Microglia as Central Protagonists in the Chronic Stress Response

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Abstract

Chronic stress is a major risk factor for developing psychiatric conditions. In addition to elevating the levels of stress hormones released in the body, chronic stress activates the immune system, resulting in increased levels of proinflammatory cytokines and innate immune cells in the circulation of rodents and humans. Furthermore, exposure to chronic stress alters the phenotype of microglia, a population of innate immune cells that reside in the CNS parenchyma. In rodent models, chronic stress activates microglia in defined brain regions and induces changes in their phenotype and functional properties. In this review, we discussed how microglia are activated in stressful situations. Furthermore, we described how microglia affect the CNS environment during chronic stress, through the production of cytokines, the induction of reactive oxygen species, and phagocytosis. We suggested that, due to their strategic location as immune cells within the CNS, microglia are important players in the induction of psychopathologies after chronic stress.

Glossary

ACTH = adrenocorticotropic hormone; **ATP** = adenosine triphosphate; **BDNF** = brain-derived neurotrophic factor; **CCL2** = chemokine (C-C motif) ligand 2; **CCR2** = CC chemokine receptor 2; **CNS** = central nervous system; **CRH** = corticotropin-releasing hormone; **CSD** = chronic social defeat; **CSF1** = colony-stimulating factor 1; **CSF1R** = colony-stimulating factor 1 receptor; **CUS** = chronic unpredictable stress; **DAMP** = danger-associated molecular pattern; **GR** = glucocorticoid receptor; **HMGB1** = high-mobility group box-1; **HPA** = hypothalamic-pituitary-adrenal; **Iba1** = ionized calcium-binding adapter molecule 1; **IL-1R1** = interleukin-1 receptor type I; **LPS** = lipopolysaccharide; **MHC-II** = major histocompatibility complex Class II; **MR** = mineralocorticoid receptor; **ROS** = reactive oxygen species; **TLR** = toll-like receptor; **TNFα** = tumor necrosis factor α.

Chronic stress increases the likelihood of developing various psychiatric conditions that affect human health such as depression, burnout, and posttraumatic stress disorder.[1] Stressful experiences activate specific brain regions and the sympathetic nervous system, causing the release of noradrenaline and adrenaline and glucocorticoid hormones into the bloodstream.[2] Repeated exposure to stress and the accompanying alterations in transmitter and hormone levels increase immune system activation. Humans exposed to high levels of chronic stress have high serum levels of the proinflammatory cytokine interleukin (IL)-6[3] and increased numbers of monocytes and neutrophils in the bloodstream.[4] Similar observations have been made in rodent models of chronic stress.[4-12] The immune system and the CNS are closely associated and regulate each other.[13] Owing to this intense communication between the immune system and the brain, activation of the immune system can cause neuroinflammation characterized by the activation of microglia and the production of proinflammatory cytokines in the brain.[14-16] Elevated brain cytokine levels in turn affect behavior and contribute to the development of psychopathologies such as depression.[15]

The communication between the immune system and cells of the CNS is mediated partly by microglia. These cells are the only myeloid immune cells residing in the CNS parenchyma during homeostasis; this strategic location facilitates their role as communicators between the immune system and the CNS. Microglia are important for immune surveillance during homeostasis and involved in the pathology of neuroinflammatory diseases.[17] The role of microglia as important players in stress sensing and responses has gained increasing attention in the past 10 years.[18] Although much literature regarding the role of microglia in stress has been published, the published studies also raise a lot of questions, such as about the functional consequences of changes in microglia phenotype and numbers and their role in the induction of pathology. Therefore, in this article, we discussed the potential mechanisms that could lead to microglial activation in stressful situations, summarized the effects of chronic stress on microglia phenotype and function, and reviewed how microglia can contribute to the establishment of chronic stress-induced psychopathologies. We suggested that as the main immune cell population within the CNS, microglia are key players in the induction of stress-induced psychopathologies.

Microglia Are Tissue-Resident Macrophages of the Central Nervous System

Microglia are innate immune cells that reside in the CNS that derive from yolk sac precursors[19,20] and maintain their population by self-renewal without major contributions from the hematopoietic system.[21,22] In the steady state, microglia have a ramified morphology with fine, branched processes that radially extend from their soma into the surrounding. Microglia processes are highly motile, constantly scanning the environment for potential threats and making contacts with neighboring cells.[23,24] In a healthy adult CNS, microglia contact neuronal synapses and phagocytose synaptic elements in response to neuronal activity, thereby shaping synaptic connections.[25-27] In addition, microglia control neurogenesis by interacting with adult neural precursor cells[28] and maintain the oligodendrocyte precursor cell pool.[29] On infection and in the diseased brain, microglia change their morphology and phagocytose debris, dead cells, and foreign material. These reactive microglia have shorter, thicker processes and can acquire an ameboid shape.[17,30] Furthermore, they upregulate the expression of ionized calcium-binding adapter molecule 1 (Iba1), CD45, and CD11b and can increase the expression of other surface immune molecules involved in antigen presentation such as major histocompatibility complex Class II (MHC-II), CD80, and CD86.[31] To fight infection or help with regeneration, microglia secrete a variety of effector molecules. These include not only proinflammatory cytokines and reactive oxygen species (ROS) but also anti-inflammatory factors and growth factors aiding regeneration.[32-34] Microglia can be activated by various molecules indicative of infection or cell death, such as proinflammatory cytokines, lipopolysaccharide (LPS), and adenosine triphosphate (ATP).[31,35,36] In addition, microglia carry receptors for neuronal ligands on their surface. Some of these are inhibitory receptors (e.g., CX₃CR1 and CD200R), which bind ligands on the surface of healthy neurons preventing the microglia from acquiring a reactive phenotype.[35,37] Taken together, microglia are important mediators of neuroinflammation, keep the CNS clean

Figure 1 Activation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis During Stress
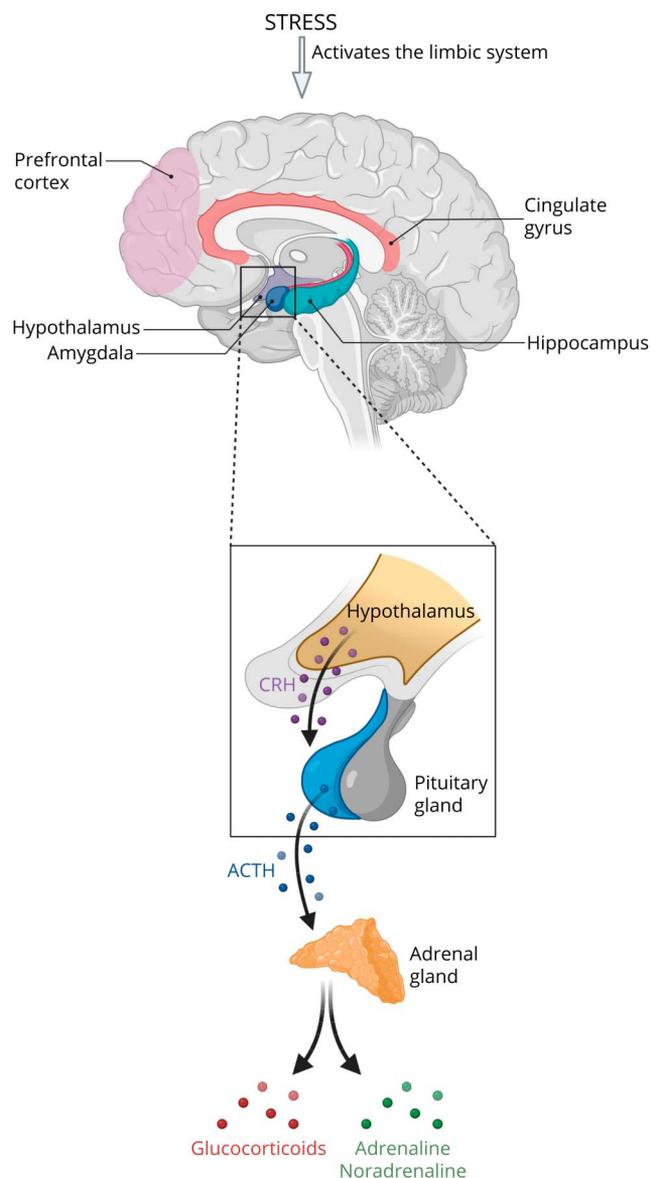
The activation of brain regions of the limbic system in stressful situations leads to the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH then acts on the pituitary gland to stimulate the release of adrenocorticotropic hormone (ACTH) into the blood. ACTH in turn stimulates the adrenal gland to release corticosterone. Furthermore, the activation of the sympathetic nervous system during stress (not shown) triggers the release of noradrenaline and adrenaline from the adrenal gland into the bloodstream.

from unneeded material, and can contribute to tissue repair and regeneration.

Potential Pathways That Activate Microglia in Chronic Stress

Neurons sense and process environmental information, initiating the body's stress response in the case of potential danger, which prepares the organism to successfully overcome threat.

Intriguingly, microglia and other immune cells can be activated during long-lasting stressful situations even in the absence of any physical trigger such as infection.[38,39] A better understanding of the mechanisms underlying microglial activation during chronic stress will be a first important step for the prevention and treatment of stress-induced psychopathologies.

In stressful situations, components of the limbic system such as the amygdala, prefrontal cortex, hippocampus, and hypothalamus are activated.[40] This causes the activation of the sympathetic nervous system, triggering the release of adrenaline and noradrenaline from the medulla of the adrenal gland into the bloodstream. The 2 catecholamines then mediate the body's reaction to stress known as the fight-or-flight response. In addition, the hypothalamic-pituitary-adrenal (HPA) axis is activated.[41] Neurons in the hypothalamus, the central regulator of the autonomic nervous system, secrete vasopressin and corticotropin-releasing hormone (CRH), which in turn stimulate the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland.[42] ACTH then stimulates the adrenal cortex to produce glucocorticoid hormones,[42] mainly cortisol in humans and corticosterone in rodents (Figure 1). In addition, signaling by members of the CRH family itself might further influence the stress response,[43] potentially also by directly affecting immune cells.[44] Altogether, the experience of stressful situations has 2 main outcomes: (1) increases in systemic levels of adrenaline and noradrenaline and (2) release of glucocorticoid hormones from the adrenal gland into the bloodstream. Catecholamines and glucocorticoids then mediate most of the effects of stress on the immune system.

Microglial Responses to Adrenergic Signaling

Inputs from stress-responsive brain regions such as the amygdala and the hypothalamus also activate the locus coeruleus, the main site of noradrenaline production within the brain.[45] The catecholaminergic axons from the locus coeruleus innervate many brain regions, resulting in a release of noradrenaline throughout the brain in stressful situations.[45] In vitro, stimulation of microglial adrenergic receptors has anti-inflammatory effects because it reduces the production of proinflammatory cytokines, superoxide anions, and nitric oxide by microglia.[46-50] By contrast, the stimulation of β-adrenergic receptors during stressful situations in vivo enhances neuroinflammation. Activation of β-adrenergic receptors elevates IL-1β levels in the brain,[51] while blocking the receptor prevents stress-induced increases in brain IL-1β.[51,52] Similarly, blockade of β-adrenergic signaling inhibits the increase in microglial Iba1 expression observed in mice exposed to chronic social defeat (CSD; Tables 1 and 2) stress[39] (Figure 2A).

Although these studies implicate β-adrenergic signaling in inducing proinflammatory responses in microglia after stress, it is not yet clear whether the microglia themselves directly respond to noradrenaline during the stress response. β-adrenergic signaling also has various effects on the activation state of the peripheral immune system during chronic stress[4,5,53] and is required for neuronal activation in CSD

Table 1 Rodent Models of Chronic Stress

Experimental models commonly used to induce chronic stress in rodents are the paradigms of chronic social defeat (CSD), chronic unpredictable stress (CUS), and repeated restraint stress (RRS) (Table 2). These models are also used to study depression because they induce depressive-like and anxiety-like symptoms including social avoidance and anhedonia, which can be reversed by chronic antidepressant treatment.[e63,e64]

CSD[e65]

    Experimental mice are subjected to social defeats by exposure to a larger, aggressive male of a different strain.[e18,e65,e66] After separation of the mice, the experimental mice either reside in their home cage until the next defeat session[e66] or are kept in the cage of the aggressor mouse separated by a wall to allow visual and olfactory contact.[e18,e65] The protocols used by different laboratories further differ regarding several other factors (Table 2).

CUS[e67]

    Mice or rats are exposed to diverse social and environmental stressors (Table 2) in an unpredictable order over weeks.[e67] This may include protocols where each of the stressors is used once a week[e67] or where 2 stressors are applied each day.[e11,e19,e20,e39]

RRS[e64]

    Stress is induced by restraining rodents in a narrow vessel for a certain time on several consecutive days. The duration of the single restraint session varies depending on the protocol (Table 2).[16,e11,e17]

stress.[39] In the studies investigating the effects of β-adrenergic receptor stimulation on microglia, the receptor activity was usually blocked in the whole organism, making it difficult to differentiate between direct effects of this blockade on microglia and secondary effects caused by other cell types. Therefore, it would be interesting to study microglial stress responses in transgenic mice lacking β-adrenergic receptors specifically in microglia, ideally in a system that allows timed deletion of the receptor in adult mice shortly before the stress exposure. Furthermore, most studies investigating the role of β-adrenergic signaling during stress only used models of acute stress; data on noradrenergic signaling in the CNS during chronic stress are scarce.

Microglial Responses to Glucocorticoids

Activation of the HPA axis during stress results in the release of glucocorticoids into the bloodstream. Glucocorticoids have anti-inflammatory functions and are used to treat a variety of inflammatory conditions and autoimmune diseases.[54] However, depending on the cell type and the glucocorticoid concentration, they can have opposing proinflammatory functions.[54] Glucocorticoids can bind and activate 2 different types of receptors, mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs), which are both expressed in a variety of tissues. Because the 2 receptor types have different affinities for glucocorticoids, glucocorticoids preferentially bind to either MRs or GRs depending on their concentration. Low levels of glucocorticoids preferentially activate MRs, whereas high levels activate GRs in most tissues.[55] Indeed, the murine microglia cell line BV-2 shows this typical concentration-response pattern to glucocorticoids: low concentrations increase the production of proinflammatory cytokines through activation of MRs, whereas higher concentrations act through GRs to inhibit cytokine production.[56,57] Moreover, in vivo, moderate corticosterone doses activate NF-κB and proinflammatory mRNA expression in the brains of rats, whereas high corticosterone doses mostly had anti-inflammatory effects[58] (Figure 2B). In line with that finding, microglia from mice with a microglia-specific deletion of the GR express higher levels of proinflammatory genes and genes associated with phagocytosis.[59] These studies further confirm the anti-inflammatory properties of microglial GR activation during steady state.

Intriguingly, in addition to exerting anti-inflammatory effects, high doses of corticosterone also prime components of the immune system to subsequent immune stimuli. Although chronic administration of high doses of corticosterone reduced IL-1β levels in the hippocampus of rats, the treatment also increased the expression levels of Iba1, MHC-II, and NLRP3 mRNAs.[60] High doses of corticosterone therefore seem to sensitize microglia to LPS, leading to exaggerated cytokine responses on subsequent stimulation.[60] The microglia gene expression profile of female mice with GR depletion in microglia after chronic unpredictable stress (CUS; Tables 1 and 2) was notably different from that of wild-type mice. The expression of genes encoding for the proinflammatory cytokine tumor necrosis factor α (TNFα) and the phagocytosis-associated protein CD68 was increased after CUS in wild-type but not in GR-depleted microglia. At the same time, gene expression associated with an anti-inflammatory microglia phenotype was significantly higher in GR-depleted microglia only.[59] Taken together, these findings support the idea that the stimulation of GRs in microglia is involved in the response to chronic stress. The consequences of GR activation in microglia, however, are rather complex and range from keeping microglia in homeostasis during steady state to inducing proinflammatory gene expression in other contexts.

Other Pathways That Activate Microglia During Chronic Stress

In addition to catecholamines and glucocorticoids as the typical players in stress, various other factors contribute to microglia activation during chronic stress. Neuronal activation in stress-responsive brain regions seems to be a prerequisite for microglia activation because inhibiting neuronal activation with the benzodiazepine clonazepam prevents CSD-induced microglial activation.[e1] Peripheral immune activation resulting in increased cytokine levels in the circulation most likely also contributes to the development of neuroinflammation during chronic stress. For example, microglia were not activated after CSD in mice deficient in IL-1 receptor type I (IL-1R1) and in IL-1R1–deficient mice reconstituted with bone marrow from wild-type mice.[10] By contrast, microglial activation after CSD occurred in mice in which the IL-1R1 was depleted only in tie2-expressing cells (this deletion mainly targets endothelial cells).[10] These findings suggest that IL-1 signaling in a cell type other than bone marrow-derived immune cells or endothelial cells is required for microglial activation during CSD stress. It is tempting to speculate that microglia themselves could respond to IL-1 released during chronic stress, especially because IL-1 signaling was shown to play a role in microglia homeostasis.[e2] However, other studies

Table 2 Protocols to Generate Chronic Stress in Rodents

	Chronic social defeat (CSD) stress[e65]	Chronic unpredictable stress (CUS)[e67]	Repeated restraint stress (RRS)[e64]
Stress generation	Male mice are subjected to a series of social defeats by a larger, aggressive male.	Animals are exposed to a variety of random stressors over weeks. The stressors include the following: tilted cage, cage shaking, isolation, crowding, wet/no bedding, food/water deprivation, noise, predator sound, rat odor, light on overnight, light off during day, restraint stress, and forced swimming.	Animals are restrained in a narrow vessel for a certain time on several consecutive days.
Duration of single stress session	Short defeat sessions (5–10 min) per day[e18]; in some cases, defeat sessions last 2 hours[e66]	Dependent on the type of stressor	30 min[16,e11] to 15 hours[e17]
Duration of entire procedure	6, 10 or 14 d	1–12 wk	1–4 wk
Differences among different protocols	Duration of single defeat sessions Number of sessions/d Duration of the entire protocol If experimental and aggressor mice are cohoused in the same cage If a new aggressor mouse is introduced for each defeat If experimental mice are single-housed or group-housed during the CSD If mandibular incisors of the aggressor mice are trimmed to avoid injuries	1 or 2 stressors/d Types of stressors Duration of the entire protocol	Duration of single restraint sessions 1 or 2 sessions of stress/d Duration of the entire protocol
Advantages & Disadvantages	+: Protocol mimics social stress −: Classic CSD model can only be applied to male rodents	+: Great variety of stressors −: More effort/equipment needed	+: Little equipment needed −: Does not truly reflect stress as it occurs in humans

indicate that microglia do not express IL-1R1 under physiologic conditions[e3] and after CSD stress.[e4]

Toll-like receptors (TLRs) are pattern recognition receptors that recognize both foreign pathogen-associated molecular patterns and endogenous danger-associated molecular pattern (DAMPs). Microglia lacking TLR2 and TLR4 failed to acquire an activated morphology after CSD stress.[e4] In addition, the activation of TLRs on microglia in the prefrontal cortex was required for the development of CSD-induced social avoidance.[e4] During stress, TLRs can be activated by endogenous DAMPs, also known as alarmins.[e5] One such alarmin is high-mobility group box-1 (HMGB1), which can activate TLR2, TLR4, and receptor for advanced glycation end products.[e6] Both acute and chronic stress induce the expression and release of HMGB1 from hippocampal microglia,[e7-e9] and inhibition of HMGB1 diminishes stress-induced increases in proinflammatory mRNA expression in rat microglia.[e7] These findings suggest that HMGB1 released during the stress response can act on microglial TLRs to activate microglia.

Taken together, the release of catecholamines and glucocorticoids as the initiators of the stress response is critical for microglial activation during stress both by direct and indirect effects. β-adrenergic signaling enhances neuroinflammation, potentially by directly activating microglia, while the direct effects of glucocorticoids on microglia are more complex and seem to be context-dependent. In addition, the release of catecholamines and glucocorticoids increases immune system activity in the periphery,[4,7] which can further contribute to microglial activation through proinflammatory cytokines such as IL-1. Finally, also local danger signals released within the CNS during stress contribute to microglial activation. These diverse mechanisms of microglial activation exemplify the complexity of the stress response in general. While some important activation factors of microglia in stress are known, their exact mode of action remains mostly unclear. Furthermore, it seems likely that additional factors and cell types are involved, making the process of microglial activation during chronic stress even more complex.

Chronic Stress Influences Microglia Phenotype and Number in Stress-Responsive Brain Regions

Exposure to chronic stress increases the expression of Iba1 in stress-responsive brain regions in repeated restraint stress (Tables 1 and 2),[16,e10,e11] CUS[e12], and CSD stress,[39,e13] demonstrating microglial activation in these models. It is of interest that Iba1 expression was significantly lower in the prefrontal cortex of mice resilient to CSD stress than in stress-susceptible and naïve mice,[e4] which points toward a role for microglial activation in rendering mice susceptible or resilient to stress. In addition, CD11b expression was increased in the brains of mice subjected to CSD or CUS,[e14] which is an additional sign of microglial activation.[31] By contrast, chronic
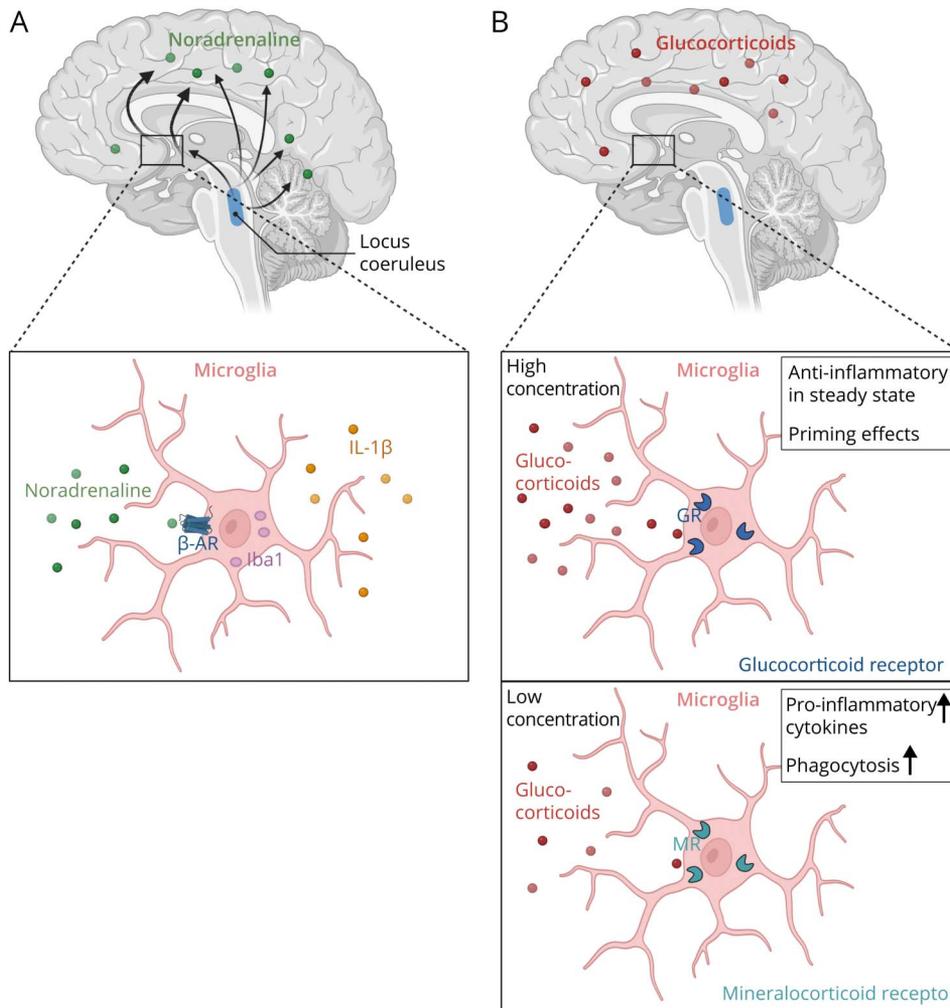
(A) In stressful situations, noradrenaline is distributed throughout the brain by neurons in the locus coeruleus and can bind to β-adrenergic receptors (β-AR). β-adrenergic signaling during stress then contributes to neuroinflammation with increased Iba1 expression in microglia and increased IL-1β levels in the brain. (B) Glucocorticoids released during the stress response can bind to 2 different types of receptors, glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), which are expressed in a variety of cell types including microglia. Because of different receptor affinities, glucocorticoids present at a high concentration preferentially activate GRs. GR activation in microglia in steady state has anti-inflammatory effects and reduces cytokine production. However, at the same time, high glucocorticoid concentrations also prime microglia to subsequent stimuli. Glucocorticoids present at low concentrations preferentially activate MRs leading to increased proinflammatory cytokine production and phagocytosis by microglia.

stress does not induce microglial expression of MHC-II,[16,39,e10] a molecule required for antigen presentation,[e15] which is expressed by microglia during neuroinflammation and CNS disease.[31] This observation is not too surprising, given that stress is a sterile inducer of inflammation. However, microglial expression of CD86, another molecule required for T-cell activation,[e16] was increased by CSD stress.[39] Similarly, the percentage of TLR4-expressing and CD14-expressing microglia was increased after CSD stress.[39,e13] The expression of CD68, a lysosomal protein expressed by monocytes and macrophages, is low during homeostasis, but is upregulated in phagocytically active microglia.[31] CD68 expression is increased in stress-susceptible mice shortly after CSD stress,[e4] indicating that microglia are more phagocytically active during chronic stress. Taken together, these findings suggest that in brain regions associated with threat appraisal and emotional responses, chronic stress activates microglia.

In addition to influencing the phenotype of individual microglia, chronic stress affects microglial proliferation and programmed cell death, resulting in alterations in microglia numbers in stressed mice.[16,e17-e19] The proliferation of microglia was detected after 2–4 days of repeated restraint, social defeat, or unpredictable stress.[e17-e19] This proliferation is associated with increased numbers of microglia in stress-responsive brain regions such as the dentate gyrus of the hippocampus, the prefrontal cortex, and the amygdala.[e18,e19] Shortly after the onset of proliferation, a fraction of microglia undergoes apoptosis,[e17,e19] leading to a decline in microglia numbers. After exposure to stress for several weeks, microglia numbers were significantly decreased in certain brain regions in the different stress models.[e19,e20] The functional consequences of these changes in microglia phenotype and numbers are only partially known and will be discussed in the remaining sections of this article.

Chronic Stress Induces Long-Lasting Priming of Microglia

Chronic stress induces an increased expression of proinflammatory mediators in microglia.[10-12,39,e1,e13,e21-e23] It is of

Table 3 The Term *Stress Resilience*

Animal studies investigating factors that contribute to the stress response often assess an outcome referred to as stress resilience. In stress research, resilience is typically used as a term to describe how well an individual can limit the detrimental effects of a stressor.[e68] Therefore, the level of resilience can be judged by measuring certain predefined biological parameters, e.g., the animals' behavior in a certain behavioral test. In that case, stress-exposed animals that behave similar to nonstressed controls are considered as stress-resilient, while stress-exposed animals that show behavioral alterations are considered as stress-susceptible. That way, the outcome of resilience or susceptibility can be used to conclude the importance of the studied factor during the stress response. However, one must keep in mind that the outcome of resilience or susceptibility only reflects the importance of that factor in influencing the specific behavioral parameter that was measured but does not allow conclusions about other, not measured, outcomes.

interest that these stress-activated microglia also show an exaggerated inflammatory response to subsequent proinflammatory stimuli such as LPS both in vitro and in vivo.[e13] This reinforces the idea that exposure to chronic stress induces a functional activation of microglia because they are more responsive to subsequent other immune stimuli. The primed (activated) microglial state is maintained as long as 24 days after the last stress and involves an increased expression of many immune-related genes and pathways such as IL-1β, IL-6, and CD14.[8,e22] Glucocorticoids are one possible mediators of stress-induced microglia priming. Increases in the proinflammatory response of microglia to LPS after acute tail shock stress were prevented by pretreating rats with a glucocorticoid receptor antagonist or by the removal of their adrenal glands before the tail shocks.[e24]

It is of importance that chronic stress does not only prime microglia for following LPS stimulation but also for subsequent acute stress exposure, indicating that the microglia response to acute stress might resemble their responses to immune stimulation by LPS. While 1 session of social defeat (acute stress) did not increase the expression of proinflammatory mediators in microglia of naïve mice, it increased the expression of proinflammatory mediators in mice subjected to CSD 24 days earlier.[8] This priming by CSD stress is also reflected in the behavior of the animals because acute stress was only sufficient to increase anxiety and social avoidance in mice that had been previously subjected to CSD.[8] To prove that microglia are involved in the increased susceptibility of CSD mice to acute stress, microglia were depleted using an inhibitor of the colony-stimulating factor 1 receptor (CSF1R), which microglia require for survival.[e22,e25] This experiment showed that CSD mice were only more susceptible to acute defeat than unstressed controls when microglia were present during the acute defeat session; the priming effect of chronic stress on the susceptibility to anxiety was erased in mice lacking microglia during the acute defeat.[e22] Surprisingly, the priming effect of chronic stress was observed in mice lacking microglia during the CSD itself. In mice lacking microglia during the CSD, but not during the acute defeat (because of repopulation), the acute defeat was sufficient to induce anxiety.[e22] Certainly, this rather unexpected observation needs to be further confirmed, ideally also by assessing anxious behavior in more than 1 test. Nevertheless,

these findings raise the following questions: (1) How is stress sensed in the absence of microglia? (2) Which persistent changes apart from microglial activation occur in the brain after exposure to chronic stress? (3) How can these changes induce a stress-sensitized microglia state once the microglia repopulate? and (4) Is it possible that residual microglia remaining after depletion can transfer the stress-sensitized phenotype to the cells they give rise to during repopulation? Intriguingly, this observation that microglia are primed by CSD stress although they were depleted was also made in a second study. Microglia were depleted with a CSF1R inhibitor during the CSD and allowed to repopulate after the last defeat session.[e26] Even without a subsequent acute stressor, microglia repopulation alone was sufficient to induce anxiety and social avoidance, while behavioral disturbances were absent in animals in which CSF1R inhibitor administration was continued after CSD had ended.[e26] This study therefore further supports the notion that either the microglia that survived the depletion or a surrounding CNS component was altered by CSD stress in a way that enabled them to reprogram the repopulating microglia. Alternatively, it is possible that the process of microglial depletion itself, which is associated with a cytokine storm,[e2] induces changes in the CNS that then reprogram the repopulating microglia, leading to a hypersensitization of the CNS to stress.

In conclusion, chronic stress induces a long-lasting priming of microglia similar to as it occurs in neurodegenerative diseases and systemic inflammation.[e27] However, some of the effects of stress on the CNS only seem to influence microglia secondarily because microglia are also primed by chronic stress if they are depleted during the stress exposure. This suggests that stress also induces other, so far unknown, changes in the CNS that in turn can induce microglia priming. Primed microglia are more susceptible to different types of secondary challenges, leading to exaggerated responses to immune stimuli or minor stress events, which otherwise would not have elicited any detrimental response.

The Role of Microglia in Stress-Induced Behavioral Disturbances

Microglia are activated during chronic stress and change their phenotype and functional properties. Studies in which microglial activation was blocked with the antibiotic minocycline or in which microglia were depleted during chronic stress demonstrate that microglia play a key role in the induction of behavioral disturbances such as anxiety, anhedonia, and despair.[e1,e19,e20,e28,e29] Considering this critical role of microglia in stress-induced psychopathologies, a better understanding of how microglial activation leads to the establishment of behavioral disturbances after stress will improve our knowledge of how stress can cause psychopathologies.

Increased brain levels of the proinflammatory cytokine IL-1β are commonly observed after chronic stress. Although brain-infiltrating

monocytes could be a potential source of this cytokine, they do not seem to be the main producer of brain IL-1β during CSD stress because IL-1β mRNA is also increased in CC chemokine receptor 2 (CCR2)-deficient mice in which the recruitment of monocytes into the brain is blocked.[9] Furthermore, several studies show that IL-1β mRNA levels are increased in brain isolates highly enriched for microglia obtained from mice subjected to CSD,[10,12,39,e13,e21,e22] further suggesting microglia as the major source of IL-1β during chronic stress. If and how microglia-derived IL-1β induces behavioral disturbances after stress remains to be revealed. In general, IL-1 signaling is a key regulator of the response to chronic stress[e30] because mice deficient in IL-1R1 do not develop anxiety after CSD.[10,39,e4] If IL-1β acts in the periphery, within the blood-brain barrier, inside the CNS, or in all these compartments to induce behavioral disturbances remains unclear. One study found that endothelial cells need to respond to IL-1β for the development of anxiety after CSD.[10] However, given the variety of IL-1β target cells and functions, it seems reasonable that its actions on more than 1 cell type are involved in the response to chronic stress.

In addition to IL-1β, microglial expression of chemokine (C-C motif) ligand 2 (CCL2) is increased during chronic stress.[10-12,e1,e23] The main cell type constitutively expressing CCR2, the receptor for CCL2, is Ly6C^{hi} monocytes.[e31] It is therefore likely that CCL2 secreted by microglia recruits monocytes to the CNS during CSD; indeed, monocyte recruitment is absent when microglial activation is blocked or when microglia were depleted during CSD.[e1] Cytokines released in the CNS are not only able to recruit peripheral immune cells but have diverse effects on various cell types and processes. For example, proinflammatory cytokines can modulate neurotransmitter systems,[e32] cause neurotoxicity,[e33] inhibit neuronal plasticity,[e33] and modulate neuronal excitability.[e34] Furthermore, cytokines can modulate the metabolic profile of astrocytes[e35] and activate astrocytes, leading to astrogliosis.[e36] Therefore, increases in cytokine production by microglia could be a critical driver of behavioral disturbances after chronic stress. Microglia also secrete other soluble factors, such as brain-derived neurotrophic factor (BDNF), which can influence surrounding CNS cells. A subset of microglia promoted adult hippocampal neurogenesis and stress resistance in a model of CUS, potentially through the secretion of BDNF.[e37]

Besides secreting proinflammatory cytokines, microglia can induce the production of ROS to cause behavioral disturbances.[e26] While CSD stress leads to increased ROS activity in the brain, this increase is prevented by microglial depletion.[e26] The administration of the antioxidant N-acetylcysteine or depletion of microglia during the CSD blocks the development of social avoidance in response to stress exposure. Intriguingly, when microglia could repopulate after the end of CSD, this was sufficient to increase ROS activity in the brain and induced a delayed development of social avoidance. To explain those results, the authors offered the following scenario: microglia produce ROS and are necessary to stimulate ROS activity in other brain cells, and this increase in ROS activity is essential for the development of social avoidance after chronic stress. Surprisingly, microglia that repopulate after CSD seem to be reprogrammed to drive ROS production, leading to the development of social avoidance in the recovery phase after CSD.[e26]

Microglia are also involved in shaping the CNS environment by phagocytosis. In recent years, it has become clear that microglia can phagocytose synapses in the postnatal CNS, thereby contributing to synaptic pruning.[25-27] Induction of CUS in mice increases microglial phagocytosis of neuronal elements such as axon terminals and dendritic spines.[e12,e38,e39] Similarly, microglia isolated from mice subjected to CSD displayed an enhanced phagocytic activity in vitro.[e18] Microglial phagocytosis of neurons is induced by neuronal expression of colony-stimulating factor 1 (CSF1), which binds to CSF1R on microglia.[e12,e39] The expression of both CSF1 and CSF1R mRNA increases in the prefrontal cortex after CUS and shRNA-mediated knockdown of CSF1 1 week before CUS blocks the development of depression-like behavior.[e12,e39] These findings propose that the remodeling of neurons by microglia is another important mechanism contributing to the establishment of behavioral disturbances after chronic stress.

Microglia express high levels of the fractalkine receptor, CX$_3$CR1, and because neurons are the main source of fractalkine (also known as CX$_3$CL1), this pathway is a major communication channel between microglia and neurons.[e40] In the healthy CNS, CX$_3$CL1-CX$_3$CR1 signaling keeps microglia in a homeostatic state, and its disruption is associated with a proinflammatory microglia phenotype and enhanced phagocytosis.[e41] This enhanced phagocytosis can have both beneficial or detrimental consequences depending on the context and disease model. For instance, the lack of CX$_3$CR1 reduces the deposition of amyloid-β in models of Alzheimer disease[e42,e43] but enhances neuronal loss in a toxic model of Alzheimer disease and a mouse model of amyotrophic lateral sclerosis.[e44] Lack of CX$_3$CR1 in the whole body during chronic stress seems beneficial because CX$_3$CR1-deficient animals are at least partly protected from developing behavioral disturbances after chronic stress.[9,e38,e45-e47] These studies suggest therefore that the enhanced phagocytosis associated with lack of CX$_3$CR1 protects the animal from stress-induced neuronal damage. However, because CX$_3$CR1 is also expressed by other immune cell types, including monocytes, some subsets of natural killer cells, and dendritic cells,[e48,e49] it is not clear whether the hyperactivation of microglia is indeed responsible for the beneficial effect of CX$_3$CR1 deletion. In addition, the stress-induced recruitment of peripheral monocytes to the brain after CSD is reduced in CX$_3$CR1-deficient animals,[9] raising the question of whether the observed resistance to chronic stress on CX$_3$CR1 deficiency might be, at least partially, due to the deletion of the gene in monocytes rather than in microglia. Therefore, further studies are needed to reveal the
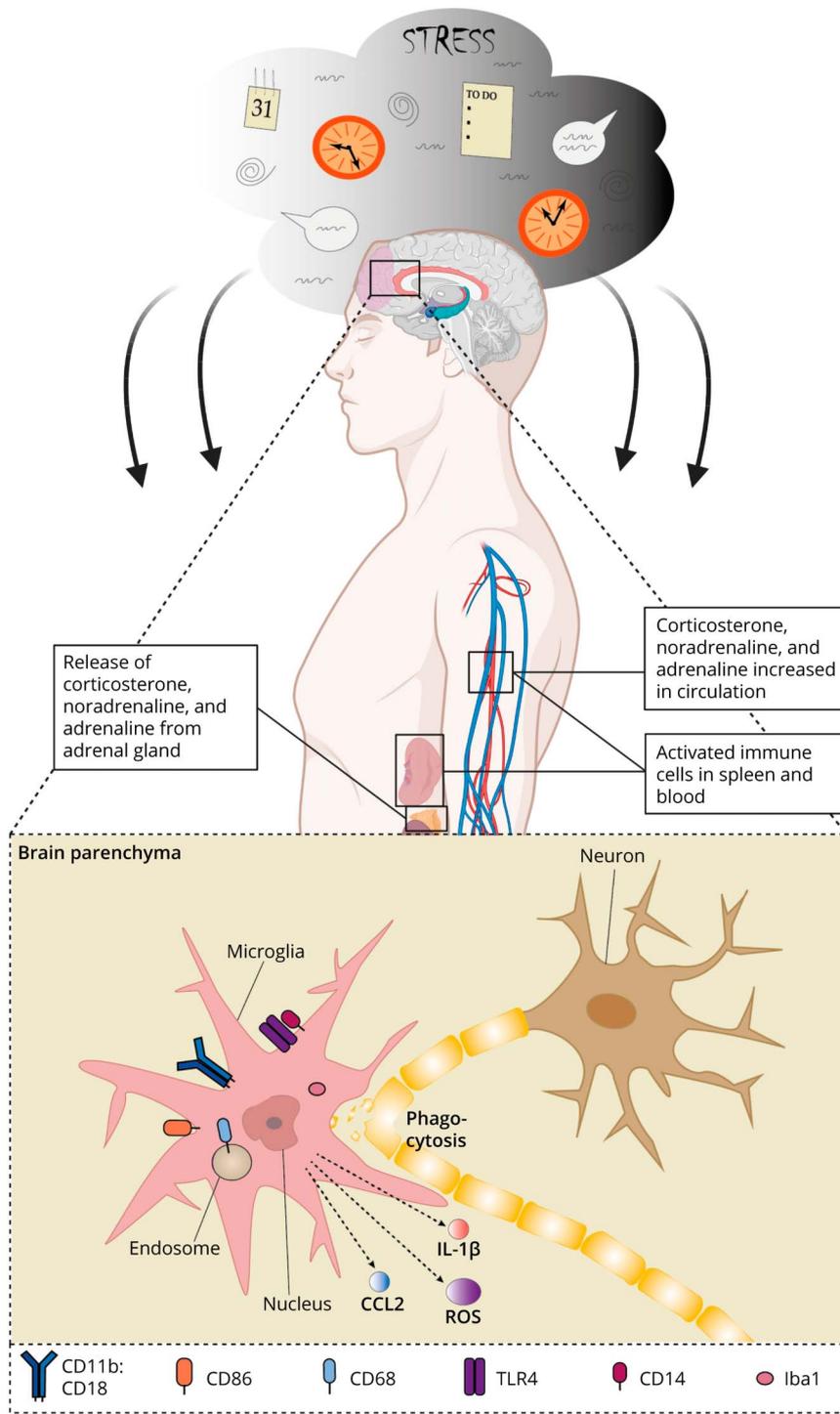
Exposure to chronic stress activates stress-responsive brain regions, the sympathetic nervous system, and the HPA axis. As a result, corticosterone, noradrenaline, and adrenaline are released from the adrenal gland into the circulation and the immune system is activated. Microglia in stress-responsive brain regions upregulate the expression of several markers associated with their activation, including Iba1, CD11b, CD86, TLR4, CD14, and CD68. Furthermore, stress-activated microglia release the proinflammatory cytokines IL-1β and CCL2, enhance ROS production in the brain, and directly phagocytose neuronal elements, thereby modulating the response to chronic stress. CCL2 = chemokine (C-C motif) ligand 2; IL = interleukin-1; HPA = hypothalamic-pituitary-adrenal; ROS = reactive oxygen species.

mechanisms by which CX$_3$CR1 deficiency protects from chronic stress, ideally using models in which the deletion of CX$_3$CR1 can be restricted to adult microglia.

Microglia are not only in contact with neurons but also with other glia cells, and this cross talk influences microglia phenotype and function.[e50] In certain brain regions of stressed rodents, astrocyte density is decreased[e51,e52] and astrocyte morphology is altered.[e52,e53] Depletion of astrocytes induced depressive-like behavior in rats, suggesting that the loss of astrocytes during chronic stress could contribute to the behavioral disturbances.[e51] While the release of ATP by astrocytes was decreased in stressed rodents, external administration of ATP could alleviate stress-induced depressive-like behavior.[e54] On the contrary, extracellular ATP was rapidly increased after the onset of restraint stress, which could trigger inflammasome activation and microglial

production of IL-1β.[e55] Taken together, while an astrocyte dysfunction is most likely involved in the pathology of chronic stress, the exact mechanism remains to be revealed. It seems likely that astrocytes exert their effects by directly influencing neighboring cells, such as microglia and neurons.[e56]

Differences in Microglia Transcriptome Between Stress-Susceptible and Stress-Resilient Mice

Intriguingly, differences in the microglia transcriptome between the microglia from stress-susceptible and stress-resilient mice (Table 3) were recently identified.[e57] According to the resilience definition used, stress-resilient mice behaved similar to nonstressed controls, while stress-susceptible mice showed decreased social interaction and decreased urine scent marking.[e57] While microglia from stress-susceptible mice had a highly inflammatory transcriptomic profile, certain genes involved in regulating emotional responses were specifically enriched in microglia of stress-resilient mice, thereby giving hints about potential mechanisms that might render these mice resilient against stress. Furthermore, the genes highly enriched in microglia from stress-susceptible mice were increased in the brains of patients with Huntington and Parkinson diseases.[e57] This finding supports the hypothesis that the transcriptome of microglia is similarly altered during chronic stress, as it is altered during some neurodegenerative diseases. Nevertheless, more studies will be needed to further uncover how chronic stress alters microglia profiles in different brain regions and to characterize microglia gene expression profiles of stress-resilient and stress-susceptible animals, ideally also on a single-cell level. In addition, it will also be interesting to investigate the possibility of epigenetic changes occurring in microglia during chronic stress.

It remains to be revealed whether the change in microglia profiles precedes the behavioral response to stress: Do the microglia profiles already differ between stress-susceptible and stress-resilient individuals before the onset of stress, thereby predicting how an individual will respond to chronic stress? Or do differences in other immune system components or differences in other CNS cell types predispose certain individuals to resilience to chronic stress? In turn, these differences could then influence the microglia activation state, leading to the observed differences in microglia signature between susceptible and resilient mice.

Conclusions

Owing to their position as innate immune cells within the CNS parenchyma, microglia are ideally located to facilitate communication between the immune system and the CNS. We suggest that microglia are important players in establishing behavioral disturbances after chronic stress; however, the role of microglia in the induction of pathology remains incompletely understood. One of the reasons for that is a scarcity of studies conducting in-depth, single-cell profiling of microglia during chronic stress. Investigations of the microglia population in the developing and healthy adult brain and in models of brain disease show that microglia are a heterogeneous population with distinct gene expression profiles.[e58-e61] In addition, the alterations in microglia phenotype that occur in disease and aging are different depending on the disease model.[e62] Therefore, it will be of great interest to uncover how chronic stress alters microglia profiles in different brain regions and to further determine how the microglia signature of stress-resilient animals differs from that of stress-susceptible animals. The lack of knowledge about the exact role of microglia during chronic stress makes it difficult to predict which microglia phenotype could be beneficial or detrimental in the context of stress and psychiatric diseases. Therefore, unbiased approaches such as genome-wide transcriptome analyses at a single-cell level are crucial to reveal distinct microglia phenotypes during chronic stress, thereby improving our understanding of how microglia contribute to the establishment of psychopathologies after chronic stress.

Disclosure
No disclosures. Go to Neurology.org/NN for full disclosure.

Appendix Authors

Name	Location	Contribution
Eva Schramm, MSc	Institute for Molecular Medicine, University Medical Center, Johannes Gutenberg University Mainz	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Ari Waisman, PhD	Institute for Molecular Medicine, University Medical Center, Johannes Gutenberg University Mainz; Focus Program Translational Neurosciences, University Medical Center of the Johannes Gutenberg-University Mainz; Research Center for Immunotherapy, University Medical Center of the Johannes Gutenberg-University Mainz, Germany	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data

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