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The deficit of oligodendrocyte family cells in layer 3 of the dorsal anterior cingulate cortex in schizophrenia: possible interactions with dysfunction and altered microanatomy

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Abstract

Current concepts suggest a close relationship between dysfunction of neuronal circuits, abnormalities of brain myelination, and alterations in the structure and function of oligodendrocyte lineage cells. Previously, we reported a significant decrease in the numerical density (Nv) of oligodendrocytes (Ol) and oligodendrocyte clusters (OlC) in layer 5 of the dorsal anterior cingulate cortex (dACC; Brodmann area 24, BA24) in schizophrenia; however, the NvOl and NvOlC in layer 3 have not yet been investigated.

Reduced connectivity between the ACC and the attention, salience, and default mode networks is characteristic of schizophrenia and is thought to underlie impaired control of affective and cognitive aspects of goal-directed behavior. These interactions are maintained through extensive cortico-cortical connectivity, with a potentially strong contribution from layer 3 pyramidal neurons. We used the optical disector method to estimate the numerical density of oligodendrocytes and oligodendrocyte clusters in layer 3 of the dACC in schizophrenia (18 cases) compared with healthy controls (13 cases). A significant reduction in the numerical density of oligodendrocytes (− 28%; $p < 0.001$) and oligodendrocyte clusters (− 29%; $p = 0.012$) was found in schizophrenia compared with controls. Strong positive correlations between NvOl and NvOlC were observed in both the control group ($R = 0.93$; $p < 0.001$) and in the schizophrenia group ($R = 0.79$; $p < 0.001$).

These findings suggest that the deficits of oligodendrocytes and oligodendrocyte clusters may contribute to altered functional connectivity in the networks involving the dACC, a key cortical hub implicated in schizophrenia.

INTRODUCTION

Current theories of schizophrenia emphasize the central role of brain network dysfunction in the pathogenesis of the disease disorder [1, 2]. The anterior cingulate cortex (ACC) occupies a critical position among the major brain networks whose disruption distinguishes patients with schizophrenia from healthy individuals, including the limbic, frontoparietal cognitive, dorsal attention, salience, and frontal eye field networks [3, 4]. Reduced connectivity between the ACC and the attention, salience, and default mode networks is a characteristic feature of schizophrenia [3, 4].

The dorsal anterior cingulate cortex (dACC), the cognitive division of the ACC, is thought to play an important role in cognitive control of goal-directed behavior [5]. It is critically involved in executive processes such as conflict monitoring, attentional control, error detection [6, 7], reward-based learning, decision-making and cost-benefit analysis [8], as well as emotional appraisal and mood regulation [9]. Accordingly, the dACC represents a key region of the limbic system and maintains extensive cortico-cortical connections with the anterior insula [10], dorsal premotor cortex [11] and amygdala [9, 12] with a potentially major contribution from layer 3 pyramidal neurons.

The dACC is consistently reported as an abnormal brain region in schizophrenia in terms of both structure and functional activity. Numerous studies have demonstrated pronounced disturbances in

dACC-related cognitive processes, including hypoactivity of the ACC in interaction with the amygdala and anterior insula during emotional processing [9, 10, 12, 13], as well as altered functional connectivity between the dACC and the precuneus during conflict monitoring [14]. Schizophrenia symptoms have also been associated with reduced connectivity between the dACC and the thalamus [15], anterior insula [16, 17], and amygdala [18].

It is generally accepted that the dysfunction of neuronal circuits is closely related to abnormalities of gray and white matter myelination and to alterations in oligodendrocyte structure and function [19–22]. Mature myelinating oligodendrocytes form myelin sheaths around axons, thereby markedly increasing conduction velocity and the number of action potentials transmitted per unit time [23, 24]. Modifications of existing myelin sheaths are also required for proper network functioning, since fine adjustment of signal propagation speed is essential for synaptic plasticity [25]. These processes are mediated by oligodendrocyte progenitors during the final stages of differentiation.

Clonal analyses have shown that mitotic division of NG2-positive oligodendrocyte progenitors results in small cell groups (approximately 2–6 cells) containing differentiating oligodendrocyte precursor cells [25]. These groups can be identified in Nissl-stained sections as clusters of cells morphologically similar oligodendrocytes (OlC). Proliferation and differentiation of oligodendrocyte progenitors are activity-dependent processes, as these cells receive synaptic input from nearby glutamatergic and GABAergic neurons and express the corresponding receptors [26].

Our previous studies demonstrated significant deficits of oligodendrocyte lineage cells in layers 3 and 5 of BA10, the rostral prefrontal cortex [27, 28], and in BA39 and BA40 of the inferior parietal lobule [29–31]. These regions constitute key nodes of the frontoparietal cognitive network (FPCN) and default mode network (DMN), dysfunction of which has repeatedly been demonstrated in schizophrenia [32, 33]. We also previously reported a significant decrease in numerical density (Nv) of oligodendrocytes (NvOl) and oligodendrocyte clusters (NvOlC) in layer 5 of the dACC [34].

The aims of the present study were therefore: (1) to determine whether the numerical density of oligodendrocytes and oligodendrocyte clusters is altered in layer 3 of the dACC in schizophrenia compared with controls, and (2) to investigate correlations between NvOl and NvOlC in this cortical layer in both groups.

MATERIALS AND METHODS

This study was performed using the same dACC tissue sections as in our previous study of oligodendrocyte lineage cells in layer 5 in schizophrenia and control subjects [34]. Postmortem brain specimens were obtained from the Departments of Pathology of Moscow Psychiatric Hospitals No. 1 and No. 15 and from Moscow Higher Medical School following consent for autopsy and research from relatives. The study complied with the Helsinki Declaration and was approved by the Local Ethics Committee of the Mental Health Research Centre.

All samples were dissected from the left hemisphere in both the schizophrenia group (18 cases) and the control group (13 cases without psychiatric pathology).

Diagnoses of schizophrenia were established according to ICD-10 and DSM-IV-R criteria independently by two psychiatrists. The schizophrenia group included 15 cases of paranoid schizophrenia (F20.0) and 3 cases of undifferentiated schizophrenia (F20.3). Data on patient age, age at disease onset, and illness duration were obtained from medical records. Demographic and clinical characteristics are presented in Table 1.

Table 1
Main demographic and clinical characteristics of controls and patients with schizophrenia

N	Diagnosis	Age, years	Gender	PMI, hours	Age at onset of disease, years	Duration of disease, years	Cause of death
1	SCH	41	M	28	27	33	Pulmonary embolism
2	SCH	60	M	25	n.a	n.a	Acute respiratory failure (aspiration)
3	SCH	60	M	28	42	18	Heart failure (CHD)
4	SCH	63	F	27	46	17	Acute respiratory failure
5	SCH	63	M	20	50	13	Pneumonia
6	SCH	62	F	14	26	36	Pulmonary embolism
7	SCH	54	M	4,5	21	33	Myocardial infarction
8	SCH	24	M	5	21	3	Pulmonary embolism
9	SCH	46	F	6	41	5	Bronchopneumonia
10	SCH	65	F	6,5	30	35	Pneumonia
11	SCH	72	M	6	29	43	Heart failure Pneumonia
12	SCH	64	F	5	28	36	Peritonitis
13	SCH	71	M	6	36	35	Heart failure (CHD)
14	SCH	73	M	7	45	28	Pulmonary embolism
15	SCH	79	F	5	32	47	Pneumonia
16	SCH	52	M	9	12	40	Heart failure (CHD)
17	SCH	74	M	7	29	45	Pneumonia
18	SCH	65	F	6	50	15	Myocardial infarction
	MEAN	60.44		13.14	33.24	28.4	
	SD	13.35		9.7	11	13.8	
1	Control	65	M	5,5			Acute respiratory failure
2	Control	81	F	7			Myocardial infarction
3	Control	48	M	5.5			Myocardial infarction

N	Diagnosis	Age, years	Gender	PMI, hours	Age at onset of disease, years	Duration of disease, years	Cause of death
4	Control	53	M	6			Heart failure (CHD)
5	Control	54	M	6			Pneumonia
6	Control	77	M	6			Heart failure (CHD)
7	Control	48	M	6			Acute respiratory failure
8	Control	61	F	7			Heart failure (CHD)
9	Control	57	M	6			Pulmonary embolism
10	Control	49	M	6			Heart failure (CHD)
11	Control	68	M	7			Heart failure (CHD)
12	Control	72	F	4			Aortic aneurism rupture
13	Control	71	M	5			Gastrointestinal hemorrhage
	MEAN	61.85		5.92			
	SD	11.34		0.84			

Abbreviations. SCH, schizophrenia; F, female; M, male; PMI, postmortem interval; Heart failure (CHD – coronary heart disease), Acute respiratory failure (aspiration); n.a. – not available.

Tissue preparation

Brains were divided midsagittally, and the dACC on the medial surface of the left hemisphere was identified according to established macroscopic landmarks [35]. Tissue blocks (approximately 1.5 cm thick and 3.0 cm^2 in area) were dissected from the medial surface of the left hemisphere beginning from the crossing of the corpus callosum and extending approximately 1.5 cm posteriorly toward the border with area 23, according to the scheme of Hoistad et al. [36].

Tissue blocks were immersion-fixed in fresh 4% paraformaldehyde in phosphate buffer (pH 7.4) and embedded in paraffin before histological processing. Each block was cut into approximately 100 serial coronal sections (20 μm thick) mounted on glass slides. The first section was selected randomly from the first 10 sections, and then every 10th section was sampled. Series of 7–10 sections were stained with cresyl violet (Nissl stain) and luxol fast blue (myelin stain). Final section thickness ranged from 14 to 16 μm.

Morphometry

Sections were examined using a Carl Zeiss Axio Imager M1 microscope equipped with AxioVision software under a 100×/1.4 oil immersion objective. Oligodendrocytes and oligodendrocyte clusters were counted in layer 3 of the dACC corresponding to Brodmann area 24.

BA24 was identified according to the cytoarchitectural criteria described by Vogt et al. [35]. Although BA24 is an agranular cortex lacking a distinct layer IV, layers 3 and 5 are readily distinguishable. The upper sublayer Va contains densely packed, well-stained pyramidal neurons with a homogeneous distribution, whereas in sublayer Vb pyramidal neurons form distinct clusters with lower overall cellular density and the presence of fusiform neurons. The presence of Von Economo neurons in layer 5 serves as a reliable marker of area 24 [37].

The numerical densities of oligodendrocytes and oligodendrocyte clusters were estimated using the optical disector method. Counting frames (250 × 340 μm) were placed systematically and randomly throughout the sampled area, with 10 frames analyzed per section. Two exclusion planes were applied: cells intersecting the left and bottom borders of the counting frame were excluded. Disector depth was 10 μm, with guard zones averaging 4 μm above and below the disector.

Oligodendrocytes were identified by their small size (nuclear diameter 4–6 μm), narrow unstained cytoplasmic rim, dense round or oval nucleus, and absence of a prominent nucleolus. Oligodendrocyte clusters were defined as pairs or groups of 2–6 morphologically similar oligodendrocytes located in close apposition.

All samples were coded, and cytoarchitectural assessments were performed blind to diagnosis.

Statistical analysis

Statistical analysis was performed using Statistica version 7. Data normality was assessed using the Kolmogorov–Smirnov test.

Preliminary correlation analysis revealed no significant effects of age or postmortem interval (PMI) on NvOl or NvOlC in either group ($R \leq 0.4$, $p \geq 0.16$). The groups did not differ significantly in age (ANOVA: $F = 0.09$, $p = 0.8$), although PMI was significantly longer in the schizophrenia group than in controls ($p = 0.013$).

The effects of diagnosis on NvOl and NvOlC were assessed using analysis of covariance (ANCOVA), with age and PMI as covariates, followed by Duncan ’s post hoc test. Correlations between NvOl and NvOlC, as well as between the measured parameters and disease duration, age at disease onset, age, and PMI, were evaluated using Pearson or Spearman correlation analyses.

RESULTS

Effects of diagnosis

One-way ANCOVA with diagnosis as the between-subject factor and age and PMI as covariates demonstrated a significant effect of diagnosis on the numerical density of oligodendrocytes [$F(1,30) = 12.5$; $p = 0.0015$; Cohen's $d = 1.22$] and oligodendrocyte clusters [$F(1,30) = 5.1$; $p = 0.03$; Cohen's $d = 1.26$]. Neither age nor PMI significantly influenced the measured parameters ($F(1,30) \leq 0.29$; $p \geq 0.6$).

Post hoc Duncan's test revealed a significant reduction in the NvOI (−29%, $p = 0.0005$) and the NvOIC (−28%, $p = 0.012$) in the schizophrenia group compared with the control group (Fig. 1A, B).

Correlation analysis

NvOIC showed strong positive correlations with NvOI in both the control group ($R = 0.93$; $p < 0.001$) and the schizophrenia group ($R = 0.79$; $p < 0.001$; Fig 2 A,B).

Within the schizophrenia group, no significant correlations were observed between the measured parameters and either disease duration or age at disease onset ($R \leq 0.28$; $p \geq 0.27$).

Potential confounding factors

Neither group demonstrated significant correlations between NvOI or NvOIC and age ($R \leq 0.27$; $p \geq 0.27$) or PMI ($R \leq 0.40$; $p \geq 0.16$).

DISCUSSION

The principal finding of the present study is a significant reduction in the numerical density of oligodendrocytes (−29%) and oligodendrocyte clusters (−28%) in layer 3 of the dACC in schizophrenia. Importantly, these alterations were independent of potential confounding factors such as age and postmortem interval, suggesting that the observed deficit is specifically associated with schizophrenia.

Our previous studies demonstrated that reduced connectivity of BA10, a major cortical hub of the FPCN, is accompanied by a significant decrease in NvOI and NvOIC in layers 3 and 5 of this region in schizophrenia [27,28]. In BA40, another important hub of the FPCN, reductions in oligodendrocyte lineage cells were observed predominantly in schizophrenia patients with poor or impaired insight [29–31], a clinical feature closely associated with cognitive dysfunction and altered inferior parietal lobule activity [33]. However, increased excitatory connectivity from the left occipitotemporal cortex to the supramarginal gyrus has also been reported in schizophrenia and has been proposed as a potential endophenotypic marker of the disorder [38].

The dACC is consistently identified as a structurally and functionally abnormal brain region in schizophrenia. The present findings, together with our previous observations in layer 5 of the dACC [34], further emphasize pronounced reductions in oligodendrocyte lineage cells in this cortical region. Collectively, these data support the hypothesis that oligodendrocyte deficits are closely linked to dysfunction of cortical hub regions in schizophrenia.

Myelination is known to increase axonal conduction velocity by more than 100-fold, reduce refractory periods, and markedly increase the number of action potentials transmitted per unit time, thereby substantially enhancing information-processing capacity [24,25]. Intracortical myelination is thought to regulate the terminal intracortical portions of axonal signal propagation and therefore critically influences network function in both healthy individuals and schizophrenia patients [39,40]. Consequently, deficits in oligodendrocyte lineage cells may contribute directly to network dysconnectivity in schizophrenia.

The dACC represents a major cortical hub within cortico–cerebellar–thalamic–cortical circuits involved in higher cognitive functions. Reduced reciprocal connectivity between the dACC and the mediodorsal nucleus of the thalamus is a characteristic feature of schizophrenia [15,41]. Such dysconnectivity may underlie disturbances in cognitive control, executive functioning, working memory, and clinical symptomatology [15,41,42].

Layer 3 pyramidal neurons and GABAergic interneurons play a key role in maintaining the temporal fidelity of dACC–thalamic interactions [43,44]. Experimental studies have demonstrated that mediodorsal thalamic projections directly excite layer 3 interneurons, which in turn mediate feedforward inhibition of pyramidal neurons in layers 3 and 5 of the dACC [43,44]. This inhibitory mechanism limits the temporal window during which pyramidal neurons integrate excitatory input and generate action potentials. Interactions between interneurons and pyramidal neurons are also essential for gamma oscillation generation and associated cognitive processes such as working memory [45,46]. Dysfunction and/or deficits of GABAergic interneurons in layer 3 of the dACC have been repeatedly implicated in schizophrenia [47]. Altered interneuron activity may additionally contribute to oligodendrocyte lineage deficits, given that interneuron axons are substantially myelinated [48].

The dACC also constitutes a key component of the salience and attention networks and contributes critically to affective and cognitive regulation [49–51]. Projections from the dACC to the dorsal premotor cortex [11] and amygdala [9,12] are predominantly cortico-cortical pathways likely involving strong participation of layer 3 pyramidal neurons. Functional neuroimaging studies consistently demonstrate ACC hypoactivity during emotional processing in schizophrenia [13], and greater negative symptom severity has been associated with reduced dACC activation during emotional tasks [18,52].

Correlation analyses demonstrated strong positive relationships between NvOlC and NvOl in layers 3 and 5 of the dACC in both groups. Similar correlations were previously identified in layer 5 of BA10 and BA40; however, in layer 3 of these cortical areas, correlations were preserved only in controls and not in schizophrenia subjects [27–31]. Layer 3 and layer 5 pyramidal neurons participate in distinct cortico-cortical and thalamocortical communication pathways and differ substantially in their glutamatergic neurophysiology [53]. Although oligodendrocyte lineage deficits are less pronounced in BA40 than in BA10, both highly interconnected cortical hubs demonstrate similar patterns of altered oligodendrocyte relationships.

We also previously observed strong positive correlations between oligodendrocyte clusters and satellite oligodendrocytes surrounding pyramidal neurons in layer 3 of BA39 [54]. BA39 is a component of the default mode network which have only weak structural connectivity with the subcortical ROIs of DMN and appears to rely predominantly on cortico-cortical connectivity mediated by layer 3 pyramidal neurons [55]. The angular gyrus functions as an integrative hub for internal and external information processing and represents one of the most functionally connected cortical regions [56]. The preserved correlation between NvOl and NvOlC in layer 3 of the dACC in schizophrenia may therefore reflect the exceptionally extensive connectivity of layer 3 pyramidal neurons in this region in accordance with continuously evolving environmental demands for ongoing behavioral adaptation [57].

Our findings suggest that abnormalities of oligodendrocyte differentiation in schizophrenia may involve both qualitative disturbances (altered maturation into myelinating oligodendrocytes or satellite oligodendrocytes) and quantitative deficits (reduced oligodendrocyte clusters). Since oligodendrocyte progenitors within clusters represent late stages of maturation and are critically involved in activity-dependent myelin remodeling necessary for neuronal plasticity [25,58], disturbances of these cells may have major consequences for cortical circuitry.

Experimental studies have demonstrated close interactions between neuronal activity and oligodendrocyte lineage cell proliferation and differentiation [58,59]. In schizophrenia, reductions in numbers of oligodendrocyte and clusters appear significant particularly in patients with severe cognitive dysfunction [29–31]. Furthermore, impaired proliferation and maturation of oligodendrocyte progenitors may contribute to deficits of mature myelinating oligodendrocytes, altered intracortical myelination, and brain dysconnectivity. Indeed, disturbances in oligodendrocyte lineage programming and maturation have been reported in schizophrenia [60,61].

The deficit of oligodendrocyte lineage cells observed in the dACC in schizophrenia may also be associated with altered intracortical myelination. Interestingly, quantitative magnetization transfer imaging studies have reported increased intracortical myelin content in the midcortical layers of the prefrontal and anterior cingulate cortex [62], as well as in the superficial and middle layers of the inferior parietal lobule [63] in schizophrenia patients. However, increased myelin content was accompanied by decreased indices of myelin organization, suggesting substantial abnormalities in cortical myeloarchitecture [62]. Our previous ultrastructural studies demonstrated marked oligodendrocyte and myelin abnormalities in schizophrenia, including axonal atrophy, swollen myelin sheaths, and accumulation of myelin-like material within glial cells [64]. Such alterations may contribute to disrupted intracortical myelin organization across cortical layers.

It is also possible that abnormal myelin organization is linked to reduced network activity. Structural plasticity of neuronal dendrites and axons is strongly activity-dependent [65]. Dendritic arborization determines the number of dendritic spines and therefore the size of neuronal receptive fields. Deficits in dendritic complexity and spine density may consequently lead to degeneration and loss of excessive presynaptic terminals [66].

In schizophrenia, marked reductions in basilar dendrite length, dendritic number, and neuronal soma size have been reported in layer 3 of the prefrontal cortex [67–69]. Alterations in layer 5 appear less pronounced and are mainly characterized by reduced dendritic field size [67,70]. In the dACC, stereological studies have demonstrated a substantial deficit of pyramidal neurons in layer 5 [71]. Together with altered connectivity between pyramidal neurons and GABAergic interneurons [47], these findings suggest major reorganization of dendritic architecture. Oligodendrocyte progenitors may also contribute to these pathological processes because they are immunocompetent cells survey their microenvironment through constant filopodia extension and capable of responding dynamically to inflammatory signals from microglia [72].

Limitations

This study has several limitations. We estimated the numerical density of oligodendrocytes and oligodendrocyte clusters but did not assess cortical thickness or dACC volume. However, previous stereological studies have not identified significant differences in these parameters within the ACC, including the dACC [36,71]. In addition, the potential effects of antipsychotic treatment remain uncertain because reliable information on medication dosage was unavailable for many patients.

Conclusion

In conclusion, our study demonstrates a significant reduction in the numerical density of oligodendrocytes and oligodendrocyte clusters in layer 3 of the dACC in schizophrenia. Together with our previous findings, these results suggest that alterations in oligodendrocyte lineage cells, as well as changes in the relationships between oligodendrocyte progenitors and their differentiated progeny across associative cortical regions, may contribute to region-specific patterns of cortical dysconnectivity and network dysfunction in schizophrenia.

Declarations

Compliance with ethical standards

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

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Author Contribution

N.K. provided cell measurements, performed statistical analysis and wrote the draft of the manuscript. N.U. revised and approved the manuscript.

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Data Availability

The data are available on the basis of request.

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Figures

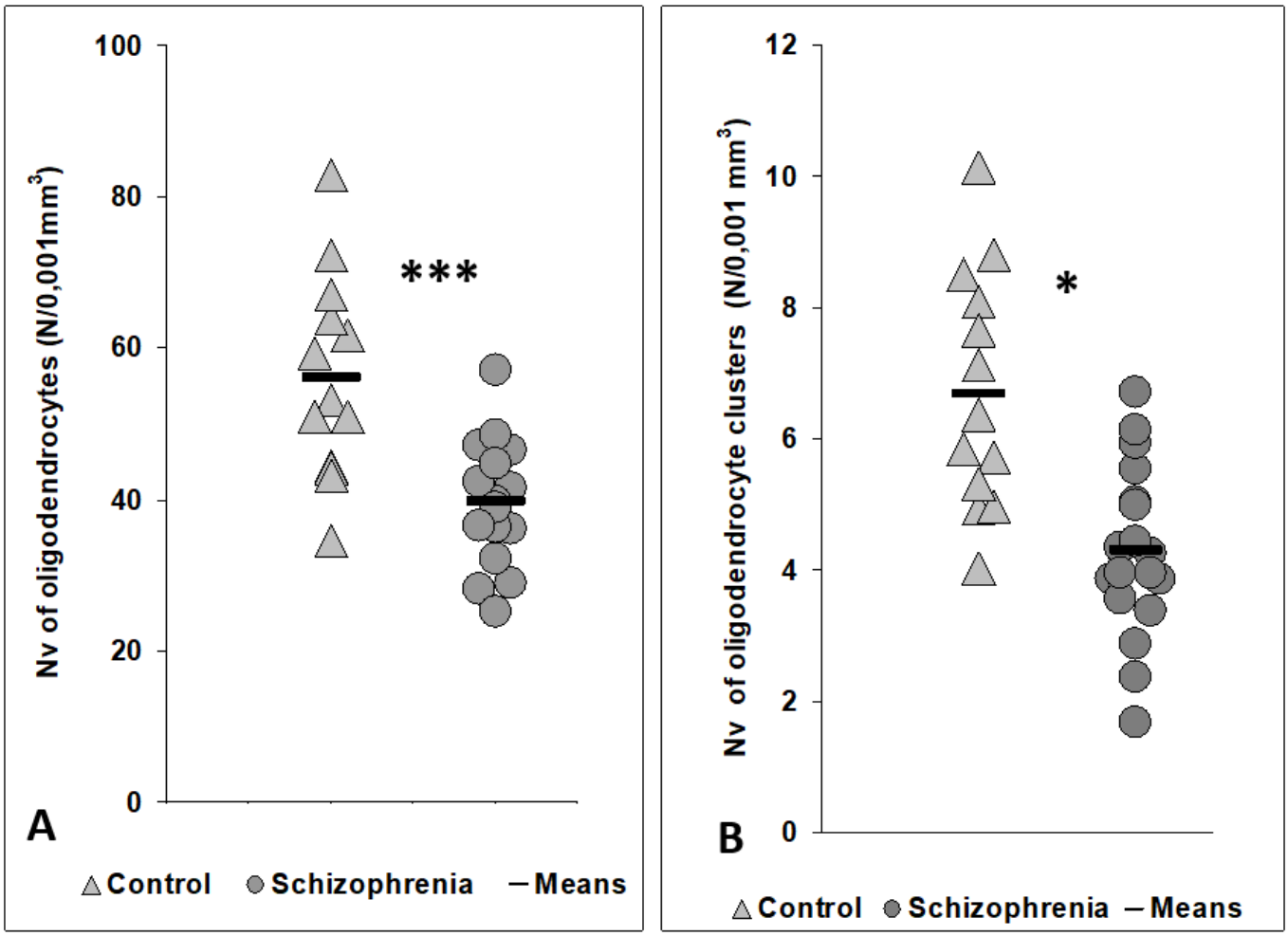
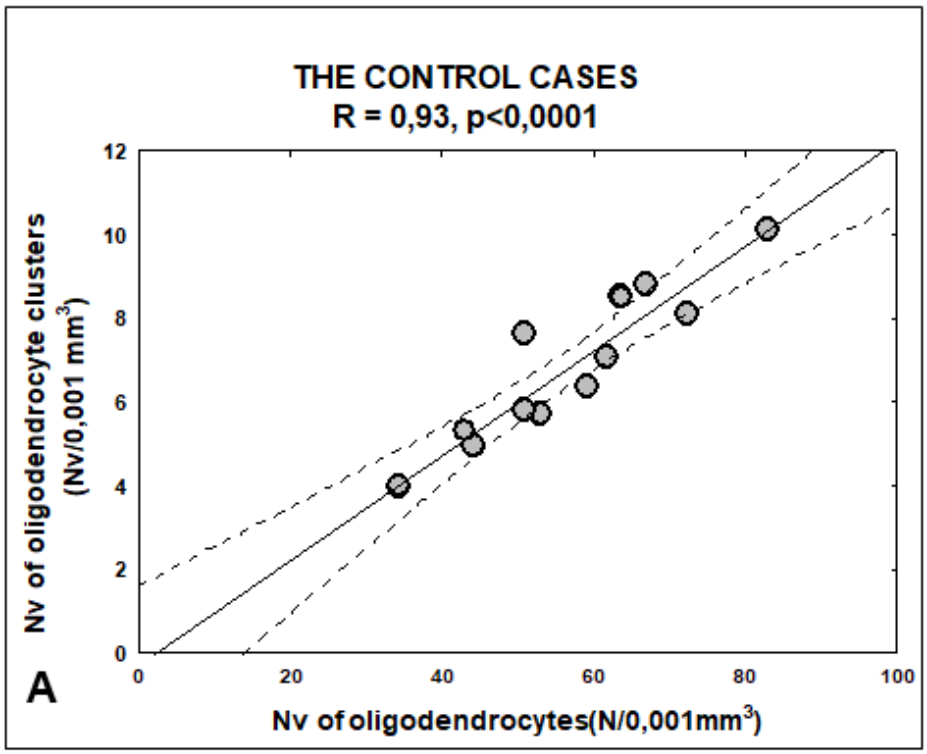


Figure 1

Plots of individual case values and means (horizontal lines) for the Nv of oligodendrocytes (A) and the Nv of oligodendrocyte clusters (B) in layer 3 of the dorsal anterior cingulate cortex in the control group and the schizophrenia group. *** $p < 0.001$, * $p = 0.012$, ANOVA.



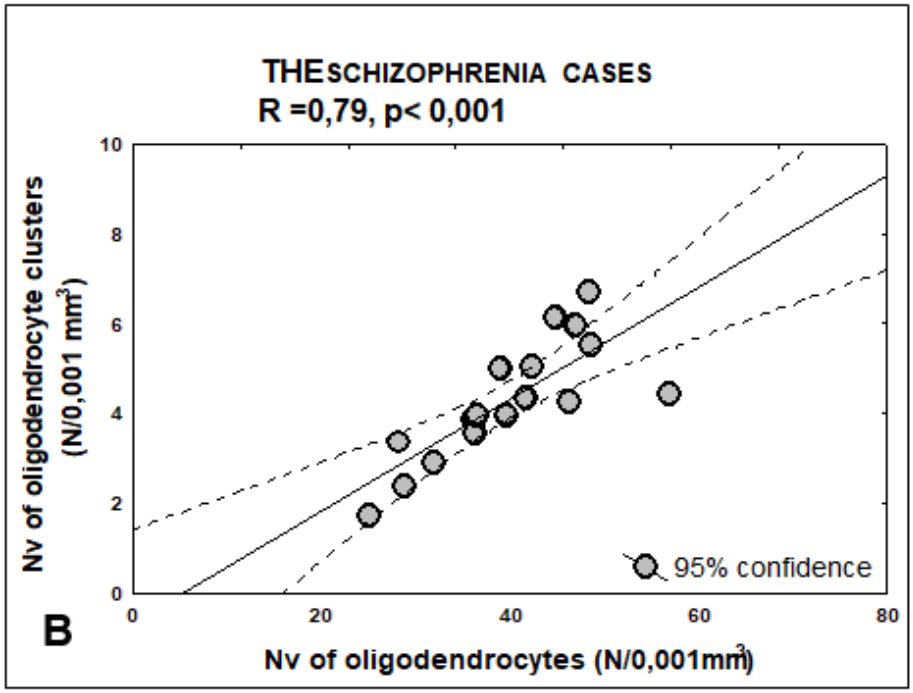


Figure 2

Positive correlations between the numerical density of oligodendrocytes and oligodendrocyte clusters in layer 3 of the dorsal anterior cingulate cortex in the control group (A) and the schizophrenia group (B).