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Microglia roles in synaptic plasticity and myelination in homeostatic conditions and neurodevelopmental disorders

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Abstract

Microglia are the immune cells of the brain, involved in synapse formation, circuit sculpting, myelination, plasticity, and cognition. Being active players during early development as well as in adulthood, microglia affect other cells directly by their long processes and unique receptors and indirectly by secreting growth factors and cytokines. In this review, we discuss the roles of microglia in neurodevelopmental disorders, synaptic plasticity, myelination, and homeostatic conditions throughout human and mouse development. Within these processes, we specifically focus on the contribution of altered microglial interactions with neurons and oligodendrocytes, altered cytokine and growth factor activities, and alterations in the complement system. We conclude by highlighting future perspectives and providing an overview of future research on microglia.

KEYWORDS

autism, microglia, myelin, neurodevelopmental disorders, synaptic plasticity

1 | MICROGLIA: INNATE IMMUNE CELLS OF THE CENTRAL NERVOUS SYSTEM

The central nervous system (CNS) consists of neurons—specialized cells that can receive and transmit chemical or electrical signals (Laughlin & Sejnowski, 2003), macroglia (astrocytes, oligodendrocytes [OLs], ependymal cells, and radial glia), and microglia. Macroglia and microglia maintain the neurons' ionic milieu (Fields et al., 2014; Walz, Ilschner, Ohlemeyer, Banati, & Kettenmann, 1993), modulate synaptic activity (Tremblay, Lowery, & Majewska, 2010; Wu, Dissing-Olesen, MacVicar, & Stevens, 2015), regulate conduction velocity in axons (Dutta et al., 2018), support neural development (Schafer & Stevens, 2013; Wu et al., 2015), and aid in recovery from CNS injury (Kreutzberg, 1996; Pineau & Lacroix, 2009). Microglia account for 5–12% of the cells in the CNS (Lawson, Perry, Dri, & Gordon, 1990); they derive from the yolk sac primitive myeloid progenitors and are maintained independently of definitive hematopoiesis (Ginhoux et al., 2010). Microglial cells arise before embryonic day 8 (E8) (Lichanska & Hume, 2000) and migrate to the brain through the circulatory system (Nayak, Roth, & McGavern, 2014). Infiltrated microglia take up residence before the differentiation of other CNS cell types and become critical regulators of CNS development (Kierdorf et al., 2013; Ransohoff & Cardona, 2010).

Microglia self-renew via proliferation and are not replaced by bone marrow-derived cells in the healthy brain (Elmore et al., 2014). Once in the CNS, microglial cells continually monitor their microenvironment (Nimmerjahn, Kirchhoff, & Helmchen, 2005) and are implicated in neuroplasticity, host defense, homeostasis, wound healing, debris scavenging, and peripheral immune cells recruitment (Aloisi, 2001) (Figure 1). Activated microglia have the ability to migrate and undergo morphological and functional changes in response to a variety of stimuli, such as cytokines and growth factors (GFs) (Nayak et al., 2014; Tremblay, Lecours, Samson, Sanchez-Zafra, & Sierra, 2015). The presence of activated microglia has been documented in a plethora of brain injury and disease conditions in humans (Ransohoff & Perry, 2009) and in related animal models (Hanisch & Kettenmann, 2007). In fact, brain pathology that is not associated with microglial function is difficult to find (Faustino et al., 2011; Kim et al., 2017; Sapp et al., 2001).

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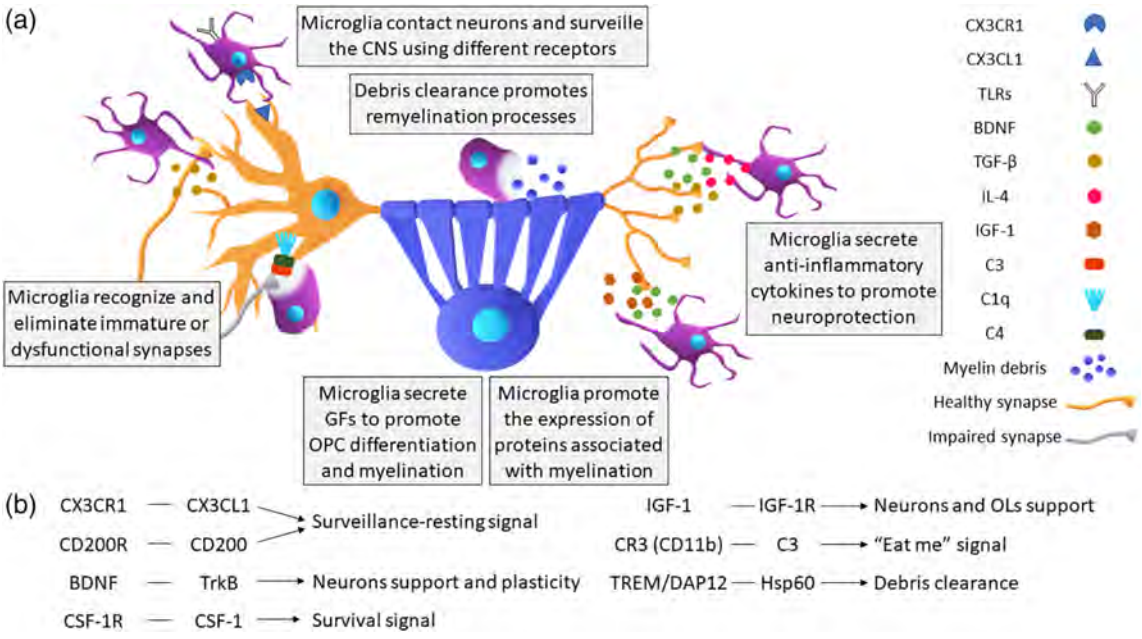

FIGURE 1 Microglial functions and molecular signaling in a normal physiological state. (a) In a normal physiological state, microglia contact neurons and surveille their environment using different receptors, such as CX3CR1 (Cardona et al., 2006) and TLRs (Olson & Miller, 2004). They eliminate immature or impaired synapses using their CR3 receptor which recognizes the complement system's C3 protein, and clear debris (Schafer et al., 2012). Microglia also secrete different cytokines and GFs to promote cell survival, maturation and proliferation (Nayak et al., 2014). IGF-1, secreted by microglia, promotes OPC differentiation and myelination (Wlodarczyk et al., 2017) and supports layer V neurons (Ueno et al., 2013). BDNF, also secreted by microglia, promotes survival of neurons and synaptic plasticity (Parkhurst et al., 2013), and regulates OPC differentiation and OL survival by positively modulating promyelinating transcription factors such as olig2 and PLP (Ramos-Cejudo et al., 2015; Zhou et al., 2015). (b) Microglia-related molecular signaling in the CNS and the outcome process

2 | MICROGLIAL POLARIZATION

Microglia are able to polarize into an activated state, such that their mode of action is situation-dependent (Ransohoff & Perry, 2009), resulting in varied and context-dependent microglial transcriptome profiles (Wes, Holtman, Boddeke, Moller, & Eggen, 2016). Microglial function results from a combination of variables, such as age, neuropathological condition, disease stage, and environmental factors (Colonna & Butovsky, 2017; Gosselin et al., 2017) (Figure 2). Microglia can produce and secrete proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), which have been shown to be beneficial during development (Shigemoto-Mogami, Hoshikawa, Goldman, Sekino, & Sato, 2014) but harmful in several pathological states in the CNS (Kim & Joh, 2006; Patterson, 2015). Conversely, microglia can produce and secrete anti-inflammatory cytokines and neurotrophic factors, including IL-4, IL-10, insulin-like growth factor-1 (IGF-1), and brain-derived neurotrophic factor (BDNF) (Cherry, Olschowka, & O'Banion, 2014). Microglia are affected by cytokines such as IL-4 and IL-13, leading to suppressed production of the proinflammatory cytokines IL-1β, IL-6, and TNF-α, reduced nitric oxide production, and enhanced tissue remodeling/repair (Colton, 2009). Importantly, microglia may not display a significant bias toward pro- or anti-inflammatory phenotypes. It is increasingly accepted that this dichotomy is inadequate to describe microglia *in vivo* (Ransohoff, 2016).

Many studies have characterized microglia and their roles in different brain pathologies (Perry, Nicoll, & Holmes, 2010; Prinz, Priller, Sisodia, & Ransohoff, 2011), where activated microglia demonstrate a marked change in morphology from ramified to amoeboid (Giulian & Baker, 1986). Once activated, microglia have been implicated in both protective and destructive functions (Ekdahl et al., 2009; Hanisch & Kettenmann, 2007), with their action depending on the perceived signals. Therefore, microglia are equipped with numerous pattern-recognition receptors (PRRs) (Kigerl, de Rivero Vaccari, Dietrich, Popovich, & Keane, 2014), such as toll-like receptors (TLRs) and the mannose receptor expressed on innate immune cells (Barak, Feldman, & Okun, 2014; Bianchi, 2007).

To perform their diverse functions, microglia express all types of TLRs, as shown in mice (Olson & Miller, 2004), rats (Zhang et al., 2013), and humans (Barak et al., 2014; Bsibsi, Ravid, Gveric, & van Noort, 2002). Damage-specific microglial activation and reaction, also mediated by the PRRs, is an essential early cellular response to brain injury (Giulian & Baker, 1985). For instance, TLR2 has a high affinity for many pathogen-associated molecular patterns (PAMPs) (Drouin-Ouellet & Cicchetti, 2012), whereas TLR4 can be triggered by lipopolysaccharide and recognizes damage-associated molecular patterns (DAMPs)—endogenous molecules released by injured tissue (Bianchi & Manfredi, 2009; Okun et al., 2012). As there is strong overlap between the signaling pathways (Zhang et al., 2013), microglia may not be able to discriminate between invading pathogens, stress, or aberrant endogenous molecular patterns (Mariani & Kielian, 2009). Overall, the activation of microglia through TLRs and their coreceptors initiates an immune response that is geared toward protecting the brain (Fellner et al., 2013; Latz, Xiao, & Stutz, 2013).

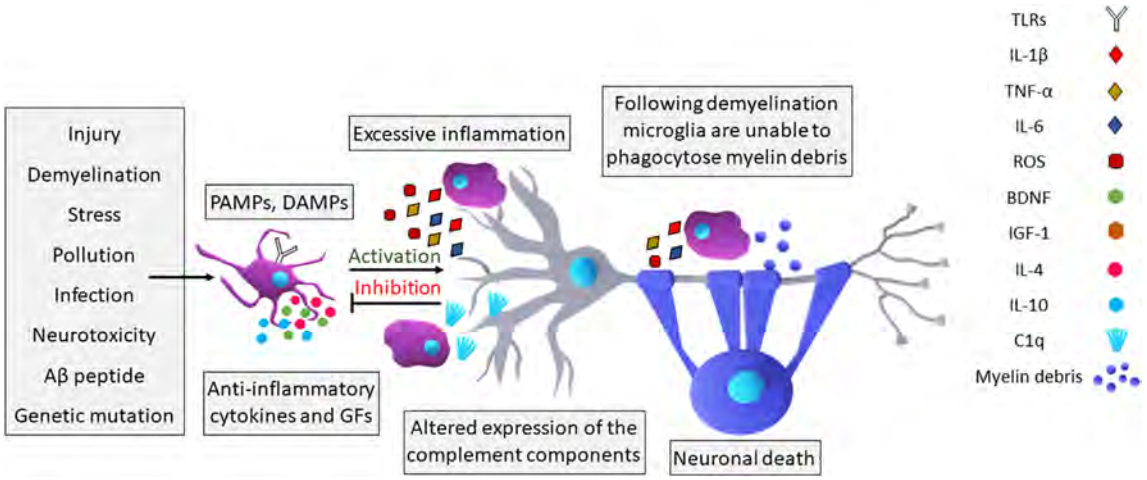

FIGURE 2 Alteration of microglial properties and molecular signaling in pathology. Upon pathological stimulation, microglia may change from a ramified to amoeboid form, secrete anti- or proinflammatory factors, and phagocytose harmful debris (Tremblay, 2014). However, in disorders involving myelination deficits, microglia may be compromised in their ability to phagocytose myelin debris and support OLs (Butovsky et al., 2006b; Zhou et al., 2015). In other pathological conditions, microglia can be overactivated and secrete high levels of inflammatory factors and radicals (Ekdahl, Kokaia, & Lindvall, 2009; Groh, Klein, Berve, West, & Martini, 2018; Kim, Hong, & Bae, 2018). This excess inflammation may eventually lead to neurotoxicity and neuronal death. Microglia-related treatments that result in microglial regulation have been shown to be effective in ameliorating deficits and promoting remyelination in pathological conditions (Butovsky et al., 2006a; Groh et al., 2018; Janova et al., 2018)

However, under certain circumstances (Fu, Shen, Xu, Luo, & Tang, 2014; Jones et al., 2015; Nair & Bonneau, 2006), microglia might be exposed to nonphysiological levels of immune stimulators (Ekdahl et al., 2009; Yao et al., 2013), affecting their typical responses. Impaired microglial activity at different stages of life can severely impair plasticity-related processes and cognitive functions (Morris, Clark, Zinn, & Vissel, 2013). For instance, elevated microglial activation has been shown in response to a range of psychosocial stressors in early life, as well as in adulthood (Calcia et al., 2016), known to increase the risk of mental illness mediated by microglial inflammatory activation (Frick, Williams, & Pittenger, 2013; Nair & Bonneau, 2006).

2.1 | Microglial polarization in autism spectrum disorder

Alterations in microglial activity, morphology, and gene expression have been associated with neurodevelopmental disorders (Garey, 2010; Gupta et al., 2014; Tetreault et al., 2012) (Figure 3). This is logical, given the crucial role played by microglia during development and adulthood in the elimination and maturation of synapses (Paolicelli et al., 2011). Several studies have shown that children with autism spectrum disorder (ASD) suffer from an ongoing neuroinflammatory process in different regions of the brain mediated by microglial activation (Chez, Dowling, Patel, Khanna, & Kominsky, 2007; Vargas et al., 2005).

Indeed, microglial activation has been reported in multiple studies focusing on ASD. For example, neuroimaging studies using positron-emission tomography or magnetic resonance imaging (MRI) found putative inflammation in the brains of ASD subjects (Pardo, Vargas, & Zimmerman, 2005; Suzuki et al., 2013; Vargas et al., 2005). Similarly, postmortem studies found increased density of microglia in the gray matter, along with morphological abnormalities and altered neuronal interactions in ASD subjects (Morgan et al., 2010). A study examining the prefrontal cortex (PFC) in ASD subjects demonstrated a neuron-directed microglial activation response in ASD (Morgan et al., 2012). Microglial activation, which leads to neuroinflammation, was reported in autistic children, with increased levels of oxidative stress mediators and proinflammatory cytokines such as IL-6, TNF-α, and interferon-gamma (IFN-γ) (Vargas et al., 2005). Increased protein levels of microglial IL-6 were measured in the cerebellar cortex of subjects with ASD (Wei et al., 2011), disrupting neuronal migration, an important process in establishing proper brain wiring (Wei et al., 2011). Finally, using transcriptome analysis, it was shown that genes related to microglial activation are upregulated in autistic subjects (Gupta et al., 2014; Voineagu et al., 2011).

2.2 | Maternal immune activation and ASD

One of the proposed risk factors for ASD involves maternal immune activation (MIA) (Ponzio, Servatius, Beck, Marzouk, & Kreider, 2007; Smith, Li, Garbett, Mirnics, & Patterson, 2007). A recent study modeled MIA by acute administration of lipopolysaccharide to E12 mouse embryos and found significant elevation of IL-1β, TNF-α, and IL-6 in the fetal brain, suggesting long-term microglial activation (O'Loughlin, Pakan, Yilmazer-Hanke, & McDermott, 2017). Another study modeled MIA by viral infection and similarly found alterations in microglial activation, density, migration, and maturation properties in the rat offspring (Zhang, Jing, Zhang, Bilkey, & Liu, 2018). Interestingly, both studies suggested prolonged microglial activation, as it was also evident postnatally. The potential link between MIA and microglial activation was also examined using a few novel treatments in human and animal trials. Microglial inhibition using luteolin decreased

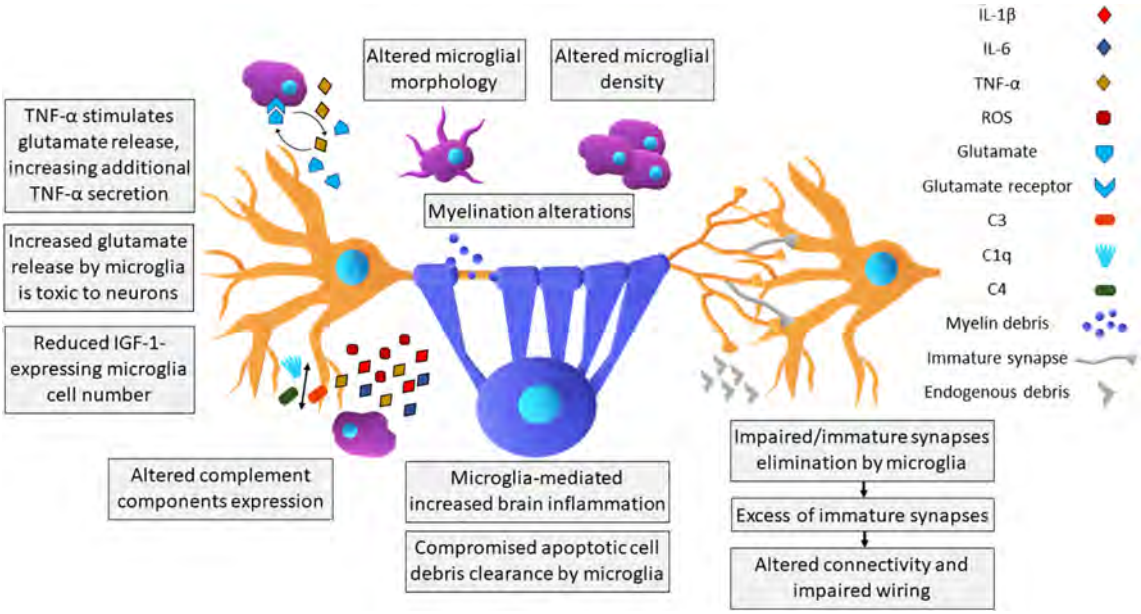

FIGURE 3 Alteration of microglial properties and molecular signaling in neurodevelopmental disorders. Microglial alterations, such as morphological abnormalities, altered microglial density and cell number (Morgan et al., 2010), high levels of inflammatory cytokines (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005) and glutamate (Maezawa & Jin, 2010), compromised phagocytosis (Sekar et al., 2016), excess synapses, and altered connectivity (Filipello et al., 2018; Sellgren et al., 2019), have been shown to occur in neurodevelopmental disorders. Moreover, molecular alterations, such as upregulation of SHANK proteins and Psd95 in neurons (Kim et al., 2017), altered TREM2 expression (Edmonson, Ziats, & Rennert, 2014; Filipello et al., 2018), and elevated levels of CX3CR1 and BDNF in microglia have been associated with ASD (Edmonson et al., 2014; Ricci et al., 2013). Conversely, a reduction in microglial BDNF levels is seen in RTT (Katz, 2014), and a reduction in myelin-related genes (*CNP*) has been measured in postmortem brains of schizophrenic and major depressive subjects (Aston, Jiang, & Sokolov, 2005; Peirce et al., 2006). Microglia-related treatments, such as inhibition of microglial activity, have been shown to be effective in ameliorating deficits in neurodevelopmental disorders (Bertolino et al., 2017; Taliou, Zintzaras, Lykouras, & Francis, 2013)

their inflammatory effect, improved sociability in humans (Taliou et al., 2013; Theoharides, Asadi, & Panagiotidou, 2012), and attenuated autistic-like behaviors in mice (Bertolino et al., 2017). Interestingly, gastrointestinal disturbances have also been suggested to influence the severity of symptoms in children with ASD (Adams, Johansen, Powell, Quig, & Rubin, 2011). Of relevance, a MIA-induced ASD mouse model presented altered gut microbiota which was reversed after treatment with *Bacteroides fragilis* (*Hsiao* et al., 2013). The gut microbiota was suggested to reduce microglial secretion of proinflammatory cytokines in ASD (Kim et al., 2018), and specifically, microbiota-derived bacterial fermentation products were suggested to regulate microglial homeostasis (Erny et al., 2015). Apart from their role in development, microglial actions play a crucial part in maintaining CNS homeostasis and synaptic plasticity (Napoli & Neumann, 2009) (Figure 4).

3 | MICROGLIA, NEURON, AND OL CROSSTALK UNDER HOMEOSTATIC CONDITIONS AND IN SYNAPTIC PLASTICITY

3.1 | Microglia promote neurogenesis and oligodendrogenesis

Neurogenesis and oligodendrogenesis in the CNS serve to maintain its function. In the rat subventricular zone (SVZ), from postnatal days 1 through 10 (P1–P10), activated microglia are densely populated and provide optimal levels of IL-1β, IFN-γ, and IL-6 to stimulate both neurogenesis and oligodendrogenesis (Shigemoto-Mogami et al., 2014; Wong, Stowell, & Majewska, 2017). Accordingly, inhibition of microglia with minocycline decreased microglial activation, reduced proinflammatory cytokine levels (i.e., IL-1β, IL-6, TNF-α, and IFN-γ), and subsequently significantly inhibited neurogenesis and oligodendrogenesis in the SVZ (Shigemoto-Mogami et al., 2014).

Overall, these findings suggest that microglial activation status affects the proliferation of SVZ neural progenitor cells (Matarredona, Talaveron, & Pastor, 2018). Specifically, it was shown that IL-1β, IFN-γ, and IGF-1 enhance neurogenesis, whereas only IL-1β and IL-6 enhance oligodendrogenesis (Shigemoto-Mogami et al., 2014). Therefore, it can be concluded that the cytokines' roles and functions depend on their context.

3.2 | Microglial fine sculpting of neuronal connections during development and in the mature CNS

Following their establishment in the CNS, microglia are highly mobile and primarily use an amoeboid morphology to regulate neural circuits (Nayak, Roth, & McGavern, 2014). For example, most of the cerebellar Purkinje cells that undergo developmental apoptosis are engulfed by amoeboid microglia, which release superoxide ions to trigger this process (Marin-Teva et al., 2004).

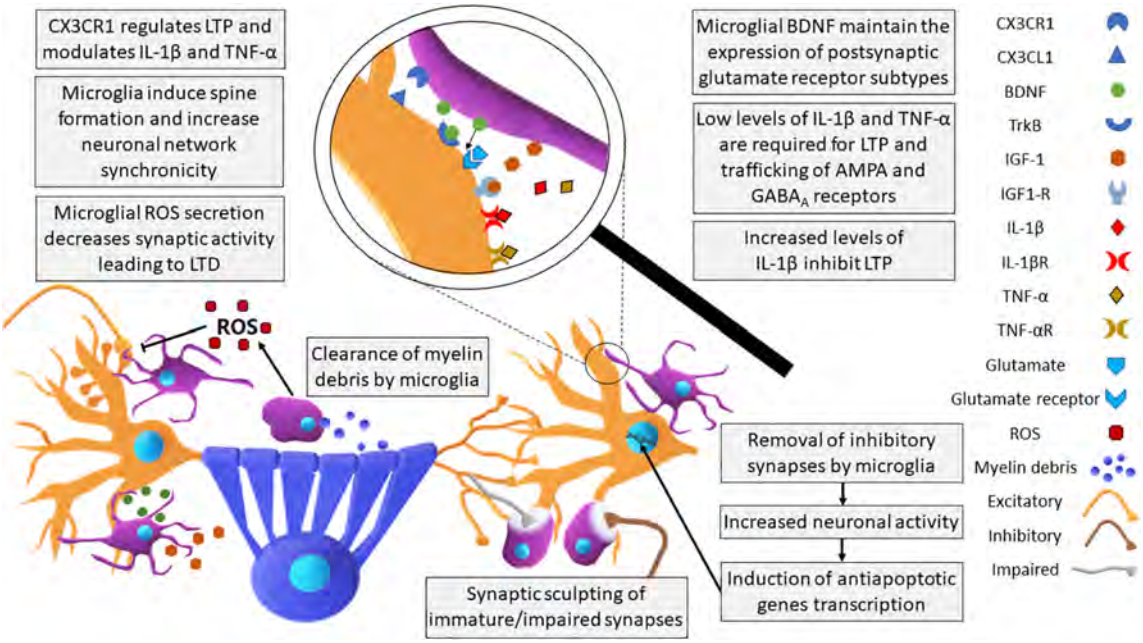

FIGURE 4 Microglial functions and molecular signaling in synaptic plasticity. Microglia regulate the molecular signaling that can affect synaptic plasticity processes such as LTP and LTD (Arnoux & Audinat, 2015; Maggi et al., 2009; Rogers et al., 2011). Microglia can also mediate the removal of impaired or inhibitory synapses from neurons (Arnoux & Audinat, 2015; Trapp et al., 2007), and however, induce spine formation (Ji, Akgul, Wollmuth, & Tsirka, 2013). These modifications can alter neuron survival and activity, which may lead to altered neuronal network activity and synchronicity

During brain development, neurons form an excess number of synaptic connections; many of these are subsequently removed during synapse sculpting (Figure 1), a critical process for appropriate brain connectivity (Kettenmann, Kirchhoff, & Verkhratsky, 2013; Paolicelli et al., 2011). Microglia are key regulators of synapse elimination during development via refinement of immature synapses (Schafer & Stevens, 2013; Sierra, Abiega, Shahraz, & Neumann, 2013) (Figure 4). Microglia were shown to engulf presynaptic (i.e., axonal terminals) and postsynaptic elements during developmental periods of circuit refinement in the CNS (Bilimoria & Stevens, 2015; Paolicelli et al., 2011). Contradictory results showed no evidence of elimination of postsynaptic material, although microglial contact on dendritic spines was suggested (Weinhard et al., 2018). Using in vivo two-photon imaging, it was suggested that the microglial contact on spines can increase the synchronization of neuronal populations by enhancing synaptic activity (Akiyoshi et al., 2018). Furthermore, it was shown *in vitro* that adding microglia to neuronal cultures decreases synaptic activity, synapse density, spine numbers, expression of AMPA receptor (GluA1), and levels of synaptic adhesion molecules (Ji et al., 2013). These findings demonstrate that "surveilling" microglia can modulate synaptic activity by regulating the number of synapses.

In the adult brain, microglia remove synapses from damaged neurons (Cullheim & Thams, 2007; Trapp et al., 2007) and are also key regulators of neuronal and synapse function in the healthy brain (Bilimoria & Stevens, 2015; Paolicelli & Ferretti, 2017) (Figure 1). Such remodeling of neuronal synapses occurs constantly throughout life (Wu et al., 2015), with synaptic connections in many areas constantly undergoing remodeling based on experience, resulting in synaptic plasticity (Tremblay et al., 2010). Connectivity-refinement deficits may lead to the impairment of brain wiring as implicated in the etiology of several neurodevelopmental disorders (Sekar et al., 2016; Thion, Ginhoux, & Garel, 2018; Zhan et al., 2014), including ASD (Filipello et al., 2018) and schizophrenia (McGlashan & Hoffman, 2000) (Figure 3). A recent study utilized microglia-like cells through cellular reprogramming of monocytes from schizophrenia subjects (Sellgren et al., 2019). Excessive synaptic pruning was shown to occur in this subject-derived cellular model (Sellgren et al., 2019). Moreover, synaptic elimination affects age-associated cognitive decline and the development of several neurodegenerative disorders (Kim & Joh, 2006). Interestingly, synapse connectivity might also be affected by alterations in myelination (Schain, Hill, & Grutzendler, 2014). Similar to synaptic elimination, demyelination might disrupt the communication between neurons and has also been suggested to play a role in neurodegenerative disorders (Nave & Ehrenreich, 2014; Trapp & Nave, 2008).

3.3 | Microglia–OL crosstalk in myelination

Microglial interactions with OLs can affect OL functionality and myelination properties. A recent study (Wlodarczyk et al., 2017) identified a CD11c + microglial subset that predominates in primary myelinating areas of the developing brain, and expresses genes for neuronal and glial survival, migration, and differentiation. In contrast to healthy adult and inflammation-activated cells, neonatal CD11c + microglia

show unique myelinogenic and neurogenic phenotypes (Wlodarczyk et al., 2017). These cells are the major source of IGF-1 (Rodriguez-Perez, Borrajo, Diaz-Ruiz, Garrido-Gil, & Labandeira-Garcia, 2016), and its selective depletion from CD11c + microglia leads to impairment of primary myelination (Wlodarczyk et al., 2017). Interestingly, microglia produce and secrete IGF-1 to support the survival of layer V cortical neurons during postnatal development (Ueno et al., 2013), yet OLs do this as well (Wilkins, Chandran, & Compston, 2001). Therefore, microglia could be contributing to cell survival indirectly by supporting oligodendrogenesis or through an additive effect on OL-derived GFs.

Evidence of the microglia's role in oligodendrogenesis can be found in rodents with acute or chronic experimental autoimmune encephalomyelitis (EAE)—an experimental model of brain inflammation and multiple sclerosis (MS). Injection of IL-4-activated microglia into the cerebrospinal fluid of rodents with EAE resulted in increased oligodendrogenesis in the spinal cord and improved clinical symptoms (Butovsky, Landa, et al., 2006a). The newly formed OLs were spatially associated with microglia expressing major histocompatibility complex class II proteins and IGF-1 (Butovsky, Landa, et al., 2006a). Treatment with IGF-1 was also suggested to restore spine density and synaptic amplitude, increase Psd95-expression levels, and stabilize cortical plasticity in a mouse model for Rett syndrome (RTT) (Tropea et al., 2009). Moreover, a reduced number of IGF-1-expressing microglia was implicated in a mouse model of Tourette syndrome and was suggested to mediate neuronal loss, although such a reduction was not shown in human subjects (Frick & Pittenger, 2016). Thus, beneficial consequences of microglia on the pathological conditions in which myelin is impaired, being mediated by GF secretion, should be considered as a possible therapeutic approach (Hagemeyer et al., 2012).

3.4 | Roles of microglia and myelination in synaptic plasticity

Aside from the well-known myelin-related neurological disorders, such as MS (Trapp & Nave, 2008) and central pontine myelinolysis (Lampl & Yazdi, 2002), myelin deficits resulting from altered glia–neuron interactions are associated with altered neuronal plasticity and cognitive impairments (McKenzie et al., 2014; Nave & Ehrenreich, 2014).

Microglia secrete cytokines and GFs and eliminate synapses in part by monitoring synaptic transmission (Wake, Moorhouse, Miyamoto, & Nabekura, 2013; Ziv et al., 2006); as such, they play a key role in neuronal connection properties, in accordance with neuronal function (Schafer et al., 2012). OLs greatly increase the speed of electrical transmission through nerve axons by forming the axonal myelin sheath and clustering ion channels at the nodes of Ranvier, where action potentials are propagated (10.1038/nature09614, 2010). Myelination is finely and locally modified to orchestrate the timing of action potentials that may require both high and low conduction velocities (Waxman, 1997). Microglia are also involved in myelin debris clearance in normal aging (Shobin et al., 2017) and in disease conditions, as shown in cuprizone-induced demyelination models (Poliani et al., 2015; Skripuletz et al., 2010). The importance of myelin debris clearance by microglia was demonstrated by blocking microglia-specific phagocytosis through inhibition of Rab7 (a key regulator in endolysosomal trafficking (Kiral, Kohrs, Jin, & Hiesinger, 2018)). This manipulation resulted in enhanced accumulation of myelin fragments in microglial endosomes and prevented remyelination (Safaiyan et al., 2016), emphasizing the microglia's key role in synaptic plasticity.

3.5 | Microglia and myelin-associated proteins

Early studies using microglia and OL cocultures showed that microglia stimulate the expression of myelin basic protein (Mbp) and proteolipid protein (Plp) in OLs, suggesting a positive role for microglia in myelination (Hamilton & Rome, 1994).

A recent study showed that in a *Plp1*-mutant mouse model for progressive MS, targeting microglia by oral administration of colony stimulating factor-1 receptor (CSF-1R) inhibitor substantially reduced inflammation-related demyelination, axonopathic alterations, and neuronal degeneration (Groh et al., 2018).

2′,3′-Cyclic-nucleotide 3′-phosphodiesterase (*CNP*) is another myelin-associated gene whose mRNA levels are significantly reduced in postmortem brains of schizophrenic and major depressive subjects (Aston et al., 2005; Flynn et al., 2003; Peirce et al., 2006). Moreover, a significant decrease in CNP protein levels has been shown in postmortem brains of schizophrenic patients (Flynn et al., 2003).

In humans and mice, reduced expression of *CNP* is associated with catatonic signs in an age-dependent manner (Hagemeyer et al., 2012). Depletion of microglia in *Cnp*-deficient mice prevented catatonia onset in young and mature mice (Janova et al., 2018). These findings, from postmortem tissues and the mouse model, revealed microglia and low-grade inflammation of myelinated tracts as the triggers for this previously unexplained mental condition (Janova et al., 2018). Thus, specific microglia-targeting anti-inflammatory therapies might help in treating other disorders associated with catatonia, such as mood-induced psychotic disorders and malignant neuroleptic syndrome (Tandon et al., 2013).

4 | MICROGLIAL ALTERATIONS IN WILLIAMS SYNDROME AND NEUROLOGICAL CONDITIONS

We recently showed multifaceted myelin deficits in Williams syndrome (WS) subjects and a mouse model for WS (Barak et al., accepted to *Nature Neuroscience*, in press; Barak, B. et al., 2019), a genetic neurodevelopmental disorder that affects social behavior and fine motor skills (Barak & Feng, 2016). These myelination-related deficits, a result of *Gtf2i* deletion in forebrain excitatory neurons, are mediated by abnormal neuron–glia interactions and are ameliorated following administration of FDA-approved drugs such as 4-aminopyridine and clemastine. We also measured a significantly increased number of microglia (Iba1-positive cells) in the mutant mouse cortex (data not published), where we characterized myelination deficits. This opens an exciting

research avenue that connects the interplay between myelination and microglial abnormalities to other neurodevelopmental disorders, as increased microglial density has also been shown in ASD (Morgan et al., 2010), schizophrenia (Garey, 2010), and WS (Wilder, Hanson, Lew, Bellugi, & Semendeferi, 2018) (Figure 3).

Moreover, activated microglia-mediated brain inflammation has been observed in attention deficit hyperactivity disorder (Anand, Colpo, Zeni, Zeni, & Teixeira, 2017) and Tourette syndrome (Lennington et al., 2016), whereas impaired synapse refinement has been seen in schizophrenia (Sekar et al., 2016), and significant microgliosis has been observed in subjects with depression who committed suicide (Steiner et al., 2008).

5 | CONSEQUENCES OF ALTERED MICROGLIAL ACTIVITY ON COGNITION AND SYNAPTIC PLASTICITY IN THE CNS

5.1 | Microglia and the complement system in synaptic plasticity

The complement system is an evolutionarily conserved branch of the innate immune system. The mammalian complement family consists of more than 30 soluble and cell-associated factors. These factors are engaged in a cascade that converges in the cleavage of C3 to release the anaphylactic peptide C3a and the opsonin C3b, followed by downstream events (Zipfel & Skerka, 2009). Several studies have suggested that microglia participate in synapse elimination through a phagocytic engulfment mechanism involving complement receptor 3 (CR3) (Fu et al., 2012; Ramaglia et al., 2012; Schafer et al., 2012). CRs bind to the complement fragments C3b and C4b—hub molecules of the complement-activation cascade—and regulate clearance of immune complexes and cell debris (Groves, Dart, Covarelli, & Caron, 2008; Khera & Das, 2009). CRs are also involved in activity-dependent synapse sculpting, where key proteins of the complement cascade, namely C1q and C3, were implicated in tagging "weaker" synapses that are normally pruned (Stevens et al., 2007).

Microglia-mediated synaptic elimination depends on neuronal activity, as microglia preferentially phagocytose less active presynaptic inputs (Stevens et al., 2007). *C1q*- and *C3*-mutant mice have excess synaptic connections in the mouse retinogeniculate system, a commonly studied area in research on developmental synaptic elimination (Stevens et al., 2007). This complement-dependent synaptic sculpting is significantly downregulated in the mature visual thalamus, suggesting a highly regulated process that is likely restricted to the refinement stages of development (Schafer et al., 2012; Xavier, Menezes, Goldman, & Nedergaard, 2014).

5.2 | Microglial CR3 and CR4 in neuropsychiatric disorders

C4 promotes C3 activation, allowing the latter to covalently attach to its targets and promote their engulfment by phagocytic cells (Fu et al., 2012). *C4* deficiency compromises synaptic elimination in mice (Sekar et al., 2016). The *C4A* variant is significantly upregulated in postmortem tissue of schizophrenic subjects (Gandal et al., 2018). The frequency of *C4B* variant deficiency is significantly higher in ASD subjects compared to controls (Odell et al., 2005), and the mRNA levels of *C1q*, *C3*, and *C4* are significantly decreased in the PFC of ASD subjects (Fagan, Crider, Ahmed, & Pillai, 2017). Overall, these alterations might affect the microglia's ability to recognize and engulf defective synapses.

Further studies are needed on the *C3* on *C4* risk variants and other complement system components, to reveal how they shape behaviors relevant to psychiatric disorders. A transgenic animal model that conditionally overexpresses *C3* or *C4* in the CNS has yet to be examined. Such a transgenic model would enable studying whether overtagging of synapses for microglial engulfment can enhance synaptic elimination, shedding light on neuropsychiatric disorders with altered connectivity.

5.3 | Autophagy and the functional role of TREM2–DAP12 in development and ASD

Triggering receptor expressed on myeloid cells 2 (TREM2) and its adapter protein DAP12 are expressed exclusively by microglia in the CNS (Bechade, Cantaut-Belarif, & Bessis, 2013; Chertoff, Shrivastava, Gonzalez, Acarin, & Gimenez-Llort, 2013). TREM2 interacts with DAP12 and stimulates microglial migration, cytoskeletal reorganization, and increased phagocytosis associated with secretion/reduction of cytokines, depending on the ligand to which the complex binds (endogenous or exogenous) (Takahashi, Rochford, & Neumann, 2005). TREM2 signaling has a variable impact in different brain regions, depending on their myelin content, their level of TREM2 expression, and the presence of alternative TREM2 ligands (Mecca, Giambanco, Donato, & Arcuri, 2018; Poliani et al., 2015). In *Trem2*$^{-/-}$ mice, microglial reduction was significant in the hippocampus, accompanied by defective synapse elimination (Filipello et al., 2018). In the cuprizone model, which mainly affects the corpus callosum, TREM2 was required for microglial response to prolonged demyelination, removal of damaged myelin sheaths, and secretion of trophic factors that support differentiation of OL precursor cells (OPCs) (Poliani et al., 2015).

Consistent with these findings, in an EAE mouse model, blocking TREM2 function resulted in the accumulation of myelin debris that continuously recruited non-engulfing microglia (Piccio et al., 2007). *Dap12*-deficient microglia in embryos resulted in upregulation of immune gene expression, and downregulated expression of genes involved in nervous system development and function (Pont-Lezica et al., 2014). This included neurite development and function, demonstrating a key role for microglia in corpus callosum development. Interestingly, defective synaptic refinement and dysfunctional microglia are associated with ASD (Kim et al., 2017; Tang et al., 2014; Wang et al., 2017).

Findings from postmortem brains of subjects with idiopathic ASD displayed a significant reduction in TREM2 compared to healthy subjects (Filipello et al., 2018). This was particularly evident in 5- to 23-year-old subjects, an age range that represents the developmental

period coinciding with synapse refinement in humans (Stiles & Jernigan, 2010). *Trem2*$^{-/-}$ mice show increased expression of synaptic proteins such as Psd95 and Shank2, an increased number of dendritic spines, increased functional connectivity between multiple brain regions, and increased miniature excitatory postsynaptic currents (mEPSCs) (Filipello et al., 2018).

These changes in *Trem2*$^{-/-}$ mice suggest circuit hyperexcitability and reduced long-range functional connectivity, converging in the observed altered sociability and repetitive behaviors that parallel those of human ASD symptoms (Filipello et al., 2018). Interestingly, an autistic-like behavior was observed in mice lacking the *Atg7* gene, a key component in autophagy, in cells of the myeloid lineage, including microglia (Kim et al., 2017). This was accompanied by significantly higher levels of Psd95 and Shank3 proteins and a significant elevation in the number of dendritic spines, attributed to an impairment in synapse elimination by microglia (Kim et al., 2017).

SHANK proteins encode a family of postsynaptic scaffolding proteins present at glutamatergic synapses in the CNS (Amal et al., 2018; Barak & Feng, 2016; Bozdagi et al., 2010; Monteiro & Feng, 2017; Peca et al., 2011; Zhou et al., 2016). Impairments in microglia's ability to sculpt synapses by phagocytic function could potentially lead to abnormal expression of SHANK proteins in the synapses, perturbing neurodevelopment. Interestingly, conflicting results showed a significant increase in *TREM2*, *DAP12*, and *CX3CR1* gene expression in the PFC of idiopathic ASD subjects (Edmonson et al., 2014).

Together, these findings suggest that the TREM2–DAP12 axis is essential for CNS homeostasis (Neumann & Takahashi, 2007) and may be fundamental in regulating microglial phagocytic function during their lifespan.

5.4 | Role of microglial fractalkine receptor in synaptic plasticity and ASD

CX3CR1 is a Gi-protein-coupled receptor that is encoded by the *Cx3cr1* gene and is expressed mostly by microglia in the brain (Cardona et al., 2006). However, its ligand, CX3CL1, also known as fractalkine, is largely expressed in neurons (Tarozzo et al., 2003) and is considered an OFF signal, keeping microglia in a nonactivated state (Biber, Neumann, Inoue, & Boddeke, 2007; Cardona et al., 2006). CX3CL1–CX3CR1 signaling represents a substantial communication channel between neurons and microglia, mediating fundamental microglial functions (Limatola & Ransohoff, 2014; Paolicelli, Bisht, & Tremblay, 2014) (Figures 1 and 4).

Cx3cr1-deficient mice at different stages of development (P8, P15, and P28) presented a transient decrease in the density of microglial cells, which were compromised in their capacity to engulf synaptic material (Paolicelli et al., 2011). In addition, a transient increase in dendritic spine density and a higher density of Psd95 were measured in microglial processes in the mouse hippocampus (Paolicelli et al., 2011). These alterations led to immature connectivity, augmented long-term depression (LTD), and impaired functionality of the excitatory synaptic network during postnatal development in the hippocampus (Arnoux & Audinat, 2015). Both juvenile and adult mice showed decreased functional brain connectivity and weak synaptic transmission, leading to deficits in social interactions and increased repetitive behavior (Paolicelli et al., 2011; Zhan et al., 2014), traits linked to ASD in humans (Barak & Feng, 2016). In juvenile *Cx3cr1*-deficient mice, this behavior was correlated with the observed transient circuit-sculpting deficits (Zhan et al., 2014).

Fractalkine is also involved in synaptic plasticity processes. For instance, fractalkine expression is upregulated in the hippocampus during memory-associated synaptic plasticity (Sheridan & Murphy, 2013). Yet, in *Cx3cr1*-deficient mice, reduced long-term potentiation (LTP) was recorded (Rogers et al., 2011), whereas another study showed increased LTP (Maggi et al., 2011). Moreover, deletion or reduction of *Cx3cr1* also led to elevated levels of the inflammatory cytokine IL-1β, which triggered a reduction of LTP in the brain (Wu et al., 2015). Ventricular infusion of an IL-1β receptor antagonist for 4 weeks reversed this reduction (Rogers et al., 2011), whereas infusion of an inactivated antagonist did not (Rogers et al., 2011). Therefore, intact chemokine signaling between neurons and microglia and appropriate levels of CNS cytokines are crucial for the maintenance of normal plasticity mechanisms.

6 | ROLES OF MICROGLIAL CYTOKINES AND BDNF IN SYNAPTIC PLASTICITY AND COGNITION

6.1 | BDNF in synaptic plasticity

BDNF is one of the most important neurotrophins secreted by neurons and glial cells, contributing to many aspects of CNS function, including cell differentiation, normal developmental apoptosis, brain connectivity, neuronal survival and migration, dendritic arborization, synaptogenesis, and activity-dependent forms of synaptic plasticity (Coull et al., 2005; Teng et al., 2005; Wu et al., 2015). Specifically, microglial BDNF can be released to directly affect the structure and function of nearby synapses (Parkhurst et al., 2013). Uncleaved pro-BDNF expression levels at early postnatal stages (<4 weeks) are high, leading to neuronal death and the removal of unnecessary neurons (Deinhardt & Chao, 2014). Pro-BDNF selectively activates its high-affinity receptor, the neurotrophin receptor p75 (p75NTR), leading mainly to the induction of proapoptotic signaling pathways and has been shown to facilitate LTD in the mouse hippocampus (Rosch, Schweigreiter, Bonhoeffer, Barde, & Korte, 2005; Woo et al., 2005).

In adult mice, mature BDNF is the prominent isoform (Greenberg, Xu, Lu, & Hempstead, 2009), and secretion of mature BDNF by microglia increases phosphorylation of neuronal tropomyosin kinase receptor type B (TrkB) (Parkhurst et al., 2013), a key mediator of synaptic plasticity. Mature BDNF binds to its highly specific receptor TrkB, increasing neuronal survival, and facilitating LTP (Deinhardt & Chao, 2014) (Figure 4). These actions are determined via interactions between the two transmembrane receptors, separately or together, determining cell fate. Indeed, in human studies, polymorphism in the *BDNF* gene has been associated with variations in hippocampal volume (Pezawas et al., 2004), memory performance (Egan et al., 2003),

and susceptibility to plasticity-inducing brain-stimulation protocols (Cheeran et al., 2008).

The importance of BDNF secretion by microglia was also demonstrated in a study (Parkhurst et al., 2013) showing that depletion of microglia leads to impaired activity of AMPA and NMDA receptors. This suggests a role for microglia in regulating the level of synaptic proteins that are associated with the glutamatergic excitatory synapse function. Moreover, microglial depletion led to severe deficits in multiple learning tasks and motor learning-induced synaptic remodeling (Parkhurst et al., 2013). Similar effects were discovered in genetically depleted microglial *BDNF* (*Parkhurst* et al., 2013). Elevated levels of the proinflammatory cytokine IL-1β (experimentally or induced by social isolation) were shown to decrease *BDNF* mRNA levels following learning, inhibit LTP in several regions of the hippocampus in young animals, and impair performance in behavioral paradigms such as the Morris water maze (Morris, 1984) and contextual fear conditioning (Barrientos et al., 2003), commonly used to examine hippocampus-dependent memory (Yirmiya & Goshen, 2011). Importantly, administration of IL-1 receptor antagonist before the social-isolation period prevented both *BDNF* downregulation and memory impairments produced by the isolation (Barrientos et al., 2003).

6.2 | BDNF involvement in myelination and neurodevelopmental disorders

BDNF was shown to affect growth in neurons by stimulating axonal sprouting toward a wound edge (Batchelor et al., 2002). Deficiency of *BDNF* can lead to a reduced number of neuron/glial antigen 2-positive OPCs and decreased expression of MBP and PLP in the CNS (Vondran, Clinton-Luke, Honeywell, & Dreyfus, 2010). In subjects with MS lesions, BDNF is primarily present in immune cells, such as microglia and reactive astrocytes (Stadelmann et al., 2002). The number of BDNF-immunopositive cells correlates with lesion demyelinating activity. In an EAE mouse model, administration of 18β-glycyrrhetinic acid (GRA) significantly reduced disease severity, mediated by a regulatory effect on microglia (Zhou et al., 2015). In addition, GRA treatment promoted remyelination by reducing inflammation that might inhibit BDNF expression in microglia and enhancing OPC proliferation (Zhou et al., 2015).

Furthermore, following CNS injury, BDNF becomes a potent extrinsic regulator of OPC differentiation and OL survival by positively modulating promyelinating transcription factors such as Olig2 and promoting expression of PLP (Ramos-Cejudo et al., 2015). BDNF in the injured spinal cord induced the formation of new OLs and promoted upregulation of MBP protein levels and prompt behavior recovery (Ikeda et al., 2002; McTigue, Horner, Stokes, & Gage, 1998).

BDNF might also play a role in RTT and ASD (Katz, 2014; Ricci et al., 2013), disorders with several intriguing differences, as well as similarities (Castro, Mellios, & Sur, 2013; Fombonne, 2009). There is evidence for immune system dysregulation early in life and altered myelination in both conditions (Ameis & Catani, 2015; Nguyen et al., 2013; Ricci et al., 2013). Decreased levels of BDNF have been implicated in RTT in both humans and mice (Katz, 2014; Schaevitz, Moriuchi, Nag, Mellot, & Berger-Sweeney, 2010). Moreover, impaired phagocytosis of apoptotic cell debris along with a toxic increase in glutamate release by microglia has been suggested in the RTT mouse model (Derecki et al., 2012; Maezawa & Jin, 2010). In contrast, BDNF was found to be elevated in subjects with ASD (Ricci et al., 2013), although conflicting results showed an association between reduced BDNF release from neurons and ASD (Sadakata et al., 2012).

Taken together, these findings underscore the importance of microglial BDNF as an essential regulator of learning-induced synaptic formation, functional connectivity, myelination, and behavioral performance (Barrientos et al., 2003; Chen, Dowlatshahi, MacQueen, Wang, & Young, 2001; McTigue et al., 1998) and suggest that BDNF may have significant potential in therapeutic approaches.

7 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Microglia are sensors of the CNS and playing a crucial role in health and in pathological conditions (Napoli & Neumann, 2009) (Figures 1 and 2). Numerous studies have implicated microglia in supporting neurons (Ueno et al., 2013), OLs and remyelination (Miron, 2017), highlighting these cells as an important therapeutic target. Equipped with PRRs, CRs, GFs, and cytokines, microglia take part in many processes occurring in the CNS, with their response fitting the specific conditions encountered (Olson & Miller, 2004; Stevens et al., 2007; Ueno et al., 2013). In this review, we summarize microglial functions in synaptic plasticity processes and neurological disorders, with special emphasis on ASD. However, this is just the tip of the iceberg. During development and throughout life, microglia promote myelination (Wlodarczyk et al., 2017), sculpt neural circuits (Yirmiya & Goshen, 2011), and help shape proper connectivity by remodeling based on experience, resulting in synaptic plasticity (Paolicelli et al., 2014) (Figures 1 and 4). Impairments in microglial components can have major consequences for the CNS, such as effects on circuit connectivity, homeostasis, immunological response, debris clearance, and remyelination (Kim et al., 2017; Lampron et al., 2015; Streit, Braak, Xue, & Bechmann, 2009). Impaired microglial activity at different stages of life can severely impair plasticity processes and cognitive functions, as seen in a variety of disorders, such as ASD (Suzuki et al., 2013), Alzheimer's disease (Wendt et al., 2017), MS (Zrzavy et al., 2017), and schizophrenia (Fillman et al., 2013).

7.1 | Which comes first? Microglial alterations or ASD?

The microglia's contribution to primary damage in neurodevelopmental disorders is still not fully understood. In this review, we mention a few microglial alterations that are suggested to occur in ASD: MIA, increased secretion of inflammatory cytokines (Vargas et al., 2005; Wei et al., 2011), increased density (Morgan et al., 2010), and increased expression of microglial activation-related genes (Gupta et al., 2014). However, these abnormalities might act as secondary effects. Some of the factors

supporting this are: (i) the above-cited studies measured activity and density using markers that are not specific to microglial cells (Vargas et al., 2005; Wei et al., 2011). For example, infiltrating macrophages can also be detected using those markers and are also able to secrete the detected cytokines (Arango Duque & Descoteaux, 2014); (ii) cytokines from the peripheral immune system have already been suggested to be involved in ASD (Masi et al., 2017); and (iii) studies examining MIA reported no obvious changes in microglial activation (Garay, Hsiao, Patterson, & McAllister, 2013; Giovanoli, Weber-Stadlbauer, Schedlowski, Meyer, & Engler, 2016).

Nevertheless, malfunctioning microglia have the potential to cause damage, such as connectivity problems and impaired myelination, which might result in behavioral changes (Akiyoshi et al., 2018; Bennett & Barres, 2017). As already noted, a reduction in TREM2 protein was observed in postmortem brains of autistic subjects (Filipello et al., 2018), and increased connectivity was detected in *Trem2*$^{-/-}$ mice (Filipello et al., 2018). Conversely, another study showed elevated *TREM2* gene expression in postmortem brains of autistic subjects (Edmonson et al., 2014).

Therefore, it is important to further investigate both transcription and translation levels, to get a better perspective on the source of the problem: to better define the microglia's role in ASD, or in any disorder for that manner, microglial-specific genes should be detected and recognized as risk factors. Interestingly, a recent study identified a rare variant of the microglia-specific *CX3CR1* gene and suggested its role in some pathophysiological mechanisms of ASD and schizophrenia (Ishizuka et al., 2017). Recent studies have revealed microglial subpopulations (Wlodarczyk et al., 2017), specific genes (Bennett et al., 2016), and proteins (Satoh et al., 2016). Use of advanced transcriptomic and proteomic techniques will help distinguish microglia from peripheral immune cells and might give a clearer picture of their multifaceted roles in health and pathology. Future work should focus on sorting subpopulations, manipulating genetic microglial aspects, and examining whether this might lead to behavioral defects.

Evidence has emerged showing that microglia do not consist of one identical population. Using a variety of methods, such as single-cell RNA-Seq, fractal analysis, and mass cytometry (Karperien, Ahammer, & Jelinek, 2013; Keren-Shaul et al., 2017; Mrdjen et al., 2018), subpopulations are starting to be characterized and their roles better defined, emphasizing the importance of the microglia's location and target.

Specific plasticity-related processes could potentially be affected by different microglial subpopulations with unique signatures of biological properties. Therefore, the pursuit of unique subsets of microglial signatures would have an enormous impact on the way we classify and study microglia, ultimately enabling development of better pathology-specific treatment.

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