diagnostic and clinical assessment

Clinical assessments were conducted by trained physicians, psychiatrists, or clinical psychologists. Diagnoses were verified using the Structured Clinical Interview for the DSM-IV Axis I disorders (SCID-IV; Spitzer, Williams, Gibbon, and First, 1992). Current symptoms were rated using the Positive and Negative Syndrome Scales (PANSS; Kay, Fiszbein, and Opler, 1987). Scores for positive, negative, disorganized, excited, and depressed symptoms were calculated according to the five-factor model by Wallwork, Fortgang, Hashimoto, Weinberger, and Dickinson (2012). Current medication use was obtained by interview or chart review and included information on antipsychotic, antiepileptic, antidepressant, and anxiolytics/hypnotic medication. For each medication, type and dose were recorded. Antipsychotic medication dosages were converted to chlorpromazine equivalent doses (CPZ; Andreasen, Pressler, Nopoulos, Miller, and Ho, 2010). Intelligence quotient (IQ) was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI-II; Wechsler, 2007), and general psychosocial functioning was rated using the split version of the global assessment of functioning scale (GAF; Pedersen, Hagtvet, and Karterud, 2007). The median time from clinical assessment (defined as the day of the PANSS interview) to MRI acquisition among patients was 12 days, with an interquartile range of 7–25 days.

MRI acquisition

Patients and healthy controls were scanned using a 3 T General Electric Discovery MR 750 system, equipped with a 32- channel head coil, between 2015 and 2019. T1w and T2w sequences were both acquired with 1 mm isotropic resolution. The T1w sequence was a 3D inversion recovery-prepared fast spoiled gradient echo recall (BRAVO) sequence with the following parameters: Repetition time (TR) = 8.16 ms; Echo time (TE) = 3.18 ms; Inversion time (TI) = 450 ms; Flip angle = 12°; Bandwidth = 244 Hz/px; ARC = 2; Acquisition time (TA) = 04:43. The T2w sequence was a 3D fast spin echo (CUBE) sequence with the following parameters: TR = 2500 ms; TE = 71.68 ms; FA = 90°; Bandwidth = 488 Hz/px; Echo train length (ETL) = 100; ARC = 2 × 2; TA = 04:23. Phased array uniformity enhancement (PURE) was enabled for both sequences. MRI images were inspected by a neuroradiologist and excluded if pathological findings were present.

MRI post-processing

FreeSurfer (v6.0.0; https://surfer.nmr.mgh.harvard.edu/) was used to reconstruct cortical surfaces, representing the boundary between gray and white matter (i.e. the inner gray–white surface of the cortex) and between gray matter and cerebrospinal fluid (i.e. the outer surface of the cortex or 'pial surface'), based on T1w images. FreeSurfer is open source and has been described in detail previously (Fischl, 2012). Reconstructed surfaces were visually inspected and edited according to standard guidelines. Images were excluded in the event of substantial motion artifacts or otherwise poor image quality.

Calculation of the T1w/T2w-ratio

To compute the T1w/T2w-ratio, we rigidly registered T2w images to T1w images using *bbregister* in FreeSurfer with FSL initialization (Greve & Fischl, 2009). We then applied N4ITK field bias correction and normalized intensities with the WhiteStripe algorithm. The T1w image was then divided by the T2w image to form the T1w/T2w-ratio, which was corrected for partial volume effects (Shafee, Buckner, & Fischl, 2015). Next, T1w/T2w-ratio voxel values were projected onto the gray–white surface by sampling along layers representing equivolumetric distances of 10% to 80% of the vertex-wise cortical thickness (Waehnert et al., 2016). Finally, we performed surface-based outlier correction based on a previously published approach (Glasser & Van Essen, 2011). This pipeline was shown in a previous study to be robust to the presence of field inhomogeneities and to improve test–retest reliability whilst preserving inter-individual variation (Nerland et al., 2021).

We visually inspected each T1w/T2w-ratio map. If the maps deviated from known myeloarchitecture, the T1w and T2w volumes were inspected. If artifacts or low image quality were found in either of the scans, the participant was excluded.

Statistical analyses

Sample characteristics were examined using descriptive statistics for demographical and clinical variables and we examined if the groups differed using analysis of variance (ANOVA), t- or X^2-tests. To examine which groups differed, *post hoc* Bonferroni tests were used where appropriate.

In the primary analyses, we examined if either patient group differed from healthy controls with respect to average T1w/T2w ratio values or their age trajectories. In these analyses, we used *mri_glmfit* in FreeSurfer to fit age- and sex-adjusted general linear

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models for each vertex of the cortical surface. We specified contrasts to examine: (1) main effects of diagnosis (SCZ v. CTR, BPD *v.* CTR), and (2) diagnosis × age interaction effects. T1w/T2w-ratio maps were concatenated and smoothed (10 mm FWHM) before running the analyses. We applied cluster-wise correction for multiple testing with a cluster-forming threshold of 0.001, a cluster-wise probability of 5%, and correction for analysis across both hemispheres (Greve & Fischl, 2018). If significant diagnosis × age interaction effects were found, we further examined if the age slope differed from zero within each diagnostic group separately. The latter were regarded as follow-up analyses, and we chose a liberal p-value threshold of $p < 0.01$. Results from these analyses are presented as statistical t-maps.

Further, we aimed to examine whether T1w/T2w-ratio values were associated with antipsychotic medication use or psychotic symptoms in regions where significant differences were found in the primary analyses. We first extracted the mean T1w/T2w-ratio values for each significant cluster. These were defined as dependent variables. To examine associations with antipsychotic medication use, antipsychotic medication status (current use/no use) as well as medication status × age interaction terms were entered as predictors of interest in the first set of linear regression models conducted in the patient sample ($n = 155$). In the second set of models, we examined only patients who were using antipsychotic medication and where information about dosage was available ($n = 86$) and entered CPZ and CPZ × age interaction terms as predictors. We then performed separate linear regression analyses among all patients ($n = 155$) using the PANSS total score and each of the five Wallwork factor scores as predictors of interest. All models were adjusted for age, sex, and diagnosis (SCZ/BPD). The analyses were conducted in SPSS version 28. False discovery rate (FDR) set at 5% was used to correct for multiple testing (Benjamini & Hochberg, 1995).

Results

Description of the study sample

The study sample consisted of 64 patients with SCZ, 91 patients with BPD and 155 CTR. The mean age did not differ between the groups. The sex distribution differed between groups, and *post hoc* tests indicated a non-significant trend towards more males in the SCZ group and more females in the BPD group.

The distributions of other demographic and clinical variables are shown in Table 1. Briefly, years of education and estimated IQ differed between the groups. Patients with SCZ had higher current PANSS positive, negative, and disorganized symptom scores, but not excited or depressive symptom scores, compared to patients with BPD. Patients with SCZ also had lower GAF scores compared to patients with BPD.

Medication use in the patient sample

The use of antipsychotics was more prevalent in SCZ than in BPD, whereas BPD had a more frequent use of antiepileptic drugs. Other medication categories did not differ between groups (Table 1).

Patients with SCZ used higher doses and were more often treated with multiple antipsychotic agents or long-acting injectables than patients with BPD (Table 1). Further information is found in online Supplementary Table 1.

The association between age and current antipsychotic dose (CPZ) was not significant ($\rho = 0.18$, $p = 0.09$).

No group differences in regional T1w/T2w-ratio values

When examining the main effects of diagnosis (SCZ *v.* CTR, BPD *v.* CTR), we found no differences in regional T1w/T2w-ratio values after cluster-wise correction for multiple testing (CWP > 0.05).

Different age trajectories of regional T1w/T2w-ratio values

In the group-wise comparison of T1w/T2w-ratio age slopes (i.e. diagnosis x age interaction terms), patients with SCZ had more positive age slopes compared to CTR in 22 clusters. These included clusters in frontal and temporal regions, e.g. bilateral regions of the superior frontal and insular cortices, as well as parietal and occipital regions. There were no significant differences in age slopes between patients with BPD and CTR. An overview of significant clusters is shown in Table 2 and Fig. 1. See online Supplementary Figure 1 for further details.

Follow-up analyses of the linear age slopes in each group showed that CTR had predominantly negative age slopes in medial frontal and temporal regions, with positive age slopes only in the central sulcus. In contrast, patients with SCZ had several regions with positive age slopes, including frontal lobe regions (Fig. 2).

Age trajectories of the T1w/T2w-ratio and antipsychotic medication use

We found significant interaction effects indicating a more positive age slope in patients using antipsychotic medication compared to patients who did not. This was found in temporal lobe regions, insular regions, the precuneus bilaterally, the left precentral gyrus, the right superior and middle frontal lobe, and the postcentral gyrus (Table 3).

When analyses were further restricted to patients using antipsychotic medication only ($n = 86$), we found more positive age slopes of T1w/T2w-ratio values in patients using a higher current dose (CPZ). Significant CPZ × age interaction effects were found in all except two of the 22 significant clusters (Table 3).

We also conducted cluster-wise analyses in patients with SCZ and BPD separately. In these analyses, there were no significant associations after correction for multiple testing. In SCZ, trends towards more positive age slopes were observed in patients who used antipsychotic medication in two clusters and, among medicated patients, with higher CPZ in six clusters (all $p < 0.05$, uncorrected). In BPD, there were no significant associations with medication use or dose. See online Supplementary Tables 2 and 3 for further details.

No association with clinical symptoms

We found no associations between T1w/T2w-ratio values and PANSS total scores, nor with any of the five symptom factors after correction for multiple testing. See online Supplementary Table 2 for details. Similarly, when PANSS scores were examined in SCZ and BPD separately, no association was significant after correction for multiple testing; however, in SCZ one cluster showed a trend towards a positive association with positive symptoms and in BPD six clusters showed trends towards positive

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Table 1. Sample characteristics

Sample characteristics	SCZ ($n = 64$)	BPD ($n = 91$)	CTR ($n = 155$)	Statistics	Post hoc tests
Demographic					
Age, years (M, S.D.)	30.4 (9.8)	31.0 (10.2)	31.9 (9.1)	$F = 0.6$, N.S.	
Sex (male, %)	37 (58%)	34 (37%)	73 (47)	$X^2 = 6.4$, $p = 0.04$	
Education, years (M, S.D.)	12.6 (2.2)	13.6 (2.1)	14.8 (2.0)	$F = 27.1$, $p < 0.001$	SCZ < BPD, CTR. BPD < CTR.
WASI IQ (M, S.D.)	104.9 (13.3)	111.9 (11.6)	115.4 (11.9)	$F = 19.0$, $p < 0.001$	SCZ < BPD, CTR.
Clinical					
Age at onset, years (M, S.D.)	23.4 (7.6)	17.9 (5.9)		n.a.	
Duration of illness, years (M, S.D.)	7.2 (8.5)	13.1 (8.9)		n.a.	
PANSS total score (M, S.D.)	59.2 (14.6)	44.0 (8.0)		$t = 7.6$, $p < 0.001$	
Positive factor	8.6 (3.6)	5.1 (1.7)		$t = 8.0$, $p < 0.001$	
Negative factor	13.3 (5.2)	8.5 (3.0)		$t = 7.2$, $p < 0.001$	
Disorganized factor	5.4 (2.4)	4.0 (1.3)		$t = 4.8$, $p < 0.001$	
Excited factor	5.3 (1.7)	5.0 (1.3)		$t = 1.4$, $p = 0.17$	
Depressive factor	7.8 (2.8)	7.9 (2.7)		$t = -0.25$, $p = 0.8$	
GAF – symptoms	50.4 (11.6)	62.4 (9.6)		$t = -7.0$, $p < 0.001$	
GAF – functioning	49.3 (11.8)	63.8 (11.0)		$t = -7.2$, $p < 0.001$	
Medication use					
Antipsychotic agents (n, %)	56 (89%)	31 (34%)		$X^2 = 45.4$, $p < 0.001$	
SGA / FGA / both (n)	53 / 0 / 3	30 / 0 / 1		n.a.	
Oral / depot / both (n)	41 / 7 / 8	30 / 1 / 0		$X^2 = 7.62$, $p = 0.01$[1]	
Antipsychotic monotherapy[2]	39 (70%)	29 (94%)		$X^2 = 6.68$, $p = 0.01$[1]	
CPZ-equivalent dose (M, S.D.)	318 (158)	191 (115)		$t = 3.9$, $p < 0.001$	
SGA (M, S.D.)	305 (162)	190 (113)		$t = 3.5$, $p < 0.001$	
FGA (M, S.D.)	254 (185)	30 (n.a.)		n.a.	
Lithium (n, %)	3 (5%)	11 (12%)		$X^2 = 2.4$, N.S.	
Antiepileptic agents (n, %)	8 (13%)	25 (28%)		$X^2 = 4.8$, $p = 0.03$	
Antidepressive agents (n, %)	16 (25%)	25 (28%)		$X^2 = 0.1$, N.S.	
Anxiolytics/hypnotic agents (n, %)	3 (5%)	7 (8%)		$X^2 = 0.5$, N.S.	

Abbreviations: M, Mean; SD, Standard deviation; SCZ, Schizophrenia; BPD, Bipolar disorders; CTR, Healthy controls; WASI, Wechsler abbreviated scale of intelligence; PANSS, Positive and negative syndrome scale; GAF, Global assessment of functioning scale; CPZ, Chlorpromazine; SGA, Second generation antipsychotics; FGA, First-generation antipsychotics; N.S., Not significant; n.a., Not applicable.
[1]Calculated using Fisher's exact test.
[2]Defined as the current use of one antipsychotic medication type.
Missing values: Education: $n = 12$. WASI IQ: $n = 14$. Age at onset: $n = 2$. Duration of illness: $n = 2$. GAF – functioning: $n = 1$. PANSS total score: $n = 1$. PANSS negative factor score: $n = 1$. Medication use: $n = 1$. CPZ-equivalent dose: $n = 1$.

associations with the excited, disorganized, or negative symptom factors ($p < 0.05$, uncorrected). See online Supplementary Tables 5 and 6 for further details.

Discussion

We did not find lower T1w/T2w-ratio values in either of the patient groups compared to healthy controls. Thus, insofar as the T1w/T2w-ratio is a measure of intracortical myelin, our results provide little support for intracortical myelin deficits in these disorders. However, we observed divergent age trajectories in patients with schizophrenia spectrum disorders. Antipsychotic medication status and dose were both associated with divergent age slopes within the patient sample, which is consistent with a possible promyelinating effect of antipsychotic medication.

The absence of lower regional T1w/T2w-ratio values in patients contrasts with our previous study on the GWC (Jørgensen et al., 2016). While these are different measures, they show moderate to high correlations, with a reported overall correlation of 0.73 (Parent et al., 2023). Our results also differed from previous findings of lower global and regional T1w/T2w-ratio values in patients with schizophrenia spectrum disorders (Ganzetti et al., 2015; Iwatani et al., 2015). However, it is worth noting that only the study by Ganzetti et al. (2015) reported lower *regional* T1w/T2w-ratio values. In this study, data was pooled from three different sites, which may have influenced the results given the known effects of scanner on the

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Table 2. Significant clusters based on vertex-wise analysis of schizophrenia × age interaction effect

Region	Maximal significance value	Cluster size (mm^2)	Coordinates		
			x	y	z
Left hemisphere					
Superior frontal	1.98×10^{-6}	1744	−8.1	44.3	35.4
Pars opercularis	1.56×10^{-6}	1239	−52.0	12.9	7.6
Caudal anterior cingulate	7.29×10^{-6}	532	−7.3	18.9	29.5
Precuneus	6.49×10^{-5}	507	−12.2	−55.1	29.2
Insula	8.17×10^{-5}	349	−35.9	−20.9	−4.1
Middle temporal	7.41×10^{-5}	249	−53.8	−9.0	−23.1
Precentral	2.72×10^{-4}	229	−27.5	−11.1	47.0
Superior temporal	3.00×10^{-4}	210	−54.0	−23.9	−3.7
Fusiform gyrus	2.51×10^{-4}	156	−38.5	−51.4	−20.0
Supramarginal	1.53×10^{-5}	139	−60.4	−32.5	36.3
Lateral occipital	4.43×10^{-4}	125	−40.5	−70.9	−8.1
Banks of the superior temporal sulcus	1.88×10^{-4}	116	−56.0	−48.7	1.0
Right hemisphere					
Rostral middle frontal	4.66×10^{-6}	1239	18.6	56.0	−5.3
Superior parietal	1.22×10^{-4}	428	16.7	−72.3	45.2
Insula (1)	9.11×10^{-5}	364	34.0	5.7	5.9
Superior temporal	7.91×10^{-5}	220	57.4	−8.0	−7.7
Superior frontal (1)	2.25×10^{-4}	205	9.6	−7.1	67.6
Precuneus (1)	2.47×10^{-4}	167	10.5	−48.4	61.9
Precuneus (2)	3.84×10^{-4}	130	5.2	−58.9	27.3
Insula (2)	1.04×10^{-4}	124	34.0	−25.5	6.5
Superior frontal (2)	4.93×10^{-4}	105	10.5	23.3	56.6
Postcentral	3.16×10^{-5}	100	27.9	−30.3	58.9

Maximal significance value refers to the *p*-value at the vertex showing the largest difference in age slopes between SCZ and CTR within each cluster.

T1w/T2w-ratio (Nerland et al., 2021). Furthermore, the calibration method based on small masks covering the eyes and the temporal muscles may be unreliable, especially for low-resolution data. In the study by Iwatani et al. (2015), a large smoothing kernel was used for computing the T1w/T2w-ratio, and a large portion of the sensorimotor cortices was excluded from the analyses. Notably, both these previous studies used low-resolution T2w images, which may introduce partial volume effects (Shafee et al., 2015).

In two recent studies on first-episode treatment-naïve patients with schizophrenia spectrum disorders (FEP) by Wei et al. (2022; 2020), a layer-dependent regional pattern was reported, with lower T1w/T2w-ratio values in the left cingulate and insula and higher values in the left superior temporal gyrus. Notably, these regions belong to the salience network and the language and auditory processing circuitry, respectively, both thought to be affected in psychotic disorders. Interestingly, the patients with FEP differed from healthy controls in the superficial and middle layers of the cortex, but not in the deep layer. In the present study, T1w/T2w-ratio values were sampled at distances of 10–80% of cortical thickness from the gray–white surface and depth-dependent analyses were not performed. Furthermore, Wei et al. (2020) normalized each individual T1w/T2w-ratio map by subtracting the subject-wise mean T1w/T2w-ratio and dividing by the variance, which makes the comparison to the present study difficult.

We observed more positive age trajectories of the T1w/T2w-ratio in patients with schizophrenia spectrum disorders. Furthermore, patients currently treated with antipsychotics showed more positive age trajectories compared with patients not currently on antipsychotics, with evidence suggesting a dose-response relationship, although a sensitivity analysis performed in each diagnostic group separately did not confirm this. It has been proposed that some antipsychotic medications have myelin-promoting properties (Bartzokis, 2012) and that their lipogenic effects are related to clinical efficacy (Kim et al., 2019; Leucht et al., 2013; Procyshyn et al., 2007). Indeed, several psychotropic drugs are known to induce cholesterol synthesis (Ferno et al., 2011) and in two preclinical studies in rodents, the antipsychotic agents quetiapine and risperidone had ameliorating effects after experimentally induced demyelination (O'Sullivan et al., 2014; Xiao et al., 2008). Similarly, clozapine and haloperidol were found to inhibit myelin loss through modulating autophagic processes in a recent study (Patergnani et al., 2021). However, in a previous study of long-term treatment with

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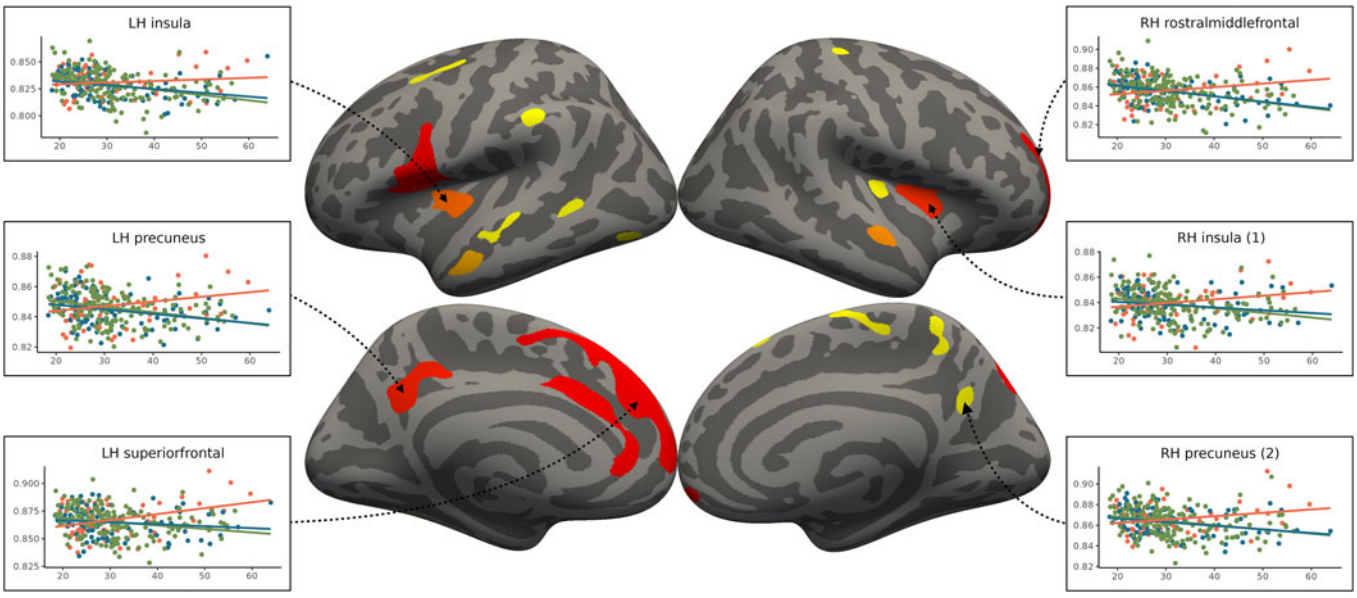

Figure 1. Clusters shown in red to yellow colors on the inflated cortical surfaces signify cortical regions where associations with age differed between SCZ and CTR. The cluster-forming threshold was 0.001 and the cluster-wise probability set at $p < 0.05$ with correction for two hemispheres. In the left and right boxes, scatterplots illustrate the association with age among SCZ (red line), BPD (blue line) and CTR (green line) with age on the x-axes and mean T1w/T2-ratio values within the cluster on the y-axes.

olanzapine and haloperidol in macaque monkeys, a reduction of glial cells was found, although the oligodendrocyte density was not reduced after treatment (Konopaske et al., 2008). Some evidence suggests similar effects are present in human settings (Barth et al., 2020; Bartzokis et al., 2007; Gjerde et al., 2018b; Tishler et al., 2018). Thus, the interpretation that divergent age trajectories in patients reflect an effect of antipsychotic treatment is plausible. However, the observed association with antipsychotic medication could also be due to factors that influence antipsychotic dosing and use, such as illness severity and chronicity, sex, or treatment response (Moilanen et al., 2013; Sommer et al., 2023). To examine this further, we encourage future studies to assess intracortical myelination longitudinally in patients with FEP who are drug-naïve at baseline.

Previous studies indicate that the myelination of the cerebral cortex follows a pattern of rapid myelination in early life, stabilization in early-to-mid adulthood, and subsequent decline in late adulthood (Callaghan et al., 2014; Whitaker et al., 2016). Notably, this myelination cycle varies between different regions of the brain (Grydeland et al., 2019), with an earlier myelination peak for the primary sensory and motor cortices than for the association, insular, and limbic cortices. Although our findings indicated a modest linear decline with age in the T1w/T2w-ratio in healthy controls, the age range in our dataset did not include the period of rapid myelination in early life. If a broader age range was included, we would expect to capture non-linear myelination trajectories. Finally, it is possible that the divergent age trajectories observed in the present study reflect a different maturational trajectory of myelination in patients with schizophrenia spectrum disorders.

Strengths and limitations

Strengths of this study include the use of a clinically well-characterized sample where all participants were scanned on the same MRI system. We used a well-tested pipeline for computing the T1w/T2w-ratio, which showed good test–retest reliability and agreement with known myeloarchitecture using scan acquisitions from the same MRI scanner system and pulse sequence parameters.

To compute the T1w/T2w-ratio, we used an intensity normalization procedure, WhiteStripe, based on intensities in normal-appearing white matter (NAWM). While this was previously shown to improve test–retest reliability whilst preserving individual variation in T1w/T2w-ratio distributions, it may introduce dependencies between cortical T1w/T2w-ratio values and T1w and T2w intensity values in NAWM. We cannot rule out the possibility that the observed age-by-diagnosis interactions reflect age trajectories of NAWM rather than gray matter. Quantitative MRI pulse sequences, such as inversion recovery imaging, may be used to rule out this possibility. Such methods estimate biophysically meaningful properties of the MRI measurements and can be used for between-subject comparisons without the need for intensity normalization or calibration.

The T1w/T2w-ratio shows spatial correlation with cortical myeloarchitecture (Glasser, Goyal, Preuss, Raichle, & Van Essen, 2014) but is based on T1w and T2w image intensities which are inherently non-dimensional measures. Recent studies have indicated that the correlations between the T1w/T2w-ratio and other indices of myelination vary between brain regions. For instance, low correlations have been found with the myelin-water fraction (MWF) in densely myelinated regions in white matter (Sandrone et al., 2023; Uddin, Figley, Solar, Shatil, & Figley, 2019). High correlations have, however, been found between the T1w/T2w-ratio and T1 relaxation time mapping of the cerebral cortex (Parent et al., 2023; Shams, Norris, & Marques, 2019). Still, strong conclusions regarding microstructural tissue properties should be avoided since the T1w/T2w-ratio remains a complex measure and other tissue properties than myelin content, such as iron content or dendritic density, may also influence it (Righart et al., 2017).

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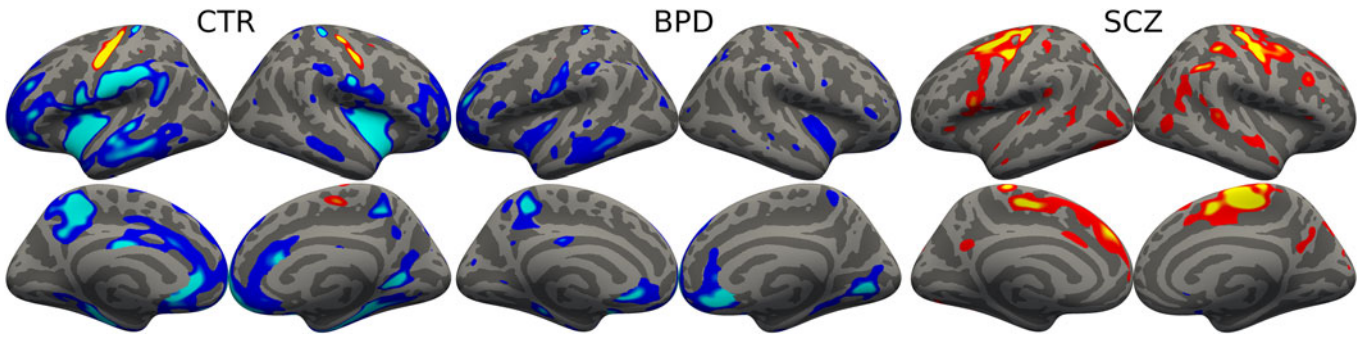

Figure 2. The figure displays results from a vertex-wise general linear model adjusted for age and sex. Contrasts were specified to examine age slopes within each group separately. Colored regions indicate where the association with age deviated from the null hypothesis (i.e. no association) at the threshold $p < 0.01$, uncorrected. Blue to light blue colors denote negative age slopes (i.e. lower T1w/T2w-ratio in older individuals). Red to yellow colors denote positive age slopes (i.e. higher T1w/T2w-ratio values in older individuals).

Table 3. Analysis of cluster-wise T1w/T2w values, antipsychotic medication use and interaction with age

	AP			AP × age			CPZ			CPZ × age		
Region	β	p	p_{corr}	β	p	p_{corr}	β	p	p_{corr}	β	p	p_{corr}
Left hemisphere												
Superior frontal	0.00	0.99	0.99	0.30	0.02	0.06	−0.04	0.71	0.89	0.32	0.002	**0.02**
Pars opercularis	0.00	0.97	0.99	0.29	0.02	0.06	−0.12	0.30	0.51	0.26	0.02	**0.05**
Caudal anterior cingulate	0.04	0.66	0.86	0.27	0.04	0.10	0.00	0.97	0.99	0.26	0.02	**0.05**
Precuneus	0.07	0.70	0.73	0.36	0.006	**0.03**	−0.06	0.63	0.85	0.27	0.01	**0.04**
Insula	−0.05	0.62	0.85	0.32	0.01	**0.05**	0.03	0.77	0.90	0.26	0.02	**0.05**
Middle temporal	0.04	0.64	0.85	0.33	0.01	**0.04**	−0.09	0.45	0.70	0.25	0.02	**0.05**
Precentral	−0.03	0.75	0.90	0.37	0.004	**0.03**	0.08	0.43	0.68	0.33	0.0007	**0.02**
Superior temporal	0.05	0.63	0.85	0.29	0.03	0.06	−0.13	0.27	0.48	0.31	0.005	**0.03**
Fusiform gyrus	−0.04	0.67	0.86	0.24	0.08	0.15	−0.21	0.06	0.13	0.28	0.007	**0.03**
Supramarginal	0.00	0.98	0.99	0.31	0.02	**0.05**	−0.08	0.46	0.71	0.32	0.003	**0.02**
Lateral occipital	−0.04	0.71	0.89	0.28	0.03	0.07	−0.21	0.05	0.12	0.29	0.004	**0.03**
Banks of the superior temporal sulcus	0.04	0.70	0.89	0.43	0.001	**0.02**	−0.17	0.12	0.23	0.33	0.002	**0.02**
Right hemisphere												
Rostral middle frontal	−0.03	0.76	0.90	0.37	0.005	**0.03**	−0.01	0.95	0.99	0.31	0.005	**0.03**
Superior parietal	−0.02	0.83	0.94	0.21	0.12	0.23	−0.03	0.80	0.92	0.38	0.0004	**0.02**
Insula (1)	−0.08	0.40	0.64	0.31	0.02	0.05	−0.04	0.73	0.89	0.24	0.03	0.06
Superior temporal	−0.02	0.87	0.95	0.34	0.01	**0.04**	−0.07	0.54	0.80	0.33	0.002	**0.02**
Superior frontal (1)	−0.02	0.85	0.95	0.42	0.001	**0.02**	−0.12	0.29	0.50	0.27	0.01	**0.04**
Precuneus (1)	0.07	0.45	0.70	0.39	0.003	**0.02**	0.02	0.88	0.96	0.27	0.01	**0.04**
Precuneus (2)	0.05	0.62	0.85	0.40	0.002	**0.02**	−0.15	0.19	0.34	0.33	0.002	**0.02**
Insula (2)	0.00	0.97	0.99	0.34	0.009	**0.04**	0.02	0.86	0.95	0.19	0.08	0.16
Superior frontal (2)	0.01	0.95	0.99	0.48	0.0001	**0.01**	0.06	0.57	0.82	0.23	0.01	**0.04**
Postcentral	0.14	0.16	0.29	0.32	0.01	**0.04**	−0.10	0.37	0.62	0.20	0.06	0.12

Linear regression models ($n = 154$) adjusted for age, sex, and diagnosis. The age and CPZ variables were centered prior to analysis. p-values below 0.05 (FDR-corrected) are marked in bold. Information about antipsychotic medication use was missing for one participant.
Abbreviations: AP, Antipsychotic medication status; CPZ, Chlorpromazine-equivalent dose.

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Neuroimaging findings in schizophrenia and BPD show considerable heterogeneity (Wolfers et al., 2021). Recent studies have suggested the existence of pathophysiological subtypes based on structural and functional neuroimaging markers, which may reflect different neurodevelopmental trajectories (Clementz et al., 2022; du Plessis et al., 2023; Dwyer et al., 2023). Of note, a recent study found a spatial correlation between cortical thickness deviations and glial-specific gene expression profiles to be present in some, but not all, patients with schizophrenia (Di Biase et al., 2022). Examining the covariation with other imaging markers, such as cortical thickness, in a large-scale context and investigating longitudinal T1w/T2w-ratio change from early illness phases would be important avenues to pursue; however, in the present study this was not possible due to sample size limitations and the cross-sectional nature of the study.

The T1w and T2w sequences we used both had 1 mm isotropic resolution; however, for cortical myelin mapping, images with submillimeter resolution would be optimal. Furthermore, while our optimized pipeline improved reliability (Nerland et al., 2021), correction for field inhomogeneities through the acquisition of B1 + field maps is an alternative approach (Glasser et al., 2022). Lastly, although our findings did not confirm an intracortical myelin deficit in schizophrenia spectrum disorders, such deficits could be present in early illness phases or in treatment-naïve individuals.

Conclusions

While our findings did not support the hypothesis of intracortical myelin deficits in schizophrenia spectrum or BPD, they were consistent with the hypothesized promyelinating effect of antipsychotic medication. The possibility that this effect could also mask an intracortical myelin deficit in patients cannot be ruled out. The findings should be followed up by applying quantitative MRI measures and assessing longitudinal trajectories of intracortical myelination in patients who are drug-naïve at baseline.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000503.

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Competing interests. Author OAA has received speaker's honoraria from Lundbeck, Janssen and Sunovion and is a consultant for Cortechs.ai. Author IA has received a speaker's honorarium from Lundbeck. The other authors report no conflict of interest.

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