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ORIGINAL PAPER

Reduced oligodendrocyte density in layer 5 of the prefrontal cortex in schizophrenia

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Abstract

Neuroimaging and post-mortem studies have implicated altered myelin integrity and oligodendrocyte abnormalities in the dysfunction of neuronal network in schizophrenia, including the prefrontal cortex, Brodmann area (BA) 10. Pyramidal neurons in layer 5 of BA10 are the important link of reciprocal frontal cortical—basal ganglia—thalamic circuits altered in schizophrenia. Previously, we found ultrastructural dystrophic and degenerative alterations of oligodendrocytes in layer 5 of BA10 in schizophrenia. The aim of the study was to estimate the numerical density (Nv) of oligodendrocytes in layer 5 of BA10 in schizophrenia as compared to normal controls. 17 chronic schizophrenia subjects and 22 healthy matched controls were studied in Nissl-stained sections using optical disector method. Group differences were analyzed using ANCOVA followed by post hoc Duncan's test. The Nv of oligodendrocytes was significantly lower (− 32%, $p < 0.001$) in the schizophrenia group as compared to the control group. Young controls (age < 50 years old) showed significantly higher Nv of oligodendrocytes as compared to elderly controls (age > 50 years old). Young and elderly schizophrenia subgroups did not differ significantly. Both control subgroups have significantly higher Nv of oligodendrocytes as compared to the schizophrenia subgroups. Decreased Nv of oligodendrocytes found in layer 5 of BA10 may be the result of dystrophic and destructive alterations and/or disrupted development of oligodendrocytes in schizophrenia.

Keywords Prefrontal cortex BA10 · Schizophrenia · Oligodendrocyte density · Optical disector

Introduction

Growing evidence coming from neuroimaging, genetic and post-mortem studies have implicated oligodendrocyte abnormalities and compromised myelin integrity in the dysfunction of neuronal network in schizophrenia [1–4]. While myelin produced by oligodendrocytes is a component of white matter, grey matter is also extensively myelinated, and a link between intracortical myelin and cognitive performance has been demonstrated in humans [5, 6]. Neuroimaging studies have identified deficits in cortical myelination in schizophrenia particularly prominent in the frontal lobes and tightly linked with cognitive impairments in patients with schizophrenia [7–9]. Post-mortem and genetic studies also support the presence of the prefrontal intracortical myelin deficit in schizophrenia including reduced myelin staining [10], decreased expression of intracortical myelin markers [11], myelin and oligodendrocyte genes [1, 12, 13].

Pyramidal neurons in layer 5 of Brodmann area (BA) 10 are the important link of reciprocal frontal cortical—basal ganglia—thalamic circuits in primates [14] and in humans [15, 16]. High-resolution neuroimaging studies revealed reduced connectivity and the dysfunction of this network in patients with schizophrenia [17–20].

Deficits of oligodendrocytes in layer 6 of the prefrontal BA10 and in the adjacent white matter have been reported in schizophrenia [21, 22]. Post-mortem electron microscopic morphometric studies showed ultrastructural damage of myelinated fibers, dystrophy and degeneration of oligodendrocytes in layers 5 and 6 of BA10 in schizophrenia [23, 24]. We hypothesized that such changes might lead to the deficit of oligodendrocytes in schizophrenia. The aim of the study was to estimate the numerical density (Nv) of oligodendrocytes in layer 5 of BA10 in schizophrenia as compared to normal controls.

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Materials and methods

Brain specimens

Human brain specimens were obtained from the Departments of Pathology of Moscow Psychiatric Hospitals no. 1 and no. 15 and Moscow Higher Medical School. The samples from 22 control and 17 schizophrenia subjects were studied. After receiving consent for autopsy and research and approval for the study from the Ethics Committee of Mental Health Research Centre, samples from the prefrontal BA10 from the left hemisphere were dissected.

ICD-10 diagnostic criteria for schizophrenia were used. The schizophrenia patients were diagnosed independently by two psychiatrists. 12 cases with paranoid schizophrenia (F20.00/F20.01), 3 cases with undifferentiated schizophrenia (F 20.30/20.31) and 2 cases with catatonic schizophrenia (F20.21) were studied. Data on age at onset, duration of disease and neuroleptic exposure were obtained from medical records and interviews with family members. Mean age at the time of death was (mean ± SD) 55.2 ± 16.7 years old for the control group and 57.9 ± 17.7 years old for the schizophrenia group. Average post-mortem interval (PMI) was 5.8 ± 1.0 h for the control group and 8.7 ± 6.4 h for the schizophrenia group. Duration of disease ranged from 5 to 49 years (mean ± SD 29.4 ± 10.6). Medication records were used to determine chlorpromazine equivalents (CPZ) of mean daily doses of antipsychotic medication for the last month of life available for the schizophrenia subjects [25–27]. Complete demographic and clinical data are given in Table 1.

Table 1 Demographic and clinical data of patients with schizophrenia and healthy control subjects

Characteristic	SCH ($n=17$)	HC ($n=22$)	p value*
Age (years)	57.9 ± 17.7	55.2 ± 16.7	0.6
Gender (male/female)	8/9	13/9	
PMI (hours)	8.7 ± 6.4	5.8 ± 1.0	0.04
Formalin fixation time (month)	1.2 ± 0.3	1.4 ± 0.4	0.3
Duration of illness (years)	29.4 ± 10.6	–	–
Age at onset of illness (years)	28.6 ± 13.0	–	–
CPE (mg)	332 ± 331.3	–	–

SCH schizophrenia patients, *HC* healthy control subjects, *PMI* post-mortem interval, *CPE* chlorpromazine equivalents of mean daily doses of antipsychotic medication, (mg) for the last month of life

*ANCOVA test

Tissue preparation

Macroscopic landmarks were used for BA 10 excision [28, 29]. Anterior part of the left hemisphere ~ 2 cm caudal the frontal pole was dissected in coronal plane. Tissue blocks covering the most anterior portion of the superior frontal gyrus were separated, fixed by immersion in 4% formalin and embedded in paraffin wax. Then each block was cut into continuous serial 20 µm sections perpendicular to the gyrus surface. Every 20th section was systematically sampled, the first section being sampled randomly from the first 20 sections. For the morphometric study ten sections per brain were systematically randomly sampled and Nissl (cresyl violet) and myelin (luxol fast-blue) stained. The brain specimens were coded, and all cytoarchitectural assessments were done blind to diagnosis.

Stereology

The Nv of oligodendrocytes in layer 5 was estimated using optical disector method [30]. BA 10 was identified cytoarchitectonically as a thick highly granular cortex with clearly distinct thick laminae II and IV, overall low neuronal density, wade laminae Ill and V [31]. Layer 5 was readily identified by the presence of big pyramidal cells. In Nissl-stained sections lines were drawn through the middle of layer 5, and the counting frame was moved along the line at regular intervals with a systematically random starting point.

Oligodendrocytes were readily identified as cells containing small round nucleus and a small rim of cytoplasm. The sections were viewed on Carl Zeiss Axio Imager M1 microscope with AxioVision microscope software. The optimal parameters for counting box size were determined in previous experiments generating approximately 600 counted oligodendrocytes, giving the coefficient of errors (CE) < 0.1.

Optical disector method has been described previously [21, 32]. Section thickness was measured on slides and ranged 14–16 µm. Grid size was 55 × 55 µm, disector depth was 10 µm, and guard distance above and below the disector averaged 4 µm. Sections were examined using a 100 × 1.4 oil immersion objective. To ensure that oligodendrocytes were not over counted, two exclusion planes were used: cells crossing the left and bottom surfaces of the box were not counted. 100 fields of view per case were counted. For the intra-rater reliability five cases randomly selected were re-evaluated. The intra-class correlation coefficient was 0.852.

Data analyses

Statistical analysis was performed using Statistica (Version 7). The data were examined using Kolmogorov–Smirnov

test for normality. Preliminary analysis of potential confounding factors was performed. Correlations between the parameter measured and age, PMI, formalin storage interval for both comparison groups were estimated. The groups did not differ significantly by age and formalin storage interval (ANOVA, $p \geq 0.3$). PMI was significantly ($p < 0.04$) longer in the schizophrenia group (8.7 ± 6.4) as compared to control group (5.8 ± 1.0). Since it is known that age has a nonlinear (quadratic) relationship with intracortical myelin development in healthy individuals over the age with increasing myelin content that peaks in the fourth decade followed by rapid decrease in the fifth decade [33] both groups were subdivided by the age into two subgroups (age < > 50 years old).

The CE was calculated for each group and ranged from 0.04 to 0.07. The analysis of covariates (ANCOVA) with diagnosis, age group and gender as the independent variables and with PMI and formalin storage interval as covariates was performed. ANCOVA was followed by post hoc Duncan's test. Correlation analysis was also performed between the parameter measured and CPZ, age at onset and duration of disease.

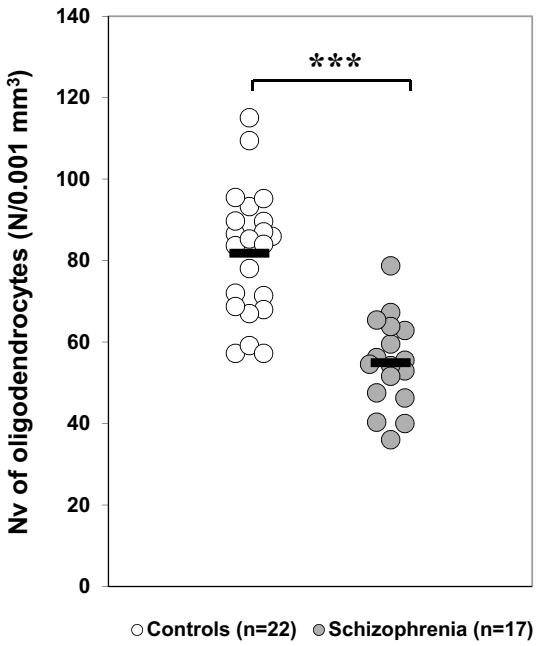

Fig. 1 Plots of individual case values and means (lines) for the Nv of oligodendrocytes in layer 5 of BA 10 in the control group and in the schizophrenia group. ***$p < 0.001$, ANCOVA test

Results

There were a significant effect of diagnosis [$F(2,29) = 24.2$; $p < 0.001$] and significant diagnosis × age interaction [$F(2,29) = 4.8$; $p = 0.03$] but not diagnosis × gender interaction on the Nv of oligodendrocytes in layer 5 of BA 10.

Effect of diagnosis

Post-hoc analysis showed a significant decrease in the Nv of oligodendrocytes (− 32%, $p < 0.001$) in the schizophrenia group as compared to the control group (Fig. 1). There were no significant correlations between the Nv of oligodendrocytes and duration of disease or age at disease onset ($R \leq 0.17$, $p \geq 0.5$).

Effect of age

A significant effect of age on the Nv of oligodendrocytes in the control group was found in post-hoc test. The Nv of oligodendrocytes was higher (+ 15%, $p = 0.02$) in young control subgroup as compared to elderly control subgroup. There was no difference between the two tested age subgroups within the schizophrenia cohort ($p = 0.36$). Both control subgroups differed significantly ($p < 0.001$) from the schizophrenia subgroups (Fig. 2).

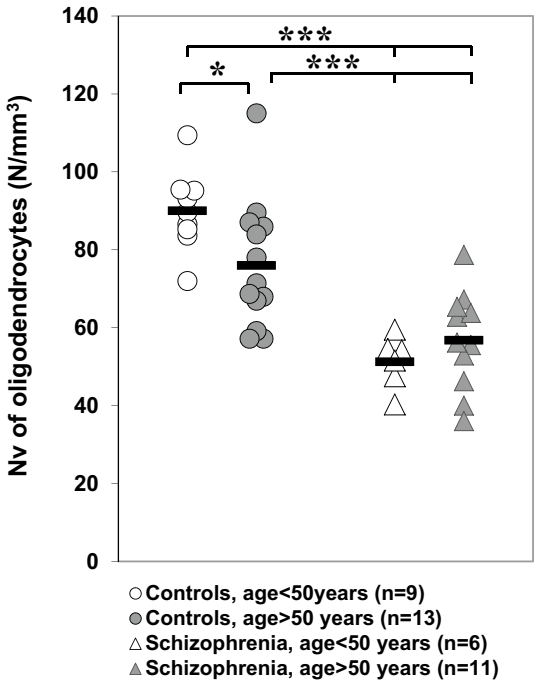

Fig. 2 Plots of individual case values and means (lines) for the Nv of oligodendrocytes in layer 5 in BA10. Young controls (age < 50 years old) showed significantly higher Nv of oligodendrocytes as compared to old controls (age > 50 years old). There were no significant differences between young and old schizophrenic subgroups for the Nv oligodendrocytes. Both control subgroups have significantly higher Nv of oligodendrocytes as compared to schizophrenia subgroups. *$p < 0.05$, ***$p < 0.001$; ANCOVA test

Confounders

Correlation analysis detected no effects of the confounding factors (age, PMI, formalin storage interval) on the parameter measured for both groups (all $p \geq 0.07$). No significant correlations between the Nv of oligodendrocytes and chlorpromazine equivalents in the schizophrenia group were found ($R = 0.01$, $p = 0.9$).

Discussion

The present study showed 32% deficit of oligodendrocytes in layer 5 of BA10 in the schizophrenia group as compared to controls. This finding extends the results of our previous studies reported a pronounced decrease in the Nv of oligodendrocytes in layer 6 (−25%) and underlying white matter (−10%) of BA 10 [21] as well as similar decrease in oligodendrocyte number in layer 3 of BA 9 (−22%) [32] and in layers 3 and 5 of the parietal cortex BA39 but not in BA40 [34, 35] in schizophrenia as compared to normal controls.

Lowered oligodendrocyte densities in white and grey matters were also found in the anterior cingulate cortex (BA 24) [36]. Additionally, the deficit of oligodendrocytes in schizophrenia was repeatedly detected in the hippocampus [37–39]. However, the reduction of oligodendrocyte density was not found in BA 32 of the anterior cingulate cortex [36], in the cingulum bundle [40]. Most of these authors used Nissl-stained sections for oligodendrocyte counting. Interestingly, Hof et al. [41] have reported a similar decrease of oligodendrocyte density in BA9 in schizophrenia using Nissl-stained sections and CNP-ase immunocytochemistry. Taken together with the results of the present study, the data point out that the prefrontal cortex is one of the brain structures where the most prominent deficit of oligodendrocytes was found in schizophrenia.

Lowered Nv of oligodendrocytes found in the present study assumes lowered myelin content in BA10 in schizophrenia. Some data support the suggestion. Decreased intracortical myelination in the prefrontal cortex of chronic schizophrenia subjects was found in post-mortem morphometric study using Luxol fast blue staining [10]. Reduced neuropil volume in layer 5 of BA10 found in schizophrenia [42] may also arise from the deficit of oligodendrocytes and myelin content. Besides, neuroimaging studies have reported a significantly smaller intracortical myelin volume in the frontal lobe in patients with schizophrenia [7–9]. The present data is in line with the results of our previous electron microscopic morphometric study [23, 24]. The studies demonstrated damage of myelin sheath lamellae and myelin/axon disruption in layer 5 of BA10 in schizophrenia. Schizophrenia subjects differed from normal controls by a significantly higher frequency of pathological myelinated fibers in layer 5 of the prefrontal BA10. Since myelin is produced by oligodendrocytes, these data suggest that the pathology of myelinated fibers in schizophrenia might be due to oligodendrocyte abnormalities. Dystrophic changes and degeneration of oligodendrocytes have been described in layer 5 and 6 of BA10 in schizophrenia [23, 24]. These data suggest that decreased Nv of oligodendrocytes found in layer 5 of BA10 may be the result of dystrophic and destructive alterations of oligodendrocytes in schizophrenia.

On the other hand, recently it has been shown that in the adult mammalian (including human) brain new oligodendrocytes continue to be generated from proliferating and differentiating precursors forming small clusters [43, 44]. Genetic association and microarray studies provide evidence for many genes with altered expression related to oligodendrocyte progenitor proliferation and differentiation in the prefrontal cortex in schizophrenia [45, 46]. Lower Nv of oligodendrocyte clusters (−40%, $p < 0.01$) was found in the inferior parietal cortex (BA39, 40) in the subgroup with adolescent onset of schizophrenia as compared to controls [47, 48]. Additionally, we did not reveal any correlations between Nv of oligodendrocytes and duration of disease or age at onset of disease in the present study. The data suggest that the decreased oligodendrocyte density may occur before the illness onset or in an early phase of schizophrenia as a result of altered proliferation and/or differentiation of oligodendrocyte progenitors during brain development and continue in the course of disease when oligodendrocyte degeneration may also occur.

Another interesting finding of the present study is the age effect on the Nv of oligodendrocytes. This parameter was higher in young control subgroup as compared to elderly control subgroup. These interactions were disturbed in schizophrenia: there were no differences between young and elderly subjects for the Nv of oligodendrocytes. Both control subgroups differed significantly ($p < 0.001$) from the schizophrenia subgroups. The result is in agreement with the decrease in oligodendrocyte number in neocortical regions of the aged human brain revealed by stereological morphometry and immunohistochemical methods [49–51]. It should be noted that some contradictory results have been reported. Previously Vostrikov and Uranova [52] using the same stereological method revealed a significant positive correlation between the Nv of oligodendrocytes and age in layer VI and the adjacent white matter of BA10 in the control group but not in the schizophrenia group. The discrepancy may be due to different cases, age range and the number of cases per young and elderly subgroups included in these studies. It is known that intracortical myelination trajectory in the human brain is complex, inverted U-shaped: an accelerated myelination process until 30 years of age, followed by a period of relative stability, before a decrease in myelin

content from the 50 s [5, 33]. Rajkowska et al. [53] have reported a strong positive correlation between the density of glial fibrillary acidic protein (GFAP)—immunoreactive astrocytes and age only in the depressed patients but not in healthy controls. Taken together, these data suggest that diagnosis by age interaction may be disease specific.

Interestingly, age-dependent decrease in the density of GFAP—immunoreactive astrocytes was observed in the prefrontal cortex of younger depressed subjects as compared to young control subjects and elderly depressed subjects [53]. The authors proposed that a combination of genetic and environmental (e.g. stress) factors at the early stages of depressive illness could lead initially to the pathology of glial cells, and consequently to the pathology of neurons later in life as depressive illness progresses. Koutsouleris et al. [54] studied the neuroanatomical age determined by a machine learning system trained to individually estimate age from the MRI study of healthy controls, schizophrenia, major depression and bipolar disorder patients. The authors have provided evidence for "accelerated aging" effects in early schizophrenic psychosis and other mental disorders supporting the hypothesis that the disruption of normal brain maturation is crucial in the pathogenesis of severe mental disorders, schizophrenia in particular.

We did not find any effects of PMI, time storage in formalin and gender on the Nv of oligodendrocytes in two groups using correlation analysis. When PMI and time storage in formalin were included as the covariates in ANCOVA test significant group differences on the parameter measured were found. In addition, ANCOVA test did not show any effects of gender or gender × diagnosis interactions on the parameter measured. Both young and elderly control subgroups differed significantly ($p < 0.001$) from the age schizophrenia subgroups.

As to the effects of antipsychotic drugs, Konopaske et al. [55] found a nonsignificant 12.9% decrease of oligodendrocyte number in the parietal grey matter after chronic exposure of macaque monkeys to haloperidol or olanzapine whereas another study demonstrated increased volume and glial density in primate prefrontal cortex after chronic antipsychotic drug exposure [56]. Protective effects of haloperidol and clozapine on oligodendrocytes [57, 58] and stimulation of progenitor proliferation by neuroleptics [59–61] have also recently been reported. Neuroimaging studies provide evidence for "promyelination" effects of atypical neuroleptics on intracortical myelin volume in the schizophrenia patients [8, 9, 62]. Thus, the reduction in oligodendrocyte density found in layer 5 of BA10 in the present study is probably not attributable to neuroleptic exposure and may be associated with schizophrenia. However, we cannot exclude the influence of neuroleptic medication on the parameter measured. Animal studies are needed to estimate the medication effects.

Intracortical myelination has been proposed to exert a marked influence on speed and synchronicity of action potential arrival across functional networks via the regulation of the short intracortical portion of axonal propagation [9]. The findings in primates and humans suggest a compelling role for intracortical myelin in cognition [5, 6]. Reduced intracortical myelination could result in cognitive and behavioral inefficiencies and disorganization that are part of the clinical manifestations of schizophrenia [9]. Recently Falkai et al. [39] in a post-mortem stereological study have reported decreased oligodendrocyte number in the hippocampus in schizophrenia subjects associated with cognitive deficits. Poor insight in schizophrenia is associated with cognitive dysfunction and more severe negative symptoms [63, 64]. Previously in a post-mortem study [34, 35] we found that a significant reduction in the Nv of oligodendrocytes in layers 3 and 5 of the inferior parietal cortex (BA 39) was associated with lack of insight in the schizophrenia subjects. A link of poor insight in schizophrenia with the structure and function of BA 10 has been reported [65]. A number of cognitive abilities including episodic memory, mentalizing and multitasking associated with rostral prefrontal cortex (BA10 among them) function have been observed to be impaired in the schizophrenia patients and may be associated with current symptoms such as delusions [66, 67]. It was found that reduced basal ganglia-thalamo-cortical connectivity [17, 18] and the dysfunction of this network may be associated with altered executive functioning and working memory deficits in patients with schizophrenia [19, 20]. Pyramidal neurons of layer 5 of BA 10 are the important link of reciprocal thalamo-cortical and basal ganglia-cortical interactions in primates [14] and in humans [15, 16]. Smaller basilar dendritic field size of layer 5 pyramidal neurons in BA 10 reported in schizophrenia [68] may contribute to reduced neuropil and prefrontal connectivity in schizophrenia. Our data point out that lowered oligodendrocyte density may lead to myelin deficiency and contribute to the dysfunction of neuronal network in BA 10 and to cognitive disturbances in patients with schizophrenia.

Our study has some limitations. First, we estimated the Nv of oligodendrocytes in Nissl-stained sections. Immunohistochemical markers to identify oligodendrocytes were not used. Second, the effects of neuroleptic treatment remain uncertain. Future studies of the role of oligodendrocytes in the pathophysiology of schizophrenia and of their relations to clinical symptoms are needed to consider these cells as a target for new treatment strategy of schizophrenia.

Thus, present study provides evidence for the reduction of oligodendrocyte density in layer 5 of BA10 in schizophrenia as compared to controls. Age-dependent decrease of oligodendrocytes was found in healthy subjects but not in subjects with schizophrenia. The deficit in the Nv of oligodendrocytes might contribute to reduced intracortical myelination

and the dysfunction of this cortical area in schizophrenia. Decreased Nv of oligodendrocytes may be the result of dystrophic and destructive alterations and/or disturbed development of oligodendrocytes in schizophrenia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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