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Microglia under psychosocial stressors along the aging trajectory: Consequences on neuronal circuits, behavior, and brain diseases

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ABSTRACT

Mounting evidence indicates the importance of microglia for proper brain development and function, as well as in complex stress-related neuropsychiatric disorders and cognitive decline along the aging trajectory. Considering that microglia are resident immune cells of the brain, a homeostatic maintenance of their effector functions that impact neuronal circuitry, such as phagocytosis and secretion of inflammatory factors, is critical to prevent the onset and progression of these pathological conditions. However, the molecular mechanisms by which microglial functions can be properly regulated under healthy and pathological conditions are still largely unknown. We aim to summarize recent progress regarding the effects of psychosocial stress and oxidative stress on microglial phenotypes, leading to neuroinflammation and impaired microglia-synapse interactions, notably through our own studies of inbred mouse strains, and most importantly, to discuss about promising therapeutic strategies that take advantage of microglial functions to tackle such brain disorders in the context of adult psychosocial stress or aging-induced oxidative stress.

1. Introduction

The reciprocal relationships between the nervous and immune systems have been intensively investigated in recent years, attracting more and more research interest, especially regarding the brain resident innate immune cells – microglia (Prinz and Priller, 2014; Ueno and Yamashita, 2014; Yirmiya et al., 2015). Microglia and the immune genes they express are now being recognized as key mediators of neuronal circuitry formation, function, and plasticity during normal physiological conditions (Hong et al., 2016; Salter and Beggs, 2014; Tay et al., 2016). Abnormality of these crucial microglial processes contributes to neurodevelopmental defects resulting in several mental disorders such as autism, schizophrenia, and depression (Laskaris et al., 2016; Yirmiya et al., 2015).

Microglia are derived from yolk-sac myeloid progenitors invading the brain during embryonic development (Ginhoux et al., 2010; Kierdorf et al., 2013). They are the only immune cells that permanently reside in the brain, alongside neurons, astrocytes, and oligodendrocytes. Microglial interactions with synapses were first described during development, and subsequently across the lifespan (Bisht et al., 2016; Paolicelli et al., 2011; Schafer et al., 2012; Tremblay et al., 2010, 2012; Wake et al., 2009). Microglia-synapse interactions are crucial for remodeling of neuronal circuits in the mature brain, and involve several mechanisms of which the best characterized are: 1) synaptic stripping, i.e. the physical separation of pre- and post-synaptic elements by intervening microglial processes, and 2) the phagocytic elimination or 'pruning' of axon terminals and dendritic spines (reviewed in Kettenmann et al., 2013). Recently, variations of the complement component (C)4 resulting in increased brain levels of C3, a known mediator of microglial synaptic pruning, were strongly linked to the susceptibility to schizophrenia in humans (Sekar et al., 2016). In addition, microglia release a number of neurotrophic factors such as glia-derived growth factor, brain-derived neurotrophic factor (BDNF), and insulin growth factor-1 (IGF-1) that are essential for neurogenesis, as well as neuronal circuit maturation and function (Parkhurst et al., 2013; Sierra et al., 2014; Ueno et al., 2013; Ziv and Schwartz, 2008).

Psychosocial stress is a state of mental or emotional strain or tension that results from adverse or demanding circumstances. It has

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multifaceted causes and occurs frequently over the course of a lifetime with varying dimensions and intensity, irrespective of a person's occupation or position within a society (Machado et al., 2014). Persistent maladaptive response to stress is associated with anxiety, depression, and several other neuropsychiatric manifestations (McEwen et al., 2015; Prenderville et al., 2015). The relationship between psychosocial stress and microglial phenotypic transformation, defined in terms of increased density, change of morphological indices, and exaggerated pro-inflammatory gene expression, is documented across animal and human studies. Microglial transformation has been identified in the hippocampus, prefrontal cortex (PFC), amygdala, and paraventricular nucleus of the hypothalamus, among other brain regions associated with emotion and the development of mental disorders. For instance, adult rats previously exposed to prenatal psychosocial stress display an increased density of ionized calcium-binding adaptor molecule 1 (Iba1)-immunopositive (+) microglia, enhanced levels of pro-inflammatory cytokines and reactive nitrogen species, as well as lowered levels of neurotrophic factors in the hippocampus and PFC (Slusarczyk et al., 2015). Chronic exposure to psychosocial stress may, therefore, utilize this arm to trigger and/or exacerbate mental disorders (Calcia et al., 2016; Lehmann et al., 2016; McKim et al., 2016; Ramirez et al., 2015).

When psychosocial stress becomes a chronic condition, people are more likely to develop and experience a more rapid progression of aging and various age-related diseases (Fidler et al., 2011; Hou et al., 2014; Mo et al., 2014). Aging can 'prime' microglial transformation – defined as a phenotypic imprinting that occurs upon exposure to stressful challenges of physiological or psychological nature – and exacerbate neuroinflammation (Cornejo and von Bernhardi, 2016; Niraula et al., 2017). Psychosocial stress and aging similarly potentiate cellular aging, oxidative stress, and neuroinflammation (Prenderville et al., 2015), and may thereby jointly accelerate cognitive aging and neurodegenerative diseases (Miller and Sadeh, 2014). Anxiety and depression are being increasingly recognized as risk factors for the development of neurodegenerative diseases that comprise the highly-prevalent Alzheimer's disease (AD) (Alkadhi, 2012; Norton et al., 2014), and preclinical studies demonstrate that chronic stress decreases the levels of memory-related signaling molecules in the hippocampus and exacerbates cognitive impairment in AD animal models (Alkadhi and Tran, 2015; Srivareerat et al., 2009).

Psychosocial stress triggers activation of the hypothalamic-pituitary-adrenal (HPA) axis leading to the release of glucocorticoid hormones from the adrenal glands, and prolonged exposure to corticosterone, which is the main glucocorticoid in rodents, was shown to exert detrimental changes in the brain inducing atrophy of neuronal dendrites (Sapolsky et al., 1985), synaptic loss (Liston and Gan, 2011; Tata et al., 2006), and eventually *N*-methyl-D-aspartate (NMDA) receptor-mediated excitotoxic death of neurons (Takahashi et al., 2002), caused by an excessive release of glutamate (Stein-Behrens et al., 1994). Synaptic loss is considered the best pathological correlate of cognitive decline across a myriad of brain disorders that include stress-induced major depression, schizophrenia, and neurodegenerative diseases such as AD (Duman and Aghajanian, 2012; Jurgens et al., 2016; McEwen et al., 2015; Spires-Jones and Hyman, 2014).

In this review, we explore the relevance of targeting microglia-synapse interactions to spare cognitive functions, which can be compromised along the aging trajectory by psychosocial stress. We hereby present the characteristics of microglia under psychosocial stressors, their implication in mental disorders occurring on the aging trajectory, through phenotypic alterations, remodeling of neuronal circuits (via synaptic formation, pruning, and neurogenesis), and mediation of oxidative stress and neuroinflammation. Our own studies using inbred strains of mice are discussed. We propose therapeutic avenues to promote stress resilience of microglia for a healthy cognitive aging.

2. Microglial transformation upon psychosocial stress across the lifespan

Chronic psychosocial stress is an environmental risk factor that exerts a profound influence on microglia and the brain's inflammatory milieu. Over the past ten years, various stress models induced by maternal separation, social isolation, chronic restraint, repeated social defeat, forced swim, foot shock and an unpredictable series of varying stressors, etc., have been used to study how stress affects microglia and thereby leads to exacerbated behavioral deficits in rodents (Calcia et al., 2016; Lehmann et al., 2016; McKim et al., 2016; Ramirez et al., 2015).

The impact of stress on microglia already occurs at early stages of brain development, especially when the exposure takes place during critical time windows of vulnerability (Bilbo and Schwarz, 2012; Castanon et al., 2015). Maternal stress profoundly affects the physiological and behavioral characteristics of the offspring, and has been linked to symptoms of depression and anxiety later in life (Knuesel et al., 2014). However, the responsible mechanisms remain largely undetermined. In a recent study, a 72-hour sleep deprivation occurring during the last gestational trimester in rats was shown to significantly increase $Iba1^+$ microglial density in the hippocampus of pre-puberty male offspring, alongside a decline in neurogenesis and an impairment of hippocampus-dependent spatial learning and memory (Zhao et al., 2015). These alterations could be reversed by pre-treatment with minocycline, a broad spectrum tetracycline-derived antibiotic commonly used to prevent microglial transformation, suggesting a role for microglia in mediating maternal sleep deprivation-induced cognitive deficits (Zhao et al., 2015). Similarly, prenatal stress induced by exposure to bright light for 45 min in mice was shown to adversely exacerbate microglia-mediated inflammatory response in the hippocampus of adult female offspring (Diz-Chaves et al., 2012). The hippocampus expresses a higher level of glucocorticoid receptor (GR) as compared to other brain regions (Reul and de Kloet, 1985), and since GR is the main receptor for the stress hormone corticosterone, the hippocampus is highly vulnerable to the harmful effects of psychosocial stress (McEwen et al., 1992).

Following lipopolysaccharide (LPS) injection, prenatally stressed adult mice compared with non-stressed mice showed an increased density of microglia with amoeboid cell bodies and numerous shorter and thicker processes in the dentate gyrus (DG) (Diz-Chaves et al., 2012). Prenatal stress, induced through 20 min of maternally forced swim on embryonic days 10–20, also increased microglial density in newborn rats across several brain areas that include the frontal, entorhinal and parietal cortices, as well as the subcortical basal ganglia, thalamus, medulla, septum, corpus callosum and internal capsule (Gomez-Gonzalez and Escobar, 2010). At postnatal day 10, this increased microglial density returned to baseline level, similar to non-stressed control rats, among all brain areas, with the exception of the corpus callosum where a reduction of ramified microglia was retained in the prenatal stress group (Gomez-Gonzalez and Escobar, 2010). Similarly, neonatal maternal separation led to alterations of microglial morphology in the somatosensory cortex, which persisted into adulthood, suggesting that microglial priming results in their exaggerated response to secondary stressful stimuli occurring later in life (Takatsuru et al., 2015). Microglial priming by stressful events during prenatal periods was proposed to explain their involvement in a number of affective disorders and schizophrenia (Hanamsagar and Bilbo, 2016).

In adulthood, a number of studies using various murine stress models revealed that exposure to acute and chronic psychosocial stressors at maturity can prime microglia at both morphological and molecular levels, as will be elaborated below. Several other recent reviews covering related topics are also available for readers (Calcia et al., 2016; Delpech et al., 2015a; Pearson-Leary et al., 2015; Reader et al., 2015; Walker et al., 2014).

2.1. Changes of density and morphology

The effects of stress on microglia can be multiple, depending on the type, duration, and frequency of the stressor-exposure. Nevertheless, many studies using various rodent models and stress paradigms consistently demonstrated that psychosocial stress can alter microglial cell density and morphology, using the OX-42 and Iba1 markers, which do not only label microglia, but also the bone marrow-derived monocytes and macrophages found in the brain under certain conditions. Considering that resident microglia represent the majority of brain myeloid cells, for simplicity we will solely refer to microglia in the subsequent paragraphs. For more information regarding the respective contributions of microglia *vs* bone marrow-derived monocytes to the stress response, our readers are referred to a recent review by Wohleb and Delpech (2017).

In particular, chronic unpredictable stress (CUS) induced by restraint or forced swim in rats and mice has been shown to significantly increase microglial density among the hypothalamus, thalamus, and hippocampus, as assessed by immunostaining for OX-42, which labels both CD11b and CD11c (Sugama et al., 2007). CD11b composes the complement receptor 3 that is expressed by microglia and is involved in synaptic pruning (Schafer et al., 2012), while CD11c is considered a marker of dendritic cells throughout the brain and periphery (D'Agostino et al., 2012). Similarly, an increased number of Iba1$^+$ microglia was observed in the prelimbic and infralimbic cortices following chronic restraint stress (30-minute daily exposure for 14 days) (Kopp et al., 2013). After chronic restraint stress in rats, Tynan et al. also observed a significant increase in Iba1$^+$ microglial density among a number of brain regions implicated in the stress response, including the anterior cingulate cortex (ACC), infralimbic and prelimbic medial PFC, nucleus accumbens, medial amygdala, bed nucleus of the stria terminalis, CA3 region of the hippocampus, and periaqueductal grey (Tynan et al., 2010). A significant increase in Iba+ microglial density was additionally observed in response to another stress paradigm — acute social defeat stress, in which the experimental mice were repeatedly stressed for 3 days. These changes were encountered within different stress-responsive brain regions, namely the infralimbic, prelimbic and ACC cortices, the basolateral amygdala, DG, nucleus accumbens, and the piriform cortex (Lehmann et al., 2016).

Kreisel et al. further revealed that microglial density varies over the course of stress response. The initial increase of Iba1$^+$ microglial density induced by 2 days of CUS in mice was followed, 2 days later, by a return to baseline density within the DG (Kreisel et al., 2014). In this case, the appearance of caspase–3$^+$ microglia 3 days after CUS also suggested that a subset of stressed microglia would undergo apoptosis (Kreisel et al., 2014). An increased proportion of microglia displaying morphological alterations was found to accompany these changes in density. For instance, alongside an increased density, a significant although partial decrease of OX-42$^+$ microglia showing an increased surface area and number of thick and short processes was described in the periaqueductal grey, a region modulating pain, upon restraint or forced swim stress in rats and mice (Sugama et al., 2007). These changes were not observed in mice deficient for the pro-inflammatory cytokine interleukin (IL)-18, indicating that microglial response to stress is partially mediated by IL-18, at least under this paradigm (Sugama et al., 2007).

In other rodent studies, chronic stress was similarly shown to alter microglial morphology in a subset of stress-responsive brain regions, inducing either hyper-ramification – as characterized by an increase in the total number of branching points and an elongation of processes (Hinwood et al., 2012, 2013) – or dystrophic morphologies – defined by a retraction of processes and a decrease in their branching points or arborization area (Kreisel et al., 2014; Milior et al., 2015; Wohleb et al., 2014). Microglial hyper-ramification was recently described in the mouse DG following 5 days of repeated forced swim stress (Hellwig et al., 2016). On the opposite, repeated social defeat was found to de-ramify microglia in the mouse amygdala and hippocampus within 8 days, and in the PFC after 24 days of stress (Wohleb et al., 2014). CUS, induced either conventionally or by an Intellicage system designed for behavioral monitoring with minimal human intervention, similarly reduced microglial process length and arborization area, in the hippocampus CA1 or DG after 2 or 5 weeks of exposure (Kreisel et al., 2014; Milior et al., 2015). For both hyper-ramified and dystrophic phenotypes, an enlargement of microglial cell body was additionally noted (Hinwood et al., 2012, 2013; Kreisel et al., 2014), suggesting an increased transcriptional activity (Dungrawala et al., 2010), which might be related to microglial release of either anti- or pro-inflammatory mediators, as well as trophic factors. Kreisel et al. additionally revealed that the initial increase in microglial cell body area observed after 2 days of CUS in mice returned to baseline when measured another 2 days later, within the DG (Kreisel et al., 2014).

Overall, these changes of microglial density indicate a greater need for microglial interventions within the stressed brain — taking place most likely at neuronal circuits — through oxidative stress, neuroinflammation and/or synaptic remodeling, as will be discussed below. Microglial morphological changes also suggest a continuum that may represent their functional repertoire recruited along the process of stress adaptation. Nevertheless, how the phenomena of hyper-ramification *vs* de-ramification may differently modify – structurally and functionally – microglial interactions with newborn neurons, synapses and other neuronal elements in the brain parenchyma remains to be determined.

2.2. Changes of inflammatory phenotype and association with anxiety

Researchers have also applied various approaches to characterize microglial changes induced by stress exposure at the molecular level. Such knowledge will undoubtedly provide deeper insights into the pathogenesis and pathophysiology of mental disorders. In animal behavioral researches, in addition to comparing inter-individual responses to stress, inbred mice were utilized to model the inter-individual variability in behavioral traits that include, but are not limited to, anxiety and psychosocial stress responses (Hovatta and Barlow, 2008; Wahlsten, 2012). A number of research studies have used inbred strains to discover novel candidate genes related to psychiatric traits such as schizophrenia and anxiety (Mozhui et al., 2010; Stevens et al., 1996; Yang et al., 2008). A previous study showed that lipopolysaccharide-binding protein (LBP), a protein involved in the acute-phase immunologic response to gram-negative bacteria, is dramatically decreased in the hippocampus of BALB/cByj mice, an inbred strain with high anxiety-trait, when the pups were exposed to maternal separation-induced early life stress. These LBP-deficient mice additionally showed increased anxiety-like behaviors (Wei et al., 2012).

The characterization of microglial molecular 'signature' has utilized polarizing phenotypes inspired by previous investigation on macrophages. Macrophages were divided into the classic, pro-inflammatory (M1) phenotype — defined as an increased release of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), IL-1β, IL-6, IL-12 and IL-18, as well as a reduction in microglial phagocytosis — *vs* the alternative, anti-inflammatory (M2) phenotype — defined as an increased production of anti-inflammatory IL-4, IL-10, IL-13 and transforming growth factor-beta (TGF-β), along with an increase in phagocytic ability. These M1 *vs* M2 phenotypes should, however, be considered as representing the opposing ends of a wide and mutually non-exclusive spectrum of myeloid phenotypic states (Sica and Mantovani, 2012), especially *in vivo*, a view that is reaching consensus both in the fields of microglia and macrophages (Murray et al., 2014; Ransohoff, 2016a).

Increasing evidence suggests that microglial transformation is finely tuned to the physiological and pathophysiological needs of the central nervous system (CNS), in which these cells adopt various intermediate phenotypes depending on the nature of the activating stimuli (Franco and Fernandez-Suarez, 2015). As a consequence, the M1 *vs* M2 categorization may under-represent the versatility of microglial functions. Even though the distinctive features of M1 and M2 microglia still need

to be better defined *in vivo*, cumulative evidence indicates that microglia can travel the alternative activation pathway, express M2-type markers, and promote neuroprotection under particular contexts (Franco and Fernandez-Suarez, 2015). Whether psychosocial stress may promote microglial polarization towards one *vs* another extreme remains to be determined, but accumulating evidence has emerged. For instance, enriched environment in a mouse model of depression induced by chronic corticosterone administration was shown to block pro-inflammatory cytokine gene induction and promote arginase 1 (*Arg1*) mRNA expression in sorted microglia, indicating an M2a-type of transition, and the effect was abolished in adiponectin-knock-out (KO) microglia (Chabry et al., 2015).

We additionally used inbred mice to study the relationship between microglial transformation and anxiety levels, which revealed that strains showing higher anxiety, such as DBA/2J and 129S2/Sv mice, had higher ratios of the pro-inflammatory major histocompatibility complex (MHC) class II$^+$ M1-like *vs* the anti-inflammatory CD206$^+$ M2-like microglia, compared with strains with lower anxiety, such as C57Bl/6J and FVB/NJ mice. These differences between inbred strains were found to be exacerbated after a peripheral LPS challenge known to prime the M1 polarization of macrophages and microglia (Orihuela et al., 2016). Furthermore, we found that the pro-inflammatory cytokines *Il1b*, *Il6*, and *Tnf*, and ratio of the M1/M2 marker genes, *Nos2/Arg1*, were elevated in the high anxiety strains undergoing LPS challenge (Li et al., 2014).

By further comparing transcriptomic microarray data of eight inbred strains, we identified a cluster of 23 brain immune genes that are constitutively expressed at different levels among these strains, most of which were innate immune genes that have been either demonstrated or speculated to be associated with microglial functions (Ma et al., 2015a, 2015b). Out of these inbred mouse strains, we and other researchers have found that C57BL/6 and DBA/2 mice, which are the most extensively studied ones, differ in many basal behavioral properties including increased anxiety (Hovatta et al., 2005; Kulesskaya et al., 2014; Mozhui et al., 2010; Voikar et al., 2005) and reduced sociability (Ma et al., 2015b; Moy et al., 2007). We also found that C57BL/6 and DBA/2 mice responded differently to psychosocial stress in changing their social and cognitive behaviors (Kulesskaya et al., 2014). Notably, our work revealed that these two strains differed in their expression of several genes shown to regulate synaptic pruning or plasticity, such as *C1qb*, *Cx3cl1*, *H2-d1*, and *H2-k1* (Ma et al., 2015a, 2015b). *C1qb* is an important subcomponent of the classical complement system demonstrated to mediate microglial synaptic pruning in development, aging, and AD (Hong et al., 2016). *Cx3cl1* encodes the fractalkine (CX_3CL1), a ligand that, along with its receptor CX_3CR1 expressed on microglia, is essential for healthy neuron-microglial crosstalk (Arnoux and Audinat, 2015; Paolicelli et al., 2014). *H2-d1* and *H2-k1*, which encode the MHC class I antigen D-B-alpha-chain and antigen A, respectively, are important for the presentation of foreign antigens to the immune system (Neefjes et al., 2011), and also for synaptic elimination, neuronal wiring, and long-term synaptic plasticity during brain development (Adelson et al., 2016; Lee et al., 2014).

Besides ours, a few other previous studies have identified that psychosocial stress can induce changes in microglial gene expression, with different outcomes depending on the stress paradigm. Although some studies using chronic restraint stress on rats did not find any evidence of increased IL-1β, MHC class II and CD68 (a marker of lysosomal activity) in rat microglia (Hinwood et al., 2013; Tynan et al., 2010), acute stress induced by tail- or foot-shock in rats was shown to upregulate microglial MHC class II, *Il1b* or *Cd14*, a monocyte marker, and to downregulate *Cd200r* (Blandino et al., 2009; Frank et al., 2007). *Cd200r*, encoding a receptor regulating myeloid functions, was found to exert a calming influence on microglial phenotype upon binding to its ligand CD200 (Hanisch and Kettenmann, 2007; Jenmalm et al., 2006). In addition, the activity of P2X7R purinergic receptor expressed by microglia was shown to result in proliferation and transformation of rat primary hippocampal microglia even in the absence of pathological insult (Monif et al., 2009). By using a P2X7R antagonist or KO mice of the inflammasome component Nlrp3, Iwata et al. recently demonstrated that the release of IL-1β and TNF-α normally induced by acute restraint stress can be completely blocked in the hippocampus (Iwata et al., 2016). Moreover, administration of the P2X7R antagonist reversed anhedonic and anxiety-like behaviors caused by CUS (Iwata et al., 2016). Conversely, an inflammation restricted to the insular cortex, as induced by LPS infusion, was shown to enhance associative taste memory through a purinergic modulation of glutamatergic AMPA (but not NMDA) receptors (Delpech et al., 2015b). In another paradigm of CUS, depression-susceptible C57BL/6J mice, when compared to their resilient counterparts, showed elevated expression of TNF in the PFC and indoleamine-2,3-dioxygenase (IDO) in the raphe, accompanied by an increased density of Iba1$^+$ microglia in the PFC (Couch et al., 2013). In addition, various stress paradigms can potentiate microglia to produce more pro-inflammatory cytokines upon stimulation with LPS (de Pablos et al., 2014; Frank et al., 2007; Johnson et al., 2013; Wohleb et al., 2012), while a combination of innate immune challenge and psychosocial stressors was shown to summate into exaggerated anxiety and social deficits in rodents (Bilbo and Schwarz, 2012; Giovanoli et al., 2013; Wohleb et al., 2012).

Recently, repeated social defeat in mice was revealed to increase expression of a selection of microglial, or strictly saying, CD11b$^+$-cell-specific genes in the brain. Notably in these studies, the pro-inflammatory cytokines *Il1β* and *Tnfα* were found to be upregulated at early stages (within 12 h) of stress, contrary to *Il6*, which was only upregulated after 8 days of stress, and to *Cd14* and *Cx3cr1*, which were elevated throughout the 24 days of stress (McKim et al., 2015; Wohleb et al., 2011, 2014). The above-described effects have been accredited to an activation of the sympathetic nervous system, as blocking its activity by subcutaneous injection of propranolol (a β blocker) or guanethidine (a norepinephrine release inhibitor) counteracted the stress-induced upregulation of pro-inflammatory cytokines in the brain (Blandino et al., 2009; McKim et al., 2015), whereas intracerebroventricular administration of the β-adrenergic agonist isoproterenol amplified it (Johnson et al., 2013). Intriguingly, such effect was found to be opposite to the anti-inflammatory effect exerted by epinephrine and norepinephrine on immune cells in the periphery, since the expressions of both early and late genes induced for instance by LPS, including *Tnf* and *Il6*, were dampened in rodents (Bellinger and Lorton, 2014; Martelli et al., 2014). Whether such discrepancy is due to the differential expression and activity of adrenergic receptors or to some other confounding factors in microglia *vs* splenic macrophages is currently unclear.

The above data reporting changes in microglial density, morphology, and gene expression upon psychosocial stress have motivated the development of microglial modulators to tackle various brain diseases including mental disorders (Biber et al., 2016). Under stress paradigms, minocycline was demonstrated to reverse *Il1b* upregulation (Blandino et al., 2009), induce expression of M2 microglial markers, which include Arg1 — an enzyme that contributes to wound healing, Ym1 (Chi3l3) — a heparin-binding lectin, FIZZ1 — a cysteine-rich protein that promotes extracellular matrix deposition, and CD206 — a scavenging mannose receptor (Burke et al., 2014; Zhao et al., 2015). It also prevented microglial morphological transformation (Hinwood et al., 2012; Kreisel et al., 2014), and rescued cognitive deficits and depression-like behaviors, of stressed rodents (Burke et al., 2014; Hinwood et al., 2013; Kreisel et al., 2014). However, in these studies, minocycline exerted beneficial effects only when it was administered in prophylaxis prior to stress induction, showing minimal therapeutic outcomes after the onset of stress-related symptoms (Kreisel et al., 2014).

3. Microglial implication in mental disorders across the lifespan

3.1. Evidence from human studies

Given the importance of microglia and their mediators for normal brain homeostasis, it is not surprising that disturbances in these cells

are encountered across various mental disorders, such as schizophrenia and depression. Primary and secondary 'microgliopathologies' are considered to be implicated in numerous diseases and have been extensively studied in recent years (Biber et al., 2016; Prinz and Priller, 2014; Yirmiya et al., 2015). In humans, changes in microglial phenotypic transformation under psychiatric disturbance were observed in post-mortem brain samples (Steiner et al., 2008; Torres-Platas et al., 2014). For example, microglial cells showing increased staining for Iba1 and de-ramified morphologies were encountered in the white matter of the dorsal PFC and dorsal ACC of suicide-committers (Schnieder et al., 2014; Torres-Platas et al., 2014). In both regions, there was also an increased density of $CD45^+$ myeloid cells around the blood vessels (Schnieder et al., 2014; Torres-Platas et al., 2014). In addition, increased 'microgliosis' or density of MHC class II^+ cells was reported in the dorsolateral PFC, ACC, and mediodorsal thalamus in suicide-committers, irrespective of their schizophrenia or depression diagnosis (Steiner et al., 2008).

In parallel, clinical researchers have been employing the latest imaging technologies to visualize microglial activity *in vivo* and to correlate changes in their expression of phenotypic markers with cases of depression and other psychiatric disorders. For example, positron emission tomography (PET) imaging has been conducted by using ^{11}C-PK11195 – a ligand for the neuroinflammation marker translocator protein 18 kDa (TSPO) – to find a microglial association with depression (Setiawan et al., 2015). Compared to ^{11}C-PK11195, the second-generation TSPO radiotracers enable wider use in different research facilities and improve the signal-to-noise ratio (Vivash and O'Brien, 2016). Expressed on the outer mitochondrial membrane, TSPO, which is mainly but not exclusively expressed by microglia, is essential for steroid hormone synthesis by allowing the flow of cholesterol into mitochondria and is therefore involved in mitochondrial functioning, and shows lower expression in the healthy brain as compared to neuropathological conditions (Rupprecht et al., 2010). Overall, increased microglial density and morphological phenotypic transformation (such as enlarged cell bodies and de-ramified processes) and increased TSPO expression were widely documented in post-mortem brain specimens across autism (Morgan et al., 2010), schizophrenia (Bloomfield et al., 2016; Steiner et al., 2008; van Berckel et al., 2008), depression (Steiner et al., 2008) and bipolar disorder (Haarman et al., 2014) patients.

3.2. Microglial remodeling of neuronal circuits

In the absence of pathological insult, microglia continuously scan the brain parenchyma with their profusion of highly ramified, motile processes. This extreme dynamism has been discovered using non-invasive transcranial two-photon *in vivo* imaging of transgenic mice, in which microglia are fluorescently labeled (reviewed in Tay et al., 2016). Subsequently, ultrastructural analyses revealed that 94% of all microglial processes directly contact synaptic elements in the healthy brain (Tremblay et al., 2010). Axon terminals, dendritic spines, perisynaptic astrocytic processes, and synaptic clefts were found to be contacted, in decreasing order of frequency, in the adolescent mouse cerebral cortex (Tremblay et al., 2010). These synaptic interactions are far from being random but rather continuously modulated by synaptic plasticity, as well as by sensory and behavioral experiences (Milior et al., 2015; Pfeiffer et al., 2016; Tremblay et al., 2010, 2012). Overall, these findings led to the proposition that microglial 'immune' surveillance targets mainly synaptic elements under normal physiological conditions. In terms of molecular underpinnings, purinergic signaling – through the microglial P2RY12 (Haynes et al., 2006) – was shown to drive microglial response to a laser-induced injury in the mouse cerebral cortex *in vivo* (Davalos et al., 2005). Recently, microglial dynamics were also found to be controlled by the TAM receptor tyrosine kinases MerTK and Axl, known to regulate the innate immune responses of dendritic cells and macrophages and the engulfment of apoptotic cells by phagocytes (Lemke, 2013; Zagorska et al., 2014). Precisely, microglia from TAM-deficient mice displayed reduced process motility and delayed convergence towards sites of laser-induced injury in the cerebral cortex *in vivo* (Fourgeaud et al., 2016). However, how purinergic signaling could interact with the TAM receptor signaling pathways still remains elusive.

Surveilling microglia actively maintain health – a homeostatic process that strongly relies on their involvement with the guidance of axonal projections, the maturation, function and plasticity of synapses, and the integration of newborn neurons into the hippocampal and olfactory bulb circuitries (Cunningham et al., 2013; Hong et al., 2016; Salter and Beggs, 2014; Sierra et al., 2013; Squarzoni et al., 2014; Tay et al., 2016). Pre-synaptic axonal terminals, post-synaptic dendritic spines, and even entire synapses are engulfed by microglia in the healthy brain, as revealed using electron microscopy and/or super-resolution imaging within different regions (Paolicelli et al., 2011; Schafer et al., 2012; Tremblay et al., 2010). In the context of adult neurogenesis, surveilling microglia eliminate – by means of phagocytosis – the excess of newborn neurons dying by apoptosis in both neurogenic niches (Fourgeaud et al., 2016; Ribeiro Xavier et al., 2015; Sierra et al., 2010). For more information, our readers are referred to recent specialized reviews on the microglial regulation of neurogenesis, synaptic maturation, function and plasticity (Hong and Stevens, 2016; Valero et al., 2016).

In terms of underlying molecular mechanisms, CX_3CL1-CX_3CR1 signaling — which is the best-characterized axis of neuron-microglia interaction (Ransohoff and El Khoury, 2015) — was shown to mediate all the above-described physiological roles of microglia (reviewed in Arnoux and Audinat, 2015; Paolicelli et al., 2014) that are also profoundly affected by psychosocial stress (Knuesel et al., 2014; Lemaire et al., 2000; Takeuchi and Kawashima, 2016). Indeed, microglial CX_3CR1 is now considered to be crucially involved in developmental and adult neurogenesis, axon guidance, as well as synapse formation, maturation, function, and plasticity under normal physiological conditions, as notably demonstrated by the various defects described in CX_3CR1-KO mice (Hoshiko et al., 2012; Maggi et al., 2009, 2011; Paolicelli et al., 2011; Rogers et al., 2011; among others). In addition, studies in mice showed that microglial release of BDNF promotes the formation of dendritic spines in the cerebral cortex during motor learning on a rotarod (Parkhurst et al., 2013), the classical complement cascade induces microglial pruning of axon terminals and dendritic spines across several brain regions during development, schizophrenia, aging, and in AD (Hong et al., 2016; Sekar et al., 2016; Shi et al., 2015; Stevens et al., 2007), and purinergic signaling through microglial P2RY12 mediates experience-dependent plasticity in the visual system (Sipe et al., 2016).

Under pathological states that include psychosocial stress response in mice, our work recently uncovered the existence of an ultrastructurally distinct microglial phenotype, especially with respect to synaptic interactions (Bisht et al., 2016). These cells appeared to be extremely active, frequently reaching for synaptic clefts, while extensively encircling axon terminals, dendritic spines and entire synapses with their highly ramified and thin processes. They strongly express CD11b, which is involved in microglia-mediated synaptic pruning (Schafer et al., 2012), specifically in their processes encircling synaptic elements. These cells also express myeloid-cell-specific triggering receptor expressed on myeloid cells (TREM2), when associated with amyloid-β plaques in an APP-PS1 mouse model (Bisht et al., 2016). In AD pathology, $TREM2^+$ cells were recently shown to express the phagocytic effectors MerTK and Axl (Savage et al., 2015). These cells were rare under steady state conditions, but became prevalent upon CUS and repeated social defeat, as well as in CX_3CR1-deficiency, aging and AD pathology, and account for almost one-third of the microglial population under stress (Bisht et al., 2016). They exhibit several signs of oxidative stress including a condensed (electron-dense) cytoplasm and nucleoplasm, giving them a 'dark' appearance in electron microscopy, accompanied by endoplasmic reticulum dilation — the best characterized sign of oxidative stress at the ultrastructural level, mitochondrial disruption and heterochromatin-remodeling associated with epigenetic alteration (Bisht et al., 2016). These findings indicate that the 'dark' microglia could represent a subset of cells that become

stressed under adaptive pressure, and as a result of their hyperactivity, leading to abnormal (or perhaps specialized) interactions with synapses. As previously discussed, synaptic loss is the best pathological correlate of cognitive decline across a myriad of neurological disorders associated with chronic psychosocial stress, including depression, schizophrenia, and neurodegenerative diseases (Duman and Aghajanian, 2012; Jurgens et al., 2016; McEwen et al., 2015; Spires-Jones and Hyman, 2014).

Microglial involvement with the gradual impairment of learning and memory during normal aging has been revealed by several studies. In particular, microglial priming by aging (Cornejo and von Bernhardi, 2016; Niraula et al., 2017), as characterized by a more pro-inflammatory basal state accompanied by increased expression of MHC class II and a decline in anti-inflammatory profile, is detrimental to neurogenesis, synaptic plasticity, as well as learning and memory (Ekdahl et al., 2003; McPherson et al., 2011; Vallieres et al., 2002). In addition, the aged brain, and especially the hippocampus, shows a decline in the levels of fractalkine (Bachstetter et al., 2011; Rogers et al., 2011) that may, in turn, affects healthy neuron-microglial crosstalk and hence contribute to the reduced synaptic plasticity and neurogenesis during normal aging (Sheridan and Murphy, 2013; Sierra et al., 2014).

3.3. Microglial mediation of oxidative stress

Apart from their mediation of inflammation and roles at synapses, microglia normally function as a redox-signaling center in the brain, which suggests additional mechanisms by which these cells could mediate neuronal damage upon psychosocial stress (and normal aging). Activation of two rate-limiting enzymes involved with the formation of L-kynurenine, tryptophan 2,3-dioxygenase (TDO) and IDO, was shown to increase kynurenine levels in the blood and cerebrospinal fluid (CSF) and to decrease serotonin production during depression in humans (Oxenkrug, 2010). Stress, corticosterone signaling and several inflammatory cytokines induced the IDO-kynurenine pathway in rodent and human microglial cells, resulting in the production of neurotoxic kynurenine metabolites, such as 3-hydroxy kynurenine and quinolinic acid, which in return could exacerbate inflammation, oxidative stress, as well as depressive behavior (reviewed in Capuron and Castanon, 2016; Dantzer et al., 2011). Likewise, administration of L-kynurenine to mice resulted in the emergence of a depression-like phenotype, while in LPS-treated mice, depression-like symptoms were attenuated by administration of either the IDO-antagonist 1-methyl-tryptophan (1 MT) or the microglial inhibitor minocycline (Dobos et al., 2012; Kiank et al., 2010; O'Connor et al., 2009).

Both rodent and human microglia express NADPH oxidase (NOX) 2 and NOX4 to regulate redox balance and stimulate oxidative stress upon neuronal injury or pathogen invasion, while NOX1 is exclusive to rodent microglia (Cheret et al., 2008; Cooney et al., 2013; Harrigan et al., 2008; Jadhav et al., 2014; Li et al., 2009; Mead et al., 2012). Neuronal injury increased microglial migration towards the damaged neurons (Heppner et al., 1998). As a neuroprotective mechanism, microglia generated inducible nitric oxide synthase (iNOS, NOS2) and release reactive oxygen species (ROS) and proteinases to clear neuronal debris (Banati et al., 1993). Each oxidase system works differently to regulate oxidative stress. NOX1 and NOX2 both contributed to LPS-induced microglial generation of intracellular superoxide (O_2^-) radical and NO, while only NOX1 triggered microglial production of IL1β *in vitro* and *in vivo* in mice (Cheret et al., 2008). NOX1 deletion reduced microglial production of cytotoxic nitrite species and the loss of presynaptic proteins within the striatum of KO mice (Cheret et al., 2008). In addition, NOX2 was specifically upregulated in rodent microglia after traumatic brain injury and within the postmortem brain specimens of patients with Creutzfeldt-Jakob disease, a degenerative neurological disorder (Cooney et al., 2013; Sorce et al., 2014). Although NOX4 was not measured in rodent microglial cells after ischemic stroke (Kleinschnitz et al., 2010; Vallet et al., 2005), it was shown to be constitutively expressed in human microglia and to generate ROS as well as stimulate IL-6 expression (Li et al., 2009), suggesting that NOX subtypes contribute differently to the induction of oxidative stress in rodents *vs* humans. For more information regarding the relationships between oxidative stress and inflammation in the context of mental disorders, our readers are referred to an excellent review on the topic (Miller and Raison, 2016).

3.4. Aging effect on microglial oxidation (and inflammation) along with psychosocial stress

Oxidative stress is measured in adults having experienced psychosocial stress or psychiatric diseases in childhood or at maturity. Adults with childhood abuse, war or divorce experience had shorter telomeres in blood cells due to glucocorticoid-associated oxidative stress damage (Ceccatelli et al., 2007; Schiavone et al., 2013; Tyrka et al., 2010), and increased susceptibility to ROS and brain cancers due to an elevation of ROS and NOS levels in the CNS (Bukhtoyarov and Samarin, 2009). Patients diagnosed with anxiety disorders, depression, schizophrenia or bipolar disorder also demonstrated decreased protein expressions of antioxidants Cu,Zn-superoxide dismutase (SOD1), glyoxalase (GLO)-1, glutathione reductase (GSR)-1 and glutathione, alongside increased immunoreactivities for the oxidative markers NOXs, DNA oxidation marker 8-hydroxy-2′-deoxyguanosine (8-oxo-dG), and exacerbated lipid peroxidation, within the cerebral cortex, hippocampus, and amygdala (Andreazza et al., 2008; Brown et al., 2014; Bruce-Keller et al., 2010; Gawryluk et al., 2011; Nunes et al., 2013; Sugama et al., 2016). Similar findings were also obtained in the blood and serum from patients having these psychiatric disorders (Altuntas et al., 2000; Bahceci et al., 2015; Kunz et al., 2008; Ranjekar et al., 2003; Zhang et al., 2006). On the other hand, reduced oxidative damage has been associated with resilience to psychosocial stress in humans (Aschbacher et al., 2013).

Similarly, in animals undergoing psychosocial stress, microglial phenotypic transformation was accompanied by exacerbated immunoreactivities against the antioxidants SOD1, GLO-1, and GSR-1, and the oxidative markers nitrotyrosine and NOXs, within the cerebral cortex, hippocampus, substantia nigra, and locus coeruleus (Gerecke et al., 2013; Nunes et al., 2013; Schiavone et al., 2009; Schiavone et al., 2012; Seo et al., 2012; Sugama et al., 2016; Vollert et al., 2011; Yoo et al., 2011). In addition, 7-weeks of social isolation was shown to exacerbate oxidative stress and NOX2 expression, increase the density of $Iba1^+$ microglia, and the oxidative damage to neurons, in the nucleus accumbens and PFC, leading to enhance locomotor activity and impair memory (Schiavone et al., 2009). The relationship between microglial oxidative stress and inflammation has been characterized *in vivo* using ozone exposure, among several other paradigms, in rodents. For instance, ozone-depletion by the solvent 1-bromopropane and low-dose ozone exposure specifically increased oxidative stress and the density of $Iba1^+$ microglia in the substantia nigra, leading to a progressive death of dopaminergic neurons, a hallmark feature of Parkinson's disease (PD) (Rivas-Arancibia et al., 2015). Upon ozone exposure, the neuroinflammation markers nuclear factor kappa B (NFκB) and cyclic oxygenase 2 (COX-2) were also upregulated alongside an overproduction of ROS (Rivas-Arancibia et al., 2015). Intracerebroventricular injection of thrombin, a coagulation factor acting as a potent microglial phenotypic modulator both *in vitro* and *in vivo*, similarly increased iNOS expression, O_2-derived oxidant production, and protein oxidation, leading to neurotoxicity in the CA1 of rat hippocampus (Choi et al., 2005).

Several studies indicate that microglial impairment induced by psychosocial stress over the lifespan can accelerate brain aging and trigger the onset of neurodegenerative diseases that include AD and PD. Both psychological stress and aging potentiate oxidative stress (Miller and Sadeh, 2014; Rodrigues et al., 2014) and neuroinflammation (Cohen et al., 2012), which play together an important role in the pathogenesis of neurodegenerative diseases (Herrup, 2015; Kooi Ong et al., 2016; Ransohoff, 2016b). A mild restraint stressor that had little or no effects in young adult mice has been shown to disrupt spatial memory and

elicit a significant neuroinflammatory response in aged mice, notably by triggering increased expressions of IL1β and MHC class II (Buchanan et al., 2008). Adult wild-type male mice undergoing repeated restraint stress (20 h per week for 6 weeks) further showed suppression of microglial neuroprotective functions, accompanied by a loss of dopaminergic neurons and the aggregation of α-synuclein, another hallmark feature of PD, as a result of increased oxidative stress (Kooi Ong et al., 2016). Dopaminergic neurons constitute a population of cells highly vulnerable to the effects of oxidative stress, for various reasons that include not only their elevated mitochondrial bioenergetics and increased axonal arborization size (Pacelli et al., 2015), but also their dopaminergic content itself (Hastings et al., 1996; Kim et al., 2005; Offen et al., 1996).

Providing further support to this synergistic effect of inflammation and oxidative stress in the pathogenesis of neurodegenerative diseases, LPS injection in animals undergoing CUS also increased Iba1$^+$ microglial density, pro-inflammatory markers expression and neuronal loss, and caused a prominent activation of stress-related signaling pathways in the rodent substantia nigra and hippocampus (de Pablos et al., 2014; Espinosa-Oliva et al., 2011). The mechanisms by which microglia trigger oxidative stress and inflammation-induced neuronal dysfunction and/or degeneration were recently summarized (Rojo et al., 2014; von Bernhardi et al., 2015). Upon aging and psychosocial stress, the reduced brain levels of anti-inflammatory and immunoregulatory factors shift the CNS microenvironment towards a pro-inflammatory state (Jurgens and Johnson, 2012). Microglial priming described in the aged brain (Kettenmann et al., 2011) additionally involves the recruitment of region-specific modifications at the transcriptional level (Grabert et al., 2016). In particular, several genes mediating immune cell phenotypic transformation and energy production were found to be upregulated during aging, with microglia from the cerebellum and hippocampus maintaining a more immune-alert state as compared to the microglia from striatum or cerebral cortex (Grabert et al., 2016).

4. Proposed therapeutic targets to prevent stress- and aging-induced microglial impairment

4.1. Oxidative stress

The above findings demonstrate the potential of using antioxidants as a therapeutic approach to suppress neuroinflammation and restore the redox balance of the brain in the context of aging and neurodegenerative diseases, which could also be utilized to prevent and/or treat neuropsychiatric disorders triggered by chronic psychosocial stress. Antioxidants were shown to inhibit inflammation, NO production, iNOS protein expression, intracellular ROS production/level and lipoxygenase activity induced by LPS in both BV2 and primary rodent microglial cells (Lee et al., 2016; Onasanwo et al., 2016; Salemme et al., 2016). In addition, antioxidants mediate their anti-inflammatory effects through upregulation of the anti-oxidative enzyme Heme oxygenase 1 (HO-1) and the oxidative enzyme inhibitor tissue metallopeptidase inhibitor 2 (TIMP2) via the Nrf2/ARE pathway in microglia (Lee et al., 2016; Onasanwo et al., 2016; Townsend and Johnson, 2016; Wang et al., 2016). A similar phenomenon was observed across *in vivo* studies. An antioxidant, biochanin A, suppressed the exaggerated Iba1$^+$ microglial density, in addition to rescuing the neuronal loss and behavioral deficits in mouse models of AD and PD challenged with LPS (Justin Thenmozhi et al., 2016; Wang et al., 2015). Similarly, L-carnitine, a free radical scavenger, readily crossed the blood–brain barrier (Nalecz et al., 2004), reduced oxidative stress damage in brain tissues, and enhanced the functional outcomes in patients with mood disorders, neurometabolic disorders, or AD (Pettegrew et al., 2000; Ribas et al., 2014; Sitta et al., 2011). However, beneficial effects of antioxidants are still unclear and remain to be investigated in the context of psychosocial stress and neurodegenerative diseases (Ellwanger et al., 2016; Feng and Wang, 2012; Galasko et al., 2012; Mecocci and Polidori, 2012; Polidori and Nelles, 2014). Encouragingly, inhibition of the oxidative stress-neuroinflammatory cascade was shown to rescue the behavioral deficits associated with depression, bipolar disorder, and schizophrenia, in addition to restoring the redox balance in animal models (Deslauriers et al., 2014; Eren et al., 2007; Gawali et al., 2016; Jangra et al., 2016; Kulak et al., 2013; Masood et al., 2008; Ribeiro et al., 2013; Zugno et al., 2014) and humans (Berk et al., 2008; Galecki et al., 2009; Gautam et al., 2012; Khanzode et al., 2003; Lavoie et al., 2008; Magalhaes et al., 2016; Michalakeas et al., 2011; Ozcan et al., 2004; Reddy and Reddy, 2011).

4.2. Neuron-microglia communication

Unarguably, microglial pro-inflammatory properties should be restricted by using counter-regulatory mechanisms, while their homeostatic functions and synaptic interactions should be normalized to help cope with psychosocial stress. These functions are mainly regulated through bidirectional communication with neurons. Fractalkine signaling was found to exert anti-inflammatory properties almost two decades ago (Harrison et al., 1998). Intracerebroventricular injection of fractalkine-neutralizing antibodies greatly increased inflammatory response to TNF-α (Zujovic et al., 2001). Deficiency of CX_3CR1 caused a massive phenotypic transformation of microglia upon repeated LPS injection (Cardona et al., 2006), increased IL-1β expression in the hippocampus, and worsened neurodegenerative progression in mouse models of AD (Bhaskar et al., 2010; Shaftel et al., 2007), although beneficial effects on neuronal survival were reported as well (Fuhrmann et al., 2010). Furthermore, profound impairment of hippocampal-dependent learning and social interactions was detected in adult CX_3CR1-KO animals, possibly due to altered synaptic pruning by microglia (Paolicelli et al., 2011; Zhan et al., 2014) or to an increased inflammation within the CNS (Rogers et al., 2011).

Studies in mice showed that deficiency in CX_3CR1 or BDNF, as well as microglial depletion, similarly affected motor learning and fear conditioning (Parkhurst et al., 2013; Rogers et al., 2011). CX_3CR1-deficiency also altered spatial learning and memory (Maggi et al., 2011; Rogers et al., 2011). Microglial depletion by using clodronate or oral administration of the inhibitor of colony-stimulating factor 1 receptor (CSF1R) transiently impaired spatial memory without disturbing social interactions when tested after 7 days of treatment (Torres et al., 2015). However, early microglial depletion by using clodronate liposomes (up to 70% by postnatal day 6) had long-lasting consequences on social, mood-related and locomotor behavior, when tested with the elevated plus maze and open field paradigms (Nelson and Lenz, 2017). Recently, a mouse model in which an activating enzyme that is essential for autophagy — Atg7 — was selectively defective in microglia, was similarly shown to display an increased density of dendritic spines and synaptic markers in the cerebral cortex, accompanied by impaired social and repetitive behaviors reminiscent of autism (Kim et al., 2016), suggesting that a defect of neuronal circuitry remodeling could be at cause.

Unexpectedly, CX_3CR1-deficiency prevented the effects of CUS on microglial de-ramification and short- and long-term neuronal plasticity in the hippocampus CA1 region, as well as the emergence of depressive-like behavior (Milior et al., 2015). Furthermore, microglial phagocytosis of axon terminals and dendritic spines was basally elevated in the CA1, targeting synaptic elements in a non-specific manner, and was unmodulated by chronic stress (Milior et al., 2015). The CX_3CR1-deficient mice were also found to be resistant to stress-induced microglial hyper-ramification in the DG and to depression-like behavior and antidepressant treatment effect under the forced swim paradigm in another recent study (Hellwig et al., 2016). These findings indicate that microglia-regulated mechanisms could underlie the differential susceptibility to chronic stress and consequently the vulnerability to disorders, including major depression, triggered by stressful events.

Besides CX_3CL1-CX_3CR1 signaling, several other molecular axes have been identified to mediate neuron-microglia interaction by targeting microglial receptors, including CD200R (Costello et al., 2011;

Dentesano et al., 2014; Hoek et al., 2000; Meuth et al., 2008; Wright et al., 2000), sialic acid-binding immunoglobulin superfamily lectins (Siglecs) such as signal-regulatory-protein-alpha (SIRPα) (Gitik et al., 2011; Linnartz and Neumann, 2013; Zhang et al., 2015), and TREM2 (Jiang et al., 2013; Takahashi et al., 2005; Walter, 2015). These receptors have been shown to prevent microglial transformation upon binding to their respective neuronal counterparts. Interaction between the neuronal ligand CD200 and microglial receptor CD200R was found to be essential for maintaining a healthy neuron-microglial crosstalk (Hoek et al., 2000; Neumann, 2001). Disruption of this interaction resulted in the emergence of microglial amoeboid morphologies associated with an increased expression of pro-inflammatory molecules *in vitro* (Zhang et al., 2011). Similarly, the constitutive relationships between neuronal CD47 and CD22 onto the microglial receptors SIRP-α and CD45 are considered to be important for controlling neuroinflammation (Gitik et al., 2011; Linnartz and Neumann, 2013; Zhang et al., 2015).

A number of secreted neuronal proteins were additionally shown to attenuate microglial phenotypic transformation, these include anti-inflammatory cytokines such as TGF-β (Boche et al., 2006; Brionne et al., 2003; Wahl et al., 2006) and IL-34 (Greter et al., 2012; Luo et al., 2013; Mizuno et al., 2011; Wang et al., 2012), neuropeptides (Delgado and Ganea, 2008; Reinke and Fabry, 2006; Waschek, 2013) and neurotrophins (Kerschensteiner et al., 2009; Neumann et al., 1998; Wei and Jonakait, 1999). Our own previous study also identified a neuronal adhesion molecule – ICAM-5 – that showed immune-dampening function too when cleaved from neurons by metalloproteinases (Tian et al., 2008). However, all of these studies were conducted under physiological or pathological conditions that are not strictly related to stress and anxiety.

4.3. Neurotransmission and neuromodulation

Several neurotransmitters, and especially monoamines, may represent potent target molecules to regulate microglial transformation and restore their physiological functions, as evidenced by drugs that modulate their synthesis, release, and recycling in both clinical studies and animal models of stress-related mental disorders, such as depression and anxiety. In patients suffering from acute depression, the elevated plasma levels of IL-6 were reduced after treatments with fluoxetine, a selective serotonin reuptake inhibitor (SSRI) (Sluzewska et al., 1995). Recently, fluoxetine administered in an enriched environment was shown to increase the expression of pro-inflammatory markers in the hippocampus and in isolated microglia, while treatment in a stressful condition produced anti-inflammatory effects. In addition, these beneficial effects of fluoxetine in the stressful situation were accompanied by increased microglial cell body area, which is suggestive of an exacerbated transcriptional activity (perhaps anti-inflammatory), and by reduced process arborization area indicating that de-ramified morphologies are not exclusive to pro-inflammatory phenotypes (Alboni et al., 2016). In animal models, several anxiolytics and antidepressants have been reported to dampen neuroinflammation, as well as microglial morphological transformation in stressed animals. Fluoxetine was previously demonstrated to suppress the LPS-induced production of cytokines such as TNF-α, IL-1β, and IL-6 by cultured microglial cells (Ha et al., 2006; Lim et al., 2009; Liu et al., 2011). Imipramine (a tricyclic antidepressant) inhibited IFN-γ-stimulated microglial production of IL-6 and NO (Hashioka et al., 2007) and TNF-α (Hwang et al., 2008) *in vitro*, and ameliorated the LPS-induced depression-like behaviors in rats *in vivo* (i.p., 10 mg/kg daily) (Yirmiya et al., 2001). Recently, Imipramine (i.p. or via drinking water, 20 mg/kg daily) was further shown to block microglial morphological transformation and pro-inflammatory gene expression in the brain under the CUS and repeated social defeat paradigms in mice (Kreisel et al., 2014; Ramirez et al., 2015).

It should be noted that the mechanisms underlying the immune-regulatory roles of these drugs can be multiple in the brain, e.g. despite that the drugs may have a direct influence on microglia, the possibility that their effects are achieved indirectly through modulation of neurons cannot be excluded. This is reinstated by a recent report showing that a γ-aminobutyric acid (GABA)-ergic anxiolytic and antidepressant clonazepam, a selective agonist of GABAA-R with high affinity for the central benzodiazepine binding site, which does not bind with high affinity to the TSPO expressed by microglia, blocked the accumulation of macrophages into the brain without affecting the production of pro-inflammatory cytokines in the spleen (Ramirez et al., 2016). GABA itself was shown to attenuate the pro-inflammatory response of microglial cultures (Kuhn et al., 2004). Additionally, receptors for acetylcholine and norepinephrine have been shown to be expressed by cultured microglial cells and therefore could regulate microglial functions as well (Blandino et al., 2009; Carnevale et al., 2007; McKim et al., 2015).

5. Conclusion

Heterogeneity in the individual response to psychosocial stress suggests that resilience is a complex neurobiological process that emerges

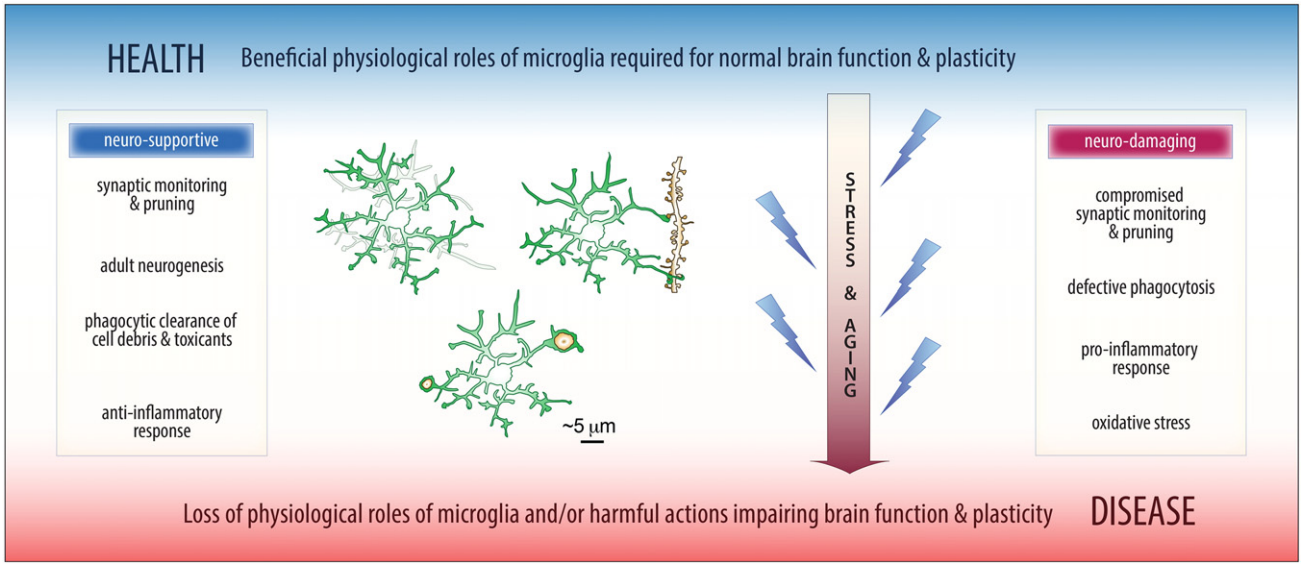

Fig. 1. Microglial dysfunction upon psychosocial stress and aging may have detrimental consequences on neuronal connectivity and behavior, thus contributing to brain diseases.

from a multitude of gene-gene and gene-environment interactions. Several mechanisms were proposed to underlie the individual differences in stress resilience and vulnerability, involving the interactions of immune cells and their inflammatory mediators with various neurotransmitter and other neuromodulatory systems (Pfau and Russo, 2015).

The integrative network formed by neurons and (micro)glia plays a major role in mediating the normal adult brain functions. Here, we have recounted current advances in this research field and discussed mechanisms underlying microglial regulation of neuronal synapses and conversely, the neuronal regulation of microglial phenotypic transformation at morphological and molecular levels. From the above discussions, one can see that microglia (as well as other immune and glial cells that are not covered by us here) are pivotal for actively shaping neuronal structural and functional plasticity. The responsible mechanisms include the clearance of cellular debris and toxicants, neurogenesis, anti-inflammatory response, as well as synaptic monitoring and pruning (see Fig. 1 for a schematic representation). Reciprocally, neurons play important roles in nurturing microglia and maintaining their inflammatory gene production, oxidative stress response, and phagocytosis at an appropriate level, in order to keep their own homeostasis under normal physiological conditions. However, both neurons and microglia are sensitive to psychosocial stress and persistent stress may compromise the dynamic balance of neuron-microglia interaction, disturb synaptic neurotransmission and hence increase the susceptibility to mental disorders.

Similar to chronic psychosocial stress, the aging process also potentiates oxidative stress and neuroinflammation, leading to compromised synaptic monitoring and pruning functions, notably through a defective phagocytosis (see Fig. 1). Chronic psychological stress is an environmental risk factor well known for accelerating aging, predisposing to neuropsychiatric and neurodegenerative diseases, as well as accelerating their progression, and exacerbating their symptoms. If depression is the devastating outcome of psychosocial stress, a considered risk factor and a comorbidity in neurodegenerative diseases, stress resilience, on the other hand, is the positive outcome of stress adaptation associated with healthy aging (Charney, 2004; Pfau and Russo, 2015). Since microglia act as a critical cellular component in the stress response, therapeutic interventions promoting resilience of these immune cells to aging and psychosocial stress could allow delaying the onset and/or progression of mental disorders.

Abbreviations

ACC	anterior cingulate cortex
BDNF	brain-derived neurotrophic factor
CNS	central nervous system
CSF	cerebrospinal fluid
CUS	chronic unpredictable stress
DG	dentate gyrus
GABA	γ-aminobutyric acid
IDO	indoleamine-2,3-dioxygenase
IFN	interferon
IL	interleukin
KO	knock-out
LPS	lipopolysaccharide
LBP	lipopolysaccharide-binding protein
MHC	major histocompatibility complex
NOS	nitric oxide synthase
PFC	prefrontal cortex
ROS	reducing oxidative species
Siglec	sialic acid-binding immunoglobulin superfamily lectin
SIRPα	signal-regulatory-protein-alpha
TGF-β	transforming growth factor-beta
TNF	tumor necrosis factor
TREM	triggering receptor expressed on myeloid cells
TSPO	translocator protein

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