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Deficit of perineuronal oligodendrocytes in the inferior parietal lobule is associated with lack of insight in schizophrenia

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ABSTRACT – *Background and Objectives:* Previously we reported a significant reduction in the numerical density of oligodendrocytes and oligodendrocyte clusters in the inferior parietal lobule (IPL) in schizophrenia that was associated with lack of insight. We also found a significant decrease in the number of perineuronal oligodendrocytes (PnOl) in the prefrontal cortex in schizophrenia and therefore we hypothesized that there may also be a deficit of PnOl in the IPL in schizophrenia and that it could be associated with poor insight.

Methods: We estimated the number of PnOl adjacent to pyramidal neurons in layer 3 of BA39 and BA40 in Nissl stained sections from 24 males with schizophrenia and 24 normal male controls from the Stanley Parietal Collection. The schizophrenia group was divided into three subgroups based on level of insight: poor, fair or good.

Results: We found a significant deficit of PnOl in layer 3 of BA39 and BA40 in the schizophrenia group as compared to the control group ($p<0.01$). In the control group but not in the schizophrenia group in BA39 the number of PnOl was significantly higher in the left hemisphere compared to the right hemisphere. In schizophrenia, in BA39 the number of PnOl was decreased in the subgroup with poor insight vs. controls. In BA40 the subgroups with both poor and fair insight were decreased vs. controls ($p<0.01$). In BA40 the subjects with fair insight also differed from those with good insight ($p<0.01$).

Conclusions: The reduction of PnOl in the IPL in schizophrenia is associated with impaired insight and lack of hemispheric asymmetry.

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Introduction

Neuroimaging, genetic and postmortem studies have all provided evidence that a dysfunction and deficits of oligodendrocytes may be involved in further abnormalities of neuronal connectivity in schizophrenia[1,2] and may also contribute to the various clinical symptoms of schizophrenia including impaired insight into their disorder[3-7]. Impaired insight is a core feature of schizophrenia and an important predictor of functional outcome, prognosis, and treatment adherence[8]. Impaired insight is associated with dysfunction of specific brain structures, including the prefrontal cortex (PFC) as well as the IPL in particular[9,10]. Poor insight is associated with deficient prefrontal cognitive functioning, lower prefrontal volumes and reduced gray matter volume in the IPL in schizophrenia patients[10]. Previously we reported a significant 15% reduction in the numerical density of oligodendrocytes[6] and 25% reduction in oligodendrocyte clusters[7] in the IPL in schizophrenia and the association of these measures with the lack of insight.

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[10-13]. A significant lateralization of oligodendrocyte density was detected in layer 3 of the IPL (BA39) (L>R) in the control group but not in the schizophrenia group[6].

The IPL and the PFC have extensive interconnections and common cortical and subcortical target regions[14]. Previously we reported a reduction in the number of PnOl in layer 3 of the dorsolateral PFC in schizophrenia[15]. Based on these findings, we hypothesized that a deficit of PnOl may also occur in the IPL in schizophrenia, and that it may be more pronounced in the left hemisphere and in the schizophrenia subjects with poor insight as compared to those with good insight.

The aims of the study were: 1) to estimate the number of PnOl in layer 3 of the IPL (BA39, BA40) in schizophrenia and normal controls; 2) to analyze hemispheric effect on the number of PnOl and 3) to study the effect of diagnosis and insight on the number of PnOl.

Materials and Methods

Samples

Human brain specimens were donated by the Stanley Medical Research Institute's 'Parietal Collection'. The samples consisted of 48 male subjects (24 controls and 24 with schizophrenia). Diagnosis was made according to DSM-IV criteria. A postmortem estimate of each person's awareness of illness (insight) based on the person's clinical records has been previously reported[6]. The mean age at the time of death was 44.3 ± 9.3 years for the control group and 39.8 ± 10.7 years for the schizophrenia group. The average postmortem interval was 24.4 ± 10.8 hours for the control group and 29.1 ± 11.6 hours for the schizophrenia group. Fourteen cases were from the left hemisphere and ten cases were from the right hemisphere. Tissue of the IPL was available from one hemisphere of each brain. Complete demographic and clinical data were reported in the previous paper[6].

The brain specimens were coded, and all cytoarchitectural assessments were done blindly. The angular gyrus (BA39) and the supramarginal gyrus (BA40) were identified according to macroscopic landmarks[16]. Ten serial sections through the IPL (every 17th section) were mounted on slides and Nissl-stained.

Morphometric analysis

The sublayers of layer 3 (a, b and c) in BA39 and BA40 were easily identified based on cytoarchitectural features. The number of PnOl was counted in each sublayer of layer 3 in BA39 and BA40. PnO1 were defined as all oligodendrocytes located within <5 μm of pyramidal neurons. Pyramidal neurons were identified by their triangular shape, oval shaped clear nucleus with a prominent nucleolus, presence of intensively stained cytoplasm and vertical apical dendrite. Oligodendrocytes were identified by the presence of a small round or oval nucleus, with relatively dense nuclear staining (more chromophilic than astroglial nuclei) and a narrow unstained rim of cytoplasm. One hundred pyramidal neurons with identifiable nucleolus were systematically randomly sampled for each sublayer. The number of pyramidal cells sampled from each subject was 300, from each group 7200, total 14,400. The number of PnOl was expressed as the number of oligodendrocytes per neuron.

Statistical analyses

Statistical analysis was performed using Statistica 7. The data were examined using the Kolmogorov-Smirnov test for normality. A Pearson correlation analysis was performed to assess possible correlations between the parameters measured and age, postmortem interval, pH, refrigerator interval, brain weight, total lifetime antipsychotics, age at onset and duration of disease. Comparisons between patients with schizophrenia and controls were performed using two-way ANOVA with the number of PnOl in 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 to compare the control group and the three insight schizophrenia subgroups. A correlation analysis was also performed to assess possible correlations between the number of PnOl and the numerical density of oligodendrocyte clusters as estimated previously in the same sections[7].

Results

Effects of disease and hemispheres

The mean numbers of PnOl and the results of their comparisons between the schizophrenia and the control groups for each sublayer of layer 3 are shown in Fig. 1. The ANOVA revealed a significant effect of diagnosis on the number of PnOl in all sublayers in BA39 [$F(3,44) = 4.57$, $p = 0.007$] and in all sublayers in BA40 [$F(3,44) = 3.71$, $p = 0.018$]. A decrease in the mean values of the parameter was found in BA39 in sublayer 3a (-21%, $p = 0.004$), in sublayer 3b (-20%, $p = 0.013$), in sublayer 3c (-24%, $p = 0.004$) and in BA40 in sublayer 3a (-13%, $p = 0.059$), in sublayer 3b (-16%, $p = 0.007$) and in sublayer 3c (-18%, $p = 0.003$) in the schizophrenia group as compared to the control group. Correlation analysis did not reveal significant effects of postmortem interval, refrigerator interval, brain weight, brain pH, age at onset or duration of disease on the number of PnOl in BA 39 and BA 40.

There was a significant hemispheric effect on the number of PnOl in BA39 in layer 3 [$F(3,43) = 2.89$, $p = 0.046$]. A post hoc test demonstrated a significant hemispheric difference in the control group but not in the schizophrenia group: the number of PnOl was significantly higher in the left hemisphere as compared to the right hemisphere in 3a (23%), 3b (25%) and in 3c (23%). There were no significant hemispheric differences in BA 40 (Table 1, Fig. 2).

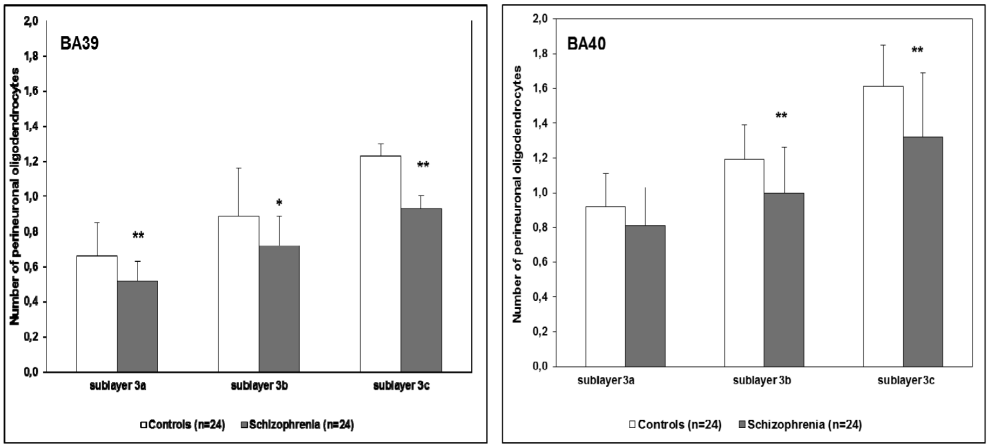

Figure 1. The number of perineuronal oligodendrocytes in three sublayers of layer 3 in BA39 and BA40 in the control group and in the schizophrenia group. p-values: * $p<0.05$, ** $p<0.01$.

Table 1
The number of perineuronal oligodendrocytes (means ± SD), hemispheric effect

Sublayers	Controls			Schizophrenia		
	Left hemisphere (n = 14)	Right hemisphere (n = 10)	p	Left hemisphere (n = 14)	Right hemisphere (n = 10)	p
BA 39						
3a	0.73 ± 0.17	0.56 ± 0.17	0.024	0.54 ± 0.08	0.51 ± 0.15	0.6
3b	0.98 ± 0.21	0.74 ± 0.29	0.03	0.73 ± 0.14	0.69 ± 0.21	0.5
3c	1.36 ± 0.35	1.05 ± 0.28	0.03	0.97 ± 0.23	0.88 ± 0.44	0.5
BA 40						
3a	0.92 ± 0.23	0.92 ± 0.11	0.9	0.79 ± 0.22	0.82 ± 0.25	0.7
3b	1.15 ± 0.23	1.24 ± 0.13	0.4	0.99 ± 0.26	1.02 ± 0.26	0.7
3c	1.53 ± 0.25	1.72 ± 0.19	0.16	1.32 ± 0.39	1.33 ± 0.35	0.9

Effects of insight

There was a significant effect of insight on the number of PnOl in both BA39 and BA40. In BA 39 the subgroup with poor insight had a significantly lower number of PnOl in each of three sublayers of layer 3 [23-33%, $F(3,44) \geq 3.0$, $p<0.02$] as compared to the control group (Fig. 3) but there were no significant differences between the three insight subgroups. In BA 40 the number of PnOl in the subgroups of subjects with both poor insight and fair insight were significantly lower than in the control group ($p<0.02$). The subjects with fair insight also had significantly lower number of PnOl than subjects with good insight ($p<0.02$) (Fig. 3). Comparing the results of this study with the results of our previous

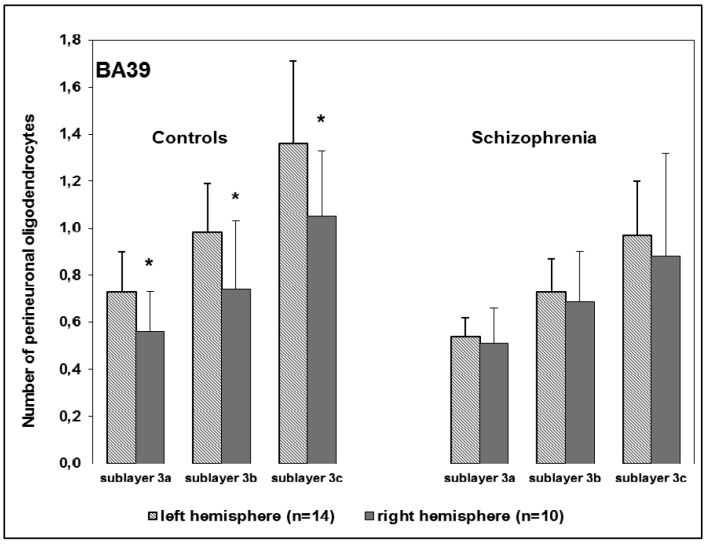

Figure 2. Hemispheric differences in the number of perineuronal oligodendrocytes in three sublayers of layer 3 of BA39 in the control group are absent in the schizophrenia group. p-values: * p<0.05.

Table 2
The number of perineuronal oligodendrocytes (means ± SD), effect of insight

Sublayers	Controls (n = 24)	Poor insight (n = 10)	Fair insight (n = 5)	Good insight (n = 9)	F(3.44)	p
BA39						
3a	0.66 ± 0.19	0.46 ± 0.09	0.54 ± 0.07	0.59 ± 0.12	4.25	0.01
3b	0.89 ± 0.27	0.62 ± 0.14	0.74 ± 0.21	0.81 ± 0.13	3.59	0.02
3c	1.24 ± 0.35	0.74 ± 0.28	1.03 ± 0.33	1.10 ± 0.30	5.45	0.002
BA40						
3a	0.92 ± 0.19	0.81 ± 0.25	0.63 ± 0.17	0.89 ± 0.20	2.99	0.04
3b	1.19 ± 0.20	0.97 ± 0.26	0.84 ± 0.21	1.13 ± 0.23	4.93	0.005
3c	1.61 ± 0.24	1.29 ± 0.37	1.04 ± 0.22	1.53 ± 0.33	7.06	0.0006

study on these same sections, the number of PnOl correlated significantly with the numerical density of oligodendrocyte clusters in three sublayers of layer 3 in BA39 in both control and schizophrenia groups and in BA40 (sublayer c) in the control group but not in the schizophrenia group (Fig. 4).

Discussion

Patients versus controls

We found a significant deficit of PnOl in all sublayers of layer 3 in both BA39 (-23%) and BA40 (-17%) in the schizophrenia group

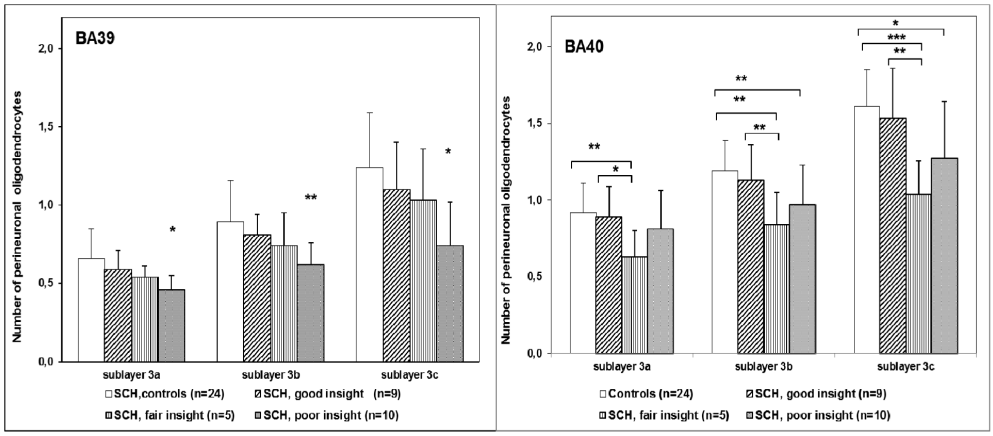

Figure 3. The number of perineuronal oligodendrocytes in the control group and in different insight subgroups in BA39 and BA40. * p<0.05, ** p<0.01, *** p<0.001.

as compared to the control group. The number of PnOl was not correlated with postmortem interval, refrigerator interval, brain weight, brain pH, age at onset or duration of disease in BA 39 and BA 40.

There was no effect of total lifetime antipsychotics on the number of PnOl. However, antipsychotics have been shown to promote the differentiation of oligodendrocyte progenitor cells by regulating oligodendrocyte lineage transcription factors 1 and 2[17]. They have also been shown to improve myelin/oligodendrocyte-related dysfunction[18], and to enhance oligodendrocyte regeneration and myelin repair after cuprizone-induced demyelination[19]. Together these data would indicate that the decrease in the number of PnOl to not be due to the effects of medication but rather to be associated with the diagnosis of schizophrenia.

We applied a two-dimensional method for the assessment of the number of PnOl. Although this method does not allow for the counting of all oligodendrocytes adjacent to neurons, it does allow for successful comparing of this parameter between the control and disease groups, and our current data concurs with data previously obtained by the stereological optical dissector method[6] showing the deficit of the numerical density of oligodendrocytes in layer 3 of the IPL (BA39). The present data are also consistent with the reduced number of PnOl found in layer 3 of the dorsolateral PFC in schizophrenia[15], and with the reduction of the numerical density of oligodendrocyte clusters found in the IPL in schizophrenia that was associated with insight in schizophrenia[7]. The findings of this study are also consistent with the results of Byne *et al.*[20] who reported a decrease in the ratio of oligodendrocytes to neurons in the anterior thalamic nucleus in schizophrenia.

Kim and Webster[21,22] using a genome-wide correlation analysis explored the genes and biological processes associated with the number of PnOl in the PFC in schizophrenia (using the data from our previous study[15]). A correlation analysis between genome-wide expression levels and cytoarchitectural traits revealed that 818 genes were significantly correlated with a decrease in the number of PnOl in schizophrenia subjects as well as in the subjects with bipolar disorder and major depression. Several oligodendrocyte-related

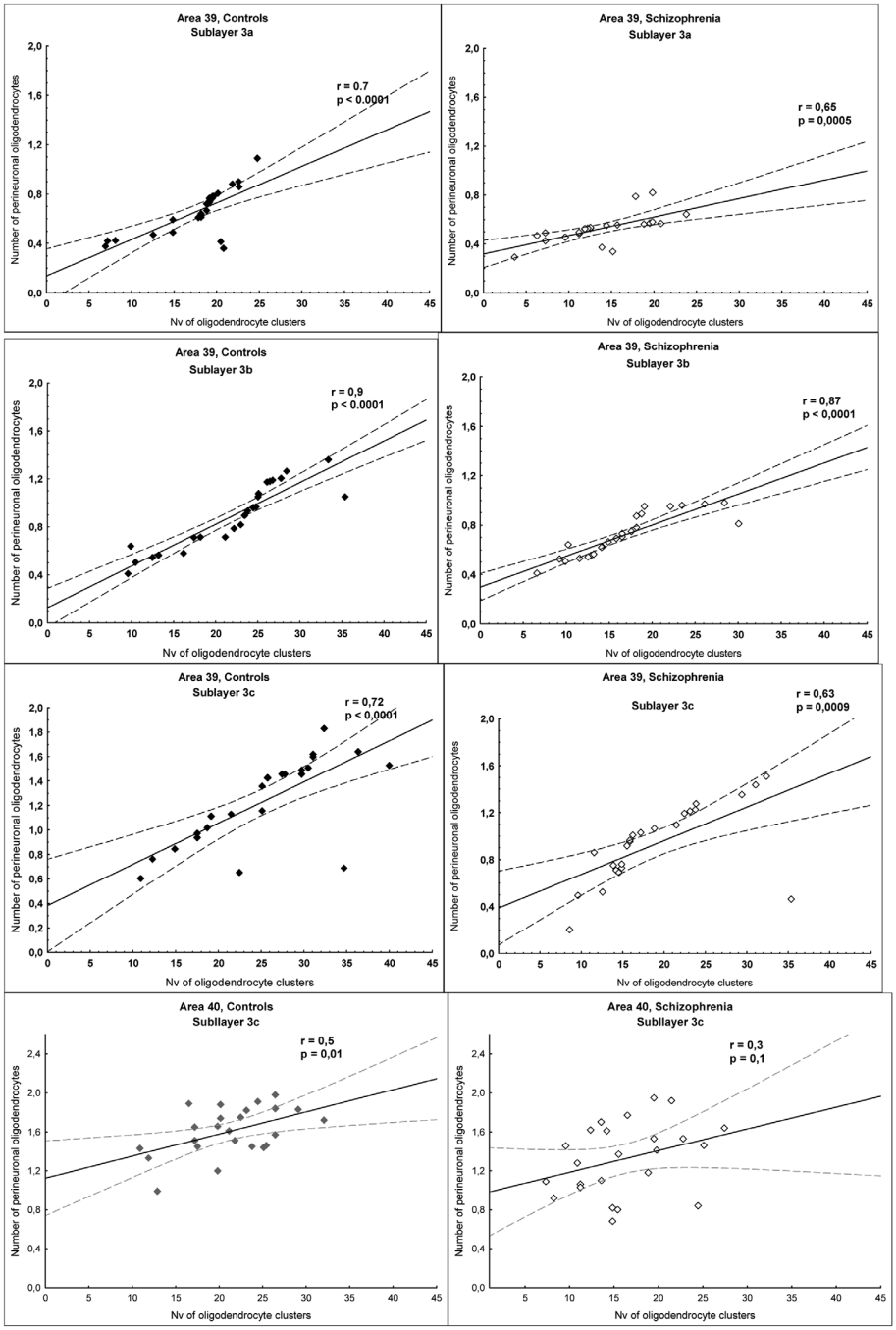

Figure 4. Significant positive correlations between the number of perineuronal oligodendrocytes and the numerical density of oligodendrocyte clusters in BA39 and BA40 in the control group and in the schizophrenia group.

mRNA, including the mRNA levels for the schizophrenia susceptibility gene ERBB3, showed significant correlations with the number of PnOl. Genome-wide correlation analysis also identified apoptosis as one of the potential mechanisms that may underlie the decrease in the number of PnOl in the PFC of subjects with schizophrenia. The authors suggest that apoptosis, perhaps associated with cytotoxicity mediated by a glutamate abnormality, may contribute to the reduced numbers of PnOl in the PFC of subjects with major psychiatric disorders. A further analysis[23] also indicated that several SNPs, including one associated with the glutamine transporter gene SLC38A1 and one with RAB-2A, were associated with the number of PnOl thus providing novel insights into the possible genetic causalities associated with the deficit of PnOl in schizophrenia and affective disorders.

Lack of asymmetry of PnOl in schizophrenia

The present study showed that the number of PnOl was significantly higher in the left hemisphere than in the right hemisphere in all three sublayers of BA39 in the control group but not in the schizophrenia group. This data is consistent with the results of the previous study that demonstrated a significant lateralization of oligodendrocyte density in layer 3 of the IPL (BA39) (L>R) in the control group but not in the schizophrenia group[6]. The IPL is among the most highly lateralized areas of the brain, and both decreased cerebral lateralization and reversed asymmetry of the IPL, particularly in the angular gyrus, have been reported in schizophrenia[10-13]. Together with the results of the present study, these data provide evidence for the involvement of the oligodendrocytes and of PnOl in particular in the decreased lateralization of the angular gyrus (BA39) in schizophrenia.

Effects of insight

We found that in BA39 the number of PnOl was significantly decreased in the schizophrenia subgroup with poor insight as compared to the control group. In BA40 the number of PnOl was significantly decreased in the subgroups with both poor and fair insight as compared to controls. However, in both areas BA39 and BA40 schizophrenia subjects with poor insight did not differ from subjects with good insight. Although in BA40 the subgroup with fair insight had a significantly lower number of PnOl than subjects with good insight. Thus, the present study shows for the first time that the decreased number of PnOl in the IPL in schizophrenia is associated with the patient's lack of insight into their disorder. The data are important because the IPL is implicated in neurocognitive impairment in schizophrenia[8] and cognitive insight can be a useful prognostic indicator, and thus should be considered in future studies and as a potential focus for treatment[24].

Density of PnOl and oligodendrocyte clustering in schizophrenia

In BA39 we found decreased number of PnOl (-23%), we previously found that the numerical density of oligodendrocyte clusters was also decreased (-23%)[7]. Moreover, in BA39 the number of PnOl correlated significantly with the numerical density of oligodendrocyte clusters in three sublayers of layer 3 in both control and schizophrenia groups. However, in BA40 the correlations were only in the control group but not in the schizophrenia group. Szuchet *et al*.[25] in molecular genetic study showed that cortical perineuronal cells are the progeny of oligodendrocyte progenitors and, hence, are member of the oligodendrocyte lineage. Recent experi-

mental data demonstrated that cell clusters in adult rodent and primate brain contain oligodendrocyte progenitors at different stages of maturation[26,27].

In addition cell cycle abnormalities and incomplete differentiation of oligodendrocytes have been reported in schizophrenia[28-30]. Together these data suggest that the reduced number of PnOl in schizophrenia may be associated with the reduced proliferation of oligodendrocyte progenitors. Recent cytochemical and cytological data suggest that PnOl in the somatosensory cortex support neuronal survival, differentiation, and function, and that they provide protection against neuronal apoptosis (Takasaki *et al*., 2010)[31]. Thus, the significant decrease in the number of PnOl may have negative consequence for neuronal activity. In conclusion, the results of the present study suggest that normal oligodendroglia-neuronal relationships in the IPL are likely dysregulated in subjects with schizophrenia primarily due to a decrease of the number of PnOl. The deficit of PnOl is associated with impaired insight and may play a key role in the pathophysiology of schizophrenia. It may also have important implications for the development of treatment strategies.

Authors' contributions

Dr. Vostrikov designed the study, carried out data collection and interpretation and wrote the manuscript. Dr. Kolomeets contributed to the study design, data collection and interpretation, and preparation of the manuscript. Dr. Uranova designed the study, performed statistical analysis, wrote and revised the manuscript.

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