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Special Section on Sexual Dimorphism in Neuroimmune Cells

Neuroimmune Mechanisms and Sex/Gender-Dependent Effects in the Pathophysiology of Mental Disorders

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ABSTRACT

Innate and adaptive immune mechanisms have emerged as critical regulators of CNS homeostasis and mental health. A plethora of immunologic factors have been reported to interact with emotion- and behavior-related neuronal circuits, modulating susceptibility and resilience to mental disorders. However, it remains unclear whether immune dysregulation is a cardinal causal factor or an outcome of the pathologies associated with mental disorders. Emerging variations in immune regulatory pathways based on sex differences provide an additional framework for discussion in these psychiatric disorders. In this review, we present the current literature pertaining to the effects that disrupted immune pathways have in mental disorder pathophysiology, including immune dysregulation in CNS and periphery, microglial activation, and disturbances of the blood-brain barrier. In addition, we present the suggested origins of such immune dysregulation and discuss the gender and sex influence of the neuroimmune substrates that contribute to mental disorders. The findings challenge the conventional view of these disorders and open the window to a diverse spectrum of innovative therapeutic targets that focus on the immune-specific pathophenotypes in neuronal circuits and behavior.

SIGNIFICANCE STATEMENT

The involvement of gender-dependent inflammatory mechanisms on the development of mental pathologies is gaining momentum. This review addresses these novel factors and presents the accumulating evidence introducing microglia and proinflammatory elements as critical components and potential targets for the treatment of mental disorders.

Introduction

Psychiatric or mental disorders include several syndromes manifested through physiologic, behavioral, emotional, and cognitive symptoms. Over a billion people worldwide suffer from mental disorders, with anxiety-related disorders, major depressive disorder (MDD), bipolar disorder (BD), post-traumatic stress disorder (PTSD), and schizophrenia (SCZ) accounting for more than 80% GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018). The World Health Organization estimates that the global burden of mental disorders translates to ~32% of years lived with disability (Vigo et al., 2016), as the current pharmacotherapies prove ineffective for up to 50% of patients (Pfau et al., 2018). Insufficient understanding of underlying disease mechanisms as well as gender influence in disease manifestation is thought to cause the observed treatment resistance.

A growing body of evidence suggests that neuroimmunologic processes affect both neuronal integrity and neuropathology, revealing new targets for the development of effective therapeutics (Russo and Nestler, 2013; Miller et al., 2017; Pape et al., 2019). Multiple clinical studies have reported through genome-wide association studies (GWASs) (Howard et al., 2019; Marques et al., 2019) and postmortem histopathological

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ABBREVIATIONS: ACC, anterior cingulate cortex; ACTH, adrenocorticotropic hormone; AMY, amygdala; BBB, blood-brain barrier; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CRH, corticotropin releasing hormone; CRP, C-reactive protein; CSF, cerebrospinal fluid; EAAT, excitatory amino acid transporter; GR, glucocorticoid receptor; GWAS, genome-wide association study; HPA, hypothalamic-pituitary-adrenal; HPC, hippocampus; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IL, interleukin; KYN, kynurenine; MAPK, mitogen-activated protein kinase; MDD, major depressive disorder; MHC, major histocompatibility complex; PFC, prefrontal cortex; NF-κB, nuclear factor–κB; NMDAR, *N*-methyl-D-aspartate receptor; PD, panic disorder; PET, positron emission tomography; PTSD, post-traumatic stress disorder; ROS, reactive oxygen species; RSDS, repeated social defeat stress; SCZ, schizophrenia; SERT, serotonin reuptake transporters; SNS, sympathetic nervous system; SSRI, selective serotonin reuptake inhibitor; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; TSPO, translocator protein.

findings (Mechawar and Savitz, 2016) that many patients with mental disorders exhibit chronic inflammation and immune system dysregulation accompanied by increased peripheral and central nervous system (CNS) inflammatory markers (Sandiego et al., 2015; Goldsmith et al., 2016; Wohleb et al., 2016).

Here, we provide an overview of the interplay between neuroinflammation and CNS homeostasis during neuropsychiatric dysfunctions. CNS neuroinflammation is predominantly initiated by the resident immune macrophage-like cells, the microglia, along with brain macrophages and astrocytes (Prinz and Priller, 2014). We discuss upstream causes of immune dysregulation in mental disorders, focusing on recent insights suggesting that inflammatory mechanisms are implicated in the mental disorder pathophysiology. We also summarize the sex and gender effects upon mental disorder prevalence and severity through the prism of neuroinflammatory mechanisms and suggest the necessity to take them into account in mental disorder therapeutics.

Neuroimmune Interactions in Brain Homeostasis

The CNS has been considered an "immune-privileged" system guarded by the blood-brain barrier (BBB) (Forrester et al., 2018). Despite its protection, the brain exhibits significant immunologic properties and is in constant interaction with the peripheral immune system (Pape et al., 2019). The immune system along with neurons and glial cells orchestrate the cognitive, emotional, and social properties in the healthy brain (Blank and Prinz, 2013). Significantly, although microglia account only for ~10% of the cells in CNS, they have emerged as crucial neuroinflammatory effectors of these functions (Tay et al., 2018; Pape et al., 2019). They continuously survey their microenvironment with their short, fine, and highly motile processes, regulating CNS homeostasis (surveillance state) (Davalos et al., 2005; Nimmerjahn et al., 2005) from development through adulthood (Blank and Prinz, 2013; Prinz and Priller, 2014; Forrester et al., 2018). In the healthy adult brain, homeostatic microglia phagocytose cellular debris (Fourgeaud et al., 2016), modulate myelin levels (Miron et al., 2013; Safaiyan et al., 2016; Hagemeyer et al., 2017), monitor neurogenesis (Sierra et al., 2010; Gemma and Bachstetter, 2013), release cell signaling factors (Parkhurst et al., 2013), and act as vital components of synapse formation, plasticity, and function (Hanisch and Kettenmann, 2007; Wake et al., 2009; Tremblay et al., 2011; Bialas and Stevens, 2013). Acting as professional phagocytes of the CNS, microglia engulf axon parts, terminals, and dendritic spines, thereby contributing to synaptic activity modulation in CNS areas implicated in behavioral experiences (such as learning/memory, fear-anxiety, anhedonia, and social tasks) via a transforming growth factor-β–dependent complement cascade (Paolicelli et al., 2011; Tremblay et al., 2011; Schafer et al., 2012; Miyamoto et al., 2016; Torres et al., 2016; Tay et al., 2018). Their process motility can dramatically change in response to neuronal activity and neurotransmitter levels (Li et al., 2012; Abiega et al., 2016). Interestingly, a recent study demonstrated that microglia-mediated synaptic reorganization is responsible for the dissociation of hippocampal engrams during adulthood and affects previously encoded memories (Wang et al., 2020).

Microglial activation drives the neuroinflammation evident in neurologic (Ransohoff, 2016a) and neuropsychiatric diseases (Mondelli et al., 2017; Li and Barres, 2018). Microglia respond swiftly to a variety of environmental cues (e.g., immune challenges, injury, diseases) through various cell surface receptors, including toll-like receptors (TLRs), complement receptors (CR3, CR4), and scavenger receptors (CD36, CD91). During this response, they significantly alter their morphology and release cytokines, chemokines, reactive oxygen species (ROS)/reactive nitrogen species, and trophic factors. Previously, microglial activation was conceptually categorized into a bimodal scheme based on the study of peripheral macrophages, resulting in either "cytotoxic" effects on neurons and oligodendrocytes (M1 type) or "protective" effects through phagocytic capacity and support of neurite outgrowth (M2 type) (Ransohoff, 2016b). More recently, however, microglial activation is considered multidimensional, with several activation stages and overlap in gene expression (Ransohoff, 2016b; Salter and Stevens, 2017; Li and Barres, 2018).

There are three other CNS macrophage types: perivascular, meningeal, and choroid plexus macrophages, located at the interface between the circulation and the parenchyma (Prinz et al., 2017). Furthermore, circulating myeloid cells, such as monocytes, granulocytes, and dendritic cells, reside in the CNS vasculature network (Li and Barres, 2018). In several diseases or injuries, monocytes may promptly infiltrate the brain parenchyma and differentiate into microglia-like cells to alleviate or exacerbate disease progression (Ginhoux et al., 2010; Prinz and Priller, 2014; Li and Barres, 2018).

Another piece of the neuroimmune cross talk is regulated by astrocytes that express chemokine, cytokine, and complement receptors, allowing them to interact with microglia and macrophages and get activated to serve several functions, including neurotrophic support, synaptic homeostasis, mitigating oxidative stress, neuron-glia signaling, and others (Sofroniew and Vinters, 2010; Khakh and Sofroniew, 2015; Liddelow and Barres, 2015). Acute astrocytic activation may exert both reparative functions [e.g., through secretion of neurotrophic factors (BDNF, neurotrophic growth factor) and glutamate clearance] or neurotoxic functions, leading to neuronal loss and behavioral alterations (Sanacora and Banasr, 2013; Khakh and Sofroniew, 2015; Liddelow and Barres, 2015; Haroon et al., 2017). Astrocytes can also act as "gate keepers" through their BBB regulation, controlling trafficking of peripheral immune cells to the CNS (Abbott et al., 2006).

Involvement of Immune Dysregulation in Mental Disorders: An Evolutionary Perspective

Recent converging human and animal data show that stress-related neurocircuitry and immune system coevolved to act synergistically and shield organisms from environmental threats. During a stressful experience, a "fight or flight" reaction is usually observed, involving activation of inflammatory pathways [e.g., nuclear factor–κB (NF-κB)] and leading to significant increases in circulating levels of proinflammatory cytokines, such as interleukin-6 (IL-6) (Pace et al., 2006; Koo et al., 2010; Sasayama et al., 2013; Wohleb et al., 2016; Felger et al., 2020). These inflammatory responses do not target specific

pathogens but rather environmental stressors, commonly observed in acute inflammatory diseases and mental disorders (such as MDD, SCZ, BD) (Pace and Miller, 2009; Derry et al., 2013; Goldsmith et al., 2016).

From an evolutionary perspective, it is hypothesized that modern humans have a hereditary genomic predisposition toward inflammation as a defensive response to environmental dangers and threatening stimuli (psychosocial stressors). The behavioral responses that are now adapted to mental disorders may have been used to enhance survival and reproduction in highly pathogenic and threatening environments many years ago (the pathogen-host hypothesis) (Miller and Raison, 2016). Consequently, mammals had to conserve energy for healing wounds and infections (social avoidance and anhedonia support this metabolic shunt) while maintaining hypervigilance against an attack from enemies (hyperalertness in stress and manic disorders) (Raison and Miller, 2013; Slavich and Irwin, 2014).

Equally important to the pathogen-host hypothesis of mental disorders is our detachment from an array of microbes that were previously ubiquitous in our microbiota (skin, gut, oral, and nasal) (Rook et al., 2015). Studies suggest that these microbes (commensals and symbiotes) have significantly contributed to the suppression of inflammatory responses through transforming growth factor-β signaling (Raison et al., 2010b; Rook et al., 2015). In modern times, sanitized urban environments resulted in decreased exposure to microbes and their immunoregulatory input. In the absence of these inflammatory regulators, the increased current psychosocial challenges and stressors have elicited increased immune responses, accounting for the high comorbidity of mental and inflammatory disorders (Prinz and Priller, 2014; Mechawar and Savitz, 2016; Miller and Raison, 2016; Wohleb et al., 2016).

Causal Factors of Immune Dysregulation in Mental Disorders

Two broad etiologic factors have been recognized as causes of mental disorder pathology: genetic susceptibility and environmental factors (Smoller, 2016). The latter include chronic stress, traumatic life events (physical, emotional, sexual abuse, bullying), malnutrition, drug abuse, social isolation, and prenatal environment (poor nutrition, exposure to drugs or toxins, and maternal infections or stress) (Wong and Licinio, 2001). Genetic sensitivity to environmental risks (Jaffee and Price, 2007; Belsky et al., 2009) can induce epigenetic changes at different levels, (e.g., neuroinflammatory, neurotransmitter, and brain connectivity), thus modifying the ability to adapt to subsequent stressors (Arango et al., 2018). Below, we discuss several causal factors of immune dysregulation affecting mental disorders.

Stress. Stress is believed to trigger psychiatric symptoms through immune system overactivation and escalation of the risk of mental disorder occurrence (Bergink et al., 2014). The immune system swiftly responds to stress through hormones (cortisol, epinephrine, and norepinephrine) and sympathetic nervous system (SNS). This can happen via the hypothalamic-pituitary-adrenal (HPA) axis activation, which is the cardinal stress-mediated neuroendocrine system, resulting from corticotropin releasing hormone (CRH) and arginine vasopressin secretion, which stimulate the secretion of adrenocorticotropic hormone (ACTH) (Faravelli et al., 2012). ACTH can then stimulate glucocorticoid release, specifically cortisol, from the adrenal cortex, mobilizing immune cell trafficking in the body (Dhabhar et al., 2012; Faravelli et al., 2012). This acute reaction can potentially cause chronic low-grade inflammatory responses characterized by intensified proinflammatory responses of tumor necrosis factor-α (TNF-α), IL-6, and interferon-γ (IFN-γ) (Glaser and Kiecolt-Glaser, 2005) (Fig. 1).

Recurrent stress (chronic stress) affects the production, reactivity, and circulation of immune cells, promoting detrimental inflammatory responses (Trottier et al., 2008). Several animal studies have demonstrated that chronic stress can induce immune dysregulation via glucocorticoid receptor (GR) resistance and inhibition of the HPA axis feedback loop, leading to proinflammatory cytokine production and a concomitant suppression of anti-inflammatory cytokines and immunosuppressive pathways (Stark et al., 2001; Frank et al., 2007; Engler et al., 2008; Heidt et al., 2014).

Early human studies in long-term social anxiety (bullying, social status changes, or hierarchy) reported higher rates of persistent anxiety, depression, low self-esteem, and incidence of illness (Marmot and Feeney, 1997; Griffin et al., 2002; Stansfeld et al., 2003). Correspondingly, clinical studies have concluded that chronic or early-life stress can induce transcriptional changes that promote susceptibility to hyperinflammatory responses, leading to a "biological imprinting" (Pace et al., 2006; Miller et al., 2008; Danese et al., 2011). For instance, teenagers with a history of childhood adversity have high IL-6 levels, correlating with subsequent development of depression (Miller and Cole, 2012). Peripheral C-reactive protein (CRP) and proinflammatory cytokine levels were shown to predict future PTSD development after traumatic and acute stressful events (Pervanidou et al., 2007; Eraly et al., 2014). Similarly, a meta-analysis of clinical studies revealed an enhanced proinflammatory profile (CRP, IL-6, and TNF-α) in adults with early-life childhood trauma and maltreatment (Baumeister et al., 2016). Changes in inflammatory gene expression mediated by epigenetic mechanisms [e.g., FK506 binding protein 5 (FKBP5), a factor associated with glucocorticoid sensitivity and mental disorders] have been linked with childhood traumatic experiences and elevated inflammatory responses (Jones, 2013; Klengel et al., 2013).

In the CNS, preclinical data have indicated that repeated psychosocial stress and early-life traumatic events can induce microglial activation (through stress hormones, cytokines, pattern recognition receptor agonists, and neurotransmitters), raising the risk of mental disorders later in life (Giovanoli et al., 2013; Howes and McCutcheon, 2017). In the hippocampus (HPC) and prefrontal cortex (PFC), psychosocial stress increases the levels of extracellular ATP, which induces the NLRP3-dependent inflammasome, leading to microglial interleukin IL-1β release (Pantazatos et al., 2017). Likewise, toll-like receptors TLR-2 and TLR-4 can mediate repeated stress-induced gene expression and TNF-α/IL-1α secretion from the PFC microglia (Wohleb et al., 2012; Nie et al., 2018; Furuyashiki and Kitaoka, 2019). Finally, restraint stress induces alterations to neurotransmitters such as glutamate and GABA, which influence microglial activation, proliferation, and motility (Nair and Bonneau, 2006; Fontainhas et al., 2011). Together, these findings suggest causal relationships between psychosocial stressors and early-life stress/trauma

with immune dysregulation, inflammation, and development of mental disorders.

Genetic Factors. Since genetics, along with stress, are the most important psychopathological contributors, the "diathesis-stress" (diathesis being the genetic component) model constitutes the principal etiologic hypothesis for mental disorders (Smoller, 2016). The diathesis-stress model suggests that genetic vulnerability and environmental stressors can escalate the predisposition to disorder, which in turn occurs once the threshold of sufficient liability is crossed. Previous studies using family members and twins revealed that mental disorders had heritable components to varying degrees. More recently, molecular studies have started identifying specific genetic variations related with psychiatric disorder phenotypes.

Significantly, genome studies have associated MDD with immune-related genes involved in the IL-6, IFN, and natural killer cell signaling pathways. Specifically, genes upregulated

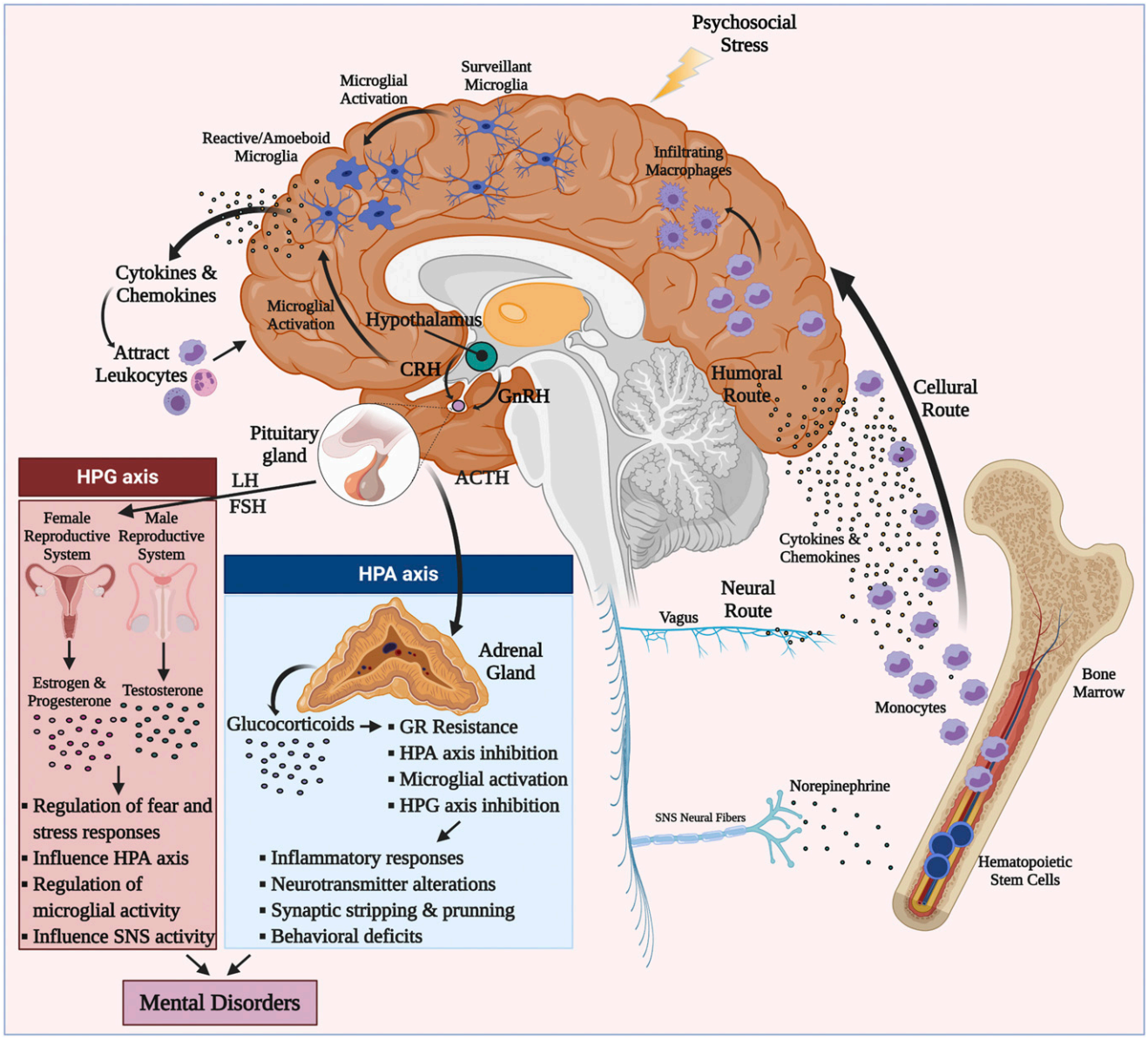

Fig. 1. Sex hormone influence and neuroimmune interplay in mental disorders. The HPA and hypothalamic-pituitary-gonadal (HPG) axes interact with each other and shape the downstream inflammatory responses, neurotransmitters, synaptic plasticity, and behavioral deficits observed in mental disorders. During psychosocial environmental stressors, microglia are stimulated through activation of immune receptors (TLRs, CRH receptors, and cytokine and chemokine receptors). Subsequent cytokine and chemokine secretion attracts activated myeloid cells to the brain via the *cellular* route. Once in the brain, infiltrating macrophages can drive central inflammatory responses. During psychosocial stress, catecholamines (e.g., noradrenaline released by activated SNS fibers) stimulate increases in myeloid cells (e.g., monocytes) in the periphery. Through induction of inflammatory signaling pathways (such as NF-κB and NLRP3 inflammasome), more proinflammatory cytokines and chemokines are produced that contribute to glucocorticoid resistance through glucocorticoid receptor cleavage. Proinflammatory cytokines and chemokines can access CNS through humoral and neural routes. Monocytes then infiltrate CNS through a compromised blood-brain barrier and differentiate to activated macrophages. Sex hormones affect risk for mental disorders by modulating these pathways at several levels: they 1) influence the perception, processing, and regulation of threat and fear; 2) modulate SNS/HPA reactivity to psychosocial stressors; and *importantly* 3) alter microglial and macrophage signal transduction through post-translational modifications and epigenetic changes. FSH, follicle stimulating hormone; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone.

in MDD include TNF-α receptor (*TNFRSF10C*), mitogen-activated protein kinase (MAPK) 14, IL-6 receptor, STAT3 (Wong et al., 2017), and several IFN-related genes (e.g., *MX1*, *OAS1*, *IFIT3*, *PTPN6*, and *IRF7*) (Mostafavi et al., 2014). Natural killer–related genes are downregulated (*GZMB*, *KLRK1*, *PRF1*, *SH2D1B*, *KLRD1*, and *NFATC2*) (Jansen et al., 2016). The *TRPM2* gene (which influences reactive oxygen species production and exacerbates NLRP3 inflammasome) was also significantly associated with MDD (Wong et al., 2017). Finally, a recent study points to a stress-related neuroinflammatory association with MDD, potentially via p75NTR/neurotrophic growth factor (nerve growth factor) and innate immune TLR signaling (Chan et al., 2020). These results support and link the neurotrophic (Duman and Li, 2012) and neuroimmune hypotheses of depression (Hodes et al., 2015).

SCZ typically emerges in early adulthood and is characterized by episodic or continuous alterations of the perception of reality, behavior, and cognition (Foley et al., 2017). GWASs have identified promising target genes that are widely involved in dopaminergic (*DRD2*) and glutamatergic neurotransmission (*GRM3*, *GRIN2A*, *SRR*, *CLCN3*, and *GRIA1*), neuronal calcium signaling (e.g., *CACNB2*, *CACNA1l*, *CACNA1C*, *RIMS1*), and synaptic function (*PAK6*, *KCTD13*, *CNTN4*) (Foley et al., 2017). Significantly, the top genetic correlations in schizophrenia come from the major histocompatibility complex (*MHC*) and B-cell activation loci (*CD19*, *CD20*), rendering immune pathways at the center of schizophrenia research (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015).

BD is a manic-depressive disorder that causes sudden changes in mood, concentration, energy, and activity levels, ranging from manic to depressive episodes. Several studies have associated BD within single-nucleotide polymorphisms (SNPs) in genes encoding cytokines or immune function (*IFN-γ*, *IL-6*, *IL-1*, *TLR2*, *TLR4*, *PTGS2*, *CCL2*, and *CCL3*) (Fries et al., 2019). A transcriptome-wide analysis included 1600 patients with SCZ and BD and reported the upregulation of members of IFN and NF-κB pathways (Guan et al., 2019).

Based on these studies, inflammatory, monoaminergic, and glutamatergic elements constitute the genetic "diathesis" and interact to coordinate the genetic predisposition of individuals to mental disorders.

Pathogen-Related Inflammation and Autoimmunity. Chronic disturbances in the innate and adaptive immunity systems are likely to dysregulate CNS function and alter cognitive performance. Frequently, pathogenic infection of the CNS drives the adaptive systemic inflammation, called "sickness behavior," which is manifested as social withdrawal, depressed mood, anhedonia, irritability, fatigue, impaired concentration, muscle pain, and fever. The symptoms overlap significantly with those observed in several mental disorders and are considered the result of reallocating energy resources to combat infection and enhance host survival. Evidence from long-term studies has demonstrated that hospitalization due to infection increases the risk for major depression by 62% (Benros et al., 2011). In rodents, perinatal infection and systemic inflammatory responses induce cognitive deficits comparable to the psychosis observed in young adults after early infection (Khandaker et al., 2015). Similarly, *Streptococcus pyogenes* infection is frequently correlated with subsequent mental and autoimmune psychiatric disorders.

In a prospective study of severe infection [*Helicobacter pylori*, *Chlamydia pneumoniae*, Cytomegalovirus (CMV), Herpes simplex virus (HSV-1, and HSV-2)], high viral burden was associated with cognitive decline (Katan et al., 2013). In addition, high CMV antibody titers have been identified in MDD subjects relative to controls (Rector et al., 2014), whereas infection with the protozoan *Toxoplasma gondii* has been associated with increased risk for SCZ (Torrey et al., 2007), MDD, and manic and suicidal behavior (Dickerson et al., 2014; Sugden et al., 2016). Studies suggest that *T. gondii* encodes proteins homologous to neurotrophic factors and dopamine metabolism, possibly modulating dopaminergic neurotransmission (Carruthers and Suzuki, 2007), leading to activation of kynurenine (KYN) pathway metabolites in the brain (Notarangelo et al., 2014).

The mechanistic associations between inflammation and mental disorders remain incomplete. Microglial inflammasome activation constitutes a potential response to proinflammatory mediators (Heneka et al., 2018; Zhang et al., 2018), thereby increasing the risk for mental disorders (Misiak et al., 2019). The systemic proinflammatory cytokine (such as TNF-α, IL-1β, and IL-6) released in response to infection or injury can also affect the CNS through activation of cerebral endothelial cells and microglia (D'Mello and Swain, 2017). Cytokines can exert neurotoxic effects through ROS production and alterations of glutamatergic and monoamine transmission.

The equilibrium between CNS and the immune system resembles a double-edged sword: on one side are the positive effects of the evolutionarily advantageous sickness behavior; on the other side are the detrimental effects of chronic inflammation, which lead to neurotoxicity, cognitive decline, and mental dysfunction.

Such equilibrium imbalances are observed in autoimmune inflammatory responses and mental disorders. In fact, there is significantly higher comorbidity of autoimmune disorders with patients with mental disorders than there is in the general population (Vonk et al., 2007; Korczak et al., 2011; Kosmidis et al., 2012). At the same time, autoimmune diseases have a high risk factor for subsequent diagnosis of mental disorder (45% increase) (Benros et al., 2013). A subset of patients with mental disorders exhibit increased levels of circulating autoantibodies: patients with MDD and BD may present comorbidity with autoimmune thyroiditis, evident by the presence of thyroperoxidase antibodies (Pop et al., 1998; Kupka et al., 2002); patients with multiple sclerosis may experience neuropsychological alterations and chronic anxiety, as in MDD (Feinstein et al., 2014) or SCZ (Andreassen et al., 2015).

Whether autoimmune antibodies are a causal factor or outcome of the psychopathological process of mental disorders is still unknown. Nevertheless, there are cases of psychosis and depression that report the presence of autoantibodies targeting neurotransmission in patients with limbic encephalitis (Dalmau et al., 2011; Kayser et al., 2013). Therefore, it becomes gradually recognized that a subset of patients with mental disorders may in fact suffer from an autoimmune disease. Lennox et al. (2012) and Dahm et al. (2014) wrote the following in an editorial: "Antibody screening in young people presenting with psychosis, seizures and cognitive disturbance is now part of routine clinical practice in neurological and intensive care settings."

Integrating Neuroimmune Systems in Mental Disorder Pathogenesis

Neuroinflammatory Mechanisms in Anxiety and Depressive Disorders

Anxiety and depressive disorders represent the leading class of mental disorders, with MDD affecting yearly 300 million people worldwide (Ferrari et al., 2013; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). They persist throughout life and have high comorbidity with other disorders, including PTSD, BD, and SCZ (Conway et al., 2006; Hettema et al., 2011). Family and GWASs implicate genetic factors [~30% contribution (Otte et al., 2016)] in the etiology of the disorders (monoaminergic, glutamatergic, neurotrophic, and stress hormone genes) (Smoller, 2016). However, exposure to chronic stress, traumatic experiences, and environmental factors are the most essential contributors for the onset of these disorders (Abelson et al., 2007; Dieleman et al., 2015).

In anxiety and depressive disorders, the fear-emotion processing network is stimulated in frontal [such as anterior cingulate cortex (ACC)] and limbic areas [amygdala (AMY)] (Gorman et al., 2000). Enhanced AMY-ACC connectivity has been correlated with augmentation of threatening stimuli in anxiety disorders, MDD, and PTSD (Killgore et al., 2014; Fonzo et al., 2015) and is accompanied by increased IL-6 levels (Muscatell et al., 2015). These increases are linked to social withdrawal, cognitive disturbances, depression (Harrison et al., 2009; Muscatell et al., 2015), and lower serotonin status (Hornboll et al., 2018). Exposure to stressful and traumatic events induces the HPA axis and cortisol release to counteract the norepinephrine-induced immune system activation and proinflammatory responses via NF-κB inhibition (Fig. 1). This balance is dysregulated during chronic activation of the HPA axis, leading to negative feedback and GR resistance.

In anxiety disorders, studies have demonstrated that patients with generalized anxiety disorder, panic disorder, and phobias have significantly increased cortisol levels (Mantella et al., 2008; Staufenbiel et al., 2013) and subsequent upsurges of sympathetic tone (Blechert et al., 2007; Alvares et al., 2013), leading to immune activation and inflammation. Patients with anxiety disorders (children and adults) exhibit elevated proinflammatory (CRP, TNF-α, IL-1β, and IL-6) and reduced anti-inflammatory (IL-2, IL-4) responses when compared with healthy controls (Brambilla et al., 1999; Hoge et al., 2009; Copeland et al., 2012; Vogelzangs et al., 2013; Wagner et al., 2015), as well as increased and highly sensitized lymphocytic T-cell populations (T helper 17) (Boscarino and Chang, 1999; Vieira et al., 2010). However, some other reports have described small or no changes in proinflammatory responses (Brambilla et al., 1999; Vogelzangs et al., 2013; Wagner et al., 2015). These discrepancies could be attributed to 1) the wide phenotypic and etiologic spectrum of anxiety disorders, 2) notions that only severe anxiety cases manifest increased inflammatory responses, 3) gender, and 4) comorbid mental or physical health problems.

In depressive disorders, early hypotheses had proposed that pathology stems from monoaminergic (Heninger et al., 1996) and glutamatergic alterations in the CNS (Kendell et al., 2005; Northoff and Sibille, 2014). However, approximately 40%–50% of patients with MDD are not responsive to antidepressants (Krishnan and Nestler, 2008), potentially reflecting that other disease mechanisms may be at play. The initial association between inflammation and depression was formed after the development of depression symptoms after long-term IFN-α treatment in patients with hepatitis C (Renault et al., 1987; Conversano et al., 2015). In a subsequent study that investigated the association of peripheral immune system and depression, Maes et al. (1992) identified elevated numbers of Ly6C^{hi} monocytes and neutrophils in the blood of patients with MDD, proposing the inflammatory hypothesis of depression (Smith, 1991; Maes, 1995).

Since then, a plethora of studies have reported high levels of proinflammatory markers (CRP, TNF-α, IL-6, and IL-1β) in patients with depression (Maes et al., 1997; Howren et al., 2009; Miller et al., 2009; Dowlati et al., 2010; Khandaker et al., 2014; Mostafavi et al., 2014; Strawbridge et al., 2015; Goldsmith et al., 2016; Miller and Raison, 2016; Felger et al., 2020). Epidemiologic studies (Whitehall II) on large community samples (>3000 individuals) and a decade of follow-up demonstrated that elevated blood levels of IL-6 and CRP could be used as prognostic markers of depressive symptoms (Gimeno et al., 2009). In support of that, elevated cortisol levels, GR insensitivity and dysregulation of the HPA axis have been consistently correlated with the inflammatory manifestations during MDD (Turecki and Meaney, 2016). In a recent single-nucleus RNA sequencing study of PFC in patients with MDD, co-chaperones of GRs (Heat shock protein 90 and FKBP5) were downregulated (Nagy et al., 2020), whereas in a systematic meta-analysis, it was demonstrated that increased inflammation (TNF-α, IL-6) is correlated with glucocorticoid resistance and elevated levels of cortisol in patients with MDD (Perrin et al., 2019).

Respective increases of innate immune markers (TNF-α, IL-1β, IL-6, TLR3, and TLR4) (Miller et al., 2009; Miller and Raison, 2016), along with microglial and astrocytic activation in several brain areas (PFC, HPC, and ACC), have been reported in postmortem MDD brain samples (Steiner et al., 2008; Rao et al., 2010; Torres-Platas et al., 2014; Nagy et al., 2015). Microarray analyses of MDD individuals identified significant upregulation of immune transcripts (cytokines, complement) (Shelton et al., 2011; Kim et al., 2016). Neuroinflammation in patients with MDD has also been visualized by positron emission tomography (PET) using the translocator protein (TSPO; microgliosis and astrogliosis marker) (Setiawan et al., 2015).

In animal studies, exposure to psychosocial/environmental stressors (stress section) has similarly revealed high cortisol and ACTH levels in plasma, elevated hypothalamic CRH expression, and concomitant increases of proinflammatory plasma cytokines (Engler et al., 2005; Ramirez et al., 2016). Chronic stress can induce neuronal activation in the anxiety/threat appraisal areas (PFC, AMY, and HPC) through glutamatergic and norepinephrine signaling (Perrotti et al., 2004; Musazzi et al., 2015), leading to neuroendocrine stimulation and glucocorticoid release (Ulrich-Lai and Herman, 2009). In a mouse depression model [repeated social defeat stress (RSDS)], innate immune GR resistance was correlated with high cortisol levels (Avitsur et al., 2002) and increased IL-6 plasma levels (Janssen et al., 2010), and these effects were dependent on Il-1β or adrenergic signaling (Jankord et al., 2010). Accordingly, chronic stress–induced activation of β3 adrenergic receptor and downregulation of chemokine ligand-12 have been shown to induce increases in hematopoietic stem cell activity and

peripheral elevation of monocytes and neutrophils (Engler et al., 2004; Wohleb et al., 2013; Heidt et al., 2014).

Microglial Interplay in Anxiety and Depressive Disorders

Microglia and macrophages are believed to have a pivotal role in depressive-like behavior (Wohleb et al., 2014b, 2015; Reader et al., 2015; Ramirez et al., 2016, 2017; Stein et al., 2017; Bollinger and Wohleb, 2019). Early work has demonstrated that in chronic stress models, β-adrenergic receptor signaling can induce microglial hypertrophy, proinflammatory cell activation (CD14, CD86, and TLR4), and cytokine expression (IL-6, IL-1β, TNF-α, and IL-1β), leading to depressive phenotype (Johnson et al., 2005; Blandino et al., 2006; Wohleb et al., 2011). These microglial-mediated effects are reduced by 1) GR antagonist RU486 (Wohleb et al., 2018; Horchar and Wohleb, 2019), 2) propranolol administration (β-adrenergic receptor antagonist), or 3) knocking out IL-1R in mice (Wohleb et al., 2011). These results suggest that chronic stress–induced inhibition of HPA axis may readily engage microglia and propagate inflammatory responses, driving associated behavioral consequences (Fig. 1).

Contributors to the chronic stress signal propagation are the pattern recognition receptor family of TLRs, associated with increased release of damage-associated molecular patterns, which in turn promote NLRP3 inflammasome activation, TSPO increase (Wang et al., 2018), and IL-1β release (Pan et al., 2014; Fleshner et al., 2017). Recently, a study by Nie et al. (2018) reported that RSDS can activate microglia through TLR2 and TLR4 and increased IL-1α and TNF-α expression, leading to atrophy of PFC neurons and social avoidance (Nie et al., 2018). The use of a double-knockout mouse model (TLR double knockout) or neutralizing antibodies for the cytokines rescued those effects, highlighting the pivotal role of TLRs on microglial activation during chronic stress.

Associated with microglial activation and concomitant inflammatory responses are activation markers (CD68), specific morphologic features (e.g., branch length and number, soma volume), phagocytic activity, and oxidative stress. Interestingly, RSDS studies have demonstrated that microglial activation (CD68), ROS production, and phagocytic activity (ex vivo) are upregulated in groups susceptible to stress, suggesting microglia-mediated neuronal dysfunction (Lehmann et al., 2016, 2018, 2019; Nie et al., 2018). Several studies have also attempted to visualize stress-induced morphologic changes in microglia, but the results are mixed (Wohleb et al., 2011, 2012, 2013, 2014a; Hinwood et al., 2012; Walker et al., 2013; Lehmann et al., 2016; McKim et al., 2016). Possible reasons for these discrepancies in the literature might be the differences in the stress paradigms [the nature and intensity of stressor (acute or chronic)] as well as lack of sensitivity and inconsistencies in the quantification of microglial morphology.

To examine the role of microglia in the onset of depression, some studies used an a priori microglial ablation (~95%) by the colony stimulating factor-1 receptor antagonist PLX5622 (McKim et al., 2018; Lehmann et al., 2019; Weber et al., 2019). Ablation before RSDS resulted in resilience to chronic stress, reductions of ROS formation, monocyte recruitment, proinflammatory cytokines, and depression-related behavioral tests (McKim et al., 2018; Weber et al., 2019; Lehmann et al., 2019). Remarkably, repopulation of microglia after PLX5622 withdrawal [clonal expansion of microglia (Tay et al., 2017)] was sufficient to reinitiate this cascade of events and recapitulate the depression-like effects in mice. These results, however, unveil more questions regarding the role of microglia during depression: 1) Could chronic stress potentially induce microglial epigenetic changes at depression onset? 2) Is the neuronal sensitization (adverse activated areas) also contributing to a microglial "re-education" after repopulation? 3) What are the significance and microglial phenotype of the relatively uncharacterized resilient-to-stress animals? And 4) what is the contribution of peripheral leukocytes in these processes?

Regarding the latter, bone marrow–derived leukocytes can enter the brain through the BBB epithelial lining and contribute to depression pathophysiology (Banks et al., 1994, 1995), a finding both in postmortem studies in patients with MDD (Torres-Platas et al., 2014) and in RSDS animals (CNS infiltration and differentiation of proinflammatory Ly6C^{hi} monocytes to macrophages) (Varvel et al., 2012; Wohleb et al., 2013) (Fig. 1). A recent study exhibited that this recruitment can be mediated by neurovascular adhesion of IL-1β–producing monocytes (vascular cell adhesion molecule-1 and ICAM-1) to the CNS parenchyma (McKim et al., 2018). This finding is of particular interest, considering that chronic stress may disrupt BBB integrity through alterations in the tight junction protein claudin-5 (Reader et al., 2015; Menard et al., 2017; Lehmann et al., 2018; Dudek et al., 2020). Interestingly, microglial activation and extracellular matrix degradation are believed to significantly contribute to BBB leakiness (Lehmann et al., 2016, 2018).

However, immune activation is not consistently reported in all depression cases (Lamers et al., 2013; Gold, 2015). For instance, a recent study by de Punder et al. (2018) demonstrated that only the patients with MDD with history of childhood adversity exhibited heightened inflammation, whereas microglial activation in postmortem studies is detectable in patients with MDD who committed suicide (Steiner et al., 2008, 2011, (Schnieder et al., 2014)). These observations suggest that immune activation may manifest only in moderate to severe depressive cases, accounting also for the treatment resistance reported in them (Fig. 2).

Neuroinflammatory Highlights in Traumatic, Bipolar, and Schizophrenia Disorders

Post-Traumatic Stress Disorder. PTSD is a severe and heterogeneous psychiatric condition that develops in individuals who have experienced traumatic or dangerous events (i.e., threat of death, injury, sexual violence) and is characterized by significant comorbidities with MDD and panic disorder (Dedert et al., 2010; Norrholm et al., 2011). Innate immune response genes and anxiety/stress vulnerability genes are thought to contribute to PTSD heritability (Hauger et al., 2012; Skelton et al., 2012; Smoller, 2016), whereas exposure to trauma is a risk factor for dysregulated HPA axis function (elevated CRH levels) (Carpenter et al., 2004; Lee et al., 2005; Michopoulos et al., 2017) and inflammation (Michopoulos et al., 2015a). In fact, individuals exposed to childhood abuse, maltreatment, socioeconomic difficulties, or parental separation may exhibit increased proinflammatory activity during adulthood (Taylor et al., 2006; Hartwell et al., 2013; Lacey et al., 2013; McDade et al., 2013; Matthews et al., 2014; Tursich et al., 2014; Baumeister et al., 2016; Lin et al., 2016; Michopoulos et al., 2017). Studies have reported in patients with PTSD

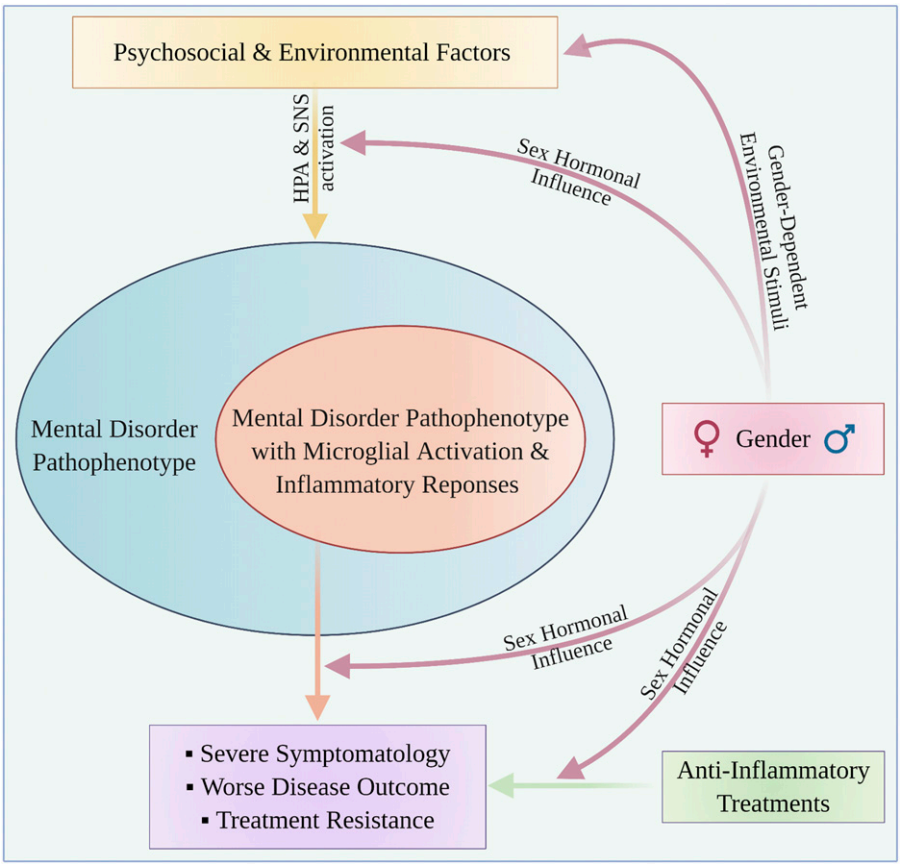

Fig. 2. Gender influence and neuroimmune interplay in mental disorders. This conceptual model proposes that a wide range of psychosocial and environmental factors (e.g., stress, trauma, abuse, discrimination) induce CNS/peripheral inflammatory responses and microglial activation in a subset of patients with mental disorders. These patients exhibit moderate to severe pathophenotype, worse disease outcome, and resistance to conventional treatments. The gender can influence the underlying disease and treatment mechanisms on several levels, either via gender-dependent environmental factors or sex hormonal effects. Anti-inflammatory treatments can be used to supplement the current therapeutic regimens in this subset of patients.

elevated circulating concentrations of TNF-α, INF-γ, IL-1β, IL-2, IL-6, and ICAM-1, which correlated positively with PTSD symptoms (von Kanel et al., 2007; Hoge et al., 2009; Oganesyan et al., 2009; Vidovic et al., 2011; Guo et al., 2012; Plantinga et al., 2013; Newton et al., 2014; Bersani et al., 2016). Respectively, cerebrospinal fluid (CSF) levels of CRP and IL-6 have been found elevated in PTSD (Baker et al., 2001; Heath et al., 2013; Plantinga et al., 2013; Lindqvist et al., 2014; Bersani et al., 2016), constituting risk factors for diagnosis (Michopoulos et al., 2015b). However, there are also studies that have described no change or even decreased levels of CRP, IL-6, and IL-2 in individuals with PTSD (Song et al., 2007; McCanlies et al., 2011; Muhtz et al., 2011). Similar discrepancies have been reported in studies examining anti-inflammatory plasma cytokine levels in patients with PTSD (IL-4, IL-8, and IL-10) (von Kanel et al., 2007; Hoge et al., 2009; Smith et al., 2011; Guo et al., 2012; Lindqvist et al., 2014; Jergovic et al., 2015; de Oliveira et al., 2018).

A meta-analysis of 20 PTSD independent studies sought to address these inconsistencies, revealing that proinflammatory markers (IL-1β, IL-6, TNF-α, and IFN-γ) are elevated and positively correlated with the illness duration in patients with PTSD (Passos et al., 2015). Another recent correlational study in traumatized women reported significant associations between higher concentrations of CRP, disease severity, and PTSD symptoms (Powers et al., 2019).

To summarize, these findings suggest that pharmaceutical interventions targeting inflammatory responses could potentially supplement the traditional psychotropic medications for severe cases of PTSD.

Bipolar Disorder. BD is a mental disorder characterized by frequent shifts in mood, activity levels, and concentration, ranging from manic episodes to depressive states. Studies have reported immune dysregulation during acute manic or depressive episodes, which is characterized by increased plasma levels of proinflammatory cytokines (TNF-α, IL-1β, IL-2R, IL-6, and IL-10) (Hope et al., 2011; Soderlund et al., 2011; Cetin et al., 2012; Munkholm et al., 2013; Stertz et al., 2013; Muneer, 2016). Similarly, postmortem analyses in the frontal cortices of patients with BD have demonstrated elevated mRNA and protein levels of IL-1b, CD11b, and inducible nitric oxide synthase (iNOS) (Rao et al., 2010).

Exacerbated inflammatory responses have been recorded by PET imaging, showing a significant increase of TSPO binding in the HPC of patients with BD (Haarman et al., 2014). Interestingly, studies have found microglial and monocytic activation with subsequent serum BDNF losses during manic or depressive phases, suggesting synaptic alterations between episodes (Drexhage et al., 2011; Parkhurst et al., 2013).

At present, research regarding the cross talk between inflammatory responses and cognitive performance in BD is extremely limited. The above studies, however, provide preliminary evidence of proinflammatory contributions on BD pathophysiology.

Schizophrenia. SCZ is a chronic, heterogeneous, and severe mental disorder affecting 1%–3% of the general population worldwide. It presents positive (hallucinations and movement disorders), negative (anhedonia, fatigue, asocial or atonic behavior), and cognitive symptoms (executive and memory functions) (van Os and Kapur, 2009). Epidemiologic studies have

reported that prenatal maternal infection (influenza, *T. gondii*, herpes simplex virus type 2, and cytomegalovirus) constitutes a risk factor for the offspring to develop SCZ during adulthood (Brown and Derkits, 2010; Khandaker et al., 2013; Canetta et al., 2014). This correlation between maternal infection and SCZ is also supported by rodent models of maternal immune activation with polyinosinic:polycytidylic acid in midgestation (Hui et al., 2018), with the offspring displaying SCZ behavioral phenotypes (Meyer et al., 2009; Patterson, 2009; Giovanoli et al., 2013).

Equally important, SCZ pathophysiology has been associated with the genetic loci of MHCII (Shi et al., 2009; Stefansson et al., 2009), predominantly genes involving complement C4, suggesting microglial involvement (Sekar et al., 2016). High C4 expression has been detected in neuron and astrocyte subsets from postmortem samples from patients with SCZ (HPC and PFC), whereas C4 knockout mice display impaired synaptic refinement (Sekar et al., 2016). Significantly, PET studies reveal increased TSPO binding in the HPC and frontal cortex of patients with SCZ (van Berckel et al., 2008; Doorduin et al., 2009; Bloomfield et al., 2016; Marques et al., 2019), whereas the density of MHCII-positive amoeboid microglia is increased (Wierzba-Bobrowicz et al., 2005; Busse et al., 2012; Fillman et al., 2013).

A meta-analysis of blood cytokine levels in patients with SCZ revealed elevated expression of IFN-γ, IL-6, IL-8, IL-1RA, IL-1β, IL-10, and TNF-α during psychotic episodes (Goldsmith et al., 2016), whereas a recent study of frontal cortex areas in patients with SCZ demonstrated elevated macrophage numbers and vascular adhesion molecules expression (ICAM-1, vascular cell adhesion molecule-1), further highlighting the presence of inflammation in SCZ (Cai et al., 2020).

Inflammatory Effects on Neurotransmitter Metabolism

There are several proposed inflammatory mechanisms by which monoamine (serotonin, dopamine) and glutamate neurotransmission may be affected.

Monoamines. Compelling evidence supports the idea that monoamine synaptic deficits result from excessive inflammatory cytokine levels in mental disorders. Many studies have focused on the impact of inflammatory cytokines on serotonin reuptake transporter (SERT) function, a primary target for anxiety- and depression-related disorders. In a lipopolysaccharide-induced depressive-like model, interleukin-1β (IL-1β) and TNF-α induction resulted in induction of SERT expression (through p38 MAPK) and diminished serotonin synaptic levels (Zhu et al., 2010). This has been replicated in human studies, correlating blood TNF-α concentrations with increased SERT binding activity (Krishnadas et al., 2016), supporting the hypothesis that inflammation promotes resistance to selective serotonin reuptake inhibitors (SSRIs), as observed in patients with mood and anxiety disorders (Strawbridge et al., 2015).

Cytokine-induced activation of the immunosuppressive enzyme indoleamine 2,3 dioxygenase also significantly alters serotonin production. Indoleamine 2,3 dioxygenase activity can be induced by several inflammatory signaling mechanisms, such as NF-κB, and can divert tryptophan metabolism from serotonin into KYN (Muller and Schwarz, 2007), which is metabolized to neurotoxic quinolinic acid by activated microglia and brain-infiltrating macrophages (Raison et al., 2010a). Studies of patients with MDD demonstrated direct correlation of plasma inflammatory markers (e.g., TNF-α) with plasma KYN and CSF KYN/tryptophan levels, exhibiting greater depression severity in those patients (Haroon et al., 2020).

Dopamine is a monoamine neurotransmitter with essential roles in the regulation of reward, motivation, and psychomotor activity (Haber, 2014). Alterations in dopamine levels are responsible for some of the most characteristic symptoms of mental disorders: anhedonia, persistent fatigue, loss of interest, and psychomotor deficits. Within weeks after administration of the cytokine IFN-α, patients experience symptoms (Capuron et al., 2002; Capuron and Miller, 2004) due to dopamine loss (Capuron et al., 2012). Similar results were reported in animal studies (Felger et al., 2007, 2013) in which lipopolysaccharide or cytokine administration (IL-1β or IL-6) in mice resulted in loss of interest and reduction in reward sensitivity (Yohn et al., 2016; Bartlett et al., 2018). Another essential cofactor in monoamine synthesis, tetrahydrobiopterin, decreases in response to inflammation-induced oxidative stress (ROS and reactive nitrogen species), inducing anxiety and depressive symptoms (Neurauter et al., 2008; Haroon et al., 2012; Felger et al., 2013).

Despite the rich literature reporting dopamine level alterations in response to cytokine administration, little research has been conducted to associate inflammation with analogous dopamine responses in patients with mental disorders. For instance, patients with MDD and chronic fatigue syndrome with elevated inflammatory markers (such as CRP and cytokines) demonstrated aberrant connectivity within reward-related corticostriatal neurocircuitry (Miller et al., 2014; Felger et al., 2016).

Altogether, these data suggest that the current first-line treatment regimens, which activate monoamine receptors, support dopamine synthesis, and block dopamine reuptake, would ultimately have greater likelihood of success and longer efficacy if they were to be combined with anti-inflammatory medications. In agreement with that, patients with MDD with high inflammation exhibit greater responses to SSRIs used in combination with the dopamine transporter blocker bupropion than to SSRI monotherapy (Jha et al., 2017).

Glutamate. Glutamatergic neurotransmission is another system through which cytokines influence reward-, motor-, and threat-related circuitry (Tilleux and Hermans, 2007; Ida et al., 2008; Miller et al., 2009; Vezzani and Viviani, 2015; Birey et al., 2017; Murrough et al., 2017). Inflammatory cytokines at physiologic levels can induce synaptogenesis by 1) inducing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid activity postsynaptically, 2) promoting glutamate clearance [through excitatory amino acid transporters (EAAT)], and 3) maintaining and protecting synapses by NMDAR stimulation through cytokine receptor activation (Santello et al., 2011; Pribiag and Stellwagen, 2014; Haroon et al., 2017).

During chronic inflammatory diseases, cytokine levels can dramatically increase, resulting in persistent NF-κB activity and neurotoxicity (Santello and Volterra, 2012): TNF-α and IL-1β enhance risk for excitotoxicity by activating NMDAR signaling, (Vezzani and Viviani, 2015) or inhibiting EAATs (which clear glutamate) in HPC slices (Zou and Crews, 2005). Interestingly, use of NMDAR antagonists blocks the cytokine-potentiated glutamate neurotoxicity, signifying the role of

N-methyl-D-aspartate signaling in inflammatory-mediated neurotoxicity and mental disorders (Zou and Crews, 2005).

Inflammatory cytokines and related components have been shown to induce glutamate neurotoxicity through microglia and astrocytes (Tilleux and Hermans, 2007; Ida et al., 2008; Haroon et al., 2017). Importantly, upon cytokine stimulation and subsequent microglial activation, large quantities of glutamate can be synthesized and released into synapses (Takeuchi et al., 2006). In addition, glutamate can be directly trafficked from microglia into astrocytes (through gap junctions), leading to EAAT dysfunction (Takeuchi et al., 2008). This glial glutamate release can stimulate extrasynaptic neuronal NMDARs and lead to BDNF loss and excitotoxicity (Hardingham et al., 2002; Hardingham and Bading, 2010).

Sex and Gender Differences in Immunoneuropsychiatry

The definition and usage of the terms sex and gender in the literature of mental disorders have sometimes been elusive and difficult to define. The term "sex differences" describes the biologic dissimilarities between male and female subjects, whereas the term "gender differences" describes the differential effects that psychosocial, cultural, and environmental factors have on men and women (Muehlenhard and Peterson, 2011). As such, the term sex is used for the animal studies assessing sex hormone influences (progesterone, estrogen, estradiol) or genetics of mental disorders, and both the sex (biologic) and gender (environment and experience) components are used in human cases (Oertelt-Prigione, 2012; Kuehner, 2017).

Justifying the Gender Gap in Mental Disorders

Differences in the epidemiology and symptomatology of mental disorders in men and women are well established, and with the exception of late-onset schizophrenia, women have significantly higher chronic prevalence of anxiety, depressive, and bipolar disorders (Boyd et al., 2015; Riecher-Rössler, 2017a,b; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; Yu, 2018; Rehm and Shield, 2019). A compelling body of evidence suggests that women are more vulnerable to psychosocial environmental stressors (due to sex hormone influence and blunted HPA axis stress responses), leading to higher prevalence of mental disorders.

Sex hormones can regulate various brain neurotransmitter pathways (serotonergic, dopaminergic, and GABAergic), modulating the sensitivity toward psychosocial influences. For instance, estradiol and progesterone fluctuations during menstrual cycle augment vulnerability of women toward psychosocial stressors but also significantly promote the overactivation, consolidation, and nonextinction of stressful experiences (Li and Graham, 2017). Stressful and emotion-negative stimuli (Kemp et al., 2004) induce greater activation of locus coeruleus (nucleus responding to stress and panic) in women compared with men (Filkowski et al., 2017; Bangasser et al., 2018).

Animal studies suggest that this difference in coping with anxiety and trauma stems from a sex-dependent HPA axis hypoactivation (Kajantie and Phillips, 2006). Specifically, low estradiol and progesterone levels (during menstruation, postpartum, and postmenopausal periods) attenuate the SNS-adrenal and HPA axis responsiveness, leading to repressed stress-coping capability (Fig. 1) (Kajantie and Phillips, 2006; Shansky et al., 2010). Studies demonstrate, however, that the decrease in cortisol release after stress exposure leads to lack of buffering mechanisms in emotional pathways (PFC-AMY) (Het et al., 2012; Kuehner, 2017). The most compelling evidence is the increased anxiety and depression prevalence postpuberty/-menarche (Kessler, 2003; Angold and Costello, 2006; Bale and Epperson, 2015), attributing these effects on ovarian hormonal level fluctuation (Costello et al., 2007). Similarly, atypical depression (a characteristic example of HPA hypoactivation predominantly observed in women) also presents this pathophenotype (Albert, 2015; Kuehner, 2017). Estradiol fluctuations can also exert pronounced effects on fear/memory and emotional extinction in anxiety-related and PTSD pathophysiology (Li and Graham, 2017).

Environmental and psychosocial influence is equally responsible for the gender differences observed in mental disorders (Kuehner, 2017; Riecher-Rössler, 2017b). Notably, reports demonstrate that domestic violence, sexual abuse (Kuehner, 2017; Oram et al., 2017), discrimination, and other risk factors can also contribute to the higher incidence of mental disorder in women (Hankin et al., 2007; Zahn-Waxler et al., 2008). As the prevalence of childhood sexual and emotional abuse is significantly higher in women than men, it constitutes an important contributor to gender differences in mental disorders (Kuehner, 2017).

Sex Influence and Inflammation in Mental Disorders

Several physiologic systems (HPA axis, immune dysregulation, neuroplasticity) have been implicated in the etiopathogenesis of mental disorders, and sex differences (hormone regulation and genetics) significantly modulate these processes (Rubinow and Schmidt, 2019) (Fig. 2). Importantly, sex hormones are key regulators of both innate and adaptive immune cell function (Rubinow and Schmidt, 2019; Slavich and Sacher, 2019), affecting immune cell progeny, proliferation, and cytokine production (Oertelt-Prigione, 2012; Trigunaite et al., 2015).

Anxiety and Depressive Disorders. Epidemiologic studies show robust gender-related differences in prevalence (2- to 3-fold higher in women), severity, and comorbidity reported in anxiety and traumatic and depressive disorders (Li and Graham, 2017; Rehm and Shield, 2019). Sex hormonal fluctuations are associated with heightened inflammatory responses in women compared with men (Giletta et al., 2018). In a meta-analysis of 26 studies, women were more prone to developing MDD after IFN-α treatment (Udina et al., 2012). Similar sensitivity to inflammatory components (endotoxin exposure) was observed in women with MDD, more than men, despite the similar magnitude in cytokine responses (IL-6, TNF-α) (Moieni et al., 2015). A recent longitudinal study highlighted the association between systemic inflammation and depression, demonstrating higher depression scores and inflammatory levels (CRP, IL-6, and fibrinogen) in women compared with men (Beydoun et al., 2020). Recently, a study focusing on severe suicidal peripartum depression implicated KYN pathway dysregulation followed by increased plasma inflammatory responses (IL-6, IL-8, IL-2, and quinolinic acid) and serotonergic system alterations (Achtyes et al., 2020).

Besides the demonstrated gender-based differences of inflammatory expression, a recent study reported gender-dependent

molecular signatures in the transcriptome of patients with MDD (Seney et al., 2018). Both genders revealed elevated expression levels for MHC and antigen-processing genes in corticolimbic areas (AMY, PFC, cingulate gyrus), but microglial-related gene expression showed significant region-dependent decreases in women and respective increases in men. Gender differences were also reported in synaptic function and plasticity genes (higher in women than men), suggesting increased microglial phagocytosis of dendritic neuronal spines (Seney et al., 2018). However, considering the grave effects that gonadal hormones exert in mental disorders during adolescence, it is important to further explore the gender differences emerging in early adulthood.

Microglia have been considered in the past as a homogeneous cell population (Ginhoux and Guilliams, 2016). However, single-cell RNA sequencing has revealed signatures associated with distinct physiologic microglial functions and subtypes (Li and Barres, 2018; Hammond et al., 2019). Interestingly, Homeobox B8 (Hoxb8)-expressing microglia, which account for one-third of all microglia in the adult mouse brain, could be related to sex differences in mood disorder pathophysiology (De et al., 2018): loss of function of microglial Hoxb8 caused anxiety-related symptoms and obsessive compulsion with higher severity in female mice, potentially regulated by progesterone and β-estradiol (Tränkner et al., 2019).

Animal work has provided additional insights on the sex differences observed in microglia-mediated immune mechanisms during mental disorders. Restraint stress can augment microglial density and affect microglial fractalkine receptor (CX3CR1) expression only in the PFC of female rats (Bollinger et al., 2016). Microglia-related transcriptional alterations in iNOS, Arginase1, and CD200 suggested that male and female rat microglia respond differently (Bollinger et al., 2016). Sex differences were also obvious in microglial morphologic features in several brain regions (AMY, orbitofrontal cortex, and HPC) (Bollinger et al., 2017), possibly affecting differentially neuronal plasticity.

Traumatic and Schizophrenia Disorders. Females have higher PTSD prevalence than males (Olff et al., 2007) and higher heritability (Duncan et al., 2018). Sex hormones influence the noradrenergic response to aversive stimuli (Segal and Cahill, 2009; Lithari et al., 2010) and show greater AMY sensitivity after threatening stimuli (Williams et al., 2005), corroborating previous reports of inflammatory gender-dependent differences in PTSD individuals (Neylan et al., 2011). A recent PTSD transcriptome mega-analysis of seven types of trauma (intrapersonal, assault, combat, childhood, and others) demonstrated a shared molecular convergence in inflammatory cytokine, innate immune, and IFN-signaling cascades in both genders (Breen et al., 2018). However, the study also revealed gender-dependent alterations in several signaling modules (IL-12, MAPK, wound healing, and lipid metabolism), which were associated with specific modes of trauma (Breen et al., 2018). Correspondingly, in a recent PTSD rodent model, researchers detected sex-specific transcriptional responses to trauma involving NF-κB activation (TNF-α upregulation) and dysregulated synaptic plasticity in female HPC (Kim and Uddin, 2020).

In SCZ, higher disease severity and frequency is evident in men (Abel et al., 2010), and the mean disease onset is 5 years earlier than women (Andersen, 2003). Interestingly, there is an increase of SCZ psychotic episodes in women when postpartum (when estrogen levels drop suddenly) (Riecher-Rössler, 2017a), as well as around menopause (Castle and Murray, 1993). These data support the "estrogen hypothesis," which postulates that estrogen can exert a protective effect in SCZ (Grigoriadis and Seeman, 2002).

The SCZ etiopathogenesis, compared with other mental disorders, involves predominantly neurodevelopmental abnormalities correlated with genetic factors and maternal infections as pathogenic contributors. It is believed that estrogen modulates microglial receptors and activity (Sierra et al., 2008), reducing inflammation (Sarvari et al., 2011). This sex-dependent hypothesis in SCZ human studies has focused on MHCII-microglial activation, evident in postmortem studies of patients with SCZ (Sekar et al., 2016; Mondelli et al., 2017). In a recent study, variations of complement component C4 in blood, brain, and lymphoblastoid cells drove stronger vulnerability and severity in men than in women (Kamitaki et al., 2020). Both C4 and its effector, complement component 3, are found at higher levels in plasma and CSF from men aged between 20 and 50 years, whereas in women, this increase occurs after menopause (40–50 years) (Ritchie et al., 2004; Gaya da Costa et al., 2018). As C4 increase occurs during the same time frame as disease vulnerability, it is suggested that microglial complement receptors in SCZ disorder may be affected differently by sex.

This hypothesis is also supported by several rodent maternal immune activation studies, in which male offspring are more vulnerable than female (Mattei et al., 2014; Deane et al., 2017; Hui et al., 2018; Notter et al., 2018). Interestingly, studies have revealed sex-based increases of inflammatory responses and "dark" microglial density (the cells appear dark in electron microscopy and interact with blood vessels and synapses), as well as extensive synapse interaction and oxidative stress in the HPC of males after exposure to prenatal polyinosinic:polycytidylic acid. Therefore, prenatal infection may differentially affect microglial responses in each gender (Hui et al., 2018).

Overall, microglia emerge as key players in traumatic and schizophrenia disorder onset, but it is still not clear whether these inflammatory effects occur only in a subset of severe disease cases or whether these mechanisms are exerted in a sex-dependent manner (Fig. 2).

Conclusions

Increasing evidence supports inflammatory mechanisms underlying the pathophysiology of mental disorders. Immune mechanisms have pronounced regulatory effects on the psychosocial stressor–genetic diathesis interaction (Fig. 1), demonstrating heightened inflammatory load in mental disorders. However, despite the evident induction of peripheral and CNS immune components and mediators in patients with mental disorders, these effects are not consistently reported. Could this possibly mean that inflammatory responses and microglial activation are evident only on a subset of patients with distinct pathophenotype or disease severity (Fig. 2)?

Postmortem studies from severe cases of depression, trauma, and psychoses have reported association with microglial activation and increases of peripheral and central proinflammatory responses (Haarman et al., 2014; Setiawan et al., 2015; Cattaneo et al., 2016; Mondelli et al., 2017; Raison, 2017; Wittenberg et al., 2020). These observations suggest

that inflammatory cytokines, along with microglial activity, may serve as prognostic markers of disease development, severity, and expected resistance to treatment. With this in mind, anti-inflammatory regimens could be used to supplement the current antidepressant treatments: nonsteroidal anti-inflammatory drugs, minocycline, and other immunosuppressive drugs (Miller et al., 2017; Raison, 2017; Pfau et al., 2018; Wittenberg et al., 2020), targeting moderate to severe disease cases.

Sex hormones play an equally important role in mental disease modulation (Fig. 2). Gender effects have come to provide an additional layer of complexity to immunopsychiatry, integrating psychosocial, genetic, and developmental factors under the prism of sex hormonal influence. However, this complexity, if used correctly, would introduce gender as a valuable part of this equation and unveil novel pharmacological interventions for modern psychiatry.

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Wrote or contributed to the writing of the manuscript: Kokkosis, Tsirka.

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