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Reduced oligodendroglial density in the inferior parietal lobule and lack of insight in schizophrenia

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ABSTRACT – *Background and Objectives:* Alterations and deficits of oligodendrocytes reported in the grey and white matter in schizophrenia may contribute to neuronal disconnectivity. Prefrontal-parietal functional disconnections have been implicated in diverse clinical symptoms of schizophrenia, including poor insight. We studied the effects of schizophrenia diagnosis and insight on numerical density (Nv) of oligodendrocytes in the inferior parietal lobule (IPL).

Methods: Nissl-stained sections from the Stanley "Parietal Collection" from male schizophrenia subjects (n = 24) having poor, fair, or good insight and healthy matched controls (n = 24) were examined. The Nv of oligodendrocytes was estimated in layer 3 of BA 39 and BA 40 of the IPL and in white matter underlying layer 6 by optical dissector method.

Results: In BA 39 we found a significant 15% decrease in the Nv of oligodendrocytes in layer 3 in the schizophrenia group. Nv of oligodendrocytes in the poor+fair insight subgroup was 20% lower compared to controls ($p< 0.05$) and to good insight subgroup ($p = 0.055$). Nv of oligodendrocytes in the good insight subgroup did not differ from the control group. A significant lateralization of oligodendrocyte density was detected in layer 3 (L>R) only in the control group. There were no significant group differences in the Nv of oligodendrocytes in BA 40 or in the white matter underlying BA 39/40 areas.

Conclusions: Lack of insight in schizophrenia may be associated with a deficit of oligodendroglia in the grey matter of IPL.

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Background

Schizophrenia is believed to be associated with altered neuronal connectivity. Some research suggests that several neural activity deficits found in schizophrenia may be associated with prefrontal and inferior parietal lobe dysfunction[1]. The inferior parietal lobule (IPL) and the prefrontal cortex (PFC) have extensive interconnections and common cortical and subcortical target regions[2]. The IPL consists of the supramarginal gyrus (BA 40) and adjacent angular gyrus (BA 39), and it participates in sensory integration, body image, concept of self and in executive functions (see Torrey 2007 for review)[3]. The IPL is among the most highly lateralized areas of the brain, and both decreased cerebral lateralization and reversed asymmetry of the IPL have been reported in schizophrenia[4].

Imaging studies demonstrated reduced white matter integrity in the IPL in schizophrenia patients[5] a significantly greater decreases over time in parietal white matter[6] and no changes in white matter volume of parietal regions in schizophrenia subjects[4].

At least 14 studies have reported anatomical deficits associated with lack of insight in individuals with schizophrenia. A study using computerized tomography (CT) reported frontal lobe atrophy[7]. Eleven studies used magnetic resonance imaging (MRI); three reported that lack of insight was associated with ventricular enlargement[8],brain size[9] or cortical thickness[10], four reported associations with frontal lobe structures[11-14], and the cingulate and precuneus[15-17] and/or temporal and inferior parietal areas[18]. One study used functional magnetic resonance imaging (fMRI) to demonstrate improved functioning of the medial prefrontal cortex during tasks assessing awareness of illness in individuals with schizophrenia acutely ill and then clinically improved[19]. Another study used diffusion tensor imaging (DTI) to demonstrate an association between widespread white matter dysfunction and decreased awareness of illness[20]. Finally, a recent study used single photon emission computed tomography (SPECT) to demonstrate an association between decreased awareness of illness and decreased blood flow in the precuneus[21]. The present study is the first to use neuropathological methods to assess awareness of illness in individuals with schizophrenia.

Postmortem and genetic studies have reported alterations and deficits of oligodendrocytes in the pathophysiology of schizophrenia[22-26]. However, the association of oligodendrocyte abnormalities with clinical symptoms of schizophrenia, particularly poor insight, remains uncertain. Poor insight is associated with more severe negative symptoms in patients with schizophrenia, poorer prefrontal cognitive functioning, lower prefrontal volumes[27], reduced gray matter volume in the parietal regions in schizophrenia patients[4,18]. Consistent with these data is a deficit of pericapillary oligodendrocytes previously reported in the PFC in the subgroup of schizophrenia subjects with predominantly negative symptoms compared to controls[26]. Previously we reported a reduction in the number of perineuronal oligodendrocytes in layer 3 of the dorsolateral PFC in schizophrenia[25]. Based on these data, we hypothesized that a deficit of oligodendrocytes might occur in the IPL in schizophrenia similar to that in the PFC and that this deficit might be more pronounced in schizophrenia subjects having poor insight than in subjects having good insight.

We studied the effects of schizophrenia diagnosis, insight, and hemisphere on oligodendrocyte density in BA 39 and BA 40 in layer 3 and in the white matter underlying layer 6.

Materials and methods

Samples

Human brain specimens were donated by the Stanley Medical Research Institute's "Parietal Collection". The samples consisted of 48 subjects (24 controls and 24 with schizophrenia). Diagnosis was made according to DSM-IV criteria. A postmortem assessment of each person's awareness of illness (insight) was done by E. Fuller Torrey MD, a senior psychiatrist who did a diagnostic summary of each brain in the Stanley Brain Collection. Medical records and, in approximately half of all cases, interviews with family members, were utilized to make diagnoses. In the course of doing the diagnostic assessment indications of the person's awareness of illness were noted. These included such things as the person's explicit acceptance or denial of illness; acceptance of denial of the need for medication; refusal to take medication; and failure to follow treatment plans, often leading to mulitiple re-admissions. After all available information had been considered the person's awareness of illness was categorized as either good (definite evidence of acceptance of illness); poor (definite evidence suggesting non acceptance of illness); fair (suggestions of non acceptance of illness but less conclusive and/or more ambiguous); or unknown (information insufficient to make a judgment). All diagnoses and assessments of awareness of illness were finalized before any neuropathological studies were done on the brains. The demographic and clinical data are given in Table 1.

The brain specimens were coded, and all cytoarchitectural assessments were done blindly. Tissue was available from one hemisphere of each brain. The angular gyrus (BA 39) and supramarginal gyrus (BA 40) were identified according to macroscopic landmarks[28]. Ten serial sections through the IPL (each 17th section) were mounted on slides and Nissl-stained.

Stereological analysis

The sublayers of layer 3 (a, b and c) in BA 39 and BA 40 were easily identified. The numerical density (Nv) of oligodendrocytes was estimated in BA 39 and BA 40 in each sublayer of layer 3 and in the white matter underlying BA 39/40 using an optical disector method. The sections were viewed on a Carl Zeiss Axio Imager M1 microscope with a computer-guided microscopy system AxioVision. Prior to the actual analysis, the optimal parameters for counting box size were determined. Section thickness was measured on slides as ranging from 14-16 μm. Grid sizes were 55×55 μm, and dissector of depth 10μm, guard strata above and below the dissector averaged at 4μm. Sections were examined under 100×1.4 oil immersion objective. The identification of oligodendrocytes and optical dissector method have been described previously[29]. 100 fields were counted per each sublayer of layer 3 and 100 fields per white matter underlying layer 6 per case.

Statistical analyses

Statistical analysis was performed using Statistica (Version 7). The data were examined using the Kolmogorov-Smirnov test for normality. A Pearson or Spearman correlation analyses were performed to assess correlations between the parameter measured and age, postmortem interval, pH, refrigerator interval, brain weight, lifetime antipsychotics, age at onset and duration of disease. Comparisons between patients with schizophrenia and controls were performed using MANOVA with Nv of oligodendrocytes in

Table 1
Demographic and clinical information on the schizophrenia and control cases

		Group	
		Controls (n = 24)	Schizophrenia (n = 24)
Demographic	Age (yrs)	44.3 ± 9.3	39.8 ± 10.7
	Hemisphere side	10R/14L	10R/14L
	PMI (hours)	24.4 ± 10.8	29.1 ± 11.6
	Fixation time (months)	*64.7 (22-90) left* *50.4 (21-83) right*	*60.1 (19-91) left* *51.3 (24-88) right*
	Refrigerator interval (hours)	*6.1 ± 4.9 (18-1)*	*6.9 ± 4.8 (18-1)*
	Brain weight (g)	1479.3 ± 102.9	1469.5 ± 100.8
	Brain pH	6.67±0.2	6.52±0.2
Clinical	Cause of death	*a/21, b/2, c/0, d/1*	*a/13, b/0, c/6, d/5*
	Duration of illness (yrs)	*0 ± 0*	*20.8 ± 10.3* *(35-1)*
	Age of onset (yrs)	*0 ± 0*	*19.0 ± 5.8* *(34-9)*
	Time in hospital (yrs)	*0 ± 0*	*1.3 ± 2.7* *(12-0)*
	Lifetime antipsychotics	*0 ± 0*	*79002 ± 79529* *(50-300000)*
	Lifetime alcohol use	*0/15, 1/3, 2/0, 3/2,* *4/3, 5/1*	*0/6, 1/2, 2/3, 3/4,* *4/3, 5/6*
	Lifetime drug use	*0/18, 1/2, 2/1, 3/3,* *4/0, 5/0*	*0/6, 1/3, 2/3, 3/6,* *4/3, 5/3*
	Smoking at time of death	*0/12, 1/5, 9/7*	*0/2, 1/18, 9/4*

Antipsychotic dose is lifetime dose in fluphenazine equivalent (mg), lifetime alcohol use and lifetime drug use: 0 - little or none, 1 - social, 2 - moderate past, 3 - moderate present, 4 - heavy past, 5 - heavy present; smoking at time of death: 0 - no, 1 - yes, 9 - unknown. Cause of death is categorized under the following headings: a - cardio-pulmonary, b - accident, c - suicide, d - other.

three sublayers of layer 3 as the dependent variables, and diagnosis and hemispheres as the independent variables. A one-way ANOVA followed by post hoc Duncan's test was used for white matter, to compare the control group and three insight schizophrenia subgroups (poor, fair and good insight).

Results

Effects of disease and hemispheres

The mean Nv of oligodendrocytes and group comparisons for sublayers of layer 3 and for the white matter underlying layer 6 are given in Table 2. A significant effect of diagnosis on the Nv of oligodendrocytes in sublayers of layer

Table 2
Effect of diagnosis on the Nv of oligodendrocytes

Layers	Controls ± SD (n = 24)	Schizophrenia ± SD (n = 24)	F(1,44)	p
Brodmann's area 39				
3a	126.95 ± 28.0	109.83 ± 32.3	4.24	**0.045**
3b	139.66 ± 33.4	118.59 ± 34.6	4.79	**0.034**
3c	152.01 ± 35.1	130.2 ± 42.8	4.11	**0.049**
White matter	412.64 ± 69.3	392.6 ± 47.7	1.36	0.24
Brodmann's area 40				
3a	154.89 ± 29.7	148,78 ± 25.15	0.63	0.43
3b	161.96 ± 29.0	158.21 ± 24.1	0.22	0.64
3c	189.77 ± 32.2	183.99 ± 26.2	0.36	0.55
White matter	386.75 ± 54.1	398.13 ± 43.5	0.5	0.48

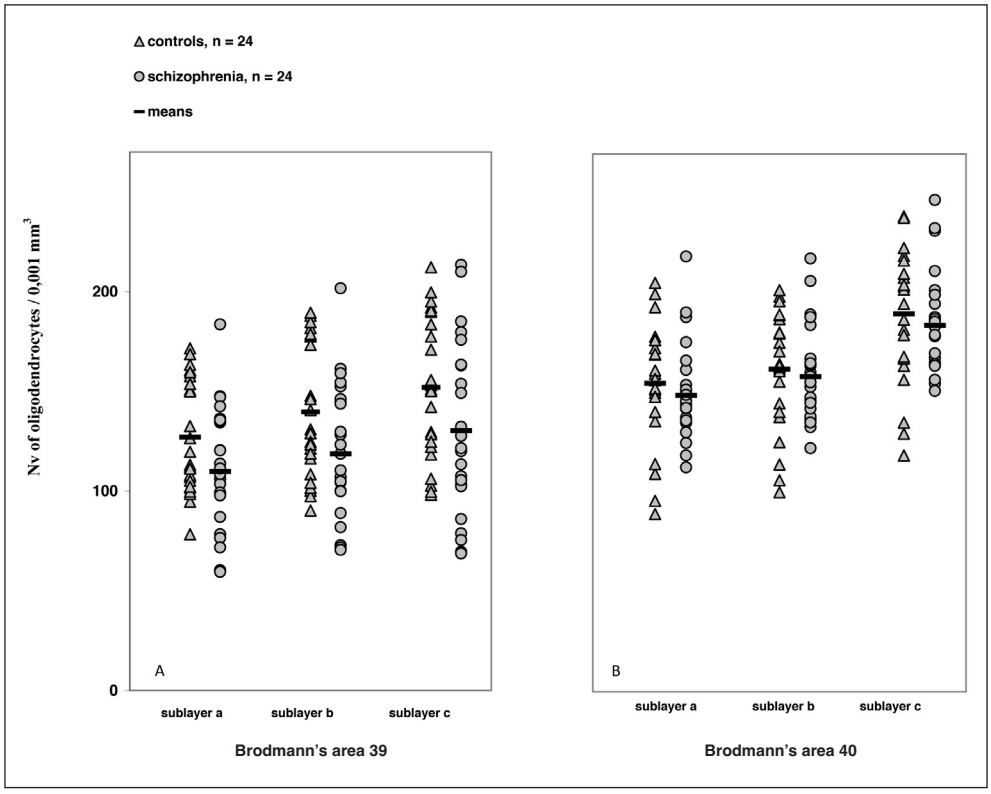

Figure 1. Plots of individual values and means (lines) of the Nv of oligodendrocytes in three sublayers of layer 3 in BA 39 (A) and in BA 40 (B).

3 was found in BA 39 but not in BA 40. There was a significant 15% decrease of the Nv of oligodendrocytes in each sublayer of BA 39 in the schizophrenia group compared to controls. The Nv oligodendrocytes did not differ significantly between the groups in the white matter underlying layer 6 of BA 39 and BA 40 (Table 2, Figure 1).

There was a significant hemisphere effect on the Nv of oligodendrocytes in layer 3 ($F \geq 7.95$, $p<0.01$ for each sublayer). A post hoc test demonstrated a significant hemispheric difference in the control group, but not in the schizophrenia group: the Nv of the oligodendrocytes was significantly higher in the left hemisphere compared to the right hemisphere in 3b and 3c (22%, $p<0.03$) and nonsignificantly higher in 3a (17%, $p<0.07$). There were no significant hemispheric differences in BA 40 (Table 3).

Table 3
Comparison of the Nv of oligodendrocytes between left and right hemispheres in BA 39

Sublayers	Control group			Schizophrenia group		
	Left hemisphere (n = 14)	Right hemisphere (n = 10)	p	Left hemisphere (n = 14)	Right hemisphere (n = 10)	p
3a	136.6 ± 28.5	113.4 ± 22.2	0.07	119.8 ± 36.4	95.9 ± 19.6	0.06
3b	153.3 ± 31.3	120.5 ± 27.2	**0.02**	128.1 ± 41.1	105.3 ± 16.7	0.1
3c	166.9 ± 29.0	131.2 ± 33.3	**0.03**	143.2 ± 51.7	112.0 ± 13.8	0.53

Effect of insight

The schizophrenia group consisted of three insight subgroups: poor (n = 10), fair (n = 5) and good (n = 9). When the three insight subgroups were included in the analysis, there were significant differences in the Nv of oligodendrocytes in layer 3 of BA 39 but not in the BA 40 compared to the control group. There were no significant differences in the white matter of BA 39/40.

Since there were only 5 cases with fair insight and since this group was also thought to have some impairment of insight, we combined the subgroups with poor and fair insight for statistical analysis. The comparison of the control group with poor+fair and good insight subgroups showed a significant effect of insight on the Nv of oligodendrocytes in BA 39 in 3b and 3c (Table 4). There were no significant differences in 3a, in each sublayer of BA 40, and in the white matter underlying layer 6 of BA 39 and BA 40. A post hoc test showed a significant decrease of the parameter in the poor+fair subgroup compared to the controls in 3b (-21%, p = 0.04) and 3c (-22%, p = 0.04). Moreover, in 3c the Nv of oligodendrocytes showed a trend to decrease in the poor+fair subgroup compared to the subgroup with good insight (-20%, p = 0.055). The subgroup with good insight did not differ from the control group.

Potentially confounding factors

There were no correlations between age, postmortem interval, refrigerator interval, brain weight, brain pH, lifetime antipsychotics, age at onset or duration of disease and the Nv of oligodendrocytes in BA 39 or BA 40.

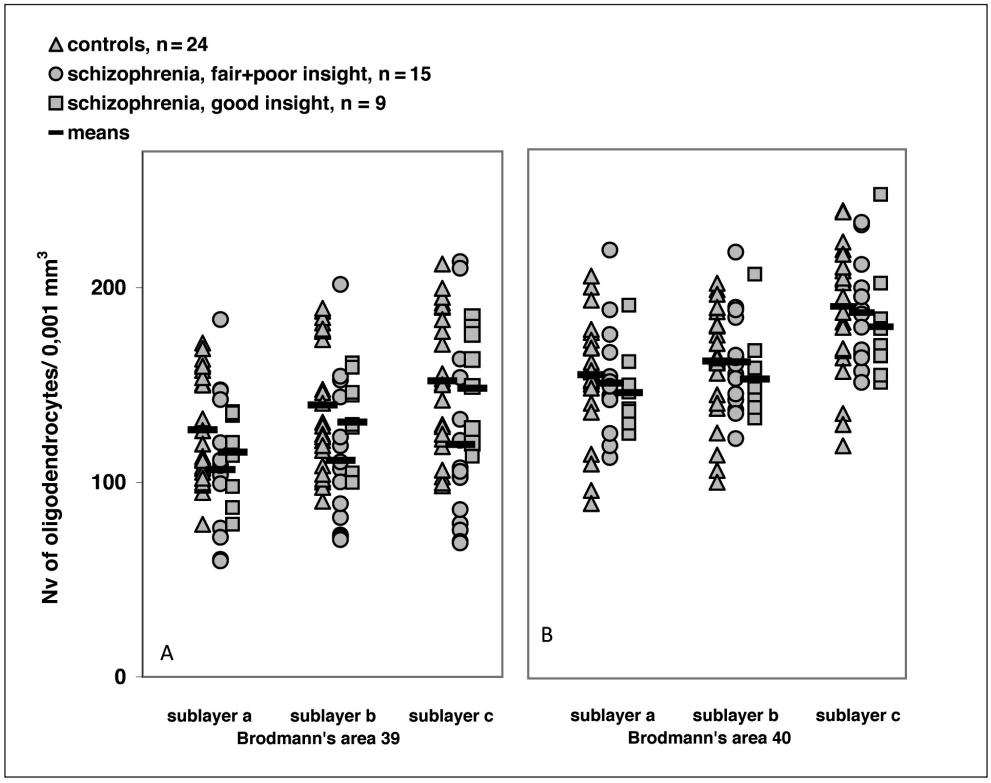

Figure 2. Plots of individual values and means (lines) of the Nv of oligodendrocytes in the three sublayers of layer 3 in control group and in the insight subgroups. BA 39 (A), BA 40 (B).

Table 4
Effect of insight on the Nv of oligodendrocytes

Layers	Controls ± SD (n = 24)	Poor+fair insight ± SD (n = 15)	Good insight ± SD (n = 9)	F(2.45)	p
		Brodmann's area 39			
3a	126.95 ± 28.0	106.51 ± 37.3	115.36 ± 22.6	2.13	0.13
3b	139.66 ± 33.4	111.20 ± 38.6	130.91 ± 23.7	3.31	**0.045**
3c	152.01 ± 35.1	119.40 ± 47.0	148.20 ± 28.6	3.54	**0.037**
White matter	412.64 ± 69.3	383.41 ± 48.9	407.91 ± 43.9	1.15	0.3
		Brodmann's area 40			
3a	154.88 ± 29.7	150.57 ± 28.3	145.77 ± 20.0	0.4	0. 7
3b	161.96 ± 29.0	161.50 ± 25.0	152.72 ± 22.9	0.4	0. 7
3c	189.76 ± 37.2	186.69 ± 24.7	179.48 ± 29.6	0.4	0. 7
White matter	386.74 ± 54.1	401.0 ± 46.2	393.4 ± 40.3	0.4	0.7

Discussion

To our knowledge, this is the first study to investigate oligodendrocyte density and effect of insight on oligodendrocyte density in the IPL in subjects with schizophrenia.

Patients versus controls

We demonstrated a 15% reduction in the Nv of oligodendrocytes in each sublayer of layer 3 of BA 39 in the schizophrenia group compared to controls. There were no changes in the Nv of oligodendrocytes in layer 3 of BA 40 or in the white matter underlying BA 39/40. These findings replicate and extend the results of our previous studies reporting pronounced ~25% decrease in the oligodendrocyte density in layer 6 of BA 9 using the Stanley Foundation Neuropathology Consortium collection[29] and in layer 6 and in the white matter of BA 10 using our brain collection[30]. The deficit of oligodendrocytes in BA 9 was associated with a loss of perineuronal oligodendrocytes in 3a, 3b and 3c[25]. Our data are also consistent with the prominent reduction of oligodendroglial cells (using Nissl staining and CNPase immunocytochemistry) in layer 3 of BA 9 previously reported in schizophrenia[22].

We did not find significant differences in the Nv of oligodendrocytes in the white matter in BA 39/40 in schizophrenia. The results of imaging studies of the white matter in the IPL are controversial. Zhou *et al*.[4] reported no changes in the white matter volume of the parietal regions in schizophrenia subjects. However, a reduced white matter integrity in the IPL[20] and a significantly greater decrease over time in frontal gray and parietal white matter[6] have been reported in schizophrenia patients. These data together with the present data suggest that the PFC might be more severely affected than IPL with respect to oligodendrocyte density in schizophrenia.

The reduction in oligodendrocyte density in IPL BA 39 and in the PFC in schizophrenia is consistent with MRI and PET studies that have demonstrated smaller gray matter volumes[31]. These data suggest that the deficit of oligodendrocytes in the gray matter of both cortical areas might contribute to the dysfunction of these cortical areas in schizophrenia.

Oligodendrocyte density and insight

As hypothesized, we found a significant reduction of oligodendrocyte density in BA 39 in sublayers 3b and 3c in the poor+fair insight subgroup compared to the control group. The differences between subgroup with poor/fair insight and with good insight approached statistical significance ($p = 0.055$), and subjects with good insight did not differ from controls. Our results are in agreement with the theory that unawareness of illness in schizophrenia may be due to atrophy of the IPL[18] and of the PFC[7,18]. The data suggest that lack of insight in schizophrenia may be associated with a deficit in oligodendrocytes in the grey matter of the IPL.

The IPL is implicated in neurocognitive impairment in schizophrenia[32]. Recent studies suggest that oligodendrocyte deficits and myelin dysfunctions might contribute to abnormal neuronal connectivity that could in turn lead to cognitive impairment in schizophrenia[33]. Poor insight in schizophrenia is associated with cognitive dysfunction and more severe negative symptoms[18,27,34]. Such data are consistent with the results of our studies of the PFC BA 10 that detected a deficit of pericapillary oligodendrocytes in the subgroup of schizophrenia subjects with predominantly negative symptoms but not in

the subjects with predominantly positive symptoms compared to controls[26]. They are also consistent with a significant increase in the volume fraction of heterochromatin in the oligodendrocyte nucleus seen only in cases with predominantly negative symptoms relative to controls[24]. Peters and Sethares[35] reported that in the PFC of monkeys, age-related alterations of myelinated fibers significantly correlated with the cognitive impairment index. Taken together with the results of the present study, these data suggest that the deficit of oligodendrocytes might contribute to cognitive disturbances and impaired insight in schizophrenia.

Oligodendrocyte density and asymmetry

We found that the oligodendrocyte density in BA 39 showed an asymmetry (L>R) in the control group but not in schizophrenia group. This result is in agreement with the neuroimaging data of Frederikse *et al*.[36] that the volume of the IPL in males is normally asymmetric (L>R), and this asymmetry is decreased in schizophrenia[3,36]. A functional MRI study[37] also demonstrated that the largest functional asymmetries (L>R) are in the IPL in healthy controls but not in schizophrenia patients during the resting state. We did not find any asymmetry in the oligodendrocyte density in BA 40 or in the white matter underlying BA 39/40. Our results provide evidence for the first time that oligodendrocyte density contributes to the normal asymmetry in the angular gyrus.

Effects of confounding factors

We did not find any effects of age, postmortem delay, pH, brain weight, age at disease onset, or duration of disease on the Nv of oligodendrocytes. No significant correlation between oligodendrocyte density and total neuroleptic usage was found. This result is in agreement with some experimental data. Konopaske *et al*.[38] found a nonsignificant lower oligodendrocyte number in parietal grey matter after chronic exposure of monkeys to haloperidol or olanzapine. However, protective effects of neuroleptics on oligodendrocytes and stimulation of oligodendrocyte proliferation by neuroleptics have recently been reported[39]. Together these data suggest that the reduction in oligodendrocyte density found in the present study is not attributable to neuroleptic exposure.

Limitations and future studies

There are several limitations to this study. First, this is a preliminary study and should be replicated with more subjects with insight ratings. Females should also be included. Second, it was difficult to estimate the effects of lifetime alcohol and drug abuse in this study: there were six alcohol and drug abuse subgroups based on qualitative criteria (from none to heavy/present), and the number of subjects per each subgroup was not comparable in the control and schizophrenia groups. Third, we found nonsignificant changes in BA 40. A possible reason is that the cytoarchitectonic areas of the human IPL are highly variable. The IPL consists of seven cytoarchitectonically distinct areas: five in the BA 40, and two in BA 39[40].

In summary, we present evidence for a reduction of the oligodendrocyte density in IPL BA 39 in schizophrenia and in subjects having poor+fair insight compared to the control group. These findings suggest that the oligodendroglial deficit in the gray matter of the IPL might be associated with impaired insight in schizophrenia.

Future studies of the neurobiological cellular basis of poor insight and the role of oligodendrocytes in impaired insight and other cognitive disturbances in schizophrenia will be useful to develop new therapeutic strategies for patients with schizophrenia.

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