Review

Biological Psychiatry

Immunity in Rodent Models of Stress

Sebastian Hachenberg, Scott J. Russo, and Flurin Cathomas

ABSTRACT

Chronic stress is a major risk factor for several psychiatric disorders, including major depressive disorder and posttraumatic stress disorder. This review synthesizes rodent-based findings showing that stress modifies immune function in the central nervous system (e.g., microglia), the neurovascular unit, and the peripheral circulation. Stress paradigms such as chronic social defeat stress or chronic variable stress induce morphological and transcriptomic changes in microglia, disrupt blood-brain barrier integrity, and mobilize immune cells (e.g., monocytes, neutrophils). These cells, in turn, secrete proinflammatory mediators, including interleukin 6 and matrix metalloproteinase 8, which can penetrate limbic brain regions and contribute to behavioral changes. Integrating next-generation molecular insights with refined behavioral models, particularly those that capture sex-related differences, holds promise for advancing personalized strategies to prevent and treat stress-related disorders.

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Our bodies constantly adapt to external conditions, and appropriate responses to environmental changes are essential for survival. This is particularly relevant when we encounter threats, during which the autonomic nervous system and the hypothalamic-pituitary-adrenal axis orchestrate the body's reaction to mediate the acute fight-or-flight response (1). While this short-term stress response is typically adaptive, repeated, prolonged, or extreme stressors can render it maladaptive (2). Consequently, chronic stress is a major risk factor for many disorders, including neuropsychiatric disorders such as major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) (3). Therefore, elucidating the mechanisms underlying stress responses is critical for understanding the etiopathophysiology of these psychiatric disorders.

In the brain, a network of interconnected regions known as the limbic system is important for regulating mood, motivation, and related emotional states under physiological conditions, as well as for driving the behavioral changes that characterize stress-related disorders defined by DSM-5 (4) or the Research Domain Criteria (5). This network encompasses the nucleus accumbens (NAc), medial prefrontal cortex (mPFC), hippocampus, amygdala, and ventral tegmental area, among other regions (6). Over the past few decades, research has revealed distinct neurophysiological and molecular alterations in both neuronal and non-neuronal cells within these brain regions (7).

It is increasingly becoming evident that the immune system contributes to mediating the deleterious effects of stress on many organ systems, including the brain (8). Accordingly, a subset of patients with MDD and PTSD exhibit a state of chronic low-grade inflammation, as evidenced by elevated levels of circulating proinflammatory cytokines, chemokines, and the acute phase protein C-reactive protein (CRP) (9–12). This proinflammatory state is also apparent in circulating immune cells, with established dysregulation of cells of the myeloid and lymphoid lineage (13). Moreover, stress has been shown to compromise key protective barriers, including the blood-brain barrier (BBB) (14) and gut lining (15).

However, the precise mechanisms by which these immune changes affect the brain and behavior remain only partially understood. Animal models, particularly rodent models, are crucial to increasing our understanding of these mechanisms. Thus, the goal of this review is to synthesize current rodent-based research on how stress modulates immune function and, in turn, how these immune alterations influence the brain and behavior (Figure 1).

RODENT STRESS MODELS

Developing valid animal models for psychiatric research is challenging due to several factors, including the wide range of symptoms characteristic of stress-related disorders and the polygenic nature of the illness. Moreover, while these disorders include measurable impairments (e.g., anhedonia, circadian disruption, appetite changes) that can often be translated into animal models, certain human-specific symptoms (e.g., feelings of guilt, suicidality) are beyond the scope of animal research (16). Thus, no single model can encompass the full spectrum of psychiatric syndromes. Instead, researchers focus on modeling various disorder dimensions, all of which require high construct or etiological validity (i.e., shared causal factors), face validity (i.e., phenomenological similarity to human disorders), and predictive validity (i.e., the degree to which an intervention in the animal model predicts outcomes in humans) (17). Figure 2 depicts the most widely used stress models, which serve as the foundation for the subsequent discussion of key psychoneuroimmunology findings.

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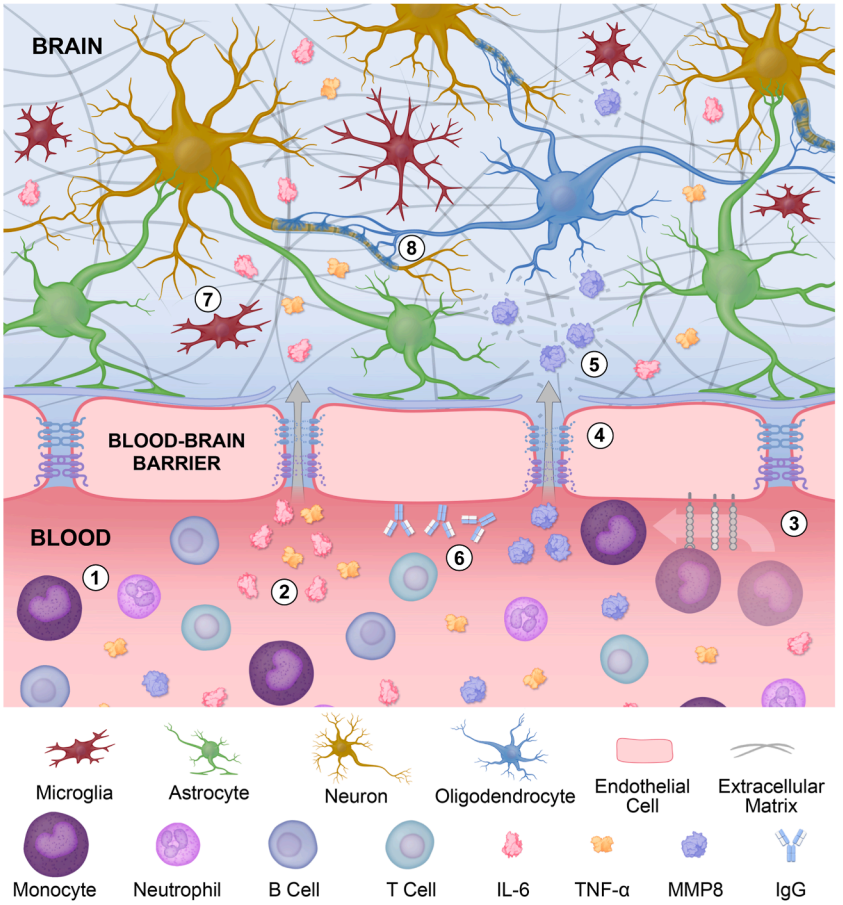

Figure 1. Key findings on stress-induced alterations in microglia, the BBB, and circulating immune cells and proteins. Stress mobilizes myeloid cells, such as monocytes and neutrophils (1), from the bone marrow into the circulation, where they secrete cytokines including IL-6 and TNF-α (2) and migrate to the vasculature of limbic brain regions (3). Stress-induced behavioral impairments are causally linked to increased BBB permeability (4), allowing these cytokines to enter the parenchyma and affect neuronal function; additionally, MMP8 can alter the brain's extracellular matrix (5). Another potential mechanism of stress susceptibility is the accumulation of brain-reactive IgG antibodies around cerebral blood vessels in limbic regions (6). In the brain parenchyma, microglia under stress exhibit morphological changes, increased phagocytic activity, and elevated expression of inflammatory cytokines (7). Peripheral factors and microglia closely interact with other glial cells, such as oligodendrocytes; however, whether the impaired myelination observed across stress paradigms (8) reflects microglial pruning or intrinsic oligodendrocyte maturation defects remains to be determined. BBB, blood-brain barrier; IgG, immunoglobulin G; IL, interleukin; MMP8, matrix metalloproteinase 8; TNF, tumor necrosis factor.

MICROGLIA

Microglia are the resident immune cells of the central nervous system (CNS), constituting approximately 5% to 12% of the adult mouse brain cells (18). In addition to their important role in brain development (e.g., synaptic pruning), they continuously monitor the CNS microenvironment (19) and help maintain homeostasis by clearing cellular debris and apoptotic cells, modulating neuronal activity, and supporting synaptic plasticity (20).

Under homeostatic conditions, microglia typically exhibit small cell bodies with extensively branched processes and a distinct transcriptional profile (21). When activated, they can alter their morphology (e.g., retracted processes and an enlarged soma), shift their transcriptome (e.g., suppression of homeostatic signatures), and secrete cytokines and growth factors that potentially affect neuronal function (22). The transition from surveilling microglia to reactive cells is not a binary process; instead, they move along a spectrum of states defined by morphology, transcription, and function (23). As a result, the traditional resting versus active and M1 versus M2 dichotomies are now considered obsolete (24), although they remain common in psychoneuroimmunology.

Chronic social defeat stress (CSDS) leads to increased soma size and shorter and thicker cell processes in the medial amygdala, PFC, and hippocampus (25). Microglia express many different receptors that can potentially integrate and respond to stress-related signals that can originate from both the brain and circulation (26). Wohleb *et al.* (25) have implicated catecholamines, and specifically β-adrenergic receptor activation, in the effects of adult stress on morphological and transcriptional changes in microglia. However, these findings rely largely on nonspecific pharmacological interventions. Microglia also express toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns and damage-associated molecular patterns (DAMPs) (27). DAMPs, also known as alarmins, such as HMGB1 or S100 proteins, are interesting candidate proteins potentially contributing to microglia activation, as they increase in the brain in response to stress (28). These signals can activate the NLRP3 inflammasome, which in turn activates caspase-1 and promotes the maturation of proinflammatory cytokines such as interleukin 1β (IL-1β) (29).

Several studies have used RNA sequencing (RNA-seq) to decipher transcriptional changes in response to adult stress. CSDS increases expression of proinflammatory cytokine

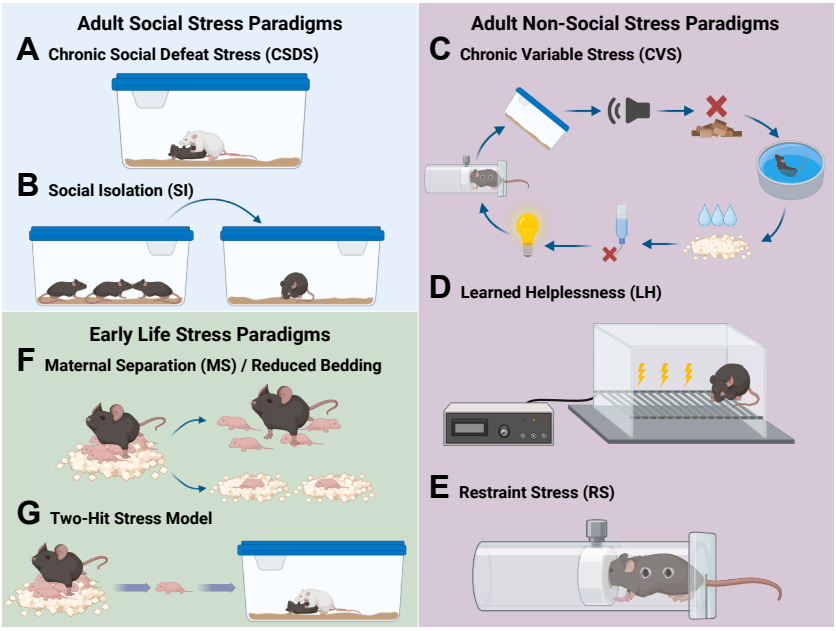

Figure 2. Rodent stress paradigms relevant to psychoneuroimmunology. Social stress, such as abuse or neglect, is a major environmental risk factor for stress-related psychiatric disorders (141). Therefore, adult rodent models based on social stressors are highly relevant. **(A)** Chronic social defeat stress: An experimental mouse is exposed for ≥10 days to brief bouts of direct physical confrontation and prolonged sensory/olfactory contact with a more dominant, aggressive mouse (e.g., CD-1) (142). CSDS offers several advantages: 1) individual variability in stress responses, with about two-thirds of mice developing behavioral alterations relevant to MDD (e.g., anhedonia, social avoidance) and about one-third remaining stress resilient, and 2) persistence of behavioral changes for several months, allowing pharmacological (e.g., antidepressants) and behavioral (e.g., environmental enrichment) interventions. Historically limited to males, CSDS application to females has expanded using novel approaches such as chemogenetic induction of male aggression (143), male odorant exposure (144), and cohousing with male aggressors (145), enabling investigation of sex difference. Physical injury is a potential confounding factor and must be controlled. Nonphysical stress models such as vicarious defeat, based on observation rather than direct confrontation, yield similar outcomes (129). **(B)** Social isolation: Mice housed individually for extended periods display reduced preferences for natural rewards and alterations in social behavior including increased avoidance and aggression (146,147). SI is straightforward to implement and models human loneliness, but the high social drive of rodents means prolonged single housing, which can induce distress beyond the intended stress exposure, raising animal welfare concerns. Several widely used models are based on nonsocial stressors. **(C)** Chronic variable stress, chronic mild stress, chronic unpredictable stress: These paradigms are based on the principle that relatively mild but persistent unpredictable stressors can reduce responses to rewards (148). The protocol typically includes a range of mild stressors (e.g., temporary food or water deprivation, disrupted light cycles, altered bedding, cage tilting) administered over several weeks (149). CVS is relatively straightforward to include both males and females, although females often develop behavioral changes more quickly (around 6 days) compared with males (several weeks) (150), and it induces behavioral deficits that only respond to chronic antidepressant treatments. However, CVS uses stressors with lower translational validity, is time-consuming, and shows variable reproducibility across laboratories. **(D)** Learned helplessness: Following exposure to uncontrollable stressors, e.g., unescapable footshocks, animals develop a specific deficit in behavioral control over aversive stimuli (151). Animals displaying this helpless phenotype exhibit behaviors with face validity to depressive symptoms, including weight loss, disrupted sleep, and HPA axis alterations (152). Limitations include the short duration of behavioral effects in many strains and their reversibility by acute antidepressant treatment. **(E)** Restraint stress: Restraint restricts the animal's mobility (e.g., using a Plexiglas cone) (153). This approach requires relatively low expenditure and produces robust behavioral alterations, particularly with respect to anhedonia (154), although it has clear limitations regarding construct validity and leads to desensitization of the HPA axis. Exposure to chronic or severe stress during early childhood, commonly referred to as ELS, has profound and lasting effects on neurodevelopment (155). ELS paradigms are essential for understanding the neurobiological consequences of stress. Many individuals with stress-related psychiatric disorders experience multiple stress exposures before symptom onset, and cumulative stress across the lifespan markedly increases the risk of depression (156). This association is particularly pronounced when stressors occur during childhood or adolescence, increasing susceptibility to later stress and depression in adulthood. These patterns are addressed by double-hit or 2-hit stress models (157). **(F)** Early-life stress: This is most frequently modeled via MS or reduced bedding/nesting (158). **(G)** Two-hit stress models combine stressors at different developmental stages (e.g., MS in early life followed by adult social defeat stress) to model cumulative stress exposure across the lifespan. ELS and the 2-hit models are translationally very relevant but labor intensive, and outcomes depend heavily on stressor type, timing, and sequencing, making cross-study comparisons challenging (159). A wide range of both early-life and adult stress models is available. Although this diversity allows researchers to address a variety of experimental questions, it also introduces substantial variability and, in some cases, inconsistency in the resulting biological data. A central question in the field is the extent to which different paradigms capture distinct facets of human stress-related disorders. Interestingly, analyses of data obtained from RNA sequencing from bulk brain tissue from the prefrontal cortex and nucleus accumbens comparing different adult stress models (CSDS, SI, CVS) reveal that while some genes are similarly affected in all stress paradigms (approximately 25%), the overall transcriptomic responses differ substantially (160), indicating that every model captures unique aspects of the heterogeneous disease. However, further research is required to determine which models are best suited to specific research questions, and incorporating a combination of different paradigms may be an optimal approach. CMS, chronic mild stress; CSDS, chronic social defeat stress; CUS, chronic unpredictable stress; CVS, chronic variable stress; ELS, early-life stress; HPA, hypothalamic-pituitary-adrenal; MDD, major depressive disorder; MS, maternal separation; SI, social isolation.

messenger RNA (mRNA) (25). However, this proinflammatory shift seems to be primarily found in models of social defeat and not in nonphysical adult stress models; for example, a recent study using chronic unpredictable mild stress (CUMS) did not find upregulation of proinflammatory cytokines but rather microglia-specific transcriptional repression of genes in interferon-signaling pathway (30). More advanced techniques such as single-cell RNA-seq (scRNA-seq) could potentially provide more detailed insights (31). In contrast to neurodegenerative disorders such as Alzheimer's disease, where disease-associated microglia (DAM) subtypes have been identified (32), findings from rodent stress models have been less consistent. Few studies have applied scRNA-seq to examine microglia in adult stress models. In the hippocampus, scRNA-seq following social defeat stress in mice revealed stress-enriched microglial clusters characterized by transcriptional signatures associated with inflammatory processes, including cytokine and chemokine signaling, endoplasmic reticulum stress, phagocytosis, and antigen presentation (33). In the striatum, single-nucleus RNA-seq in rats exposed to an acute

inescapable footshock stressor demonstrated persistent transcriptional alterations in microglia 6 weeks after exposure (34). In contrast, other studies have reported no major transcriptional changes in microglia. In the NAc, CSDS did not produce significant alterations in either inflammatory or homeostatic genes (35). Similarly, acute restraint stress (RS) in mice did not induce changes in microglial gene expression within the paraventricular nucleus of the hypothalamus (36). Further research is required to determine whether stress-associated microglia subtypes analogous to DAMs exist.

Similarly, human transcriptomic studies have yielded mixed findings: While some have indicated microglial activation and elevated cytokine production in depression (37,38), more recent postmortem data focusing on microglia specifically have not consistently found immune marker upregulation (39,40). It remains unclear whether these microglial changes in humans are confined to particular depressive subtypes (e.g., patients who died by suicide or patients who showed increased circulating immune markers) (38) or whether they reflect methodological differences among studies.

Mechanistic studies that probe microglia function in stress responses are still sparse. In a recent study, Nie *et al.* (41) showed that combined microglial knockdown of TLR2 and TLR4 in the PFC attenuated repeated social defeat stress (RSDS)–induced social avoidance. This shows that concurrent disruption of TLR2 and TLR4, but not global deletion of either receptor alone, attenuates RSDS-induced social avoidance, suggesting that both receptors contribute in a partially redundant or convergent manner to stress-induced behavioral changes, most likely through shared downstream MyD88-dependent signaling. While TLR2 and TLR4 recognize distinct canonical ligands, both can be engaged by certain DAMPs such as S100A8/A9 (42,43), which are upregulated following defeat stress (41). The necessity of knocking down both receptors to alter behavior implies that stress may trigger multiple, possibly overlapping, innate immune-sensing pathways in microglia that converge on similar molecular outputs. These mechanisms seem to be different in different compartments; for example, depleting TLR4 specifically in circulating leukocytes was sufficient to at least partially protect against CSDS-induced social avoidance (44).

Another important receptor on microglia is the CSF1R (colony stimulating factor 1 receptor), which regulates microglial survival and proliferation, synaptic remodeling, and phagocytosis of neuronal elements (45). Anxiety- and depression-like behaviors of stressed animals have been linked to increased expression of *Csf1r* in the mPFC, mirroring postmortem findings in individuals with depression (46). Pharmacological inhibition of CSF1R by PLX5622 has been shown to diminish social stress–induced behavioral deficits (47,48). However, these outcomes are limited by PLX5622's off-target effects on peripheral immune cells and its broad depletion of microglia (49).

Acute and chronic stressors increase the number of cells immunopositive for microglial/macrophage-associated proteins such as Iba-1 (25). Some researchers interpret this as an increase in microglial cell numbers, but it may indicate higher protein expression rather than true proliferation. Other microglia-enriched proteins that have been found to be increased in different brain regions include CD11b (50), CD86 (25), and CD68 (51). CD68 is a phagocytosis-associated protein; microglial phagocytic function is upregulated across various models of chronic stress, implying potential neuronal remodeling via elevated microglial phagocytosis (46,52). Alternatively, chronic stress could cause neuronal death or apoptosis, resulting in a heightened phagocytic response to clear dying cells and limit the release of proinflammatory signals, such as DAMPs.

Furthermore, the CX3CL1/CX3CR1 signaling pathway is integral to neuron–glia communication. CX3CL1, a chemokine primarily produced by neurons, binds to the CX3CR1 receptor predominantly expressed on microglia (53). This interaction is essential for microglial hyperramification (54). CX3CR1-deficient mice show resilience to stress-induced behavioral alterations and do not develop anhedonia after stress exposure (54). These mice exhibit increased basal phagocytosis alongside enlarged somas and expanded branching but lack the typical stress-related morphological and plasticity changes observed in stressed wild-type mice (55). However, these results are complicated by the constitutive nature of the knockout, which may also affect other immune cells expressing CX3CR1, e.g., circulating monocytes (56). The extent to which microglia communicate with other glial cells in the context of stress remains to be elucidated. Microglia shape oligodendroglial dynamics by phagocytosing viable oligodendrocyte precursor cells in a CX3CR1-dependent manner and supporting adult myelin integrity (57), but whether the reduced oligodendrocytic gene expression and impaired myelination seen after chronic social stress and social isolation reflect microglial pruning or intrinsic oligodendrocyte maturation defects remains unresolved (58).

There is growing interest in how early-life stress (ELS) alters microglia, although findings vary by stressor. With limited bedding, microglia show reduced ramification and impaired synaptic engulfment in the developing hippocampus (≈ postnatal day 17 [P17]; some effects persist to P29), as well as reductions in microglial cell volume (59,60). Maternal separation (MS) results in an immature microglial transcriptional signature in the juvenile hippocampus, with altered immune- and synapse-related gene expression and increased phagocytic activity (61). In contrast, MS increases ramification/activation shortly after stress and alters pruning extending into adolescence/early adulthood (62). Most of these assessments were directly after ELS. Complementing these acute findings, Reemst *et al.* (63) observed no immediate microglial transcriptomic change at P9 after limited bedding but robust alterations at P200, including reduced synaptosome phagocytosis and upregulation of inflammatory-response programs. Epigenetic mechanisms (e.g., region- and cell type–specific DNA methylation) likely contribute to these durable shifts (64). Interestingly, ELS impairs microglial pruning of excitatory inputs onto CRH^{+} hypothalamic neurons, yielding excessive excitatory synapses within stress-responsive circuits and aberrant adult stress responses (65). The only scRNA-seq study related to ELS models did not report microglial changes (66), and no

study is available that used scRNA-seq in the double-hit paradigm.

THE NEUROVASCULAR UNIT

The BBB is a protective structure formed by brain microvascular endothelial cells (BECs), which are sealed by junction proteins maintaining selective permeability to circulating factors (67). The BBB is supported by the basement membrane, pericytes, astrocytes, neurons, microglia, and oligodendrocytes, collectively forming the neurovascular unit (NVU) (68).

A growing body of evidence indicates that stress profoundly affects both the BBB and the NVU. CLDN5, an endothelial cell-specific tight-junction protein (69), is consistently downregulated in various stress paradigms, contributing to increased BBB permeability. In CSDS, stress-susceptible but not resilient male mice exhibited decreased *Cldn5*/CLDN5 expression in the NAc (70). This downregulation compromised the BBB, allowing peripheral IL-6 to enter the brain. Notably, stress, such as CSDS, appears to exert sex-specific effects on the BBB; female mice demonstrate increased permeability in the PFC and NAc, whereas male mice primarily show such damage in the NAc (70,71). Although CLDN5 has been the focus of most research, additional tight-junction proteins (e.g., occludins and ZO-1) have also been reported to decrease in response to stress, particularly in the hippocampus and amygdala (72–74).

Stress-induced BBB breakdown has been linked to inflammatory signaling and epigenetic repression; for example, CSDS triggers inflammation in endothelial cells and activates HDAC1 (histone deacetylase 1), an epigenetic repressor that suppresses *Cldn5* expression, thereby weakening tight junctions (75). Similarly, chronic stress reduces *Cldn5* expression in the hippocampus via increased H3K27me3 at the Cldn5 promoter, facilitating TNF-α (tumor necrosis factor α) infiltration into the brain (76). Another potential contributor is VEGF (vascular endothelial growth factor). Elevated *Vegfa* expression, coupled with enhanced BBB permeability and reduced *Cldn5*, suggests that stress may induce cerebrovascular constriction, leading to hypoxia and subsequent BBB disruption (77). In turn, hypoxia stimulates VEGF production, promoting angiogenesis but also weakening endothelial tight junctions, which can create a self-perpetuating cycle of BBB leakage. RS and CSDS upregulate VEGFA in several limbic regions (78,79), and pharmacologically blocking VEGFR2 prevented BBB permeability and anhedonic behavior induced by chronic RS (78).

ELS can also alter BBB function. In rats, MS increased BBB permeability during development, with heightened Evans blue entry across multiple regions at P10 and increased caveolae-mediated transcytosis in hippocampal capillaries between P10 and P20; permeability normalized by P30 (80,81). Findings have not been fully consistent, however. Solarz *et al.* (82) reported a transient MS-induced increase in BBB permeability in the dorsal striatum of juvenile males that did not persist into adulthood; adult females in the same study exhibited lower permeability than males. This work also found sex- and region-specific changes in tight-junction and transporter gene expression (e.g., *Cldn3*, *Cldn5*, *Ocln*, *Slc2a1*) and altered astrocyte endfoot marker profiles (e.g., *Aqp4*), indicating that ELS can influence multiple components of the NVU. No studies reported to date have investigated BBB function in a double-hit paradigm.

BECs also mediate adhesion and transmigration of circulating immune cells (83). Elevated expression of adhesion molecules such as ICAM-1, VCAM-1, and E-selectin, associated with endothelial dysfunction, has been implicated in depression (84). ICAM-1 facilitates the initial adhesion of leukocytes to the endothelium, enabling their subsequent migration across the BBB (85). VCAM-1 similarly supports leukocyte-endothelial interactions and triggers signaling pathways that temporarily open junctions, allowing leukocyte passage (86). VCAM-1 engagement also promotes NADPH oxidase–dependent reactive oxygen species (ROS) production in BECs, driving actin reorganization around migrating lymphocytes (87). These adhesion molecules are upregulated at both the mRNA and protein levels following social defeat in regions such as the amygdala and hippocampus (88,89).

Astrocytes and oligodendroglial cells contribute directly to NVU function and BBB integrity, and stress can recruit these pathways. Astrocytic endfeet are central to BBB maintenance and neuron-endothelium signaling, and astrocytic CB_1 signaling limits stress-induced BBB alterations while promoting behavioral resilience (90). An open question involves the mechanisms that drive region-specific BBB alterations following chronic stress. Some indirect evidence has been presented in humans (e.g., increased vascular markers in circulation or cerebrospinal fluid) (91,92) and decreased levels of Claudin-5 in postmortem brain tissue (75). Additionally, a recent dynamic contrast–enhanced MRI study of patients with MDD showed increased BBB permeability in certain brain areas (compared with healthy control participants) (93). However, further human studies are needed.

CIRCULATING IMMUNE CELLS AND PROTEINS

The immune system comprises innate and adaptive arms that are functionally specialized yet interdependent. The innate arm includes barrier tissues (skin, gastrointestinal tract), myeloid and innate lymphoid cells, and soluble mediators (cytokines, chemokines, complement system) that recognize pathogens via germline-encoded receptors and initiate inflammation that primes the adaptive system, while the adaptive arm (T and B cells) uses antigen-specific receptors generated by clonal gene rearrangements to mount targeted responses, including antibody production (94).

Most studies linking stress to peripheral immune alterations have focused on innate immunity (Table 1). Numerous stress paradigms induce the mobilization of myeloid cells from the bone marrow into circulation (95–97). Monocytes arise from hematopoietic precursors in the bone marrow and can be classified into homeostatic or inflammatory subsets. The inflammatory subset ($Ly6C^{high}$) is characterized by high expression of certain markers such as CCR2 (98). CSDS increases monocytes in both stress-resilient and susceptible mice (35,99,100). However, only monocytes in susceptible mice exhibit distinct proinflammatory gene expression profiles (35), resembling patterns observed in other paradigms (e.g., chronic variable stress [CVS]) (97). Stress also alters innate immune cell reactivity; for example, stressed mice release more proinflammatory cytokines following in vitro exposure to

Table 1. Summary of the Most Important Alterations in Circulating Leukocyte Subpopulations and Proteins in the Different Stress Models Discussed and Examples of Potential Drug Repurposing Options in Humans

Circulating Immune Factors	Findings in Rodent Models	Examples of Potential Drug Repurposing Opportunities in Humans
Monocytes	CSDS ↑ (35,99,100), SI (NA), CVS ↑ (35), LH (NA), RS ↑ (121), ELS (NA), THS (NA)	Cenicriviroc (dual CCR2/CCR5 antagonist) (163), rosuvastatin (statin) (164)
Neutrophils	CSDS ↑ (35,100), SI (NA), CVS ↑ (95), LH (NA), RS (NA), ELS (NA), THS (NA)	Brensocatib (oral dipeptidyl peptidase 1 inhibitor) (165)
B Cells	CSDS ↓ (35,100), SI (NA), CVS (NA), LH (NA), RS ↓ (107), ELS (NA), THS (NA)	Rituximab (anti-CD20) (166)
T Cells	CSDS ↓ (99,100), SI (NA), CVS (NA), LH (NA), RS → (121), ELS (NA), THS (NA)	Alemtuzumab (anti-CD52) (167)
IL-6/IL-6R	CSDS ↑ (25,129), SI (NA), CVS ↑ (109), LH (NA), RS ↑ (112), ELS → (132), THS → (132)	Siltuximab (anti-IL-6) (168), tocilizumab (anti-IL-6R) (168)
IL-17	CSDS (NA), SI (NA), CVS ↓ (109), LH (NA), RS ↑ (112), ELS (NA), THS (NA)	Secukinumab (anti-IL17A) (168)
IL-23	CSDS (NA), SI (NA), CVS ↓ (110), LH (NA), RS (NA), ELS (NA), THS (NA)	Guselkumab (anti-IL-23 p19) (168)
TNF-α	CSDS ↑ (119), SI (NA), CVS ↑ (76), LH (NA), RS → (112,169), ELS → (132), THS → (132)	Infliximab (anti-TNF) (168)
MMP8	CSDS ↑ (35), SI (NA), CVS ↑ (35), LH (NA), RS (NA), ELS (NA), THS (NA)	Doxycycline (antibiotic) (170)

↑ Indicates increase; ↓ indicates decrease; → indicates no change.

CSDS, chronic social defeat stress; CVS, chronic variable stress; ELS, early-life stress; IL, interleukin; LH, learned helplessness; NA, not available; RS, restraint stress; SI, social isolation; THS, two-hit stress; TNF, tumor necrosis factor.

lipopolysaccharide (LPS) (101). In addition, epigenetic regulation of monocytes may change under stress: Mice exposed to CSDS showed modulation of several microRNAs in Ly6C^{high} monocytes, including miR-25-3p from the miR-106b-25 cluster, the selective knockout of which in peripheral leukocytes promoted resilience (99). Another mechanism by which innate immunity may affect behavior is the migration of monocytes to brain regions of the limbic system. In animal models, proinflammatory monocytes migrate to the brain in a CCL2/CCR2-dependent manner; genetic deletion of *Ccr2* prevented their recruitment and the associated stress-induced behavioral phenotypes (102). Additionally, there is close interaction among microglia, BECs, and peripheral monocytes. Microglia can actively recruit peripheral monocytes via an IL-1β–dependent mechanism, guiding them to stress-sensing brain regions where they regulate anxiety-like behaviors. Depletion of microglia with a CSF1R inhibitor disrupts this monocyte trafficking and prevents anxiety-like behavior (103). Notably, it is well established that in most stress paradigms, monocytes do not penetrate into the brain parenchyma but accumulate at the level of the vasculature (35,70). Future work must clarify the extent to which monocyte accumulation at border regions (e.g., meninges) or within circumventricular organs contributes to stress-induced behavioral changes (35).

CSDS also increases circulating neutrophils (35,100), as do other paradigms such as chronic unpredictable stress (CUS) (95). This mobilization appears largely mediated by the sympathetic nervous system: Noradrenaline released in the bone marrow under stress reduces local CXCL12 levels, prompting neutrophils to enter circulation (104). Blocking β_3-adrenergic receptors can prevent stress-induced reductions in hematopoietic stem cell growth and circulating neutrophil mobilization (95). Neutrophils produce proinflammatory mediators such as IL-1 and ROS that increase following RS (105) and can potentially affect neuronal functions. CUMS leads to higher neutrophil numbers in whole-brain homogenates and the neutrophil adhesion molecule CD177 (106). Adoptive transfer of CD177$^+$ neutrophils from stressed mice boosted brain neutrophilia, increased microglial activation, and elevated proinflammatory signaling in the NAc, providing evidence of a potential role of neutrophils in stress behaviors (106).

Like RS, CSDS reduces circulating B cells (35,100,107), with fewer transcriptional changes observed relative to inflammatory monocytes (35). However, because B cell–mediated antibody responses primarily occur in secondary lymphoid organs, blood measurements may underestimate the full impact of stress on these cells. CSDS has been shown to expand germinal center B cells and plasma cells in brain-draining lymph nodes, which receive antigens via meningeal lymphatic vessels (108), and these expansions correlate with stress-induced social avoidance and anhedonia. Susceptible mice exhibit elevated brain-reactive IgG antibodies accumulating around cerebral blood vessels in limbic regions, and depleting B cells confers stress resilience and brain-reactive antibodies correlated with anhedonia in individuals with MDD (108). While the notion that stress can induce autoimmune responses against the brain is compelling, more research is needed to determine the origin of these antigens and the underlying mechanisms.

Several studies highlight a critical role for Th17 cells in stress-related pathology: CUS is associated with reduced splenic CD4$^+$/Th17 numbers and lower IL-17/IL-23 (109,110), whereas RS or learned helplessness is associated with Th17 infiltration into the dorsal striatum and hippocampus (111,112). These findings suggest that Th17 cells may influence the CNS either via cytokine signaling across an intact BBB or via IL-17A–mediated BBB disruption (113,114), and within the brain, IL-17A activates astrocytes and microglia to

drive inflammatory cascades (115). Consistently, adoptive Th17 transfer induces depression-like behavior, and RORγt inhibition or IL-17A neutralization is protective (111,113), yet $CD4^+$ T cell–specific RORγt knockout mice in CUMS show no behavioral protection (116), implying additional IL-17 sources or compensatory mechanisms. Early rodent studies suggest a neuroprotective or resilience-promoting role for T cells. In one experiment, immunizing rats with modified myelin basic protein prior to chronic mild stress improved immobility and restored hippocampal BDNF (brain-derived neurotrophic factor) levels (117,118). T-cell infiltration of the choroid plexus, where ICAM-1 levels were elevated, also correlated with stress resilience (118). Furthermore, lymphocyte-depleted (*Rag2*$^{-/-}$) mice that received adoptively transferred lymphocytes from defeated donors displayed lower anxiety-like behavior, reduced proinflammatory cytokine levels, and a shift in microglia toward an anti-inflammatory phenotype compared with mice that received no cells or cells from nonstressed donors (119). These findings imply that psychosocial stress imprints on the adaptive immune system and influences future stress responses. Thus, it has been proposed that behavioral immunization, akin to vaccination, could potentially protect against subsequent stressors (120). How these findings align with the multiple lines of evidence from various stress models indicating that stress decreases T-cell frequencies in circulation (99,100,121) and only leads to relatively limited transcriptional alterations (35) requires further study. Notably, RAG2-deficient mice present several limitations. In addition to their lack of mature T and B lymphocytes, they display physiological and behavioral alterations, including increased fatigue (122), reduced anxiety- and depression-like behaviors, and impaired fear memory (123). They also exhibit neurodegeneration-like changes in the cortex and hippocampus (124) and elevated numbers of natural killer cells and megakaryocytes (125). Moreover, Rag2$^{-/-}$ mice often show a diminished susceptibility to stress-induced behavioral changes.

Numerous studies have reported elevated circulating cytokines in stressed animals (Table 1). Most consistent is the upregulation of IL-6, a pleiotropic molecule involved in immune defense, inflammation, and tissue regeneration (126). IL-6 is predominantly produced by immune cells in response to TLR activation and proinflammatory signals (e.g., IL-1), generating a feedforward loop that amplifies inflammation (127,128). Various stress paradigms, including CSDS, CVS, and witness defeat, elevate IL-6 levels (25,129). In one of the first studies causally linking increased circulating cytokines and stress-induced behavioral changes, the systemic neutralization of IL-6 with an antibody or the depletion of IL-6 from bone-derived leukocytes in chimeric mice both promoted resilience (129). These findings are consistent with studies of patients with comorbid depression and rheumatoid arthritis where IL-6 monoclonal antibodies improved depression (130). Additionally, predefeat inflammatory markers predicted how mice would respond to RSDS: Mice susceptible after defeat displayed higher baseline circulating leukocyte levels than resilient mice, and IL-6 release upon stimulation with the bacterial endotoxin LPS negatively correlated with social interaction scores (129). Although elevated IL-6 levels are a consistent finding in stress-related conditions and have been implicated in depression-like behaviors, direct causal evidence of its function, e.g., linking IL-6 to BBB disruption or neuronal dysfunction is limited. IL-6 can enter the brain when the BBB is already compromised by stress, and direct infusion of IL-6 into the NAc increases vulnerability to subthreshold social defeat stress (70). However, whether IL-6 actively drives BBB breakdown in stress or simply crosses when the BBB is already impaired remains unclear. Similarly, the role of circulating IL-6 in stress-related neuronal dysfunction is still unclear, although there is recent evidence for a direct link: CSDS increased PSD-95 puncta (as a marker of synaptic structural changes) in NAc in wild-type bone marrow chimeras compared with unstressed wild-type or IL-6$^{-/-}$ bone marrow chimeras, supporting a potential direct link between circulating IL-6 and neuronal dysfunction (131). Future studies, such as genetic deletion or pharmacological blockade of IL-6 in relevant stress models with simultaneous assessment of BBB permeability and neuronal function, will be essential to confirm the precise role of IL-6 in these processes. Recent advances in omics approaches allow for more precise characterization of stress-induced immune changes in the periphery. One example is a study that identified MMP8 produced by circulating myeloid cells, which was found at elevated levels in both circulation and the NAc of stress-susceptible mice, as well as in serum of individuals with MDD. Depleting MMP8 in peripheral leukocytes promoted resilience, possibly by preventing MMP8-driven extracellular matrix remodeling and associated neurophysiological changes (35).

MS generally produces transient peripheral cytokine effects, however, without lasting changes (132,133). Beyond cytokines, MS can alter peripheral immune cells: Early work showed reduced lymphocyte mitogenic responses and lymphopenia in adolescence after premature separation (134), and more recent data show peripheral blood mononuclear cell alterations across the lifespan in MS-exposed female rats (135). Very few models combine MS or limited nesting with subsequent stressors, and one study that combined MS and RS did not observe changes in circulating cytokine levels (132). For limited bedding/nesting, most published work has emphasized region-specific brain cytokine changes, with few studies directly measuring circulating factors (136,137). This represents a gap for blood-based immune phenotyping in ELS and double-hit models. In humans, ELS is associated with elevated circulating inflammatory markers such as IL-6, TNF-α, and CRP (138) as well as altered immune cell transcriptional profiles (139).

One important open point is that in psychoneuroimmunology, cytokine changes during and after stress are typically within physiological ranges and far lower than those seen in infection or systemic disease. Such low-grade, sustained inflammation is mechanistically distinct from acute inflammatory responses, and its long-term impact on brain and behavior likely depends on the magnitude and duration of exposure.

CONCLUSIONS

Stress disrupts immune function at multiple levels within the CNS, in circulating immune cells and proteins, and at the NVU.

Table 2. Examples of Future Directions and Experiments in the Field of Psychoneuroimmunology

Area	Key Gaps	Future Directions
Stress Models	Protocol heterogeneity; limited data on sex differences; poor cross-species validity	Standardize protocols for different stress models; detailed reporting of housing conditions, etc.; consistent inclusion of both sexes; improve stress models regarding etiologic validity
Behavioral Readouts	Emphasis on simple assays with limited face validity	Include readouts of complex behaviors (e.g., decision making, cognitive tasks)
Longitudinal Designs	Lack of time-course of stress-induced neuroimmune changes; sparse early-life to adult interaction data	Use serial behavioral, immune, and brain function measurements across acute, subacute, and chronic stress paradigms; combination of early-life and adult stressors
Resident Myeloid Cells	Inconsistent molecular and functional characterization of microglia and border-associated macrophages	Use single-cell and spatial omics approaches; apply region- and cell type–specific manipulations
Circulating Immune Factors	Single-analyte focus; sparse mechanistic links to brain function; low-grade vs. acute effects unresolved	Apply large-scale proteomics; manipulate cytokines with cell type–specific knockouts or blockade and combine with readouts of brain function and behavior; quantify dose-duration kinetics
Meningeal Immunity, Skull Hematopoiesis, and Lymphatic/Glymphatic Drainage	Incomplete understanding of skull-derived immune cells; roles of meningeal lymphatics and glymphatic flow in stress poorly defined	Fate map from skull and vertebral marrow to meninges and choroid plexus; single-cell and spatial profiling; perturb meningeal lymphatics and glymphatic flow
Blood-Brain Barrier	Causes of increased permeability unclear (peripheral vs. central); unknown mechanisms of differences between brain regions	Include blood-brain barrier readouts after cell type–specific manipulations of immune and nonimmune cells; perform endothelial cell–specific omics in different brain regions

Advancing our understanding of the underlying neuroimmune mechanisms of stress and depression requires studies with humans as well as animal models with high translational validity that are applicable in both sexes (Table 2). While this review focuses on various established stress paradigms, it will also be essential in the future to develop more robust cross-species behavioral readouts for complex behaviors (140). Furthermore, a major priority is determining how sex differences in immune and NVU biology contribute to the approximately twofold higher incidence of stress disorders in females. Although early transcriptomic data suggest notable sex-specific immune and endothelial responses, their functional significance, such as whether PFC damage induces more severe cognitive and emotional disturbances in females,

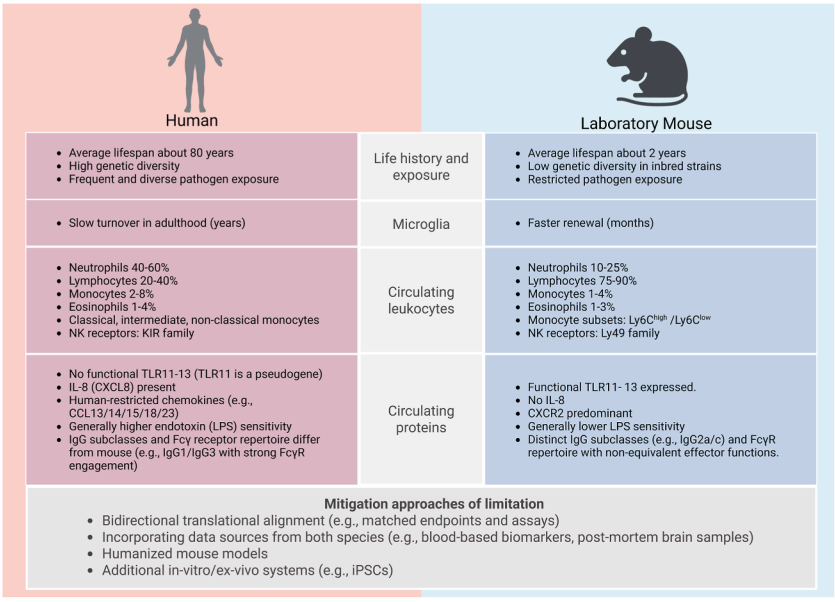

Figure 3. Major differences in the immune system between humans and mice and potential mitigation strategies (161,162). IL, interleukin; iPSC, induced pluripotent stem cell; LPS, lipopolysaccharide; NK, natural killer cell; TLR, toll-like receptor.

remains unclear. Tools such as scRNA-seq of immune cells in the brain and circulation and advanced omics integration in combination with novel tools to precisely perturb the identified molecular mechanisms will be essential for identifying these pathophysiological signatures. However, species differences in immune cell composition warrant consideration (Figure 3). While the functional consequences of this divergence are not yet fully understood, such differences influence the translational relevance of rodent models for studying immune-brain interactions. Finally, the brain exerts top-down control over immune processes, underscoring a bidirectional relationship that remains only partially understood.

Circulating immune factors offer especially promising therapeutic targets, given their greater accessibility to medications compared with structures in the brain parenchyma. Combining next-generation molecular insights with refined behavioral models that replicate stress-induced alterations in both sexes can lay the groundwork for innovative, personalized approaches to preventing and treating stress-related disorders.

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ARTICLE INFORMATION

From the Department of Adult Psychiatry and Psychotherapy, University Hospital of Psychiatry Zurich, University of Zurich, Zurich, Switzerland (SH, FC); Nash Family Department of Neuroscience, Brain and Body Research Center, Icahn School of Medicine at Mount Sinai, New York, New York (SJR); and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York (SJR).

Address correspondence to Flurin Cathomas, M.D., at flurin.cathomas@pukzh.ch.

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