Basic Concept of Microglia Biology and Neuroinflammation in Relation to Psychiatry

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Abstract The hypothesis that the neuroimmune system plays a role in the pathogenesis of different psychiatric disorders, including schizophrenia, depression, and bipolar disease, has attained increasing interest over the past years. Previously thought to have the sole purpose of protecting the central nervous system (CNS) from harmful stimuli, it is now known that the central immune system is critically involved in regulating physiological processes including neurodevelopment, synaptic plasticity, and circuit maintenance. Hence, alterations in microglia – the main immune cell of the CNS – and/or inflammatory factors do not unequivocally connote ongoing neuroinflammation or neuroinflammatory processes per se but rather might signify changes in brain homoeostasis. Despite this, psychiatric research tends to equate functional changes in microglia or alterations in other immune mediators with neuroinflammation. It is the main impetus of this chapter to overcome some of the current misconceptions and possible oversimplifications with respect to neuroinflammation and microglia activity in psychiatry. In order to do so, we will

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first provide an overview of the basic concepts of neuroinflammation and neuroinflammatory processes. We will then focus on microglia with respect to their ontogeny and immunological and non-immunological functions presenting novel insights on how microglia communicate with other cell types of the central nervous system to ensure proper brain functioning. And lastly, we will delineate the non-immunological functions of inflammatory cytokines in order to address the possible misconception of equating alterations in central cytokine levels with ongoing central inflammation. We hereby hope to help unravel the functional relevance of neuroimmune dysfunctions in psychiatric illnesses and provide future research directions in the field of psychoneuroimmunology.

Keywords Cytokines · Microglia · Microglia Sensome · Neuroinflammation · Psychiatry · Schizophrenia

1 Introduction

The neuroimmune hypothesis in schizophrenia has experienced a reappraisal. The possible role of inflammatory processes in psychiatric disorders, which in the context of the central nervous system (CNS) is frequently referred to as neuroinflammation, has attained increasing interest over the past decade (Graeber 2014; Masgrau et al. 2017). In particular, functional abnormalities in microglia – the resident, myeloid immune cell of the CNS – have attained increasing interest in psychiatry in general and schizophrenia in particular (Laskaris et al. 2016). Microglia act as the first line of defence against invading pathogens and play a key role in central infections and central inflammation (Kettenmann et al. 2011). Similar to monocytes/macrophages in the periphery, they constantly survey the CNS and rapidly respond to invading pathogens, changes in the physiological microenvironment, and CNS injury (Gomez-Nicola and Perry 2015; Hanisch and Kettenmann 2007). Upon activation by pathological insults, microglia can rapidly alter their transcriptional profiles and morphological appearance, increase their motility and phagocytic activity, and produce and secrete various factors that are integral for combating pathogens and/or initiating and promoting tissue remodelling and repair (Gomez-Nicola and Perry 2015; Graeber and Streit 1990; Lawson et al. 1992; Ransohoff and Engelhardt 2012; Svahn et al. 2014; Wolf et al. 2017). The functional diversity and dynamics of microglia are enormous, and their activation is heterogeneous and critically depends on the nature of the pathological insult (Gomez-Nicola and Perry 2015; Graeber and Streit 1990; Lawson et al. 1992; Ransohoff and Engelhardt 2012; Svahn et al. 2014; Wolf et al. 2017). However, while microglia play a key role in inflammatory processes, their activation does not equal neuroinflammation per se (Graeber 2014; Masgrau et al. 2017). In fact, microglia can detect, process, and respond to signals in an entirely noninflammatory way (Salter and Beggs 2014). Comparative to peripheral macrophages, microglia support normal tissue function, which in the case of the CNS is neuronal integrity (Hanisch and Kettenmann 2007; Kettenmann et al. 2011; Nimmerjahn et al. 2005; Ransohoff

and Perry 2009; Scheffel et al. 2012). We now know that microglia are involved in the regulation of neuronal development, synaptic plasticity, and circuit maintenance (Arnold and Betsholtz 2013; Bilimoria and Stevens 2015; Reemst et al. 2016; Salter and Beggs 2014). As discussed in detail below, there is substantial commonality in the molecular signalling cascades used by microglia to exert its different functions. Thus, alterations in microglia and inflammatory factors do not unequivocally convey ongoing neuroinflammation or neuroinflammatory processes but might instead signify changes in brain homoeostasis (Estes and McAllister 2014; Reemst et al. 2016; Salter and Beggs 2014; Thion and Garel 2017). These novel findings critically challenge the concept that disorders involving changes in microglia or inflammatory mediators are de facto neuroinflammatory disorders (Estes and McAllister 2014; Salter and Beggs 2014). Despite this, psychiatric research tends to equate changes in microglia activity with neuroinflammation (Biesmans et al. 2013; Brites and Fernandes 2015; Doorduin et al. 2009; Gracia-Rubio et al. 2016; Haarman et al. 2014, 2016; Kenk et al. 2015; Monji et al. 2013; Na et al. 2014; Najjar and Pearlman 2015; Nakatomi et al. 2014; Setiawan et al. 2015; Suridjan et al. 2014). Such oversimplifications could obscure the functional complexity of immune cells and molecules in physiological brain processes beyond that of their classically defined roles in inflammation resulting in possible misconceptions of disease aetiology.

In the spirit of John Maynard Keynes: 'The difficulty lies not in the new ideas, but in escaping the old ones'. The main incentive for writing this chapter was to overcome some of the current misconceptions and oversimplifications with respect to neuroinflammation and microglia activity in psychiatry. In the first sections, we will provide an overview of the basic concepts of neuroinflammation and microglia. We will then present key immunological and non-immunological functions of microglia and inflammatory mediators in order to increase the awareness of the complexity and difficulty to interpret changes in microglia and immune mediators in psychiatric disorders.

2 Basic Concept of Neuroinflammation and Neuroinflammatory Processes in Relation to Psychiatry

Associations between psychiatric diseases and immune system dysfunctions have been postulated more than 100 years ago (Kraepelin 1890; Menninger 1919) and have remained a matter of discussion ever since. With the reconceptualization of the 'immune privilege' of the CNS, the field of psychoimmunology has experienced a reappraisal. Advances in the fields of immunology and genetics, as well as the increasing understanding of how immunological processes can influence brain development and functions (Reemst et al. 2016; Thion and Garel 2017), have further contributed to the growing interest and recognition of immune system dysfunction in psychiatry. Indeed, abnormal neuroimmune functions have been implicated in the

aetiology and pathophysiology of a number of psychiatric disorders, including depression (Dantzer et al. 2008; Du Preez et al. 2016; Miller and Raison 2016; Muller and Schwarz 2007), schizophrenia (Horvath and Mirnics 2014; Khandaker et al. 2015; Muller et al. 2000; Yolken and Torrey 2008), autism spectrum disorders (Ashwood et al. 2006; Estes and McAllister 2015; Meltzer and Van de Water 2017), and bipolar disorder (Isgren et al. 2017; Wang and Miller 2017; Watkins et al. 2014).

The possible role of aberrant immune functions involving altered inflammatory and neuroinflammatory processes is currently among the timeliest topics in psychiatry. In this field, however, immunological changes that are being revealed in the CNS are frequently (and often misleadingly) referred to as neuroinflammation (Graeber 2014; Masgrau et al. 2017). The extent to which the brain is considered to be 'inflamed' is typically evaluated against the background of altered expression of secreted inflammatory mediators (including cytokines and chemokines) together with numerical, morphological, and/or functional abnormalities of astrocytes and microglia (Graeber 2014; Masgrau et al. 2017).

The word inflammation was coined by the ancients and is derived from the Latin word *inflammare* ('to set on fire') (Scott et al. 2004). The Roman Celsus is considered the first to have described the four cardinal signs of inflammation more than 2,000 years ago: rubor et tumor cum calore et dolore (redness and swelling with heat and pain) (Rocha e Silva 1978). In the late nineteenth century, the German pathologist Rudolf Virchow added the fifth cardinal sign: loss of function (Scott et al. 2004). This early definition was based on the assumption that inflammation represents a purely pathological process, which was later revised to acknowledge that it encompasses concomitant beneficial effects on tissue healing. Hence, inflammation denotes a complex cascade of concurrent processes that cause both tissue damage and repair (Schwartz and Baruch 2014; Serhan and Savill 2005).

Today, inflammation is considered an integral part of the body's homoeostatic repair and defence mechanisms and engages physiological interactions between resident and recruited immune cells, soluble factors, and tissue-specific elements (Schwartz and Baruch 2014; Serhan and Savill 2005). Upon initiation and proper orchestration, it limits the spread of infection and/or tissue damage and is typically followed by a resolution phase. The latter ensures that the affected tissues are structurally and functionally restored and that the immunological components attain their original functional state (Schwartz and Baruch 2014; Serhan and Savill 2005).

In general, the processes of classical inflammation can occur in the CNS like in any other organ and show largely the same characteristics on the cellular and molecular level (Denes et al. 2010; Filiou et al. 2014; Graeber 2014; Masgrau et al. 2017; Schwartz and Baruch 2014). Illustrative examples of neurological conditions where this occurs are multiple sclerosis, stroke, traumatic brain injury, and CNS infections (Filiou et al. 2014; Graeber 2014; Masgrau et al. 2017). The immune-driven CNS responses underlying these pathologies have been the cornerstones of defining 'neuroinflammation' and involve (1) initiation of a local immune response by CNS-resident immune cells, (2) increased production of pro-inflammatory cytokines and chemokines, (3) additional recruitment of CNS-resident immune cells to the primary site of trauma or infection, (4) blood-brain barrier (BBB) leak and infiltration of blood-derived leucocytes into the brain

parenchyma, and (5) resolution of inflammation and tissue remodelling. Hence, the term 'neuroinflammation' was historically well defined and mirrored the hallmarks of classical inflammation in the periphery (Estes and McAllister 2014; Masgrau et al. 2017). Over the past decade, however, the term 'neuroinflammation' has been frequently used to describe isolated aspects of neuroinflammatory processes with no known causative insult or overt changes in the BBB integrity (Graeber 2014; Masgrau et al. 2017). This has led to the oversimplified assumption that a wide range of psychiatric and neurodegenerative disorders underlie neuroinflammatory dysfunctions. The increasing understanding of how microglia and inflammatory mediators exert regulatory functions in brain development and maturation independent of inflammation adds another level of complexity on how to interpret central immune dysfunction in these different disorders (Reemst et al. 2016; Thion and Garel 2017).

As suggested by Estes and McAllister (2014), we therefore propose that the denotation 'neuroinflammation' should only be applied when all five signs of pathological inflammation – increased cytokines and chemokines, activated microglia and astrocytes, disturbance in BBB integrity and blood leucocyte infiltration, degenerative tissue damage, and resolution of inflammation and tissue remodelling – are present. For alterations in isolated inflammatory mediators within the CNS, we suggest to refer to the terms 'changes in neuroinflammatory mediators or processes' or 'changes in microglia activity states' and specify them separately. Clarifying the term 'neuroinflammation' is warranted in order to prevent oversimplifications, which in turn could result in the false assumption that various psychiatric and neurodegenerative diseases involve the same or similar pathologies. Such oversimplifications may, in fact, impede scientific progress regarding the understanding of disease-specific aetiologies and, consequently, developing adequate interventions with maximal therapeutic benefits.

3 Microglia: Historical Perspective

Microglia were first described by the German psychiatrist and neuropathologist Franz Nissl in the late nineteenth century as 'Stäbchenzellen' (rod cells) that represent reactive glial elements with migratory, phagocytic, and proliferative potential (Ginhoux et al. 2013). During the same time, W. Ford Robertson introduced the term 'mesoglia', which attempted to denote phagocytic elements with mesodermal origin. In 1913, Santiago Ramón y Cajal introduced the classification of central elements as 'the first element' (neurons), 'the second element' (neuroglia, a term introduced by Rudolf Virchow, which comprise astrocytes and oligodendrocytes), and 'the third element of the nervous system' (cells with small round nuclei), whereby he too stated that cells of the latter were probable to have a mesodermal origin (Ginhoux et al. 2013; Ransohoff and Cardona 2010). In 1920, the Spanish neuroscientist, and student of Ramón y Cajal, Pio del Rio Hortega, coined the term 'microglia' (Perez-Cerda et al. 2015). del Rio Hortega's early observations and descriptions were of tremendous accuracy. He observed the invasion of amoeboid

microglia into the developing brain during early embryonic development and hypothesized that they originated from meningeal macrophages and/or peripheral monocytes penetrating the CNS (Ginhoux et al. 2013; Kettenmann et al. 2011). He also described that microglia change their appearance during brain maturation into ramified cells, with a small round soma and an intricate network of fine ramifications. Furthermore, he reported that in the mature brain, microglia are present throughout the entire brain parenchyma occupying defined, non-overlapping territories (Kettenmann et al. 2011). Upon pathological events, he observed that they were able to retract their processes, become amoeboid, and display migratory and phagocytic functions (Ginhoux et al. 2013; Kettenmann et al. 2011). Astonishingly, most of these early observations and interpretation from Rio Hortega largely hold true until today (Kettenmann et al. 2011).

4 Microglia: Ontogeny and General Facts

Although the ontogeny of microglia has been the subject of debates for decades, their origin – primitive yolk sac (YS) macrophages – was only fully established in 2010 (Ginhoux et al. 2010). By applying an inducible lineage-tracing model using the runt-related transcription factor 1 (Runx1) to label YS progenitors, including YS macrophages, Ginhoux et al. could show that adult microglia arise unequivocally from YS macrophages that invade the developing CNS at embryonic day (E) 9.5 through the bloodstream, where they proliferate in situ and are maintained throughout adulthood (Ginhoux et al. 2010, 2013; Salter and Stevens 2017). The lack of foetal monocyte contribution to the microglia progenitor pool could be explained by the inaccessibility of foetal monocytes to the developing brain, as embryonic tissue colonization of foetal monocytes starts at around E13.5, which coincides with the formation of the BBB (Daneman et al. 2010).

YS macrophages represent an independent lineage and arise before the development of other myeloid cells that differentiate from definitive haematopoietic stem cells (Hoeffel et al. 2015; Orkin and Zon 2008). In contrast to other macrophage populations, they have a unique development in the sense that they can bypass the monocyte stage (Hoeffel et al. 2015; Takahashi et al. 1989). Hence, although microglia may be considered to be similar to tissue-resident macrophages in peripheral tissues, they are the only 'myeloid' cells that are derived solely from yolk sac precursors under 'normal' conditions (Hoeffel et al. 2015; Sheng et al. 2015).

Recent genome-wide chromatin and expression profiling coupled with single-cell transcriptomic analyses throughout development revealed that microglia undergo three distinct developmental stages along with brain development: early, pre-, and adult microglia, which were shown to underlie distinct regulatory circuits (Matcovitch-Natan et al. 2016). Morphologically, microglia undergo maturational changes as well. While microglia during early brain development display an amoeboid cell morphology, they mature into ramified cells with numerous thin processes at around postnatal day 15 (Cunningham et al. 2013; Harry 2013; Salter and Beggs

2014). In a healthy mouse brain, depending on the region analysed, microglia account for 10–15% of all brain parenchymal cells (Gomez-Nicola and Perry 2015; Graeber and Streit 1990; Lawson et al. 1990; Ransohoff and Engelhardt 2012; Svahn et al. 2014; Wolf et al. 2017). In contrast to this, their density shows marked regional differences in the non-diseased adult human brain parenchyma, ranging from approximately 0.5 to 16% of all cells (Mittelbronn et al. 2001).

The unique ontogeny of microglia with no contribution of foetal monocytes suggests that microglia population persist in the brain parenchyma through self-renewal of resident microglia. Previous estimates based on [^{3}H]thymidine, 5-ethynyl-2′-deoxyuridine (EdU), or 5-bromo-2′-deoxyuridine (BrdU) incorporation suggested that 0.05–1.04% of microglia in adult healthy mice of different strains and 2.35% of microglia in the young adult healthy macaque were entering cell cycle each day (Lawson et al. 1992; Shankaran et al. 2007; Tonchev et al. 2003). A recent report in humans using C^{14} retrospective birth dating of microglia isolated from postmortem brains of adults born across six decades estimated that 0.08% of microglia entered cell cycle per day in the healthy human brain, confirming the slow rate in microglia renewal (Reu et al. 2017). However, more recent studies performed in mice challenged the assumption that microglia are long-lived cells with slow proliferation rates. Using a multicolour fluorescence fate mapping system approach, Tay et al. revealed that microglia displayed higher and heterogeneous turnover rates in different brain compartments that occurred in a context-dependent manner (Tay et al. 2017). Another recent report confirmed a high region-dependent turnover rate for murine microglia revealing that proliferation is temporally and spatially coupled to intrinsic apoptosis (Askew et al. 2017). In this study, on average 0.69% of the total microglial cells were estimated to be proliferating, suggesting that the whole population is renewed several times during a lifetime.

In the healthy brain, microglia form a near-regular three-dimensional lattice in which each microglial cell occupies a unique territory. For decades, ramified microglia have been mistakenly denoted as ‘resting’ cells. Recent studies, however, revealed ramified microglia to be the opposite of resting: They constantly scan the brain parenchyma for potential insults (Davalos et al. 2005; Hristovska and Pascual 2015; Nimmerjahn et al. 2005). Estimates suggest that microglia scan the entire brain volume within a few hours (Nimmerjahn et al. 2005). While scanning the brain, the fine microglial processes continuously contact neurons, axons, and dendritic spines (Salter and Stevens 2017; Sierra et al. 2013; Tremblay et al. 2011). Furthermore, process motility was shown to dramatically change in response to adenosine triphosphate (ATP), neuronal activity, and neurotransmitters, whereas the latter is partly indirectly mediated through ATP (Davalos et al. 2005; Dissing-Olesen et al. 2014; Eyo et al. 2014; Fontainhas et al. 2011; Li et al. 2012). Although microglia process motility and interaction with neuronal synaptic elements is an established phenomenon, the functional implications remain to be discovered.

5 Microglia: The CNS Immune Cell

Microglia represent the central immune cell with the potential to sense and initiate active immune defence in the CNS (Gomez-Nicola and Perry 2015; Graeber and Streit 1990; Ransohoff and Engelhardt 2012; Svahn et al. 2014; Wolf et al. 2017). They express numerous cell surface and intracellular receptors including pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) as well as damage-associated molecular patterns (DAMPs) (Kettenmann et al. 2011; Santoni et al. 2015) through which they can virtually sense any pathological event or changes in homoeostatic conditions and respond accordingly (Kettenmann et al. 2011; Ransohoff and Cardona 2010; Ransohoff and Perry 2009).

Upon sensing a pathological insult, microglia rapidly alter their morphological appearance and transcriptional programme in a context-dependent manner. In vivo two-photon microscopy studies revealed that upon brain injury, microglial processes rapidly and autonomously assemble on the site of injury without cell body movement, establishing a potential barrier and thereby protecting the surrounding, healthy tissue (Davalos et al. 2005; Hines et al. 2009; Szalay et al. 2016). This process assembly was shown to be mediated by ATP (released either by damaged cells or in a more regulated manner by astrocytes) and the microglia purinoreceptor $P2Y_{12}$ (Haynes et al. 2006). Subsequent to this immediate barrier formation, microglia are known to retract the processes adopting a more amoeboid-like morphology. These morphological changes were found to be associated with a downregulation of $P2Y_{12}$, a conversion of ATP to adenosine by microglia ectoenzymes CD73 and CD39, and an increase in expression of adenosine A2A receptors (Orr et al. 2009). At the end of the range of morphological changes upon 'activation', microglia display a rounded cell body with an increase in soma size and only sparse processes, which is termed 'amoeboid' (Kettenmann et al. 2011). Similar to peripheral immune responses, the density of microglia increases at the site of an insult in order to provide more immune cells to fight invading pathogens, as well as to assure the protection and restoration of tissue homoeostasis. Microglia can become motile and actively migrate to the sight of insult following chemotactic gradients as well as increase their density through local proliferation (Kettenmann et al. 2011). As tissue macrophages, microglia increase their phagocytic activity to engulf invading pathogens and toxic molecules as well as to promote and regulate tissue remodelling and repair by phagocytizing apoptotic cells and cellular debris (Kettenmann et al. 2011). During neuroinflammation, microglia can also act as antigen-presenting cells (APCs) to activate invading lymphocytes of the adaptive immune system (Kettenmann et al. 2011). Lastly, microglia produce and secrete various immune-mediating factors, including pro- and anti-inflammatory cytokines and chemokines, as well as neurotrophic factors, that are crucial for coordinating the combat against pathogens and/or initiating and promoting tissue remodelling and repair (Gomez-Nicola and Perry 2015; Graeber and Streit 1990; Kettenmann et al. 2011; Ransohoff and Cardona 2010; Ransohoff and Engelhardt 2012; Svahn et al. 2014; Wolf et al. 2017).

Descriptive studies of microglia morphology in a variety of different diseases and animal models suggested that their 'activation' pattern follows a linear range (Perry et al. 2010). This hypothesis, however, has been replaced by the macrophage-derived polarization terminology (Perry et al. 2010). This concept of activation was based on findings in peripheral macrophages where different stimuli could induce different activation states termed M1 (classically activated) and M2 (alternatively activated), whereby M2 phenotypes were further refined into M2a, M2b, and M2c (Martinez and Gordon 2014). The classically activated M1 macrophages are designated to specialize in pathogen elimination, whereas alternatively activated M2 macrophages are involved in tissue remodelling and repair (Geissmann et al. 2010; Mantovani et al. 2005). However, this schema of activation has several limitations (as explained by Martinez and Gordon 2014), which undermines the possibility of applying the M1/M2 framework to microglia (Ransohoff 2016). Despite this, there are numerous publications that employ M1/M2 terminology in order to characterize microglia 'activation' states.

We now know that the functional diversity and dynamics of microglia are enormous, and their activation is heterogeneous and critically dependent on the nature of the pathological insult (Gomez-Nicola and Perry 2015; Graeber and Streit 1990; Ransohoff and Engelhardt 2012; Svahn et al. 2014; Wolf et al. 2017). Thus, identifying the diverse phenotypes and functions they can adopt in response to an insult or in different diseases remains to be a major challenge. Novel technologies including two-photon imaging, whole-genome transcriptomic and epigenomic analysis with complementary bioinformatics and unbiased proteomics, and cytometry by time of flight (CyTOF; Fluidigm) have been able to shed light into the complex world of microglia and microglia 'activation' (Ransohoff 2016). Despite these major advances and exciting new insights, most of the research published today still relies on morphological analyses and measurements of specific cellular markers in order to identify microglia-specific phenotypes. While these measures can, to a certain extent, detect alterations in microglia activation states, they fail to adequately identify all the diverse phenotypes and functions that these cells can adopt (Gomez-Nicola and Perry 2015; Graeber and Streit 1990; Perry et al. 2010; Ransohoff 2016; Ransohoff and Engelhardt 2012; Svahn et al. 2014; Wolf et al. 2017).

6 Microglia Function: Beyond Central Immune Cell

For decades, microglia were regarded as the brain-resident immune cells having the sole purpose to sense and protect the brain from harmful stimuli. In the past years, however, the functional roles of microglia have been extended to non-immunological functions, including the regulation of neurogenesis, myelination, angiogenesis, and synaptic pruning (Arnold and Betsholtz 2013; Bilimoria and Stevens 2015; Reemst et al. 2016; Salter and Beggs 2014; Thion and Garel 2017). A large body of evidence accumulated suggest that microglia are critically involved in neurodevelopmental

processes throughout prenatal stages up to postnatal maturation of the CNS (Paolicelli and Ferretti 2017; Reemst et al. 2016).

During embryonic development, microglia were shown to regulate the size of the neural precursor cell (NPC) pool through phagocytosis of NPCs in the subventricular zone (SVZ) of the developing cerebral cortex (Cunningham et al. 2013). Besides controlling the neuronal progenitor cell pool, microglia were implicated in regulating the wiring of forebrain circuits during embryonic development (Squarzoni et al. 2014). In utero perturbations of microglia activity resulted in impaired outgrowth of dopaminergic axons in the forebrain and affected the laminar positioning of subsets of neocortical interneurons (Squarzoni et al. 2014). Furthermore, in utero microglia depletion resulted in defective fasciculation of the axonal tracts in the dorsal corpus callosum (Pont-Lezica et al. 2014).

In postnatal developmental periods, microglia were shown to continue regulating the NPC pool in the SVZ. Besides microglia-dependent regulation of NPC numbers through phagocytosis, microglia were shown to promote neurogenesis and oligodendrogenesis through the production and release of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and IFN-γ (Shigemoto-Mogami et al. 2014). Microglia were further shown to control developmental cell death in the hippocampus during early postnatal development in mice by means of phagocytosis of apoptotic neurons (Wakselman et al. 2008). Moreover, microglia were implicated to support the survival of layer V cortical neurons during postnatal development (Ueno et al. 2013).

Besides regulating survival and death, migration, and positioning, as well as axonal guidance of neurons, microglia are now known to actively participate in synaptic pruning in a complement-dependent manner (Schafer et al. 2012; Wu et al. 2015). The complement system is a major effector of the innate immune system and an adjuvant for the adaptive immunity (Parkin and Cohen 2001). It consists of numerous soluble and cell-surface proteins that can recognize endogenous and foreign materials (Mayilyan et al. 2008; Parkin and Cohen 2001). In the context of CNS circuit refinement, the complement system is critical for the tagging, recognition, and elimination of synapses (Orsini et al. 2014; Presumey et al. 2017; Stephan et al. 2012). As of today, microglia-dependent synaptic pruning has been best studied in the mouse retinogeniculate system. This system has proven to be an excellent model system for studying developmental CNS synapse elimination as it involves the removal of excess synapses in the dorsal lateral geniculate nucleus (dLGN) of the thalamus in an activity-dependent manner (Stephan et al. 2012; Stevens et al. 2007). The findings from these studies suggest that microglia-dependent pruning is mediated by the synaptic deposition of the complement component C1q, which initiates the proteolytic cascade of the complement system ultimately resulting in the deposition of the activated C3 fragment on synapses, which itself is recognized by the complement receptor 3 (CR3) expressed by microglia inducing phagocytosis (Schafer et al. 2012; Stevens et al. 2007). Intriguingly, this process is not random but has been shown to be activity-dependent, as microglia cells engulf weaker, less active synapses only and sparing the strong ones (Schafer et al. 2012).

Besides the complement system, fractalkine (CX3CL1) has been implicated to regulate microglia-dependent synaptic pruning (Arnoux and Audinat 2015; Paolicelli et al. 2011). CX3CL1 is produced by neurons and astrocytes and present in a membrane-bound ('do-not-eat-me' signal) or soluble ('find-me' signal) form and the ligand for the microglia-specific receptor CX3CR1 (Table 1). Findings in CX3CR1 knock-out mice demonstrated that the lack of fractalkine-mediated chemoattraction resulted in delayed recruitment of microglia and impaired synapse formation of pyramidal cells of the CA1 region of the hippocampus (Paolicelli et al. 2011), resulting in long-term alterations of hippocampal functional connectivity (Zhan et al. 2014), and the impaired functional development of thalamocortical synapses of the barrel cortex (Hoshiko et al. 2012).

Glia-dependent pruning of excess or weak synapses has been proposed to contribute to synapse elimination during two distinct phases of postnatal development: the first phase including the first 3 weeks after births in rodents and approximately the first 5 postnatal years in human infants (Johnson 2001; Neniskyte and Gross 2017) and a second phase spanning week 3–8 in rodent development, which represents adolescence in humans (Blakemore 2012; Konrad et al. 2013; Neniskyte and Gross 2017). During the first phase, sensory circuits along with circuits associated with cognition and behaviour are being refined (Johnson 2001; Neniskyte and Gross 2017). The second phase of refinement is crucial for the establishments of circuits involved in goal-directed behaviour, planning, and impulse control in associated brain regions such as the medial prefrontal cortex (mPFC) (Blakemore 2012; Konrad et al. 2013; Neniskyte and Gross 2017). In support of the notion that microglia-dependent synaptic pruning is involved in later postnatal development and maturation are recent findings where transient microglia depletion in mice at postnatal day 19 or 30 altered the development and fine-tuning of synapses necessary for proper learning and memory tasks (Parkhurst et al. 2013).

In the healthy adult brain, microglia have been primarily studied with regard to their role as immune cell of the CNS. However, the few studies assessing the non-immunological function of microglia have shown that microglia continue to participate in the regulation of the NPC pool in regions with adult neurogenesis (Sierra et al. 2010, 2014). The extent to which microglia regulate synaptic pruning and remodelling in the adult brain, on the other hand, remains ill defined. However, recent findings suggest that microglia are involved in regulation of behaviour. Temporal microglia depletion in the hippocampus of adult mice resulted in cognitive deficits and impaired social behaviour (Torres et al. 2016). Furthermore, microglia processes have been shown to make temporary contacts with elements of the neuropil, including dendritic spines and axonal terminals (Salter and Stevens 2017; Sierra et al. 2013; Tremblay 2011). Confocal and immuno-gold electron microscopy studies have identified both pre- and postsynaptic elements within microglia processes following such brief contacts with synapses, suggesting that microglia could actively participate in synaptic remodelling and pruning (Linnartz et al. 2012; Paolicelli et al. 2011; Tremblay et al. 2010).

Against this background, it becomes evident that the neuroimmune system, and microglia in particular, critically regulates proper neuronal development and

Table 1 Overview of the regulatory signals based on their response they evoke in microglia

Ligands/signals	Expression	Microglia receptor	Reference
'Do-not-eat-me'			
CD47 (integrin-associated protein)	Various cell types including neurons and myelin	Signal regulatory protein-alpha (SIRP-a)	Zhang et al. (2015)
Polysialic acid residues	Neuronal glycocalyx	Sialic acid-binding immunoglobulin-like lectins (SIGLECs)	Brown and Neher (2014), Claude et al. (2013), and Wang and Neumann (2010)
Membrane-bound fractalkine ligand (CX3CL1)	Neurons	CX3CR1	Brown and Neher (2014), Paolicelli et al. (2014), and Cardona et al. (2006)
'Find-me'/'help-me'			
Adenosine triphosphate (ATP) ('find-me')	Released by neurons and astrocytes	$P2Y_{12}$	Dissing-Olesen et al. (2014), Haynes et al. (2006), Hristovska and Pascual (2015), and Eyo et al. (2014)
Soluble CX3CL1 ('find-me')	Released by neurons	CX3CR1	Garton et al. (2001), Noda et al. (2011), Maciejewski-Lenoir et al. (1999), Liang et al. (2009), and Zhang et al. (2012)
Interleukin-34 (IL-34) (find-me/help-me)	Released by neurons	Colony-stimulating factor-1 receptor (CSFR-1)	Xing and Lo (2017), Mizuno et al. (2011), and Luo et al. (2013)
Fibroblast growth factor-2 (FGF-2) (find-me/help-me)	Released by neurons	Fibroblast growth factor-3 (FGFR3) (chemotaxis) FGFR1 (restorative microglia phenotype)	Noda et al. (2014) and Xing and Lo (2017)
'Eat-me'			
Phospholipid phosphatidylserine	Exposed on cell surface of neurons	Brain-specific angiogenesis inhibitor-1 (BAI-1)	Brown and Neher (2014), Wakatsuki and Araki (2017), Marker et al. (2012), and Mazaheri et al. (2014)
Opsonin (milk fat globule factor-E8 (MFG-E8)-tagged phospholipid phosphatidylserine	Released by microglia and astrocytes	Vitronectin receptors (VNRs)	Cardona et al. (2006), Fricker et al. (2012), and Neniskyte and Brown (2013)
Membrane debris	Apoptotic cells	Triggering receptor expressed on myeloid cells-2 (TREM2)	Fu et al. (2014) and Takahashi et al. (2005)
Complement component C1q-tagged glycoproteins	Neuronal surface	Complement receptor 3 (CR3)	Schafer et al. (2012), Linnartz et al. (2012), Stephan et al. (2012), and Brown and Neher (2014)

refinement of brain circuitry during embryonic and postnatal development and possibly as well in the adult brain (Arnold and Betsholtz 2013; Bilimoria and Stevens 2015; Reemst et al. 2016; Thion and Garel 2017; Wu et al. 2015). It is therefore conceivable that alterations in the neuroimmune system could impact neurodevelopment and therefore play an important role in the aetiology of neurodevelopmental psychiatric disorders. To what extent dysfunctions in the neuroimmune system and microglia contribute to the pathogenesis of neurodevelopmental disorders, however, warrants further examination.

7 The Microglia 'Sensome'

A crucial prerequisite for the functions of microglia is its proper communication with CNS cells, in particular neurons. Diverse microglia receptors have been identified that recognize and respond to specific neuronal ligands (both soluble and membrane-bound). The set of receptors expressed by microglia in order to enable them to sense brain environment and neuronal states and respond accordingly is highly complex and can be referred to as the 'microglia sensome' (Brown and Neher 2014; Diaz-Aparicio et al. 2016). The microglia sensome is not stable but rather has been shown to adapt to changing brain environments such as present during the development of the CNS (Hickman et al. 2013; Matcovitch-Natan et al. 2016). The regulatory signals (ligands), on the other hand, can be classified based on the response they evoke in microglia (Table 1). These include 'do-not-eat-me' signals presented by healthy neurons to prevent microglial phagocytosis, 'find-me'/'help-me' signals from neurons that induce microglial chemotaxis and adhesion to neuronal components (e.g. dendritic spines), and 'eat-me' signals that initiate phagocytosis (Brown and Neher 2014; Sierra et al. 2013).

Phagocytosis is not only important for the physiological maintenance of the CNS, but it is also a crucial mechanism during inflammation to engulf invading pathogens, injured neurons, and cellular debris (Rosales and Uribe-Querol 2017). Although triggered by different signals that induce different intracellular signalling cascades, the phagocytic cascades under noninflammatory or inflammatory conditions both depend on the activation of small GTPases including Rac and Rho, which catalyse cytoskeletal rearrangement in order to enable the formation of a phagocytic cup and eventually (Gumienny et al. 2001; Lee et al. 2007; Patel et al. 2011; Rosales and Uribe-Querol 2017; Sierra et al. 2013; Underhill and Goodridge 2012).

Neurotransmitter receptors expressed by microglia have been suggested to be an integral part of the 'microglia sensome' to mediate the bidirectional communication between neurons and microglia (Liu et al. 2016). Indeed, evidence suggests that neurotransmitter signalling can modulate 'microglia activation', phagocytic clearance, and phenotypic polarization (Liu et al. 2016). For example, microglia express both ionotropic and metabotropic glutamate receptors, which were shown to alter cytokine release (Noda et al. 2000), chemotaxis (Liu et al. 2009), as well as process motility (Fontainhas et al. 2011) in an ATP-dependent and ATP-independent

manner. Furthermore, microglia express both ionotropic GABA(A) and metabotropic GABA(B) receptors (Liu et al. 2016), which were both shown to decrease the release of pro-inflammatory cytokines upon an inflammatory stimulus (Kuhn et al. 2004; Lee et al. 2011). Microglia also express both α-1/2 and as β-1/2 adrenergic receptors (Liu et al. 2016). Depending on the receptors expressed, noradrenaline (NA) was shown to regulate the microglia immune profile in response to an inflammatory stimulus (Johnson et al. 2013; Liu et al. 2016), chemotaxis, and phagocytosis (Heneka et al. 2010), as well as ATP-dependent process motility and cell mobility (Gyoneva and Traynelis 2013). Moreover, microglia were shown to express functional serotonin receptors, which promote injury-induced and ATP-mediated microglia process motility and cell mobility, as well as inhibit phagocytosis (Krabbe et al. 2012). Lastly, histamine was also identified as a regulator of microglia motility, migration, and cytokine release (Ferreira et al. 2012), as well as modifying their morphological appearance and immune response in specific brain regions (Frick et al. 2016).

Considering the above, we are only now starting to appreciate the complexity of neuron-microglia interactions and how neuronal activity governs microglia activity and vice versa. Neurotransmitters otherwise designated to regulate our mood, wakefulness, and cognitive processes are now known to directly or indirectly interact with brain-resident immune cells and thereby modulate a broad array of microglia functions including chemotaxis, process motility, phagocytosis, and cytokine release. The latter is of particular interest, as changes in cytokine levels measured in the brain or cerebral spinal fluid (CSF) of psychiatric patients are often interpreted as ongoing inflammatory processes or neuroinflammation. It is, however, only now becoming clear that inflammatory cytokines in the brain are constantly produced at low levels in a region-specific and diurnal manner whereby they exert various physiological tasks independent of immunological processes (Cearley et al. 2003; Krueger et al. 2011).

8 The Role of Central Cytokines Beyond Inflammation

Besides orchestrating and controlling the function of immune cells (Parkin and Cohen 2001), cytokines have been increasingly recognized to be involved in the regulation of various physiological processes of the CNS including sleep, learning, memory, neural plasticity, and neurogenesis (Cearley et al. 2003; Donzis and Tronson 2014; Krueger et al. 2011; Yirmiya and Goshen 2011).

The two prototypical pro-inflammatory cytokines IL1β and TNFα were found to be constitutively expressed in the healthy adult rat brain following a diurnal expression pattern in specific brain regions (Cearley et al. 2003) and were shown to stimulate non-rapid eye movement (NREM) sleep (Krueger 2008). Furthermore, hippocampal IL1β gene expression was shown to regulate contextual fear memory formation (Goshen et al. 2007). Hippocampal IL-1β levels were shown to increase 24 h after contextual fear conditioning and that interfering with IL-1 signalling

(excess or blocking the IL-1 signalling pathway) could impede hippocampus-dependent memory formation (Goshen et al. 2007). Intriguingly, sleep deprivation, which is associated with cognitive decline, was shown to cause an increase in central IL-1β and TNF-α levels, which was suggested to contribute to the cognitive deficits evident after excessive lack of sleep (Krueger et al. 2011). The notion that IL-1β is involved in regulating cognitive processes was further strengthened by a study that found hippocampal IL-1β to be increased in an ATP- and microglia-dependent manner after a spatial recognition task (Labrousse et al. 2009). ATP was identified as a key regulator of central IL-1 induction through binding to the microglia-specific purinergic receptor P2X7 (Ferrari et al. 2006; Mingam et al. 2008). Indeed, mice lacking the P2X7 receptor showed no task-dependent IL-1β induction, which was associated with impaired spatial learning (Labrousse et al. 2009). These findings are in line with previous studies showing that impaired IL-1 signalling impeded hippocampus-dependent learning and memory processes, including long-term potentiation (LTP) (Avital et al. 2003; Yirmiya et al. 2002). The chemokine fractalkine (CX3CL1) was also suggested to be involved in learning and memory processing, more specifically to play a role in the protective plasticity process of synaptic scaling (Sheridan et al. 2014). CX3CL1 was shown to be upregulated in the rat hippocampus during a brief temporal window following spatial learning and LTP-inducing stimulation of the dentate gyrus. Furthermore, physiologically relevant levels of CX3CL1 inhibited LTP maintenance and were shown to dampen glutamate-mediated calcium increase in both neurons and microglia (Sheridan et al. 2014). The cytokine TNF-α, on the other hand, was implicated in regulating the NPC pool in adult neurogenesis (Chen and Palmer 2013). NPCs were shown to express TNF receptors (TNFR) 1 and 2, which differentially regulate NPC cell fate, whereby TNFR1 signalling favours proliferation and TNFR2 signalling favours apoptosis (Chen and Palmer 2013).

In light of this book chapter and the presented physiological functions of cytokines described above, there is a need to carefully consider how to interpret alterations in cytokine levels measured between patient groups and controls. Indeed, numerous studies have identified significant changes in cytokine levels both in brain tissue and CSF of psychiatric patients (Miller and Raison 2016; van Kesteren et al. 2017; Wang and Miller 2017). However, although significant, the observed changes are very small in comparison to the neurological conditions that underlie neuroinflammation: For example, a significant increase of CSF IL-6 levels was detected in a subgroup of schizophrenic patients where the levels in healthy controls were found to be at 3 pg/mL and that of patients 4.5 pg/mL (Garver et al. 2003). Also in chronic schizophrenic patients, CSF IL-6 levels were significantly increased, with a mean CSF IL-6 concentration of 1.5 pg/mL in controls and 2.68 pg/mL in patients (Schwieler et al. 2015). Furthermore, significant increased CSF IL-6 levels were measured in recent-onset schizophrenic patients (median 0.85 pg/mL) relative to controls (median 0.52 pg/mL) (Coughlin et al. 2016). Another study found that patients who attempted violent suicide had significantly higher CSF IL6 levels (5.26 pg/mL) as compared to control (0.64 pg/mL) (Lindqvist et al. 2009). In contrast to this, CSF IL-6 levels measured in multiple sclerosis (MS) patients have

been found to increase from a mean of 0.87 pg/mL in controls to 13.4 pg/mL in MS patients (Stelmasiak et al. 2000). Furthermore, CSF IL-6 levels measured in patients suffering from meningitis have been found to peak up to 500 pg/mL (Pinto Junior et al. 2011). Similar to IL-6, CSF IL-1β levels have been found to be increased in schizophrenic patients relative to controls, whereby schizophrenic patients displayed a median IL-1β of 4.37 pg/mL and controls 0.78 pg/mL (Soderlund et al. 2009). IL-1β was also found to be elevated in the CSF of patients with acute depression, where the mean level was 1.14 pg/mL in patients as compared to controls who had an average level of 0.14 pg/mL (Levine et al. 1999). In comparison to this, meningitis patients displayed CSF levels of IL-1β that can reach a peak of 1,000 pg/mL (Coutinho et al. 2013). Lastly, in patients with traumatic brain injury, the levels of CSF pro-inflammatory cytokines can increase up to several 100-fold in comparison to controls (Sordillo et al. 2016).

It becomes evident that there is a substantial difference with respect to the measured levels of pro-inflammatory cytokines in patients suffering from conditions or diseases with ongoing neuroinflammation or psychiatric patients. The question arises as to whether these observed alterations in psychiatric patients truly reflect ongoing inflammatory processes or changes in the general physiological state of the brain. To answer this question, future studies are needed to expand our knowledge of the physiological roles of pro-inflammatory cytokines in health and disease.

9 Concluding Remarks

The growing understanding that central immune mediators are functionally involved in regulating physiological processes of the CNS has revolutionized the field of neuroimmunology. Microglia and cytokines have been implicated in the regulation of neurodevelopment, neuronal wiring, and synaptic plasticity. The functional relevance and underlying mechanisms of these non-immunological functions remain, however, largely unknown and await further investigation. It is, however, clear that the reductive conception of microglia as merely central immune cells is too simplistic. Rather, they emerge as a distinct but heterogeneous cell population of the CNS with a high degree of functional diversity and complexity. Unequivocally implying changes in microglia activity profiles and/or inflammatory factors with ongoing neuroinflammation or neuroinflammatory processes may therefore be too simplistic and could result in misconceptions. In contrast, alterations in neuroimmune systems – particularly in neurological and psychiatric diseases where there is no apparent ongoing inflammation that is evident – should be interpreted in relation to the functional complexity of immune cells and molecules in physiological brain processes. This could help unravelling the functional relevance of neuroimmune dysfunctions in psychiatric illnesses and aid defining future research directions in the field of psychoneuroimmunology.

References

Arnold T, Betsholtz C (2013) Correction: The importance of microglia in the development of the vasculature in the central nervous system. Vasc Cell 5:12. https://doi.org/10.1186/2045-824x-5-12

Arnoux I, Audinat E (2015) Fractalkine signaling and microglia functions in the developing brain. Neural Plast 2015:689404. https://doi.org/10.1155/2015/689404

Ashwood P, Wills S, Van de Water J (2006) The immune response in autism: a new frontier for autism research. J Leukoc Biol 80:1–15. https://doi.org/10.1189/jlb.1205707

Askew K et al (2017) Coupled proliferation and apoptosis maintain the rapid turnover of microglia in the adult brain. Cell Rep 18:391–405. https://doi.org/10.1016/j.celrep.2016.12.041

Avital A, Goshen I, Kamsler A, Segal M, Iverfeldt K, Richter-Levin G, Yirmiya R (2003) Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity. Hippocampus 13:826–834. https://doi.org/10.1002/hipo.10135

Biesmans S et al (2013) Systemic immune activation leads to neuroinflammation and sickness behavior in mice. Mediat Inflamm 2013:271359. https://doi.org/10.1155/2013/271359

Bilimoria PM, Stevens B (2015) Microglia function during brain development: new insights from animal models. Brain Res 1617:7–17. https://doi.org/10.1016/j.brainres.2014.11.032

Blakemore SJ (2012) Development of the social brain in adolescence. J R Soc Med 105:111–116. https://doi.org/10.1258/jrsm.2011.110221

Brites D, Fernandes A (2015) Neuroinflammation and depression: microglia activation, extracellular microvesicles and microRNA dysregulation. Front Cell Neurosci 9:476. https://doi.org/10.3389/fncel.2015.00476

Brown GC, Neher JJ (2014) Microglial phagocytosis of live neurons. Nat Rev Neurosci 15:209–216. https://doi.org/10.1038/nrn3710

Cardona AE et al (2006) Control of microglial neurotoxicity by the fractalkine receptor. Nat Neurosci 9:917–924. https://doi.org/10.1038/nn1715

Cearley C, Churchill L, Krueger JM (2003) Time of day differences in IL1beta and TNFalpha mRNA levels in specific regions of the rat brain. Neurosci Lett 352:61–63

Chen Z, Palmer TD (2013) Differential roles of TNFR1 and TNFR2 signaling in adult hippocampal neurogenesis. Brain Behav Immun 30:45–53. https://doi.org/10.1016/j.bbi.2013.01.083

Claude J, Linnartz-Gerlach B, Kudin AP, Kunz WS, Neumann H (2013) Microglial CD33-related Siglec-E inhibits neurotoxicity by preventing the phagocytosis-associated oxidative burst. J Neurosci 33:18270–18276. https://doi.org/10.1523/jneurosci.2211-13.2013

Coughlin JM et al (2016) In vivo markers of inflammatory response in recent-onset schizophrenia: a combined study using [(11)C]DPA-713 PET and analysis of CSF and plasma. Transl Psychiatry 6:e777. https://doi.org/10.1038/tp.2016.40

Coutinho LG, Grandgirard D, Leib SL, Agnez-Lima LF (2013) Cerebrospinal-fluid cytokine and chemokine profile in patients with pneumococcal and meningococcal meningitis. BMC Infect Dis 13:326. https://doi.org/10.1186/1471-2334-13-326

Cunningham CL, Martinez-Cerdeno V, Noctor SC (2013) Microglia regulate the number of neural precursor cells in the developing cerebral cortex. J Neurosci 33:4216–4233. https://doi.org/10.1523/jneurosci.3441-12.2013

Daneman R, Zhou L, Kebede AA, Barres BA (2010) Pericytes are required for blood-brain barrier integrity during embryogenesis. Nature 468:562–566. https://doi.org/10.1038/nature09513

Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9:46–56. https://doi.org/10.1038/nrn2297

Davalos D et al (2005) ATP mediates rapid microglial response to local brain injury in vivo. Nat Neurosci 8:752–758. https://doi.org/10.1038/nn1472

Denes A, Thornton P, Rothwell NJ, Allan SM (2010) Inflammation and brain injury: acute cerebral ischaemia, peripheral and central inflammation. Brain Behav Immun 24:708–723. https://doi.org/10.1016/j.bbi.2009.09.010

Diaz-Aparicio I, Beccari S, Abiega O, Sierra A (2016) Clearing the corpses: regulatory mechanisms, novel tools, and therapeutic potential of harnessing microglial phagocytosis in the diseased brain. Neural Regen Res 11:1533–1539. https://doi.org/10.4103/1673-5374.193220

Dissing-Olesen L, LeDue JM, Rungta RL, Hefendehl JK, Choi HB, MacVicar BA (2014) Activation of neuronal NMDA receptors triggers transient ATP-mediated microglial process outgrowth. J Neurosci 34:10511–10527. https://doi.org/10.1523/jneurosci.0405-14.2014

Donzis EJ, Tronson NC (2014) Modulation of learning and memory by cytokines: signaling mechanisms and long term consequences. Neurobiol Learn Mem 115:68–77. https://doi.org/10.1016/j.nlm.2014.08.008

Doorduin J, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA, Klein HC (2009) Neuroinflammation in schizophrenia-related psychosis: a PET study. J Nucl Med 50:1801–1807. https://doi.org/10.2967/jnumed.109.066647

Du Preez A, Leveson J, Zunszain PA, Pariante CM (2016) Inflammatory insults and mental health consequences: does timing matter when it comes to depression? Psychol Med 46:2041–2057. https://doi.org/10.1017/s0033291716000672

Estes ML, McAllister AK (2014) Alterations in immune cells and mediators in the brain: it's not always neuroinflammation! Brain Pathol (Zurich, Switzerland) 24:623–630. https://doi.org/10.1111/bpa.12198

Estes ML, McAllister AK (2015) Immune mediators in the brain and peripheral tissues in autism spectrum disorder. Nat Rev Neurosci 16:469–486. https://doi.org/10.1038/nrn3978

Eyo UB, Peng J, Swiatkowski P, Mukherjee A, Bispo A, Wu LJ (2014) Neuronal hyperactivity recruits microglial processes via neuronal NMDA receptors and microglial P2Y12 receptors after status epilepticus. J Neurosci 34:10528–10540. https://doi.org/10.1523/jneurosci.0416-14.2014

Ferrari D et al (2006) The P2X7 receptor: a key player in IL-1 processing and release. J Immunol (Baltimore, MD: 1950) 176:3877–3883

Ferreira R, Santos T, Goncalves J, Baltazar G, Ferreira L, Agasse F, Bernardino L (2012) Histamine modulates microglia function. J Neuroinflammation 9:90. https://doi.org/10.1186/1742-2094-9-90

Filiou MD, Arefin AS, Moscato P, Graeber MB (2014) 'Neuroinflammation' differs categorically from inflammation: transcriptomes of Alzheimer's disease, Parkinson's disease, schizophrenia and inflammatory diseases compared. Neurogenetics 15:201–212. https://doi.org/10.1007/s10048-014-0409-x

Fontainhas AM et al (2011) Microglial morphology and dynamic behavior is regulated by ionotropic glutamatergic and GABAergic neurotransmission. PLoS One 6:e15973. https://doi.org/10.1371/journal.pone.0015973

Frick L, Rapanelli M, Abbasi E, Ohtsu H, Pittenger C (2016) Histamine regulation of microglia: gene-environment interaction in the regulation of central nervous system inflammation. Brain Behav Immun 57:326–337. https://doi.org/10.1016/j.bbi.2016.07.002

Fricker M, Neher JJ, Zhao JW, Thery C, Tolkovsky AM, Brown GC (2012) MFG-E8 mediates primary phagocytosis of viable neurons during neuroinflammation. J Neurosci 32:2657–2666. https://doi.org/10.1523/jneurosci.4837-11.2012

Fu R, Shen Q, Xu P, Luo JJ, Tang Y (2014) Phagocytosis of microglia in the central nervous system diseases. Mol Neurobiol 49:1422–1434. https://doi.org/10.1007/s12035-013-8620-6

Garton KJ, Gough PJ, Blobel CP, Murphy G, Greaves DR, Dempsey PJ, Raines EW (2001) Tumor necrosis factor-alpha-converting enzyme (ADAM17) mediates the cleavage and shedding of fractalkine (CX3CL1). J Biol Chem 276:37993–38001. https://doi.org/10.1074/jbc.M106434200

Garver DL, Tamas RL, Holcomb JA (2003) Elevated interleukin-6 in the cerebrospinal fluid of a previously delineated schizophrenia subtype. Neuropsychopharmacology 28:1515–1520. https://doi.org/10.1038/sj.npp.1300217

Geissmann F, Gordon S, Hume DA, Mowat AM, Randolph GJ (2010) Unravelling mononuclear phagocyte heterogeneity. Nat Rev Immunol 10:453–460. https://doi.org/10.1038/nri2784

Ginhoux F et al (2010) Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science (New York, NY) 330:841–845. https://doi.org/10.1126/science.1194637
Ginhoux F, Lim S, Hoeffel G, Low D, Huber T (2013) Origin and differentiation of microglia. Front Cell Neurosci 7:45. https://doi.org/10.3389/fncel.2013.00045
Gomez-Nicola D, Perry VH (2015) Microglial dynamics and role in the healthy and diseased brain: a paradigm of functional plasticity. Neuroscientist 21:169–184. https://doi.org/10.1177/1073858414530512
Goshen I et al (2007) A dual role for interleukin-1 in hippocampal-dependent memory processes. Psychoneuroendocrinology 32:1106–1115. https://doi.org/10.1016/j.psyneuen.2007.09.004
Gracia-Rubio I, Moscoso-Castro M, Pozo OJ, Marcos J, Nadal R, Valverde O (2016) Maternal separation induces neuroinflammation and long-lasting emotional alterations in mice. Prog Neuro-Psychopharmacol Biol Psychiatry 65:104–117. https://doi.org/10.1016/j.pnpbp.2015.09.003
Graeber MB (2014) Neuroinflammation: no rose by any other name. Brain Pathol (Zurich, Switzerland) 24:620–622. https://doi.org/10.1111/bpa.12192
Graeber MB, Streit WJ (1990) Microglia: immune network in the CNS. Brain Pathol (Zurich, Switzerland) 1:2–5
Gumienny TL et al (2001) CED-12/ELMO, a novel member of the CrkII/Dock180/Rac pathway, is required for phagocytosis and cell migration. Cell 107:27–41
Gyoneva S, Traynelis SF (2013) Norepinephrine modulates the motility of resting and activated microglia via different adrenergic receptors. J Biol Chem 288:15291–15302. https://doi.org/10.1074/jbc.M113.458901
Haarman BC et al (2014) Neuroinflammation in bipolar disorder - a [(11)C]-(R)-PK11195 positron emission tomography study. Brain Behav Immun 40:219–225. https://doi.org/10.1016/j.bbi.2014.03.016
Haarman BC et al (2016) Volume, metabolites and neuroinflammation of the hippocampus in bipolar disorder - a combined magnetic resonance imaging and positron emission tomography study. Brain Behav Immun 56:21–33. https://doi.org/10.1016/j.bbi.2015.09.004
Hanisch UK, Kettenmann H (2007) Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat Neurosci 10:1387–1394. https://doi.org/10.1038/nn1997
Harry GJ (2013) Microglia during development and aging. Pharmacol Ther 139:313–326. https://doi.org/10.1016/j.pharmthera.2013.04.013
Haynes SE, Hollopeter G, Yang G, Kurpius D, Dailey ME, Gan WB, Julius D (2006) The P2Y12 receptor regulates microglial activation by extracellular nucleotides. Nat Neurosci 9:1512–1519. https://doi.org/10.1038/nn1805
Heneka MT et al (2010) Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. Proc Natl Acad Sci U S A 107:6058–6063. https://doi.org/10.1073/pnas.0909586107
Hickman SE, Kingery ND, Ohsumi TK, Borowsky ML, Wang LC, Means TK, El Khoury J (2013) The microglial sensome revealed by direct RNA sequencing. Nat Neurosci 16:1896–1905. https://doi.org/10.1038/nn.3554
Hines DJ, Hines RM, Mulligan SJ, Macvicar BA (2009) Microglia processes block the spread of damage in the brain and require functional chloride channels. Glia 57:1610–1618. https://doi.org/10.1002/glia.20874
Hoeffel G et al (2015) C-Myb(+) erythro-myeloid progenitor-derived fetal monocytes give rise to adult tissue-resident macrophages. Immunity 42:665–678. https://doi.org/10.1016/j.immuni.2015.03.011
Horvath S, Mirnics K (2014) Immune system disturbances in schizophrenia. Biol Psychiatry 75:316–323. https://doi.org/10.1016/j.biopsych.2013.06.010
Hoshiko M, Arnoux I, Avignone E, Yamamoto N, Audinat E (2012) Deficiency of the microglial receptor CX3CR1 impairs postnatal functional development of thalamocortical synapses in the barrel cortex. J Neurosci 32:15106–15111. https://doi.org/10.1523/jneurosci.1167-12.2012

Hristovska I, Pascual O (2015) Deciphering resting microglial morphology and process motility from a synaptic prospect. Front Integr Neurosci 9:73. https://doi.org/10.3389/fnint.2015.00073
Isgren A et al (2017) Markers of neuroinflammation and neuronal injury in bipolar disorder: relation to prospective clinical outcomes. Brain Behav Immun. https://doi.org/10.1016/j.bbi.2017.05.002
Johnson MH (2001) Functional brain development in humans. Nat Rev Neurosci 2:475–483. https://doi.org/10.1038/35081509
Johnson JD, Zimomra ZR, Stewart LT (2013) Beta-adrenergic receptor activation primes microglia cytokine production. J Neuroimmunol 254:161–164. https://doi.org/10.1016/j.jneuroim.2012.08.007
Kenk M et al (2015) Imaging neuroinflammation in gray and white matter in schizophrenia: an in-vivo PET study with [18F]-FEPPA. Schizophr Bull 41:85–93. https://doi.org/10.1093/schbul/sbu157
Kettenmann H, Hanisch UK, Noda M, Verkhratsky A (2011) Physiology of microglia. Physiol Rev 91:461–553. https://doi.org/10.1152/physrev.00011.2010
Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB (2015) Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2:258–270. https://doi.org/10.1016/s2215-0366(14)00122-9
Konrad K, Firk C, Uhlhaas PJ (2013) Brain development during adolescence: neuroscientific insights into this developmental period. Dtsch Arztebl Int 110:425–431. https://doi.org/10.3238/arztebl.2013.0425
Krabbe G, Matyash V, Pannasch U, Mamer L, Boddeke HW, Kettenmann H (2012) Activation of serotonin receptors promotes microglial injury-induced motility but attenuates phagocytic activity. Brain Behav Immun 26:419–428. https://doi.org/10.1016/j.bbi.2011.12.002
Kraepelin E (1890) Über Psychosen nach Influenza. Dtsch Med Wochenschr 16:209–212
Krueger JM (2008) The role of cytokines in sleep regulation. Curr Pharm Des 14:3408–3416
Krueger JM, Majde JA, Rector DM (2011) Cytokines in immune function and sleep regulation. Handb Clin Neurol 98:229–240. https://doi.org/10.1016/b978-0-444-52006-7.00015-0
Kuhn SA et al (2004) Microglia express GABA(B) receptors to modulate interleukin release. Mol Cell Neurosci 25:312–322. https://doi.org/10.1016/j.mcn.2003.10.023
Labrousse VF, Costes L, Aubert A, Darnaudery M, Ferreira G, Amedee T, Laye S (2009) Impaired interleukin-1beta and c-Fos expression in the hippocampus is associated with a spatial memory deficit in P2X(7) receptor-deficient mice. PLoS One 4:e6006. https://doi.org/10.1371/journal.pone.0006006
Laskaris LE et al (2016) Microglial activation and progressive brain changes in schizophrenia. Br J Pharmacol 173:666–680. https://doi.org/10.1111/bph.13364
Lawson LJ, Perry VH, Dri P, Gordon S (1990) Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. Neuroscience 39:151–170
Lawson LJ, Perry VH, Gordon S (1992) Turnover of resident microglia in the normal adult mouse brain. Neuroscience 48:405–415
Lee WL, Mason D, Schreiber AD, Grinstein S (2007) Quantitative analysis of membrane remodeling at the phagocytic cup. Mol Biol Cell 18:2883–2892. https://doi.org/10.1091/mbc.E06-05-0450
Lee M, Schwab C, McGeer PL (2011) Astrocytes are GABAergic cells that modulate microglial activity. Glia 59:152–165. https://doi.org/10.1002/glia.21087
Levine J, Barak Y, Chengappa KN, Rapoport A, Rebey M, Barak V (1999) Cerebrospinal cytokine levels in patients with acute depression. Neuropsychobiology 40:171–176. https://doi.org/10.1159/000026615
Li Y, Du XF, Liu CS, Wen ZL, Du JL (2012) Reciprocal regulation between resting microglial dynamics and neuronal activity in vivo. Dev Cell 23:1189–1202. https://doi.org/10.1016/j.devcel.2012.10.027

Liang KJ, Lee JE, Wang YD, Ma W, Fontainhas AM, Fariss RN, Wong WT (2009) Regulation of dynamic behavior of retinal microglia by CX3CR1 signaling. Invest Ophthalmol Vis Sci 50:4444–4451. https://doi.org/10.1167/iovs.08-3357

Lindqvist D et al (2009) Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. Biol Psychiatry 66:287–292. https://doi.org/10.1016/j.biopsych.2009.01.030

Linnartz B, Kopatz J, Tenner AJ, Neumann H (2012) Sialic acid on the neuronal glycocalyx prevents complement C1 binding and complement receptor-3-mediated removal by microglia. J Neurosci 32:946–952. https://doi.org/10.1523/jneurosci.3830-11.2012

Liu GJ, Nagarajah R, Banati RB, Bennett MR (2009) Glutamate induces directed chemotaxis of microglia. Eur J Neurosci 29:1108–1118. https://doi.org/10.1111/j.1460-9568.2009.06659.x

Liu H, Leak RK, Hu X (2016) Neurotransmitter receptors on microglia. Stroke Vasc Neurol 1:52–58. https://doi.org/10.1136/svn-2016-000012

Luo J et al (2013) Colony-stimulating factor 1 receptor (CSF1R) signaling in injured neurons facilitates protection and survival. J Exp Med 210:157–172. https://doi.org/10.1084/jem.20120412

Maciejewski-Lenoir D, Chen S, Feng L, Maki R, Bacon KB (1999) Characterization of fractalkine in rat brain cells: migratory and activation signals for CX3CR-1-expressing microglia. J Immunol (Baltimore, MD: 1950) 163:1628–1635

Mantovani A, Sica A, Locati M (2005) Macrophage polarization comes of age. Immunity 23:344–346. https://doi.org/10.1016/j.immuni.2005.10.001

Marker DF, Puccini JM, Mockus TE, Barbieri J, Lu SM, Gelbard HA (2012) LRRK2 kinase inhibition prevents pathological microglial phagocytosis in response to HIV-1 Tat protein. J Neuroinflammation 9:261. https://doi.org/10.1186/1742-2094-9-261

Martinez FO, Gordon S (2014) The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000prime Rep 6:13. https://doi.org/10.12703/p6-13

Masgrau R, Guaza C, Ransohoff RM, Galea E (2017) Should we stop saying 'glia' and 'neuroinflammation'? Trends Mol Med 23:486–500. https://doi.org/10.1016/j.molmed.2017.04.005

Matcovitch-Natan O et al (2016) Microglia development follows a stepwise program to regulate brain homeostasis. Science (New York, NY) 353:aad8670. https://doi.org/10.1126/science.aad8670

Mayilyan KR, Weinberger DR, Sim RB (2008) The complement system in schizophrenia. Drug News Perspect 21:200–210. https://doi.org/10.1358/dnp.2008.21.4.1213349

Mazaheri F, Breus O, Durdu S, Haas P, Wittbrodt J, Gilmour D, Peri F (2014) Distinct roles for BAI1 and TIM-4 in the engulfment of dying neurons by microglia. Nat Commun 5:4046. https://doi.org/10.1038/ncomms5046

Meltzer A, Van de Water J (2017) The role of the immune system in autism spectrum disorder. Neuropsychopharmacology 42:284–298. https://doi.org/10.1038/npp.2016.158

Menninger KA (1919) Psychoses associated with influenza, I: general data: statistical analysis. JAMA 72:235–241

Miller AH, Raison CL (2016) The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 16:22–34. https://doi.org/10.1038/nri.2015.5

Mingam R, De Smedt V, Amedee T, Bluthe RM, Kelley KW, Dantzer R, Laye S (2008) In vitro and in vivo evidence for a role of the P2X7 receptor in the release of IL-1 beta in the murine brain. Brain Behav Immun 22:234–244. https://doi.org/10.1016/j.bbi.2007.08.007

Mittelbronn M, Dietz K, Schluesener HJ, Meyermann R (2001) Local distribution of microglia in the normal adult human central nervous system differs by up to one order of magnitude. Acta Neuropathol 101:249–255

Mizuno T et al (2011) Interleukin-34 selectively enhances the neuroprotective effects of microglia to attenuate oligomeric amyloid-beta neurotoxicity. Am J Pathol 179:2016–2027. https://doi.org/10.1016/j.ajpath.2011.06.011

Monji A et al (2013) Neuroinflammation in schizophrenia especially focused on the role of microglia. Prog Neuro-Psychopharmacol Biol Psychiatry 42:115–121. https://doi.org/10.1016/j.pnpbp.2011.12.002

Muller N, Schwarz MJ (2007) The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. Mol Psychiatry 12:988–1000. https://doi.org/10.1038/sj.mp.4002006

Muller N, Riedel M, Gruber R, Ackenheil M, Schwarz MJ (2000) The immune system and schizophrenia. An integrative view. Ann N Y Acad Sci 917:456–467

Na KS, Jung HY, Kim YK (2014) The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. Prog Neuro-Psychopharmacol Biol Psychiatry 48:277–286. https://doi.org/10.1016/j.pnpbp.2012.10.022

Najjar S, Pearlman DM (2015) Neuroinflammation and white matter pathology in schizophrenia: systematic review. Schizophr Res 161:102–112. https://doi.org/10.1016/j.schres.2014.04.041

Nakatomi Y et al (2014) Neuroinflammation in patients with chronic fatigue syndrome/myalgic encephalomyelitis: an (1)(1)C-(R)-PK11195 PET study. J Nucl Med 55:945–950. https://doi.org/10.2967/jnumed.113.131045

Neniskyte U, Brown GC (2013) Lactadherin/MFG-E8 is essential for microglia-mediated neuronal loss and phagoptosis induced by amyloid beta. J Neurochem 126:312–317. https://doi.org/10.1111/jnc.12288

Neniskyte U, Gross CT (2017) Errant gardeners: glial-cell-dependent synaptic pruning and neurodevelopmental disorders. Nat Rev Neurosci 18:658–670. https://doi.org/10.1038/nrn.2017.110

Nimmerjahn A, Kirchhoff F, Helmchen F (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science (New York, NY) 308:1314–1318. https://doi.org/10.1126/science.1110647

Noda M, Nakanishi H, Nabekura J, Akaike N (2000) AMPA-kainate subtypes of glutamate receptor in rat cerebral microglia. J Neurosci 20:251–258

Noda M et al (2011) Fractalkine attenuates excito-neurotoxicity via microglial clearance of damaged neurons and antioxidant enzyme heme oxygenase-1 expression. J Biol Chem 286:2308–2319. https://doi.org/10.1074/jbc.M110.169839

Noda M et al (2014) FGF-2 released from degenerating neurons exerts microglial-induced neuroprotection via FGFR3-ERK signaling pathway. J Neuroinflammation 11:76. https://doi.org/10.1186/1742-2094-11-76

Orkin SH, Zon LI (2008) Hematopoiesis: an evolving paradigm for stem cell biology. Cell 132:631–644. https://doi.org/10.1016/j.cell.2008.01.025

Orr AG, Orr AL, Li XJ, Gross RE, Traynelis SF (2009) Adenosine A(2A) receptor mediates microglial process retraction. Nat Neurosci 12:872–878. https://doi.org/10.1038/nn.2341

Orsini F, De Blasio D, Zangari R, Zanier ER, De Simoni MG (2014) Versatility of the complement system in neuroinflammation, neurodegeneration and brain homeostasis. Front Cell Neurosci 8:380. https://doi.org/10.3389/fncel.2014.00380

Paolicelli RC, Ferretti MT (2017) Function and dysfunction of microglia during brain development: consequences for synapses and neural circuits. Front Synaptic Neurosci 9:9. https://doi.org/10.3389/fnsyn.2017.00009

Paolicelli RC et al (2011) Synaptic pruning by microglia is necessary for normal brain development. Science (New York, NY) 333:1456–1458. https://doi.org/10.1126/science.1202529

Paolicelli RC, Bisht K, Tremblay ME (2014) Fractalkine regulation of microglial physiology and consequences on the brain and behavior. Front Cell Neurosci 8:129. https://doi.org/10.3389/fncel.2014.00129

Parkhurst CN et al (2013) Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 155:1596–1609. https://doi.org/10.1016/j.cell.2013.11.030

Parkin J, Cohen B (2001) An overview of the immune system. Lancet (London, England) 357:1777–1789. https://doi.org/10.1016/s0140-6736(00)04904-7

Patel M, Pelletier A, Cote JF (2011) Opening up on ELMO regulation: New insights into the control of Rac signaling by the DOCK180/ELMO complex. Small GTPases 2:268–275. https://doi.org/10.4161/sgtp.2.5.17716

Perez-Cerda F, Sanchez-Gomez MV, Matute C (2015) Pio del Rio Hortega and the discovery of the oligodendrocytes. Front Neuroanat 9:92. https://doi.org/10.3389/fnana.2015.00092

Perry VH, Nicoll JA, Holmes C (2010) Microglia in neurodegenerative disease. Nat Rev Neurol 6:193–201. https://doi.org/10.1038/nrneurol.2010.17

Pinto Junior VL, Rebelo MC, Gomes RN, Assis EF, Castro-Faria-Neto HC, Boia MN (2011) IL-6 and IL-8 in cerebrospinal fluid from patients with aseptic meningitis and bacterial meningitis: their potential role as a marker for differential diagnosis. Braz J Infect Dis 15:156–158

Pont-Lezica L, Beumer W, Colasse S, Drexhage H, Versnel M, Bessis A (2014) Microglia shape corpus callosum axon tract fasciculation: functional impact of prenatal inflammation. Eur J Neurosci 39:1551–1557. https://doi.org/10.1111/ejn.12508

Presumey J, Bialas AR, Carroll MC (2017) Complement system in neural synapse elimination in development and disease. Adv Immunol 135:53–79. https://doi.org/10.1016/bs.ai.2017.06.004

Ransohoff RM (2016) A polarizing question: do M1 and M2 microglia exist? Nat Neurosci 19:987–991. https://doi.org/10.1038/nn.4338

Ransohoff RM, Cardona AE (2010) The myeloid cells of the central nervous system parenchyma. Nature 468:253–262. https://doi.org/10.1038/nature09615

Ransohoff RM, Engelhardt B (2012) The anatomical and cellular basis of immune surveillance in the central nervous system. Nat Rev Immunol 12:623–635. https://doi.org/10.1038/nri3265

Ransohoff RM, Perry VH (2009) Microglial physiology: unique stimuli, specialized responses. Annu Rev Immunol 27:119–145. https://doi.org/10.1146/annurev.immunol.021908.132528

Reemst K, Noctor SC, Lucassen PJ, Hol EM (2016) The indispensable roles of microglia and astrocytes during brain development. Front Hum Neurosci 10:566. https://doi.org/10.3389/fnhum.2016.00566

Reu P et al (2017) The lifespan and turnover of microglia in the human brain. Cell Rep 20:779–784. https://doi.org/10.1016/j.celrep.2017.07.004

Rocha e Silva M (1978) A brief survey of the history of inflammation. Agents Actions 8:45–49

Rosales C, Uribe-Querol E (2017) Phagocytosis: a fundamental process in immunity. Biomed Res Int 2017:9042851. https://doi.org/10.1155/2017/9042851

Salter MW, Beggs S (2014) Sublime microglia: expanding roles for the guardians of the CNS. Cell 158:15–24. https://doi.org/10.1016/j.cell.2014.06.008

Salter MW, Stevens B (2017) Microglia emerge as central players in brain disease. Nat Med 23:1018–1027. https://doi.org/10.1038/nm.4397

Santoni G, Cardinali C, Morelli MB, Santoni M, Nabissi M, Amantini C (2015) Danger- and pathogen-associated molecular patterns recognition by pattern-recognition receptors and ion channels of the transient receptor potential family triggers the inflammasome activation in immune cells and sensory neurons. J Neuroinflammation 12:21. https://doi.org/10.1186/s12974-015-0239-2

Schafer DP et al (2012) Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 74:691–705. https://doi.org/10.1016/j.neuron.2012.03.026

Scheffel J et al (2012) Toll-like receptor activation reveals developmental reorganization and unmasks responder subsets of microglia. Glia 60:1930–1943. https://doi.org/10.1002/glia.22409

Schwartz M, Baruch K (2014) The resolution of neuroinflammation in neurodegeneration: leukocyte recruitment via the choroid plexus. EMBO J 33:7–22. https://doi.org/10.1002/embj.201386609

Schwieler L et al (2015) Increased levels of IL-6 in the cerebrospinal fluid of patients with chronic schizophrenia--significance for activation of the kynurenine pathway. J Psychiatry Neurosci 40:126–133

Scott A, Khan KM, Cook JL, Duronio V (2004) What is "inflammation"? Are we ready to move beyond Celsus? Br J Sports Med 38:248–249

Serhan CN, Savill J (2005) Resolution of inflammation: the beginning programs the end. Nat Immunol 6:1191–1197. https://doi.org/10.1038/ni1276

Setiawan E et al (2015) Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. JAMA Psychiat 72:268–275. https://doi.org/10.1001/jamapsychiatry.2014.2427

Shankaran M et al (2007) Measurement of brain microglial proliferation rates in vivo in response to neuroinflammatory stimuli: application to drug discovery. J Neurosci Res 85:2374–2384. https://doi.org/10.1002/jnr.21389

Sheng J, Ruedl C, Karjalainen K (2015) Most tissue-resident macrophages except microglia are derived from fetal hematopoietic stem cells. Immunity 43:382–393. https://doi.org/10.1016/j.immuni.2015.07.016

Sheridan GK et al (2014) CX3CL1 is up-regulated in the rat hippocampus during memory-associated synaptic plasticity. Front Cell Neurosci 8:233. https://doi.org/10.3389/fncel.2014.00233

Shigemoto-Mogami Y, Hoshikawa K, Goldman JE, Sekino Y, Sato K (2014) Microglia enhance neurogenesis and oligodendrogenesis in the early postnatal subventricular zone. J Neurosci 34:2231–2243. https://doi.org/10.1523/jneurosci.1619-13.2014

Sierra A et al (2010) Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell Stem Cell 7:483–495. https://doi.org/10.1016/j.stem.2010.08.014

Sierra A, Abiega O, Shahraz A, Neumann H (2013) Janus-faced microglia: beneficial and detrimental consequences of microglial phagocytosis. Front Cell Neurosci 7:6. https://doi.org/10.3389/fncel.2013.00006

Sierra A, Beccari S, Diaz-Aparicio I, Encinas JM, Comeau S, Tremblay ME (2014) Surveillance, phagocytosis, and inflammation: how never-resting microglia influence adult hippocampal neurogenesis. Neural Plast 2014:610343. https://doi.org/10.1155/2014/610343

Soderlund J et al (2009) Activation of brain interleukin-1beta in schizophrenia. Mol Psychiatry 14:1069–1071. https://doi.org/10.1038/mp.2009.52

Sordillo PP, Sordillo LA, Helson L (2016) Bifunctional role of pro-inflammatory cytokines after traumatic brain injury. Brain Inj 30:1043–1053. https://doi.org/10.3109/02699052.2016.1163618

Squarzoni P et al (2014) Microglia modulate wiring of the embryonic forebrain. Cell Rep 8:1271–1279. https://doi.org/10.1016/j.celrep.2014.07.042

Stelmasiak Z, Koziol-Montewka M, Dobosz B, Rejdak K, Bartosik-Psujek H, Mitosek-Szewczyk K, Belniak-Legiec E (2000) Interleukin-6 concentration in serum and cerebrospinal fluid in multiple sclerosis patients. Med Sci Monit 6:1104–1108

Stephan AH, Barres BA, Stevens B (2012) The complement system: an unexpected role in synaptic pruning during development and disease. Annu Rev Neurosci 35:369–389. https://doi.org/10.1146/annurev-neuro-061010-113810

Stevens B et al (2007) The classical complement cascade mediates CNS synapse elimination. Cell 131:1164–1178. https://doi.org/10.1016/j.cell.2007.10.036

Suridjan I et al (2014) Quantitative imaging of neuroinflammation in human white matter: a positron emission tomography study with translocator protein 18 kDa radioligand, [18F]-FEPPA. Synapse (New York, NY) 68:536–547. https://doi.org/10.1002/syn.21765

Svahn AJ, Becker TS, Graeber MB (2014) Emergent properties of microglia. Brain Pathol (Zurich, Switzerland) 24:665–670. https://doi.org/10.1111/bpa.12195

Szalay G et al (2016) Microglia protect against brain injury and their selective elimination dysregulates neuronal network activity after stroke. Nat Commun 7:11499. https://doi.org/10.1038/ncomms11499

Takahashi K, Yamamura F, Naito M (1989) Differentiation, maturation, and proliferation of macrophages in the mouse yolk sac: a light-microscopic, enzyme-cytochemical, immunohistochemical, and ultrastructural study. J Leukoc Biol 45:87–96

Takahashi K, Rochford CD, Neumann H (2005) Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. J Exp Med 201:647–657. https://doi.org/10.1084/jem.20041611

Tay TL et al (2017) A new fate mapping system reveals context-dependent random or clonal expansion of microglia. Nat Neurosci 20:793–803. https://doi.org/10.1038/nn.4547

Thion MS, Garel S (2017) On place and time: microglia in embryonic and perinatal brain development. Curr Opin Neurobiol 47:121–130. https://doi.org/10.1016/j.conb.2017.10.004

Tonchev AB, Yamashima T, Zhao L, Okano H (2003) Differential proliferative response in the postischemic hippocampus, temporal cortex, and olfactory bulb of young adult macaque monkeys. Glia 42:209–224. https://doi.org/10.1002/glia.10209

Torres L et al (2016) Dynamic microglial modulation of spatial learning and social behavior. Brain Behav Immun 55:6–16. https://doi.org/10.1016/j.bbi.2015.09.001

Tremblay ME (2011) The role of microglia at synapses in the healthy CNS: novel insights from recent imaging studies. Neuron Glia Biol 7:67–76. https://doi.org/10.1017/s1740925x12000038

Tremblay ME, Lowery RL, Majewska AK (2010) Microglial interactions with synapses are modulated by visual experience. PLoS Biol 8:e1000527. https://doi.org/10.1371/journal.pbio.1000527

Tremblay ME, Stevens B, Sierra A, Wake H, Bessis A, Nimmerjahn A (2011) The role of microglia in the healthy brain. J Neurosci 31:16064–16069. https://doi.org/10.1523/jneurosci.4158-11.2011

Ueno M, Fujita Y, Tanaka T, Nakamura Y, Kikuta J, Ishii M, Yamashita T (2013) Layer V cortical neurons require microglial support for survival during postnatal development. Nat Neurosci 16:543–551. https://doi.org/10.1038/nn.3358

Underhill DM, Goodridge HS (2012) Information processing during phagocytosis. Nat Rev Immunol 12:492–502. https://doi.org/10.1038/nri3244

van Kesteren CF et al (2017) Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Transl Psychiatry 7:e1075. https://doi.org/10.1038/tp.2017.4

Wakatsuki S, Araki T (2017) Specific phospholipid scramblases are involved in exposure of phosphatidylserine, an "eat-me" signal for phagocytes, on degenerating axons. Commun Integr Biol 10:e1296615. https://doi.org/10.1080/19420889.2017.1296615

Wakselman S, Bechade C, Roumier A, Bernard D, Triller A, Bessis A (2008) Developmental neuronal death in hippocampus requires the microglial CD11b integrin and DAP12 immunoreceptor. J Neurosci 28:8138–8143. https://doi.org/10.1523/jneurosci.1006-08.2008

Wang AK, Miller BJ (2017) Meta-analysis of cerebrospinal fluid cytokine and tryptophan catabolite alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder, and depression. Schizophr Bull. https://doi.org/10.1093/schbul/sbx035

Wang Y, Neumann H (2010) Alleviation of neurotoxicity by microglial human Siglec-11. J Neurosci 30:3482–3488. https://doi.org/10.1523/jneurosci.3940-09.2010

Watkins CC, Sawa A, Pomper MG (2014) Glia and immune cell signaling in bipolar disorder: insights from neuropharmacology and molecular imaging to clinical application. Transl Psychiatry 4:e350. https://doi.org/10.1038/tp.2013.119

Wolf SA, Boddeke HW, Kettenmann H (2017) Microglia in physiology and disease. Annu Rev Physiol 79:619–643. https://doi.org/10.1146/annurev-physiol-022516-034406

Wu Y, Dissing-Olesen L, MacVicar BA, Stevens B (2015) Microglia: dynamic mediators of synapse development and plasticity. Trends Immunol 36:605–613. https://doi.org/10.1016/j.it.2015.08.008

Xing C, Lo EH (2017) Help-me signaling: non-cell autonomous mechanisms of neuroprotection and neurorecovery. Prog Neurobiol 152:181–199. https://doi.org/10.1016/j.pneurobio.2016.04.004

Yirmiya R, Goshen I (2011) Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav Immun 25:181–213. https://doi.org/10.1016/j.bbi.2010.10.015

Yirmiya R, Winocur G, Goshen I (2002) Brain interleukin-1 is involved in spatial memory and passive avoidance conditioning. Neurobiol Learn Mem 78:379–389

Yolken RH, Torrey EF (2008) Are some cases of psychosis caused by microbial agents? A review of the evidence. Mol Psychiatry 13:470–479. https://doi.org/10.1038/mp.2008.5

Zhan Y et al (2014) Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. Nat Neurosci 17:400–406. https://doi.org/10.1038/nn.3641

Zhang M, Xu G, Liu W, Ni Y, Zhou W (2012) Role of fractalkine/CX3CR1 interaction in light-induced photoreceptor degeneration through regulating retinal microglial activation and migration. PLoS One 7:e35446. https://doi.org/10.1371/journal.pone.0035446

Zhang H, Li F, Yang Y, Chen J, Hu X (2015) SIRP/CD47 signaling in neurological disorders. Brain Res 1623:74–80. https://doi.org/10.1016/j.brainres.2015.03.012