



The role of microglia in neuropsychiatric disorders and suicide

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Abstract

This narrative review examines the possible role of microglial cells, first, in neuroinflammation and, second, in schizophrenia, depression, and suicide. Recent research on the interactions between microglia, astrocytes and neurons and their involvement in pathophysiological processes of neuropsychiatric disorders is presented. This review focuses on results from postmortem, positron emission tomography (PET) imaging studies, and animal models of schizophrenia and depression. Third, the effects of antipsychotic and antidepressant drug therapy, and of electroconvulsive therapy on microglial cells are explored and the upcoming development of therapeutic drugs targeting microglia is described. Finally, there is a discussion on the role of microglia in the evolutionary progression of human lineage. This view may contribute to a new understanding of neuropsychiatric disorders.

Keywords Microglia · Schizophrenia · Major depressive disorder · Bipolar disorder · Affective disorders · Suicide · Dorsal raphe nucleus · Serotonin · Evolution of human lineage

Abbreviations

AD	Affective disorders	AMPA	(S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazole)-propionic acid
ALS	Amyotrophic lateral sclerosis	APOE	Apolipoprotein type E
APSM	Abnormal spindle-like microcephaly-associated protein	ASDs	Autism spectrum disorders
		ATP	Adenosine triphosphate
		BDNF	Brain-derived neurotrophic factor
		CXCL1	Fractalkine
		CD	Cluster of differentiation
		CNS	Central nervous system
		CSF	Cerebrospinal fluid
		DAT	Dementia of Alzheimer's type
		DRN	Dorsal raphe nucleus
		DRD	Dopamine receptors
		ECT	Electroconvulsive therapy
		ER	Endoplasmic reticulum
		HLA-DR	Human leukocyte antigen
		IBA1	Ionized calcium-binding adaptor molecule 1
		IFN- α	Interferon-alpha
		IL	Interleukin
		KYN	Kynurenine
		LPS	Lipopolysaccharide
		MHC	Major histocompatibility complex
		MDD	Major depressive disorder
		NMDAR	N-methyl-D-aspartate receptors
		NO	Nitric oxide
		NOX2	NADPH oxidase 2

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NRCAM	Neuronal cell adhesion molecule
PAL	Physical activity level
PATHOS-D	Pathogen host defence
PFC	Prefrontal cortex
PD	Parkinson's disease
PSA	Polysialic acid
PET	Positron emission tomography
PND	Postnatal day
PGE2	Prostaglandin E2
SN	Substantia nigra
SIGLEC11	Sialic acid-binding Ig like lectin 11
SIRT 2	Silent information regulator 2
SSRI	Selective serotonin reuptake inhibitors
SZ	Schizophrenia
TEE	Total energy expenditure
TGF- α	Transforming growth factor alpha
TH-1	T-helper cells 1
TH-2	T-helper cells 2
TNF- α	Tumor necrosis factor alpha
TSPO PET	Translocator protein positron emission tomography

Introduction

Microglial cells originate from myeloid precursors in the yolk sac and are regarded as resident macrophages of the central nervous system (CNS) [1]. During the development of the CNS, microglial cells have various functions: they phagocytose apoptotic neurons, and induce neuronal apoptosis, prune weak synapses, form new synapses, promote the survival of pyramidal neurons in the white matter, direct the expression of (S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazole)-propionic acid—(AMPA) and N-methyl-D-aspartate—(NMDA) receptors at thalamocortical synapses and regulate the production and migration of cortical inhibitory neurons [1]. Activated microglia produce cytokines and nitric oxide (NO). Activated microglial cells are polarized towards the M1 or M2 phenotype. While polarization towards the M1 phenotype, also called the proinflammatory phenotype, is caused by cytokines such as interferon-alpha (IFN- α) and tumor necrosis factor-alpha (TNF- α), polarization towards the M2 phenotype, also termed the anti-inflammatory phenotype, is triggered by various cytokines such as interleukin IL-4, IL-13 and IL-25 [2–11]. The differences between the M1 and M2 phenotypes have been critically discussed and might be reevaluated in the future [10, 12].

Microglial cells and neuroinflammation

Neuroinflammation is inflammation of nervous tissue [13]. The hallmark of neuroinflammation in schizophrenia (SZ) is overactivation of microglial cells [14]. Acute

neuroinflammation during fetal development causes neuropathological abnormalities in the cerebellum, insular cortex, fusiform gyrus and deficits in neuronal activation in the right amygdala and fusiform gyrus, and ventrolateral prefrontal cortex (PFC) [15]. Neuroinflammation is mainly facilitated by microglial cells and to some extent by astrocytes and mast cells [16]. Microglial cells are divided into amoeboid and ramified cells. The so-called dark microglial cells, which are highly phagocytic cells under oxidative stress around the vasculature showing an electron-dense, condensed cytoplasm, are either overactivated microglial cells or a novel type of myeloid cell infiltrating the brain [16]. Neuroinflammation is linked to white matter pathology in patients with schizophrenia and is caused by microglial cells [17, 18]. Furthermore, focal neuroinflammation occurs in the hippocampi of patients with schizophrenia with an acute psychosis [19]. Disruption of the interaction between mast cells and microglial cells increases neuroinflammation [20]. However, the term neuroinflammation is not interchangeable with the term inflammation: microarray analyses of postmortem cerebral cortices of patients with Alzheimer's disease (DAT), Parkinson's disease (PD), patients with schizophrenia and patients with inflammatory diseases have demonstrated no relationship between these conditions [21].

When microglial cells become activated during neuroinflammation, they become enlarged and phagocytic. Microglial cells contribute to synaptic plasticity by releasing neuroactive molecules such as adenosine triphosphate (ATP), glutamate, D-serine, nitric oxide (NO), brain-derived neurotrophic factor (BDNF), TNF- α , free radicals, prostaglandin E2 (PGE2), and ILs; and microglial cells communicate with astrocytes through glutamatergic neurotransmission [2]. Furthermore, glutamate controls the function of microglial cells via ionotropic and metabotropic receptors located in these cells [22]. Microglial cells also communicate with neurons, promoting neuronal cell death, neurogenesis, and synaptic interactions [7, 23, 24]. Activated microglia control inhibitory inputs from parvalbumin containing interneurons onto the basilar dendritic spines of deep layer 3 pyramidal neurons in the PFC in patients with schizophrenia [25]. Microglia–neuronal interactions involve various signals such as cytokines, neurotransmitters, and neuron–microglia inhibitory factors, such as fractalkine (CXCL1) and cluster of differentiation (CD200) [26, 27]. Microglial cells are also connected with astrocytes and oligodendrocytes, and these interactions might also cause neuropathic pain [28]. Dystrophic microglial cells contribute to substantial dystrophies in adjacent oligodendrocytes in the PFC (layer 5) in patients with schizophrenia with predominately negative symptoms and to a lesser extent in patients with schizophrenia with mainly positive symptoms but not in healthy control subjects [29]. Disruption of the balance between microglial cells and astrocytes (e.g., type-1/type-2 imbalance) causes a

dysregulation of the immune response in schizophrenia [30, 31]. T-helper 1 cells (TH-1) and certain macrophages/monocytes (M1) produce cytokines (IL-2, IL-12, IL-18, IFN- α , TNF- α) and this immune response is called type-1 immune response. T-helper 2 cells (TH-2) and certain macrophages/monocytes (M2) create cytokines (IL-4, IL-10, IL-13) and this immune response is termed type-2 immune response. Type-1 and type-2 cytokines irritate each other with a down-regulation in schizophrenia [30].

The various roles of microglial cells in neuropsychiatric disorders

Microglial cells play an important role in the pathology of neuropsychiatric disorders such as schizophrenia and major depressive disorder (MDD) [31–35]. Microglial cells are also involved in the cerebral cortex with autism spectrum disorders (ASDs), which are also regarded as neurodevelopmental disorders [36, 37]. Activated microglia and neuroinflammation are also pathological hallmarks of neurodegenerative diseases such as DAT and PD [38]. Original research on postmortem and PET studies demonstrating the presence or absence of microglial activation using different microglial markers in brain regions of interest, predominantly, in patients with schizophrenia, bipolar disorder, and affective disorders, respectively, is summarized in Table 1.

The role of microglial cells in schizophrenia

Glucocorticoid levels are increased during stress, and influence microglial response with pro- and anti-inflammatory activity [9]. Stress-induced release of glutamate from neurons results in the stimulation of microglial cells through the activation of N-methyl-D-aspartate receptors (NMDARs) by glucocorticoids [8, 9].

Microglial cells induce the loss of cortical gray matter in patients with schizophrenia by pruning synapses, phagocytosing stressed neurons, and preventing the release of neurotrophic factors such as BDNF [39].

In a systematic review by Trépanier et al. [40], many of the studies (11 of 22) reported an increase in the expression of microglial markers in the postmortem brains from patients with schizophrenia compared with those of control subjects. Moreover, a meta-analysis by van Kesteren et al. [41] revealed an increase in the number of microglia in specific brain areas, such as the temporal cortex, in postmortem brains of patients with schizophrenia compared with those of control subjects. Calprotectin is expressed in microglial cells and is considered a nonspecific marker of inflammation. Calprotectin expression is significantly increased in patients with schizophrenia compared with healthy control subjects [42]. The level of ionized calcium-binding adaptor

molecule 1 (IBA1), a marker showing specific immunostaining of resting and activated microglia, is increased in specific brain areas such as the amygdala, hippocampus, nucleus accumbens, and PFC in patients with schizophrenia [9, 43]. A lateralization of IBA1 immunopositive microglial cells was observed towards the right anterior midcingulate cortex in patients with schizophrenia and bipolar disorder compared with healthy control subjects [44]. A study by Bloomfield et al. [45] using translocator-protein positron emission tomography (TSPO PET) demonstrated that microglial activity is increased in total and frontal and temporal lobe gray matter in patients with schizophrenia and ultrahigh risk individuals compared with healthy control subjects. Nevertheless, an 18 kDa TSPO PET study revealed no increase in microglial activity in the dorsolateral PFC and hippocampus in first-episode psychosis patients compared with healthy control subjects [46]. Moreover, another TSPO PET study by Di Biase et al. [47] did not show any differences among individuals at risk for schizophrenia, patients with schizophrenia and healthy control subjects. A meta-analysis by Marques et al. [48] of TSPO PET studies and microglial activation exposed a moderate effect on gray matter relative to other brain tissue in schizophrenia when using binding potential as an outcome measure but no difference when using volume of distribution as an outcome measure. The TSPO PET study by Conen et al. [49] found no microglial activation in patients with recent onset and established schizophrenia compared with healthy control subjects in the ACC, PFC, parietal cortex, and brainstem, but significant changes in the thalamus and putamen.

Activated microglial cells are linked to the increased expression of peripheral benzodiazepine binding sites (PBBS). (R)-PK1195 is a specific ligand for the PBBS and combines with carbon-11 in PET studies in schizophrenia, which can be used as a novel PET biomarker of activated microglial cells in schizophrenia [50].

The discrepancies in findings related to microglia activation in schizophrenia obtained by PET- and postmortem studies may have been caused by effects of confounding factors (e.g., tissue quality and aging) and comorbid factors (e.g., use of antipsychotic medication, suicidal tendencies, smoking, or drug abuse) [24].

Human leukocyte antigen (HLA-DR) is a class II antigen, and different gene loci code for the alpha (α)- and beta (β)-chains. Other important genes, namely, TNF- α and tumor necrosis factor beta (TNF- β) are distributed throughout the HLA-complex [51]. Steiner et al. [52] (2008) found that the density of HLA-DR, which reacts with activated microglia, was increased in the PFCs of suicidal patients. Bayer et al. [53] reported that three late-onset out of 14 patients with schizophrenia, 1 out of 6 patients with affective disorders (AD), and four out of 8 patients with dementia of Alzheimer's type (DAT)

Table 1 Postmortem and PET studies demonstrating the presence or absence of microglial activation using different microglial markers in brain regions of interest in patients with schizophrenia, bipolar disorder and affective disorders

Study	Subjects	Methods	Brain regions	Results
Bayer et al. [53]	14 SZ, 8 AD 13 CTR,	Histology, HLA-DR	HPC, PFC	Activation of HLA-DR ↑
Radewicz et al. [54]	8 chronic SZ, 10 CTR (area 9), 7 chronic SZ, 6 CTR (area 22)	Histology, HLA-DR	DLPFC (Brodmann's area 9), STG (area 22), ACC (area 24)	Area 9 ↑, Area 22 ↑
Wierzb-Bobrowicz et al. [55]	9 SZ, 6 CTR	Histology, HLA-DR	Frontal and temporal cortices	HLA-DR ↑
Steiner et al. [57]	16 SZ 16 CTR	Histology, HLA-DR	DLPFC, ACC, MD	DLPFC ↔ ACC ↔, MD ↔, cerebral lateralization of amoeboid microglia in SZ ↓, ↑ ACC, ↑ MD in SZ, who committed suicide
Steiner et al. [52]	16 SZ	Histology, HLA-DR	DLPFC, ACC, MD, HPC	Significant differences in microglial cell densities ↔ among the groups; significant increases ↑ in DLPFC, ACC and MD in patients, who committed suicide
Doorduyn et al. [19]	14 AD 10 CTR 7 SZ	Pet with ¹¹ C-(R)-PK1195	Frontal, occipital, temporal, parietal lobes, basal ganglia, thalamus, HPC, midbrain, cerebellum, pons	Binding of ¹¹ C-(R)-PK1195 ↑ in the HPC in SZ
Busse et al. [59]	8 CTR 17 SZ	Histology, CD3 + T-lymphocytes, CD20 + B-lymphocytes, HLA-DR + microglia	Posterior HPC	CD3 +, CD20 + ↑ in residual SZ versus paranoid SZ, HLA-DR ↑ in paranoid SZ versus residual SZ
Fillman et al. [58]	11 CTR 37 SZ	Histology, HLA-DR	DLPFC	Density in the white matter ↑ in SZ, density in gray matter ↔ in SZ
Kenk et al. [188]	37 CTR 16 SZ	PET with TSPO	Gray matter: striatum, HPC, PFC, DLPFC, TC, white matter: CC, CING, SLF, PLIC	Significant difference in neuroinflammation ↔
Najjar and Pearlman [17]	27 CTR 15 studies: 350 SZ, 49 BD, 37 MDD, 10 AD, 346 CTR	Systematic review, neuropathological and neuroimaging studies	Gray and white matter	Microglial activation in the white matter in SZ,
Busse et al. [175]	12 AD (6 MDD, 6 BD)	Histology, microglial QUIN	HPC (CA1, CA2/3 areas)	QUIN ↓ in the right CA1 area in MDD and BD
Bloomfield et al. [45]	14 ultra-high risk SZ	PET with TSPO	Total gray matter, volume, frontal and temporal lobe gray matter	Microglial activity ↑ in ultra-high risk SZ
	14 CTR			

Table 1 (continued)

Study	Subjects	Methods	Brain regions	Results
Di Biase et al. [47]	10 ultra-high risk SZ 18 patients recently diagnosed with SZ 15 chronic SZ 27 CTR 18 SZ	PET with TSPO	Dorsal frontal, orbital frontal, medial temporal cortex, ACC	Significant difference in TSPO expression ↔, microglial activation ↔
Brisch et al. [104]	15 MDD 12 BD 22 CTR 14 first-episode SZ	Histology, HLA-DR	DR	Microglial reaction ↓ in nonsuicidal patients compared with suicidal patients and CTR
Hafizi et al. [46]	20 CTR 783SZ	PET with TSPO	DLPFC, HPC, medial prefrontal and temporal cortices, total gray matter	Significant difference in TSPO expression ↔, microglial activation ↔
van Kesteren et al. [41]	762 CTR 20 ROS	Meta-analysis, histology, various microglial markers	TC, PFC, OC, diencephalon, basal ganglia, ACC	Significant increase in microglial cell density ↑
Conen et al. [49]	21 ES 21CTR 17 SZ	PET with TSPO	ACC, PFC, PC, putamen, thalamus, and brainstem	Microglial activation ↔ in ACC, PFC, PC, and brainstem; microglial activation ↓ in thalamus and brainstem in ROS and ES
Petrasch-Parwez et al. [44]	13 BD 17 CTR	Histology, Iba-1	aMC	No significant differences in IBA1 microglial densities between SZ, BD, and controls. A lateralization towards the right anterior midcingulate cortex was observed in SZ, BD, not in controls

Abbreviations: ACC anterior cingulate cortex, AD patients with affective disorders, aMC anterior midcingulate cortex, BD patients with bipolar disorder, CC corpus callosum, CING cingulum, CTR healthy control subjects, DAT patients with dementia of Alzheimer's type, DLPFC dorsolateral prefrontal cortex, DR dorsal raphe nucleus, ES patients with established schizophrenia, HPC hippocampus, HLA-DR human leukocyte antigen, MD mediodorsal thalamus, MDD patients with major depressive disorder, OC occipital cortex, PC parietal cortex, PET positron emission tomography, PFC prefrontal cortex, PLIC posterior limb of the internal capsule, QUIN quinolinic acid, ROS patients with recent onset schizophrenia, SLF superior longitudinal fasciculus, TSPO translocator protein, TC temporal cortex

Arrows: ↑ increase, ↔ no alteration ↓ decrease

exhibited increased HLA-DR immunostaining in the frontal cortex and hippocampus. Radewicz et al. [54] observed an increase in HLA-DR density in the frontal and temporal cortices in patients with schizophrenia compared with control subjects, and Wierzbica-Bobrowicz et al. [55] detected a greater expression of HLA-DR in the anterior cingulate and temporal cortices in patients with schizophrenia compared with control subjects. Additionally, Krause et al. [56] found that the number of HLA-DR immunopositive cells was increased in patients with schizophrenia compared with healthy control subjects. Steiner et al. [57] reported decreased cerebral lateralization of HLA-DR in patients with schizophrenia compared with healthy control subjects. Fillman et al. [58] found an increased HLA-DR in the dorsolateral prefrontal cortex in patients with schizophrenia compared with control subjects. A study by Busse et al. [59] also demonstrated that HLA-DR immunostaining was increased in the posterior hippocampus in patients with paranoid schizophrenia compared with patients with residual schizophrenia and healthy control subjects. Moreover, patients with residual schizophrenia showed a greater concentration of CD3⁺ and CD20⁺ lymphocytes in the posterior hippocampus [59]. No significant differences in microglial density using the microglial marker IBA1 in the medial frontal gyrus in patients with bipolar disorder compared with healthy control subjects have been demonstrated [60]. A correlation has also been found between HLA-DR and alcoholism or even alcoholism withdrawal [61–64].

These discrepancies in the results of postmortem studies could be explained by methodological differences such as the immunohistochemical markers used, the methods used to count microglial cells, the brain regions studied, the cortical layers in which the expression of the markers was measured, and technical issues such as the postmortem interval and brain pH. Other confounding variables including age differences, sex, age at death, cause of death, clinical variables, illness history and duration, medication history, diagnosis method and inclusion and exclusion criteria also exist [14, 65]. Recently, microglial activation rather than microglial density has been investigated [65]. Microglial activation reflects innate immune memory (history of life events) including prenatal and perinatal influences and genetic background [14, 66]. Furthermore, the use of a single microglial marker (such as HLA-DR) for phenotypic identification is problematic, since detailed knowledge of the time course of death is crucial [14]. Multiple markers must be used to identify the functional state [14]. The association between microglial activation and reduced synaptic plasticity, and neuropil alterations and reduced neuroplasticity needs to be studied in a multimodal manner combining imaging studies and postmortem

brain analyses of patients with schizophrenia with various immunological markers [14].

Research conducted by Goudriaan et al. [67] has demonstrated that genes that are involved in microglial activation do not contribute genetically to schizophrenia susceptibility. However, there is an association between the HLA-DRB1 gene and schizophrenia in the human population [68–70].

Maternal infection during pregnancy is known to be an environmental risk factor for the development of neuropsychiatric disorders such as schizophrenia and ASDs in offspring. The causative role of immunological processes that interfere with brain development in schizophrenia have been discussed [71–73]. Sex differences in processes related to microglial cells exist and might contribute to the sex differences in neuropsychiatric disorders such as schizophrenia [74, 75] and in a neonatal rat animal model of early-life infection [76].

Although Smolders et al. [77] demonstrated that a single or double injection of poly(I:C) in pregnant mice does not result in a fetal microglial activation during mid- or late embryonic development, other research groups have found an involvement of microglial cells in maternal immune activation. In an animal study using pregnant mice injected with poly(I:C) on gestational day 9 as an animal model of schizophrenia, the number and shape of microglia in several brain regions were assessed in the offspring on postnatal day (PND) 30 using immunofluorescence with an anti-IBA1 antibody [78]. There were more microglial cells in the hippocampus and striatum in the offspring of poly(I:C)-injected mice than in the offspring of vehicle-treated mice. Additionally, these microglial cells were morphologically characterized by reduced arborization, which is indicative of a greater activation. This is supported by studies showing that microglial cells from control animals show greater microglial arborization, which is indicative for a noninflammatory state of microglia than those from offspring from poly(I:C) treated mice, which were characterized by no or few branched cells, indicating an activated and inflammatory or phagocytic microglial state [79, 80]. Furthermore, in a pilot study comparing the offspring of poly(I:C) treated mice on PND10 and PND100, the mouse pups displayed no microglial alterations in response to prenatal exposure to poly(I:C), whereas adolescent mice showed a significant increase in the number of microglial cells in the frontal association cortex, ventral striatum, dentate gyrus of the hippocampus and secondary visual cortex. In contrast, in adult mice (PND100), immunological activation was only observed in the frontal association cortex [81]. Prenatal poly(I:C) treatment in mice prevents an increase in the number of microglial cells in the cortex [82]. These studies support the hypothesis that maternal infection during embryogenesis contributes to an increase in the number of microglial cells in offspring, which in subsequent periods

of life results in decreases in dopamine and the stimulation of high-affinity dopamine receptors (involving DRD3 and DRD5). These alterations in dopamine levels may, therefore, cause a neuroinflammatory response, which contributes to the pathogenesis of schizophrenia [83].

The involvement of microglial cells in depression and suicide

Suicide is a major public health problem [84] with a prevalence of 5.92% and is supported by ongoing neurobiological research [85], suicide behavior is listed as an independent mental disorder in the fifth edition of the Diagnostic Statistical Manual of Mental Disorders-DSM V [86]. The dorsal raphe nucleus (DRN) comprises the caudal and rostral subregions, which are further divided into the dorsal, ventral, interfascicular, ventrolateral, and caudal subregions [87]. The DRN sends serotonergic projections to the striatum, frontal cortex, thalamus, lateral septal nuclei, nucleus accumbens, habenular complex, and hippocampus [88–93]. The dorsal raphe nucleus is implicated in the pathology of schizophrenia, major depression, suicidal behavior [94–104] and even alcoholism [105]. Disruption of serotonergic functions is implicated in the pathophysiology of stress, MDD, and suicide [106–110], while serotonin deficiency contributes to suicidal behavior and MDD [111–126]. Additionally, a link between smoking, suicide, and low serotonin levels has been demonstrated [127]. Nicotine-induced microglial activation in reward seeking brain regions such as nucleus accumbens and basolateral amygdala increases cocaine reinforcement in adolescent rats but not adult rats [128].

Microglial cell activation correlates with transcriptional activity in the DRN neurons in the non suicidal depressed subgroup [104]. In addition, microglial activation induced by interferon-alpha (IFN- α) is associated with depressive-like behavior and the expression of proinflammatory surface markers such as major histocompatibility complex-II (MHC-II) and CD86 in a mouse model of immune-mediated depression, demonstrating that microglia are polarized towards the M1-phenotype [129]. A study by Steiner et al. [52] demonstrated that microglial density is increased in the dorsolateral prefrontal cortex, anterior cingulate cortex, and mediodorsal thalamus in suicidal patients with schizophrenia and suicidal patients with depression compared with healthy control subjects. Schnieder et al. [130] also observed that microglial density is augmented in the white matter of the PFC in suicidal patients with schizophrenia and depression compared with nonsuicidal subjects. Various studies (e.g., postmortem analysis, PET imaging studies, and analysis of the cerebrospinal fluid and serum/plasma of patients) have provided evidence for a role of microglial cells in suicide, which can be used for a new therapeutic target for suicide prevention [131]. Adolescence is a significant period for

the development of neuropsychiatric diseases. During this period microglial synaptic pruning occurs in the PFC and contributes to pathological alterations that are evident in schizophrenia [132]. An increase in the number of microglial cells leads to depression through the neuroinflammatory pathway. Activated microglia are also involved in post-stroke depression [133]. Additionally, a decrease in the number of microglial cells causes depression by inducing neuronal degeneration, leading to inhibition of neurogenesis in the hippocampus [134].

Most studies have demonstrated an association between suicidal behavior and alterations in IL-2, IL-6, IL-8, TNF- α and VEGF levels [135]. Elevation of IL-6 levels is one of the most prominent findings in patients exhibiting suicidal behavior. However, future research should focus on the association between cytokines, suicidal behavior, and depression [136, 137]. Moreover, the number of primed microglial cells is increased in the white matter of the dorsal anterior cingulate cortex in depressed suicidal patients compared with healthy control subjects [138].

In an animal model of depression, prenatal stress may be linked to increased activity of microglial cells in the hippocampus and frontal cortex and depression-like disturbances [139, 140]. The hippocampus, especially the CA1 region, is characterized by an elevated number of microglial cells, which are activated by stress [7, 141]. The adult microglial transcription factor MafB is involved in the expression of the adult gene program during inflammatory responses under stress as demonstrated by experiments with knockout mice [142]. Another brain region that is affected by microglial cell activation is the postnatal amygdala, which is involved in emotion, as maternal immune activation causes the activation of microglial cells in the amygdala [143].

The neuroprotective role of microglial cells has been extensively discussed [144–147]. For example, microglial cells exert neuroprotective effects through anti-inflammatory responses in depression [148, 149] and schizophrenia [150]. Microglia also have neuroprotective effects after ischemia [151]. On one hand, microglial cells are responsible for maintaining neuronal structure and plasticity via clearance of cellular debris, neurogenesis, anti-inflammatory responses, and synaptic pruning [149]. On the other hand, neurons play a vital role in the functions of microglial cells by maintaining inflammatory gene production, the oxidative stress response, and synaptic pruning [149, 152]. Therefore, if the balance between microglial cells and neurons is disturbed, neuropsychiatric disorders may result [149, 153–155]. Microglial cells have also been demonstrated to play a neurodegenerative role [156]. For example, a disturbance of the interplay between microglial cells and cytokines may cause neurodegenerative processes in neuropsychiatric diseases such as schizophrenia [34]. Peripheral blood mononuclear cells were combined

with neural progenitor cells and pluripotent stem cells to produce microglia-like cells, which express specific markers and function as microglial cells [157]. Microglial cells and monocytes interact with each other to regulate the expression of genes, cytokines, and surface markers through the blood–brain barrier and neuronal networks, and these interactions might be useful for the developing peripheral biomarkers for psychiatric disorders [157].

Prenatal immune challenge by poly(I:C) causes microglial cell alterations in different structures such as microglial clusters, including changes in morphology, the arborization index and the number of dark microglia in the dentate gyrus of the hippocampus, mainly in male mice. These changes are features of cellular stress [158]. Hinwood et al. [159] observed that microglia facilitate the effects of stress on neurons in the medial PFC. Stress exposure correlates with increased microglial activation in the PFC but not antigen presentation [159]. Similarly, microglia are responsible for the impact of stress on neuronal branching in the PFC. Treatment with minocycline eliminates these effects [160]. In patients with depression, repeated stress exposure can lead to microglial inflammation or even suicidal behavior [161]. It has been shown that increased apoptosis causes a reduction in microglial cell number [26].

In the CNS, the kynurenine (KYN) pathway is affected by astrocytes, microglial cells, and macrophages. KYN can be converted to kynurenic acid or quinolinic acid [162–164]. Abnormal KYN levels are implicated in neurodevelopmental disorders through the proliferation, specification, and differentiation of radial glial cells [165] and the pathophysiology of schizophrenia and affective disorders [166–171]. By exploring the inflammatory process and hence the kynurenine pathway, novel therapeutic targets and biomarkers for suicidal depressed patients [172] and patients with schizophrenia [173] might be developed. For example, Steiner et al. [174] reported an increase in the level of quinolinic acid, which is produced by microglial cells, in subregions of the anterior cingulate gyrus in depressed patients. Furthermore, investigations by Busse et al. [59, 175] revealed that quinolinic acid levels are decreased in the hippocampus of suicidal depressed patients compared with healthy control subjects and in patients with paranoid schizophrenia compared with patients with residual schizophrenia [176].

Early postnatal lipopolysaccharide (LPS) administration in a rat animal model of early immune stimulation causes a reduction in hippocampal volume, activation of the KYN pathway of tryptophan metabolism, astrogliosis, and a decrease in tyrosine hydroxylase levels in the substantia nigra demonstrating a link between early immune stimulation and neuropsychiatric disorders [177]. LPS-induced maternal immune activation causes an increase in cytokine levels in the fetal brain, which results in elevation

of microglial activation, astrogliosis and cytoarchitectural changes in the postnatal amygdala [143].

The effects of antidepressants, antipsychotics, and electroconvulsive therapy (ECT) on microglial cells

The long-term influences of antidepressants and antipsychotics on microglial cells in various brain regions should not be ignored, as they might offer new options for drug treatment. Therefore, we will discuss the effects of antidepressants, antipsychotics, and electroconvulsive therapy on microglial cells. Typical and atypical antipsychotics suppress microglial activity by inhibiting the secretion of cytokines [178]. Specific interleukins (IL-10, IL-18, and TGF- α) are state markers and increase during acute phases of schizophrenia, but are normalized with antipsychotic medication. Both IL-12, IL-2, interferon- α , and TNF- α are characterized as trait markers and continue to be high during acute phases independent of antipsychotic medication [179]. Typical and atypical antipsychotics influence the intracellular Ca²⁺ mobilization and signaling in the endoplasmic reticulum (ER) of microglial cells in different ways. Thus, these processes might be targets for antipsychotic therapy [180].

Specifically, inhibitors of microglial activity such as minocycline are regarded as potential antipsychotic drugs [181–183]. Riazi et al. [184] showed that minocycline decreased the effects of inflammation and abolished the effects of peripheral inflammation in the hippocampi of rats. For example, minocycline selectively inhibits the expression of M1-polarized microglia in vivo and in vitro in amyotrophic lateral sclerosis (ALS) [185].

Cotel et al. [186] reported that chronic antipsychotic use increases microglial activation and proliferation in the rat brain. Cotel et al. [186] revealed that antipsychotic treatment not only reduced the gray matter volume in the hippocampus, anterior cingulate cortex, corpus striatum, and secondary somatosensory cortex but also increased the density of microglial cells in the hippocampus and somatosensory cortex but surprisingly not in the anterior cingulate cortex. The reason why the microglial density was not increased in the anterior cingulate cortex by chronic antipsychotic use requires further research. In rat experiments, clozapine was shown to increase microglial activation in the striatum and hippocampus, mainly the CA2 and CA3 regions [187]. In contrast, antipsychotics inhibit the release of proinflammatory cytokines and NO by microglial cells [188, 189]. In summary, microglial activity plays a role in the pathophysiology of schizophrenia and anti-inflammatory drugs such as minocycline might be useful for targeting the increased microglial activation in schizophrenia and thus be new treatment options [190, 191]. Regulation of microglial activation

site-specifically and function-specifically might be a novel target for the development of new drugs for patients with schizophrenia [192, 193].

For example, studying single-cell screening from blood serum taken from drug-naïve patients with schizophrenia the phenotypic modification of microglial cell signaling in vitro was demonstrated [193]. Overactivated epitopes in blood sera of patients with schizophrenia can be ameliorated by microglial proinflammatory activation inhibitors such as minocycline to improve negative symptoms in schizophrenia [194]. Antagonists of the ATP-gated P2X7 receptor, which is a microglial receptor found in the CNS, might be used as monotherapies or adjunct therapies for the treatment of schizophrenia, bipolar disorder or depression [194]. Activated microglia can be used as biomarkers for predicting the course in bipolar disorder and pharmacological responses [195]. Stertz et al. [196] argued that the inflammatory changes that occur in bipolar disorder patients are associated with disease progression rather than causative. Additionally, the selective serotonin reuptake inhibitor (SSRI) fluoxetine protects neurons against the neurotoxic effects of microglial cells [197]. SSRIs increase TNF- α levels, and when used at low concentrations for a long period of time, SSRIs have slight proinflammatory effect [198]. In contrast, Horikawa et al. [199] reported that SSRIs inhibit the production of NO and TNF- α in microglial cells. Additionally, the SSRI fluoxetine and its metabolite norfluoxetine reduce the viability of microglia and increase the expression of the apoptotic marker cleaved-caspase 3 in microglial cells [200]. Depression is also considered a microglial disease and drugs that either suppress or stimulate microglial cells are regarded as novel drugs in the treatment of depression [147]. Various antidepressants and antipsychotics overturn microglial activation. Antidepressants inhibit the release of proinflammatory cytokines from activated microglial cells [201]. The antidepressant drug venlafaxine can partially protect the viability of microglial cells [202]. Antidepressants cause microglial cell disturbances in the dorsal raphe nucleus [104]. A positive correlation between antidepressants and microglial density in non-suicidal depressed patients in the dorsal raphe nucleus has been reported [104] (Figs. 1 and 2).

Glutamate has neurotoxic effects on activated microglial cells [203]. For example, an inhibition of glutamine synthetase increases the activity of activated microglial cells [204]. However, a general blockade of microglial cells as a therapeutic intervention might have risky effects, since glutamate and activated microglial cells are involved in dendritic apoptosis. An excessive synaptic pruning during late adolescence and early adulthood might cause severe negative symptoms and a cognitive decline in patients with schizophrenia [205, 206].

Additionally, the use of induced microglial cells (iMG) from the peripheral blood [207] and the use of

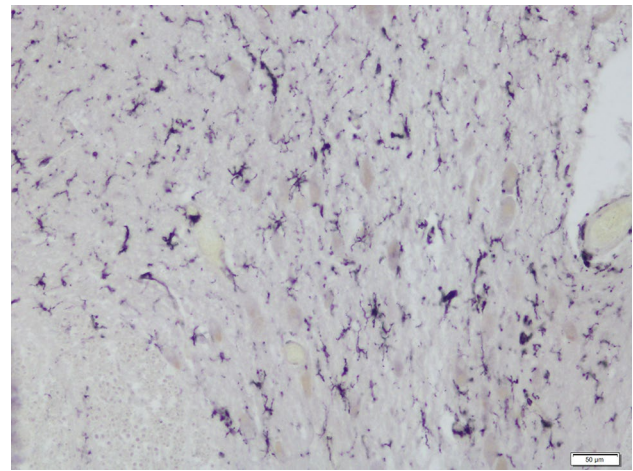


Fig. 1 Microglial reaction in the DRN (caudal subdivision) in suicidal depressed patient as shown by HLA-DR antigen, scale bar 50 μ m

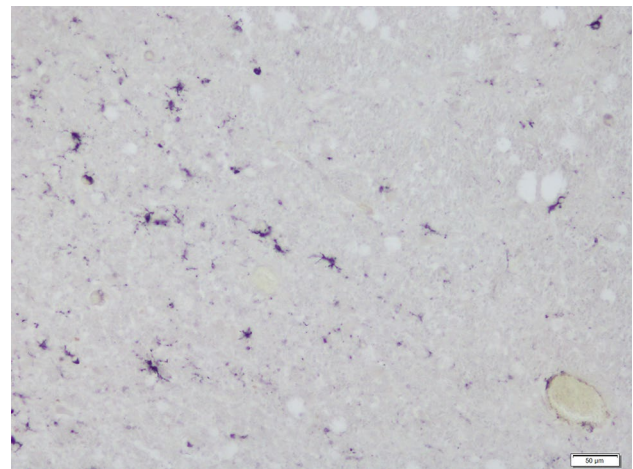


Fig. 2 Microglial reaction in the DRN (caudal subdivision) in non-suicidal depressed patient as shown by HLA-DR antigen, scale bar 50 μ m

human-induced pluripotent stem cells for microglial cell culture methods [208] might represent novel directions for psychopharmacological screening or schizophrenia modeling. Cannabis and cannabidiol reduce the oligodendrocyte, astrocyte, and microglial activity in schizophrenia [209, 210]. For example, activated cannabinoid type -2 (CB2) receptors located on microglial cells decrease the effects of activated microglial cells such as neuroinflammation and synaptic pruning [211]. ECT either reduces microglial cell density in the hippocampus [212] or activates microglial cells [213]. It has been demonstrated that microglial cell activation in the hippocampus is inhibited by ECT in a rat model [214].

Evolutionary role of microglial cells in neuropsychiatric disorders

Microglia probably arose during the Cambrian period (500–540 Ma ago) with the propagation of multicellular animals. Microglia have been evolutionarily conserved in both invertebrates and vertebrates [215–217]. It has been argued that early microglia contributed to the protection of the CNS in emerging vertebrates, and informed axonal coverage, thus increasing action potential transmission and speed and thereby improving CNS efficiency [218].

It is worth noting that human neuronal density is much lower than that of chimpanzees and other apes and primates [219]. This means a greater volume of glial cells, likely also microglia in proportion to neurons. Such an arrangement allows for greater role of glial cells in processing of information in the human brain. It has been shown that working memory is different in humans than in chimpanzees. In humans, there is evidence that genes of abnormal spindle-like microcephaly-associated protein (ASPM), neuronal cell adhesion molecule (NRCAM) and sialic acid-binding Ig like lectin 11 (SIGLEC11) are involved in neural proliferation, promotion of neural connections, and glial expression, respectively [220, 221]. There is a difference in ASPM and SIGLEC-11 in the human lineage expression compared to chimpanzee lineage. SIGLEC-11 is a human-specific microglial gene that is not found in other primates [222]. A study by Wang et al. [223] using human brain tissue demonstrated that human SIGLEC-11 ectopically expressed by a lentiviral vector system in cultured murine microglial cells interacts with polysialic acid (PSA) residues on neurons, reduces LPS-induced gene transcription of proinflammatory mediators, impairs phagocytosis and alleviates microglial neurotoxicity.

The pathogen host defence (PATHOS-D) theory suggests that the immune responses that occur in MDD are proinflammatory and that specific risk alleles for MDD generate a proinflammatory response, which is a driving force in human evolution [224]. Divergence from microglial stability due to inflammatory conditions that trigger microglial activity (e.g. infections, neurodegenerative diseases, stress, brain trauma) are risk factors for depression [147].

It should be noted that during the last 2 million years there have been notable changes in the neurohormonal regulation of the human brain due to self-amplifying feedback processes that contributed not only to the size and capacity of the modern human brain but also to its susceptibility to psychopathologies. *H. erectus* (1–8 Ma) exhibited a marked increase in physical activity levels

(PALs) and total energy expenditure (TEE) compared to australopithecine and the great ape lineages [225, 226]. Selective processes enhanced aerobic mechanisms and modified the thermoregulatory response (i.e., hairlessness in humans facilitated evaporative sweating and increased UV exposure) [227, 228] to optimize the bodies of archaic hominins for persistent hunting in hot environments, thereby increasing the production of growth factors, such as BDNF [229, 230]. Selection for characteristics important for persistent hunting and endurance is biased towards muscle composition changes and the development of more efficient energy systems involving peroxisome proliferator-activated receptor γ coactivator (PGC-1 α) and myocyte enhancer factor-2 (MEF2) gene regulation, which stimulate BDNF factor activity [227]. In archaic hominins, BDNF informed brain evolution in cortical and subcortical areas [231, 232]. BDNF also contributes to neurogenesis in the hippocampus, memory and learning. Synaptic plasticity is associated with prenatal brain development [233, 234] and neuroprotection, and ~80% of synaptic plasticity is dependent on exercise [235]. Furthermore, BDNF mediates microglial proliferation, promotes microglia and astrocyte activation and has potential to increase neuroinflammation [233]. It can be speculated that changes in thermoregulatory processes that were crucial for increasing the PALs of *Homo erectus* onwards may have come at an evolutionary cost, altering the expression of BDNF dependent microglia and consequentially that of proinflammatory CNS markers implicated in neuropsychiatric disorders [232]. Thus, there is evidence for a role of microglial cells in the evolution of neuropsychiatric disorders. Therefore, this view suggests that evolutionary psychiatry may become a novel and distinct area of research and doctrine in the field of biological psychiatry [236]. Due to the mismatch between prehistoric and modern environments, humans are becoming susceptible to inflammatory markers due to chronic stress. Evolutionary psychiatry offers an explanatory model for understanding modern psychiatric disorders and their evolutionary antecedents. Psychiatry has reached a critical point where it needs to develop therapeutic methods that integrate evolutionary thinking. This will be especially important in the advent of novel biotechnologies that may alter psychoneuroendocrinological mechanisms in ways that are beyond our current understanding.

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Declarations

Conflict of interest The authors declare that the research was conducted in absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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