Review

Beyond the neuron: Role of non-neuronal cells in stress disorders

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SUMMARY

Stress disorders are leading causes of disease burden in the U.S. and worldwide, yet available therapies are fully effective in less than half of all individuals with these disorders. Although to date, much of the focus has been on neuron-intrinsic mechanisms, emerging evidence suggests that chronic stress can affect a wide range of cell types in the brain and periphery, which are linked to maladaptive behavioral outcomes. Here, we synthesize emerging literature and discuss mechanisms of how non-neuronal cells in limbic regions of brain interface at synapses, the neurovascular unit, and other sites of intercellular communication to mediate the deleterious, or adaptive (i.e., pro-resilient), effects of chronic stress in rodent models and in human stress-related disorders. We believe that such an approach may one day allow us to adopt a holistic "whole body" approach to stress disorder research, which could lead to more precise diagnostic tests and personalized treatment strategies.

INTRODUCTION

Stress-related disorders, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD), are among the world's greatest public health problems. However, their etiology and pathophysiology remain incompletely understood. Although there are many effective treatments for these disorders, more than half of affected individuals are not fully treated by available antidepressant medications or other therapies (Gaynes et al., 2009; Rush et al., 2006). All existing antidepressants, which act initially on either the brain's monoamine or glutamate systems, exert their eventual therapeutic actions through unknown mechanisms: many prominent theories suggest that the drugs' therapeutic effects are not mediated via changes in monoaminergic or glutamatergic neurotransmission per se but require neuroplastic adaptations to these initial actions (Berton and Nestler, 2006; Duman and Monteggia, 2006; Kavalali and Monteggia, 2020; Peña and Nestler, 2018; Slattery et al., 2004). Challenges in treating these disorders also reflect the fact that they are highly heterogeneous syndromes, diagnosed today solely on the basis of behavioral abnormalities, with no biological endpoints used for diagnosis or to guide treatment (Goldberg, 2011; Zimmermann et al., 2009). Moreover, the exclusive focus on monoaminergic and glutamatergic transmission has ignored unbiased transcriptomic studies pointing to broad perturbations in non-neuronal mechanisms in stress-related disorders beyond changes observed in neurons (Girgenti et al., 2021a; 2021b; Labonté et al., 2017; Pantazatos et al., 2017; Zhu et al., 2019). Our review examines emerging evidence that is providing a fundamentally more complete view of the non-neuronal contributions to stress action in rodent models, related human disorders, and their treatment. We focus on technological advances that have allowed for a multiscale understanding of unique biological changes in a range of non-neuronal cells that contribute to an individual's risk—or resilience to—stress over the lifetime.

GENERAL OVERVIEW

Considerable evidence supports the view that a series of highly inter-connecting brain structures—referred to as limbic regions—are important in regulating mood, motivation, and related emotional states under normal conditions and the abnormalities in these behavioral domains that characterize stress-related disorders as defined by DSM5 or by RDoC (Dunlop and Mayberg, 2014; Epstein et al., 2006; Price and Drevets, 2010; Sheline et al., 2002). These include the nucleus accumbens (NAc), medial prefrontal cortex (mPFC), hippocampus (HIP), amygdala (AMY), and ventral tegmental area (VTA) among other regions. We focus here largely on NAc and mPFC—based on the robust published data for these two regions—but whenever possible we discuss studies of other regions where evidence is available. In recent years, investigators have focused on molecular abnormalities in these structures that are induced in rodent stress models, with increasing investigation of human postmortem brain tissue as well. Early
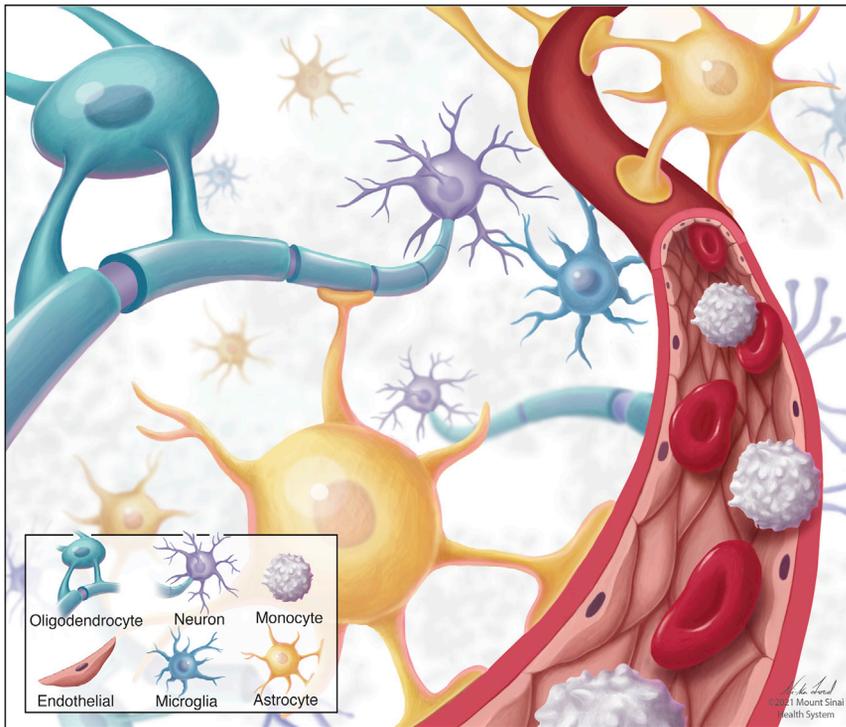
Figure 1. Interactions among non-neuronal cells in brain
Non-neuronal cells interact at cellular barriers, including the blood-brain barrier (BBB), synapses, and other sites of intercellular communication in the brain. Oligodendrocytes (turquoise); astrocytes (yellow); monocytes (white); microglia (blue); endothelial cells (brown); neurons (purple).

models and in human stress-related disorders, with some shared but many distinct mechanisms operating in males versus females.

Major themes discussed in this review

The review focuses on the role of 4 distinct non-neuronal cell types in stress action stated earlier: astrocytes, myeloid cells, endothelial cells, and oligodendrocytes. Although at first they may appear distinct, in reality, we will discuss how non-neuronal cells interact within the central nervous system (CNS) and at particular sites of intercellular communication (e.g., blood-brain barrier [BBB]) to ultimately affect neural networks and complex stress-related behaviors (Figure 1). Three major themes related to intercellular communication are woven across the review sections. First, a major focus is on the ability of non-neuronal cells to affect neural connectivity in limbic brain regions by regulating synaptic inputs and myelination of axons. Second, we focus on the interactions at the BBB, which is permeabilized in specific brain regions by stress in susceptible individuals and serves as a critical site of communication between blood-derived signals and the CNS. Third, we focus on how the cross talk between non-neuronal cells and neurons ultimately controls stress behaviors.

Non-neuronal cells in stress action

Over many decades, stress research has focused almost exclusively on mechanisms of neuronal dysfunction from a cell-intrinsic perspective, that is, to identify a cellular or molecular change within a given neuronal cell type and then test whether that change is causally linked to the deleterious effects of stress on behavior. Although this approach has yielded many important insights into stress action, it has largely ignored the contribution of non-neuronal cell types, which exist in high numbers throughout the brain of mammalian and non-mammalian species (Christoffel et al., 2015; Deyama et al., 2019; Donahue et al., 2014; Friedman et al., 2017; Golden et al., 2013; Hokenson et al., 2021; Issler et al., 2020; Tye et al., 2013). There are, however, considerable differences in the ratio of neuronal versus non-neuronal cells across species that must be accounted for in basic research (Vasile et al., 2017): For example, the nervous system of *C. elegans* has more than 5 neurons per glia. In mammals, the glial:neuron

studies took a candidate gene approach, examining alterations in one or at most a few proteins or mRNAs, mostly of neuronal origin (Barrot et al., 2002; Covington et al., 2009; Golden et al., 2013; Menard et al., 2017; Monteggia et al., 2007; Vialou et al., 2010). The past decades have seen the increasing use of genome-wide methods—first microarrays and more recently RNA sequencing (RNA-seq)—to provide a global view of alterations in gene expression in limbic brain regions of rodents and humans (Andrus et al., 2012; Bagot et al., 2016; Berton et al., 2006; Chang et al., 2014; Chaudhury et al., 2014; Hernandez et al., 2021; Hodes et al., 2015b; Kronman et al., 2021; Li et al., 2021; Seney et al., 2022; Yoshino et al., 2021). Such global approaches are essential, as they provide an unbiased view of the genes that are most regulated by stress, as opposed to relying on our still very limited knowledge of human stress disorder pathophysiology. These unbiased screens—performed initially on bulk tissue dissections—have shown that some of the most highly regulated genes and molecular pathways are enriched not only in neurons but also in astrocytes, myeloid cells, endothelial cells, or oligodendrocyte lineage (OL) cells (Girgenti et al., 2021b; Labonté et al., 2017). Limitations of these early data include their analysis of whole tissue extracts without first enriching for a given cell type and use of a single-rodent stress model and small cohorts of human brains, with generally inadequate attention given to sex differences. In this review we discuss established and emerging roles for non-neuronal cells in limbic regions of the brain that interface at synapses, the neurovascular unit, and other sites of intercellular communication to mediate the deleterious effects, as well as the adaptive, protective (i.e., pro-resilient) effects of different forms of chronic stress in rodent

ratio varies considerably across brain regions. In the cerebral cortex of humans, the glial:neuron ratio is approximately 4:1, whereas it is inverse in the cerebellum (Herculano-Houzel, 2014). Adding to the complexity, there is increasing evidence that there are sex differences among non-neuronal cells in both rodents and humans (Guneykaya et al., 2018). Here, we discuss four major non-neuronal cell types (Figure 1) that are affected by stress and altered in human stress disorders as well as their interface with neurons in limbic brain regions that mediate the effects of stress on behavior. Decades of research have implicated myeloid cells (monocytes, macrophages, and microglia) of the immune system in mediating responses to stress in both mouse models (Gallagher et al., 2019; Kronenberg et al., 2019; Lehmann et al., 2016; Pfau et al., 2019b; Wohleb et al., 2013; Woodburn et al., 2021; Yin et al., 2019) and human stress disorders (Bekhbat et al., 2020; Böttcher et al., 2020; Chiang et al., 2019; Hasselmann et al., 2018; Lago et al., 2020; Syed et al., 2018). Work in mice has shown that stress activates myeloid cells in the periphery, some of which then traffic to the brain to mediate stress-induced behavioral abnormalities. Translational studies in human patients and mouse models show that a subset of individuals with stress disorders exhibit a heightened immune response to stress and neuroimmune interactions with certain brain regions through damaged endothelial cells of the BBB that ultimately affects reward-related behaviors (Cathomas et al., 2022; Hodes et al., 2014; Menard et al., 2017; Pfau et al., 2019a). In addition, glial cells in the brain, which have been historically described as support cells, are now being recognized to control many aspects of synaptic and circuit function and they serve as a critical link between peripheral organ systems, the BBB, neuronal signaling, and ultimately behavior. The primary classes of glia include astrocytes, microglia, and OL cells. Astrocytes and microglia are both capable of directly regulating synaptic transmission by shaping neuronal synapses (Liddelow et al., 2020; Schafer et al., 2012; Stevens et al., 2007). Astrocytes further regulate synaptic transmission by controlling extracellular levels of glutamate and can interface with myeloid cells of the periphery via the BBB (Kofuji and Araque, (2021); Moura et al., 2017; Ross et al., 2020; Wang et al., 2021). Loss of astrocyte integrity can damage the BBB and allow for entry of peripheral factors that impact behavior (Abbott et al., 2006). Oligodendrocytes provide myelin sheathing to facilitate neural conductance, and serve as a metabolic interface with neurons, while oligodendrocyte progenitor cells (OPCs) receive direct synaptic inputs from neurons and facilitate cross talk with other glial cell types (Domingues et al., 2016; Simons and Nave, 2015). Several recent papers (Bonnefil et al., 2019; Cui et al., 2018; Dudek et al., 2020; Hodes et al., 2014; Liu et al., 2012, 2018, 2020; Menard et al., 2017; Nagy et al., 2020; O'Leary and Mechawar, 2021; Rajkowska and Stockmeier, 2013; Woodburn et al., 2021) have shown that human stress disorders or rodent stress models are associated with alterations in many of these processes, including the following: (1) trafficking of peripheral myeloid cells to the brain, (2) altered myelin content and OL cell dynamics, (3) alterations in glial- and myeloid-mediated synaptic alterations, and (4) impaired BBB integrity.

Animal models of stress disorders

A major challenge in psychiatry research, more so than in other branches of medicine, is the challenge in generating animal models since all psychiatric syndromes today are still diagnosed solely on the basis of behavioral abnormalities, many of which are inaccessible in animals. This challenge holds for stress-related disorders (Bale et al., 2010; Bliss-Moreau and Rudebeck, 2021; Fitzgerald et al., 2021; Nestler and Hyman, 2010; Simmons et al., 2021), including both translationally valid stress paradigms and behavioral readouts of stress exposure with high face and predictive validity. Although certain tests (e.g., forced swim test) have proven useful in predicting clinical efficacy of currently available monoamine-acting antidepressants, results from these tests have not yielded major breakthroughs in developing novel antidepressants with better efficacy and faster onset (Nestler and Hyman, 2010). Many stress paradigms used in preclinical stress research typically involve acute stress—or chronic physical stress—in normal rodents, which is very different from the increased vulnerability to stress, typically emotional, seen in most patients with stress-related disorders. That vulnerability is thought to be due to a combination of genetic factors and life experiences. Genetic factors remain an intense area of research, and recent GWAS studies have at long last begun to identify potentially interesting genomic loci involved in increasing risk for these disorders (Cai et al., 2020; Wray et al., 2018). However, it is clear that genetic risk for stress disorders is highly polygenic, involving many hundreds of genes acting in synergy, with each gene contributing a minute amount and heredity only accounting for 30%–40% of the overall risk for developing an illness. Therefore, human genetic risk for stress disorders cannot be reproduced in rodent models. By contrast, the best-established risk factor for these conditions is a lifetime history of stress exposure most commonly repeated or chronic emotional stress (Albert and Newhouse, 2019; Belleau et al., 2019; Otte et al., 2016), which is driving the field increasingly to focus on the latter (Kuske and Trainor, 2021; Russo and Nestler, 2013). For a comprehensive discussion on these preclinical stress paradigms across the lifespan see (Kuske and Trainor, 2021; Lopez and Bagot, 2021; Nestler and Hyman, 2010; Planchez et al., 2019; Schmidt et al., 2011; Torres-Berrío et al., 2019). In the present review, we discuss emerging evidence that chronic stress across the life cycle, via alterations in neuronal and non-neuronal cell types, affects complex behaviors that tap into translationally relevant domains and brain mechanisms that have been shown or are hypothesized to be disrupted in stress-related mental illnesses, such as depression or PTSD.

Role of astrocytes in stress disorders

Astrocytes—the most prevalent type of glia in the brain—are best known for their roles in regulating synaptic signaling, metabolic coupling with neurons, and maintaining the BBB. Crucial to the astrocyte function is their so-called star-shaped morphology, whereby astrocytes extend multiple primary branches that elongate into increasingly fine peripheral processes (Ben Haim and Rowitch, 2017; Sofroniew and Vinters, 2010). It is at these peripheral processes that astrocytes (1) contact nerve terminals

and dendritic spines to form the "tripartite synapse," (2) form gap-junctions with other astrocytes, (3) engage with neurons to control their metabolic state and availability of certain neurotransmitters, and (4) form endfeet to enwrap blood vessels. Research in stress disorders shows consistent alterations in astrocyte number and morphology, loss of gap-junction coupling, and regulation of neuronal excitability and synaptic communication both in animal models and in human brain tissue. Recent studies have also highlighted the involvement of astrocytes, along with microglia, in mediating neuroinflammatory-like responses, synaptic dysfunction, and a damaged BBB in stress and MDD.

Changes in astrocyte number and morphology

One of the most common ways to investigate astrocytic involvement in stress disorder subjects and rodent stress models has been to examine astrocyte density and morphological complexity. Reports demonstrate a reduction in the number and complexity of astrocytes across multiple brain regions, including the PFC and NAc (Banqueri et al., 2019). These studies have largely utilized glial fibrillary acidic protein (GFAP), a cytoskeletal protein specific to astrocytes, to stain and visualize astrocytes. However, it is important to note that not every astrocyte expresses GFAP at appreciable levels, and GFAP expression itself varies by brain region. Thus, there is some debate about whether there is a true reduction in the number of astrocytes, or instead a reduction in the number of GFAP+ astrocytes or in the expression levels of GFAP with an unchanged number of total astrocytes. Studies identifying astrocytes by other methods, such as Nissl, S100B, or vimentin staining, have reported mixed results, with some confirming that stress or MDD is associated with loss of astrocytes, while others reporting no change (Kim et al., 2018; Tynan et al., 2013). Notably, decreased GFAP expression is one of the most consistent findings in MDD patients and across chronic stress models in rodents, including chronic variable stress (CVS), early life stress, and genetic rodent models of anxiety-like behavior. Nevertheless, the utilization of GFAP allows for the concomitant examination of astrocyte morphology and demonstrates loss of astrocyte branch complexity—including both branch number and arborization in multiple brain regions in both human MDD patients and rodent models (Bender et al., 2016; Kim et al., 2018). No change in branch complexity has been observed in response to acute stress (Bender et al., 2016; Kim et al., 2018). Importantly, treatment with a range of antidepressants has been shown to reverse changes in astrocyte branch morphology in rodents (Wang et al., 2017b).

The majority of astrocyte morphological complexity occurs at peripheral processes. Indeed, the cytoskeletal structure revealed by GFAP staining only encompasses roughly 10%–15% of total astrocyte volume (Bushong et al., 2002). Examination of astrocyte peripheral process morphology is technically complex, given that these processes are thinner than the diffraction limit of normal microscopy techniques. Therefore, cellular reconstruction and estimates of astrocyte volume are most commonly used as a proxy for astrocyte complexity. To date, human postmortem studies have utilized sparse Golgi staining to report on overall astrocyte cell soma size with mixed results. Hypertrophic

astrocytes were found in the dorsolateral PFC of MDD patients and in the anterior cingulate cortex (ACC) in MDD patients who committed suicide (Kim et al., 2018). In contrast, no change in astrocyte size was observed in the frontal cortex (Kim et al., 2018).

Influence of astrocytes on synapses and neuronal activity

Astrocyte peripheral processes enwrap upward of 90% of synapses in the brain, which ideally positions astrocytes for monitoring and controlling neuronal and circuit activity, including maintaining ionic and neurotransmitter homeostasis, providing structural support, and facilitating elimination of synapses. To our knowledge, only one study has investigated astrocyte peripheral processes and synapse localization in the context of stress. The authors found that acute stress in rats decreased the number of presynaptic nerve terminals within astrocyte domains in the NAc core (Garcia-Keller et al., 2021). Interestingly, this acute stress paradigm did not alter overall astrocyte volume, suggesting that the loss of astrocytic contact of synapses could be driven by retraction of astrocytes from synapses rather than decreased astrocyte morphology per se. Thus, changes in the number of astrocyte peripheral processes may not be required for the loss of astrocytic control over synapses.

Astrocytes passively influence neuronal activity via neurotransmitter and ionic homeostasis. For example, the glutamate transporter solute carrier family 1 member 2 (SLC1A2; also referred to as GLT1 or EAAT2), which is highly enriched in astrocytes in rodent and human brain, accounts for upward of 90% of glutamate recycling at synapses, and loss of SLC1A2 is associated with disruptions of glutamate uptake and subsequent excitation-inhibition imbalances (Bechtholt-Gompf et al., 2010; Tanaka et al., 1997). Glutamate taken up by the astrocytes via SLC1A2 is also converted to glutamine and shuttled to neurons to be converted back into glutamate. Importantly, loss of SLC1A2 is consistently found in multiple rodent stress models, as well as in human MDD subjects at both the mRNA and protein levels, including in the PFC and NAc (reviewed in Rajkowska and Stockmeier, (2013) and Rappeneau et al. (2016); Figure 2). Genetic deletion or pharmacological inhibition of SLC1A2 has been shown to elicit or exacerbate depressive-like behavioral phenotypes in rodents (Bechtholt-Gompf et al., 2010; Blacker et al., 2020; Fullana et al., 2020; John et al., 2012; Kofuji and Araque, 2021). Additionally, imbalances in the glutamate-glutamine cycle are found in both rodent models and human MDD patients (Rappeneau et al., 2016). Given the recent shift in the field from monoamine-based treatments of MDD to the ones focused on glutamate (based on the approval of ketamine—an NMDA glutamate receptor antagonist among other actions—for treatment-resistant depression), these findings further support the utility in targeting glutamatergic mechanisms in treating depression and shed light on the involvement of astrocytes in the pathophysiology of this syndrome (Sanacora et al., 2012).

Astrocytes also influence neuronal activity by buffering extracellular K^+ after neuronal action potentials. The inward-rectifying K^+ channel, KCNJ10 (also referred to as KIR4.1), is thought to be the main mediator of astrocytic extracellular K^+ buffering
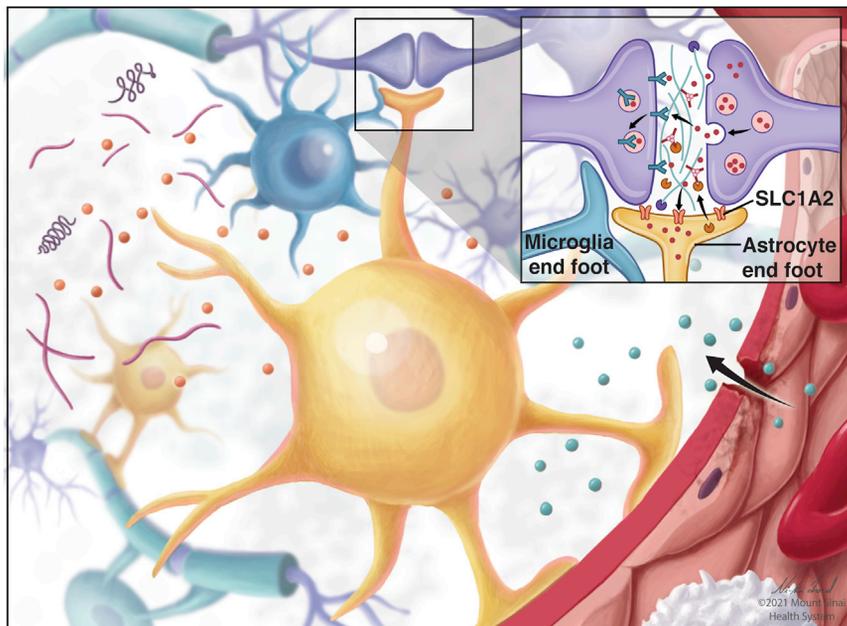
Figure 2. Stress effects on astrocytes
Stress affects astrocytes (yellow) and their interaction with the blood-brain barrier (BBB). As shown in the inset, SLC1A2 (also known as GLT1 or EAAT2) removes glutamate from the extracellular space. SLC1A2 is downregulated in both humans and rodent models of stress and depression. Additionally, loss of astrocyte endfeet integrity may loosen the BBB and allow peripheral factors into the brain.

(Nwaobi et al., 2016). Within the lateral habenula of genetically derived learned helpless rats, KCNJ10 was upregulated and contributed to the modulation of neuronal burst firing. Furthermore, overexpression of KCNJ10 in astrocytes alone was sufficient to induce a depressive-like behavioral phenotype (Cui et al., 2018). In addition, KCNJ10 expression was increased in the parietal cortex of human MDD subjects (Xiong et al., 2019). Several antidepressants have been shown to inhibit KCNJ10 function, albeit at high supra-therapeutic concentrations (Furutani et al., 2009; Ohno et al., 2007; Su et al., 2007). Although the specific role of Ca^{2+} in astrocytes is still a topic of debate (Bazargani and Attwell, 2016; Khakh and McCarthy, 2015), Ca^{2+} signaling is thought to be the main mode of astrocyte communication, including the surveying and integration of neuronal activity, astrocyte-to-astrocyte communication, and release of factors that influence neurons. Ca^{2+} signaling in astrocytes is largely generated through two mechanisms: extracellular Ca^{2+} entry via plasma membrane ion channels or ionotropic glutamate receptors and the release of Ca^{2+} from internal stores (e.g., endoplasmic reticulum). Genetic deletion of IP3R2 in astrocytes, a major mechanism of releasing Ca^{2+} from internal stores, increased susceptibility to a depressive-like phenotype after chronic social defeat stress (CSDS) (Cao et al., 2013). Additionally, CSDS in rodents impaired Ca^{2+} responses and subsequent ATP release in the PFC (Cao et al., 2013), and fluoxetine treatment increased ATP release by astrocytes in the HIP (Kinoshita et al., 2018). Furthermore, transcranial direct current stimulation reduced chronic restraint stress-induced behavioral abnormalities in mice, as well as increased cortical astrocyte Ca^{2+} signaling (Monai et al., 2016). Serotonin-selective reuptake inhibitor (SSRI) antidepressants also increase Ca^{2+} signaling in PFC astrocytes regardless of neuronal activity, suggesting a direct effect of SSRIs on astrocytes, which express certain serotonin receptor subtypes (Schipke et al., 2011). Finally, multiple studies of

chemogenetic activation or attenuation of Ca^{2+} signaling in astrocytes have demonstrated an influence on both neuronal synapse activity and complex behaviors—including learning and memory, decision-making, fear conditioning, and goal-directed behavior (Kang et al., 2020; Kofuji and Araque, 2021; Nagai et al., 2021).

Astrocytes and microglia
More recently, interactions between astrocytes and other types of non-neuronal cells have been investigated. The most prominent ones are the bidirectional communications between astrocytes and microglia to regulate neuronal synapse number as stated earlier (Han et al., 2021; Vainchtein and Molofsky, 2020). For example, astrocyte-derived interleukin-33 (IL-33) promotes microglia engulfment of hippocampal synapses during normal neurodevelopment (Vainchtein et al., 2018). While this astrocyte-microglia pathway has not been directly examined in the context of stress and depression, IL-33 expression is increased in rat PFC in response to acute footshock stress (Kudinova et al., 2016), and microglia engulfment of synapses is increased after 14 days of CVS (Woodburn et al., 2021). Furthermore, females diagnosed with recurring MDD exhibited higher peripheral levels of IL-33 than females with only one episode or no history of MDD (Kudinova et al., 2016). Conversely, reactive microglia are capable of inducing a reactive astrocyte transcriptional profile (termed A1/A2 astrocytes) in vitro (Liddelow et al., 2017). The microglia-induced effect has been attributed to a combination of cytokines, such as IL-1a, tumor necrosis factor (TNF), and complement C1q (Liddelow et al., 2017). Notably, TNF and IL-1 have both been previously implicated in depression in both MDD patients and rodent models (Dowlati et al., 2010; Goshen and Yirmiya, 2009).

Astrocytes and BBB
The BBB is tightly maintained via tight junctions between adjacent endothelial cells, surrounded by pericytes and finally enwrapped by astrocyte endfeet. Indeed, nearly the entire vascular network within the brain is covered by astrocytic endfeet (Abbott et al., 2006; Lundgaard et al., 2014; Mathiisen et al., 2010; Petzold and Murthy, 2011), underscoring that astrocytes contribute importantly to the physical barrier between the periphery and brain. Increasing evidence indicates that this barrier is impaired by chronic stress in rodents and in human MDD. For example,

within the orbitofrontal cortex, immunofluorescence of AQP4 (an isoform of aquaporin that is enriched in astrocytes) revealed a 50% decreased colocalization between astrocytes and blood vessels in MDD patients (Rajkowska et al., 2013). Similar results were determined in rodents after chronic stress (Hallof-Büstrich and Di Benedetto, 2019). AQP4 expression itself is decreased in MDD (Rajkowska and Stockmeier, 2013), and single-nucleotide polymorphisms (SNPs) in AQP4 have been found in a subset of patients diagnosed with atherosclerotic disease and a comorbid depression diagnosis (Westermair et al., 2018). AQP4 expression may be regulated by pericytes; astrocytic endfeet nearby pericytes exhibit higher levels of AQP4 than those nearby endothelial cells do (Gundersen et al., 2014). Astrocytes additionally contribute to the BBB and its permeability via the release of several cytokines, chemokines, and other factors. Acute stress increases the number of astrocytes expressing IL-1β (Sugama et al., 2011). In response to IL-1β stimulation, astrocytes release vascular endothelial growth factor (VEGF), leading to greater BBB permeability and entry of leukocytes into the brain parenchyma (Rudzki and Maes, 2020). Additionally, CSDS in mice decreases endothelial cell tight junction protein claudin-5 and subsequently increases BBB permeability and the infiltration of peripheral IL-6 into the brain (Menard et al., 2017). Cell culture experiments demonstrate that astrocytes stimulated with IL-6 increase the production of cytokines associated with the recruitment of T cells to the brain (Meares et al., 2012), which could further increase BBB permeability.

Transcriptomic mapping of astrocytes in stress and depression

The earlier discussion highlights several astrocytic genes and functions that have been implicated in depressive-like phenotypes or their treatment. Genome-wide transcriptomic data identify numerous additional genes enriched in astrocytes as being among the most highly regulated in specific brain regions in mouse stress models and human MDD subjects during postmortem examination (Bagot et al., 2016; Bagot et al., 2017; Labonté et al., 2017; Pantazatos et al., 2017; Writing Committee for the Attention-Deficit/Hyperactivity et al., 2021). Gene co-expression network analysis, which clusters genes based on coordinated regulation into "modules" and identifies key hub or driver genes deduced to play a coordinating role within a module, found modules in both human MDD and mouse stress models that include large numbers of astrocyte-enriched genes (Bagot et al., 2016; Labonté et al., 2017; Pantazatos et al., 2017). Such a role for astrocyte-enriched modules was particularly prominent in NAc and mPFC. Furthermore, a correlation between differences in cortical structure and cell-type-specific transcriptomics in MDD patients revealed that the highest number of overlapping genes were astrocytic (Li et al., 2018). Changes in astrocyte gene expression occur even after acute stressors, indicating a potential role for astrocytes in the development of depression and other stress-related disorders. For example, microarray analysis after acute footshock demonstrated differentially expressed genes enriched in astrocytes from rats, with persistent changes out to 20 days post-stressor (Ponomarev et al., 2010). Furthermore, RNA-seq of the "translatome" (RNAs associated with ribosomes) in mouse cortical astrocytes revealed a robust

change in astrocytes 90 min after a forced swim test (Murphy-Royal et al., 2020). In particular, astrocytic expression of *Cxn30*—which encodes one of the major connexins for gap-junction function—was decreased. Loss of *Cxn30* and *Cxn43* has also been demonstrated in the dorsolateral PFC of individuals who died by suicide (Ernst et al., 2011). These findings together provide support for the hypothesis that stress alters gene expression in astrocytes within the NAc and mPFC and presumably other brain regions not yet investigated. The current work is focused on delineating the precise mechanisms by which regulation of such genes alters astrocyte function and consequently controls neuronal, synaptic, and circuit function to contribute to stress-related behavioral abnormalities.

Role of myeloid cells in stress disorders

Resident immune cells account for ~10% of all CNS cells. Tissue resident macrophages in the CNS, which belong to the mononuclear phagocytic system, can be divided into two subgroups: microglia (whose name stems from their relatively small soma), which are located in the parenchyma of the brain, and CNS-associated macrophages (CAMs), which are located at brain border regions (thus, also called border-associated macrophages [BAMs]), such as the meninges, choroid plexus, and perivascular spaces (Li and Barres, 2018). Of note, although microglia are the only myeloid cells within the CNS parenchyma, several other types of immune cells of both the myeloid (e.g., monocytes and neutrophils) and lymphoid (e.g., B cells and T cells) lineage populate brain border regions (Mrdjen et al., 2018). These immune cells not only interact closely with each other but they also interact with other neuronal and non-neuronal cells of the CNS and play a crucial role in tissue homeostasis under physiological conditions, development, and disease.

Role of brain-resident myeloid cells in stress action

Microglia and a majority of CAMs originate during embryogenesis from erythromyeloid progenitor cells from the yolk sac, beginning around embryonic day 7.5 in mice and gestation week 4.5 in humans (Menassa and Gomez-Nicola, 2018), although the latter is much less well characterized (Bian et al., 2020). They maintain themselves by self-renewal, with little contribution from bone marrow-derived cells in peripheral circulation (Ginhoux et al., 2010). One exception is CAMs of the choroid plexus that are replenished by peripheral monocytes through fenestrated capillaries (Goldmann et al., 2016). Microglia implant in the developing brain around the same time as early neuronal development, consistent with the view that they are important in regulating and guiding embryonic neurogenesis and neuronal migration (Prinz et al., 2021). However, this microglial-neuron interaction is not restricted to prenatal development. Under homeostatic conditions, there is bidirectional communication between the two cell types to maintain neuronal function (Koo and Wohleb, 2021). Neurons release soluble factors, such as fractalkine (CX3CL1) (Cardona et al., 2006) or colony-stimulating factor 1 (CSF1) (Elmore et al., 2014), whereas microglia release cytokines, such as IL-1β or TNF-α (Schneider et al., 1998; Stellwagen and Malenka, 2006). Microglial TNF-α has been shown to regulate activity-dependent plasticity at established functioning synapses (Stellwagen and Malenka, 2006).
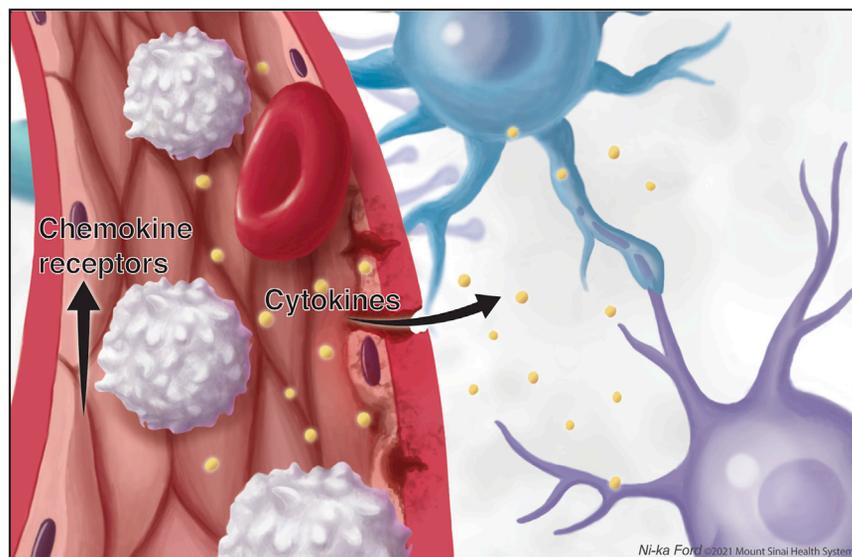
Figure 3. Stress effects on central and peripheral myeloid cells
Stress results in trafficking of peripheral monocytes (white) to the brain via upregulation of chemokine receptors. In the brain, stress leads to activation of microglia (blue) and increased secretion of cytokines and production of reactive oxygen species.

In addition to cytokines, microglia secrete several other factors, including brain-derived neurotrophic factor (BDNF), which modulates synaptic plasticity via tropomyosin-related kinase receptor B (TRKB) (Parkhurst et al., 2013). Another important aspect of microglial-neuron interactions is the ability of microglia to phagocytize synapses to shape neuronal plasticity (Wilton et al., 2019).

Microglia also play a role in surveillance and respond to a variety of stimuli indicative of changes in physiological homeostatic conditions. Thus, it is not surprising that they are involved in many pathological conditions, including the response to stress. While dynamic changes of microglia can be both neuroprotective "disease attenuating" and neurotoxic "disease promoting" (Shemer et al., 2015), early studies have shown that chronic stress changes microglia morphology, characterized by increased soma size and shorter and thicker cell processes and is associated with increased phagocytic activity in limbic brain regions, such as the PFC, HIP, and AMY (McKim et al., 2016; Tynan et al., 2010; Wohleb et al., 2011). Although phagocytic removal of apoptotic cells and cellular debris through phagocytosis from the brain is crucial to maintain brain homeostasis (Lauber et al., 2004), recent studies have shown that stress can increase phagocytic activity of microglia and thereby promotes stress-related behaviors (Figure 3). For example, Wohleb et al. (2018) demonstrated that stress-induced anxiety- and depressive-like behaviors were associated with increased expression of CSF1 gene expression in the PFC, which is necessary for development and maintenance of microglia. This increased CSF1 expression was also found in postmortem dorsolateral PFC of MDD patients compared with healthy controls. In addition, the authors described increased phagocytosis of neuronal elements and coinciding decreased dendritic spine density on apical dendrites of pyramidal neurons in the mPFC. In line with this study, CSDS increased the proportion of microglia and expressed high levels of CD68, a marker of phagocytic activity, and they displayed increased phagocytic activity in an *ex vivo* culture preparation (Lehmann et al., 2016).

Stress can also directly increase expression of several cytokines and chemokines or other damage-associated molecules in microglia (Avitsur et al., 2005). For example, a recent study using CSDS showed that microglia can be a source of reactive oxygen species, which have been associated with stress-induced behavioral changes in both rats and mice (Lehmann et al., 2019; Salim, 2014; Seo et al., 2012). Functional changes of microglia can be induced by molecules from both within the brain and from circulation. Chronic stress can activate microglia through local glucocorticoid and noradrenergic signaling (Frank et al., 2012; Iwata et al., 2013), as well as the nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3 (NLRP3) inflammasome. Microglia express pattern recognition receptors (e.g., phylogenetically conserved, germ-line encoded Toll-like receptors) (Qureshi and Medzhitov, 2003) and can thus bind pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), molecules induced in the CNS by stress (Fleshner et al., 2017). This leads to an activation of the NLRP3 inflammasome resulting in activation of the enzyme caspase-1, which proteolytically cleaves pro-inflammatory cytokines, such as IL-1β (Wohleb et al., 2016). Several forms of rodent stress have been shown to activate NLRP3 inflammasome, both via DAMPs (such as high-mobility group box 1 [HMGB1] or ATP) and PAMPs, resulting in the expression of stress-related behaviors.

One of the more exciting recent findings is that microglia can directly shape synaptic plasticity through synaptic pruning processes (Schafer et al., 2012). Synaptic pruning describes the process during development by which excessive synapses are removed in a controlled and timely manner to achieve a refined mature neural circuitry (Neniskyte and Gross, 2017). Such pruning can be regulated via the complement system where, for example, C1q or C3 expressed on immature synapses can be recognized by corresponding receptors on microglia, thereby marking them for phagocytosis (Stevens et al., 2007). Synaptic pruning continues throughout life and is thought to be an important dimension of normal synaptic and behavioral plasticity. Abnormalities in synaptic pruning have been reported in both neurodegenerative disorders, such as Alzheimer's disorder and psychiatric disorders, such as schizophrenia (Hong et al., 2016). Although synaptic pruning has been implicated in developmental changes in limbic brain regions involved in stress disorders, such as the NAc (Kopec et al., 2018), whether and how

stress-induced changes in synaptic pruning is affected across the lifespan remain to be elucidated.

Role of brain-resident myeloid cells in human stress disorders

Initially, the field hypothesized that human stress disorders and their resultant behavioral pathologies were mediated by aberrant microglia activation and increased local production of pro-inflammatory cytokines (Shelton et al., 2011; Torres-Platas et al., 2014). However, emerging studies of microglia cells in human stress disorders are far more variable, with some showing microglia activation and neuroinflammation and others showing no change or even an anti-inflammatory profile (Holmes et al., 2018; Li et al., 2018; Richards et al., 2018; Setiawan et al., 2015; Steiner et al., 2011; Su et al., 2016; Torres-Platas et al., 2014). Part of the inconsistency stems from multiple factors, including the marker used to assess microglia activation, small sample size, and postmortem factors, such as cause of death (e.g., suicide versus non-suicide). Much of what we know regarding the microglia activation in human stress disorder subjects comes from the studies using positron emission tomography (PET) with radioligands that bind to translocator protein (TSPO), a microglia- and endothelial cell-enriched protein (Albrecht et al., 2016; Enache et al., 2019; Holmes et al., 2018; Li et al., 2018; Richards et al., 2018; Setiawan et al., 2015; Su et al., 2016). Although several studies and a recent meta-analysis consistently show increased TSPO binding in MDD patients, which is interpreted as increased microglia activation, the specificity of TSPO to distinguish between activated microglia versus other cell types has come into question (Perry, 2018; Veronese et al., 2018). Postmortem molecular studies have provided important additional information to better the understanding of the mechanisms of neuroinflammation in depression, although again the studies are mixed and a more nuanced interpretation is warranted (Bayer et al., 1999; Böttcher et al., 2020; Shelton et al., 2011; Snijders et al., 2020). For example, several studies argue that microglia activation and neuroinflammation is not a ubiquitous neuropathological change defining all types of depression, but rather it only occurs in depressed patients experiencing suicidality (Steiner et al., 2011; Torres-Platas et al., 2014). Gene expression analysis of isolated microglia from postmortem brain tissue in largely non-suicidal depressed subjects did not find upregulation of markers of immune activation associated with depression (183). In fact, a recent single-cell analysis of microglia activation in MDD subjects suggests that they exhibit a "non-inflammatory" signature compared with healthy control subjects (Böttcher et al., 2020). Given the incomplete and often contradictory results observed in studies of microglia in patients with depression and related stress disorders, far more studies are needed to clarify their roles.

Brain-resident myeloid cells and oligodendrocyte interactions

Microglia also closely interact with oligodendrocytes and are important at various stages of oligodendrocyte development. For example, Nicholas et al. (2001) has shown that microglia produce soluble factors that promote oligodendrocyte development through an effect on the platelet-derived growth factor-alpha (PDGF-α) receptor-signaling pathway. A subpopulation of microglia located in the white matter of the brain contribute to myelination (Hagemeyer et al., 2017). Similar to the synaptic pruning processes described earlier, microglia can phagocytose OPCs, a process that seems to be dependent on microglia CX3CR1 (Nemes-Baran et al., 2020). Interestingly, although there is clear evidence from both preclinical animal models and human postmortem studies that stress disorders, such as MDD, are associated with impaired myelination (Liu et al., 2012; Lutz et al., 2017), it is still unknown whether this is due in part to increased phagocytosis of OPCs by microglia.

Peripheral myeloid cells in stress disorders

It is now well accepted that a subset of patients with stress-related disorders show increased peripheral immune system activation (Cathomas et al., 2019; Dantzer et al., 2008). Early studies mainly focused on the role of peripheral cytokines in mediating stress-relevant behaviors, which has, analogous to the "monoamine hypothesis of depression," led to the "cytokine hypothesis of depression" (Hodes et al., 2015a; Raison et al., 2006). Although cytokines are mainly produced by cells of the immune system, several other cell types in the periphery (adipocytes, hepatocytes) and CNS (neurons, astrocytes) also produce cytokines (Turner et al., 2014).

Studies investigating the interaction between peripherally derived cytokines of the immune system with the brain in preclinical mouse models have mainly used two different strategies: (1) activation of the immune system by administration of exogenous immune system activators, such as the bacterial endotoxin lipopolysaccharide (LPS), and (2) mouse models of social stress that produce strong elevations of systemic inflammation. Both the preclinical stress studies and the studies of human stress disorder patients have pointed toward a major disturbance in peripheral myeloid cells (i.e., monocytes and neutrophils). Social stress mobilizes bone marrow-derived peripheral myeloid cells into circulation (Heidt et al., 2014; Powell et al., 2013). Several studies using transcriptional analysis of peripheral blood in humans with depression or related stress disorders have revealed important transcriptional changes indicative of systemic immune disturbances (Glahn et al., 2012; Jansen et al., 2016; Leday et al., 2018; Mostafavi et al., 2014; Savitz et al., 2013; Spijker et al., 2010; Yi et al., 2012). In the largest RNA-seq study to date (almost 500 cases and controls), Mostafavi et al. (2014) showed that the interferon α/β pathway was among the most highly regulated in MDD subjects. Leday et al. (2018) compared data from two different whole blood microarray datasets and showed that 90 genes that were upregulated in both cohorts were significantly enriched for the gene ontology (GO) term "immune response to infection." Most genes were affiliated with the gene network specialized for innate immune response, including neutrophils, monocytes, and dendritic cells. Interestingly, the downregulated genes were enriched for GO terms related to T cell function and adaptive immunity and clusters of strongly co-expressed genes were enriched in T cells, B cells, and NK-cells (Leday et al., 2018). These findings indicate that peripheral immune system dysfunction is associated with both activation of the innate immune system and relative suppression of the adaptive immune system.

In addition to these peripheral effects, animal models show that pro-inflammatory monocytes traffic to the brain in a CCL2/CCR2-dependent manner (Figure 3): genetic deletion of *Ccr2*

prevented the recruitment of monocytes to the brain and associated stress-induced behavioral changes (Wohleb et al., 2013). Importantly, there is a close interaction among microglia, BBB endothelial cells, and peripheral monocytes. In fact, microglia can actively recruit peripheral monocytes, through an IL-1β-dependent mechanism, to stress-sensing brain regions where they regulate anxiety-like behaviors (McKim et al., 2018). Depletion of microglia with the CSF1R inhibitor plexxikon prevents such monocyte trafficking and anxiety-like behavior. A subsequent study confirmed the important role of endothelial IL-1 signaling in mediating sickness behavior: endothelial IL-1R1 was necessary and sufficient for mediating sickness behavior and monocyte recruitment to the CNS, whereas ventricular IL-1R1 was critical for monocyte recruitment to the CNS (Liu et al., 2019).

Another important cytokine associated with stress-induced behavioral alterations is IL-6. Together with TNF-α, IL-6 is the cytokine most consistently elevated in circulation of patients with stress disorders (Dowlati et al., 2010; Miller et al., 2011). CSDS increases peripheral IL-6 specifically in susceptible mice, with no effect seen in resilient mice that are subjected to the same stress but avoid most behavioral abnormalities (Hodes et al., 2014). Both IL-6 neutralization with a systemically administered antibody and depleting IL-6 from bone marrow-derived leukocytes prevented susceptibility (Hodes et al., 2014). This was one of the first studies causally linking stress-induced cytokine changes in the periphery with behavioral alterations. Although cytokines have extensively been shown to be increased in stress disorders, our knowledge of the exact mechanisms is sparse. Most neuronal and non-neuronal cells in the brain express cytokine receptors and several potential pathways have been proposed to link peripheral inflammation and neuronal function. One candidate pathway is tryptophan, the precursor of serotonin, and its catabolites (referred to as TRY-CATs) (Savitz, 2020). Cytokines activate several enzymes of the kynurenine pathway, which are derived from tryptophan, not only depleting tryptophan but also leading to neuroactive catabolites affecting dopamine and glutamate (Savitz, 2020). Song et al., for example, demonstrated that systemic administration of IL-6 decreases extracellular levels of dopamine in the NAc (Song et al., 1999). A potential mechanism downstream of IL-6 important for its behavioral effects is the NFκB signaling pathway. Previous studies demonstrated that NFκB signaling is activated by IL-6 in the NAc of susceptible mice following CSDS. Neuronal NFκB is necessary for increased excitatory synaptic plasticity induced by CSDS (Christoffel et al., 2011, 2015; Hodes et al., 2016). Pro-inflammatory cytokines, such as IL-6, TNF, and IL-1β, also have a direct effect on stress-evoked changes in neurogenesis and neuronal differentiation, suggesting that inflammatory signaling may play a broad role across multiple brain regions and neuronal cell types to regulate maladaptive plasticity (Borsini et al., 2015; Levin and Godukhin, 2017). Although beyond the scope of the current review, it is important to note that neurons express a large number of cytokine receptors themselves; thus, their function can be directly modulated by cytokines from both within the CNS and from the periphery (Salvador et al., 2021). The importance of such interactions in stress-related disorders was recently described by DiSabato et al.

(2021), where they showed that IL-1R1 on glutamatergic neurons in the HIP were causally linked to stress-induced impairments in social interaction and working memory deficits. Future work to more broadly define additional neuroimmune mechanisms across brain regions and cell types is needed.

Role of the endothelial barrier in stress disorders

The CNS has traditionally been viewed as an immune-privileged organ (Galea et al., 2007). However, there is increasing evidence that the brain interacts extensively with the peripheral immune system, both directly and indirectly (Louveau et al., 2015). The BBB tightly controls the bidirectional communication between the CNS and the peripheral circulation and is therefore vital for brain protection and function. This complex selective interface—referred to as the neurovascular unit—consists of several specialized cell types: non-fenestrated brain endothelial cells that are characterized by highly specific tight junctions sealing the para-cellular space, pericytes, and smooth muscle cells that play a major role in controlling the cerebral blood flow, and astrocytic endfeet covering most of the vasculature (Abbott et al., 2010). The immune system and BBB are tightly intertwined (Abbott, 2000). Although under physiological conditions, most peripheral cytokines or immune cells cannot penetrate the BBB or depend upon specialized transporters regulating their passage, pathological conditions, such as acute or chronic inflammatory states, can lead to increased BBB leakiness (Abbott, 2000).

The BBB in stress and depression

Although early studies in mouse models showed that inflammation (e.g., via TNFα) compromises BBB integrity (Danielski et al., 2018), animal studies linking BBB dysfunction to depression-like behaviors have only recently been performed. Menard et al. showed that CSDS in stress-susceptible but not stress-resilient mice downregulated the endothelial tight junction gene and its protein product claudin-5 (Menard et al., 2017). This results in the disruption of the BBB, allowing for the influx of potentially neurotoxic proteins, such as peripheral IL-6. Claudin-5 gene expression was also shown to be downregulated in postmortem tissue from patients with MDD (Dudek et al., 2020; Menard et al., 2017). Interestingly, there is a sex-specific effect of stress on the BBB, where female mice exhibit endothelial damage and BBB permeability in the frontal cortex and NAc, whereas males only exhibit such damage in the NAc (Dion-Albert et al., 2022). In both cases, however, BBB damage is dependent upon a loss of endothelial integrity via downregulation of claudin-5 (Figure 4). Claudin-5 downregulation exhibits sex-specific effect in postmortem human PFC and NAc of MDD subjects similar to mice following chronic stress. The link among stress, systemic inflammation, and BBB permeability was further substantiated in a study showing that hippocampal BBB permeability was increased in mice that underwent learned helplessness and that BBB permeability and behavioral abnormalities could be reversed by systemic injection of a TNFα inhibitor (Cheng et al., 2018).

In humans, BBB permeability can be assessed by neuroimaging to directly visualize infiltration of contrast dyes into the brain parenchyma or by indirect measures to examine the concentration of plasma versus cerebrospinal fluid (CSF) proteins (Heye et al.,
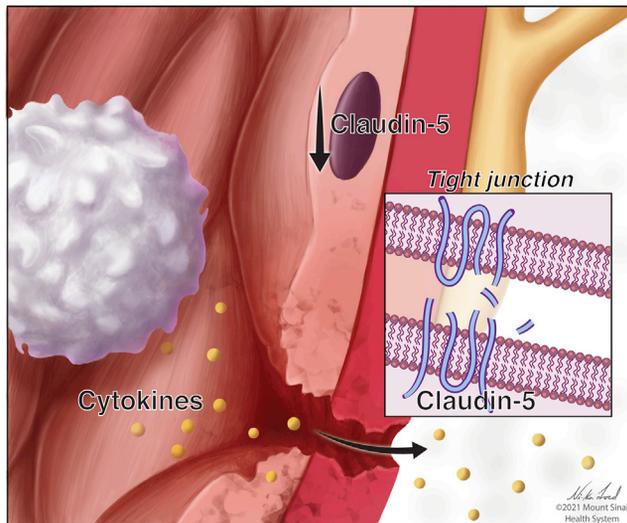
Figure 4. Stress impairs function of the blood-brain barrier (BBB)
Stress leads to a damage of endothelial cells (brown), including brain-region-specific downregulation of the tight junction protein claudin-5 (inset), resulting in an increased permeability of the BBB and infiltration of peripheral factors, such as cytokines.

2014; Marchi et al., 2003). To our knowledge, no study has thus far investigated BBB differences in MDD patients versus controls using neuroimaging approaches. Therefore, the evidence linking neurovascular dysfunction and MDD stems from the studies that have used indirect measures, such as examining vascular markers in circulation or ratios between blood and CSF proteins, such as the CSF albumin/serum albumin quotient (Andersson et al., 1994). Because albumin is not synthesized centrally, albumin measured in CSF stems from the circulation, and this measure can therefore be used as a proxy to assess blood-CSF or BBB dysfunction. In a study performed in elderly women, those with MDD had a higher CSF/serum albumin ratio (Gudmundsson et al., 2007). Another peripheral marker of BBB dysfunction is S100β. This Ca^{2+}-binding protein, which is mainly expressed in glial cells, is normally not detectable in serum; however, it is elevated in the presence of BBB damage (Kanner et al., 2003). To date, several studies have reported increased levels of S100β in patients with MDD compared with controls and have shown associations with treatment response to antidepressants (Ambrée et al., 2015; Polyakova et al., 2015; Schroeter et al., 2002). The related protein, S100A10 (also known as p11), is highly enriched in endothelial cells in humans and also implicated in MDD and antidepressant action (Milosevic et al., 2017). In a recent prospective cohort study, low-grade inflammation (assessed by CRP, serum amyloid A [SAA], intercellular adhesion molecule 1 [ICAM-1], IL-6, IL-8, and TNF-α) and endothelial dysfunction (assessed by vascular cell adhesion molecule 1 [VCAM-1], E-selectin, von Willebrand factor [VWF], and ICAM-1) were associated with depressive symptoms, whereas endothelial dysfunction was further associated with chronicity of depressive symptoms (Janssen et al., 2021). In addition, an early study showed increased markers of BBB permeability in MDD compared with controls (Niklasson and Agren, 1984). In summary, since there is a bidirectional interaction between peripheral inflammation and endothelial cell func-

tion, it can be hypothesized that both contribute to the etiology and pathophysiology of MDD.

Role of oligodendrocyte lineage cells in stress disorders

OL cells include several unique cell subtypes that differ at the transcriptional, morphological, and functional level. OL cells are the only myelinating cell type in the CNS. They are characterized by a specialized membrane, called myelin, with a unique proteolipid composition and the ability to wrap around axons, thereby creating areas of insulated axonal segments called internodes (Baumann and Pham-Dinh, 2001; Simons and Nave, 2015). The discrete regions between internodes, called nodes of Ranvier, are characterized by high expression levels of voltage-gated Na^+ channels and other specialized proteins, which together mediate saltatory conduction of action potentials. Myelinating OL cells also serve a main role in providing metabolic support to neurons. During development, OL cells are generated from neonatal OPCs, which continue to persist in the adult brain. OPCs are very dynamic and electrically responsive, characterized by the ability to proliferate, migrate, and differentiate in response to neural activity. They respond to signals from glutamatergic, GABAergic, and potentially other neuronal subtypes.

OL cells respond to stressful events throughout the lifespan

There is a large literature, both in humans and rodents, supporting the age-dependent response of myelin and OL cells to distinct types of stressors. Evidence ranges from MRI and histological studies in postmortem human or rodent brains to transcriptional studies using punch biopsies or sorted cells from human brains or animal models. Within the prenatal and neonatal periods, exposure to parental stress has been shown to alter white matter microstructures in the frontal lobe (Dean et al., 2018) and AMY (Rifkin-Graboi et al., 2013) of infants from mothers with reported depression and anxiety symptoms. Additional reports further validated the concept that developmental myelination of neural tracts is negatively impacted by maternal depression (Posner et al., 2016; Scheinost et al., 2016) or exposure to stress (Lautarescu et al., 2020), highlighting the importance of myelination in favoring the development of connectivity involved in emotional regulation. Important information on the role of early life exposure to stress and the development of psychiatric symptoms in adulthood are also emerging from studies on preterm babies (Lammertink et al., 2020). Although recent evidence argues against a generalized effect of prematurity on overall volume of brain structures (Lautarescu et al., 2021), it is becoming clear that prematurity and exposure to the stressful environment of the neonatal intensive care unit interfere with autonomic nervous system development and especially with myelination of vagal fibers from the nucleus ambiguus (Porges and Furman, 2011; Sachis et al., 1982), which may in part explain the higher propensity for long-term dysregulation of vagal inhibitory control over heart rate and respiration detected in individuals who were born preterm. In addition, evidence supporting the critical role of stress during the period of developmental myelination includes studies on maternal

separation reporting aberrant PFC myelin formation (Carlyle et al., 2012; Yang et al., 2017).

Childhood and adolescence are periods of significant risk related to the impact of stress on OL cell development and function. Imaging studies in children subjected to the stress of institutionalization revealed correlations between white matter changes detected by MRI and time spent in orphanages prior to adoption (Govindan et al., 2010; Kumar et al., 2014). Studies of adoptees highlighted reduced size of major white matter tracts, such as corpus callosum, as potentially related to behavioral adjustments of children to their new environment (Mehta et al., 2009). The long-term consequences of early life stress on white matter abnormalities have been shown to persist into adulthood in the brains of MDD subjects (Choi et al., 2009, 2012; Hanson et al., 2015; Lutz et al., 2017; Siehl et al., 2018; Tanti et al., 2018). Furthermore, other forms of stressful experience in adolescence, such as social isolation or sleep deprivation, significantly impact adolescent white matter tract development (Jamieson et al., 2021a, 2021b). The functional consequences of these alterations during such a critical period for psychological and emotional development is just beginning to be elucidated but are likely to be catastrophic, as indicated by high rates of suicide among teenagers associated with early stress exposure (Mayne et al., 2021). In summary, stressful experience during critical developmental periods in humans severely impairs white matter tract development in the PFC, a finding that is consistent with previous reports in rodents (Liu et al., 2012; Makinodan et al., 2012).

Most of the literature on the effect of stress on white matter integrity in the adult brain refers to alterations detected in patients with MDD or other stress-related disorders, such as PTSD or anxiety disorders, with results consistently showing decreased myelin content in frontal cortical circuitry (Baur et al., 2011; Murphy and Frodl, 2011; Phan et al., 2009; Sacchet and Gotlib, 2017), as well as in the corpus callosum and thalamic tracts (Gunning-Dixon et al., 2008; Kumar et al., 2004; Miyata et al., 2016; Siehl et al., 2018). Histopathological studies of postmortem brains from stress disorder subjects are largely consistent with in vivo imaging findings: they show reduced myelin content, fewer oligodendrocyte cells, reduced levels of myelin gene transcripts, and in some cases micro-alterations in the length of the internodal segments (see further on) (Aston et al., 2005; Boda, 2021; Hamidi et al., 2004; Hayashi et al., 2011; Miyata et al., 2016; Rajkowska et al., 2015; Seney et al., 2018; Tham et al., 2011; Williams et al., 2019). The relationship between demyelination in areas of the limbic system and depressive symptoms was suggested by studies in multiple sclerosis (MS) patients, who display increased risk of depression and anxiety (Habek et al., 2006; Pham et al., 2018; Rocca et al., 2018; Sanders and van Lieshout, 1992; Simpson et al., 2016). Moreover, stress is known to alter the course of MS, including precipitating relapse during symptom remittance and exacerbation (Ackerman et al., 2002; Buljevac et al., 2003; Mitsonis et al., 2008). Exposure of adult mice to CVS, social isolation, or CSDS also revealed overall decreased myelin transcript levels (Bonnefil et al., 2019; Lehmann et al., 2017; Liu et al., 2012, 2018), although important differences were observed between the distinct stress models. The most notable difference is the reported number of neuron glial antigen 2+ (NG2+) OPCs, which was found to be reduced in CVS models (Banasr et al., 2007; Liu et al., 2018; Yang et al., 2016) but increased in susceptible mice following CSDS (Bonnefil et al., 2019). The functional relevance of these differences have yet to be elucidated. OPCs in the brains of stressed mice were also characterized by the presence of abnormal histone marks, suggestive of an overall defective mechanism of epigenetic repression (71). Interestingly, a recent transcriptomic analysis of single nuclei isolated from the PFC of MDD subjects identified a cluster of immature OPCs with dysregulated gene expression (Nagy et al., 2020). This cluster included a profile indicative of a very immature population of OPCs, displaying higher levels of transcripts and the immature OPCs were previously reported to be downregulated during differentiation into OL cells by repressive histone marks (Liu et al., 2015).

Mechanisms of dysregulation in OL cells in response to stress

As shown in Figure 5, stress affects myelination in three ways: (1) myelin loss or reduced thickness of existing sheath, (2) impaired "de novo" myelination and OPC differentiation, or (3) adjusted internodal length. Although these changes may all have been detected in distinct studies, they do not necessarily occur in concert. Human studies provide ample evidence for the integrity of myelin, as well as transcriptional alterations in stress disorders, whereas animal studies provide further characterization of the ultrastructural alterations of white matter tracts and dysregulated OL cell population dynamics, thereby suggesting several potential explanations of the effect of stress on this lineage. The mechanisms underlying each type of change in myelin require investigation.

Inflammatory mechanisms of myelin and OL cell loss in response to stress

The link between demyelinating disorders, such as MS, and depression suggests that dysregulation of the immune system and elevated levels of pro-inflammatory cytokines may be a common mechanism between them (Beurel et al., 2020; Pucak et al., 2007). Pro-inflammatory cytokines, released by T cells and astrocytes, such as interferon-gamma (IFNγ) and IL-17, have been shown to inhibit the ability of OPCs to exit from the cell cycle and differentiate (Balabanov et al., 2007; Pucak et al., 2007; Wang et al., 2017a), while promoting their ability to serve as putative antigen-presenting cells and eventually leading to apoptosis (Wang et al., 2017a). An additional signal responsible for decreased progenitor numbers and impaired differentiation into myelinating cells is the upregulation of death receptor 6 (DR6), a member of TNF receptor superfamily, in OPCs in mice exposed to chronic stress (Yang et al., 2016). OL cells may also be a direct target for T-cell-derived metabolites induced by stress, such as xanthine, a purine derivative elevated in patients with MDD and in mice exposed to chronic stress (Ali-Sisto et al., 2016; Fan et al., 2019). Using metabolic profiling along with single-cell transcriptomics, it was reported that CD4+ T-cell-derived xanthine acts directly on OPCs in the AMY via adenosine A1 receptors whose activation promoted OPC proliferation and resulted in a reduced number of mature OL cells (Fan et al., 2019). Silencing A1 receptor specifically in OL cells rescued anxiety-like behavior,
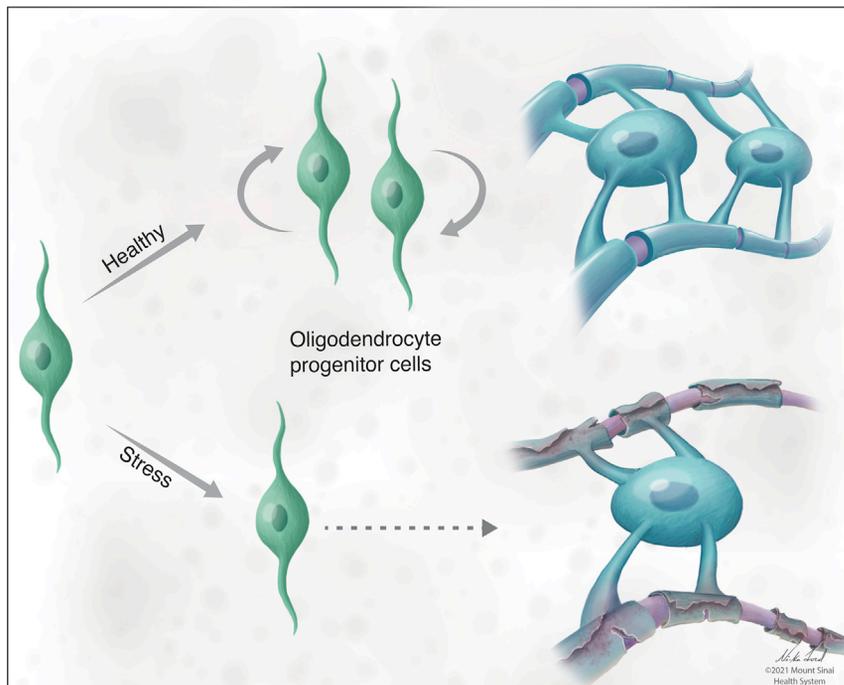
Figure 5. Stress effects on oligodendrocyte lineage (OL) cells
Stress induces brain-region-specific impairments of myelination that is a result of reduced OL cell differentiation and maturation potentially through mechanisms, such as oxidative stress or immune dysregulation in the periphery.

a well-known regulator of myelination (de Faria et al., 2019). Neuronal activity induces OPC proliferation, differentiation, and *de novo* myelination (de Faria et al., 2019; Gibson et al., 2014) and also affects the stability of newly formed myelin sheaths on axons (Gibson et al., 2014; Mensch et al., 2015). Conversely, decreasing neuronal activity with pharmacological treatment or optogenetics leads to reduced OPC proliferation, lower number of myelinating OL cells, and overall decreased *de novo* myelination (Demerens et al., 1996; Mensch et al., 2015; Wake et al., 2011). The reported loss of excitatory synapses in frontal cortex of MDD patients and animal stress models (Duman and Aghajanian, 2012; Liu et al., 2017) may be related to the reduced OL cells and myelin content in conditions of chronic stress. The concept is perhaps best exemplified in the model of social isolation of juvenile mice, which is associated with reduced excitatory synaptic inputs on PFC pyramidal neurons and with hypomyelinated neurons (Makinodan et al., 2012, 2017; Tan et al., 2021; Yamamuro et al., 2018). Conversely, enriched environments that promote stress resilience increase PFC neuronal activity and promote myelinogenesis (Goldstein et al., 2021; Nicholson et al., 2020). However, when stress is experienced during certain critical developmental period, environmental enrichment is not capable of restoring impaired myelination (Makinodan et al., 2012), which might due in part to premature OPC differentiation that exhausts the pool of existing progenitor cells in adulthood (Teissier et al., 2020).

At a molecular level, impaired OPC differentiation as detected in stress disorder patients and in animal stress models can be partly explained by alterations of the epigenome and consequent changes in gene expression. For instance, whole genome DNA methylation profiles in the ACC of MDD individuals with a history of child abuse identified altered DNA methylation in OL lineage genes and a global impairment of the OL-related transcriptional program (Lutz et al., 2017). Aberrant nuclear chromatin structure and altered expression levels of histone modifiers were also reported in OL cells in the PFC of socially isolated mice (Liu et al., 2012), whereas treatment with clemastine, a muscarinic receptor antagonist, promoted histone methyltransferases activity and was sufficient to restore myelination and social behavior (Liu et al., 2016). Reduced heterochromatin content and repressive histone marks were also detected in mice susceptible to CSDS, but not in resilient mice (Bonnefil et al., 2019), suggesting that stress may disrupt the epigenetic program in OL cells,

even in mice with elevated levels of xanthine, providing a direct link between T cell metabolism and OL cells in stress-driven anxiety-like behavior. Finally, oxidative stress, consequent to microglia activation and inflammation, is frequently detected both in MDD (Spaas et al., 2021; Yirmiya et al., 2015) and in MS (Lassmann and van Horssen, 2016; Schuh et al., 2014) brains. This is of relevance because oxidative DNA damage and protein and lipid peroxidation in OL cells (Giacci and Fitzgerald, 2018; Jana and Pahan, 2007) impair OPC maturation (French et al., 2009) and lead to decreased levels of myelin and lower numbers of oligodendrocytes. As mentioned earlier, pro-inflammatory cytokines can diffuse into the brain of stressed individuals due to stress-induced neurovascular damage and increased BBB permeability (Menard et al., 2017). Whether or not OL cells play a role in the effects of stress on BBB permeability remains unknown; however, a recent study linked OPC-derived matrix metalloproteinase 9 (MMP9) to BBB opening and neutrophil infiltration in early stages of white matter injury (Seo et al., 2013).

Impaired "*de novo*" myelination and OPC differentiation in response to stress

Decreased OL cell number and impaired OPC differentiation are commonly observed in MDD patients and stressed animals (Bonnefil et al., 2019; Hamidi et al., 2004; Liu et al., 2016; Yang et al., 2016) and several mechanisms, including hormonal signals and neuronal activity, have been implicated. Glucocorticoids and their receptors are expressed by both OPC and OL cells (Matsusue et al., 2014) where they have been shown to inhibit OPC proliferation (Alonso, 2000) and induce abnormal branching of OL cells (Miyata et al., 2011). A separate mechanism, possibly relevant to decreased myelin levels in animals and humans subjected to social isolation, is decreased neuronal activity, which is

thereby promoting maladaptive behavioral consequences in susceptible individuals.

Remodeling of internodes in response to stress

Micro-alterations of myelin structure have been reported in several animal stress models. Shorter internodal length was detected in mice susceptible to CSDS and was significantly correlated with social interaction behavior (Bonnefil et al., 2019). The length of nodes of Ranvier, as well as their boundary regions, the paranode, was shortened in mice subjected to chronic restraint stress (Miyata et al., 2016). This was characterized by a diffused distribution of contactin-associated protein (Caspr) and the voltage-dependent K$^+$ channel Kv1.1, suggesting a disruption of axon-myelin adhesion. Interestingly, in socially isolated adult mice, expression of neuronal-specific nodal and paranodal genes was unaffected, whereas expression of OL cell-specific paranodal genes was decreased in the PFC (Liu et al., 2012), suggesting a cell-type-specific response.

Summary and future directions

As discussed throughout this review, important advances have been made recently in uncovering the role of non-neuronal cells in stress-related disorders, such as MDD and PTSD. However, it is also clear that the field needs a far better understanding of non-neuronal mechanisms, both under normal and pathological conditions. Available data suggest that non-neuronal mechanisms play very diverse roles in brain function. In astrocytes, studies have confirmed that stress alters their number and morphology and influences their interactions with neurons, microglia, and the BBB. Although we continue to learn about the roles of astrocytes in brain function, there remains many unknowns regarding the true extent of their involvement in stress-related illnesses. Both peripheral and central myeloid cells (monocytes and microglia), through interactions with several other non-neuronal cell types, play crucial roles in mediating stress-induced effects on brain and behavior, although much additional research is needed. For example, a majority of the studies that characterize microglia state after stress still use relatively simple markers of activation or classification approaches, such as M1 (i.e., activated, pro-inflammatory) versus M2 (i.e., anti-inflammatory) phenotypes, which do not account for the complexity and heterogeneity of these resident immune cells (Borsini et al., 2015). Additionally, we need a better understanding about how peripheral monocytes interact with the brain. Although evidence suggests that they are recruited to the brain endothelium and may initiate endothelial-specific inflammatory signaling to the brain, several important questions remain. For example, do they play a direct role in stress-induced disruption of endothelial cells? Are they actively trafficked to specific places within the brain endothelium and is this why stress seems to affect the BBB in some but not all brain regions? We know from recent single-cell RNA-sequencing (scRNA-seq) studies that the gene expression signature of endothelial cells is highly dependent on the size and type of blood vessel and brain region. However, we do not know how these translate to the observed differences in BBB leakiness in the context of stress disorders. Finally, the evidence suggests that impaired myelination by oligodendrocytes in response to stress associates with stress-induced behavioral and neuronal al-

terations, which is consistent with the idea that stress-related signals eventually cause loss of myelin in areas related to emotional regulation and executive function. These signals may include oxidative stress or cytokine signaling from the periphery, resulting in a myelinotoxic environment in the brain. In contrast, the regional specificity (i.e., within PFC) of stress-induced myelination defects appears to challenge such an interpretation, given that research has shown little BBB damage or subsequent peripheral cytokine infiltration in the PFC. The recent identification of immature OPC transcriptional signatures in PFC of MDD subjects and stressed mice (Bonnefil et al., 2019; Liu et al., 2012; Nagy et al., 2020; Seo et al., 2013) may suggest that stress affects epigenetic mechanisms intrinsic to OPCs. Whether or not such OL cell dysfunction is causally linked to the onset of depression remains an active area of investigation. In sum, although non-neuronal cells are likely to be key factors in stress-related disorders, there are many gaps in the preclinical and clinical literature, including the need for a much broader understanding of non-neuronal perturbations in both sexes throughout the brain and periphery. Further on, we have highlighted important avenues for future investigation.

One important aspect of future research will be the identification of blood and CSF biomarkers with high sensitivity and specificity to detect and quantify alterations in non-neuronal cells. While a few biomarkers, such as astrocyte-derived S100B and endothelial cell adhesion molecules exist, several open questions need to be addressed: Are these markers that have mainly been used in disorders, such as traumatic brain injury or MS, sensitive enough to measure the more subtle changes associated with stress disorders? How specific are these biomarkers given that although enriched in certain cell types, they could also be derived from sources outside the CNS, e.g., S100B from adipocytes (Gonçalves et al., 2010)?

Another important avenue of research is the development of novel *in vivo* neuroimaging techniques in both rodents and humans to assess non-neuronal cells with far greater precision and specificity. Currently, most approaches utilized to date are not able to specifically identify individual cell types; one example is the use of radiolabeled ligands binding to the TSPO (Notter et al., 2018), which are incapable of distinguishing between astrocytes, microglia and endothelial cells. In addition, existing neuroimaging modalities, such as PET and MRI, could be better integrated with blood-based biomarkers and clinical and behavioral phenotyping to obtain much higher resolution clinical information about the role of non-neuronal cells in stress disorders.

Ultimately, the development and application of tools to manipulate non-neuronal cells in preclinical animal models is crucial to establish causal mechanisms. Indeed, recent advances have been made to enable the cell-type-specific genetic manipulation of non-neuronal cells with transgenic Cre driver lines and viral vectors (Dumas et al., 2021; Galichet et al., 2021; Yu et al., 2020). Studies have also begun to apply optogenetic and chemogenetic approaches to manipulate non-neuronal cells. Much of the work to date has focused on astrocytes and have utilized designer receptors exclusively activated by designer drugs (DREADDs) to regulate Ca^{2+} signaling (Yu et al., 2020). Activation of astrocytes using Gq DREADDs in the central AMY decreased the firing rate of neighboring neurons and reduced fear expression in a fear-conditioning paradigm (Martin-

Fernandez et al., 2017). Although limited, some studies are beginning to apply these approaches to other non-neuronal cells, including bone marrow-derived immune cells (Bohineust et al., 2020). Such work has shown that optogenetic activation of T cells can alter intracellular Ca^{2+} signaling, T cell migration, adhesion, and chemokine release. While much more work is needed, such approaches offer promising new avenues for controlling non-neuronal cells throughout the body.

A major need in the field is to understand the extent to which sex differences in non-neuronal cells influences the ~2-fold greater risk for stress disorders in girls and women. Several early lines of evidence from large-scale transcriptomic studies described earlier point to a host of sex differences in non-neuronal cell types throughout the brain and body. For example, as mentioned earlier, data from rodent stress models point toward sex differences in endothelial dysfunction after stress. The importance of such sex differences in the behavioral response to stress have yet to be elucidated, including whether PFC damage in females is associated with more profound disturbances in PFC-dependent behaviors than what is observed in males. From a therapeutic perspective, we will need to gain a very high-dimensional understanding of non-neuronal mechanisms perturbed in stress disorders if we aim to develop personalized medications optimized for the unique physiology of women versus men. Novel molecular tools, such as brain-region-specific scRNA-seq, should be applied to appropriately identify stress-related phenotypic signatures. Advanced bioinformatic analyses integrating multimodal "omics" data will be required to elucidate underlying mechanisms.

Lastly, the field continues to struggle with development and validation of preclinical models of complex behavior with greater translational relevance to human disease. We need to double down and advance efforts in this area. There has been some early successes in developing cross-species effort-based models that tap into a limited number of key behavioral domains disrupted in human stress disorders, but we need a much broader array of these tests to reflect the highly complex biological and behavioral domains disrupted in MDD and related disorders. Studies should assess multiple stress paradigms in both sexes to elucidate shared and dissociable mechanisms underlying the effects of stress on non-neuronal cell types and pathways. Such advances in combination with a better understanding of the non-neuronal cellular and molecular perturbations that define stress disorders will usher in a new era of discovery efforts to conquer these debilitating illnesses.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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