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Quantitative analysis of activated microglia, ramified and damage of processes in the frontal and temporal lobes of chronic schizophrenics

Teresa Wierzba-Bobrowicz, Eliza Lewandowska, Waldemar Lechowicz, Tomasz Stępień, Elżbieta Pasennik

Department of Neuropathology, Institute of Psychiatry and Neurology, Warsaw, Poland

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Abstract

Under pathological conditions, microglial cells undergo activation, which is manifested by the expression of histocompatibility locus antigens class II (HLA II) on their surface as well as by proliferation and varied morphological forms. In schizophrenia, characterised by an essential role played by immunological mechanisms, quantitative analysis of activated microglia – with well-developed ramification (RM), degenerative traits and damaged processes (from their shortening to their complete lack) (DM) – may contribute to better understanding of schizophrenia etiopathogenesis. Quantitative analysis was performed on slices derived from the frontal and temporal lobes of 9 brains of schizophrenics and 6 control brains. The nonparametric Mann-Whitney U test was used to assess quantitative differences in the distribution of microglia in these regions of the brain. Statistical analyses were performed with STATISTICA 6.5 Programme.

In both structures of the brain, the number of activated microglial cells was higher in schizophrenic brains than in control brains. Except for the first layer of the cerebral cortex with the same amounts of RM and DM, the number of DM cells in the remaining regions was several-fold higher than that of RM cells. It is most likely that disturbances in calcium metabolism and energetic balance as well as antibodies produced in the course of schizophrenia are the agents able to trigger a cascade transforming RM into DM. Quantitative differences in RM and DM, observed between the studied structures and cortical regions, could depend not only on functioning of inter-neuronal and inter-structural links. Our study suggests a pivotal role of microglial cells in repair processes and/or etiopathogenesis of schizophrenia and indicates that they undergo substantial damage in the course of chronic schizophrenia.

Key words: *microglia, HLA II, schizophrenia, frontal lobe, temporal lobe, quantitative analysis*

Introduction

In the central nervous system (CNS), microglial cells make 15-20% of the total number of cells [7,36]. Although microglial cells appear prior to the brain vascularisation and monocytes, it is generally thought that they originate from the hematopoidal line [7,23]. From the eighth week of intrauterine life,

Communicating author:

doc. dr hab. Teresa Wierzba-Bobrowicz, Department of Neuropathology, Institute of Psychiatry and Neurology, Sobieskiego 9, 02-957 Warsaw, Poland, e-mail: bobrow@ipin.edu.pl

Table I. Cases of schizophrenia

Case No.	Age (years)	Duration of disease (years)	Cause of death	Concomitant diseases
1	32	no data	pneumonia	No data
2	55	20-30	cardio-respiratory failure	post-trauma epilepsy
3	69	25	cardio-respiratory failure	diabetes, Hashimoto's goitre
4	54	35	gastric ulcer perforation	no data
5	54	18	circulatory failure	hyperthyroidism
6	66	14	sudden circulatory arrest pulmonary embolism	diabetes
7	58	20	circulatory failure	no data
8	67	10	sudden circulatory arrest	no data
9	46	21	sudden circulatory arrest	no data

they emerge in all CNS structures evenly distributed in the grey and white matter.

Microglia exhibit an extensive morphological plasticity. Activated microglia may assume different morphological forms, depending on morphoarchitecture of their structure, in which they occur, on the function performed in a given moment as well as on pathological agent exerting its effect [23,24]. Activated microglial cells most frequently assume the form of buscy microglia and/or ramified microglia (RM). However, spindle, rod and ameboid cells of different shapes, cytoplasm abundance, thickness, and the number of processes are also visible [19,26].

Microglia are also multifunctional cells. During the CNS development, they play a crucial role in eliminating necrotic neurons in the mechanism of apoptosis. They are also involved in vasculogenesis, migration and functional differentiation of neurons [7,23]. In the mature CNS, they primarily play the role of immunocompetent cells equipped with the fagocyting ability. The recent reports suggest their new role of multipotential stem cells [16,36]. Under pathological conditions, microglial cells are rapidly activated, which is mostly manifested by showing on their surface the expression of the major histocompatibility complex class II (MHC II), and also by their proliferation and appearance in new/different morphological forms [3,4,26].

Proliferation of microglia has also been reported in schizophrenia although its etiopathogenesis has not yet been conclusively elucidated [21,18,35]. Their proliferation is particularly observed in structures

Table II. Cases of controls

Case No.	Age (years)	Cause of death	Concomitant diseases
1	57	sudden circulatory arrest, pulmonary embolism	miocardiopathy
2	38	sudden circulatory arrest, pulmonary embolism	hyperthyroidism
3	57	pneumonia	no data
4	77	circulatory failure	coronary heart disease
5	65	sudden circulatory arrest	miocardiopathy
6	44	circulatory failure	coronary heart disease

Table III. Schizophrenia. Density of active microglia cells (N/mm^2) in cerebral cortex of the frontal lobe (gyrus cinguli), **RM** – ramified microglia cells, **DM** – active microglia without processes. SE – standard error of arithmetic mean

Case number according to Tab. I		Distance through neocortex from the lobe margin (mm)									
		0.35	0.7	1.05	1.4	1.75	2.1	2.45	2.8	3.15	3.5
1_{sch}	RM	14.38	15.69	11.76	3.92	3.92	6.54	5.23	9.15	7.84	7.84
	DM	69.28	13.07	15.69	15.69	19.61	18.30	24.84	32.68	20.92	22.22
2_{sch}	RM	39.22	14.38	7.84	11.76	9.15	16.99	13.07	24.84	24.84	13.07
	DM	9.15	6.54	11.76	14.38	23.53	16.99	14.38	20.92	11.76	27.45
3_{sch}	RM	11.76	3.92	2.61	0.00	3.92	5.23	1.31	7.84	2.61	2.61
	DM	9.15	7.84	14.38	0.00	1.31	1.31	3.92	6.54	5.23	9.15
4_{sch}	RM	28.76	6.54	6.54	7.84	7.84	1.31	2.61	2.61	3.92	0.00
	DM	11.76	7.84	11.76	5.23	5.23	5.23	18.30	11.76	13.07	15.69
5_{sch}	RM	45.75	19.61	13.07	7.84	11.76	6.54	10.46	5.23	9.15	5.23
	DM	44.44	27.45	27.45	30.07	33.99	62.75	62.75	52.29	58.82	60.13
Mean	RM±SE	27.97±3.89	12.03±2.17	8.37±1.61	6.27±1.50	7.32±1.68	7.32±1.69	6.54±1.36	9.93±2.81	9.67±2.07	5.75±1.40
Mean	DM±SE	28.76±4.49	12.55±1.67	16.21±2.35	13.07±2.80	16.73±2.45	20.92±4.11	24.84±3.76	24.84±3.42	21.96±3.71	26.93±3.35

whose abnormal functioning suggests clinical and neurochemical symptoms [1,2,28,30]. A diminished volume of individual structures of the brain, most frequently linked functionally, as well as the reduced number of neuronal processes, axons, dendrites, and synapses, and the decreased level of neurotransmitters have already been described [6,28]. Our previous study showed the presence of activated microglial cells, ramified and damage of processes, which exhibited some degenerative traits in both frontal and temporal lobes. These structures are linked with each other by inhibitory and excitatory projections via mammilary bodies and anterior thalamus [8,10,27]. These changes suggested a secondary damage of the former normal, activated microglial cells in the course of chronic schizophrenia [31,35], which indicates their involvement in exacerbation of structural changes in the long-term morbid process. The aim of the present study was to perform a quantitative analysis of activated microglia, normally ramified and exhibiting degenerative traits, in both frontal and temporal lobes in chronic schizophrenics. The quantitative assessment of both morphological forms of microglia may contribute to better understanding of agents participating in pathogenesis of schizophrenia.

Material and methods

The quantitative analysis was performed on serially cut slices, derived from the temporal lobe (gyrus temporal inferior, Brodmann's area 20) and the frontal lobe (gyrus cinguli, Brodmann's area 24). The study material was obtained from 9 brains of female chronic schizophrenics (Table I). Control brains were obtained from 6 patients of the same age group and free from neurological illnesses with extracerebral causes of their deaths (Table II).

The brains were fixed in 4% paraformaldehyde in 0.1 M phosphorane- buffer saline, pH 7.4. Frontal and temporal lobe slices were cut serially at 8 µm. Expression of MHC II was visualised immuno-histochemically, using anti-human HLA-DP, DQ, DR (DAKO 1:50). The quantitative analysis was performed on three consecutive preparations of each series. Microglial cells were counted in 10 not overlapping regions of 0.076 mm^2 (Neofluar 40x, Axiophot Zeiss), localised axially along five segments of 3.5 mm, running from the surface deep into the cortex at intervals of 0.5

Table IV. Schizophrenia. Density of active microglia cells (N/mm^2) in cerebral cortex of the temporal lobe (gyrus temporal inferior), **RM** – ramified microglia cells, **DM** – active microglia cells without processes. SE – standard error of arithmetic mean

Case number according to Tab. I		Distance through neocortex from the lobe margin (mm)									
		0.35	0.7	1.05	1.4	1.75	2.1	2.45	2.8	3.15	3.5
Sch1	RM	11.76	10.46	11.76	13.07	9.15	13.07	15.69	15.69	10.46	15.69
	DM	50.98	30.07	37.91	35.29	45.75	48.37	54.90	49.67	60.13	62.75
Sch2	RM	1.31	9.15	26.14	15.69	10.46	15.69	11.76	39.22	60.13	45.75
	DM	0.00	2.61	10.46	6.54	7.84	9.15	14.38	16.99	13.07	15.69
Sch6	RM	44.44	45.75	50.98	49.67	49.67	41.83	39.22	39.22	44.44	49.67
	DM	37.91	53.59	54.90	65.36	65.36	53.59	66.67	79.74	75.82	57.52
Sch7	RM	7.84	7.84	10.46	24.84	40.52	65.36	92.81	94.12	104.58	70.59
	DM	14.38	26.14	30.07	35.29	45.75	52.29	56.21	48.37	44.44	50.98
Sch8	RM	57.52	19.61	9.15	11.76	11.76	15.69	16.99	22.22	53.59	40.52
	DM	49.67	53.59	57.52	75.82	81.05	96.73	111.11	100.65	91.50	70.59
Sch9	RM	58.82	20.92	19.61	32.68	32.68	47.06	54.90	50.98	65.36	60.13
	DM	33.99	36.60	39.22	49.67	40.52	41.83	35.29	60.13	45.75	37.91
Mean	**RM±SE**	**30.28±4.52**	**18.95±2.39**	**21.35±2.70**	**24.62±2.63**	**25.71±2.97**	**33.12±3.63**	**38.56±4.67**	**43.57±5.12**	**56.43±5.81**	**47.06±4.34**
Mean	**DM±SE**	**31.15±3.62**	**33.77±3.11**	**38.34±3.13**	**44.66±3.70**	**47.71±4.29**	**50.33±4.58**	**56.43±5.43**	**59.26±4.81**	**55.12±5.35**	**49.24±3.93**

mm (Fig. 1). The values of arithmetic mean (±SE) of the identified numbers are given in summary tables. The nonparametric Mann-Whitney U test was used to assess quantitative differences in the distribution of microglia in the studied regions of the brain. Statistical analyses were performed with STATISTICA 6.5 Programme (Stat Soft USA).

Results

The quantitative analysis of microglial cells was performed (neocortex) on the frontal lobe (gyrus cinguli, Brodmann's area 24) and the temporal lobe (gyrus temporal inferior, Brodmann's area 20). The increase in the number of activated microglial cells, ramified and with damaged processes (from their shortening to their complete lack (DM)), was observed in both structures (Table III, Fig. 1).

In gyrus cinguli, the majority of microglia, both RM and DM, was localised in the submeningeal region (0.35), where the numerical values of both morphological forms were comparable (Fig. 2). In the layers localised deep into the cortex (0.7-3.5 mm), the number of RM cells was 2-3 times higher than that observed in the control material, whereas the amount of microglia damage of processes was 3-7 times higher than that in the cortex of control brains. In the regions between 0.7 and 3.5 mm, microglial cells with damaged processes largely outnumbered RM cells.

In gyrus temporal inferior in the subcortical layer (0.35), the numbers of RM and DM were similar and only slightly exceeded the control values (Fig. 3). The number of activated microglial cells increased with calculations descending deeper into the cortex, from 0.7 to 3.5 mm (Table IV). In those regions of the cortex, DM cells were definitely superior in numbers to RM cells. Only in the deepest regions (3.15-3.5 mm) the numbers of RM and DM cells were similar, however, they substantially exceeded the control values. The control results showed that the number of both RM and DM cells was over twice as high in the temporal lobe as that in the frontal lobe (Tables V and VI).

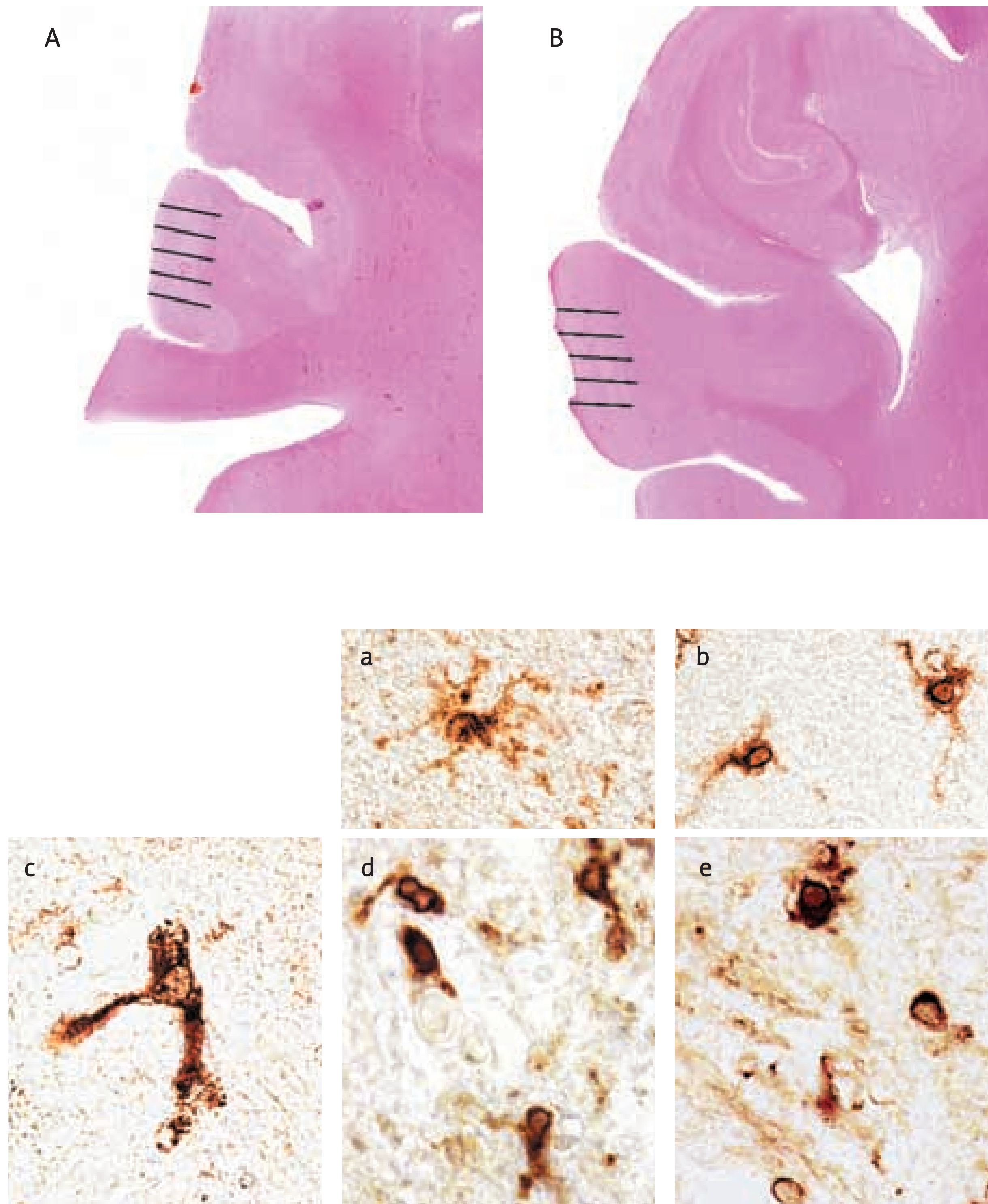

Fig. 1. A. Frontal lobe (gyrus cinguli); **B.** Temporal lobe (gyrus temporal inferior): **a, b** – microglia cells described as ramified microglia /RM/; **c, d, e** – cells of microglia described as microglial with damage of processes /DM/. Bars indicate area's distance of analysis inside the cortex (0-3.5 mm). Range of bars indicates distance between areas of analysis (0.5 mm)

Table V. Controls. Density of active microglia cells (N/mm²) in cerebral cortex of the frontal lobe (gyrus cinguli), **RM** – ramified microglia cells, **DM** – active microglia without processes. SE – standard error of arithmetic mean

Case number according to Tab. II		Distance through neocortex from the lobe margin (mm)									
		0.35	0.7	1.05	1.4	1.75	2.1	2.45	2.8	3.15	3.5
1_C	RM	7.84	7.84	1.31	1.31	1.31	0.00	0.00	2.61	2.61	2.61
	DM	31.37	15.69	7.84	9.15	13.07	7.84	13.07	22.22	20.92	15.69
2_C	RM	0.00	0.00	2.61	1.31	0.00	0.00	1.31	1.31	0.00	1.31
	DM	1.31	0.00	2.61	0.00	2.61	0.00	1.31	1.31	1.31	3.92
3_C	RM	15.69	5.23	3.92	2.61	11.76	13.07	16.99	7.84	22.22	20.92
	DM	16.99	6.54	9.15	1.31	6.54	6.54	3.92	9.15	10.46	14.38
4_C	RM	2.61	1.31	0.00	0.00	0.00	0.00	2.61	0.00	0.00	0.00
	DM	3.92	0.00	0.00	0.00	0.00	1.31	0.00	0.00	0.00	1.31
6_C	RM	0.00	0.00	1.31	1.31	1.31	0.00	0.00	0.00	0.00	0.00
	DM	2.61	2.61	0.00	1.31	1.31	0.00	1.31	5.23	2.61	1.31
Mean	RM±SE	5.23±1.34	2.88±0.86	1.83±0.75	1.31±0.56	2.88±1.14	2.61±1.49	4.18±1.69	2.35±1.03	4.97±1.71	4.97±1.75
Mean	DM±SE	11.24±2.75	4.97±1.28	3.92±1.07	2.35±0.80	4.71±1.16	3.14±1.09	3.92±1.41	7.58±1.79	7.06±1.63	7.32±1.54

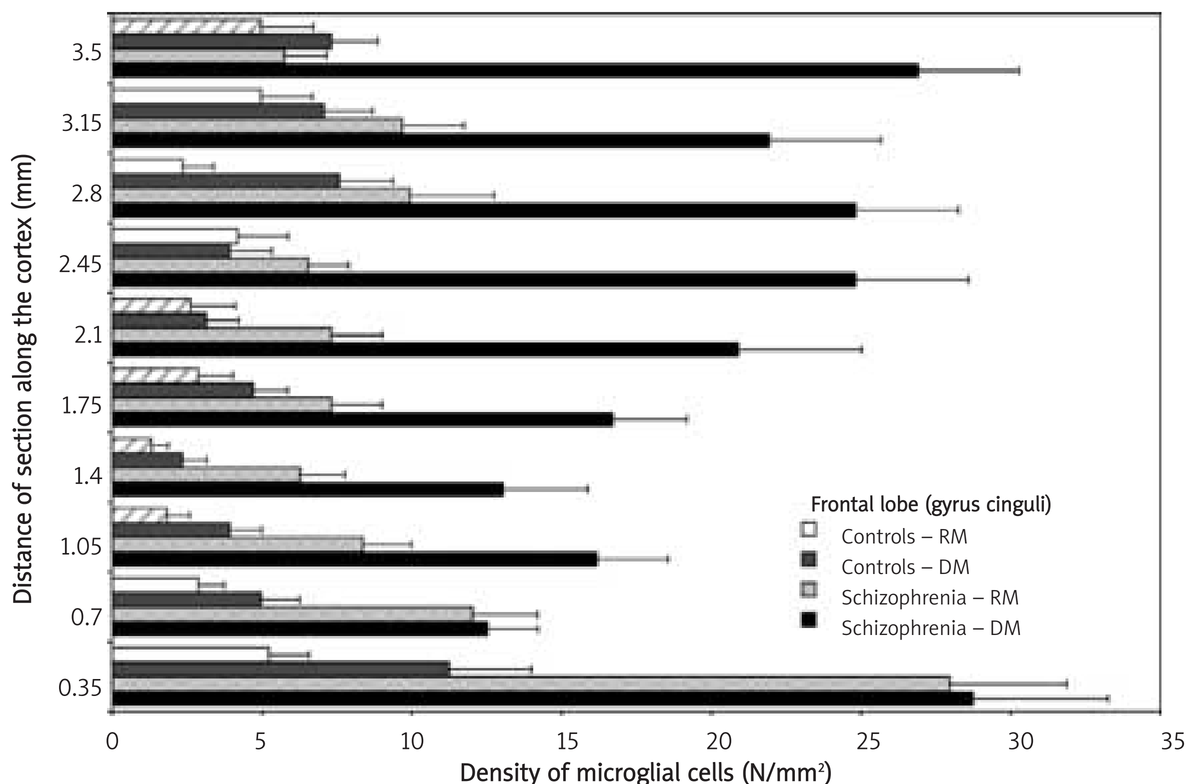

Fig. 2. Frontal lobe (gyrus cinguli)

Table VI. Controls. Density of active microglia cells (N/mm²) in cerebral cortex of the temporal lobe (gyrus temporal inferior) **RM** – ramified microglia cells, **DM** – active microglia without processes. SE – standard error of arithmetic mean

Case number according to Tab. II		Distance through neocortex from the lobe margin (mm)									
		0.35	0.7	1.05	1.4	1.75	2.1	2.45	2.8	3.15	3.5
1_C	RM	15.69	11.76	7.84	6.54	2.61	6.54	3.92	5.23	5.23	5.23
	DM	18.30	10.46	16.99	23.53	24.84	40.52	45.75	44.44	37.91	49.67
2_C	RM	20.92	3.92	2.61	5.23	0.00	0.00	0.00	0.00	3.92	2.61
	DM	13.07	5.23	2.61	2.61	5.23	2.61	0.00	3.92	5.23	9.15
4_C	RM	18.30	11.76	33.99	90.20	116.34	28.76	5.23	14.38	19.61	28.76
	DM	11.76	9.15	5.23	18.30	16.99	5.23	13.07	10.46	13.07	7.84
5_C	RM	22.22	5.23	3.92	3.92	2.61	2.61	2.61	7.84	6.54	1.31
	DM	36.60	7.84	5.23	7.84	10.46	11.76	5.23	6.54	6.54	5.23
6_C	RM	19.61	2.61	2.61	1.31	0.00	1.31	2.61	6.54	5.23	14.38
	DM	43.14	3.92	5.23	2.61	2.61	0.00	10.46	3.92	5.23	11.76
Mean	RM±SE	19.35±2.31	7.06±1.41	10.20±2.99	21.44±5.10	24.31±7.61	7.84±2.82	2.88±0.77	6.80±1.80	8.10±1.66	10.46±1.97
Mean	DM±SE	24.58±3.11	7.32±1.79	7.06±1.40	10.98±1.80	12.03±2.04	12.03±2.68	14.90±3.10	13.86±2.70	13.59±2.44	16.73±3.56

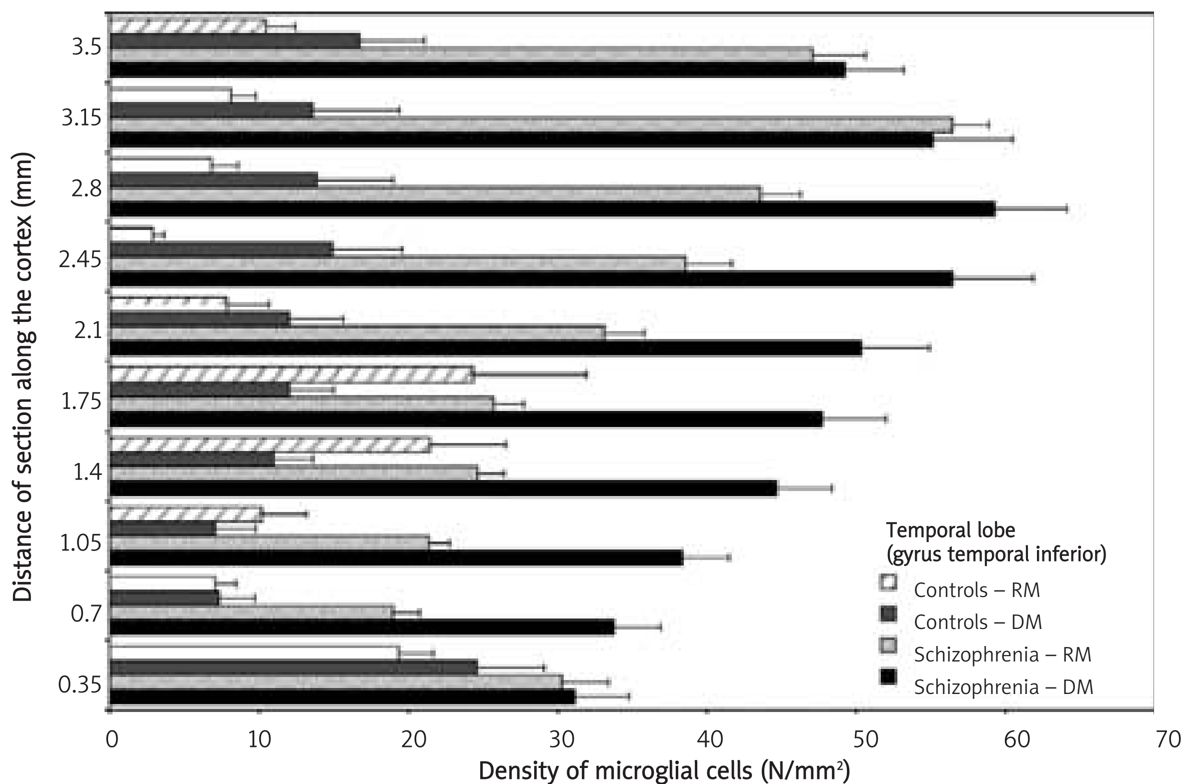

Fig. 3. Temporal lobe (gyrus temporal inferior)

Discussion

The quantitative analysis of ramified microglia and microglia with diversified damage to processes, which exhibited the expression of histocompatibility locus antigens class II (HLA II) for a specific immunohistochemical marker of activated microglia, showed a significant increase in the pool of microglial cells in the brain of chronic schizophrenics. This form of activity was observed in both morphological forms of microglia (RM and LM) in the frontal lobe as well as in the temporal lobe. It seems that the possibility of producing HLA II at the genic and molecular levels is not impaired by agents responsible for schizophrenia generation, duration of the disease, or long-term use of psychotropic drugs [11,21]. There is a number of agents that can influence proliferation and activation of microglial cells in the frontal and temporal lobes of patients with chronic schizophrenia [24,25,29]. They may include unknown causes possibly fundamental for etiopathogenesis of schizophrenia (e.g., neurodevelopmental disorders, infections), structural changes (e.g., defects of neuronal and glial cells, loss of axons and dendrites), and the decline in highly energetic compounds (ATP below 30-50 μM), or disturbances at the level of neurotransmitters [1,5,6,13,20,21]. On the other hand, activated microglia show the ability to generate bioactive, protective (e.g., plasminogen, IL-6) and structural agents in the CNS. The majority of microglia devoid of processes were characterised by more or less advanced degenerative traits. Abnormalities in toxic molecules such as IL-1β or TNF-α, which may be fundamental to structural and functional damages to neurones and oligodendroglia in chronic schozophrenia, may be regarded as agents able to trigger a cascade transforming RM into DM [12,17].

In all studied regions of both temporal and frontal lobes, activated DM cells outnumbered RM cells. In the brain of schizophrenics, the DM frequently multiplied RM values, especially in the frontal lobe. Only in the submeningeal region (0.35 mm) (first cortical layer), the numbers of both morphological forms of microglia were balanced, which may suggest that this region is structurally privileged in terms of the ”inflow” and/or the absence of effects exerted by agents involved in the transformation of RM into DM. Cerebral meninges like periventricular region and vessels are described as places where microglia penetrate the CNS [7,23,33,34]. Moreover, in the first layer of neocortex, intra-layer links are not expanded as this layer is mostly composed of Calaj cells with processes running in parallel to meninges and astroglial cells [32].

Morphological forms of cerebral microglia/ /macrophages with a limited number of processes or completely devoid of them, frequently exhibited the ability to phagocytose damaged CNS structural fragments. The majority of forms of microglia devoid of processes were characterised by more or less advanced degenerative traits. The disturbed calcium metabolism (Ca^{2+}) and energetic balance as well as generation of antibodies described in schizophrenia (e.g, antibrain antibodies, antibodies to basic myelin-protein, antibodies to a brain glycoprotein fraction) may be regarded as agents able to trigger a cascade transforming RM into DM [9,11,15,20]. There were quantitative differences in morphological forms of microglia (RM and DM) between the frontal and temporal lobes as well as between the studied individual regions localised in different layers of neocortex. The observed differences could be not only due to different advancement of cellular and molecular changes, and the effect of pathological agents, but also due to altered functioning of inter-neuronal and inter-structural links [14,22,32].

The present study may indicate a pivotal role of microglial cells in repair processes and/or generation and development of structural, molecular and functional changes in chronic schizophrenia. It also suggests that a substantial amount of microglia may be subjected to considerable damage in the course of chronic schizophrenia.

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