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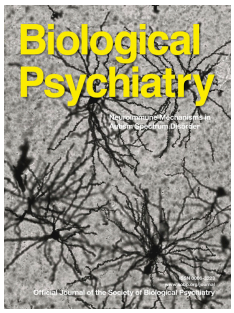

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Immunity in rodent models of stress

Short Title: Immunity and stress

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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 pro-inflammatory 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.

Key Words: Stress; Animal Models; Major Depressive Disorder; Microglia; Blood-Brain Barrier, Peripheral Immune System

Introduction

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 (HPA) 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). Elucidating the mechanisms underlying stress responses is therefore 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 the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (4) or the Research Domain Criteria (RDoC) (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 pro-inflammatory cytokines, chemokines, and the acute phase protein C-reactive protein (CRP) (9–12). This pro-inflammatory 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 in 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) lie 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** discusses the most widely used stress models, which serve as the foundation for the subsequent discussion of key psychoneuroimmunology findings.

Microglia

Microglia are the resident immune cells of the central nervous system (CNS), comprising approximately 5-12% in the adult mouse brain (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 vs. active” and “M1 vs. M2” dichotomies are now considered obsolete (24), although they remain common in psychoneuroimmunology.

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. have implicated catecholamines, and specifically β-adrenergic receptor activation, in the effects of adult stress on morphological and transcriptional changes in microglia (25). However, these findings rely largely on nonspecific pharmacological interventions. Microglia also express Toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (27). DAMPs, also known as alarmins, such as high-mobility group box-1 (HMGB1) or S100 proteins, are interesting candidate proteins potentially contributing to microglia activation, as they increase in the brain upon 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-1 β (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 mRNA (25). This proinflammatory shift seems, however, to be primarily found in models of social defeat and not in non-physical adult stress models, as for example a recent study using CUMS did not find upregulation of pro-inflammatory cytokines but microglia-specific transcriptional repression of genes in IFN-signaling pathway (30). More advanced techniques such as single-cell (sc)RNA-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 are less consistent. Only 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 six weeks after exposure (34). By 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 yield mixed findings: while some indicated microglial activation and elevated cytokine production in depression (37,38), while 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 that show 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. showed that combined microglial knockdown of TLR2 and TLR4 in the PFC attenuated RSDS-induced social avoidance (41). 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, as 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 colony-stimulating factor 1 receptor (CSF1R), 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 like ionized calcium-binding adapter molecule (Iba-1) (25). Some researchers interpret this as an increase in microglial cell numbers, but it may instead indicate higher protein expression rather than true proliferation. Other microglia-enriched proteins 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 hyper-ramification (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 might also affect other immune cells expressing CX3CR1, e.g., circulating monocytes (56). To what extent 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), yet 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 ELS alters microglia, though findings vary by stressor. With limited bedding, microglia show reduced ramification and impaired synaptic engulfment in the developing hippocampus (≈P17; some effects persist to P29), and 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. 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 (63). 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. Claudin-5 (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 instance, CSDS triggers inflammation in endothelial cells and activates HDAC1, 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 infiltration into the brain (76). Another potential contributor is vascular endothelial growth factor (VEGF). 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. Indeed, RS and CSDS upregulate VEGFA in several limbic regions (78,79) and pharmacologically blocking VEGF receptor 2 (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 are not fully consistent, however. Solarz et al. report a transient MS-induced increase in BBB permeability in the dorsal striatum of juvenile males that does not persist into adulthood; adult females in the same study exhibit lower permeability than males (82). 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 neurovascular unit. No studies have so far 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 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 neurovascular unit function and BBB integrity, and stress can recruit these pathways. Astrocytic endfeet are central to BBB maintenance and neuron-endothelium signaling, and astrocytic CB1 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 CSF) (91,92) and decreased levels of Claudin-5 in postmortem brain tissue (75). Additionally, a recent DCE-MRI study in patients with MDD showed increased BBB permeability in certain brain areas (compared to healthy controls) (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) 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 focus 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 markers such as CCR2, CD62L, and CX3CR1 (98). CSDS increases monocytes in both stress resilient

and susceptible mice (35,99,100). However, only monocytes in susceptible mice exhibit distinct pro-inflammatory gene expression profiles (35), resembling patterns observed in other paradigms (e.g., chronic variable stress) (97). Stress also alters innate immune cell reactivity; for example, stressed mice release more pro-inflammatory cytokines following in vitro exposure to lipopolysaccharide (LPS) (101). In addition, epigenetic regulation of monocytes may change under stress: mice exposed to CSDS showed modulation of several miRNAs in Ly6C^{high} monocytes, including miR-25-3p from the miR-106b-25 cluster, whose selective knockout in peripheral leukocytes promoted resilience (99). A further mechanism by which innate immunity may affect behavior is the migration of monocytes to brain regions of the limbic system. In animal models, pro-inflammatory 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). Of note, 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 well as in other paradigms like chronic unpredictable stress (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 β3-adrenergic receptors can prevent stress-induced reductions in hematopoietic stem cell growth and circulating neutrophil mobilization (95). Neutrophils produce pro-inflammatory mediators such as IL-1 and ROS which 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 pro-inflammatory signaling in the NAc, providing evidence of a potential role of neutrophils in stress behaviors (106).

CSDS, as well as chronic RS 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. Indeed, 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: chronic unpredictable stress is associated with reduced splenic $CD4^+$/Th17 numbers and lower IL-17/IL-23 (109,110) whereas RS or LH report 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 (MBP) prior to chronic mild stress improved immobility and restored hippocampal BDNF 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 pro-inflammatory cytokine levels, and a shift in microglia toward an anti-inflammatory phenotype compared to mice receiving no cells or cells from non-stressed donors (119). These findings imply that psychosocial stress imprints on the adaptive immune system and influences future stress responses. It has thus 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 (NK) cells and megakaryocytes (125). Moreover, $Rag2^{-/-}$ mice often show a diminished susceptibility to stress-induced behavioral changes.

Numerous studies report 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 pro-inflammatory signals (e.g., IL-1), generating a feedforward loop that amplifies inflammation (127,128). Various stress paradigms, including CSDS, chronic variable stress, 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 in line with studies in patients with comorbid depression and rheumatoid arthritis where IL-6 monoclonal antibodies improved depression (130). Additionally, pre-defeat 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 correlated negatively 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, however, with recent evidence for a direct link: CSDS increased PSD-95 puncta (as a marker of synaptic structural changes) in NAc in wildtype bone marrow chimeras compared to unstressed wildtype 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 for 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 identifying metalloproteinase 8 (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 report 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, one study combining MS and RS did not observe changes in circulating cytokine levels (132). For limited bedding/nesting, most published work emphasizes region-specific brain cytokine changes, with few studies directly measuring circulating factors (136,137). This represents an open gap for blood-based immune phenotyping in early life stress 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.

Conclusion

Stress disrupts immune function at multiple levels within the CNS, in circulating immune cells and proteins, and at the NVU. Advancing our understanding of the underlying neuroimmune mechanisms of stress and depression requires studies in 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 moving forward 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 roughly 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, remains unclear. Tools like scRNA-seq of immune cells in the brain and circulation, 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 to 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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Figure Legends

Figure 1. Key findings on stress-induced alterations in microglia, the blood–brain barrier (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 interleukin-6 (IL-6) and tumor necrosis factor-α (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, matrix metalloproteinase-8 (MMP-8) 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.

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). Adult rodent models based on social stressors are therefore highly relevant. **A) Chronic Social Defeat Stress (CSDS):** 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: i. 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; ii. 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 like chemogenetic induction of male aggression (143), male odorant exposure (144), and co-housing with male aggressors (145), enabling investigation of sex difference studies. Physical injury is a potential confounding factor and must be controlled. Non-physical stress models like vicarious defeat, based on observation rather than direct confrontation, yield similar outcomes

(129). **B) Social Isolation (SI):** 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 non-social stressors: **C) Chronic Variable/ Chronic Mild/ Unpredictable Stress (CVS/CMS/CUS):** 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, though females often develop behavioral changes more quickly (around six days) compared to 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 (LH):** 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 short duration of behavioral effects in many strains and their reversibility by acute antidepressant treatment. **E) Restraint Stress (RS):** 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 two-hit stress models (157). **F) Early-Life Stress (ELS):** Most frequently modeled via maternal separation or reduced bedding/nesting (158). **G) Two-hit stress models:** Combine stressors at different developmental stages (e.g., maternal separation in early life followed by adult social defeat stress) to model cumulative stress exposure across the lifespan. ELS and the two-hit models are translationally very relevant but laboursome 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 prefrontal cortex (PFC) and NAc comparing different adult stress models (CSDS, social isolation, CVS) reveal that while some genes are similarly affected in all stress paradigms (approximately 25%) the overall transcriptomic responses differ substantially (160), indicating that indeed 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.

Figure 3: **Major differences in the immune system between humans and mice, and potential mitigation strategies** (161,162). Abbreviations: CL: CC chemokine ligand; CXCL: Chemokine (C-X-C motif) ligand; IgG: Immunoglobulin G; IL: Interleukin; iPSCs: induced pluripotent stem cells; LPS: Lipopolysaccharide; NK: Natural killer cells; TLR: Toll-like receptor.

Circulating immune factors	Findings in rodent models	Examples of drug repurposing opportunities in humans
Monocytes	CSDS ↑ (35,99,100), SI (N/A), CVS ↑ (35), LH (N/A), RS ↑ (121), ELS (N/A), THS (N/A)	Cenicriviroc (dual CCR2/CCR5 antagonist) (163), Rosuvastatin (Statin) (164)
Neutrophils	CSDS ↑ (35,100), SI (N/A), CVS ↑ (95), LH (N/A), RS (N/A), ELS (N/A), THS (N/A)	Brensocatib (oral dipeptidyl peptidase 1 inhibitor) (165)
B Cells	CSDS ↓ (35,100), SI (N/A), CVS (N/A), LH (N/A), RS ↓ (107), ELS (N/A), THS (N/A)	Rituximab (anti-CD20) (166)
T cells	CSDS ↓ (99,100), SI (N/A), CVS (N/A), LH (N/A), RS → (121), ELS (N/A), THS (N/A)	Alemtuzumab (anti-CD52) (167)
IL-6/IL-6R	CSDS ↑ (25,129), SI (N/A), CVS ↑ (109), LH (N/A), RS ↑ (112), ELS → (132), THS → (132)	Siltuximab (anti-IL-6) (168), Tocilizumab (anti-IL-6R) (168)
Il-17	CSDS (N/A), SI (N/A), CVS ↓ (109), LH (N/A), RS ↑ (112), ELS (N/A), THS (N/A)	Secukinumab (anti-IL17A) (168)
IL-23	CSDS (N/A), SI (N/A), CVS ↓ (110), LH (N/A), RS (N/A), ELS (N/A), THS (N/A)	Guselkumab (anti-IL-23 p19) (168)
TNF-α	CSDS ↑ (119), SI (N/A), CVS ↑ (76), LH (N/A), RS ↑ (169) → (112), ELS → (132), THS → (132)	Infliximab (anti-TNF) (168)
MMP8	CSDS ↑ (35), SI (N/A), CVS ↑ (35), LH (N/A), RS (N/A), ELS (N/A), THS (N/A)	Doxycycline (antibiotic) (170)

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.

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 etiological 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	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 non-immune cells; perform endothelial-cell specific omics in different brain regions

Table 2: Examples of future directions and experiments in the field of psychoneuroimmunology.

References

1. Ulrich-Lai YM, Herman JP (2009): Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* 10: 397–409.

2. Selye H (1956): Endocrine reactions during stress. *Curr Res Anesth Analg* 35: 182–193.

3. Hammen C (2005): Stress and depression. *Annu Rev Clin Psychol* 1: 293–319.

4. American Psychiatric Association, American Psychiatric Association (Eds.) (2013): *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*, 5th ed. Washington, D.C: American Psychiatric Association.

5. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, *et al.* (2010): Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* 167: 748–751.

6. Price JL, Drevets WC (2010): Neurocircuitry of mood disorders. *Neuropsychopharmacology* 35: 192–216.

7. Bagot RC, Cates HM, Purushothaman I, Lorsch ZS, Walker DM, Wang J, *et al.* (2016): Circuit-wide Transcriptional Profiling Reveals Brain Region-Specific Gene Networks Regulating Depression Susceptibility. *Neuron* 90: 969–983.

8. Cathomas F, Murrough JW, Nestler EJ, Han M-H, Russo SJ (2019): Neurobiology of Resilience: Interface Between Mind and Body. *Biol Psychiatry* 86: 410–420.

9. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL (2010): A Meta-Analysis of Cytokines in Major Depression. *Biological Psychiatry* 67: 446–457.

10. Leighton SP, Nerurkar L, Krishnadas R, Johnman C, Graham GJ, Cavanagh J (2018): Chemokines in depression in health and in inflammatory illness: a systematic review and meta-analysis. *Mol Psychiatry* 23: 48–58.

11. Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM (2019): Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychol Med* 49: 1958–1970.

12. Peruzzolo TL, Pinto JV, Roza TH, Shintani AO, Anzolin AP, Gnielka V, *et al.* (2022): Inflammatory and oxidative stress markers in post-traumatic stress disorder: a systematic review and meta-analysis. *Mol Psychiatry* 27: 3150–3163.

13. Foley ÉM, Parkinson JT, Mitchell RE, Turner L, Khandaker GM (2023): Peripheral blood cellular immunophenotype in depression: a systematic review and meta-analysis. *Mol Psychiatry* 28: 1004–1019.

14. Kealy J, Greene C, Campbell M (2020): Blood-brain barrier regulation in psychiatric disorders. *Neurosci Lett* 726: 133664.

15. Madison AA, Bailey MT (2024): Stressed to the Core: Inflammation and Intestinal Permeability Link Stress-Related Gut Microbiota Shifts to Mental Health Outcomes. *Biol Psychiatry* 95: 339–347.

16. Krishnan V, Nestler EJ (2011): Animal models of depression: molecular perspectives. *Curr Top Behav Neurosci* 7: 121–147.

17. Nestler EJ, Hyman SE (2010): Animal models of neuropsychiatric disorders. *Nat Neurosci* 13: 1161–1169.

18. Lawson LJ, Perry VH, Dri P, Gordon S (1990): Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. *Neuroscience* 39: 151–170.

19. Matejuk A, Ransohoff RM (2020): Crosstalk Between Astrocytes and Microglia: An Overview. *Front Immunol* 11: 1416.

20. Wu Y, Dissing-Olesen L, MacVicar BA, Stevens B (2015): Microglia: Dynamic Mediators of Synapse Development and Plasticity. *Trends Immunol* 36: 605–613.

21. Fu R, Shen Q, Xu P, Luo JJ, Tang Y (2014): Phagocytosis of Microglia in the Central Nervous System Diseases. *Mol Neurobiol* 49: 1422–1434.

22. Wolf SA, Boddeke HWGM, Kettenmann H (2017): Microglia in Physiology and Disease. *Annu Rev Physiol* 79: 619–643.

23. Soulet D, Rivest S (2008): Microglia. *Current Biology* 18: R506–R508.

24. Paolicelli RC, Sierra A, Stevens B, Tremblay M-E, Aguzzi A, Ajami B, *et al.* (2022): Microglia states and nomenclature: A field at its crossroads. *Neuron* 110: 3458–3483.

25. Wohleb ES, Hanke ML, Corona AW, Powell ND, Stiner LM, Bailey MT, *et al.* (2011): β-Adrenergic Receptor Antagonism Prevents Anxiety-Like Behavior and Microglial Reactivity Induced by Repeated Social Defeat. *J Neurosci* 31: 6277–6288.

26. Augusto-Oliveira M, Tremblay M-È, Verkhratsky A (2024): Receptors on Microglia. *Adv Neurobiol* 37: 83–121.

27. Guneykaya D, Ivanov A, Hernandez DP, Haage V, Wojtas B, Meyer N, *et al.* (2018): Transcriptional and Translational Differences of Microglia from Male and Female Brains [no. 10]. *Cell Reports* 24: 2773-2783.e6.

28. Franklin TC, Xu C, Duman RS (2018): Depression and sterile inflammation: Essential role of danger associated molecular patterns. *Brain Behav Immun* 72: 2–13.

29. Wohleb ES, Franklin T, Iwata M, Duman RS (2016): Integrating neuroimmune systems in the neurobiology of depression. *Nat Rev Neurosci* 17: 497–511.

30. Zhang Y, Dong Y, Zhu Y, Sun D, Wang S, Weng J, *et al.* (2022): Microglia-specific transcriptional repression of interferon-regulated genes after prolonged stress in mice. *Neurobiology of Stress* 21: 100495.

31. Hammond TR, Dufort C, Dissing-Olesen L, Giera S, Young A, Wysoker A, *et al.* (2019): Single-Cell RNA Sequencing of Microglia throughout the Mouse Lifespan and in the Injured Brain Reveals Complex Cell-State Changes. *Immunity* 50: 253-271.e6.

32. Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, *et al.* (2017): A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. *Cell* 169: 1276-1290.e17.

33. Goodman EJ, DiSabato DJ, Sheridan JF, Godbout JP (2024): Novel microglial transcriptional signatures promote social and cognitive deficits following repeated social defeat. *Commun Biol* 7: 1199.

34. Connolly MG, Johnson ZV, Chu L, Johnson ND, Buhr TJ, McNeill EM, *et al.* (2025): Single-Nucleus RNA Sequencing Reveals Enduring Signatures of Acute Stress and Chronic Exercise in Striatal Microglia. *Genes Brain Behav* 24: e70019.

35. Cathomas F, Lin H-Y, Chan KL, Li L, Parise LF, Alvarez J, *et al.* (2024): Circulating myeloid-derived MMP8 in stress susceptibility and depression [no. 8001]. *Nature* 626: 1108–1115.

36. Brivio E, Kos A, Ulivi AF, Karamihalev S, Ressle A, Stoffel R, *et al.* (2023): Sex shapes cell-type-specific transcriptional signatures of stress exposure in the mouse hypothalamus. *Cell Rep* 42: 112874.

37. Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, Reddy R, Aschner M, Lewis DA, Mirnics K (2011): Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. *Mol Psychiatry* 16: 751–762.

38. Torres-Platas SG, Cruceanu C, Chen GG, Turecki G, Mechawar N (2014): Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. *Brain Behav Immun* 42: 50–59.

39. Böttcher C, Fernández-Zapata C, Snijders GJL, Schlickeiser S, Sneeboer MAM, Kunkel D, *et al.* (2020): Single-cell mass cytometry of microglia in major depressive disorder reveals a non-inflammatory phenotype with increased homeostatic marker expression. *Transl Psychiatry* 10: 310.

40. Snijders GJLJ, Sneeboer MAM, Fernández-Andreu A, Udine E, Psychiatric donor program of the Netherlands Brain Bank (NBB-Psy), Boks MP, *et al.* (2021): Distinct non-inflammatory signature of microglia in post-mortem brain tissue of patients with major depressive disorder. *Mol Psychiatry* 26: 3336–3349.

41. Nie X, Kitaoka S, Tanaka K, Segi-Nishida E, Imoto Y, Ogawa A, *et al.* (2018): The Innate Immune Receptors TLR2/4 Mediate Repeated Social Defeat Stress-Induced Social Avoidance through Prefrontal Microglial Activation. *Neuron* 99: 464-479.e7.

42. Coveney AP, Wang W, Kelly J, Liu JH, Blankson S, Wu QD, *et al.* (2015): Myeloid-related protein 8 induces self-tolerance and cross-tolerance to bacterial infection via TLR4- and TLR2-mediated signal pathways. *Sci Rep* 5: 13694.

43. Vogl T, Tenbrock K, Ludwig S, Leukert N, Ehrhardt C, van Zoelen MAD, *et al.* (2007): Mrp8 and Mrp14 are endogenous activators of Toll-like receptor 4, promoting lethal, endotoxin-induced shock. *Nat Med* 13: 1042–1049.

44. Russo S, Chan K, Li L, Parise L, Cathomas F, LeClair K, *et al.* (2023): Stress-activated brain-gut circuits disrupt intestinal barrier integrity and social behaviour. *Res Sq* rs.3.rs-3459170.

45. Green KN, Crapser JD, Hohsfield LA (2020): To Kill a Microglia: A Case for CSF1R Inhibitors. *Trends in Immunology* 41: 771–784.

46. Wohleb ES, Terwilliger R, Duman CH, Duman RS (2018): Stress-Induced Neuronal Colony Stimulating Factor 1 Provokes Microglia-Mediated Neuronal Remodeling and Depressive-like Behavior. *Biological Psychiatry* 83: 38–49.

47. Weber MD, McKim DB, Niraula A, Witcher KG, Yin W, Sobol CG, *et al.* (2019): The Influence of Microglial Elimination and Repopulation on Stress Sensitization Induced by Repeated Social Defeat. *Biological Psychiatry* 85: 667–678.

48. Kokkosis AG, Madeira MM, Hage Z, Valais K, Koliatsis D, Resutov E, Tsirka SE (2024): Chronic psychosocial stress triggers microglial-/macrophage-induced inflammatory responses leading to neuronal dysfunction and depressive-related behavior. *Glia* 72: 111–132.

49. Claeys W, Verhaege D, Van Imschoot G, Van Wonterghem E, Van Acker L, Amelinck L, *et al.* (2023): Limitations of PLX3397 as a microglial investigational tool: peripheral and off-target effects dictate the response to inflammation. *Front Immunol* 14: 1283711.

50. Farooq RK, Isingrini E, Tanti A, Le Guisquet A-M, Arlicot N, Minier F, *et al.* (2012): Is unpredictable chronic mild stress (UCMS) a reliable model to study depression-induced neuroinflammation? *Behav Brain Res* 231: 130–137.

51. Picard K, Bisht K, Poggini S, Garofalo S, Golia MT, Basilico B, *et al.* (2021): Microglial-glucocorticoid receptor depletion alters the response of hippocampal microglia and neurons in a chronic unpredictable mild stress paradigm in female mice. *Brain, Behavior, and Immunity* 97: 423–439.

52. Lehmann ML, Cooper HA, Maric D, Herkenham M (2016): Social defeat induces depressive-like states and microglial activation without involvement of peripheral macrophages [no. 1]. *J Neuroinflammation* 13: 224.

53. Kettenmann H, Hanisch U-K, Noda M, Verkhratsky A (2011): Physiology of Microglia. *Physiological Reviews* 91: 461–553.

54. Hellwig S, Brioschi S, Dieni S, Frings L, Masuch A, Blank T, Biber K (2016): Altered microglia morphology and higher resilience to stress-induced depression-like behavior in CX3CR1-deficient mice. *Brain, Behavior, and Immunity* 55: 126–137.

55. Milior G, Lecours C, Samson L, Bisht K, Poggini S, Pagani F, *et al.* (2016): Fractalkine receptor deficiency impairs microglial and neuronal responsiveness to chronic stress. *Brain, Behavior, and Immunity* 55: 114–125.

56. Mrdjen D, Pavlovic A, Hartmann FJ, Schreiner B, Utz SG, Leung BP, *et al.* (2018): High-Dimensional Single-Cell Mapping of Central Nervous System Immune Cells Reveals Distinct Myeloid Subsets in Health, Aging, and Disease. *Immunity* 48: 380-395.e6.

57. McNamara NB, Munro DAD, Bestard-Cuche N, Uyeda A, Bogie JFJ, Hoffmann A, *et al.* (2023): Microglia regulate central nervous system myelin growth and integrity. *Nature* 613: 120–129.

58. Cathomas F, Azzinnari D, Bergamini G, Sigrist H, Buerge M, Hoop V, *et al.* (2019): Oligodendrocyte gene expression is reduced by and influences effects of chronic social stress in mice. *Genes Brain Behav* 18: e12475.

59. Dayananda KK, Ahmed S, Wang D, Polis B, Islam R, Kaffman A (2023): Early life stress impairs synaptic pruning in the developing hippocampus. *Brain Behav Immun* 107: 16–31.

60. Catale C, Gironda S, Lo Iacono L, Carola V (2020): Microglial Function in the Effects of Early-Life Stress on Brain and Behavioral Development. *J Clin Med* 9: 468.

61. Delpech J-C, Wei L, Hao J, Yu X, Madore C, Butovsky O, Kaffman A (2016): Early life stress perturbs the maturation of microglia in the developing hippocampus. *Brain Behav Immun* 57: 79–93.

62. Roque A, Ochoa-Zarzosa A, Torner L (2016): Maternal separation activates microglial cells and induces an inflammatory response in the hippocampus of male rat pups, independently of hypothalamic and peripheral cytokine levels. *Brain Behav Immun* 55: 39–48.

63. Reemst K, Kracht L, Kotah JM, Rahimian R, van Irsen AAS, Congrains Sotomayor G, *et al.* (2022): Early-life stress lastingly impacts microglial transcriptome and function under basal and immune-challenged conditions. *Transl Psychiatry* 12: 507.

64. Catale C, Bussone S, Lo Iacono L, Viscomi MT, Palacios D, Troisi A, Carola V (2020): Exposure to different early-life stress experiences results in differentially altered DNA methylation in the brain and immune system. *Neurobiol Stress* 13: 100249.

65. Bolton JL, Short AK, Othy S, Kooiker CL, Shao M, Gunn BG, *et al.* (2022): Early stress-induced impaired microglial pruning of excitatory synapses on immature CRH-expressing neurons provokes aberrant adult stress responses. *Cell Rep* 38: 110600.

66. Kos A, Lopez JP, Bordes J, de Donno C, Dine J, Brivio E, *et al.* (2023): Early life adversity shapes social subordination and cell type-specific transcriptomic patterning in the ventral hippocampus. *Sci Adv* 9: eadj3793.

67. Zhao Y, Gan L, Ren L, Lin Y, Ma C, Lin X (2022): Factors influencing the blood-brain barrier permeability. *Brain Research* 1788: 147937.

68. Sá-Pereira I, Brites D, Brito MA (2012): Neurovascular Unit: a Focus on Pericytes. *Mol Neurobiol* 45: 327–347.

69. Berndt P, Winkler L, Cording J, Breitkreuz-Korff O, Rex A, Dithmer S, *et al.* (2019): Tight junction proteins at the blood–brain barrier: far more than claudin-5. *Cell Mol Life Sci* 76: 1987–2002.

70. Menard C, Pfau ML, Hodes GE, Kana V, Wang VX, Bouchard S, *et al.* (2017): Social stress induces neurovascular pathology promoting depression. *Nat Neurosci* 20: 1752–1760.

71. Dion-Albert L, Cadoret A, Doney E, Kaufmann FN, Dudek KA, Daigle B, *et al.* (2022): Vascular and blood-brain barrier-related changes underlie stress responses and resilience in female mice and depression in human tissue. *Nat Commun* 13: 164.

72. Xu G, Li Y, Ma C, Wang C, Sun Z, Shen Y, *et al.* (2019): Restraint Stress Induced Hyperpermeability and Damage of the Blood-Brain Barrier in the Amygdala of Adult Rats. *Front Mol Neurosci* 12: 32.

73. Sántha P, Veszelka S, Hoyk Z, Mészáros M, Walter FR, Tóth AE, *et al.* (2016): Restraint Stress-Induced Morphological Changes at the Blood-Brain Barrier in Adult Rats. *Front Mol Neurosci* 8. https://doi.org/10.3389/fnmol.2015.00088

74. Cheng Y, Desse S, Martinez A, Worthen RJ, Jope RS, Beurel E (2018): TNFα disrupts blood brain barrier integrity to maintain prolonged depressive-like behavior in mice. *Brain, Behavior, and Immunity* 69: 556–567.

75. Dudek KA, Dion-Albert L, Lebel M, LeClair K, Labrecque S, Tuck E, *et al.* (2020): Molecular adaptations of the blood–brain barrier promote stress resilience vs. depression. *Proc Natl Acad Sci USA* 117: 3326–3336.

76. Sun Z-W, Wang X, Zhao Y, Sun Z-X, Wu Y-H, Hu H, *et al.* (2024): Blood-brain barrier dysfunction mediated by the EZH2-Claudin-5 axis drives stress-induced TNF-α infiltration and depression-like behaviors. *Brain, Behavior, and Immunity* 115: 143–156.

77. Lee S, Kang B-M, Kim JH, Min J, Kim HS, Ryu H, *et al.* (2018): Real-time in vivo two-photon imaging study reveals decreased cerebro-vascular volume and increased blood-brain barrier permeability in chronically stressed mice. *Sci Rep* 8: 13064.

78. Matsuno H, Tsuchimine S, O'Hashi K, Sakai K, Hattori K, Hidese S, *et al.* (2022): Association between vascular endothelial growth factor-mediated blood–brain barrier dysfunction and stress-induced depression. *Mol Psychiatry* 27: 3822–3832.

79. Samuels JD, Lotstein ML, Lehmann ML, Elkahloun AG, Banerjee S, Herkenham M (2023): Chronic social defeat alters brain vascular-associated cell gene expression patterns leading to vascular dysfunction and immune system activation. *J Neuroinflammation* 20: 154.

80. Gómez-González B, Escobar A (2009): Altered functional development of the blood-brain barrier after early life stress in the rat. *Brain Res Bull* 79: 376–387.

81. Gómez-González B, Larios HM, Escobar A (2011): Increased transvascular transport of WGA-peroxidase after chronic perinatal stress in the hippocampal microvasculature of the rat. *Int J Dev Neurosci* 29: 839–846.

82. Solarz A, Majcher-Maślanka I, Chocyk A (2021): Effects of early-life stress and sex on blood-brain barrier permeability and integrity in juvenile and adult rats. *Dev Neurobiol* 81: 861–876.

83. Cook-Mills JM, Deem TL (2005): Active participation of endothelial cells in inflammation. *J Leukoc Biol* 77: 487–495.

84. Van Agtmaal MJM, Houben AJHM, Pouwer F, Stehouwer CDA, Schram MT (2017): Association of Microvascular Dysfunction With Late-Life Depression: A Systematic Review and Meta-analysis. *JAMA Psychiatry* 74: 729.

85. Lawson C, Wolf S (2009): ICAM-1 signaling in endothelial cells. *Pharmacological Reports* 61: 22–32.

86. Kong D-H, Kim Y, Kim M, Jang J, Lee S (2018): Emerging Roles of Vascular Cell Adhesion Molecule-1 (VCAM-1) in Immunological Disorders and Cancer. *IJMS* 19: 1057.

87. Matheny HE, Deem TL, Cook-Mills JM (2000): Lymphocyte Migration Through Monolayers of Endothelial Cell Lines Involves VCAM-1 Signaling Via Endothelial Cell NADPH Oxidase. *The Journal of Immunology* 164: 6550–6559.

88. Sawicki CM, McKim DB, Wohleb ES, Jarrett BL, Reader BF, Norden DM, *et al.* (2015): Social defeat promotes a reactive endothelium in a brain region-dependent manner with increased expression of key adhesion molecules, selectins and chemokines associated with the recruitment of myeloid cells to the brain. *Neuroscience* 302: 151–164.

89. Zhu Y, Geng X, Stone C, Guo S, Syed S, Ding Y (2022): Forkhead Box 1(FoxO1) mediates psychological stress-induced neuroinflammation. *Neurological Research* 44: 483–495.

90. Dudek KA, Paton SEJ, Binder LB, Collignon A, Dion-Albert L, Cadoret A, *et al.* (2025): Astrocytic cannabinoid receptor 1 promotes resilience by dampening stress-induced blood-brain barrier alterations. *Nat Neurosci*. https://doi.org/10.1038/s41593-025-01891-9

91. Gudmundsson P, Skoog I, Waern M, Blennow K, Pálsson S, Rosengren L, Gustafson D (2007): The relationship between cerebrospinal fluid biomarkers and depression in elderly women. *Am J Geriatr Psychiatry* 15: 832–838.

92. Schroeter ML, Abdul-Khaliq H, Diefenbacher A, Blasig IE (2002): S100B is increased in mood disorders and may be reduced by antidepressive treatment. *Neuroreport* 13: 1675–1678.

93. Shang B, Wang T, Zhao S, Yi S, Zhang T, Yang Y, *et al.* (2024): Higher Blood-brain barrier permeability in patients with major depressive disorder identified by DCE-MRI imaging. *Psychiatry Research: Neuroimaging* 337: 111761.

94. Chaplin DD (2010): Overview of the immune response. *J Allergy Clin Immunol* 125: S3-23.

95. Heidt T, Sager HB, Courties G, Dutta P, Iwamoto Y, Zaltsman A, *et al.* (2014): Chronic variable stress activates hematopoietic stem cells. *Nat Med* 20: 754–758.

96. McKim DB, Yin W, Wang Y, Cole SW, Godbout JP, Sheridan JF (2018): Social Stress Mobilizes Hematopoietic Stem Cells to Establish Persistent Splenic Myelopoiesis. *Cell Reports* 25: 2552-2562.e3.

97. Barrett TJ, Corr EM, van Solingen C, Schlamp F, Brown EJ, Koelwyn GJ, *et al.* (2021): Chronic stress primes innate immune responses in mice and humans. *Cell Rep* 36: 109595.

98. Auffray C, Sieweke MH, Geissmann F (2009): Blood Monocytes: Development, Heterogeneity, and Relationship with Dendritic Cells. *Annu Rev Immunol* 27: 669–692.

99. Pfau ML, Menard C, Cathomas F, Desland F, Kana V, Chan KL, *et al.* (2019): Role of Monocyte-Derived MicroRNA106b~25 in Resilience to Social Stress. *Biological Psychiatry* 86: 474–482.

100. Ishikawa Y, Kitaoka S, Kawano Y, Ishii S, Suzuki T, Wakahashi K, *et al.* (2021): Repeated social defeat stress induces neutrophil mobilization in mice: maintenance after cessation of stress and strain-dependent difference in response. *British J Pharmacology* 178: 827–844.

101. Avitsur R, Kavelaars A, Heijnen C, Sheridan JF (2005): Social stress and the regulation of tumor necrosis factor-α secretion [no. 4]. *Brain, Behavior, and Immunity* 19: 311–317.

102. Wohleb ES, Powell ND, Godbout JP, Sheridan JF (2013): Stress-Induced Recruitment of Bone Marrow-Derived Monocytes to the Brain Promotes Anxiety-Like Behavior. *J Neurosci* 33: 13820–13833.

103. McKim DB, Weber MD, Niraula A, Sawicki CM, Liu X, Jarrett BL, *et al.* (2018): Microglial recruitment of IL-1β-producing monocytes to brain endothelium causes stress-induced anxiety [no. 6]. *Mol Psychiatry* 23: 1421–1431.

104. Eash KJ, Means JM, White DW, Link DC (2009): CXCR4 is a key regulator of neutrophil release from the bone marrow under basal and stress granulopoiesis conditions. *Blood* 113: 4711–4719.

105. Munalisa R, Lien T-S, Tsai P-Y, Sun D-S, Cheng C-F, Wu W-S, *et al.* (2024): Restraint Stress-Induced Neutrophil Inflammation Contributes to Concurrent Gastrointestinal Injury in Mice. *IJMS* 25: 5261.

106. Meng L, Zhou M, Wang Y, Pan Y, Chen Z, Wu B, Zhao Y (2024): CD177 on neutrophils engages stress-related behavioral changes in male mice. *Brain, Behavior, and Immunity* 120: 403–412.

107. Domínguez-Gerpe L, Rey-Méndez M (2001): Alterations induced by chronic stress in lymphocyte subsets of blood and primary and secondary immune organs of mice. *BMC Immunol* 2: 7.

108. Shimo Y, Cathomas F, Lin H, Chan KL, Parise LF, Li L, *et al.* (2023): Social stress induces autoimmune responses against the brain. *Proc Natl Acad Sci USA* 120: e2305778120.

109. Shi W, Zhang S, Lu Y, Wang Y, Zhao J, Li L (2022): T cell responses in depressed mice induced by chronic unpredictable mild stress. *J Affect Disord* 296: 150–156.

110. Hong M, Zheng J, Ding Z, Chen J, Yu L, Niu Y, *et al.* (2013): Imbalance between Th17 and Treg cells may play an important role in the development of chronic unpredictable mild stress-induced depression in mice. *Neuroimmunomodulation* 20: 39–50.

111. Beurel E, Lowell JA, Jope RS (2018): Distinct characteristics of hippocampal pathogenic TH17 cells in a mouse model of depression. *Brain Behav Immun* 73: 180–191.

112. Peng Z, Peng S, Lin K, Zhao B, Wei L, Tuo Q, *et al.* (2022): Chronic stress-induced depression requires the recruitment of peripheral Th17 cells into the brain. *J Neuroinflammation* 19: 186.

113. Beurel E, Harrington LE, Jope RS (2013): Inflammatory T helper 17 cells promote depression-like behavior in mice. *Biol Psychiatry* 73: 622–630.

114. Kebir H, Kreymborg K, Ifergan I, Dodelet-Devillers A, Cayrol R, Bernard M, *et al.* (2007): Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat Med* 13: 1173–1175.

115. Beurel E, Lowell JA (2018): Th17 cells in depression. *Brain Behav Immun* 69: 28–34.

116. Rivet-Noor CR, Merchak AR, Li S, Beiter RM, Lee S, Thomas JA, *et al.* (2022): Stress-induced despair behavior develops independently of the Ahr-RORγt axis in CD4 + cells. *Sci Rep* 12: 8594.

117. Lewitus GM, Schwartz M (2009): Behavioral immunization: immunity to self-antigens contributes to psychological stress resilience. *Mol Psychiatry* 14: 532–536.

118. Lewitus GM, Cohen H, Schwartz M (2008): Reducing post-traumatic anxiety by immunization. *Brain, Behavior, and Immunity* 22: 1108–1114.

119. Brachman RA, Lehmann ML, Maric D, Herkenham M (2015): Lymphocytes from Chronically Stressed Mice Confer Antidepressant-Like Effects to Naive Mice. *J Neurosci* 35: 1530–1538.

120. Lewitus GM, Wilf-Yarkoni A, Ziv Y, Shabat-Simon M, Gersner R, Zangen A, Schwartz M (2009): Vaccination as a novel approach for treating depressive behavior. *Biol Psychiatry* 65: 283–288.

121. Jiang W, Li Y, Sun J, Li L, Li J, Zhang C, *et al.* (2017): Spleen contributes to restraint stress induced changes in blood leukocytes distribution. *Sci Rep* 7: 6501.

122. Golumbek PT, Keeling RM, Connolly AM (2007): RAG2 gene knockout in mice causes fatigue. *Muscle Nerve* 36: 471–476.

123. Clark SM, Soroka JA, Song C, Li X, Tonelli LH (2016): CD4(+) T cells confer anxiolytic and antidepressant-like effects, but enhance fear memory processes in Rag2(-/-) mice. *Stress* 19: 303–311.

124. Jin M, Alam MM, Liu AY-C, Jiang P (2022): Rag2-/- accelerates lipofuscin accumulation in the brain: Implications for human stem cell brain transplantation studies. *Stem Cell Reports* 17: 2381–2391.

125. Kim J-I, Park J-S, Kim H, Ryu S-K, Kwak J, Kwon E, *et al.* (2018): CRISPR/Cas9-mediated knockout of Rag-2 causes systemic lymphopenia with hypoplastic lymphoid organs in FVB mice. *Lab Anim Res* 34: 166–175.

126. Tanaka T, Narazaki M, Kishimoto T (2014): IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* 6: a016295.

127. Kang S, Tanaka T, Narazaki M, Kishimoto T (2019): Targeting Interleukin-6 Signaling in Clinic. *Immunity* 50: 1007–1023.

128. Schaper F, Rose-John S (2015): Interleukin-6: Biology, signaling and strategies of blockade. *Cytokine & Growth Factor Reviews* 26: 475–487.

129. Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, Bregman D, *et al.* (2014): Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. *Proc Natl Acad Sci USA* 111: 16136–16141.

130. Sun Y, Wang D, Salvadore G, Hsu B, Curran M, Casper C, *et al.* (2017): The effects of interleukin-6 neutralizing antibodies on symptoms of depressed mood and anhedonia in patients with rheumatoid arthritis and multicentric Castleman's disease. *Brain Behav Immun* 66: 156–164.

131. Wang J, Hodes GE, Zhang H, Zhang S, Zhao W, Golden SA, *et al.* (2018): Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice. *Nat Commun* 9: 477.

132. Barouei J, Moussavi M, Hodgson DM (2015): Perinatal maternal probiotic intervention impacts immune responses and ileal mucin gene expression in a rat model of irritable bowel syndrome. *Benef Microbes* 6: 83–95.

133. Grassi-Oliveira R, Honeycutt JA, Holland FH, Ganguly P, Brenhouse HC (2016): Cognitive impairment effects of early life stress in adolescents can be predicted with early biomarkers: Impacts of sex, experience, and cytokines. *Psychoneuroendocrinology* 71: 19–30.

134. Ackerman SH, Keller SE, Schleifer SJ, Shindledecker RD, Camerino M, Hofer MA, *et al.* (1988): Premature maternal separation and lymphocyte function. *Brain Behav Immun* 2: 161–165.

135. Grigoruta M, Chavez-Solano M, Varela-Ramirez A, Sierra-Fonseca JA, Orozco-Lucero E, Hamdan JN, *et al.* (2020): Maternal separation induces retinal and peripheral blood mononuclear cell alterations across the lifespan of female rats. *Brain Res* 1749: 147117.

136. Gifford JJ, Pluchino JR, Della Valle R, Van Weele B, Brezoczky E, Caulfield JI, *et al.* (2023): Effects of limited bedding and nesting on postpartum mood state in rats. *J Neuroendocrinology* 35: e13275.

137. Walker C-D, Bath KG, Joels M, Korosi A, Larauche M, Lucassen PJ, *et al.* (2017): Chronic early life stress induced by limited bedding and nesting (LBN) material in rodents: critical considerations of methodology, outcomes and translational potential. *Stress* 20: 421–448.

138. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V (2016): Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Mol Psychiatry* 21: 642–649.

139. Schwaiger M, Grinberg M, Moser D, Zang JCS, Heinrichs M, Hengstler JG, *et al.* (2016): Altered Stress-Induced Regulation of Genes in Monocytes in Adults with a History of Childhood Adversity. *Neuropsychopharmacology* 41: 2530–2540.

140. Durand-de Cuttoli R, Martínez-Rivera FJ, Li L, Minier-Toribio A, Holt LM, Cathomas F, *et al.* (2022): Distinct forms of regret linked to resilience versus susceptibility to stress are regulated by region-specific CREB function in mice. *Sci Adv* 8: eadd5579.

141. Schneiderman N, Ironson G, Siegel SD (2005): Stress and health: psychological, behavioral, and biological determinants. *Annu Rev Clin Psychol* 1: 607–628.

142. Krishnan V, Han M-H, Graham DL, Berton O, Renthal W, Russo SJ, *et al.* (2007): Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* 131: 391–404.

143. Takahashi A, Chung J-R, Zhang S, Zhang H, Grossman Y, Aleyasin H, *et al.* (2017): Establishment of a repeated social defeat stress model in female mice. *Sci Rep* 7: 12838.

144. Harris AZ, Atsak P, Bretton ZH, Holt ES, Alam R, Morton MP, *et al.* (2018): A Novel Method for Chronic Social Defeat Stress in Female Mice. *Neuropsychopharmacology* 43: 1276–1283.

145. Newman EL, Covington HE, Suh J, Bicakci MB, Ressler KJ, DeBold JF, Miczek KA (2019): Fighting Females: Neural and Behavioral Consequences of Social Defeat Stress in Female Mice. *Biol Psychiatry* 86: 657–668.

146. Wallace DL, Han M-H, Graham DL, Green TA, Vialou V, Iñiguez SD, *et al.* (2009): CREB regulation of nucleus accumbens excitability mediates social isolation-induced behavioral deficits. *Nat Neurosci* 12: 200–209.

147. Ma X, Jiang D, Jiang W, Wang F, Jia M, Wu J, *et al.* (2011): Social isolation-induced aggression potentiates anxiety and depressive-like behavior in male mice subjected to unpredictable chronic mild stress. *PLoS One* 6: e20955.

148. Willner P (2017): The chronic mild stress (CMS) model of depression: History, evaluation and usage. *Neurobiology of Stress* 6: 78–93.

149. Wiborg O (2013): Chronic mild stress for modeling anhedonia. *Cell Tissue Res* 354: 155–169.

150. Johnson A, Rainville JR, Rivero-Ballon GN, Dhimitri K, Hodes GE (2021): Testing the Limits of Sex Differences Using Variable Stress. *Neuroscience* 454: 72–84.

151. Pryce CR, Azzinnari D, Spinelli S, Seifritz E, Tegethoff M, Meinlschmidt G (2011): Helplessness: a systematic translational review of theory and evidence for its relevance to understanding and treating depression. *Pharmacol Ther* 132: 242–267.

152. Tian X, Russo SJ, Li L (2024): Behavioral Animal Models and Neural-Circuit Framework of Depressive Disorder. *Neurosci Bull*. https://doi.org/10.1007/s12264-024-01270-7

153. Buynitsky T, Mostofsky DI (2009): Restraint stress in biobehavioral research: Recent developments. *Neuroscience & Biobehavioral Reviews* 33: 1089–1098.

154. Mao Y, Xu Y, Yuan X (2022): Validity of chronic restraint stress for modeling anhedonic-like behavior in rodents: a systematic review and meta-analysis. *J Int Med Res* 50: 3000605221075816.

155. Pechtel P, Pizzagalli DA (2011): Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology (Berl)* 214: 55–70.

156. Nanni V, Uher R, Danese A (2012): Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *Am J Psychiatry* 169: 141–151.

157. Kuhlman KR (2024): Pitfalls and potential: Translating the two-hit model of early life stress from pre-clinical non-human experiments to human samples. *Brain Behav Immun Health* 35: 100711.

158. Murthy S, Gould E (2018): Early Life Stress in Rodents: Animal Models of Illness or Resilience? *Front Behav Neurosci* 12: 157.

159. Peña CJ, Smith M, Ramakrishnan A, Cates HM, Bagot RC, Kronman HG, *et al.* (2019): Early life stress alters transcriptomic patterning across reward circuitry in male and female mice. *Nat Commun* 10: 5098.

160. Scarpa JR, Fatma M, Loh Y-HE, Traore SR, Stefan T, Chen TH, *et al.* (2020): Shared Transcriptional Signatures in Major Depressive Disorder and Mouse Chronic Stress Models. *Biol Psychiatry* 88: 159–168.

161. Mestas J, Hughes CCW (2004): Of mice and not men: differences between mouse and human immunology. *J Immunol* 172: 2731–2738.

162. Dutta S, Sengupta P (2016): Men and mice: Relating their ages. *Life Sciences* 152: 244–248.

163. Thompson M, Saag M, DeJesus E, Gathe J, Lalezari J, Landay AL, *et al.* (2016): A 48-week randomized phase 2b study evaluating cenicriviroc versus efavirenz in treatment-naive HIV-infected adults with C-C chemokine receptor type 5-tropic virus. *AIDS* 30: 869–878.

164. Funderburg NT, Jiang Y, Debanne SM, Storer N, Labbato D, Clagett B, *et al.* (2014): Rosuvastatin treatment reduces markers of monocyte activation in HIV-infected subjects on antiretroviral therapy. *Clin Infect Dis* 58: 588–595.

165. Chalmers JD, Haworth CS, Metersky ML, Loebinger MR, Blasi F, Sibila O, *et al.* (2020): Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. *N Engl J Med* 383: 2127–2137.

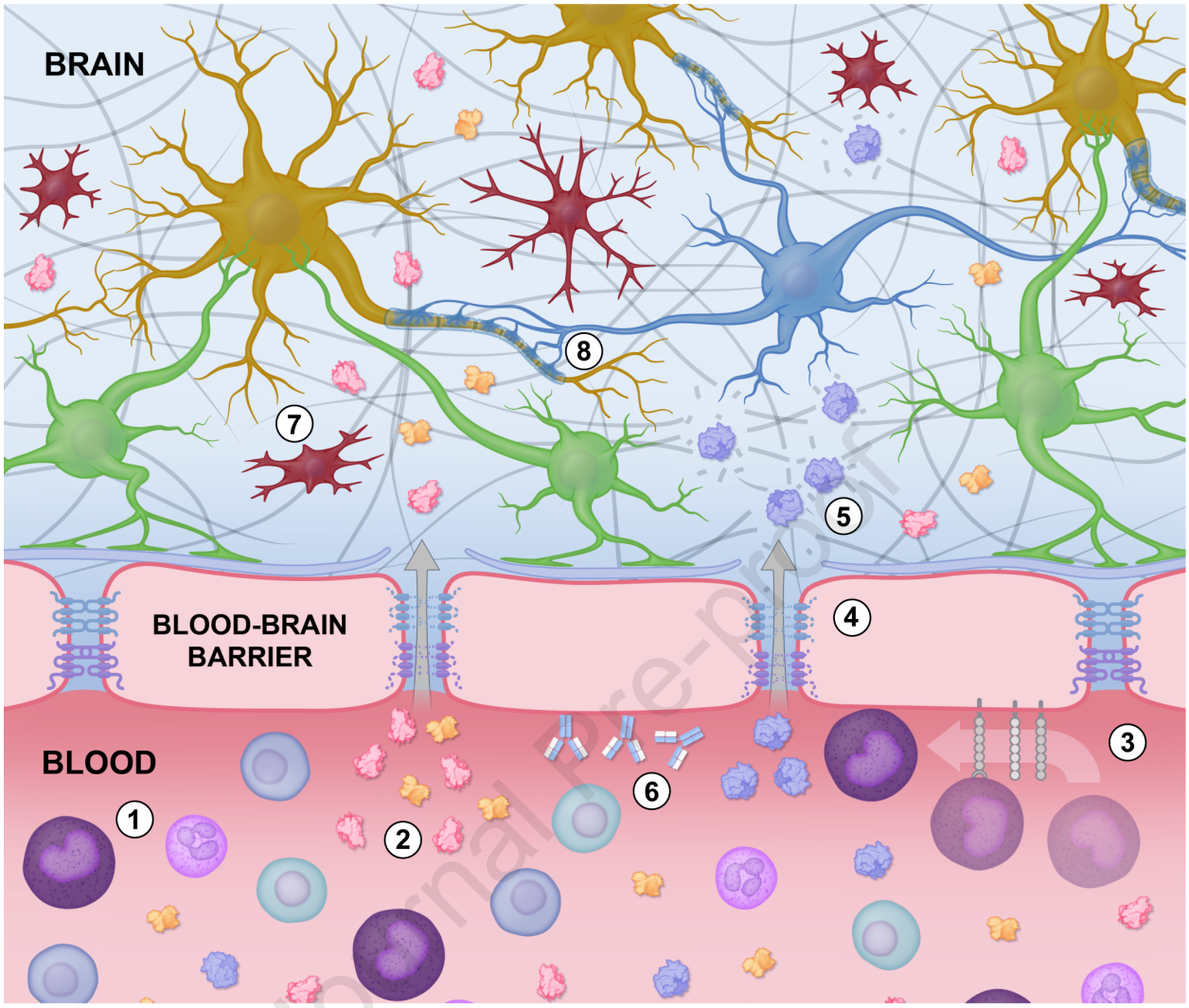
166. Nakou M, Katsikas G, Sidiropoulos P, Bertsias G, Papadimitraki E, Raptopoulou A, *et al.* (2009): Rituximab therapy reduces activated B cells in both the peripheral blood and bone marrow of patients with rheumatoid arthritis: depletion of memory B cells correlates with clinical response. *Arthritis Res Ther* 11: R131.

167. Jones JL, Phuah C-L, Cox AL, Thompson SA, Ban M, Shawcross J, *et al.* (2009): IL-21 drives secondary autoimmunity in patients with multiple sclerosis, following therapeutic lymphocyte depletion with alemtuzumab (Campath-1H). *J Clin Invest* 119: 2052–2061.

168. Rizk MM, Bolton L, Cathomas F, He H, Russo SJ, Guttman-Yassky E, *et al.* (2024): Immune-Targeted Therapies for Depression: Current Evidence for Antidepressant Effects of Monoclonal Antibodies. *J Clin Psychiatry* 85: 23nr15243.

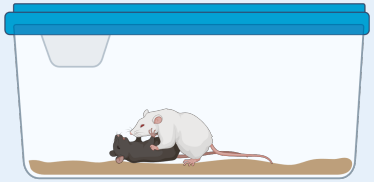
169. Voorhees JL, Tarr AJ, Wohleb ES, Godbout JP, Mo X, Sheridan JF, *et al.* (2013): Prolonged restraint stress increases IL-6, reduces IL-10, and causes persistent depressive-like behavior that is reversed by recombinant IL-10. *PLoS One* 8: e58488.

170. Choi D-H, Moon I-S, Choi B-K, Paik J-W, Kim Y-S, Choi S-H, Kim C-K (2004): Effects of sub-antimicrobial dose doxycycline therapy on crevicular fluid MMP-8, and gingival tissue MMP-9, TIMP-1 and IL-6 levels in chronic periodontitis. *J Periodontal Res* 39: 20–26.

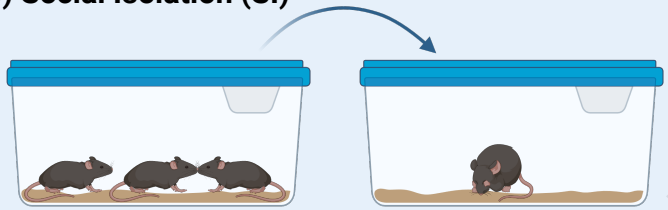


Adult Social Stress Paradigms

A) Chronic Social Defeat Stress (CSDS)

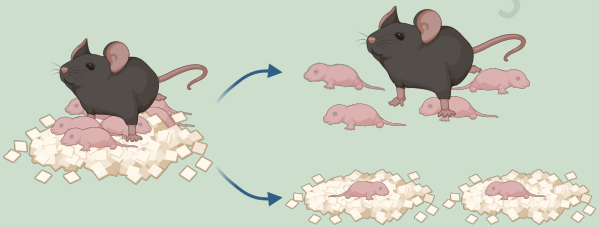


B) Social Isolation (SI)

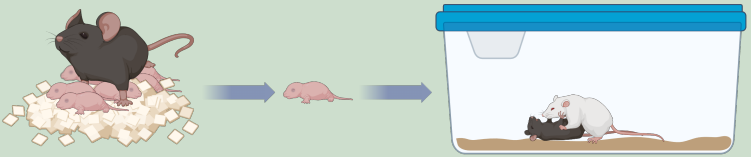


Early Life Stress Paradigms

F) Maternal Separation (MS) / Reduced Bedding

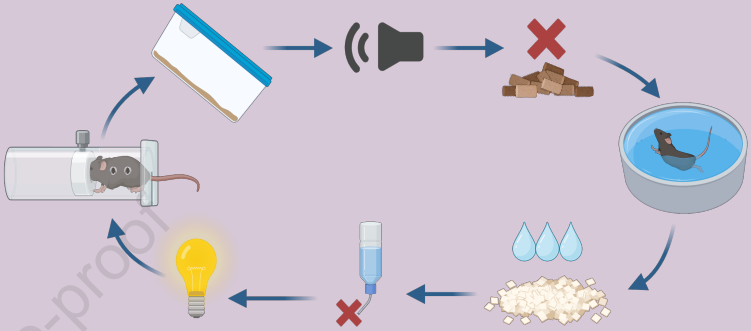


G) Two-Hit Stress Model

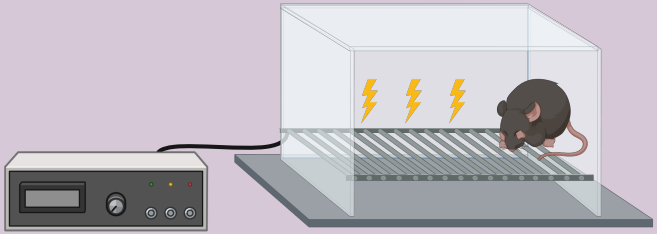


Adult Non-Social Stress Paradigms

C) Chronic Variable Stress (CVS)



D) Learned Helplessness (LH)



E) Restraint Stress (RS)

Human		Laboratory Mouse
• Average lifespan about 80 years • High genetic diversity • Frequent and diverse pathogen exposure	Life history and exposure	• Average lifespan about 2 years • Low genetic diversity in inbred strains • Restricted pathogen exposure
• Slow turnover in adulthood (years)	Microglia	• Faster renewal (months)
• Neutrophils 40-60% • Lymphocytes 20-40% • Monocytes 2-8% • Eosinophils 1-4% • Classical, intermediate, non-classical monocytes • NK receptors: KIR family	Circulating leukocytes	• Neutrophils 10-25% • Lymphocytes 75-90% • Monocytes 1-4% • Eosinophils 1-3% • Monocyte subsets: Ly6C^{high} /Ly6C^{low} • NK receptors: Ly49 family
• No functional TLR11-13 (TLR11 is a pseudogene) • IL-8 (CXCL8) present • Human-restricted chemokines (e.g., CCL13/14/15/18/23) • Generally higher endotoxin (LPS) sensitivity • IgG subclasses and Fcγ receptor repertoire differ from mouse (e.g., IgG1/IgG3 with strong FcγR engagement)	Circulating proteins	• Functional TLR11- 13 expressed. • No IL-8 • CXCR2 predominant • Generally lower LPS sensitivity • Distinct IgG subclasses (e.g., IgG2a/c) and FcγR repertoire with non-equivalent effector functions.

Mitigation approaches of limitation

- Bidirectional translational alignment (e.g., matched endpoints and assays)
- Incorporating data sources from both species (e.g., blood-based biomarkers, post-mortem brain samples)
- Humanized mouse models
- Additional in-vitro/ex-vivo systems (e.g., iPSCs)