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Stress and aging act through common mechanisms to elicit neuroinflammatory priming

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Abstract

Over the course of an animal's lifespan, there is a protracted breakdown in basic homeostatic functions. Stressors (both psychological and physiological) can accelerate this process and compromise multiple homeostatic mechanisms. For example, both stress and aging can modulate neuroinflammatory function and cause a primed phenotype resulting in a heightened neuroinflammatory profile upon immune activation. Microglia, the brain's resident myeloid cell, produce "silent" immune machinery in response to stress and aging that does not cause immediate immune activation; rather, these changes prime the cell for a subsequent immune insult. Primed microglia exhibit a hyperinflammatory response upon immune activation that can exacerbate pathology. In this review, we will explore parallels between stress- and aging-induced neuroinflammatory priming. First, we will provide a background on the basic principles of neuroimmunology. Next, we will discuss evidence that neuroinflammatory responses become primed in the context of both stress and aging. We will also describe cell-specific contributions to neuroinflammatory priming with a focus on microglia. Finally, common mechanisms underlying priming in the context of stress and aging will be discussed: these mechanisms include glucocorticoid signaling; accumulation of danger signals; dis-inhibition of microglia; and breakdown of circadian rhythms. Overall, there are multifarious parallels between stress- and aging-elicited neuroinflammatory priming, suggesting that stress may promote a form of premature aging. Further unravelling mechanisms underlying priming could lead to improved treatments for buffering against stress- and aging-elicited behavioral pathologies.

I. Background

The concept that stress and aging are interrelated has pervaded the gerontology literature in two main forms (Sapolsky et al., 1986). First, aging activates stress response pathways in a maladaptive, chronic manner, leading to reduced adaptivity to stress in senescence.

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Consequently, physiological systems in aged animals inadequately respond to stressors (Haigis and Yankner, 2010). For example, aged and young animals typically show comparable thermoregulation at baseline, but aged animals exhibit thermoregulatory impairments when heat- or cold-challenged (Degroot and Kenney, 2007; Tournissac et al., 2017). Second, chronic stress accelerates the aging process. Selye (Selye and Tuchweber, 1976) and later Sapolsky (Sapolsky et al., 1986) postulated that prolonged stress prematurely depletes an organisms energy reserves, accelerating the onset of senescence. Experimental evidence supports this theory. For example, hypocortisolism, which can develop from chronic stress exposure, is associated with shortened telomere length, a hallmark of aging (Wikgren et al., 2012).

The aging process is characterized by a protracted breakdown in basic homeostatic functions over the course of the lifespan. Stress can accelerate this process and compromise multiple homeostatic mechanisms. Of special interest here, aging and stress both have profound effects on neuroimmune regulation. For example, young animals maintain an adaptive balance between pro- and anti-inflammatory mechanisms in the brain: the healthy adult immune system is not activated at baseline but is poised for an effective immune response to infection or damage. In contrast, with aging, this balance shifts towards a potentially pathological sensitized neuroimmune state at baseline (Fonken et al., 2016b). Similarly, exposure to acute and chronic stressors can release inhibitory mechanisms that regulate immune cell activity in the central nervous system (CNS), leading to heightened neuroinflammatory responses to immune challenge (Frank et al., 2018).

This shift towards a baseline sensitized inflammatory phenotype has been termed neuroinflammatory “priming”. Priming is defined as a process whereby an antecedent condition or prior exposure to a stimulus potentiates the immune response to a subsequent condition or stimulus. In particular, priming of the neuroinflammatory response is attributed to microglia, the major CNS immune cell. Primed microglia exhibit a much stronger response to an inflammatory stimulus than that observed in stimulus-naïve microglia. Indeed, aging and stressors (both physiological and psychological) cause microglia to develop a primed phenotype, resulting in a protracted neuroinflammatory profile upon immune activation.

Here, we will explore the common mechanisms that mediate stress and aging induced neuroinflammatory priming. First, we will provide a brief background on some basic principles of neuroimmunology. Next, we will discuss cell specific contributions to neuroinflammatory priming with a focus on microglia. We will then explore evidence that neuroinflammatory responses become primed in the context of stress and aging with a focus on the common mechanisms that underlie priming in these two conditions. Finally, we will conclude by discussing the translational relevance of neuroinflammatory priming.

II. Key principles of neuroimmunology

Del Rio-Hortega provided a comprehensive characterization of the brain’s non-neuronal cellular components about 100 years ago. In particular, del Rio-Hortega was the first to identify and accurately assess the origin and role of microglia; he proposed that these cells

were of mesodermal origin and helped clear debris during CNS pathology (Somjen, 1988). A number of diverse functional roles have since been attributed to microglia. We now know that glial cells are present in healthy unstimulated brain and regulate basic homeostatic functions including synaptic development and pruning (Stogsdill and Eroglu, 2017; Wu et al., 2015), neuronal migration (Deverman and Patterson, 2009), and progenitor cell differentiation (Gonzalez-Perez et al., 2010). Microglia form and function are tightly regulated in the CNS to help regain homeostasis following activation. However, prolonged or exaggerated immune activation can cause maladaptive neuroinflammatory changes, or as del Rio-Hortega described, cause microglia to take on the phenotype of "voracious monsters". This introductory section will review the basic constituents of the brain's immune system and describe how immune activity is communicated to the CNS.

IIA. Immune to brain signaling

Neuroimmune activation can be induced by signals originating both inside and outside the CNS. Peripheral immune stimulation dramatically alters neural activity and induction of cytokines in the CNS (Dantzer et al., 2008). Exposure to pathogens or injury activates pattern recognition receptors (PRRs), that function as 'danger' sensors on peripheral innate immune cells, to initiate inflammatory cascades. PRRs bind both pathogen-associated molecular patterns (PAMPs), which are evolutionarily conserved molecular motifs from microbial organisms, as well as danger-associated molecular patterns (DAMPs), which are endogenous cellular products that are released following injury or stress. DAMPS include proteins, purine metabolites, DNA, and RNAs that are either typically found inside the cell (so once extracellular they signal damage) or are mediators that are secreted actively to drive inflammation (reviewed in (Schaefer, 2014). In response to PRR activation, innate immune cells including macrophages, monocytes, and neutrophils secrete inflammatory mediators such as pro-inflammatory cytokines [(e.g. interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interferon γ (IFNγ)]. The blood-brain barrier (BBB) generally prevents peripheral pathogens from entering the brain and directly activating CNS immune cells (Banks, 2015); however, inflammatory signals can be communicated from the periphery to the CNS through various pathways, including neural (e.g. vagus) and blood-borne (e.g. circulating PAMPs reach the circumventricular organs) routes (reviewed in (Dantzer et al., 2008).

IIB. Immune response in the CNS

In response to peripheral cytokines, a variety of changes occur in brain including *de novo* production of cytokines, chemokines, reactive oxygen species and secondary messengers that propagate CNS inflammation (Hansen et al., 1998; van Dam et al., 1992). These mediators are produced by resident CNS glia (microglia and astrocytes), endothelial cells, and peripherally-derived immune cells. The detection and propagation of an immune signal throughout the CNS causes a suite of behavioral and physiological modifications, collectively known as the sickness response (Dantzer et al., 2008). Behavioral changes associated with increased inflammatory molecules within the CNS include reduced food and water intake, decreased exploration and social behavior, hyperalgesia (pain hypersensitivity) and global changes in mood and cognition. Overall, the sickness response represents a shift in the motivational state of an organism and is considered highly adaptive and critical for

host defense (Hart, 1988). This response, however, can become pathological when immune cell activation in the CNS is exaggerated or persists long-term, such as in neurodegenerative diseases.

In addition to immune activation originating peripherally, CNS-localized injury and disease states can also lead to pathological persistent neuroinflammation. For example, spinal cord injury causes a robust CNS immune response with activation of CNS glia and recruitment of peripheral inflammatory cells to the lesion site (Popovich et al., 1997). Unfortunately, after CNS injury, the persistent inflammatory response can become increasingly pro-inflammatory over time, rather than repairing and resolving the injury, as in the periphery (Gaudet et al., 2017; Kigerl et al., 2009). Indeed, multiple CNS pathologies can be caused or exacerbated by neuroinflammation, including multiple sclerosis, ischemic stroke, Parkinson's disease, and Alzheimer's disease (Dendrou et al., 2015; Perry and Holmes, 2014; Ritzel et al., 2016).

IIC. Dynamic changes in microglia phenotype

Microglia are phagocytic myeloid cells that are distributed throughout the brain parenchyma and are the major source of cytokines and other inflammatory molecules in the CNS (Ransohoff and Perry, 2009). Microglia functions mirror those of tissue-resident macrophages but differ in a few key ways. Other types of myeloid cells in the brain, including meningeal, choroid plexus, and perivascular macrophages (Butovsky et al., 2014; Gautier et al., 2012), typically reside outside the parenchyma and have distinct developmental origins. Microglia are derived from progenitors in the yolk sac that colonize the brain around embryonic day 8 in mice (Alliot et al., 1999). Unlike monocytes, which continuously renew from bone marrow hematopoietic stem cells, microglia persist throughout adulthood by a self-renewal process (Ajami et al., 2007; Askew et al., 2017; Tay et al., 2017). Microglia numbers are tightly maintained in the adult brain by spatial and temporal coupling of proliferation and apoptosis (Askew et al., 2017). Undefined local signals cause microglia to develop region-specific phenotypes (variations in anatomical features, lysosome content, membrane properties, and transcriptomic profile) during the second postnatal week (De Biase et al., 2017). These region-specific phenotypes can cause microglia from different brain regions to demonstrate functional differences. For example, Grabert et al found that microglia isolated from the cerebellum, as compared to the cortex, have enhanced phagocytic activity *ex vivo* (Grabert et al., 2016). Microglia continuously assess their surrounding microenvironment via extension, withdrawal, and reformation of long cellular processes (Nimmerjahn et al., 2005). This active surveying of the microenvironment likely serves a housekeeping function, enabling microglia to effectively monitor and clear accumulated metabolic products and tissue debris.

Various homeostatic perturbations in the CNS can trigger microglia activation. Microglia that detect a homeostatic disturbance or "danger" signal can undergo rapid morphological and functional changes in order to: (1) phagocytose microbes and cellular debris; (2) migrate or proliferate to increase density in specific regions (Tay et al., 2017); and (3) produce and secrete inflammatory molecules (Yirmiya et al., 2015). Phenotypic shifts in microglia activity occur across a broad spectrum in the sense that microglia can synthesize a number

of both pro- and anti-inflammatory cytokines and release other molecular mediators (e.g. DAMPs).

Microglial activation in the adult CNS is tightly controlled by endogenous signaling. Notably, unstimulated microglia express much lower levels of cytoplasmic and cell surface molecules than do other types of tissue-resident macrophages, gating their transition to a pro-inflammatory state (Gautier et al., 2012). Exposure to neuronal cell-surface and soluble factors maintain microglia in a comparatively quiescent immunophenotype compared to other myeloid cells (Biber et al., 2007). The tight regulation of microglia by molecular factors in the CNS likely evolved to prevent microglia from damaging brain tissue, which is less susceptible to infection, but has more limited capacity for repair and regeneration than peripheral tissue.

III. Characteristics of neuroinflammatory priming

Before discussing priming phenomena in detail, it is important to consider the conceptual distinction between neuroinflammatory or *in vivo* priming and microglial or *ex vivo* priming. In the neuroimmune literature, this distinction is sometimes blurred, which might lead to erroneous conclusions. As mentioned above, in the context of immune-related phenomena, priming is a process whereby an antecedent condition or prior exposure to a stimulus potentiates the immune response to a subsequent stimulus. Thus, neuroinflammatory priming necessarily involves examining the effects of an antecedent condition such as aging on the immune response in the brain to a subsequent stimulus such as intra-peritoneal injection of the bacterium *E. coli.*, which elicits a robust pro-inflammatory response in the brain via immune-to-brain signaling (see section IIA). As explored in detail below, the neuroinflammatory response to *E. coli* is potentiated in aged animals compared to young animals, which demonstrates that aging serves as an antecedent priming condition (Barrientos et al., 2010). However, because *E. coli* was administered *in vivo*, determination of the cellular substrate(s) primed by aging is not possible under these experimental conditions. For example, the aging-induced potentiation of the neuroinflammatory response might be driven through enhanced immune-to-brain signaling via *E. coli* signaling at primed peripheral immune substrates (e.g. macrophages, monocytes and dendritic cells). Thus, microglia may be simply exhibiting a heightened pro-inflammatory response to increased peripheral pro-inflammatory drive via either neural (i.e. vagal) or humoral pathways. To definitively determine whether a cellular substrate is primed by an antecedent condition, it is necessary to directly expose a purified cell type to an immune challenge *ex vivo*. For example, highly pure hippocampal microglia were isolated from aged and young animals, and directly exposed to lipopolysaccharide (LPS; a cell wall component of gram-negative bacteria; *E. coli*) *ex vivo*. Microglia from aged animals exhibited a potentiated pro-inflammatory response to LPS compared to the response observed in microglia from young animals (Frank et al., 2010b) demonstrating that aging does induce a primed activation state in hippocampal microglia (Fig 1). Thus, it is important to consider the possible cellular components contributing to a primed neuroinflammatory response.

IIIA. Microglia priming

Microglia have multiple roles in the CNS and functional and morphological changes occur across a broad spectrum of activation states resulting in varying immunophenotypes and cytokine profiles (De Biase et al., 2017; Grabert et al., 2016; Ransohoff and Perry, 2009). For instance, microglia challenged with an initial minor immune stimulus can become primed – that is, predisposed to activation (Frank et al., 2016; Perry and Holmes, 2014) (Fig 2). Primed microglia maintain an intermediate inflammatory state characterized by shortened processes and expression of cell surface markers similar to activated microglia, but without producing appreciable secretion of inflammatory cytokines (Frank et al., 2007). Importantly, priming makes microglia susceptible to subsequent inflammatory stimuli. That is, primed microglia exhibit an exaggerated and/or prolonged inflammatory response to a subsequent immune challenge (Frank et al., 2007; Frank et al., 2010b). This secondary immune stimulus can arise from either peripheral or central sources of inflammation. For example, in rodents exhibiting microglia priming, injury to the brain or periphery can induce both prolonged neuroinflammatory and behavioral changes (Barrientos et al., 2012; Fenn et al., 2014a).

Microglia priming is a general process that is identified/revealed by the activity of the cell in response to an *ex vivo* secondary immune stimulus. Furthermore, whether distinct priming stimuli produce different phenotypes and molecular signatures in microglia is largely unknown. However, there are stereotypic changes in immunophenotype that may indicate that microglia are primed in the CNS, including upregulated expression of inflammatory pathway genes such as major histocompatibility complex II, toll-like receptors, NOD-like receptors, and purinergic receptors (Fonken et al., 2016a; Frank et al., 2006; Weber et al., 2015) and down-regulated expression of receptors in key anti-inflammatory pathways such as CD200R and CX3CR1 (Corona et al., 2010; Fonken et al., 2016c; Frank et al., 2017; Wynne et al., 2010).

IIIB. Other cell types contribute to neuroinflammatory priming

The CNS microenvironment strictly controls microglia activation state. Microglia communicate with other CNS cells, including neurons, astrocytes, and oligodendrocytes (Perry and Holmes, 2014) (summarized in Fig 3). Furthermore, soluble factors released by other cells can act to repress (e.g., TGF-β (Butovsky et al., 2014)) or activate (e.g., DAMPs (Venereau et al., 2015)) microglia. Additionally, the recruitment of other cells into the CNS can induce microglia activation and/or directly affect neuroinflammation.

a. Neuron-microglia interactions—Microglia-neuron interactions tightly regulate the phenotype and function of microglia. Under healthy conditions, several neuronally expressed ligands interact with inhibitory receptors on microglia to repress microglia activation. These microglia-neuron signaling dyads include CD200-CD200 receptor (CD200R) (Hoek et al., 2000), CX3CL1-CX3CR1 (Cardona et al., 2006), and CD47-SIRP-α (a “don’t eat me” signal also expressed on other cell types) (Jaiswal et al., 2009). Neuronal stress or damage can cause down-regulation of these neuronally expressed ligands leading to dis-inhibition of microglia. For example, CD200 is a membrane glycoprotein that is expressed throughout the CNS on neurons, endothelial cells, and oligodendrocytes

(Koning et al., 2009). CD200R is exclusively expressed on microglia and other myeloid cells in the CNS (Cardona et al., 2006). Interactions between CD200 and its receptor inhibit myeloid cell activity by initiating anti-inflammatory intracellular signaling cascades (Jenmalm et al., 2006) (described in more detail in section VC).

b. Microglia-astrocyte interactions—Astrocytes actively regulate microglia morphology and function and can both promote and inhibit microglia activity. Astrocytic inhibitory regulation of microglia involves the release of diffusible signals. For example, adding conditioned media from astrocytes to cultured microglia increases antioxidant activity (hemeoxygenase-1 gene and protein expression) and reduces IFN-γ-induced reactive oxygen species in microglia (Min et al., 2006). Astrocyte-derived factors promote microglia health and survival (Bohlen et al., 2017). Transforming growth factor β (TGF-β) is one such diffusible signal that can contribute to anti-inflammatory regulation of microglia by astrocytes (Brionne et al., 2003). TGF-β is synthesized and released by most cell types, including astrocytes, and is required for the development of normal adult-like microglia (Bialas and Stevens, 2013; Butovsky et al., 2014; Schachtrup et al., 2015). TGF-β can reduce the production of reactive oxygen species and cytokines in microglia (Herrera-Molina and von Bernhardi, 2005; Huang et al., 2010), likely via an NF-κB dependent mechanism (Noh et al., 2016).

There are also bi-directional pro-inflammatory interactions between astrocytes and microglia, such that activated microglia promote astrocyte activation and *vice versa* (Liu et al., 2011). For example, classically activated pro-inflammatory microglia release cytokines that act on astrocytic toll-like receptors to elicit “reactive” astrocytes (Farina et al., 2005). Reactive astrocytes become hypertrophic, upregulate intermediate filaments, can proliferate, and secrete cytokines and other mediators (Karimi-Abdolrezaee and Billakanti, 2012). Once reactive, astrocytes can lose the ability to promote neuronal survival, outgrowth, synaptogenesis and phagocytosis, and induce death of neurons and oligodendrocytes (Liddelow et al., 2017). Importantly, neuronal death can then lead to the release of DAMPs such as high mobility group box-1 (HMGB1), which in turn can contribute to microglia activation (Scaffidi et al., 2002). Astrocytes can further propagate inflammatory signals through the release of DAMPs such as adenosine triphosphate (ATP), which are detected by proximal microglia (Davalos et al., 2005).

Two recent studies by Norden et al. highlight the possibility that astrocytes contribute to priming of microglia responses (Norden et al., 2014; Norden et al., 2016). Astrocytes isolated from aged mice had reduced expression of growth factors and the receptor for the anti-inflammatory cytokine IL-10. Following an immune challenge (intraperitoneal LPS), aged astrocytes appeared insensitive to IL-10, which resulted in a failure to induce TGF-β and resolve microglia activation (Norden et al., 2016). Further, the blockade of TGF-β signaling in the brain of healthy adult mice at the time of an immune challenge (intraperitoneal LPS) increased pro-inflammatory cytokine gene expression (IL-1β, TNF-α, IL-6) in a coronal brain slice and produced an exaggerated sickness responses (social withdrawal) (Norden et al., 2014). Therefore, astrocytes can collaborate with microglia to resolve – or exacerbate – neuroinflammatory priming.

c. Infiltrating immune cells—Peripheral immune cells can infilitrate the CNS and induce microglia priming. In the healthy adult CNS, the BBB tightly regulates the entry of leukocytes (e.g. monocytes, B cells, and T cells) into the brain parenchyma. Immune cell migration across the BBB is typically controlled by the expression of chemokines and adhesion molecules. Under pathological conditions, BBB disruption and/or upregulation of chemokines and adhesion molecules can induce trafficking of peripheral immune cells into the brain (Banks and Erickson, 2010).

There are age-associated increases in the number of peripheral immune cells in the CNS (Gemechu and Bentivoglio, 2012). Both an increase in BBB permeability and an upregulation of chemokines may contribute to the increase in peripheral immune cells in the aged brain (Blau et al., 2012; Gemechu and Bentivoglio, 2012). In particular, a gradual increase in T-cell recruitment to the brain with aging is thought to activate local myeloid cell populations (Stichel and Luebbert, 2007), although see (Ritzel et al., 2016). The influx of T cells into the brain parenchyma and choroid plexus is also exaggerated following a central immune challenge (intracerebroventricular TNFα or IFNγ) in aged animals (Xu et al., 2010). The recruitment of specific populations of macrophages to the CNS with aging may also contribute to microglia priming. For example, following spinal cord injury, there is increased recruitment of potentially harmful IL-4Rα- macrophages to the CNS in aged as compared to adult mice, which may inhibit CNS repair (Fenn et al., 2014b).

Stress-induced priming of microglia can also be induced by the recruitment of peripheral myeloid cells into the CNS (McKim et al., 2016; McKim et al., 2017; Wohleb et al., 2013). Following social-defeat stress in mice, there is an exposure dependent upregulation of mRNA expression of the chemokines CXCL1 and CXCL2 and adhesion molecule E-selectin that corresponds with the recruitment of myeloid cells into the CNS (Sawicki et al., 2015). Blockade of trafficking of these inflammatory myeloid cells into the CNS can prevent elevated neuroinflammatory changes, microglia priming, and behavioral deficits in stressed mice (McKim et al., 2016; McKim et al., 2017; Wohleb et al., 2013). Of note, recruitment of peripheral myeloid cells into the brain following stress might be specific to the type and severity of the stressor and may depend on peripheral injury to the animal (i.e., if stressor model includes tissue damage (Lehmann et al., 2016)). For example, Lehmann et al demonstrated that social defeat stress induces region-specific microglia proliferation but not recruitment of myeloid cells to the CNS when tissue damage is prevented.

In some contexts, neuroinflammatory priming may occur in the absence of enhanced glial activation. For example, Ritzel et al recently found that the brain of aged (18–22 mos) C57BL/6J mice had increased T cell prevalence and a positive correlation between T cell and microglia numbers. This increase in immune cell number was associated with a primed phenotype following an ischemic insult: aged animals displayed an enhanced inflammatory signature and increased damage following experimental stroke. However, the presence of T cells was associated with a more anti-inflammatory/phagocytic phenotype in microglia, suggesting that the primed inflammatory response in this model of aging may be directly due to activation of T cells in the CNS (Ritzel et al., 2016).

IV. Neuroinflammatory priming elicited by stress and aging

IVA. Neuroinflammatory priming in the context of aging

A steady decline in homeostatic function occurs with aging. Indeed, reduced function with aging manifests at all levels of an organism, from the molecular level – e.g., shortening telomeres increases DNA lability and susceptibility to aging-related disease (Blackburn et al., 2015) – to the behavioral level – e.g., declining memory performance (Nyberg et al., 2012). In parallel, aging is associated with dysregulation of the immune and neuroimmune systems.

The neuroimmune system shows a gradual shift from a balance between pro- and anti-inflammatory functions in adulthood towards a primed neuroinflammatory environment in aging. This contrasts with the effect of aging on peripheral myeloid cells: macrophages show a senescent diminished inflammatory capacity with aging (Rawji et al., 2016). Indeed, peripheral immune challenges (e.g., intraperitoneal *E. coli*, LPS, surgery, etc.) induce blunted or comparable inflammatory responses in the periphery of aged as compared to young rats but produce an enhanced inflammatory profile in the CNS (Barrientos et al., 2009; Barrientos et al., 2012). For example, one intraperitoneal injection of *E. coli* induces a transient (< 24h) neuroinflammatory response in young rats. In contrast, aged rats display elevations in hippocampal IL-1β gene and protein expression for up to 8 days following the exact same dose of *E. coli* (Barrientos et al., 2009). That is, the amount of *E. coli* was not increased to compensate for the greater body weight of the older rats, so the neuroinflammatory difference between young and aging subjects is likely underestimated by this conservative dosing procedure. Interestingly, this enhanced immune response is specifically segregated to the CNS as initial peripheral cytokine responses are actually elevated in young as compared to aged rats (Barrientos et al., 2009). Sterile peripheral immune challenges (such as a laparotomy procedure) also induce prolonged elevations in hippocampal IL-1β in aged, as compared to young rats (Barrientos et al., 2012). Aged mice show similarly exaggerated neuroinflammatory changes in response to immune challenges (Chen et al., 2008; Godbout et al., 2005; Huang et al., 2008). For example, peripheral LPS induces enhanced IL-1β and IL-6 gene and protein expression in the brain of aged as compared to young mice (Chen et al., 2008; Godbout et al., 2005). In addition to peripheral immune challenges inducing heightened neuroinflammatory responses, direct injury to the CNS also exacerbates inflammatory responses in aged rodents. For example, spinal cord injury, traumatic brain injury, and ischemic stroke are all associated with increased neuroimmune activation in aged as compared to young rodents (Dinapoli et al., 2010; Fenn et al., 2014b; Kumar et al., 2013; Manwani et al., 2011; Onyszchuk et al., 2008; Zhang et al., 2016).

Importantly, microglia priming contributes to these heightened neuroinflammatory responses in aged mice and rats (Chen et al., 2008; Frank et al., 2010b; Huang et al., 2008). For example, following ischemic stroke, microglia activation, as measured by increased density of microglia immunoreactive for ionized calcium binding adapter molecule-1 (Iba1), is more robust in the brain of aged as compared to young mice (Manwani et al., 2011). The increase in microglia activation is also apparent *in vitro*, outside the influence of other CNS cells,

suggesting that it is due to an intrinsic change in cellular phenotype: microglia isolated from the hippocampus of aged (versus young) rats and challenged *ex vivo* with LPS display exaggerated upregulation in pro-inflammatory cytokine gene expression (Frank et al., 2010b).

However, aging-related microglia priming may vary regionally as immunohistochemical analyses reveals that aged C57/BL6 mice have greater upregulation of markers of microglia activation (CD11b, CD68, CD11c, F4/80, and FcyRI) in the white matter as compared to the grey matter (Hart et al., 2012). This may indicate that microglia are more prone to activation in the white versus the grey matter with age. Further evidence that microglia priming may be unique to specific regions of the aged brain comes from a study by Sierra et al. Microglia that were isolated from the whole brain of aged mice did not exhibit enhanced cytokine gene expression (TNFα, IL-1β, IL-6, IL-12, etc) following an intraperitoneal LPS challenge (Sierra et al., 2007). Microglia isolated from aged animals did have a modest increase in basal cytokine expression, but no age by LPS interaction was observed, indicating a lack of priming. This finding suggests that not all microglia in the aged CNS become primed with age, but rather it is possible that only microglia in vulnerable regions, such as the hippocampus, take on a primed phenotype. Indeed, Grabert et al demonstrated that the "ageing" of microglia varies in a region-specific manner. A principal component analysis of the transcriptome of microglia purified from either the cerebellum, cortex, hippocampus, or striatum of mice at 4, 12, and 22 months of age showed an age-dependent progression suggesting an interaction between age and brain region on global gene activity. This parallels the age-associated *in vivo* neuroinflammatory profile that follows an immune challenge: enhanced cytokine responses to peripheral immune challenge are only found in specific regions of the CNS (Barrientos et al., 2009).

There are important functional implications associated with neuroinflammatory priming in the aged brain. Aged mice and rats show prolonged cognitive and affective behavioral changes in response to peripheral immune stimulation such as LPS, *E. coli*, and surgery (Barrientos et al., 2012; Fonken et al., 2016a; Godbout et al., 2005) and CNS injuries including traumatic brain injury and spinal cord injury (Fenn et al., 2014b; Onyszchuk et al., 2008). The behavioral deficits follow a similar time course to the inflammatory profile in aged rats (Barrientos et al., 2009) and are likely due to the enhanced cytokine production in the CNS following immune stimulation. Indeed, central administration of IL-1 receptor antagonist (IL-1RA), which blocks the pro-inflammatory cascade initiated by IL-1β(Basu et al., 2004), attenuates the prolonged behavioral deficits following peripheral immune challenges in aged animals (Abraham and Johnson, 2009; Barrientos et al., 2012; Frank et al., 2010a). IL-1β has been designated the "master" cytokine (Basu et al., 2004) because of its pleiotropic role in the induction and propagation of the central inflammatory response and behavioral sickness response (Goshen and Yirmiya, 2009).

IVB. Stress and neuroinflammatory priming

Exposure to acute psychological and physiological stressors can rapidly alter the inflammatory milieu of the brain. Stressors can transiently induce pro-inflammatory cytokines in stress-reactive areas of the brain such as the hippocampus and hypothalamus

(Deak et al., 2003; Johnson et al., 2005; Nguyen et al., 2000; O'Connor et al., 2003) and this increase in cytokines appears dependent on catecholaminergic signaling (Johnson et al., 2005). The initial pro-inflammatory response to stress typically resolves within a few hours (Nguyen et al., 2000). However, in addition to this transient neuroinflammatory response with associated molecular and behavioral effects, stress can induce a prolonged primed neuroimmune phenotype (de Pablos et al., 2014; Espinosa-Oliva et al., 2011; Fonken et al., 2018; Fonken et al., 2016c; Frank et al., 2007; Frank et al., 2018b; Frank et al., 2012; Johnson et al., 2002; Johnson et al., 2003; Munhoz et al., 2006; Wohleb et al., 2012; Wohleb et al., 2011). For example, following a single session of inescapable tail shock stress, rats exhibit elevated hippocampal IL-1β production in response to intra-peritoneal LPS (Johnson et al., 2002; Johnson et al., 2003). Although LPS is commonly used as the immune challenge, stress also potentiates pro-inflammatory cytokine responses in the CNS following other peripheral and central immune challenges such as surgery or ischemic injury (Karelina et al., 2009; Norman et al., 2010; Wang et al., 2017; Weil et al., 2008). Potentiated neuroinflammatory responses follow a diverse array of stressors including chronic variable stress (de Pablos et al., 2014; Espinosa-Oliva et al., 2011; Yue et al., 2017), social defeat (Wohleb et al., 2012), stress from shipping/travel (Holder and Blaustein, 2017), social isolation (Gaudier-Diaz et al., 2017), chronic sleep restriction (Bellesi et al., 2017), and inescapable tail shock (Frank et al., 2007; Johnson et al., 2002) suggesting that neuroinflammatory priming may be a conserved feature of the stress response. The degree of neuroimmune activation may vary across stressors. For example, a meta-analysis revealed 20 to 200% increases in Iba1 immunoreactivity in the hippocampus in response to different stress models (Calcia et al., 2016).

Stress-induced neuroinflammatory priming is associated with exaggerated behavioral responses to an immune challenge. Indeed, prior stressor exposure enhances LPS-induced sickness responses including elevated depressive and anxiety-like behaviors, fever, and hyperalgesia (Fonken et al., 2018; Johnson et al., 2003; Loram et al., 2011; Wohleb et al., 2012). Stress can also exaggerate behavioral deficits following CNS injury. For example, social isolation stress prior to global cerebral ischemic injury was associated with enhanced CNS cytokine gene expression, greater neuronal loss, and increased depressive-like behavior (Norman et al., 2010). Social isolation also increased damage following focal cerebral ischemia (middle cerebral artery occlusion; MCAO). However, stress induced increases in damage following MCAO were associated with reduced CNS IL-6 gene and protein expression (Karelina et al., 2009).

Stress can also prime the microglia response to an *ex vivo* immune challenge. Prior exposure to stress potentiates the pro-inflammatory response to LPS in hippocampal microglia isolated from male rodents (Fonken et al., 2018; Frank et al., 2017; Frank et al., 2012; Weber et al., 2015; Wohleb et al., 2011). Interestingly, the phenomenon of stress-induced priming of microglia differs between males and females. Similar to males, female rats exhibit potentiated behavioral and neuroinflammatory responses to stress. Microglia isolated from male and female rats post-stress also show comparable changes in phagocytic activity *ex vivo* (Fonken et al, 2018). However, pro-inflammatory microglia priming *ex vivo* is not evident in microglia isolated from female rats following stress: microglia isolated from female rats following tail shock stress do not exhibit enhanced cytokine mRNA expression

following *ex vivo* challenge with LPS. This finding, along with other work, suggests that distinct cellular substrates of stress-elicited neuroinflammation might exist in females and males (Fonken et al., 2018; Pyter et al., 2013; Wohleb et al., 2018).

Stressor exposure may also induce a primed neuroinflammatory environment by increasing microglial proliferation *in vivo* (Kreisel et al., 2013; Lehmann et al., 2016; Nair and Bonneau, 2006). That is, stress may increase the pro-inflammatory response because it leads to an increase in the number of microglia that respond to a challenge. While this is a possible explanation for the neuroinflammatory priming effects of stress, increased proliferation is not responsible for the priming of microglia by stress observed in male rats as these studies controlled for the number of microglia exposed to immune challenge *ex vivo*.

The immunological and behavioral effects of stress require activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS). HPA axis activation in response to physiological and psychological stressors culminates in the release of glucocorticoids (GCs; predominately cortisol in humans and corticosterone in mice and rats) from the adrenal gland (reviewed in (Bellavance and Rivest, 2014)). GCs are released into the general circulation and are detected throughout the body and brain. For example, inescapable tailshock in rats induces profound increases in serum GC levels (Fleshner et al., 1995) as well as hippocampal GC levels (Frank et al., 2012). GCs are potent immunomodulatory molecules that act on both innate and adaptive immune cells due to the ubiquitous expression of glucocorticoid receptors (GRs) (Bellavance and Rivest, 2014; Cain and Cidlowski, 2017). GCs have powerful and well-characterized anti-inflammatory actions in a number of contexts (reviewed in (Cain and Cidlowski, 2017), but can paradoxically also contribute to neuroinflammatory priming in the context of aging and stress (described in section VA). The SNS, and in particular norepinephrine, also plays a crucial role in mediating neuroimmune changes in response to stress (Johnson et al., 2005; McKim et al., 2016; Porterfield et al., 2012; Powell et al., 2013; Wohleb et al., 2011). This conclusion stems from findings that pharmacological inhibition of noradrenergic signaling during stress (e.g. inescapable tailshock and repeated social defeat) can prevent microglia from developing a primed phenotype (Johnson et al., 2005; McKim et al., 2016; Porterfield et al., 2012; Wohleb et al., 2011). A considerable number of studies have demonstrated that stress-induced noradrenergic and GC signaling co-regulate one another in the brain (Herman et al., 2003), but the interactive effects of these stress systems in the context of neuroimmune priming has largely been unexplored (Lowrance et al., 2016). Future studies should further elucidate how the HPA axis and the SNS interact to produce stress- and aging-elicited neuroinflammatory priming.

Importantly, aging and stress can also act additively to induce neuroinflammatory priming, in that aged animals have exaggerated stress-induced cytokine production and behavioral deficits (Buchanan et al., 2008). It is possible that this compounded aging-stress priming effect could represent hyper-activation of a conserved priming pathway and/or coincident activation of parallel priming pathways.

V. Mechanisms underlying neuroinflammatory priming: common features of stress and aging

As described above, the changes in neuroinflammatory phenotype in response to aging and stress share several common features: exaggerated sickness response following an immune challenge, increased hippocampal cytokine production, microglia priming, etc. Thus, it follows that there are likely common mechanisms that mediate priming in the context of stress and aging. In this section, we discuss mediators that contribute to the shared neuroinflammatory pathways underlying stress and aging (Fig 4).

VA. Glucocorticoid signaling

GCs have traditionally been regarded as potent anti-inflammatory molecules (Cain and Cidlowski, 2017 provide an excellent comprehensive review of the pleiotropic actions of GCs on the immune system). Indeed, GCs are used therapeutically to suppress inflammation in a number of conditions including arthritis, asthma, eczema, etc. (Cain and Cidlowski, 2017). However, the clinical application of GCs has outpaced our understanding of the mechanisms that mediate GC actions, which has led, in some cases, to the inappropriate use of GCs. Clinical use of GCs has been called into question for several conditions including cardiac arrest (Jastremski et al., 1989; Sapolsky and Pulsinelli, 1985), spinal cord injury (Hurlbert et al., 2013), and Crohn's disease (Irving et al., 2007). A number of paradoxical results with GCs (Busillo et al., 2011; Dhabhar and McEwen, 1999; Frank et al., 2010c; Frank et al., 2012; Hermoso et al., 2004; Lim et al., 2007; MacPherson et al., 2005) suggest that GCs do not universally exert anti-inflammatory actions (examples follow). Both the timing (Barber et al., 1993; Frank et al., 2010c) and dose (Dhabhar and McEwen, 1999; Lim et al., 2007) of GC administration influence whether GCs exert antiinflammatory or pro-inflammatory actions. For example, humans administered GCs concomitant with LPS show reduced cytokine responses; however, GCs administered 12 h or 1 week prior to LPS enhance cytokine responses (Barber et al., 1993). Similarly, in rats, administering GCs (2.5 mg/kg subcutaneous corticosterone) 1 h following peripheral LPS suppresses IL-1β gene and protein increases in both liver and hippocampus. However, when GCs are administered 2 or 24 h prior to the immune challenge, the hippocampal IL-1β induction by LPS is potentiated (Frank et al, 2010c). Dose of GCs also critically controls their immunomodulatory activity. For example, Dhabar and McEwen demonstrated that a high pharmacological dose of corticosterone (40 mg/kg intraperitoneal) suppresses skin delayed-type hypersensitivity responses (DTH; cell-mediated immune measure), whereas a lower physiological dose of GCs (5 mg/kg) enhanced DTH responses.

Studies in both rodents and humans support the hypothesis that GCs generally promote brain aging (Landfield et al., 1981; Lupien et al., 1998). Here, we propose that GCs may more specifically prime neuroinflammatory responses in the aged brain. Barrientos et al recently demonstrated that aging selectively alters the circadian rhythm of GCs in the hippocampus. In adult rats, GCs are typically highest at the beginning of the active phase, and lowest at the beginning of the inactive phase. Aged rats exhibit increases in hippocampal corticosterone during the inactive phase of the circadian cycle (Barrientos et al., 2015). The hippocampal corticosterone values were not reflected in blood corticosterone, highlighting the importance

of evaluating brain regional changes in GCs. Importantly, dysregulated GCs in the aged CNS are a critical cause of neuroinflammatory priming. For example, blockade of GC action in the brain with an intracisternal magna injection of the GC receptor antagonist mifepristone prevents the *ex vivo* microglial priming produced by aging (Barrientos et al., 2015). Consistent with these findings, prophylactic mifepristone treatment also prevented prolonged hippocampal-dependent deficits in learning and memory following infection. Interestingly, exercise equalized corticosterone concentrations in the hippocampus of young and aged rats and also prevented aspects of age-related neuroinflammatory priming (Barrientos et al., 2011; Barrientos et al., 2015).

GCs are also critically involved in the neuroinflammatory response to stress. Various physiological and psychological stimuli activate the HPA axis, resulting in the production of GCs. GCs are a proximate signal through which stress primes inflammatory responses in rodents (Frank et al., 2013). Indeed, both acute and chronic administration of exogenous GCs can induce neuroinflammatory priming in rats (Fonken et al., 2018; Frank et al., 2014; Frank et al., 2010c; Kelly et al., 2012; Munhoz et al., 2010). For example, a single subcutaneous injection of corticosterone, at a dose (2.5 mg/kg) that mimics the serum rise in GCs produced by tail shock stress (Fleshner et al., 1995), induces heightened hippocampal cytokine gene and protein expression to later immune challenge with LPS in Sprague Dawley rats (Fonken et al., 2018; Frank et al., 2010c). In addition, priming induced by GCs is reflected in microglia isolated from male, but not female rats (Fonken et al., 2018). Establishing causality, pharmacological inhibition of GC signaling in rats blocks the stress-induced exaggeration of the neuroinflammatory response to LPS following both chronic (chronic variable stress) (de Pablos et al., 2006; Espinosa-Oliva et al., 2011) and acute (tail shock stress) stressors (Frank et al., 2012). Similarly, blockade of the stress-induced GC response via adrenalectomy in rats prevents neuroinflammatory and microglia priming in response to acute stress (Frank et al., 2012).

Several possible mechanisms that underlie GC-elicited neuroinflammatory priming have been explored. First, GCs may act through disruption of CD200 signaling (described below). In support, *ex vivo* treatment of microglia isolated from adult male rats with corticosterone downregulates CD200R (Fonken et al., 2016c). Second, neuroinflammatory priming may occur through the induction of GC resistance. Peripheral macrophages from mice that have undergone social disruption stress become hyposensitive to GCs and show potentiated inflammatory responses to an *ex vivo* LPS challenge (Avitsur et al., 2001; Stark et al., 2001), suggesting that a similar process may occur in microglia. GC resistance is mediated by diminished GR function in macrophages as evidenced by decreased nuclear translocation of GR following stress, which diminishes the inhibitory effect of GCs on the pro-inflammatory transcription factor NF-κB (Quan et al., 2003). GR downregulation is also detected in brain macrophages following stress and is dependent on the release of adrenal GCs (McKim et al., 2017; Niraula et al., 2018). However, microglia, isolated from animals that received chronic social disruption stress, failed to show GC resistance *ex vivo* (Wohleb et al., 2011). Consistent with a primed response, GC resistance following stress requires immune stimulation (i.e. injury during social defeat or LPS) (Foertsch et al., 2017). Reports on GR changes in the aged brain are conflicting (Barrientos et al., 2015; Murphy et al., 2002), and glial specific changes in GR have not been evaluated.

Finally, GCs are capable of inducing key components of the inflammasome, a multiprotein complex that is involved in the processing and maturation of IL-1β (as well as IL-18). In particular, GCs prime the NLRP3 inflammasome through upregulation of NLRP3 expression in myeloid cells *in vitro* (Busillo et al., 2011). NLRP3 inflammasome formation and activation requires a 2-step process. The first step involves increased NLRP3 gene transcription, translation and protein production. This has been called the "priming" step, and is thought to involve the ligation of TLR4 (Hornung and Latz, 2010). Once sufficient NLRP3 protein has been formed, then a second activation signal is needed that leads NLRP3 to interact with the adaptor protein, apopotosis-associated speck-like protein containing a CARD (ASC), which then recruits pro-caspase-1 through its caspase recruitment domain. This assembly of proteins is considered the inflammasome, and once formed triggers the activation/cleavage of pro-caspase 1. Mature, active caspase-1 then acts to cleave pro-IL-lβ into mature IL-1β protein. The NLRP3 inflammasome is also unusual in that it responds to a very broad range of signals as the second event that produces inflammasome formation/ activation (e.g. ATP, K+ efflux, β-amyloid, silica, uric acid crystals, ROS; (Elliott and Sutterwala, 2015). Chronic GC administration up-regulates NLRP3 expression in hippocampus concomitant with priming of the microglial pro-inflammatory response *ex vivo* (Frank et al., 2014). Taken together, these findings suggest that GC-induced neuroinflammatory priming might involve a diverse array of mechanisms of action.

VB. Accumulation of danger signals

Innate immune cells can be activated in the absence of infectious processes (i.e. sterile inflammation) by endogenous molecules, which have been termed danger associated molecular patterns (DAMPs) or alarmins (Schaefer, 2014). DAMPs signal through PRRs (e.g. TLR4) expressed by innate immune cells to activate signal transduction pathways such as NF-kB, which are pivotal in eliciting a pro-inflammatory immune response. Interestingly, in many instances PAMPs such as LPS use these same PRRs to induce a pro-inflammatory response, suggesting that DAMPs may prime these pathways to subsequent PAMP exposure (Bianchi, 2007). A number of DAMPs have been characterized including heat shock proteins, uric acid, S100 proteins, IL-lα and high mobility group box-1 (HMGB1), which are released under a variety of sterile inflammatory conditions (Bianchi, 2007). In the CNS, the neuroinflammatory effects of DAMPs have been characterized in ischemia (Yang et al., 2010), traumatic CNS injury (Corps et al., 2015), chronic pain states (Agalave et al., 2014), seizure (Vezzani, 2014), ethanol exposure (Szabo and Lippai, 2014) and methamphetamine exposure (Frank et al., 2015a). Of particular relevance here, DAMPs have also been found to play a pivotal role in the aging- and stress-induced priming of neuroinflammatory processes.

Our laboratory has recently implicated the DAMP HMGB1 in stress- and age-elicited neuroinflammatory priming (Fonken et al., 2016a; Weber et al., 2015). HMGB1 is a chromatin-binding factor localized to the nucleus that is released from the nucleus, and subsequently the cell, under pathological conditions (e.g. sepsis, stroke, Alzheimer's disease) (Lotze and Tracey, 2005). HMGB1 is released in the brain both actively by microglia and passively by necrotic or damaged cells (Scaffidi et al., 2002). Extracellular HMGB1 interacts with the key immune receptors TLR2 and 4 and the receptor for advanced glycation end products (RAGE), thereby driving priming and/or pro-inflammatory responses

(Yang and Tracey, 2010). Importantly, extracellular HMGB1 does not necessarily induce a pro-inflammatory cytokine response in the brain; rather, HMGB1 can potentiate the effects of a subsequent neuroinflammatory challenge (Weber et al., 2015).

Aged rats exhibit basal elevations in hippocampal and cerebrospinal fluid HMGB1, the latter suggesting increased extracellular release of HMGB1 (Fonken et al., 2016a). As noted above, aged rats do not exhibit an increase in basal brain cytokines, but following an immune challenge *(E. coli)* they display prolonged elevations in hippocampal cytokines and greater microglial reactivity. This phenotype is associated with age-related increases in HMGB1, and indeed, HMGB1 is required for age-related neuroinflammatory priming. Blockade of the actions of HMGB1 by CNS administration of a competitive antagonist, Box A, can prevent aging-induced neuroinflammatory priming and associated behavioral changes (Fonken et al., 2016a). Similarly, in an aged rat model of post-operative cognitive decline, systemic HMGB1 neutralization prevented neuroinflammatory and behavioral pathologies (Terrando et al., 2016). Aged rats that received anti-HMGB1 treatment exhibited a reduction in hippocampal microglia activation (Terrando et al., 2016). Interestingly, it appears that microglia in the aged brain attempt to compensate for this age-related upregulation in endogenous danger signals as microglia from aged rats downregulate genes involved in sensing endogenous ligands such as DAMPs, but not other foreign debris (Hickman et al., 2013).

As with aging, we have recently found that acute stressor exposure (tail shock stress) increases levels of HMGB1 in hippocampus (Frank et al., 2018a; Frank et al., 2018b; Weber et al., 2015) as well as amygdala of rats (Frank et al., 2018a), findings replicated in other stress paradigms (Cheng et al., 2016; Franklin et al., 2018; Lian et al., 2017). Further, acute stress increases the release of HMGB1 *ex vivo* from hippocampal microglia (Weber et al., 2015). HMGB1 likely plays a mediating role in stress-induced priming as central administration of a competitive antagonist to HMGB1 (Box A) before stress exposure blocks stress-induced priming of the microglial pro-inflammatory response to *ex vivo* LPS treatment (Weber et al., 2015). Furthermore, central administration of HMGB1 mimics the impact of stressor exposure and potentiates the neuroinflammatory, behavioral, as well as the microglia pro-inflammatory response to a subsequent immune challenge (Frank et al., 2015b). Similar effects of HMGB1 were observed *in vitro*. As noted above, HMGB1 signals through a number of innate immune receptors including RAGE. A recent study showed that stress-induced anhedonia, as assessed by reduced sucrose preference, was blocked in RAGE KO mice, suggesting that HMGB1 (or another RAGE receptor ligand) might contribute to the anhedonic effects of stress (Franklin et al., 2018). Consistent with this idea, we recently found that central administration of box A blocks the anxiogenic effects (i.e. decrements in juvenile social exploration) of inescapable tailshock (unpublished observations), suggesting that stress-induced HMGB1 is necessary for the immediate behavioral effects of stress.

In addition to increased production/secretion of DAMPs, impairments in paravascular clearance may contribute to the pathological accumulations of DAMPs in the brain following stress and aging. Indeed, the brain's glymphatic system is critical for removing extracellular solutes from the brain parenchyma and subsequently the cerebrospinal fluid (Aspelund et al., 2015; Iliff et al., 2012; Louveau et al., 2015). With aging, loss of

perivascular aquaporin-4, a critical component of the glymphatic system, is associated with a decline in cerebrospinal fluid clearance and accumulation of DAMPs such as amalyoid β (Iliff et al., 2012; Kress et al., 2014; Zeppenfeld et al., 2017). Voluntary exercise, which can diminish the maladaptive consequences of aging and stress, can promote glymphatic clearance and reduce the accumulation of amyloid plaques (He et al., 2017). Whether stressors can also dampen effectiveness of the glymphatic system remains unknown.

VC. Dis-inhibition of microglia

Exposure to neuronal cell-surface and soluble factors maintain microglia in a comparatively quiescent immunophenotype compared to other myeloid cells (Biber et al., 2007). For example, 'off' signals including the neuronally derived factors CD200 and fractalkine (CX3CL1) are constitutively expressed at high levels in healthy brain and signal through their cognate receptors on microglia, CX3CR1 and CD200R1, to inhibit activation. As discussed above, exposure to PAMPs or DAMPs amplifies release of 'on' signals, which can override or dis-inhibit these 'off' signals and lead to the pro-inflammatory shift in microglia (Katsumoto et al., 2014).

a. CD200:CD200R—Downregulation of CD200R contributes to microglia priming in the contexts of both stress (Fonken et al., 2016c; Frank et al., 2017) and aging (Cox et al., 2012). CD200 is a membrane glycoprotein that is ubiquitously expressed on neurons, endothelial cells, and oligodendrocytes (Koning et al., 2009). The cognate receptor for CD200, CD200R, is exclusively expressed on microglia and other myeloid cells in the CNS (Cardona et al., 2006). Ligation of CD200R by CD200 inhibits microglia activation and constitutively dampens myeloid cell activity (Jenmalm et al., 2006). Unlike most inhibitory receptors, the CD200R does not contain an immunoreceptor tyrosine-based inhibitory motif; rather, stimulation by CD200 leads to the phosphorylation of a cytoplasmic tyrosine residues which recruits the adaptor protein downstream of tyrosine kinase 2 (Vaine and Soberman, 2014). Disruption of this anti-inflammatory CD200:CD200R signaling potentiates microglial responses to immune stimuli (Costello et al., 2011; Denieffe et al., 2013; Hoek et al., 2000).

Alterations in the CD200:CD200R signaling dyad occur in aging and following stress. CD200 is downregulated in the hippocampus of aged rats (Cox et al., 2012; Frank et al., 2006). Administration of a soluble fragment of CD200 (CD200Fc; a CD200R agonist) into the hippocampus of aged rats decreases markers of microglia activation including MHCII immunoreactivity and CD40 gene expression (Cox et al., 2012). Stress-induced neuroinflammatory priming is associated with suppressed CD200R mRNA expression across sub-regions of the hippocampus (CA1, CA3, and dentate gyrus) as well as in isolated hippocampal microglia (Frank et al., 2017). CD200R protein is also reduced in whole hippocampus following tail shock stress (Frank et al., 2017). Moreover, administration of CD200Fc into the cisterna magna prior to tail shock stress exposure prevents *ex vivo* stress-induced microglia priming. Intriguingly, changes in CD200:CD200R signaling are also implicated in pathological neuroinflammatory responses in other context including Alzheimer's disease (Varnum et al., 2015; Walker et al., 2017), CNS injury (Cohen et al., 2017), and neuropathic pain (Hernangomez et al., 2016).

b. CX3CL1:CX3CR1—The CX3CL1:CX3CR1 signaling axis has features similar to CD200:CD200R regulation of microglia. Complementary expression of the ligand CX3CL1 (a.k.a. fractalkine) in neurons and the receptor CX3CR1 in microglia serves to regulate the activation of microglia (Cardona et al., 2006; Harrison et al., 1998; Mizutani et al., 2012). Constitutive expression and release of CX3CL1 by neurons inhibits microglia from developing a pro-inflammatory phenotype. Blocking the actions of CX3CL1 exaggerates pro-inflammatory responses to immune stimulation (Zujovic et al., 2001), whereas treatment with soluble CX3CL1 inhibits LPS-induced cytokine production (Lyons et al., 2009). Furthermore, mice lacking CX3CR1 have exaggerated neuroinflammatory and behavioral responses to an immune challenge (Corona et al., 2010). Counter-intuitively, deletion of CX3CR1 can have protective effects following CNS injury (Freria et al., 2017; Mattison et al., 2013). However, as noted in the study by Mattison et al, one limitation to using global genetic knockout models is that compensation for gene deletions may occur during development. Thus, to determine whether CX3CR1 removal is truly neuroprotective, future studies could use conditional deletion or receptor antagonist strategies.

Changes in CX3CL1 signaling have been implicated in neuroinflammatory priming. For example, CX3CL1 expression is reduced in the brain of aged rodents, an effect that is accompanied by evidence of age-related microglia priming (Bachstetter et al., 2011; Lyons et al., 2009; Wynne et al., 2010). Administering soluble or membrane-bound CX3CL1 attenuates primed immune responses in the aged rats, including blocking age-related evidence of microglial priming indicated by increased MHCII and CD40 mRNA expression (Lyons et al., 2009), deficits in LTP (Lyons et al., 2009), and the decline in neurogenesis (Bachstetter et al., 2011). CX3CL1 signaling has also been implicated in neuroinflammatory priming in the context of stress, albeit in an opposite role than expected. Stress-induced exacerbations in neuroinflammation are not apparent in CX3CR1 knockout mice and affective behavioral changes associated with stress are reduced (Hellwig et al., 2016; Milior et al., 2016; Rimmerman et al., 2017; Winkler et al., 2017). It is possible that the lack of stress induced neuroinflammation in global CX3CR1 knockout is due to a compensatory upregulation in another anti-inflammatory pathway. Overall, CX3CR1 knockouts may show a primed phenotype at baseline as they are more sensitive to LPS-induced neuroinflammation and sickness behaviors (Corona et al., 2010).

VD. Breakdown of circadian rhythms

Anticipating predictable daily events and adjusting physiology and behavior accordingly is adaptive. The circadian system synchronizes organisms to daily fluctuations in their external environment and temporally organizes internal systems to maintain homeostatic balance. For example, there are time of day variations in the risk for an organism encountering infection and injury and the circadian system regulates multiple immunological processes including the release of immunomodulatory hormones, immune cell trafficking, and cellular cytokine production (Scheiermann et al., 2013). Indeed, the time at which an immune challenge occurs can modulate the severity of the immune response (Halberg et al., 1960; Marpegan et al., 2009; Spengler et al., 2012). For example, mortality following a bacterial challenge varies depending on the time of immunostimulation (Halberg et al., 1960). Circadian regulation of immune cells includes direct regulation of microglia (Fonken et al., 2015;

Nakazato et al., 2017). Indeed, we demonstrated that microglia possess intrinsic circadian clock mechanisms and display altered immune potential over the course of the day, with peak immune activation occurring during the light phase (Fonken et al., 2015). As might be expected, disruption of the circadian system can lead to heightened peripheral and central inflammatory responses (Castanon-Cervantes et al., 2010; Fonken and Nelson, 2013; Wright et al., 2015). Indeed, circadian disruption by nighttime light exposure results in heightened microglia cytokine mRNA expression in response to a peripheral immune challenge (Fonken and Nelson, 2013). Importantly, the circadian system has notable changes in response to both aging and stress that can impact neuroimmune activity.

Aging is associated with decreased amplitude and precision of behavioral, metabolic, and other endocrine rhythms (Bonaconsa et al., 2014; Nakamura et al., 2015; Smith et al., 2005; Valentinuzzi et al., 1997). Furthermore, disruption in rhythms in immune activity also occurs in aged animals (Fonken et al., 2016b; Sato et al., 2014). Diurnal rhythms in the microglial activation signature are observed in young, but not aged rats. While microglia from young rats display diurnal differences in microglia activation potential both *in vivo* and *ex vivo*, with dampened microglial pro-inflammatory cytokine responses during the rats' active phase, microglia from aged rats exhibit constitutively elevated microglia activation potential. Changes in microglia activation parallel the intensity of neuroinflammatory responses in young and aged rats. For example, hippocampal IL-1β protein induction in response to intraperitoneal *E. coli* depends on time of day in young, but not aged rats. The erosion of this potentially beneficial diurnal fluctuation in inflammatory response may contribute to the protracted neuroinflammatory responses that are observed in aged animals. Moreover, changes in circadian clock genes/proteins are implicated in the aging process. For example, disruption of the core clock gene BMAL1 causes pre-mature aging (Kondratov et al., 2006) and neurodegeneration (Kress et al., 2018; Musiek et al., 2013), although see (Yang et al., 2016). Interestingly, strategies that strengthen circadian rhythms, such as exercise (Droste et al., 2009; Edgar and Dement, 1991; Leise et al., 2013), can prevent neuroinflammatory and microglia priming (Barrientos et al., 2011).

The circadian and stress response systems have a unique interrelated relationship. Both systems are critical for enabling acclimatization to environment challenges: while the circadian system is important for adjusting physiology and behavior to predictable daily events, the stress system exists to maintain homeostasis in response to unpredictable challenges. Responses to stressors and susceptibility to stress-related comorbidities are regulated by the circadian system (Cohen et al., 2015). For example, the time of day at which a stressor or inflammatory challenge occurs significantly defines the magnitude of the stress-elicited neuroinflammatory response (Fonken et al., 2016c; Johnson et al., 2003). Indeed, while tail shock stress induces neuroinflammatory priming when the stressor occurs during the middle of the light (rest) phase in rats, priming is significantly blunted during the animals' active phase (Fonken et al., 2016c).

Reciprocally, stress has profound effects on circadian rhythms. GCs show robust circadian oscillations that are driven by both the central clock in the SCN and local adrenal clocks (Oster et al., 2006). GCs are an important entrainment factor for extra-SCN circadian rhythms. Stress both directly induces GCs and causes longer-term dysregulation of circadian

rhythms in GCs. As discussed above (IVa), microglia are sensitive to daily or stress-induced changes in GC concentrations. Thus, the disruption of circadian rhythms with stress has the potential to dysregulate immune cells, which are sensitive to daily or stress-induced changes in GC concentrations (Borniger et al., 2017).

VE. Mechanism interactions

In section V, we introduced several mechanisms by which stress and aging can contribute to neuroinflammatory priming. An important remaining question is how do these mechanisms interact? Are distinct forms of neuroinflammatory priming induced by GCs versus danger signals versus dis-inhibition of microglia? Or are all of these elements involved at different points in the same signaling cascade that leads to neuroinflammatory priming? Here we will present evidence that the mechanisms described above can interact to induce neuroinflammatory priming.

As already noted, GCs are critical for inducing neuroinflammatory priming in a number of different stress models (de Pablos et al., 2006; Espinosa-Oliva et al., 2011; Frank et al., 2012; Wang et al., 2017) and likely are at the top of the signaling cascade that induces neuroinflammatory priming. The rapid synthesis and release of GCs in response to stressors may induce the release of the danger signal HMGB1 via disinhibition (reduced CD200:CD200R signaling) of microglia. In two recent papers from our group (Fonken et al., 2016c; Frank et al., 2018a), we demonstrated that stress (and GCs) might induce neuroinflammatory and microglia priming via downregulating CD200R signaling. Exposure to tail shock stress reduced CD200R gene and protein expression in the hippocampus. Furthermore, CAAT/enhancer binding protein (C/EBP)β, a transcription factor that binds to the CD200R and inhibits its transcription (Dentesano et al., 2012), was potently upregulated by stress exposure at both the gene and protein expression level (Frank et al., 2018a). Microglia isolated from adult rats also showed a dose dependent downregulation in CD200R in response to *ex vivo* treatment with corticosterone suggesting that GCs may act directly on microglia to target reduced CD200R (Fonken et al., 2016c). Intriguingly, the administration of CD200Fc into the cisterna magna immediately prior to stress prevented stress-induced elevations in hippocampal HMGB1 protein, suggesting that microglia disinhibition may cause increased HMGB1 synthesis in microglia (Frank et al., 2018a). Furthermore, a recent paper by Wang et al highlights the importance of GCs in CD200:CD200R signaling: reductions in CD200 in the hippocampus of rats following chronic unpredictable stress were prevented by pharmacological blockade of GC signaling produced by intraperitoneal injection of RU486 during the CUS protocol (Wang et al., 2017). Although, note that this study evaluated CD200 rather than CD200R. Taken together, these studies suggest that several of the mechanisms described above can interact to induce neuroinflammatory priming.

VI. Neuroinflammatory priming in human aging and stress

This review has primarily focused on neuroinflammatory priming in animal models of aging and stress. The majority of work that investigates neuroinflammatory priming is conducted in animal models due to the difficulty of studying this phenomenon in humans. For example,

there are serious ethical considerations when performing an immune challenge in humans, although some studies use low dose LPS, viral challenges, or measure inflammation following vaccination. Additionally, measuring neuroimmune changes following an immune challenge is not feasible in humans. However, there is indirect evidence (evidence of neuroimmune changes, studies on peripheral immune cell priming, etc.) that suggests that neuroinflammatory priming may occur in humans and contribute to pathology. Thus, here we will provide a brief discussion of evidence suggesting that neuroinflammatory priming may occur in humans in the context of aging and stress.

Extensive innate immune gene upregulation accompanies brain aging. For example, a microarray study by Cribbs et al, which profiled immune/inflammation-related genes in young (29 to 59) and aged ((60 to 99) human brain tissue, revealed that age was associated with increased expression of genes involved in complement (C1q, C3, C5, etc.), TLR (TLR2, TLR4, etc.), and inflammasome (caspase-1) pathways (Cribbs et al., 2012). The authors concluded that conditions in the aged human brain are comparable to conditions following a chronic injury (Cribbs et al., 2012). Morphologically, microglia take on a dystrophic phenotype in the aged human brain that is distinct from an activated phenotype (Streit et al., 2004). Furthermore, the transcriptomic and proteomic profile of human microglia changes with aging. Aged human microglia display downregulated genes involved in anti-inflammatory signaling (e.g. the TGFβ signaling pathway gene set) and upregulated genes involved in neurodegeneration and amyloid pathology (Olah et al., 2018). Taken together, these studies suggest a primed inflammatory signature may develop in the aged brain.

Neuroimmune changes with aging may underlie vulnerability to age-ass ociated pathologies such as cognitive decline and neurodegenerative diseases. Indeed, age is the most salient risk factor for postoperative cognitive decline (POCD) (Monk et al., 2008; Steinmetz et al., 2009), a disorder characterized by impairments in memory, concentration, and information processing that can occur following surgery. Systemic inflammation positively correlates with POCD, suggesting that changes in immune activation,at least in the periphery, may contribute to the development of this condition (Burkhart et al., 2010; Hudetz et al., 2011). Other inflammatory insults can also induce cognitive decline in aged individuals. For example, in elderly individuals with Alzheimer’s disease, an inflammatory insults such as periodontitis, is associated with cognitive decline (Ide et al., 2016). However, cognitive decline is not always associated with increased inflammation in the aged population (Hajjar et al., 2018; Knezevic et al., 2017).

Stress and GCs are also associated with primed immune cell responses in humans. Several studies have characterized the effects of stress on peripheral immune cell populations. For example, Powell et al, demonstrated that stress may induce monocyte proliferation in humans and mice (microglia are the CNS myeloid cell and monocytes are the blood myeloid cell). Indeed, chronic social stress defined by socioeconomic status in humans and repeated social defeat stress in mice was associated with selective up-regulation of a subpopulation of immature pro-inflammatory monocytes identified with a transcriptome analysis of the circulating leukocyte pool (Powell et al., 2013). Stress may also cause peripheral immune cells to become hyper-responsive by inducing GC receptor resistance. Cohen et al,

demonstrated that stressful life events were associated with GC receptor resistance in peripheral lymphocytes (Cohen et al., 2012). GC resistance positively correlated with nasal pro-inflammatory cytokine expression following a cold virus challenge (Cohen et al., 2012). Furthermore, the treatment of peripheral blood mononuclear cells from healthy donors with GCs can upregulate expression of chemokine (CCR1 and CCR2) and cytokine (IL-1R1,TNFR, IFNγR1) receptors and complement family (C1q, C3, C5) genes assessed with DNA microarray and qPCR, while repressing the expression of adaptive immune-related genes (Galon et al., 2002). In a random double-blind study, Yeager and colleagues demonstrated that prior treatment (24h prior) of human volunteers with intravenous infusion of hydrocortisone enhanced plasma concentrations of the pro-inflammatory cytokine IL-6 at 3h and 4h post-LPS treatment (Yeager et al., 2009). Notably, LPS-induced plasma levels of the anti-inflammatory cytokine IL-10 were reduced by prior hydrocortisone treatment.

Importantly, stress-induced changes in innate immune activity are likely not limited to the periphery. Stress is a predisposing factor for the development of neuropsychiatric disorders (major depressive disorder, generalized anxiety disorder, post-traumatic stress disorder, etc.) and there is evidence that enhanced neuroimmune activation may occur in a subset of patients with neuropsychiatric disorders (Dantzer et al., 2008). For example, elevated microglia density in limbic brain structures has been found in brains after suicide (Schnieder et al., 2014; Steiner et al., 2008). Moreover, myeloid cells in the brains of depressed individuals that committed suicide show a more primed phenotype (Torres-Platas et al., 2014). Consistent with these findings, imaging studies reveal that major depressive episodes are associated with increased translocator protein density, which is increased in activated microglia (Setiawan et al., 2015).

VII. Conclusions

Neuroinflammatory priming is a common mechanism linking pathology caused by stress and by aging. Homeostatic disruptions can cause direct and immediate neuroinflammatory changes, such as increases in pro-inflammatory cytokines. This pro-inflammatory response, however, is typically brief and so cannot account for long-term changes that depend on CNS immune processes. However, here we focus on a long-term and more derivative change. Through both peripheral and central signaling, CNS cells – particularly microglia – can become primed. After stress or during aging, primed microglia produce new “silent” immune machinery that does not cause immediate immune activation, but rather, this immune machinery primes the cell for a subsequent immune insult and a hyperinflammatory response that can exacerbate pathology (Fig 1 and 2). Remarkable parallels exist between stress- and aging-elicited microglial priming. Microglia priming by stress or aging can be elicited by glucocorticoid signaling, by excess release of endogenous DAMPs, by dysregulated neuron-microglia homeostatic signaling (e.g., CD200L-CD200R, CX3CL1-CX3CR1), and by disrupted circadian rhythms (Fig 4). Accumulating research highlights the probable relevance of microglial activation in stress and aging in human brains. Therefore, optimizing neuroinflammatory responses could have broad benefits for organismal responses to stress, aging, and other CNS disorders. Future research will reveal more details regarding substrates that underlie microglial priming, how priming occurs in females versus males, and

how to manipulate priming so that microglia produce effective inflammatory responses while minimizing pathology.

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Highlights

- Stress and aging can prime neuroinflammatory processes
- Priming can cause pathological neuroinflammation following an immune challenge
- Silent immune machinery produced by microglia in stress and aging may cause priming
- Here we discuss common mechanisms of priming induced by stress and aging

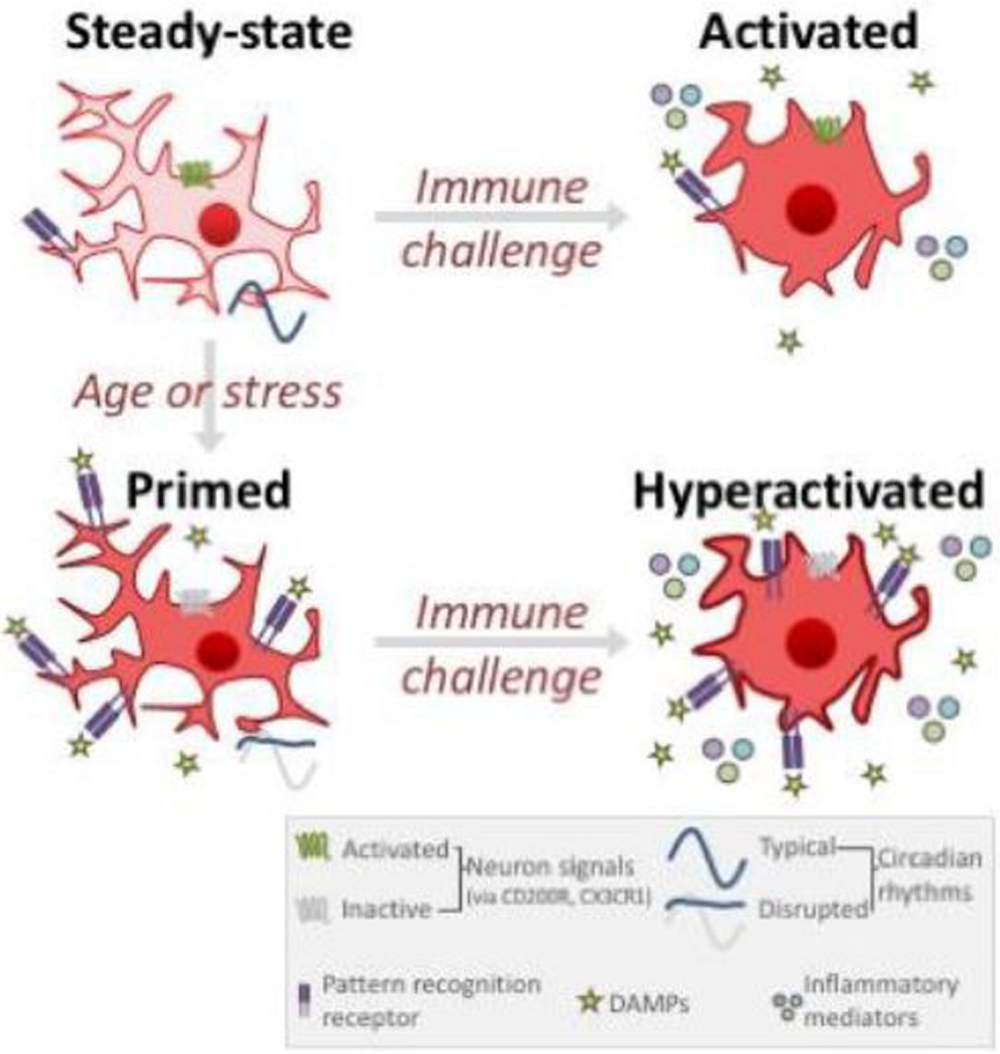

Figure 1. Microglial priming during aging and stress.

In the healthy CNS, a steady-state inactive microglial phenotype is associated with limited pattern recognition receptor expression (and low extracellular damage-associated molecular pattern (DAMP) expression), activation of neuron-microglia signaling pathways, and typical daily rhythms in circadian and inflammatory genes. During aging or after stress, microglia develop a “primed” phenotype that does not increase effector function but sensitizes the cells to subsequent stimulation. Primed microglia upregulate pattern recognition receptors, have more DAMPs in the extracellular environment, and de-activated neuron-microglia signaling (dis-inhibition of microglial). When primed microglia experience an immune challenge, the cell responds with an exaggerated inflammatory response that can be prolonged and can exacerbate pathology. Processes shown here represent key common mechanisms driving microglia priming; please see text for more details.

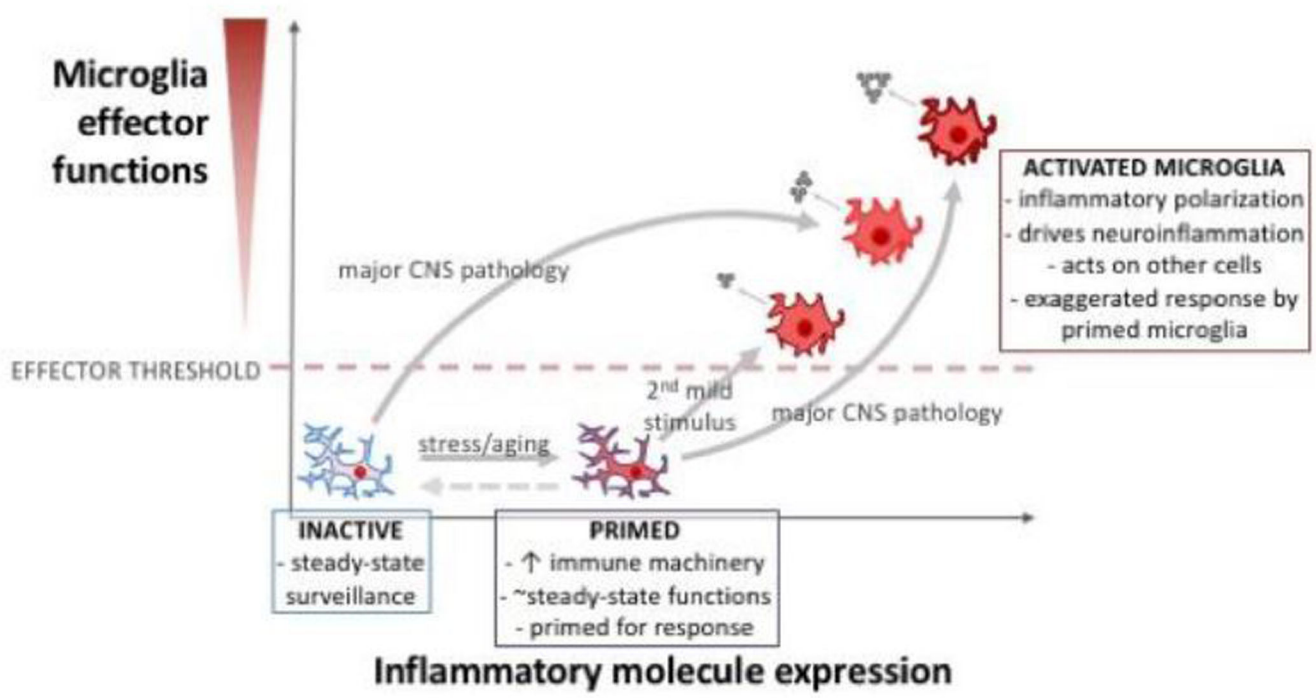

Figure 2. Microglial activation occurs along a continuum.

In healthy adult CNS tissue, microglia exist in an inactive state: these microglia survey the CNS microenvironment for infection or damage, and are involved in homeostatic regulation (e.g., synapse modulation, phagocytosis of normal debris, etc.). Following certain physiological challenges (such as stress or aging), microglia can take on a “primed” phenotype. Primed microglia modulate immune machinery involved in an inflammatory response (e.g., increased MHC II, NOD-like receptors, purinergic receptors; see text), but do not substantially increase their inflammatory effector phenotype (i.e., without further stimulus, primed microglia do not release inflammatory molecules). However, if microglia in a primed state are subjected to a stimulus, these primed microglia mount an exaggerated activated response that is maladaptive and can exacerbate pathology. Major CNS pathology (e.g., trauma or ischemia) can directly cause microglia to develop a strongly activated state, but primed microglia may fail to resolve the inflammatory response and continue to produce and secrete inflammatory molecules. By better understanding underlying mechanisms of microglia priming and activation, we may develop effective treatments that dampen aberrant microglial inflammatory phenotypes (dashed arrows).

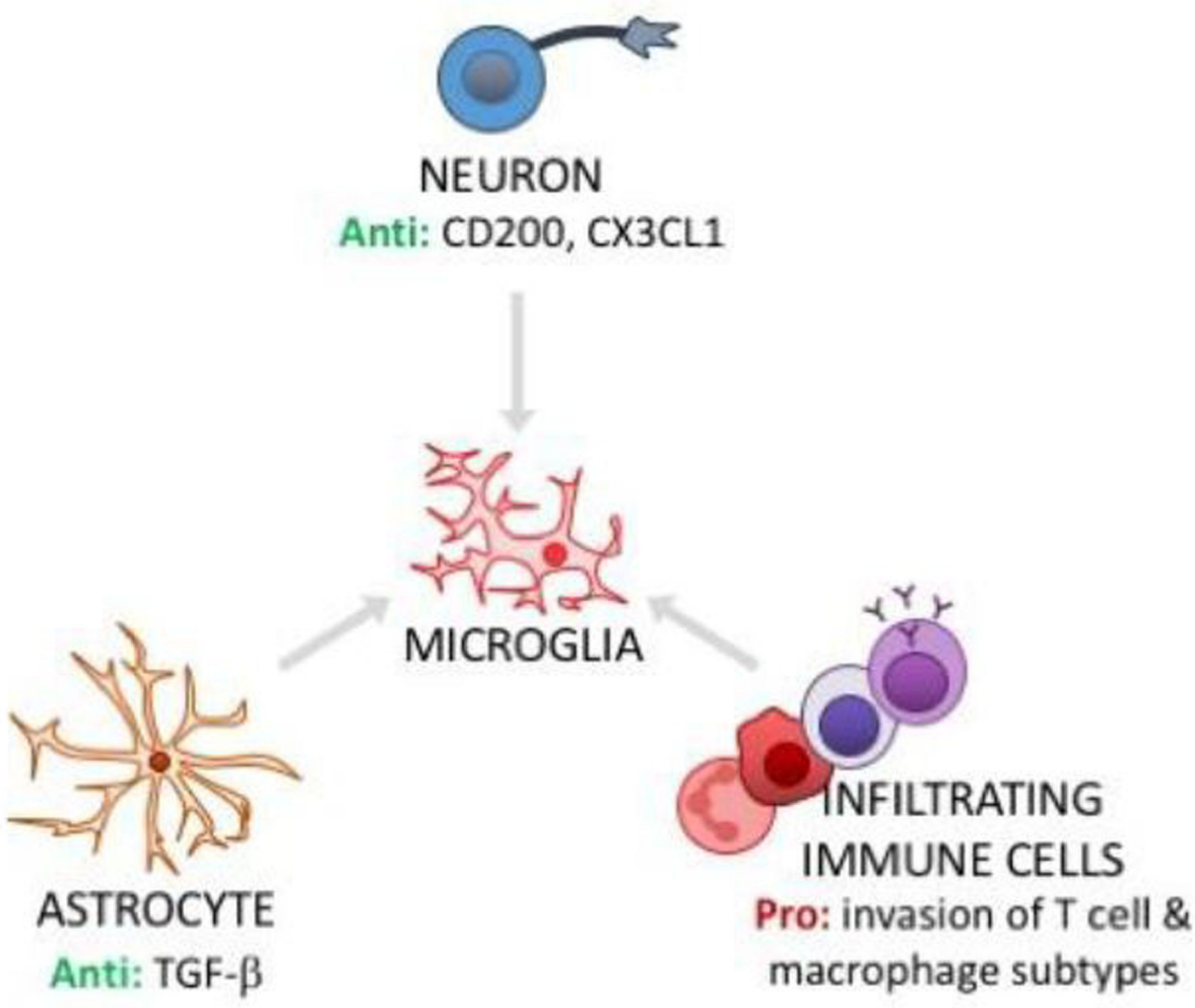

Figure 3. Microglial phenotype is regulated by other cells in the CNS.

In healthy CNS, steady-state microglial quiescence is maintained by signaling with neurons (neuron CD200L to microglia CD200R; neuron CX3CL1 to microglia CX3CR1) and astrocytes (e.g., TGF-β signaling limits microglial activation). Dysregulation of these cell-cell interactions can contribute to microglial priming. In addition, hematogenous immune cells - which typically have no/very limited access to the CNS - can invade CNS tissue in stress and aging. Pro-inflammatory subtypes of infiltrating cells, such as macrophages, can signal to microglia to elicit priming and/or activation. Anti = anti-inflammatory actions; Pro = pro-inflammatory actions.

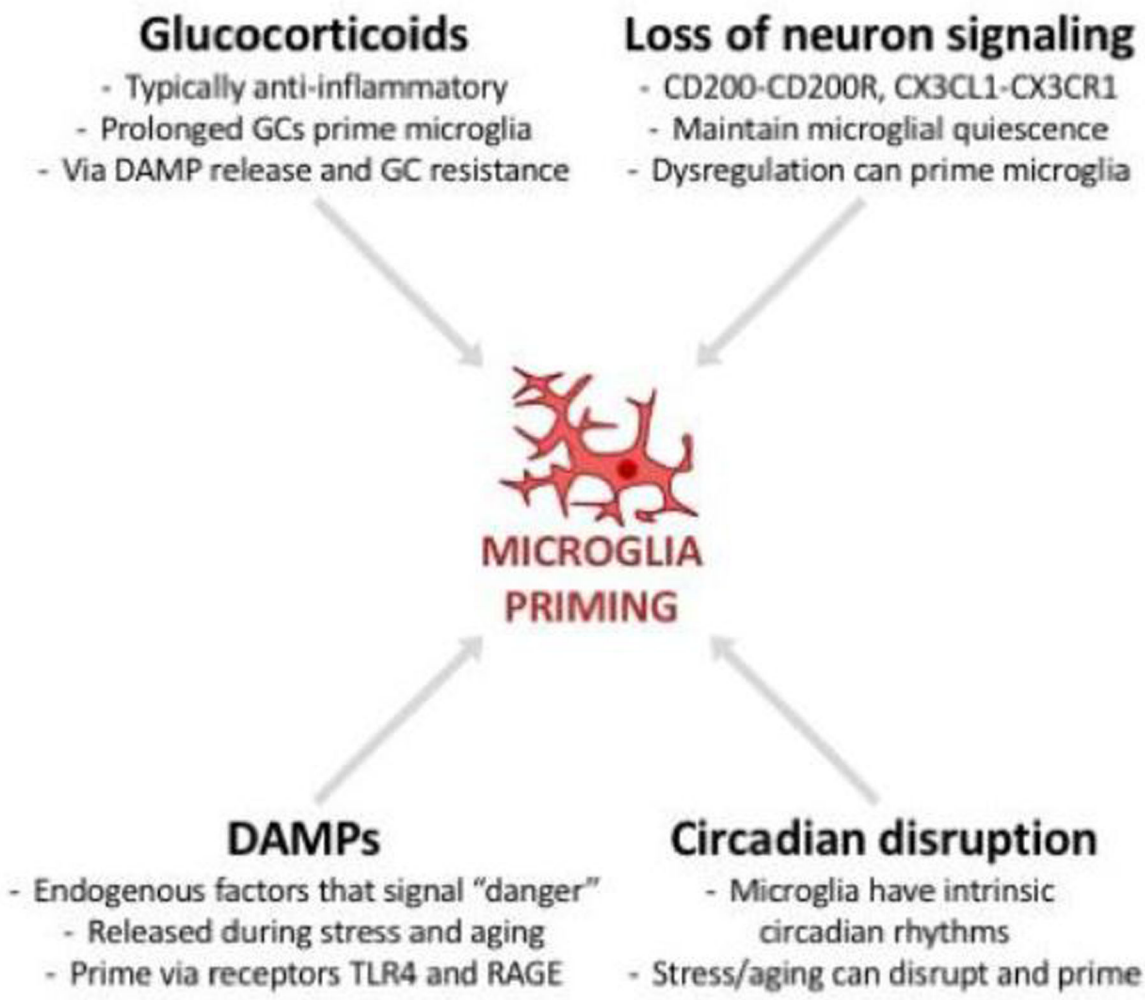

Figure 4. Microglial priming is elicited by common mechanisms in aging and stress.

Microglial priming can be caused by intense and/or prolonged glucocorticoid signaling, by excess release of damage-associated molecular patterns (DAMPs), by loss of neuron signaling (which typically helps maintain microglia homeostasis), and by circadian disruption. Aging and stress can elicit priming by any or all of these mechanisms.