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REVIEW

Immune and Neuroendocrine Mechanisms of Stress Vulnerability and Resilience

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Diagnostic criteria for mood disorders including major depressive disorder (MDD) largely ignore biological factors in favor of behavioral symptoms. Compounding this paucity of psychiatric biomarkers is a need for therapeutics to adequately treat the 30–50% of MDD patients who are unresponsive to traditional antidepressant medications. Interestingly, MDD is highly prevalent in patients suffering from chronic inflammatory conditions, and MDD patients exhibit higher levels of circulating pro-inflammatory cytokines. Together, these clinical findings suggest a role for the immune system in vulnerability to stress-related psychiatric illness. A growing body of literature also implicates the immune system in stress resilience and coping. In this review, we discuss the mechanisms by which peripheral and central immune cells act on the brain to affect stress-related neurobiological and neuroendocrine responses. We specifically focus on the roles of pro-inflammatory cytokine signaling, peripheral monocyte infiltration, microglial activation, and hypothalamic-pituitary-adrenal axis hyperactivity in stress vulnerability. We also highlight recent evidence suggesting that adaptive immune responses and treatment with immune modulators (exogenous glucocorticoids, humanized antibodies against cytokines) may decrease depressive symptoms and thus represent an attractive alternative to the current antidepressant treatments.

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INTRODUCTION

One out of five people will suffer from a mood disorder during their lifetime (Kessler *et al*, 2005; Kessler *et al*, 1993). Major depressive disorder (MDD), the most prevalent mood disorder (6.7%) (Kessler *et al*, 2005), is the leading cause of worldwide disability (Lopez and Murray, 1998). Core symptoms of MDD include depressed mood, irritability, anhedonia (defined as the reduced ability to experience pleasure from previously rewarding activities), difficulty concentrating, and disrupted appetite and sleep habits (Krishnan and Nestler, 2008). Several clinical studies report a high prevalence of MDD comorbidity with inflammatory diseases including cardiovascular diseases, diabetes, metabolic disorders, asthma, and rheumatoid arthritis, as presented in Table 1 (Fenton and Stover, 2006; Maes *et al*, 2011; Moussavi *et al*, 2007). Underscoring these data is the finding that subsets of MDD patients display higher levels of inflammatory markers such as cytokines and circulating leukocytes (Dowlati *et al*, 2010; Lanquillon *et al*, 2000; Maes, 1995; Maes *et al*, 1995a; Maes *et al*, 1992; Maes *et al*, 1995b). This observation informed the macrophage theory of depression, which argues that overactive cytokine secretion by macrophages (stimulated by allergens, chronic disease, estrogen, etc) drives the neuroendocrine disruptions observed in depressed individuals (Smith, 1991). Subsequent work has identified enhanced peripheral inflammation in post-traumatic stress disorder (PTSD) (Baker *et al*, 2001; Gill *et al*, 2008; Newton *et al*, 2014; Passos *et al*, 2015) and bipolar disorder (Fiedorowicz *et al*, 2015; Goldstein *et al*, 2009; Kalelioglu *et al*, 2015; Uyanik *et al*, 2015).

Prolonged stress induces neuroimmune and neuroendocrine responses, and individual differences in these responses likely shape behavioral vulnerability and resilience (Charney, 2004; Hodes *et al*, 2015a). In some individuals, overactive, unresolved stress responses may increase stress vulnerability and ultimately the development of mood disorders (Charney, 2004). However, most individuals mount adaptive coping mechanisms that promote resilience in the face of stress (Pfau and Russo, 2015; Russo *et al*, 2012). Here, we provide an overview of insights from human and rodent studies highlighting a role for the immune system in the development of stress vulnerability *vs* resilience and the pathogenesis of mood disorders with a focus on MDD.

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TABLE 1 Comorbidity of MDD with Inflammatory Diseases

Diseases	Prevalence of depression	References
Healthy		
General population	6.7%	Kessler *et al*, 2005
Autoimmune diseases		
Multiple sclerosis	23.7–50%	Marrie *et al*, 2015; Siegert and Abernethy, 2005
Systemic lupus	10.8–44%	Ainiala *et al*, 2001; Nery *et al*, 2007
Rheumatoid arthritis	13–48%	Dickens *et al*, 2002; Matcham *et al*, 2014
Neurodegenerative disorders		
Alzheimer's disease	30–50%	Lee and Lyketsos, 2003; Zhao *et al*, 2016
Parkinson's disease	7–76%	Veazey *et al*, 2005; Bomasang-Layno *et al*, 2015
Huntington's disease	48.2%	Wetzel *et al*, 2011
Metabolic disorders		
Obesity	20–55%	Luppino *et al*, 2010; Stunkard *et al*, 2003
Cardiovascular diseases	17–27%	Rudisch and Nemeroff, 2003; Seligman and Nemeroff, 2015
Type 2 diabetes	12.8–26%	Ali *et al*, 2006; Anderson *et al*, 2001
Infection/environmental diseases		
Chronic obstructive pulmonary disorders	6–42%	Maurer *et al*, 2008
HIV	5–42%	Cruess *et al*, 2003; Nanni *et al*, 2015
Asthma	7.6–20.2%	Jiang *et al*, 2014

This table was adapted with from Iwata *et al*, 2013 and updated to include the recent clinical findings.

DEFINITION OF STRESS VULNERABILITY *VS* RESILIENCE

The adaptive physiological response to acute stress is crucial for survival in life-threatening situations. However, the failure to resolve a physiological stress response upon cessation of an acute stressful event may create a deleterious allostatic load, leading to stress vulnerability and enhanced risk of mood disorders (Charney, 2004; Goldstein and McEwen, 2002). Allostatic load is defined as the physiological and psychological burden placed upon the brain and body by stress (Goldstein and McEwen, 2002). Conversely, resilience is defined as an integrated process involving multiple peripheral and central mechanisms that promotes an appropriate, non-pathological stress response (Charney, 2004; Pfau and Russo, 2015; Russo *et al*, 2012). Maladaptive neurobiological responses associated with mood disorders have been studied extensively for decades. Resilience was first described in at risk children in the 1970s (Garmezy, 1971; Masten, 2001) and has inspired increasing interest as a means to understand mood disorder etiology and identify novel strategies for prevention and treatment. A greater understanding of resilience biology is important, given that only 30% of patients completely remit following treatment with current first-line antidepressant therapies, making MDD a chronic, recurrent condition for many sufferers (Krishnan and Nestler, 2008). Furthermore, ~30–50% of depressed patients are unresponsive to any approved antidepressant treatment (Krishnan and Nestler, 2008). This lack of efficacy suggests that current treatments fail to address causal or secondary pathological responses, preventing complete remission. We propose here that circulating inflammatory molecules and/or exacerbated immune responses, neither of which are primary targets of current antidepressant treatments, likely contribute to both the development of mood disorders and resistance to treatment.

THE ROLE OF IMMUNE SYSTEM IN CHRONIC PSYCHOLOGICAL STRESS RESPONSE

Stress precipitates inflammatory events in both the central nervous system (CNS) and peripheral immune system that are relevant to behavioral vulnerability and resilience. Here, we will overview the major components of the immune system (innate and adaptive) before detailing the effects of stress on immune cells and cytokines, both peripherally and centrally.

The Innate Immune System

Innate immune cells (monocytes, granulocytes, macrophages, dendritic cells and innate lymphocytes) react to pathogens or injury by mounting rapid and effective responses (Hodes *et al*, 2015a; Rosenblat *et al*, 2014). They are equipped with receptors recognizing pathogen-associated molecular patterns or danger-associated molecular patterns (Frank *et al*, 2015; Portou *et al*, 2015). Activation of these receptors can induce signaling cascades that stimulate the release of inflammatory mediators such as prostaglandins, leukotrienes, bradykinin, histamines, and serotonin

(Rosenblat *et al*, 2014). These molecules produce a local inflammatory response comprising vasodilatation, pain receptor stimulation, and release of pro-inflammatory cytokines. Pro-inflammatory cytokines such as interleukin-1-beta (IL-1β), IL-6, and tumor necrosis factor-alpha (TNFα) are released by tissue-resident dendritic cells and macrophages (Hodes *et al*, 2015a; Rosenblat *et al*, 2014), leading to the recruitment of immature Ly6c^{high} monocytes and neutrophils. Recruited monocytes can further differentiate into phagocytic macrophages to enhance inflammatory processes or promote resolution of inflammation (Ginhoux and Jung, 2014; Shi and Pamer, 2011). As in trauma-related injury, psychological stress can induce monocytosis, defined as an increase in the number of monocytes circulating in blood (Ginhoux and Jung, 2014). Although the immune response to stress can be adaptive in the short term, chronic psychological stress can produce sustained, unresolved inflammation and leukocytosis, which are hallmark symptoms of depression (Maes *et al*, 1992).

The Adaptive Immune System

Adaptive immune cells (T and B lymphocytes) can induce an immune response in secondary lymphoid organs such as lymph nodes and spleen. Adaptive immunity refers to the storage of an immunological memory after an initial response to a pathogen that then enhances future responses to that pathogen (for review, refer to Mueller and Mackay, 2016). Effector memory T cells are abundant in non-lymphoid tissues and circulate in the bloodstream, while another subset of central memory T cells is predominant in secondary lymphoid organs (lymph nodes and spleen) in the absence of inflammation. Memory T cells become activated upon presentation of a previously encountered specific antigen by an antigen-presenting cell. Tissue-resident memory T cells respond rapidly to local pathogen re-encounter initiating cytokine release and recruitment of natural killer and dendritic cells (Mueller and Mackay, 2016). It is thought that the adaptive immune system may store the immunological memory of a stressor, thereby enabling a protection against future similar stress exposure (Lewitus and Schwartz, 2009a) and possibly the establishment of mood disorders (Miller, 2010).

Stress and Peripheral Immune Cells

Cells of the innate immune system. Numerous recent studies suggest that chronic stress mobilizes the innate immune system, stimulating enhanced proliferation and release of inflammatory Ly6c^{high} monocytes and neutrophils (Figure 1a). Powell *et al* (2013) utilized repeated social defeat (RSD) to investigate the effects of stress on leukocyte biology. In the RSD paradigm, a novel, aggressive CD-1 mouse is introduced into a home cage of three C57BL/6 mice for 2 h over six consecutive nights, disrupting the social hierarchy of the cage and eliciting submissive behaviors. The authors found that RSD increases monocyte and granulocyte progenitor cells within bone marrow and induces blood monocytosis and granulopoiesis. They further identified a stress-induced, β-adrenergic receptor signaling-dependent leukocyte transcriptional profile that favored the release of Ly6c^{high} monocytes and Ly6c^{intermediate} granulocytes into circulation. This occurs via enhanced expression of pro-inflammatory genes and myeloid lineage commitment genes accompanied by decreased expression of terminal myeloid differentiation genes (Powell *et al*, 2013). These findings were mirrored in human subjects of low socioeconomic status (SES), a form of chronic social stress that can activate the sympathetic nervous system. Low SES subjects had higher relative and absolute counts of monocytes in blood and displayed a leukocyte transcriptional profile favoring monocytosis and β-adrenergic signaling (Powell *et al*, 2013). Heidt *et al* (2014) reported similar findings using rodent chronic variable stress (CVS), in which mice were subjected to 3 weeks of varying, unpredictable stressors (cage tilt, wet bedding, social isolation, cage crowding, and constant illumination). Mice exposed to CVS had more monocytes and neutrophils in blood and bone marrow than did home cage controls, an effect dependent on β_3-adrenergic receptor signaling (Heidt *et al*, 2014). Stress affects not only cell number but also cell reactivity in the innate immune system. Following exposure to RSD, splenic macrophages of stressed mice exhibit enhanced release of TNFα and IL-6 in response to treatment with lipopolysaccharide (LPS, a bacterial endotoxin and toll-like receptor (TLR4) agonist), an effect mediated by stress-induced glucocorticoid (GC) resistance (Avitsur *et al*, 2005). Interestingly, Avitsur *et al* (2001) reported individual differences in splenocyte GC resistance related to social hierarchy. Submissive mice were more likely to develop splenocyte GC resistance following RSD than were control and dominant mice, suggesting that pre-existing differences in social status may underlie susceptibility *vs* resilience to stress-induced inflammation. Although these studies inform our understanding of the effect of stress on the innate immune system, more research is necessary to determine the innate immune profile of resilience.

Cells of the adaptive immune system. As mentioned above, the adaptive immune system is thought to play a protective role by 'inoculating' an individual against repeated stressors, thereby promoting resilience (Figure 1e and g). Lewitus *et al* (2009b) showed that T-cell-dependent immunization with a weak agonist of a CNS-specific myelin-derived peptide before exposure to chronic mild stress ameliorated subsequent depression-like behaviors in rats (Figure 1g). Accordingly, in a predator odor challenge that is considered a model of PTSD, mice overexpressing autoreactive T cells exhibit resilience to the stressful episode (Cohen *et al*, 2006). Conversely, T-cell-deficient mice are more vulnerable to stress, displaying enhanced social avoidance and acoustic startle response (Cohen *et al*, 2006). Inoculation with a single population of T cells reactive to CNS-associated self-antigens (cells capable of homing to the CNS) was sufficient

to protect T-cell-deficient mice and promote resilience (Cohen *et al*, 2006). These preclinical studies suggest that, like inoculation of a weak antigen for infectious disease vaccination, mild activation of the adaptive immune system before stress exposure can confer a relative protection against stress-related psychiatric disorders.

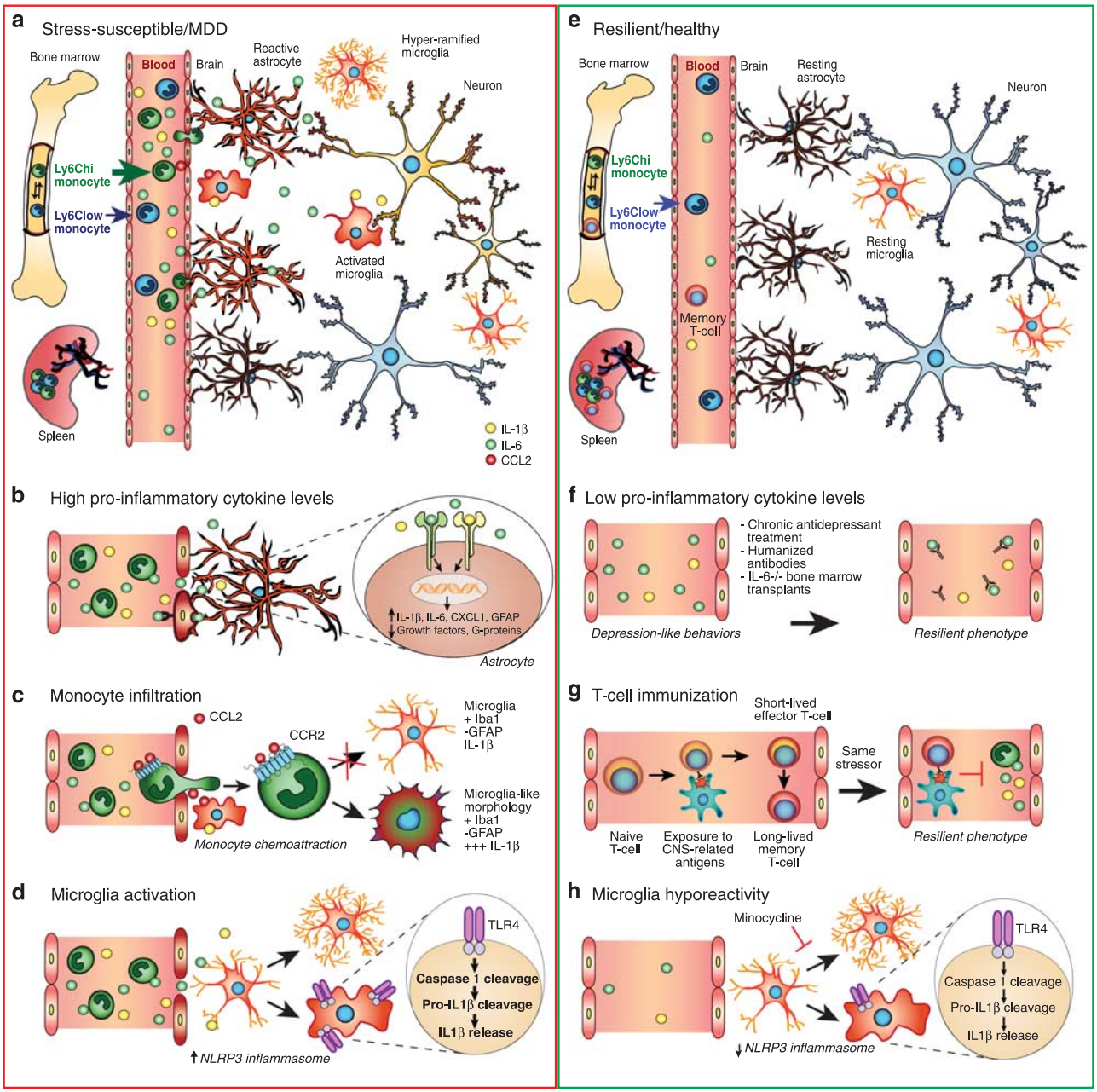

Figure 1. Immune mechanisms of stress vulnerability and resilience. (a) Circulating levels of pro-inflammatory cytokines (IL-1β and IL-6) are elevated in the blood of stress-susceptible animals and MDD patients altering neuronal, astrocytic and microglial functions. (b) Pro-inflammatory cytokines activate receptors at the cell surface of reactive astrocytes leading to enhanced expression of structural GFAP and release of inflammatory mediators and reduced expression of G-protein effectors and growth factors. (c) Activated microglia can release chemokine ligand 2 (CCL2) in the blood attracting patrolling immature Ly6C^{high} monocytes through binding of CCL2 to chemokine receptor 2 (CCR2). These monocytes can cross the blood–brain barrier and penetrate into the brain, particularly in stress-related brain regions expressing high levels of pro-inflammatory cytokine IL-1β, where they differentiate into phagocytic macrophages displaying a microglia-like morphology as assessed with microglia marker Iba1. (d) Activation of the NLRP3 inflammasome, constitutively expressed in macrophages and microglia, through Toll-like receptor 4 (TLR4) binding initiate pro-caspase-1 and pro-IL-1β cleavage leading to the secretion of pro-inflammatory IL-1β. Chronic stress also induces microglia hyper-ramification in rodent models of depression. (e) On the other hand, resilient animals do not display exacerbated immune responses following acute or chronic stressors. (f) In fact, lowering circulating pro-inflammatory cytokines levels by antidepressant treatment, humanized antibodies or IL-6$^{-/-}$ bone marrow transplants reverse depression-like behaviors and promote a resilient phenotype. (g) Immunization through production of long-lived memory T-cell after exposure to CNS-related antigens could even help to build appropriate adaptive immune responses to future stressors. (h) Lower microglia reactivity and NLRP3 inflammasome activation could also be associated with resiliency as reduction of microglial activity by administration of the inhibitor minocycline abolishes the pro-ramifying effect of stress and reverses depression-like behaviors.

TABLE 2 Studies Related To Cytokines in Mood Disorders

Cytokine	MDD	Bipolar disorders	References
IL-1β	↑ or —	n.d.	Black and Miller, 2015; Fornaro et al, 2013; Hernandez et al, 2008; Huang and Lee, 2007; Leo et al, 2006; Liu et al, 2004; Maes et al, 1993; Owen et al, 2001; Simon et al, 2008
IL-1RA	↑	↑ or ↓	Liu et al, 2004; Maes et al, 1997; Tsai et al, 2012
IL-2	↑ or —	—	Fornaro et al, 2013; Hernandez et al, 2008; Liu et al, 2004; Sutcigil et al, 2007
IL-4	↓	—	Liu et al, 2004; Sutcigil et al, 2007
IL-6	↑	↑ or ↓	Basterzi et al, 2005; Berk et al, 1997; Hodes et al, 2014; Kapczinski et al, 2011; Maes et al, 1997; Maes et al, 1995a; Munkholm et al, 2015; Sluzewska et al, 1996
IL-8	—	n.d.	Mikova et al, 2001
IL-10	↑	—	Fornaro et al, 2013; Hernandez et al, 2008; Huang and Lee, 2007; Kapczinski et al, 2011; Liu et al, 2004
IL-12	↑	n.d.	Kim et al, 2002; Lee and Kim, 2006; Sutcigil et al, 2007
IL-13	↑	n.d.	Hernandez et al, 2008
IL-17	n.d.	n.d.	
IL-18	n.d.	↑	Munkholm et al, 2015
sIL-2 R	↑	↑ or ↓	Maes et al, 1995a; Sluzewska et al, 1996; Tsai et al, 1999; Tsai et al, 2003; Tsai et al, 2001
s-IL6 R	↑	—	Maes et al, 1995a; Sluzewska et al, 1996; Tsai et al, 1999; Tsai et al, 2003; Tsai et al, 2001
TGF-β	↓	n.d.	Sutcigil et al, 2007
TNF-α	↑	↑ or ↓	Eller et al, 2008; Fornaro et al, 2013; Huang and Lee, 2007; Kapczinski et al, 2011; Su et al, 2011; Sutcigil et al, 2007
s-TNF-R1	n.d.	↑	Tsai et al, 2012
IFN-γ	↑	↓	Fornaro et al, 2013; Hernandez et al, 2008; Liu et al, 2004

Supporting the adaptive immune system stress inoculation theory, a recent study reported that transplantation of lymph node cell suspensions from previously stressed mice into *Rag2* knockout mice that lack mature lymphocytes induces a resilient phenotype characterized by prosocial behavior and reduced anxiety (Brachman *et al*, 2015). Transplanted mice displayed reduced pro-inflammatory cytokine levels in peripheral blood, while their microglia, the resident immune cells of the brain, seemed to shift toward an anti-inflammatory profile (Brachman *et al*, 2015). Despite these intriguing findings, far more work is needed to fully understand the role of adaptive immune cells in stress susceptibility and resilience.

Peripheral cytokines and depression. A potential causal link between MDD and inflammation was first revealed when clinicians reported psychiatric complications in a high percentage of patients undergoing long-term interferon-α therapy to control chronic viral hepatitis (Conversano *et al*, 2015; Renault *et al*, 1987). In line with these findings, a large body of correlative evidence from clinical studies (Table 2) (Dowlati *et al*, 2010; Fagundes *et al*, 2013; Lanquillon *et al*, 2000; Maes *et al*, 1995a), suggests that depressed individuals have higher levels of circulating pro-inflammatory cytokines such as IL-1β, IL-6 (Figure 1b) and TNFα. Increased pro-inflammatory cytokines have also been reported in rodent models of depression-like behavior (Figure 1b) (Grippo *et al*, 2005; Hodes *et al*, 2014). Moreover, systemic administration of IL-1β, TNFα, or LPS promotes the expression of pro-inflammatory cytokine genes and proteins in the brain (Laye *et al*, 1994; Quan *et al*, 1999; van Dam *et al*, 1992) and induces sickness behaviors such as social withdrawal, loss of appetite, decreased motor activity, and cognitive deficits in rodents (Dantzer *et al*, 2008). However, it is important to note that, because the behavior is directly tied to LPS- or cytokine-induced inflammatory activation and subsides following a return to baseline, behavioral changes are considered sickness behavior rather than depression-like behavior. Interestingly in humans, systemic LPS injection resulted in greater feelings of social isolation in women than men (Moieni *et al*, 2015). Although there were no sex differences in circulating levels of cytokines induced by LPS, the increased feelings of social isolation correlated with circulating levels of IL-6 and TNFα only in females.

Our group recently reported that differences in the peripheral immune system, notably the number of circulating leukocytes and leukocyte IL-6 release following LPS stimulation, predicts susceptibility or resilience to chronic social defeat stress (CSDS) in mice (Hodes *et al*, 2014). In this model, repeated social and physical subordination by a physically larger, aggressive CD-1 mouse produces depression-like behaviors, including anhedonia and social avoidance, in the majority of experimental mice—termed stress-susceptible (Golden *et al*, 2011; Krishnan *et al*, 2007). However, paralleling resilience to marked stress in humans, not all mice become susceptible and develop a depressive phenotype. This subpopulation of mice behaviorally resilient to CSDS behaves similarly to unstressed controls (Golden *et al*, 2011; Krishnan *et al*, 2007). CSDS is a useful animal model to explore stress-induced neurobiological and neuroimmune changes associated with susceptibility and resilience (Hodes *et al*, 2015a; Menard *et al*, 2016). Following a single exposure to an aggressor, IL-1β and IL-6 levels were significantly elevated two-fold and nine-fold, respectively, in

the blood of mice that subsequently became susceptible compared with mice that ultimately became resilient (Figure 1b) (Hodes *et al*, 2014). Circulating levels of IL-6 were still elevated 48 hours after the last defeat in susceptible mice and remained elevated a month later. To further explore the role of peripheral IL-6 in stress vulnerability, hematopoietic stem cells from stress-susceptible or IL-6 knockout ($IL\text{-}6^{-/-}$) mice were transplanted into wild-type mice previously subjected to irradiation to eliminate their native peripheral immune system. Stress-susceptible bone marrow chimeras exhibited social avoidance after subthreshold defeat, a paradigm that is normally not sufficient to induce depression-like behaviors (Hodes *et al*, 2014). Conversely, $IL\text{-}6^{-/-}$ chimeras and mice treated with a systemic IL-6 monoclonal antibody demonstrated enhanced resilience to CSDS (Figure 1f) (Hodes *et al*, 2014). It is important to note that the level of resilience reached by $IL\text{-}6^{-/-}$ chimeras was similar to that of whole body IL-6 knockout mice, suggesting a prominent role for peripheral IL-6 in the development of stress susceptibility (Hodes *et al*, 2014). In line with the data obtained in mice, IL-6 levels were elevated in the blood of chronically depressed patients resistant to antidepressant treatment (Hodes *et al*, 2014).

A subsequent study highlighted a role for pro-inflammatory cytokines in the development of stress vulnerability *vs* resilience in other animal models of depression. Yang *et al* (2015) showed that peripheral IL-6 is higher in rats displaying learned helplessness (LH) behavior. In this model, experimental animals are exposed to uncontrollable stress in the form of inescapable foot shock for 2 days. On the third day, rodents are subjected to foot shock in a two-way-conditioned avoidance test, in which they can choose to avoid the stressor through an easy escape mechanism. Animals who fail to escape the controllable stressor are categorized as susceptible and show a broad range of behavioral, physiological and hormonal changes associated with depression (Chourbaji *et al*, 2005; Maier, 1990). As in CSDS, LH can be reversed by chronic, but not acute, antidepressant treatment (Berton *et al*, 2006; Slattery and Cryan, 2014; Menard *et al*, 2016).

The aforementioned results, supported by clinical studies in depressed patients, suggest that stress-induced cytokine release may play an important role in the pathogenesis of depression (for review, refer to Miller and Raison (2015)). High levels of circulating inflammatory mediators may affect the brain reward circuitry leading to the establishment of depressive behaviors (Felger *et al*, 2015b). However, the effects of antidepressant treatment on inflammatory cytokine levels have been contradictory in humans with reported decreased level (Mutlu *et al*, 2012; Sluzewska *et al*, 1995), no effect (Jazayeri *et al*, 2010; Maes *et al*, 1995a) or even increased level (Kubera *et al*, 2004; Munzer *et al*, 2013) (Table 2). This lack of consistency may be attributable to the heterogeneity of treatment responses in MDD (Kessler *et al*, 2016). In addition, the sex of the patient along with the type of drug may further obfuscate the relationship between antidepressant treatment and immune response. Men given serotonin-norepinephrine reuptake inhibitors (SNRIs) displayed increased levels of IL-6 and C-reactive protein (CRP) (Vogelzangs *et al*, 2012), whereas tricyclic antidepressants increased CRP in both sexes. Treatment with serotonin reuptake inhibitors (SSRIs) decreased IL-6 levels in men only. Neither SNRIs nor SSRIs significantly altered cytokine levels in women. Although studies investigating cytokine and immune cell abnormalities associated with stress vulnerability and resilience have been informative, further studies are necessary to address outstanding questions: is it possible to establish an immune molecular signature of resilience? Is the lack of heightened inflammation in resilient individuals maintained by active mechanisms? And lastly, would it be possible to predict a stress-related phenotype by stimulating circulating leukocytes and measuring cytokine release in humans?

Stress and Central Immune Cells

Microglia. Microglia constitute 10–15% of all brain cells and are the main active immune defense of the brain. These glial cells are tissue-resident macrophages that colonize the developing brain early during embryogenesis and become trapped after the blood–brain barrier forms (Ginhoux *et al*, 2010; Ransohoff and Brown, 2012). Microglia are highly dynamic and display stress-responsive morphological changes indicative of increased activity in stress-sensitive brain regions, notably the hippocampus, prefrontal cortex, and amygdala (Tynan *et al*, 2010; Wohleb *et al*, 2011). Reduction of microglial activity by administration of the inhibitor minocycline abolishes the pro-ramifying effect of stress (Hinwood *et al*, 2013) and rescues depression-like behaviors (Figure 1h) (Kreisel *et al*, 2014). Microglia dynamically survey their surrounding environment (Nimmerjahn *et al*, 2005), promote synaptic pruning (Stevens *et al*, 2007), and the recruitment of blood circulating monocytes to help manage tissue damage and local inflammation (Ajami *et al*, 2011; Yamasaki *et al*, 2014). Repeated stress may be sufficient to induce a deleterious inflammatory response potentially driven by microglia and/or infiltrating monocytes in the brain (Figure 1c). Indeed, dendritic cells along with monocytes and lymphocytes can enter the healthy brain in small numbers through the choroid plexus, brain lymphatic system, or circumventricular organs (Baruch and Schwartz, 2013; Louveau *et al*, 2015; Shechter *et al*, 2013). Elevated circulating inflammatory molecules and/or immune cells may trigger an opening of the gates separating the brain from the blood. In fact, Wohleb *et al* (2013) reported that repeated social stress not only induces an increase in circulating monocytes and brain macrophages but also the recruitment of peripheral myeloid cells within the perivascular space and parenchyma of stress-related brain regions expressing high levels of IL-1β in mice. Interestingly, this migration is dependent upon the fractalkine receptor CX3CR1 and chemokine receptor 2 (CCR2) as mice deficient in these receptors did not develop anxiety-like behaviors and failed to recruit macrophages into the brain

following RSD (Wohleb *et al*, 2013). Infiltration of monocytes into the mouse brain was also reported in the hippocampus following 5 consecutive days of electric foot-shock exposure (Brevet *et al*, 2010). All infiltrating monocytes developed microglia-like morphological ramifications and were positive for the microglia marker Iba-1 but negative for the astrocyte marker glial fibrillary acidic protein (GFAP) (Brevet *et al*, 2010). A follow-up study demonstrated that RSD leads to infiltration of bone marrow-derived monocytes in the paraventricular nucleus of the hypothalamus of mice subjected to chronic psychological stress (Ataka *et al*, 2013). In parallel, Wohleb *et al* (2011) report a concomitant increase in the expression of surface inflammatory markers such as TLR4 on resident microglia in socially defeated mice. Thus, chronic stress exposure affects not only microglial morphology but also microglial sensitivity. Taken together, these studies indicate that microglial function and peripheral cell recruitment play an active role in stress adaptation and may represent an attractive target to develop novel antidepressant treatments.

Astrocytes. Astrocytes, glial cells that engulf synapses and surround blood vessels, respond actively to inflammatory signals, inciting a growing interest in how astrocytic function and astrogliosis communicate with the immune system (Hodes *et al*, 2015a; Menard *et al*, 2016). Like microglia, astrocytes may be actively involved in stress-induced recruitment of peripheral monocytes through the expression of the chemokine ligand 2 (CCL2), also called monocyte chemoattractant protein-1 (MCP-1). CCL2 can activate CCR2 receptors on peripheral immune cells, promoting the invasion of inflammatory monocytes into the brain (Sica *et al*, 1990; Ransohoff and Tani, 1998). Astrocyte-mediated CCL2 release is sufficient to induce monocyte transmigration in a co-culture system meant to model aspects of the human blood–brain barrier (Weiss *et al*, 1999). Panenka *et al* (2001) reported that in cultured astrocytes, activation of ATP/purinergic receptor type 2X7 (P2X7R) increases CCL2 expression through mitogen-activated protein kinase activation, an effect that can be blocked by P2X7 antagonists. Interestingly, CCL2 gene expression is upregulated in the dorsal anterior cingulate cortex of patients suffering from MDD who committed suicide (Torres-Platas *et al*, 2014). In line with these findings, Zheng *et al* (2016) recently reported that chemical dampening of peripheral Ly6C^{high} monocyte recruitment and infiltration into the brain through inhibition of astrocyte activation and CCL2 release improves depression-like behaviors induced by either inflammation or chronic social defeat in mice. Further studies, supported by clinical findings, are necessary to elucidate the role astrocytes might play in the recruitment of peripheral immune cells and establishment of mood disorders.

Central cytokines and depression. Cytokines can directly cross the blood–brain barrier via saturable transport systems to act on astrocytes, neurons and microglia (Banks *et al*, 1995; Banks *et al*, 1994; Hodes *et al*, 2015a). Brain endothelial cells have the capacity to secrete cytokines (Verma *et al*, 2006) and thus may actively participate in the inflammatory response underlying chronic stress maladaptation. However, thus far most studies have investigated the role of activated microglia in inflammation and instigation of depression-like behaviors (Kreisel *et al*, 2014). Isolated microglia from rodents vulnerable to stress produce higher levels of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α following LPS stimulation when compared with those of unstressed controls (Frank *et al*, 2007; Wohleb *et al*, 2011). Frank *et al* (2007) also showed that prior exposure to inescapable shock potentiates microglial pro-inflammatory responses 24 hours post stress in rat hippocampus. Interestingly, the effect of inescapable shock was comparable to the effect of *ex vivo* LPS stimulation, reinforcing the hypothesis that stress can prime microglial response to future psychological or physiological stressors. Conversely, treatment with SSRI and SNRI antidepressants suppresses microglial responses in murine microglial cell lines (Tynan *et al*, 2012), providing evidence that these drugs act in part by suppressing inflammation.

Acute and chronic stressors also induce activation of the NLRP3 inflammasome, which is constitutively expressed in macrophages and microglia (Figure 1d) (for review, refer to Iwata *et al* (2013)). NLRP3 is a cytosolic pattern recognition receptor that can be activated by either ATP or TLR4 binding, initiating pro-caspase-1 cleavage that subsequently cleaves pro-IL-1β to IL-1β. Secretion of pro-inflammatory IL-1β by the activated microglia inflammasome is associated with increased depression-like behaviors in rodents, while NLRP3 null mutant mice exhibit resilience (Figure 1h) (Iwata *et al*, 2015). Administration of a P2X7R antagonist blocked IL-1β release and NLRP3 activation, promoting resilience to chronic unpredictable stress (Iwata *et al*, 2015). This study highlights a role for the ATP/P2X7R-IL-1β-NLRP3 inflammasome cascade in the immune response to psychological stress. In line with these findings, IL-1β receptor inhibition via genetic or pharmacological interventions rescues anhedonia in rats exposed to chronic unpredictable stress (Koo and Duman, 2008) and prevents failure to escape in the LH paradigm (Maier and Watkins, 1995), suggesting a role for IL-1β and downstream signaling in stress vulnerability. Interestingly patients diagnosed with chronic inflammatory diseases such as diabetes, atherosclerosis, myocardial infarction and rheumatoid arthritis, who present with high rates of comorbid MDD, also tend to exhibit enhanced activation of the NLRP3 inflammasome complex (Mason *et al*, 2012).

As occurs in endothelial cells and microglia, the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α can activate receptors at the cell surface of astrocytes (Figure 1b) (Sofroniew, 2014). Astrocytes subsequently release cytokines and inflammatory mediators away from the perivascular region, affecting neighboring astrocytes, microglia, and neurons (for review, see Sofroniew, 2014). Transcriptome profiling of reactive human, rat and mouse astrocytes revealed broad changes following exposure to cytokines

and/or inflammatory mediators including altered calcium signaling, reduced expression of G-protein effectors and growth factors, antigen presentation and regulation of astrocyte production of cytokines (Figure 1b) (Hamby *et al*, 2012; Meeuwsen *et al*, 2003; Pang *et al*, 2001; Sofroniew, 2014). Although each inflammatory molecule induces a specific molecular signature, astrocytes are generally exposed to multiple inflammatory markers and thus synergistic interactions are likely to occur as previously reported in immune cells (Korn *et al*, 2009). Stress-sensitive regions of the brain are highly interconnected (Russo *et al*, 2012), suggesting that an unresolved chronic neuroimmune response in even a restricted area may induce a chain reaction precipitating the development of stress-related disorders.

Other functions of activated microglia and astrocytes in stress-related synaptic plasticity. Synaptic plasticity is a highly dynamic process involving formation, strengthening, shrinking, and elimination of neuronal synapses (Hua and Smith, 2004; Katz and Shatz, 1996). During development, an activity-dependent elimination of immature synapses called synaptic pruning occurs, a process that likely involves microglia (Dalmau *et al*, 1998; Paolicelli *et al*, 2011; Tremblay *et al*, 2011). There is evidence for a similar but slower process of experience-dependent synapse remodeling and elimination in the healthy adult mouse brain, indicating that microglia may also influence synaptic structure in adulthood (Tremblay *et al*, 2010). Synapse development is impaired in mice deficient for the microglia-expressed chemokine receptor Cx3CR1 (Paolicelli *et al*, 2011). *Cx3CR1* knockout mice are characterized by reduced microglial density and transient defects in synaptic plasticity and connectivity in the hippocampus (Paolicelli *et al*, 2011), a brain region essential for memory processes that is involved in various psychiatric disorders including MDD. At the behavioral level, mice lacking the *Cx3CR1* receptor display hippocampal cognitive dysfunction and motor deficits that can be reversed by treatment with an IL-1β antagonist (Rogers *et al*, 2011). Surprisingly, Hellwig *et al* (2015) recently reported enhanced resilience to stress-induced depression-like behavior in *Cx3CR1*-deficient mice after 5 days of repetitive swim stress. Stress induced microglial hyper-ramification in wild-type mice as reported by other groups, but these morphological changes did not occur in *Cx3CR1*-deficient mice (Hellwig *et al*, 2015). As Cx3CR1 receptor binds to a chemokine fractalkine (Cx3CL1) expressed by neurons (Harrison *et al*, 1998), these findings potentially implicate microglia-neuron interactions in the development of stress-related disorders. However, it must be noted that Cx3CR1 is also expressed on peripheral monocytes and macrophages, and that selective knockout of Cx3CR1 in those cells promotes resilience to stress by preventing their recruitment to the mouse brain (Wohleb *et al*, 2013). Thus, future studies are needed to determine whether Cx3CR1 knockout specifically in microglia affects stress-related behaviors and neuronal function.

Microglia can affect neurotransmission and glutamate release through activation of purinergic signaling in astrocytes (Tremblay *et al*, 2011). ATP is an important mediator of brain intercellular communication and activation of astrocytic purinergic receptors has been shown to initiate TNF-α and prostaglandin-dependent glutamate release (Domercq *et al*, 2006). Increased glutamatergic synaptic transmission in stress-related brain regions has been associated with depression-like behaviors in mice (Christoffel *et al*, 2011b; Christoffel *et al*, 2015; Russo and Nestler, 2013), although it remains unclear whether this is due to an astrocyte-dependent mechanism. Astrocytes also maintain homeostasis and provide trophic support to neurons and other glial cells (Ridet *et al*, 1997). Moderate inflammation can lead to morphological hypertrophy of astrocytes while severe and chronic insults induce the release of pro-inflammatory cytokines and promote glial scar formation, triggering microglia-mediated inflammation (Sofroniew, 2009; Zhang *et al*, 2010). Hung *et al* (2016) recently reported that LPS induces growth-associated protein 43 (GAP-43) expression in rat brain astrocytes through activation of TLR4, nuclear factor-κB (NF-κB), IL-6 signal transducer and activator of transcription 3 (STAT3). Knockdown of GAP-43 or inhibition of downstream NF-κB signaling aggravated astrogliosis-induced microglial activation and expression of inflammatory cytokines, suggesting that this growth factor is important for inflammation-induced glial plasticity and attenuation of microglial activation (Hung *et al*, 2016). It would be interesting to evaluate GAP-43 expression in stress-susceptible *vs* resilient mice in future studies as our laboratory has reported that NF-κB signaling is implicated in altered neuronal morphology and depression-like behaviors in socially defeated mice (Christoffel *et al*, 2011a; Christoffel *et al*, 2012). Taken together, these findings highlight the diverse roles of a single signaling pathway in different cell types, promoting either vulnerability to stress or coping mechanisms associated with resilience.

NEUROENDOCRINE MECHANISMS OF SUSCEPTIBILITY *VS* RESILIENCE AND INTERACTIONS WITH INFLAMMATORY PROCESSES

We will now shift our focus to discuss neuroendocrine processes that are relevant to behavioral susceptibility and resilience as well as stress-induced inflammation. The autonomic nervous system (ANS), hypothalamo-pituitary-adrenal (HPA) axis and immune system are by no means mutually exclusive—they interact extensively to titrate hormonal and inflammatory stress response (Amsterdam *et al*, 2002). Immune cells express both adrenergic and GC receptors, making them sensitive to ANS and HPA signals. Furthermore, MDD and numerous inflammatory diseases are characterized by HPA axis dysfunction including reduced levels of HPA hormones as well as disrupted HPA-ANS cross

talk and GC resistance (for review, refer to Straub *et al*, 2011). In this section, we will discuss co-regulation of stress response by HPA axis, ANS and immune processes, as well as the effect of gonadal sex hormones on susceptibility and resilience to stress.

HPA Axis Stress Response and Circulating Glucocorticoids in Mood Disorders

While the immune system appears to act directly on the brain during stressful situations, an appropriate response to stress exposure invariably involves the ANS and HPA axis (for comprehensive reviews, refer to McEwen *et al*, 2015; Ulrich-Lai and Herman, 2009). The ANS promotes an immediate physiological response by modulating heart rate and blood pressure through sympathetic and parasympathetic innervation. Meanwhile, slower activation of the HPA axis increases circulating GCs by promoting their synthesis and release from the adrenal cortex, resulting in widespread physiological, hormonal, and neurobiological effects. This circuit—designed to properly tune the stress response and maintain physiological homeostasis—may be altered in the chronically stressed brain, leading to the development of brain disorders (Figure 2a) (McEwen *et al*, 2015; Pfau and Russo, 2015; Ulrich-Lai and Herman, 2009). Indeed, GCs bind to steroid receptors expressed ubiquitously throughout the brain, altering gene expression and affecting synaptic plasticity, structural remodeling, and ultimately behavioral responses to stress and adaptive coping mechanisms of resilience (Figure 2e and f) (McEwen *et al*, 2015; Pfau and Russo, 2015; Russo *et al*, 2012). Moreover, GCs may produce a persistent sensitization of microglia—maintaining a pro-inflammatory state (Figure 2b) despite resolution of the stressful challenge—that primes neuroimmune responses to subsequent events (Frank *et al*, 2013). GC levels are elevated in the blood of about two-thirds of MDD patients, although an interesting subset of patients are characterized by lower GC levels and display less severe depressive symptoms according to a meta-analysis of 414 independent studies (Stetler and Miller, 2011). In this ambitious meta-analytic study, Stetler and Miller (2011) compared 671 effect sizes for parameters such as cortisol and HPA axis function-related hormones across 361 studies including over 18 000 individuals. The authors observed that while depressed individuals exhibit increased cortisol and adrenocorticotropic hormone levels, they do not display elevated corticotropin-releasing hormone. Surprisingly, age, but not gender, affected HPA outcome. This finding is supported by studies including older hospitalized individuals that report greater cortisol differences between depressed and control subjects when compared with studies focusing on younger outpatient cohorts (Stetler and Miller, 2011). Cortisol differences may also be restricted to sub-populations of patients affected by specific forms of depression (Stetler and Miller, 2011). Altogether, these findings reinforce the need for future studies that account for the heterogeneity of depression, symptoms, and peripheral immune responses. Moreover, HPA hyperactivity and resulting GC resistance may represent a promising link between MDD and diabetes or metabolic syndrome (Brown *et al*, 2004). In line with clinical findings, studies in animal models of depression suggest that the HPA axis is a critical mediator of stress response that can be shifted toward a resilient phenotype through a process termed stress inoculation. For example, rodents exposed to mild to moderate early-life stress in the form of postnatal handling, when compared with unstressed controls and rodents exposed to maternal separation (a more severe stressor) (Figure 2c), display reduced hormonal response to stress in adulthood (Plotsky and Meaney, 1993). This phenomenon has been attributed to the high levels of maternal care displayed by mothers of handled rodents compared with non-handled rodents. High levels of licking, grooming, and arched back nursing promote decreased repressive DNA methylation of the GC receptor gene promoter in handled pups, enhancing hippocampal expression of GC receptors and sensitivity to GC-negative feedback (Figure 2g) (Weaver *et al*, 2005). Interestingly, clinical studies have reported pro-resilience effects of high-dose GC administration in individuals vulnerable to PTSD, including combat-exposed veterans and patients hospitalized in intensive care units (Kearns *et al*, 2012; Schelling *et al*, 2006; Suris *et al*, 2010), suggesting that controlled intermittent exposure to stress mediators may promote resilience in humans. The mechanisms by which GC administration confers resilience in human populations are not yet fully understood but are thought to involve inhibition of traumatic memory consolidation (Kearns *et al*, 2012). Informative future experiments investigating the link between behavioral stress inoculation and the previously mentioned inoculation by exposure to activated immune cells would be valuable to the field. Important questions remain: does prior behavioral exposure to stress promote resilience through actions on adaptive immune cell compartments, and can these interactions be targeted therapeutically to treat mood disorders?

HPA Axis Stress Response and Immune Cells

GCs play a major role in attenuation of inflammatory response by inducing apoptosis in monocytes, macrophages, and T lymphocytes (Figure 2h) (Amsterdam *et al*, 2002) and suppressing NF-κB signaling (De Bosscher *et al*, 2003). They also exert a protective effect on resident cells surrounding sites of inflammation (Amsterdam *et al*, 2002). Chronic stress-induced GC resistance may dampen anti-inflammatory processes (Figure 2d) and induce prolonged production of pro-inflammatory mediators as proposed by Cohen *et al* (2012). In line with this hypothesis, Miller *et al* (2008) reported diminished expression of transcripts related to GCs coupled with heightened expression of transcripts associated with NF-κB signaling in peripheral blood monocytes of familial caregivers of brain cancer patients. Similarly, adults who were raised in low-SES households exhibit higher Toll-like receptor-stimulated

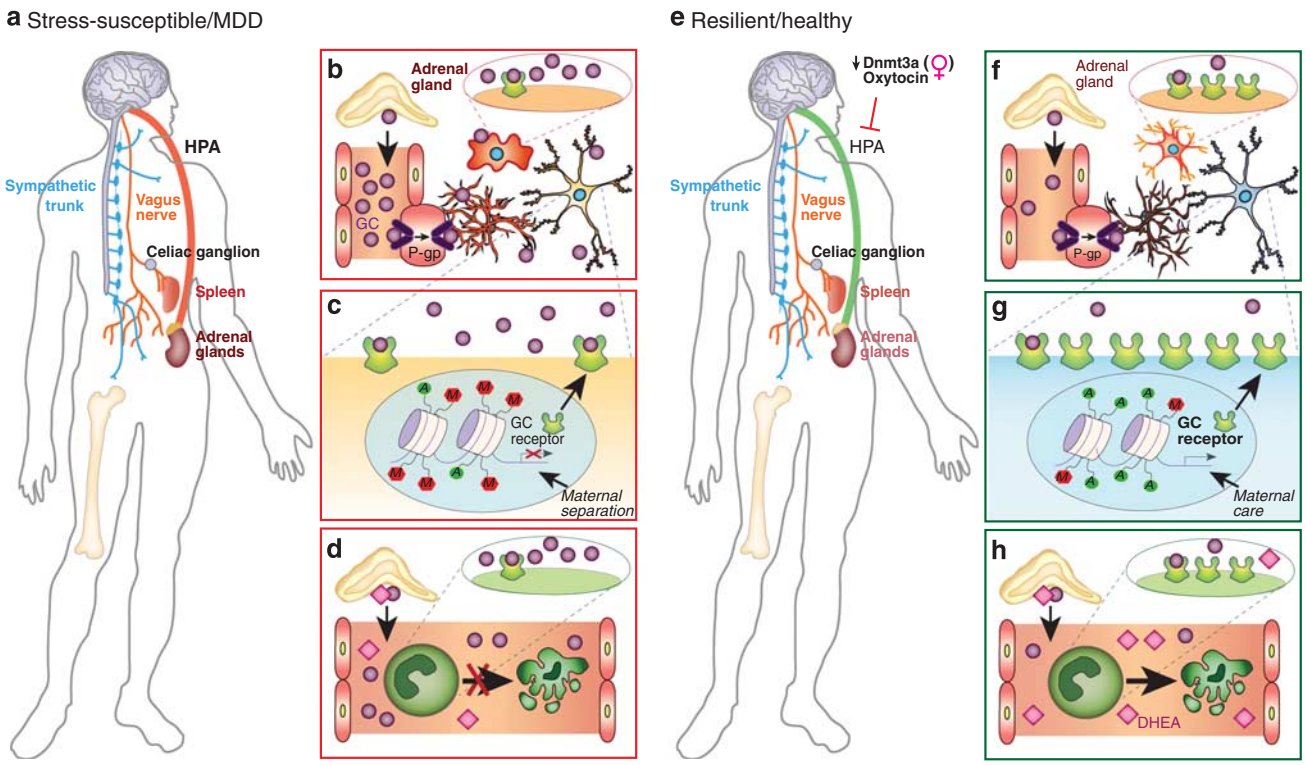

Figure 2. Neuroendocrine mechanisms of stress vulnerability and resilience. (a) Psychological stressors induce the activation of the hypothalamic-pituitary-adrenal axis (HPA), a circuit designed to properly modulate stress response and maintain physiological homeostasis that may be hyperactive in stress-susceptible animals and MDD patients. (b) Circulating glucocorticoids (GCs), which are synthetized and released from the adrenal glands following HPA activation, can cross the blood–brain barrier through P-glycoprotein (P-gp) transporters of endothelial cells and bind to GC receptors on brain cells including microglia and neurons. Prolonged GC binding on microglial receptors may maintain these CNS-resident immune cells in a pro-inflammatory state leading to the establishment of depression-like behaviors. (c) Severe early-life stressors, such as maternal separation, can affect GC receptor epigenetic regulation and promote repressive methylation reducing its expression at the cell surface and inducing GC resistance. (d) GCs play a major role in attenuation of inflammatory response by inducing apoptosis in immune cells, a process that might be involved in stress vulnerability. (e) Clinical studies reported sex differences in HPA response to stressors. Downregulation of DNA methyltransferase 3a (Dnmt3a) activity may promote resilience in a gender-specific manner by modulating gene expression in stress-related brain regions and possibly HPA axis response. The hormone oxytocin, which plays a role in social bonding, parturition and lactation, can reduce HPA axis activation inducing antidepressant effect. (f) Low circulating GC level and high expression of GC receptor in brain cells are associated with proper HPA axis response and a resilient phenotype. (g) Life experience such as high level of maternal care during childhood can positively alter epigenetic regulation of GC receptor gene, leading to enhanced GC receptor expression in brain and immune cells and reduced stress vulnerability. (h) Exogenous GC replacement with dehydroepiandrosterone (DHEA), a precursor for the synthesis of anabolic steroids released from the adrenal cortex with cortisol in response to stress, may blunt stress-induced HPA axis activation, promoting resilience.

production of IL-6 and transcriptional activation of NF-κB signaling in peripheral blood mononuclear cells (Chen *et al*, 2011). Reminiscent of rodent studies of maternal behavior by Meaney's group, subjects who experienced high maternal warmth in early life were protected from low SES-induced inflammation compared with those living in similar environments but with lower maternal warmth (Chen *et al*, 2011). A study conducted in non-human primates provided additional evidence of adverse early-life social conditions altering leukocyte transcriptional profiles. Early-life stress promoted enhanced expression of genes involved in inflammation, cytokine signaling, and T-lymphocyte activation, but suppressed genes associated with innate antimicrobial and antiviral responses (Cole *et al*, 2012). As mentioned earlier, pro-inflammatory transcriptional responses have also been reported in leukocytes of socially defeated mice (Powell *et al*, 2013). Furthermore, following SDR, splenic leukocytes from stressed mice are more sensitive to LPS stimulation and release higher levels of pro-inflammatory cytokines IL-6 and TNFα compared with unstressed controls (Avitsur *et al*, 2003). Mouse splenic macrophages and monocytes are less sensitive to the inhibitory effects of GCs after 6 days of psychosocial stress (Avitsur *et al*, 2005; Stark *et al*, 2001) indicating a dysregulation of the negative feedback mechanisms suppressing inflammatory signaling. In patients under chronic interferon-α treatment to control hepatitis C virus, interferon-α-induced inflammation was associated with reduced GC-negative feedback sensitivity and depressive symptoms (Felger *et al*, 2015a). Overall, these findings highlight an important role for immune-ANS-HPA interactions in maladaptive stress responses and shed light on the comorbidity of inflammatory diseases with MDD, as immune cell GC resistance has been raised as a major barrier to treating inflammatory diseases (Barnes and Adcock, 2009).

Sex Differences in HPA-Axis-Mediated Stress Response

MDD and mood disorders are more prevalent in women (Kessler *et al*, 1993), suggesting that sex differences may play a role in the pathogenesis of these diseases. In fact, sexual dimorphism in the stress response has been observed in various animal models of depression (for review, refer to Pfau and Russo, 2015). Overall, adult female rodents exhibit greater cognitive resilience to chronic stress, while their male counterparts display enhanced emotional resilience. In line with these behavioral observations, chronic restraint stress modifies hippocampal CA3 neuronal morphology, which is closely associated with memory formation, in male but not female rats (Galea *et al*, 1997). GC receptor density is reduced in male rat hippocampus after 21 days of restraint stress (Kitraki *et al*, 2004). However, receptor density is enhanced in females, providing a potential explanation for gender-specific spatial memory performance discrepancies in animal models of depression (Kitraki *et al*, 2004). Clinical findings paint a more complicated picture, suggesting gender-specific HPA axis dysfunction in human patients and supporting hypotheses that the experience and symptoms of depression are different in men and women (Martin *et al*, 2013). Cortisol level is significantly higher in men meeting criteria for MDD compared with healthy controls, while no difference is observed in depressed women, suggesting that HPA axis hyperactivity may be more characteristic of male depression (Sanches *et al*, 2013). Furthermore, Kirschbaum *et al* (1995) suggest that a subpopulation of healthy men may be unable to adapt their adrenocortical stress response to repeated psychological stress leading to HPA axis hyperactivity and a higher risk of developing mood disorders. Shedding additional light on these findings, Suarez *et al* (2015) evaluated corticosterone (CORT) to CRP ratio, a measure that is thought to indicate the efficiency of homeostatic HPA-immune regulatory mechanisms and predict vulnerability to MDD. CRP is synthetized by hepatocytes in response to IL-6 release and becomes elevated shortly after the onset of inflammation, while CORT is subsequently released upon activation of the HPA axis. Low CORT/CRP ratios indicate a blunted HPA axis-related response to elevation of inflammatory signals. CORT/CRP ratio was associated with severity of depressive symptoms in a gender-specific manner (Suarez *et al*, 2015). Depressed women were characterized by lower CORT/CRP ratios, suggesting insufficient release of CORT despite heightened inflammatory state. In contrast, anxiety was correlated with higher CORT/CRP ratio in men, indicating a hyperactive response of the HPA axis (Suarez *et al*, 2015). Before this study, Miller *et al* (2005) reported lower CORT release in response to acute stress-induced inflammation in depressed women when compared with healthy controls. In this study, subjects were exposed to a mock job interview and blood was drawn to assess secretion and regulation of inflammatory molecules. Stress was associated with anxious behaviors as well as mobilization of monocytes and neutrophils and enhanced stimulated release of IL-6 and TNF-α by leukocytes *in vitro* (Miller *et al*, 2005). Interestingly, before the stressful experience, depressed women displayed greater sensitivity to the anti-inflammatory properties of GC in comparison with healthy controls. However, after the stressor, GCs sensitivity decreased only among depressed women (it increased in controls), indicating impairment in HPA axis regulation of stress-related inflammation. This study focused exclusively on female subjects, but additional studies on HPA axis sensitivity in depressed men (as opposed to healthy controls exposed to acute stress) would be informative.

Animal studies suggest that initiation of sex differences in vulnerability to stress may occur even before birth. Indeed, in mice, male offspring of mothers that have been exposed to chronic unpredictable stress during early pregnancy develop depression-like behaviors while female offspring do not (Mueller and Bale, 2008). These gender-specific maladaptive behavioral responses were associated with exacerbated HPA axis response, long-term alterations in amygdala corticotropin-releasing factor (CRF) expression and decreased hippocampal GC receptor expression driven by enhanced repressive methylation at the GC receptor promoter. Placental expression profiles also suggest a role for DNA methyltransferase 1 (Dnmt1), a methylation maintenance enzyme, in the establishment of adult phenotypes (Mueller and Bale, 2008). In line with these findings, our laboratory recently reported DNA methyltransferase 3a (Dnmt3a) -dependent sex differences in adult mouse nucleus accumbens (NAc) transcriptome profiles following exposure to subchronic variable stress (SCVS) (Hodes *et al*, 2015b). This 6-day stress paradigm is sufficient to induce depression-like behaviors in female, but not male, mice, allowing us to explore mechanisms underlying sex differences in stress response. NAc RNA-sequencing revealed gender-specific stress regulation of gene expression (Hodes *et al*, 2015b). Dnmt3a was among the genes upregulated only in females and local overexpression of Dnmt3a in the NAc rendered male mice more susceptible to SCVS. Conversely, knocking down Dnmt3a in NAc rendered females more resilient. Moreover, the female transcriptome shifted toward a more male-like pattern, indicating a role for this gene in stress-related sex differences (Hodes *et al*, 2015b). Interestingly, one of the most enriched biological pathways regulated by Dnmt3a was the CRF pathway, suggesting a role for HPA axis regulation in sex differences in stress vulnerability (Figure 2e). These studies, as well as additional preclinical evidence (for comprehensive review, please refer to Hodes (2013)), suggest an important role for experience-dependent epigenetic modifications in sexual dimorphism of stress sensitivity. In contrast to clinical studies, which largely employ blood samples, most studies in animal models focus on sex differences in HPA axis response in CNS tissues. Further investigation of sex differences in neuroendocrine-immune regulation of stress vulnerability in immune cells would provide valuable insight into depression etiology and treatment.

Sex Differences in Microglial Activation

Numerous recent studies outline an interesting link between immune cells, hormonal processes, and development, suggesting that microglial activation may play a role in brain sex differences and masculinization (for review, refer to Lenz and McCarthy (2015)). Indeed, inhibition of these immune cells during the critical period for sexual differentiation in rodents can prevent morphological changes generally associated with the male brain in the preoptic area (POA), a highly sexually dimorphic nucleus involved in male sexual behavior (Lenz *et al*, 2013). At the morphological level, the POA is five- to seven-fold larger in males (Gorski *et al*, 1978) and its neurons exhibit two to three times more dendritic spines as well as more complex astrocytic processes (Amateau and McCarthy, 2002, 2004). Furthermore, neonatal male brains contain twice as many microglia cells as do female brains (Lenz and McCarthy, 2015). Although the mechanisms of sex differences in microglia-dependent masculinization are not well established, microglia express prostaglandin receptors that may be actively involved in gender-specificity of POA-mediated behaviors through direct interactions with neurons (Lenz *et al*, 2013). For example, a single exposure to prostaglandins is sufficient to not only shift neuronal morphology toward a masculine phenotype but also alter sexual behavior in adulthood (Wright and McCarthy, 2009). Conversely, inhibition of prostaglandins synthesis with a cyclooxygenase (COX) inhibitor downregulates dendritic spine density and impairs sexual behaviors in males (Amateau and McCarthy, 2004). These intriguing results provide evidence for distinct neuroimmune interactions during sexual differentiation of the brain; however, it is not clear whether similar mechanisms are involved in sex differences in stress-induced plasticity during adulthood. A few recent studies have hinted that this might be the case.

Around the beginning of puberty and into early adulthood, female rats develop more microglia than do males in select brain areas including the amygdala, parietal cortex, and hippocampus (Schwartz *et al*, 2012; Hanamsagar and Bilbo, 2015). During adulthood, females have a greater ratio of primed microglia to ramified microglia compared with males. There are also prominent sex differences in the effects of restraint stress on microglial morphology in the medial prefrontal cortex of adult rats. Exposure to either acute or chronic restraint stress reduced the proportion of primed microglia in females but not males (Bollinger *et al*, 2016). This study raises the interesting possibility that females are normally in a more activated central immune state than males, and that stress acts to suppress these responses in females. However, additional research is needed to determine the functional contribution of these basal sex differences in stress susceptibility and resilience. More research is also required to elucidate whether sex-specific stress effects on microglial activation and morphology are ubiquitous through the brain or occur only in particular regions related to emotionality.

FUTURE DIRECTIONS—ANTI-INFLAMMATORY AND HORMONAL THERAPEUTICS TO TREAT MOOD DISORDERS

Recent ongoing clinical studies are translating basic research findings regarding the role of the immune and neuroendocrine systems into clinical practice. Below, we highlight clinical findings most relevant to immune and hormonal processes.

Anti-inflammatory Therapeutics

Considering the mounting evidence supporting a role for the immune system in development of mood disorders and possibly resistance to current antidepressant treatments, clinical studies have evaluated potential benefits of anti-inflammatory agents in depressed patients (Box 1). A meta-analysis of randomized clinical trials including 10 for non-steroidal anti-inflammatory drugs (NSAIDs) and four for cytokine inhibitors provides proof-of-concept for using anti-inflammatory treatments to reduce depressive symptoms (Kohler *et al*, 2014). The selective COX-2 inhibitor celecoxib seems to be particularly effective in producing antidepressant effect, as measured by treatment response and remission. Moreover, no evidence of gastrointestinal or cardiovascular side effects was observed after chronic treatment when compared with placebo (Kohler *et al*, 2014). However, non-selective COX inhibition does not seem to be as efficient (Eyre *et al*, 2015). There have also been some reported benefits of NSAID therapy on depressive symptoms in patients suffering from osteoarthritis (Iyengar *et al*, 2013), raising the possibility of monotherapy to treat comorbid inflammatory diseases and MDD. However, it should be noted that overall the evidence supporting antidepressant effects of these more traditional non-selective anti-inflammatory medications is not very strong. In addition, some anti-inflammatory drugs could potentially interfere with the bioavailability of widely prescribed antidepressants such as SSRIs, raising concerns for clinicians and highlighting the need to carefully consider side effect profiles when combining NSAIDs with traditional antidepressants (Warner-Schmidt *et al*, 2011).

Treatment of depressed patients with humanized antibodies that more selectively target individual pro-inflammatory cytokines (Figure 1f) has also been evaluated in recent clinical trials. A double-blind, placebo-controlled randomized clinical trial revealed an improvement of depressive symptoms in patients treated with infliximab (Raison *et al*, 2013), a chimeric monoclonal antibody against TNFα generally used to treat autoimmune diseases (Willrich *et al*, 2015). However, efficacy was limited to patients presenting a high baseline level of inflammation as assessed by CRP concentration at the beginning of the trial (Raison *et al*, 2013). The therapeutic potential of IL-6 antagonism to treat bipolar and unipolar disorder has been proposed following reports of increased IL-6 level during manic and depressive episodes (Brietzke *et al*, 2011). The use of

BOX 1 Past and Ongoing Clinical Trials for MDD with Anti-inflammatory Drugs and Hormonal Therapeutics

Celecoxib is a COX-2 selective non-steroidal anti-inflammatory drug (NSAID). Two clinical trials are currently recruiting participants. One will attempt to enhance and augment the antidepressant efficacy of escitalopram by combining it with celecoxib in poorly responding bipolar depressed patients (NCT01479829). The other will evaluate antidepressant properties of 8-week celecoxib treatment in depressed patients resistant to minocycline beneficial effects by measuring depressive scores with the Hamilton Depression Rating Scale (NCT02362529).
Infliximab is a chimeric monoclonal antibody against TNF-α generally used to treat autoimmune diseases. A completed 12-week clinical trial including three infusions of either infliximab or placebo at weeks 0, 2 and 6 did not reveal generalized efficacy in treatment-resistant depression but note an overall improvement of depressive symptoms in patients suffering from MDD with high baseline inflammatory markers (NCT00463580) (Raison *et al*, 2013). Another trial not yet open for participant recruitment will soon evaluate the efficacy of 12-week infliximab treatment on bipolar I/II depression in individuals exhibiting signs of high inflammation (NCT02363738).
Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor used as an immunosuppressive drug in the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis. A clinical trial, not yet open for participant recruitment; will examine antidepressant effects of 8-week tocilizumab treatment in patients suffering from treatment-refractory MDD using the Hamilton Depression Rating Scale and remission rate (NCT02660528).
Sirukumab is a humanized monoclonal antibody against the pro-inflammatory cytokine IL-6, used to treat rheumatoid arthritis, currently in phase 2 clinical trials for the treatment of depression. This 12-week study consists of three subcutaneous injections at days 1, 28 and 56 in participants diagnosed with MDD and resistant to current standard oral antidepressant treatment but also characterized by high C-reactive protein sensitivity. Efficacy of sirukumab treatment on depressive symptoms will be compared with adjunctive placebo at the 12-week end point (NCT02473289).
Ketamine is an anesthetic uses for sedation and chronic pain relief displaying robust antidepressant effects. A search on www.clinicaltrials.gov revealed over 100 completed or recruiting trials evaluating the antidepressant effects of ketamine in MDD or treatment-resistant depression, bipolar depression, suicidal ideation, etc. However, only two trials currently recruiting participants propose to investigate if ketamine treatment affects MDD-related peripheral inflammation. The first one will evaluate the effects of repeated infusions of ketamine on severity of depressive symptoms in treatment-resistant depressed patients and inflammatory mediator's expression as a secondary outcome measure (NCT01945047). The second one will determine the efficacy of 24 hours intravenous low-dose of ketamine to improve depressive symptoms and reduce circulating IL-1 and TNFα levels (NCT02610712).
DHEA is an endogenous steroid hormone. To our knowledge no clinical trial has directly assessed its efficacy on MDD-related inflammation yet despite reported beneficial effects on depressive symptoms.
Oxytocin is an endogenous hormone involved in social bonding, reproduction and lactation. An ongoing trial will evaluate the efficacy of a single-dose administration of oxytocin on postpartum depressive symptoms and assess its effect on brain activity and connectivity in empathy-related brain regions (NCT02191423). Another trial will evaluate the efficacy of intranasal oxytocin administration during the first postpartum days in mothers at risk to develop postpartum depression (NCT02505984). Clinical trials evaluating oxytocin efficacy to treat depressive symptoms are not restricted to postpartum depression. One trial currently recruiting participants will compare the efficacy of intranasal oxytocin treatment *vs* placebo, both combined to interpersonal psychotherapy, in the treatment of major depressive disorder (NCT02405715). However according to the information available none of these trials are measuring outcomes related to peripheral inflammation.

tocilizumab, a humanized antibody against IL-6 receptor, or sirukumab, a humanized antibody against IL-6 have been proposed as novel antidepressant therapeutics (Traki *et al*, 2014; Hsu *et al*, 2015). Two ongoing clinical trials will examine the antidepressant effects of tocilizumab and sirukumab among patients with treatment-refractory major depression (www.clinicaltrials.gov).

If inflammatory processes are involved in MDD pathogenesis, one might assume that treatment with antidepressants should at least partly reduce overall inflammatory load. Recent findings suggest that ketamine, a novel antidepressant producing rapid action and long-term positive effects in treatment-resistant depressed patients (Murrough *et al*, 2013a; Murrough *et al*, 2013b), can decrease levels of the pro-inflammatory cytokines IL-1β, IL-6, and TNFα, possibly through inhibition of TLR4 (for review, refer to De Kock *et al* (2013)). Conversely, evidence assessing effects of traditional antidepressants on inflammation is mixed with studies reporting a reduction (Sluzewska *et al*, 1995), no effect (Jazayeri *et al*, 2010; Maes *et al*, 1995a), or even an increase (Kubera *et al*, 2004) in circulating IL-6 levels. These discrepancies could be related to methodological heterogeneity across variables including age, gender, depressive measures, severity of depressive symptoms, and type and duration of antidepressant treatment; as well as study design and duration, or the fact that increased inflammation is not ubiquitously treated with standard antidepressant treatments.

Hormonal Therapeutics

Clinical studies suggest a promising role for exogenous GC replacement in blunting stress-induced HPA axis activation and promoting resilience (Box 1). A study conducted in patients suffering from PTSD revealed that dehydroepiandrosterone (DHEA), a precursor for the synthesis of anabolic steroids released from the adrenal cortex with cortisol in response to stress, possesses antiglucocorticoid properties (Rasmusson *et al*, 2003; Russo *et al*, 2012). DHEA level increases rapidly in blood under acute stress, and higher DHEA-to-cortisol ratio promotes resilience (Figure 2h) (Rasmusson *et al*, 2003). In contrast, lower DHEA-to-cortisol ratio correlates with greater severity of PTSD symptoms (Figure 2d) (Yehuda *et al*, 2006). A meta-analysis of clinical studies reported lower DHEA sulfate derivative (DHEAS) in individuals diagnosed with depression. However, ethnicity-stratified analysis indicated that lower levels of DHEAS were not observed in Caucasian and Asian depressed patients (Hu *et al*, 2015). These discrepancies could explain the lack of benefit of DHEA supplementation on subjective stress in an initial randomized trial of men undergoing military survival training (Taylor *et al*, 2012). Alternatively, DHEA level decreases with normal aging and this reduction may be linked to age-related decline in immune function and increased prevalence of mood disorders. In mice, altered regulation of IL-6 production can be prevented or reversed with DHEAS supplements (Daynes *et al*, 1993). These observations were later corroborated in human: serum DHEA/DHEAS decreases while IL-6 level increases with age in both men and women, leading to a significant inverse correlation between DHEA/DHEAS and IL-6 (but not TNFα) levels in peripheral blood mononuclear cells (Straub *et al*, 1998). MDD is highly prevalent in older adults and may be a preventable risk factor for dementia (for review, refer to Wang and Blazer (2015b)). Considering the rapid growth of aged human populations, further studies are necessary to better understand and therapeutically address age-related neuroimmune and

neurobiological changes that may be associated with MDD in the elderly.

Another target that could promote resilience through direct actions on immune function is the neuropeptide oxytocin. Although conventionally viewed as a hormone responsible for parturition and lactation, oxytocin is also associated with prosocial behaviors such as social bonding, altruism, empathy, and positive communication (for reviews refer to McQuaid *et al* (2014) and Wang *et al* (2015a)). It acts as a neuromodulator in multiple brain regions involved in stress-related disorders and thus may contribute to the development of MDD. In fact, administration of oxytocin has strong antidepressant effects in rodents across multiple behavioral domains (Arletti and Bertolini, 1987; Grippo *et al*, 2009). Oxytocin reduces HPA axis activation (Figure 2e) and pro-inflammatory cytokine release in response to LPS stimulation in healthy men (Clodi *et al*, 2008). Norman *et al* (2010) showed that oxytocin administration attenuated cortical IL-1β expression and depression-like behaviors following spared nerve injury in socially isolated mice. Conversely, treatment of pair-housed animals with an oxytocin receptor antagonist induced a depressive phenotype and increases IL-1β level in the frontal cortex (Norman *et al*, 2010). Clinical studies have reported that circulating oxytocin is reduced in patients suffering from MDD (Frasch *et al*, 1995) and negatively correlates with depressive symptoms (Scantamburlo *et al*, 2007). However, no difference was measured in cerebrospinal fluid (Sasayama *et al*, 2012) and other studies reported contradictory findings (Parker *et al*, 2010) that may be related to gender-specific effects (Ozsoy *et al*, 2009; Yuen *et al*, 2014). These discrepancies may also be related to variability of subjects' depressive symptoms, antidepressant treatments and past experiences. Indeed, early-life challenges such as childhood abuse were associated with lower plasma oxytocin levels in both men (Opacka-Juffry and Mohiyeddini, 2012) and women (Heim *et al*, 2009), suggesting an inherent oxytocin-dependent vulnerability to stressors in adult life. Despite the excitement surrounding oxytocin therapeutics, far more work is needed to fully understand the role of oxytocin in proper immune function and depression.

CONCLUSIONS

Taken together, findings from both clinical studies and rodent models of depression support an active role for the neuroendocrine and immune systems in stress response and vulnerability to mood disorders. Identification and characterization of dysregulated immune and hormonal processes observed in patients suffering from MDD that have been reverse translated into rodent models to show causation has helped us to better understand the neuroimmune mechanisms of depression. Reciprocally, basic research findings have been applied to clinical research and therapeutic trials, producing encouraging results. Nevertheless, further research is required to determine key cellular and molecular mechanisms affecting stress-related immune and neuroendocrine responses and stress-induced plasticity in central and peripheral systems. For instance, future studies should investigate innate and adaptive immune responses in stress-susceptible *vs* resilient animals, and evaluate whether manipulation of inflammatory mediators is an effective means to promote resilience to stress. Although many clinical studies have been conducted in depressed patients, only a handful investigated mechanisms of resilience. Intriguing future clinical studies could recruit highly resilient individuals for comparison with depressed patients and healthy controls. Increasing insight into the biology of resilience may help us to elucidate novel targets for more broadly effective treatment of mood disorders.

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The authors declare no conflict of interest.

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