RESEARCH ARTICLE

Depth-dependent abnormal cortical myelination in first-episode treatment-naïve schizophrenia

Wei Wei[1,2] | Yamin Zhang[1,2] | Yinfei Li[1,2] | Yajin Meng[1,2] | Mingli Li[1,2] | Qiang Wang[1,2] | Wei Deng[1,2] | Xiaohong Ma[1,2] | Lena Palaniyappan[3,4] | Nanyin Zhang[5] | Tao Li[1,2]

[1]Mental Health Center and Psychiatric Laboratory, The State Key Laboratory of Biotherapy, West China Hospital of Sichuan University, Chengdu, Sichuan, China

[2]West China Brain Research Center, West China Hospital of Sichuan University, Chengdu, Sichuan, China

[3]Robarts Research Institute & Department of Psychiatry, University of Western Ontario, London, Ontario, Canada

[4]Lawson Health Research Institute, London, Ontario, Canada

[5]Department of Biomedical Engineering, The Huck Institutes of the Life Sciences, The Pennsylvania State University, University Park, Pennsylvania

Correspondence
Nanyin Zhang, Department of Biomedical Engineering, The Huck Institutes of the Life Sciences, The Pennsylvania State University, W-341 Millennium Science Complex, University Park, Pennsylvania 16802, USA.
Email: nuz2@psu.edu and Tao Li, Mental Health Center, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China.
Email: litaohx@scu.edu.cn

Abstract

Myelination is key to effective message passing in the central nervous system and is likely linked to the pathogenesis of schizophrenia (SZ). Emerging evidence indicates that a large portion of intracortical myelin insulates inhibitory interneurons that are highly relevant to pathogenesis of schizophrenia. Here for the first time, we characterized intracortical myelination across the entire cortical surface in first-episode treatment-naïve patients with schizophrenia (FES) using T1w/T2w ratio of structural MRI, FES patients exhibited significantly higher myelin content in the left inferior parietal lobe, supramarginal gyrus, and superior temporal gyrus in the superficial layer, as well as left IPL in the middle layer, but significantly lower myelin content in the left middle insula and posterior cingulate gyrus. Years of education, a proxy for onset of functional decline, significantly altered the relationship between abnormal parietal and posterior cingulate myelination and clinical symptoms, indicating that the pathoplastic role of myelination hinges on the age of onset of functional decline. In addition, higher myelination generally related to better cognitive function in younger subjects but worse cognitive function in older subjects. We conclude that FES is characterized by increased myelination of the superficial layers of the parietal–temporal association cortex, but reduced myelination of the cingulo-insular midcortical layer cortex. Intracortical myelin content affects both cognitive functioning and symptom burden in FES, with the effect conditional upon age and timing of onset of functional decline. These results suggest myelination might be a critical biological target for procognitive interventions in SZ.

KEYWORDS

cognitive development, cortical myelination, insula, schizophrenia, T1w/T2w ratio

1 | INTRODUCTION

Schizophrenia (SZ) is a severe mental disease disabling thinking, behavior and social function. Etiology of SZ has not been fully understood. Studies have shown that demyelination in the central nervous system (CNS) might be related to the pathogenesis and progress of SZ (Maas, Valles, & Martens, 2017). Myelination ensures insulation of neural axons and is important to rapid action potential propagation and nutrition supply (Emery, 2010; Funfschilling et al., 2012).

Abnormal myelination in SZ has been mainly reported in white matter (WM) based on the diffusion tensor imaging (DTI) technique (Gangadin, Nasib, Sommer, & Mandl, 2019; Hamoda et al., 2019). Structural imaging of the gray matter (GM) has identified morphological changes such as reduced volume, thickness and surface area in SZ (Barry et al., 2019; Gao et al., 2018; Storvestre et al., 2019). Some studies suggest that in SZ, changes of myelination in WM might explain the morphometric change in GM since neural fibers mostly start from or end in the GM (Sasamoto et al., 2014). In particular, frontal, parietal, and temporal association cortices are thought to show a late surge in the intracortical myelination during adolescence, a critical period for the onset of schizophrenia (Whitaker et al., 2016). Therefore, we investigate if widespread abnormalities in intracortical myelination (GM), especially affecting the multimodal association cortices, are seen in SZ before any exposure to antipsychotic medications occurs.

Postmortem studies have found evidence showing some cortical damages related to demyelination in SZ: (a) Demyelination in layer I of the dorsal lateral prefrontal cortex was observed (Uranova, Vostrikov, Orlovskaya, & Rachmanova, 2004); (b) The prefrontal cortex showed decreased density and altered microstructure of myelinated axons (Lake et al., 2017); (c) The density of oligodendrocytes in layer IV of Broadmann area 9 (BA 9) was decreased (Uranova, Vikhreva, Rachmanova, & Orlovskaya, 2011). in vivo examination of myelination in SZ, is fraught with technical challenges. Although DTI is an excellent tool for investigating WM changes, it is not suitable for quantifying cortical myelination. Magnetization transfer ratio (MTR) imaging has been used to detect signals related to myelin (Jia et al., 2017; Wei et al., 2018). However, it has recently been reported that the signal intensity in MTR mainly reflected the density of dendrites of neurons but not myelin (Patel, Shin, Gowland, Pausova, & Paus, 2019). GM/WM contrast (GWC) was also used to reflect myelination in SZ and revealed increased GWC in sensory and motor areas in SZ (Jorgensen et al., 2016), and that the GWC in the insula and cingulate was positively correlated with psychopathology in young patients (Norbom et al., 2019). Nonetheless, GWC can only detect myelination of relatively inner layers of the cortex. As most postmortem studies have found abnormal myelination in SZ to be restricted to specific cortical layers across different brain regions. We expected the abnormal myelination in SZ to be depth-dependent.

Glasser and colleagues reported that T1-weighted (T1w)/T2-weighted (T2w) ratio value could reflect cortical myelination (Glasser & Van Essen, 2011). Evidence shows that this method can precisely estimate cortical myelination: (a) Virtual boundaries of brain

regions generated based on T1w/T2w ratio were well aligned with results in prior anatomical and functional brain study (Glasser & Van Essen, 2011); (b) T1w/T2w ratio had similar cortical distribution compared to signal density pattern in neurite imaging (Fukutomi et al., 2018); (c) abnormal myelination of WM revealed by this method was highly consistent with the DTI results in patients with multiple sclerosis (Nakamura, Chen, Ontaneda, Fox, & Trapp, 2017); (d) structural covariance networks generated based on T1w/T2w ratio corresponded to functional brain network (Ma & Zhang, 2017). Hagiwara et al. also demonstrated that the correspondence between T1w/T2w ratio and myelin water fraction was strong across the gray matter (Hagiwara et al., 2018). Application of T1w/T2w ratio has also aided in elucidating diverse regional maturation patterns of cortical myelination over the lifespan (Grydeland et al., 2019; Shafee, Buckner, & Fischl, 2015). Given these regional variations in the age-specific myelin maturation in different brain regions (Grydeland et al., 2019), we expected the relationships between cortical myelination and cognitive function to differ across ages. In patients with FES, anatomical changes as well as functional decline predate illness onset, the latter often affecting years of education (EDUY) (Bolt et al., 2018). In addition to age, we also studied the moderating effect of EDUY on cortical myelination in FES.

To our knowledge, there is no study to date examining cortical myelination in patients with first-episode treatment-naïve SZ (FES). Furthermore, existing studies in chronic schizophrenia samples do not resolve depth-dependent variations in myelin content. We employ a vertex-based method, which allows us to separate the cortex to multiple layers and detect depth-dependent myelination changes in FES. In addition, we examine whether regional myelination changes are correlated with clinical symptoms or altered cognitive functions in patients. Furthermore, we apply a moderation analysis to probe whether the relationships between myelination and clinical symptom as well as cognitive functions changed for different ages or EDUY.

2 | METHOD

2.1 | Participants

A total of 109 SZ patients were enrolled from the inpatients and outpatients from Mental Health Center of West China Hospital of Sichuan University from October 2014 to June 2018. All patients were assessed with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (SCID-IP) and fulfilled with the diagnostic criteria for SZ in DSM-IV. All patients were treatment-naïve. Patients with any other Axis I disorder in DSM-IV were excluded. Then, 128 gender and age-matched healthy participants were recruited in the same institution from October 2014 to June 2018 and assessed using SCID for DSM-IV, nonpatient edition. General exclusions included nervous system diseases, severe physical diseases, personality disorders, drug abuse, alcohol abuse, or IQ < 70. The study was described in specific details to every participant, who completed and signed an informed consent

form before participating in this study. Informed consent forms of juveniles were signed by their legal guardians. This study was approved by the Institutional Review Board of West China Hospital, Sichuan University and in accordance with the Helsinki Declaration.

2.2 | Clinical ratings and cognitive assessment

All participants were Han Chinese and right-handed. Handedness was assessed with the Annett Handedness Scale (Annett, 2004). Positive and Negative Syndrome Scale (PANSS) and Global Assessment Function (GAF) were estimated when patients were recruited. We applied a consensus five-factor model which identifies symptom categories estimated by PANSS: Positive, negative, disorganization, excitement, and depression (Wallwork, Fortgang, Hashimoto, Weinberger, & Dickinson, 2012). P6 (Suspiciousness/Persecution) was analyzed alone since it was a hallmark of SZ but not included in the five-factor model. Full, verbal and performance intelligence quotient (IQ, VIQ and PIQ) were estimated using the short version of the Weschsler Adult Intelligence Scale (WAIS)—Revised in China including information, arithmetic, digital symbol, digital span test, block design, picture completion, and similarities (Gong, 1984).

2.3 | MRI acquisition

All scanning was performed on a 3.0 T MR scanner (Achieva; Philips, Amsterdam, the Netherlands) using an eight-channel phased-array head coil. We used foam padding and earplugs to minimize head movement of participants and scanner noise.

T1w images were acquired by a magnetization-prepared rapid gradient-echo sequence: Repetition time (TR): 8.1 ms, echo time (TE): 3.7 ms, flip angle: $7°$, slice thickness: 1 mm (no slice gap), 188 axial slices, matrix size: 256×256, field of view (FOV): 256×256 mm^2, voxel size: $1 \times 1 \times 1$ mm. T2w images were acquired by a turbo spin-echo sequence: TR: 2,500 ms, TE: 261 ms, flip angle: $90°$, slice thickness: 1 mm (no slice gap), 180 axial slices, matrix size: 256×256, FOV: 256×256 mm^2, voxel size: $1 \times 1 \times 1$ mm^3, strong fat suppression. Brain images were examined after each scan, and repeated if any artifact was identified. Eight fewer slices in T2w image were all located in the neck.

T1w and T2w images were judged with the quality control procedure of HCP (https://www.humanconnectome.org/storage/app/media/documentation/s1200/HCP_S1200_Release_Appendix_IV.pdf) before preprocessing. Only "good" or "excellent" images were used for processing and analysis.

2.4 | Image processing

We used three pipelines (PreFreeSurfer, FreeSurfer, and PostFreeSurfer) to generate cortical myelin maps with HCP pipelines (v4.0.0-alpha.5, https://github.com/Washington-University/HCPpipelines/tree/master),

Freesurfer (v6.0) FMRIB Software Library (FSL, v5.0.10), and workbench (v1.2.3). Details of these pipelines can be found in the reference (Glasser et al., 2013). Briefly, bias field correction and T2w image to T1w image registration were conducted using PreFreeSurfer pipeline; FreeSurfer pipeline generated untraditional pial-GM and GM-WM surfaces with additional information from T2w image. We obtained a more precise pial-GM surface through this pipeline; PostFreeFurfer pipeline was used to map voxel-wise T1w/T2w ratio value to a midplane which was generated in the middle of pial-GM surface and GM-WM surface, and individual images were then registered to standard space (32k fs LR mesh) through Multimodal Surface Matching algorithm (MSM-Sulc) based on cortical curvature and myelination (Robinson et al., 2014). The mean myelin map of the entire cortex of healthy controls was generated at last and compared with the mean myelin map of the HCP database to confirm the preprocessing results (Figure S1).

Subsequently, we determined superficial, middle and deep cortical layers in percentage terms (95–65, 65–35, and 35–5 through superficial to deep layers). Five percent of the cortex at the superficial and deep surfaces was abandoned to avoid the partial volume effect of cerebrospinal fluid and WM, respectively. To form the myelin maps of each cortical layer, T1w/T2w ratio values of three cortical layers were all mapped to the mid-plane, and corrected for partial volume, which further improved the precision of mapping (Shafee et al., 2015). At last, we normalized the myelin map (zero mean and unit variance) per cortical layer for every subject and smoothed all myelin maps with a Gaussian filter (FWHM = 10 mm).

2.5 | Statistical analysis

2.5.1 | Demographic, clinical, and cognitive data

We used chi-square tests or two-sample tests to examine gender, age, and EDUY between groups. ANCOVA tests were conducted to examine IQ, VIQ, and PIQ between groups after regressing out age, gender, and EDUY. All analyses were conducted in R (v3.6).

2.5.2 | T1w/T2w ratio values

To compare normalized T1w/T2w ratio values between groups in three myelin maps, permutation tests were conducted using Permutation Analysis of Liner Models (PALM, version alpha106). Age, gender, and EDUY were regressed out as covariates. Permutation tests were two-tailed, and were separately performed on two hemispheres according to the manual (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM) with 5,000 repetitions. Cohen's d values were calculated to represent the effect sizes. The level of significance was set at cluster-wise family-wise error (FWE)-corrected $p < .05$ ($z > 3.1$ as the cluster threshold). Multiple comparison correction for three myelin maps and two hemispheres were conducted with a built-in "corrmod" command in PALM.

After permutation tests, mean T1w/T2w ratio values of brain regions with statistically significant differences were extracted. Partial correlations with PANSS scores, GAF scores or IQ after controlling for age, gender and EDUY were also calculated. Multiple comparison correction was performed by setting the false discovery rate (FDR) threshold at $p < .05$. Partial correlation tests were performed in R (version 3.6).

2.5.3 | Moderation analysis

After determining the relationship between myelination with clinical ratings, cognitive function and EDUY, we used the Johnson–Neyman (JN) procedure with CAHOST (version 1.01) to probe the conditional effects (θ) of myelination (X) on PANSS scores, GAF scores and cognitive function (Y) in the entire age range (with gender and EDUY as nuisance covariates) or EDUY (with gender and age as nuisance covariates) as continuous moderators (M; Johnson & Fay, 1950; Miller, Stromeyer, & Schwieterman, 2013). Conventional moderation analysis is conducted by pick-a-point method, which means that the analysis only tests conditional effects of X on Y at some arbitrary-chosen points of M. JN procedure is a floodlight analysis which tests conditional effects of X on Y at multiple points across the entire range of M to get a fuller picture (Bauer & Curran, 2005). Usually, two steps are needed for JN procedure, first step is calculating the dividing point of M which let the P of the conditional effect of X on Y equal to a significant level (0.05 in the present study), second step is plotting the lower and upper bands with 95% confidence interval. In the present study, if the confidence interval contains zero at any age or EDUY

(M), the conditional effects (θ) of X on Y was interpreted as insignificant (Carden, Holtzman, & Strube, 2017). For better understanding, we also conducted moderation analysis by pick-a-point method and reported these results in the Supporting Information.

3 | RESULTS

3.1 | Demographic and cognitive data

Age, gender, and body mass index did not differ between FES patients and healthy controls. FES patients had statistically significant lower EDUY, VIQ, PIQ, and IQ (all $p < .001$). Table 1 shows those results along with GAF and PANSS scores of FES patients.

3.2 | Differences in myelination

In the superficial layer, the left supramarginal gyrus (sSMG, $-\log$[FWE-P] = 2.52, MNI $x = -61$, $y = -46$, $z = 32$), inferior parietal lobe (sIPL, $-\log$[FWE-P] = 1.76, MNI $x = -49$, $y = -68$, $z = 35$) and superior temporal gyrus (sSTG, $-\log$[FWE-P] = 1.60, MNI $x = -58$, $y = -6$, $z = -6$) showed statistically significant higher T1w/T2w ratio in FES patients. In the middle layer, the left inferior parietal lobe (mIPL, $-\log$[FWE-P] = 1.80, MNI $x = -50$, $y = -68$, $z = 35$) showed statistically significant higher T1w/T2w ratio in FES patients, while the left insula (mINS, $-\log$[FWE-P] = 1.40, MNI $x = -30$, $y = 17$, $z = -24$) and posterior cingulate gyrus (mPCG) showed statistically significant lower T1w/T2w ratio in

TABLE 1 Demographic, cognitive, and clinical data

	FES patients ($n = 109$)	Health ($n = 128$)	Statistics	p
Gender (M/F)	52/57	66/62	$X^2 = 0.35$	.554
Age (years)	23.69 ± 6.18	24.36 ± 5.18	$t = 0.91$	.364
EDUY (years)	12.40 ± 2.70	15.03 ± 2.66	$t = 7.52$	1.13E−12
BMI	21.22 ± 3.27	20.93 ± 3.16	$t = 0.67$	.501
IQ	($n = 92/109$)	($n = 118/128$)		
VIQ	98.03 ± 14.37	114.89 ± 12.89	$F = 26.297$	6.76E−07
PIQ	92.75 ± 15.48	110.75 ± 13.38	$F = 36.002$	8.86E−09
Total IQ	95.39 ± 13.75	114.36 ± 12.70	$F = 43.868$	3.03E−10
GAF ($n = 93/109$)	46.95 ± 13.72	–	–	–
PANSS ($n = 99/109$)		–	–	–
Total	93.03 ± 20.15	–	–	–
Positive	14.35 ± 4.12	–	–	–
Negative	21.55 ± 6.82	–	–	–
Disorganization	10.40 ± 3.40	–	–	–
Excitement	10.20 ± 4.95	–	–	–
Depression	7.26 ± 2.95	–	–	–
P6	4.23 ± 1.56	–	–	–

Abbreviations: BMI, body mass index; EDUY, education year; FES, first-episode treatment-naïve patients with schizophrenia; GAF, Global Assessment Function; IQ, intelligence quotient; PANSS, Positive and Negative Syndrome Scale; PIQ, performance intelligence quotient; Total IQ, Total score of intelligence quotient; VIQ, verbal intelligence quotient.

FES patients. Cohen's *d* values of all regions showing significant differences were higher than 0.6, indicating medium effect size changes. No group differences were noted in the deep cortical layer. Results were shown in Figures 1 and 2, Table 2, and Figure S2.

3.3 | Regional myelin content correlates of GAF, PANSS, and IQ

We observed several trends of correlation between regional mean T1w/T2w ratio and GAF, PANSS, and cognitive functions. The myelin content in the left sIPL and mIPL was negatively correlated with PIQ in controls and excitement factor of PANSS in FES patients, respectively. However, none of these correlations survived statistical correction for multiple comparisons (Table 3).

3.4 | Conditional effects of regional myelination on clinical ratings and IQ

We applied the JN technique to determine the age and EDUY range at which the conditional effects (θ) of regional abnormal myelination on clinical ratings and cognitive function were significant. Only correlations with significant conditional effects are shown. Higher T1w/T2w ratio of the left mIPL was significantly related to higher P6 (Suspiciousness/Persecution) and positive factor scores in patients with EDUY higher than 12.4 and 13 years (Figure 3a,b). For EDUY lower than 12.4 and 13 years, the conditional effect of myelination in the left mIPL on the Suspiciousness/Persecution (P6) and a positive factor of PANSS scores was insignificant. Higher T1w/T2w ratio of the left mIPL was also related to higher depression factor scores with EDUY higher than 16 years; an opposite effect indicating lower depression with higher T1w/T2w of left mIPL was seen
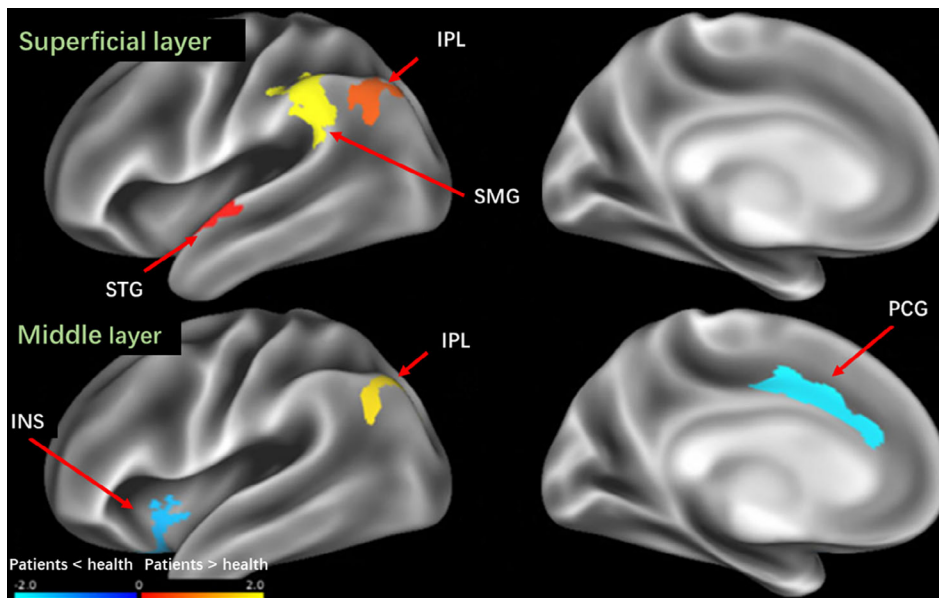

FIGURE 1 Regional differences in myelin content. IPL, inferior parietal lobe; SMG, supramarginal gyrus; STG, superior temporal gyrus; INS, insula; PCG, posterior cingulate gyrus. No significant result was found in deep cortical layer
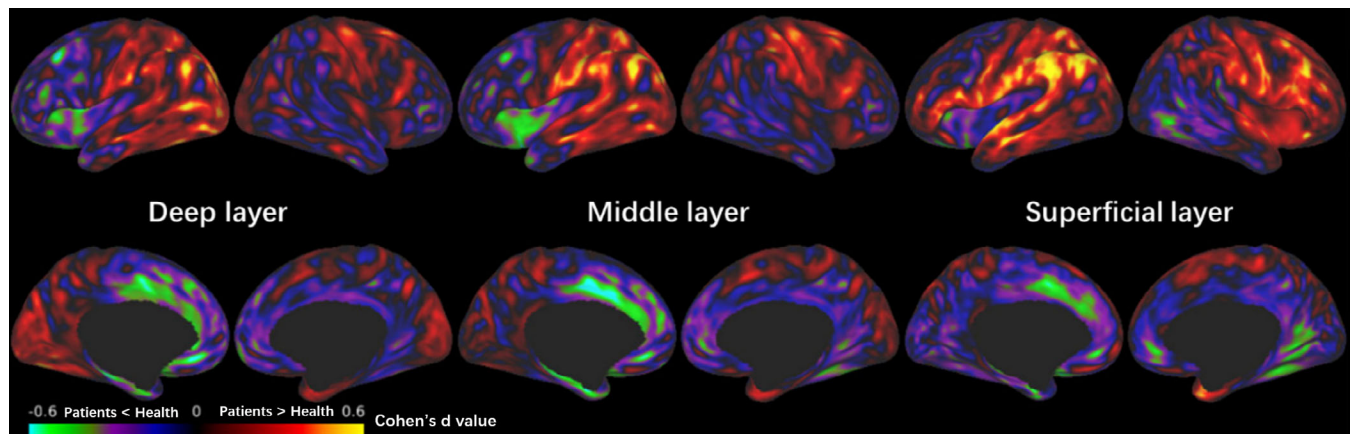

FIGURE 2 Effect size map of intergroup difference between FES patients and healthy controls. Cohen's *d* was calculated as the effect size and differed in different cortical layers. Negative Cohen's *d* values indicated fewer myelin contents in FES patients. Regions with relative high effect size could be observed in the superior frontal gyrus and ventral medial cortex though those regions did not show significant differences after multiple comparison correction

TABLE 2 Regional differences of T1w/T2w ratio value

	Peak T	Peak Cohen's *d*	−log *p* (FWE-corrected)	Number of vertex	MNI coordinate		
					x	y	z
FES patients > controls							
Left sSMG	4.85	0.72	2.52	516	−61	−46	32
Left sIPL	4.96	0.73	1.76	232	−49	−68	35
Left sSTG	4.37	0.65	1.60	160	−58	−6	−6
Left mIPL	4.92	0.73	1.80	201	−50	−68	35
FES patients < controls							
Left mINS	−4.06	−0.6	1.40	201	−30	17	−24
Left mPCG	−5.05	−0.75	1.80	300	−5	1	44

Abbreviations: FES: first-episode treatment-naïve schizophrenia; FWE: family-wise error; mINS: middle insula; mIPL: middle inferior parietal lobe; mPCG: middle posterior cingulate gyrus; sIPL: superficial inferior parietal lobe; sSMG: superficial supramarginal gyrus; sSTG: superficial superior temporal gyrus.

TABLE 3 Correlations between regional myelination and clinical ratings and IQ

	Left sSMG	Left sIPL	Left sSTG	Left mIPL	Left mINS	Left mPCG
IQ						
Health						
VIQ	−0.007 (.943)	0.028 (.769)	0.038 (.685)	−0.02 (.828)	0.124 (.186)	−0.069 (.464)
PIQ	−0.171 (.067)	−0.206 (.028)*	0.02 (.829)	−0.268 (.004)*	0.131 (.164)	0.084 (.372)
Total IQ	−0.091 (.335)	−0.083 (.38)	0.038 (.69)	−0.146 (.119)	0.154 (.101)	−0.005 (.961)
FES patients						
VIQ	−0.116 (.281)	0.101 (.347)	−0.202 (.058)	0.074 (.491)	−0.012 (.909)	−0.076 (.48)
PIQ	−0.012 (.914)	0.156 (.146)	−0.201 (.061)	0.235 (.028)*	−0.188 (.080)	−0.126 (.241)
Total IQ	−0.130 (.226)	0.059 (.585)	−0.225 (.034)*	0.090 (.401)	−0.129 (.230)	−0.109 (.308)
Clinical ratings						
GAF	0.076 (.481)	0.060 (.572)	−0.117 (.272)	0.158 (.137)	−0.098 (.356)	−0.241 (.022)*
PANSS						
Positive	−0.029 (.781)	0.003 (.973)	−0.079 (.445)	0.132 (.199)	−0.154 (.133)	0.039 (.707)
Negative	−0.001 (.996)	−0.010 (.926)	−0.011 (.912)	−0.096 (.354)	0.042 (.683)	0.128 (.214)
Disorganization	−0.011 (.913)	−0.110 (.285)	−0.087 (.397)	−0.145 (.158)	0.067 (.518)	0.064 (.535)
Excitement	−0.165 (.108)	−0.295 (.004)*	−0.083 (.422)	−0.233 (.022)*	−0.037 (.717)	0.042 (.683)
Depression	−0.056 (.587)	−0.044 (.671)	−0.289 (.004)*	−0.011 (.916)	−0.203 (.047)*	−0.117 (.256)
P6	−0.013 (.897)	0.066 (.520)	−0.193 (.059)	0.177 (.084)	−0.224 (.028)*	−0.125 (.226)

Note: *$p < .05$, not corrected. Results were represented as the correlation coefficient ρ with *p* in brackets. No correlation survived multiple-comparison correction.

Abbreviations: FES: first-episode treatment-naïve schizophrenia; GAF: Global Assessment Function; IQ: intelligence quotient; mINS: middle insula; mIPL: middle inferior parietal lobe; mPCG: middle posterior cingulate gyrus; PANSS: Positive and Negative Syndrome Scale; PIQ: performance intelligence quotient; sIPL: superficial inferior parietal lobe; sSMG: superficial supramarginal gyrus; sSTG: superficial superior temporal gyrus; VIQ: verbal intelligence quotient.

when EDUY was lower than 8.6 years (Figure 3c). For GAF scores, the myelination of the left mIPL showed a positive correlation and that of the left mPCG showed a negative correlation in patients with EDUY lower than 11.3 years, respectively (Figure 3d,e). Myelination of the left mPCG was also negatively related to the depression factor with EDUY higher than 13.6 years (Figure 3f). No age-related moderation effect was found. In summary, these results (and the regression results in the Figure S2) indicate that illness severity in FES varies with myelin quantity in a U-like manner depending on the onset of functional decline in the hypermyelinated IPL region, and in an inverted U-like manner in the hypomyelinated mPCG, region.

Myelination of the left sSTG was positively related to VIQ with healthy controls younger than 22.4 years (Figure 4a). Myelination of the left mINS was positively related to VIQ and IQ with healthy controls younger than 21.7 and 37.2 years, respectively, while the opposite relationship was found in healthy controls older than 29.1 and 30.2 years, respectively (Figure 4b,c). Myelination of the left sSMG showed a negative correlation with VIQ in FES patients younger than
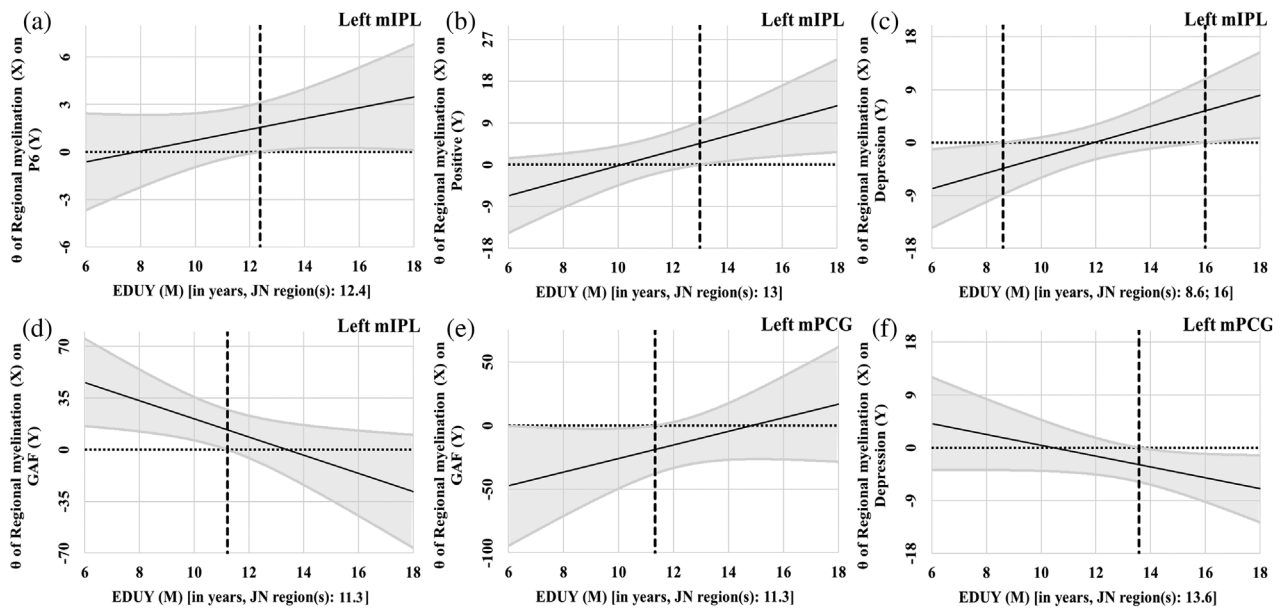
FIGURE 3 Altered regional myelination associated with clinical ratings. Conditional effects (θ) of regional myelination on clinical ratings across the entire EDUY range using the Johnson–Neyman procedure. mIPL, middle inferior parietal lobe; mPCG, middle posterior cingulate gyrus; EDUY, years of education. Gray regions indicate the 95% confidence interval. Confidence interval contained zero indicates insignificant conditional effect of regional myelination on clinical ratings at corresponding EDUY

21.5 years (Figure 4d). Myelination of left the mINS was positively related to VIQ in FES patients younger than 18.6 years, while the opposite relationship was found in VIQ and IQ in FES patients older than 28.4 and 24.9 years, respectively (Figure 4e,f). Higher myelination of the left mPCG was related to lower VIQ in FES patients older than 26.2 years (Figure 4g). Higher myelination of the left mINS was related to higher VIQ in FES patients with EDUY lower than 9.3 years, but lower VIQ and IQ in FES patients with EDUY higher than 14.9 and 13.5 years (Figure 4h,i). In summary, these results (and the conventional regression reported in the Figure S3) indicate that cognitive function has an inverted U type relationship with age-related myelin quantity in both healthy controls and in FES (with the exception of sSMG in FES, possibly due to the age-invariant higher peak levels seen in FES).

4 | DISCUSSION

Using T1w/T2w ratio as a measure of myelin content, this cross-sectional study found several brain regions with abnormal myelination in FES. Patients exhibited higher myelination in the left sIPL, sSMG, sSTG, and mIPL, but lower myelination in the left mINS and mPCG. Age had a pronounced moderating effect on the relationship between myelination and cognition, with higher myelination relating to better cognitive function in younger patients but worse cognitive function in older patients. We also noted that EDUY (a proxy for the onset of functional decline), not age, moderated the influence of cortical dysmyelination on clinical symptoms, in patients with FES. Overall these results indicate that (a) cortical dysmyelination is most pronounced at the temporoparietal and cingulo-insular regions, rather than dorsolateral prefrontal cortex, in drug-naïve FES and (b) the pathological effect

of relative excess/deficit in myelin quantity on cognition relates to age, and on clinical symptoms relates to age of onset of functional decline (measured using EDUY).

4.1 | Mean myelin map in healthy controls

In present study, we observed relatively lower than average myelination in the prefrontal cortex, insula, and anterior cingulate cortex, whereas relatively higher than average myelination in sensorimotor cortex, primary visual cortex, and PCG in the mean myelin map generated from healthy subjects. The distribution of values in our mean myelin map was consistent with the mean myelin map from the HCP database and other myelin maps reported in previous studies (Glasser et al., 2013; Glasser, Goyal, Preuss, Raichle, & Van Essen, 2014; Glasser & Van Essen, 2011). Those results confirmed the effectiveness of the HCP pipelines in analyzing myelination data.

4.2 | Depth-dependence of abnormal regional myelination in FES

The effect size maps of HC vs. FES contrast highlight the inconsistency of aberrant myelination across the various cortical layers (Figure 3). This observation is consistent with postmortem studies reporting myelin-related abnormalities in specific, not all, cortical layers of the various affected regions in FES only IPL had hyper-myelination in both superficial and middle cortical layers (Smiley, Konnova, & Bleiwas, 2012; Uranova et al., 2004). Increased myelination in superficial layer might relate to higher neuronal density, but
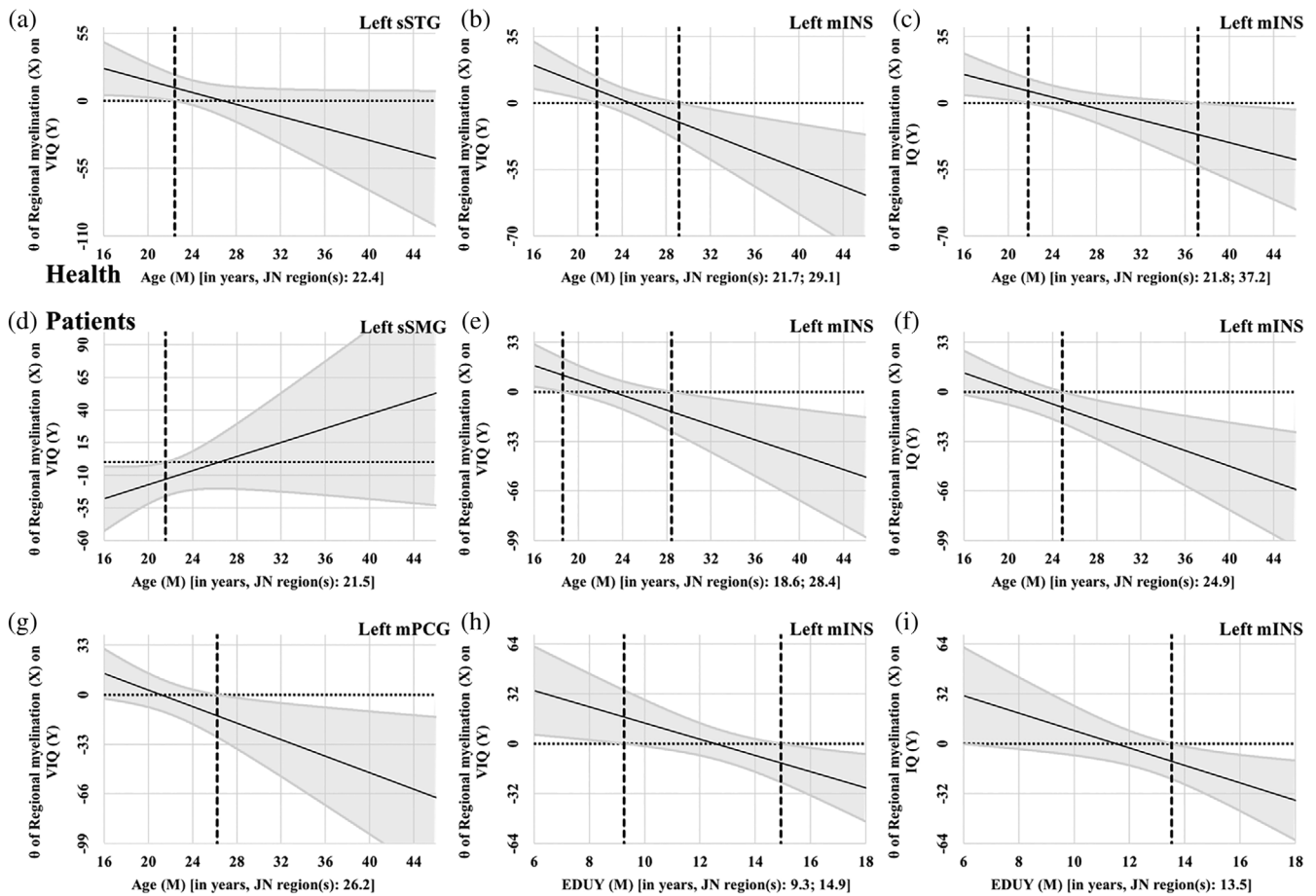
FIGURE 4 Altered regional myelination associated with cognitive function. Conditional effects (θ) of regional myelination on cognitive functions across the entire age or EDUY ranges using the Johnson–Neyman procedure. sSMG, superficial supramarginal gyrus; sSTG, superficial superior temporal gyrus; mINS, middle insula; mPCG, middle posterior cingulate gyrus. Gray regions indicate the 95% confidence interval. Confidence interval contained zero indicates insignificant conditional effect of regional myelination on cognitive functions at corresponding age

reduced dendritic arbors, reflecting loss of dendritic spines (Glasser et al., 2014). Given that the superficial cortical level tends to contain the supragranular layers that are rich in feed-forward sensory connections on pyramidal neurons, higher myelination in this layer may also reflect reduced density of sensory inputs to the multimodal association areas of temporal and parietal cortices in FES. On the other hand, reduced myelination in mid cortical level, where thalamic inputs are more prominent (Viaene, Petrof, & Sherman, 2011), may indicate aberrations in thalamocortical inputs to insula and cingulate cortex in FES. As a large fraction of cortical myelin in layers 2/3 and 4 encircles axons of parvalbumin-positive inhibitory basket cells (Micheva et al., 2016), reduced mid-cortical myelination of cingulo-insular cortex may also indicate inefficient cortical inhibitory processes in FES. Therefore, separately analyzing these data in a layer dependent manner helps reveal more specific information.

We found hypermyelination in the left sSMG, sIPL and mIPL. Traditionally IPL consists of SMG and angular gyrus in the Brodmann atlas. IPL relates to multiple cognitive function such as attention sensory integration, language, calculation and concept of self (Chieffi, Ilardi, & Iavarone, 2018; Torrey, 2007). Postmortem study observed higher neuron density in superficial layer of IPL in SZ (Smiley et al.,

2012). Frangou, Doucett, Lee, and Sprooten (2019) found higher intracortical myelin concentration in the parietal cortex in SZ. Godwin and colleagues found cortical thickness was reduced in IPL and SMG in SZ (Godwin, Alpert, Wang, & Mamah, 2018). Cortical thinning is related to higher cortical myelin content in superficial cortical layer of IPL and SMG (Shafee et al., 2015), suggesting that our results were consistent with these previous studies.

Hypermyelination was also found in the left sSTG in SZ. As STG contains the primary auditory cortex, hypermyelination in this area could affect auditory function (Tzourio-Mazoyer et al., 2018). Structural and functional abnormalities in STG were related to verbal hallucination in SZ (Kose, Jessen, Ebdrup, & Nielsen, 2018; Kunzelmann et al., 2019). Level of gamma-aminobutyric acid (GABA) was found increased in temporal gyrus in SZ patients, which may suggest that hypermyelination in the STG could relate to GABAergic pathway disruption in the disease (Galinska-Skok et al., 2018).

Reduced myelination was found in the left mPCG and mINS. The volume of both these regions decreases in the early stages of SZ, with the deficit worsening during the course of the disease (Gao et al., 2018; Koo et al., 2008). Decreased volume of INS is one of the most replicated findings in SZ (Kuo & Pogue-Geile, 2019) and related to

decreased IQ in SZ (Caldiroli et al., 2018). In addition, the centrality of INS was found to decrease in a brain network analysis in adolescents with SZ (Palaniyappan et al., 2019). Damage of neural cells, decreased density of axons or pathological degeneration of oligodendrocytes all might lead to demyelination of those two regions, which may result in reduced volume (N. Uranova et al., 2001). In addition, Norbom et al. found GWC of the INS and PCG was positively correlated with psychotic symptoms in youth, which suggests myelination of those two regions be negatively correlated with psychotic symptoms. Their results were consistent with our current observations and indicate that demyelination of PCG and INS may precede the onset of SZ and persist afterward.

4.3 | Conditional effects of abnormal regional myelination on clinical ratings and cognitive function

EDUY is usually used as a proxy for cognitive reserve in dementia (Mungas et al., 2018), but lower EDUY is best considered as a proxy for earlier onset functional decline in FES patients, as academic decline often predates the first psychotic break. Unlike degenerative disorders such as dementia, the cognitive deficits in SZ are evident early in development even before the disease onset (Bolt et al., 2018; Reichenberg et al., 2010), possibly contributing to drop-out from schools, but does not decline continuously after the first episode (Bora, 2015). We found that hypermyelination of the left mIPL was correlated with higher suspiciousness, positive and depression factor scores of PANSS with higher EDUY. Hypomyelination of the left mPCG correlated with higher depression (and lower GAF) in FES with higher EDUY. While increased GM myelination in IPL (and concomitant decrease in mPCG) was associated with less severe illness in those with earlier illness onset (i.e., low EDUY), the abnormally persistent change in myelin content in FES was associated with more severe illness in those with later onset.

Cortical myelin maturation could reflect neurodevelopment trajectory of the cortex. Grydeland et al. (2019) examined the trajectory of myelin maturation in a large sample with a wide range of age. They found that myelin of the left insula reached peak growth age at nearly 21 years old and became stable until 35 years old. We observed VIQ and total IQ positively correlated to myelination of the left mINS till 21.7 and 21.8 years old, respectively, and negatively correlated to myelination of left mINS from 29.1 and 37.2 years old in healthy controls. The time points we observed were roughly consistent with the maturation milestones in the study of Geydeland. Peak growth age of the left sSTG (about 21 years old) was also similar to the end point of simultaneity of increasing myelination and VIQ. Therefore, we speculated that after peaking in the growth of myelination, cognition development could not gain from the growth of myelin, and after myelination becomes stable, increasing myelination in the mINS was pathological and could affect cognitive function. FES patients showed earlier ending and starting points than healthy controls in the left mINS, which indicated that increasing of cognitive function gained from myelin maturation diminished earlier and decreased cognitive

function along with abnormal hypermyelination started earlier because of abnormal neural development in SZ. Our finding corresponds to Bora's theory (Bora, 2015) that the development of cognitive function of SZ patients is characterized by slower gain, earlier peaking followed by earlier onset of decline.

Finally, a number of important limitations need to be considered. There is an ongoing uncertainty about the relationship between T1w/T2w ratio and myelination. Uddin et al. reported that T1w/T2w ratio failed to reach a consistency with myelin water fraction (MWF) imaging (Uddin, Figley, & Figley, 2018; Uddin, Figley, Marrie, Figley, & CCOMS Study Group, 2018). Other pathology such as iron deposition could also affect signal of T1w or T2w image (Ogg & Steen, 1998). But, in a more recently head-to-head comparison of T1/T2 ratio and tissue relaxometry based on myelin water fraction, Hagiwara et al. (2018) demonstrated that the correspondence between these two measures were moderate to strong across the gray matter (Spearman's r = .73–.77), though it was poor for white matter (Spearman's r = .40–.50). Abnormal iron deposition was also not observed in schizophrenia (Iritani, 2007). This indicates that our results are meaningful but need confirmation in the trough alternate imaging approaches. Nevertheless, as other pathological changes can also result in alterations of T1w/T2w ratio, we urge caution in equating our results to changes restricted to the actual quantity of myelin. The range of age was limited to 16–45 years for both groups and the range of EDUY was limited to 6–18 years for FES patients. Thus, we were unable to probe conditional effects beyond those ranges. Subjects with high and low ages were also needed for precisely fitting of the JN procedure. Future studies with wider age and EDUY ranges and a larger sample size are needed for a full framework. Smoking history was not collected in the present study. Given the known effects of nicotine dependence on intracortical myelin (Tishler et al., 2018), this may be a potential confound whose effects are unknown in our data. We roughly separated the cortex into three layers in percentile terms. Those layers could not stand for any specific anatomical cortical layers. Magnetic resonance imaging with ultra-high filed strength like 7.0 T may allow recognizing more detailed anatomical cortical layers in the future, but now the "sliding-window" is still a state-of-the-art method for cortical myelination study. At last, we only used VIQ, PIQ, and IQ as general proxies for cognitive function. More specific cognitive functions need to be assessed in future studies.

5 | CONCLUSION

In conclusion, we report depth-dependent changes in intracortical myelination in several brain regions in drug-naïve FES. Both chronological age and the age of onset of functional decline are critical moderators of the intracortical myelin-related variations in clinical symptom burden and cognitive function in schizophrenia. Interventions that restore the normal maturational trajectory of myelin are likely to have a procognitive, disease-modifying effect in schizophrenia. Increased cognitive function gained from myelin maturation ended earlier and decreased cognitive function along with abnormal

hypermyelination started earlier in SZ. These results provide important and additional evidence of abnormal neural development and degeneration in SZ.

CONFLICT OF INTEREST

L.P. reports personal fees from Otsuka Canada, Janssen Canada, SPMM Course Limited, UK, Canadian Psychiatric Association; book royalties from Oxford University Press; investigator-initiated educational grants from Janssen Canada, Sunovion and Otsuka Canada outside the submitted work. All other authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Imaging data supporting the findings of this study are available from the corresponding author upon reasonable request. Demographic, clinical and cognitive data used in this study are provided as a Supplementary Data file. Source data underlying Figures 3 and 4 are provided as a Source Data file.

ORCID

Nanyin Zhang https://orcid.org/0000-0002-5824-9058
Tao Li https://orcid.org/0000-0003-3831-901X

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