Review article

The role of inflammation in core features of depression: Insights from paradigms using exogenously-induced inflammation

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ABSTRACT

A wealth of evidence has implicated inflammation in the development of depression. Yet, the heterogeneous nature of depression has impeded efforts to understand, prevent, and treat the disease. The purpose of this integrative review is to summarize the connections between inflammation and established core features of depression that exhibit more homogeneity than the syndrome itself: exaggerated reactivity to negative information, altered reward processing, decreased cognitive control, and somatic syndrome. For each core feature, we first provide a brief overview of its relevance to depression and neurobiological underpinnings, and then review evidence investigating a potential role of inflammation. We focus primarily on findings from experimental paradigms of exogenously-induced inflammation. We conclude that inflammation likely plays a role in exaggerated reactivity to negative information, altered reward reactivity, and somatic symptoms. There is less evidence supporting an effect of inflammation on cognitive control as assessed by standard neuropsychological measures. Finally, we discuss implications for future research and recommendations for how to test the role of inflammation in the pathogenesis of heterogeneous psychiatric disorders.

1. Introduction

An estimated 11–15% of the global population will experience a major depressive episode in their lifetime (Bromet et al., 2011; Kessler and Bromet, 2013). Only about half of affected individuals achieve remission under available treatments (Nemeroff, 2007), and depression remains the leading global cause of disability· (WHO Depression, 2017). Identifying biological and behavioral processes underlying depression—and the links among them—that can be targeted by interventions is a global health priority. One of the more promising research areas in this vein involves inflammation. Substantial evidence across various populations and study designs has implicated inflammation in the etiology of depression (Dantzer et al., 2008; Irwin, 2002; Miller et al., 2009; Raison et al., 2006). However, depression is an exceedingly heterogeneous disorder as evidenced by the mixed symptom phenotypes that qualify for the disorder (Fried and Nesse, 2015; Young et al., 2014) and the mixed effectiveness of existing treatments (Biesheuvel-Leliefeld et al., 2015; Cipriani et al., 2018; Piet and Hougaard, 2011;

Shea et al., 1992; Vittengl et al., 2007). Thus, it is likely that a better understanding of Major Depressive Disorder and its effective treatment will emerge by focusing on the role of inflammation in the onset and maintenance of more homogenous core features that are disrupted among depressed patients (Craske, 2012; Gottesman and Gould, 2003; Hasler et al., 2004).

The aim of the present review is to determine if exogenously-induced inflammation may cause core features of depression, or endophenotypes. Endophenotypes are quantitative traits that are heritable and reflect the functioning of a discrete biological system (Gottesman and Gould, 2003). Traits falling within the definition of an endophenotype are thought to more closely reflect the root cause of a given disease than the broad clinical phenotype represented by symptoms. First, we review the evidence that inflammation plays a role in depression, and underscore the value of an endophenotype approach to organizing the heterogeneity of psychopathology into treatment relevant, dimensional domains. Next, we identify and define several key endophenotypes for depression: reactivity to negative information,

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altered reward processing, cognitive control, and somatic syndrome. For each endophenotype, we review evidence supporting its relevance for depression and its neurobiological correlates, and then examine evidence that inflammation modulates the processes represented by the endophenotype. Evidence informing the role of inflammation in each endophenotype is drawn primarily from experimental studies employing one of three paradigms for inducing inflammation: typhoid vaccination, injection with endotoxin, or treatment with interferon (IFN)-α. The strength of limiting our review to studies using these three paradigms is that such studies can test a causal role of inflammation in each psychological construct. Finally, we propose future research directions aimed at understanding the role of inflammation in the pathogenesis of depression.

1.1. Mechanisms linking inflammation and depression

Inflammation is a key component of the innate immune system's ability to clear infection and repair injured tissue. Inflammation results from the release of pro-inflammatory cytokines from innate immune cells. In addition to their effects in the periphery, cytokines can communicate with the brain and result in a host of emotional, cognitive, and behavioral changes collectively termed "sickness behaviors" (Dantzer et al., 2008). Of particular relevance for this review, peripheral inflammation has been shown to induce depressive-like behaviors in animal models, including anhedonia (e.g., reduced sucrose consumption), decreases in exploratory, novelty-seeking and social behaviors, reduced food intake; and sleep disturbance (Anisman and Matheson, 2005; De La Garza, 2005; Dunn et al., 2005; Larson and Dunn, 2001; Pecchi et al., 2009). These sickness behaviors are considered an adaptive response intended to reduce the spread of infection and promote healing. However, prolonged inflammatory signaling, such as when the inflammatory response is maintained by ongoing psychosocial stress, can have detrimental effects that include risk for depression and other psychiatric diseases (Dantzer et al., 2008; Miller et al., 2009; Miller and Raison, 2016; Slavich and Irwin, 2014).

Research conducted over the last several decades has elucidated the mechanisms by which peripheral inflammation can access the brain to influence neural processes relevant for depression, including neuroplasticity, neurotransmitter systems, and neuroendocrine function (see Banks and Erickson, 2010; Haroon et al., 2012 for comprehensive reviews on this topic). For example, inflammatory cytokines can alter neuroplasticity by decreasing expression of the brain-derived neuroprotective hormone BDNF (Calabrese et al., 2014). Inflammation can also lead to changes in dopaminergic systems, with relevance for depression (See Felger, 2017 for review). Indeed, single injections of high doses of LPS (5 mg/kg) lead to degeneration in dopaminergic system in the brain, particularly in the substantia nigra and the striatum (Qin et al., 2007; Reinert et al., 2014). Further, chronic treatment with IFN-α in non-human primates leads to decreases in the synthesis and availability of dopamine in the striatum, which are correlated with reductions in effort-dependent sucrose consumption (Felger et al., 2013). There is a wealth of experimental research in rodents demonstrating that decreases in dopamine release and binding to the dopamine receptor is closely linked with deficits in reward-motivated behavior in depression (Nestler and Carlezon, 2006).

In addition to effects on dopamine, inflammation can influence the serotonin system through alterations in tryptophan metabolism. Under normal, healthy conditions, approximately 5% of tryptophan is metabolized into serotonin while 95% is metabolized through the kynurenine pathway. Metabolism of tryptophan through the kynurenine pathway can either be converted to neurotoxic 3-hydroxykynurenin (OHK) and quinolinic acid (QUIN) or neuroprotective kynurenic acid. How tryptophan is metabolized is determined by the presence of indoleamine-2,3-dioxygenase (IDO). In preclinical models, activation of inflammation using LPS increases the activity of IDO thereby allocating more tryptophan metabolism toward the kynurenine pathway rather

than serotonin synthesis (Zunszain et al., 2012), ultimately resulting in serotonin deficiency (See Dantzer et al., 2011; Nikkheslat et al., 2018; O'Farrell and Harkin, 2017 for a review of research on the kynurenine pathway). In preclinical models, LPS-induced depressive behavior is mediated by IDO activation (O'Connor et al., 2009). Of note, inflammation and IDO can both influence glutamate metabolism, which may also play a role in depression

Inflammation can impact almost all aspects of glutamate neurotransmission (See Haroon and Miller, 2017 for review). To summarize briefly, glutamate is released at a higher rate under conditions of stress (Goshen and Yirmiya, 2009), and excess presence of synaptic glutamate can lead to excitotoxicity and neuronal death (Ankarcrona et al., 1995). Control of synaptic glutamate concentrations depend upon release and clearance by neurons, astrocytes, microglia, and oligodendrocytes. Following the summary of the kynurenine pathway in the previous paragraph, QUIN and glutamate released by activated microglia operate synergistically to promote excitotoxicity (Dantzer and Walker, 2014). When synaptic glutamate is detected by glial cells via their glutamate receptors, they activate gliotransmission in order to maintain regulation of local excitatory activity. However, inflammatory cytokines such as TNF-α and IL-1ß interfere with the ability of glial cells to do this by altering their Ca^{2+} channels. The effect of inflammatory cytokines on calcium ion channels also leads to reverse efflux, which means that instead of glial cells taking in glutamate and detoxifying it, glutamate is released back into the extracellular space (Malarkey and Parpura, 2008).

Further, inflammation has potent effects on neuroendocrine systems. Inflammatory cytokines may indirectly upregulate glucocorticoids in the body by interfering with the functional capacity of the glucocorticoid receptor (Pace, Hu, & Miller, 2007; Raison & Miller, 2003), resulting in continued synthesis of corticotropin releasing hormone (CRH) and sustained activation of the HPA-axis which has long been implicated in the pathogenesis of depression (Lopez-Duran et al., 2009; Nikkheslat et al., 2018; Pariante and Lightman, 2008). This process can become self-perpetuating because chronically elevated glucocorticoids can stimulate production of neuroinflammation by activating microglia (Frank et al., 2013; Nair and Bonneau, 2006), the resident immune cells of the brain.

In summary, preclinical models have elegantly demonstrated the mechanisms through which inflammation can access the brain to influence neural processes relevant for depression, providing strong mechanistic support for this association. Next, we consider studies conducted in humans that have interrogated links between inflammation and depression, focusing on experimental paradigms.

1.2. Inflammation and depression in humans: experimental paradigms

There is growing evidence in humans that inflammation plays a role in the pathogenesis of depression. Markers of inflammation are elevated in depressed individuals (Dowlati et al., 2010; Haapakoski et al., 2015; Howren et al., 2009) and predict increases in depressive symptoms in longitudinal studies (Gimeno et al., 2009; Valkanova et al., 2013; van den Biggelaar et al., 2007; Wium-Andersen et al., 2013). Similarly, recent data from a study of twin pairs—which holds constant shared genetic and early environmental factors—showed that the twin with higher CRP concentrations at baseline was more likely to develop depression five years later (Huang et al., 2017). Yet, there is also evidence that the inflammation-depression pathway is bidirectional as depressive symptoms predict increases in inflammation in some samples (Huang et al., 2017; Matthews et al., 2010; Stewart et al., 2009). Experimental paradigms, such as those using exogenously-induced inflammation, are needed to inform our understanding of the directional pathways between inflammation and depression.

Causal evidence in humans supporting a role for inflammation in core features of depression comes from studies administering an inflammatory challenge and examining subsequent changes in cognitive

Table 1
Examples of the three paradigms used to examine the link between inflammation and depression, and their key features.

Paradigm	Citation	Dosing schedule	Actual or estimated[a] IL-6 increase (% increase)	Time of IL-6 assessment	Duration of increase	Strengths	Limitations
IFN-α							
Hepatitis C (3 MU/m² dose)	Dowell et al., 2016	3 days/wk, for 4 - 24 mos	2.18 pg/mL (102%)	4 hrs following initial injection	Sustained throughout treatment	Models effects of chronic, low/moderate levels of inflammation; allows for the investigation of temporal development of symptoms and relationships between symptoms	Effects of inflammation may be confounded by presence of pre-existing chronic disease. Limits generalizability of findings.
Malignant melanoma (20 / 10 MU/ m² dose)	Capuron et al., 2003	20 MU/m² 5 days/wk, for 1 month / then 10 MU/m² 3 days/wk for 12 mos	46 pg/mL (1533%)[a]	3 hrs following initial injection	Sustained throughout treatment; however, at 8 wks, IL-6 increase to injection fell to 2.33 pg/mL (233% increase from baseline)		
Endotoxin							
0.2 ng/kg of body weight dose	Krabbe et al., 2005	1x	4 pg/mL (400%)[a]	3 hrs post-injection	Resolves within 4.5 hours	Models effects of acute exposure to high levels of inflammation. Used in medically healthy samples to avoid confound of pre-existing disease.	Can cause illness symptoms. Elicits increases in inflammation higher than typically seen in individuals with depression.
0.8 ng/kg of body weight dose	Eisenberger et al., 2009	1x	145 pg/mL (28,900%)[a]	3 hrs post-injection	Resolves within 6 hrs		
2.0 ng/kg of body weight dose	Lasselin et al., 2017	1x	1000 pg/mL (49,900%)[a]	3 hrs post-injection	Did not resolve by last assessment (7 hours post-injection)		
Vaccination							
Typhoid vaccine	Wright et al., 2005	1x	0.87 pg/mL (106%)	3 hrs post-injection	Resolves within 32 hrs[b]	Models effects of acute exposure to mild elevations in inflammation, comparable to elevations seen in individuals with depression. Is safe to use in diverse samples. Does not typically cause illness symptoms.	May not be sufficient to elicit sustained increases in depressed mood or changes in behavior.
Influenza vaccine	Kuhlman et al., 2018	1x	0.33 pg/mL (29%)	24 hours post-injection	Resolves within 3-7 days[c]		

[a] Values are approximate, based on graphs.
[b] Hingorani et al., 1999.
[c] Christian et al., 2011; Tsai et al., 2005.

and behavioral functioning. Three predominant models have been used to this end: vaccination, endotoxin, and interferon-α (IFN-α) therapy. The results of studies using these paradigms will be the focus of the present review. Key features and evidence from these three models will be discussed below; Table 1 also provides a summary of the key characteristics of each of these models.

Some of the earliest evidence of a link between inflammation and depression came from clinical observations of patients with Hepatitis C or cancer, who commonly develop clinically significant depressive symptoms after the initiation of IFN-α therapy (Capuron and Miller, 2004; Raison et al., 2005). IFN-α is a cytokine released by the innate immune system, and stimulates the release of other proinflammatory cytokines such as IL-6 (Taylor and Grossberg, 1998). Studies of patients receiving this treatment have shown that IFN-α can induce symptoms of depressed mood, fatigue, sleep disturbance, loss of appetite, pain, anxiety, anhedonia, anger, hostility, cognitive impairment, and suicidal ideation (Capuron et al., 2002; Janssen et al., 1994; Lotrich et al., 2007). IFN-α treatment causes symptoms sufficient for a major depression diagnosis in up to 50% of patients (Musselman et al., 2001).

Dosing schedules for IFN-α therapy typically involve multiple treatments per week over a period of months. Thus, a key feature of the IFN-α model is that it reflects chronic inflammatory stimulation. Additionally, IFN-α treatment results in moderate to robust increases in inflammatory markers that are sustained over weeks, depending on the disease being treated and associated dosing schedule. For example, patients with Hepatitis C typically receive a relatively mild dose of IFN-α several days per week for at least 16 weeks; one study showed an IL-6 increase of 2.18 pg/mL (a 102% increase) at four hours following the initial injection (Dowell et al., 2016). Patients receiving IFN-α for malignant melanoma typically receive higher doses and a more rigorous dosing schedule; one study showed an increase in IL-6 levels of approximately 46 pg/mL (a 1533% increase) at three hours after the initial injection; by week 8 a 233% increase from pre-treatment levels persisted (Capuron et al., 2003). Thus, IFN-α studies model the effects of exposure to chronic inflammation at mild or moderate levels, depending on the indication and associated dosing regimen. Modeling chronic inflammatory exposure allows for examination of temporal manifestation of different symptoms across a time period that is similar to the development of depression, and the relationships between symptoms or symptom clusters. Yet, one limitation of this model is its use exclusively in the context of chronic disease (hepatitis C, cancer).

Experimental evidence that inflammation can contribute to the development of depression even among medically healthy individuals comes from studies in which bacterial endotoxin - which elicits a strong inflammatory response - is administered to healthy individuals. These studies have shown that endotoxin administration leads to symptoms of depression including negative mood, anhedonia, cognitive impairment, fatigue, reduced food intake, altered sleep, and social withdrawal, as well as anxiety symptoms (DellaGioia and Hannestad, 2010; Eisenberger et al., 2010a; Reichenberg et al., 2001). Additionally, the effects of endotoxin on mood and anxiety appear to manifest in a dose-dependent manner, with higher doses associated with degradations in mood and increases in anxiety (Grigoleit et al., 2011). Endotoxin results in a robust but short-term inflammatory response that ranges from 40 to 190 pg/mL (up to a 38,000% increase) two hours after injection depending on the bacterial strain and dose (Andreasen et al., 2008; Grigoleit et al., 2011). Regardless of these factors, IL-6 increases following endotoxin appear to resolve within six hours of administration. Thus, the endotoxin model can inform our understanding of the acute effects of exposure to high levels of inflammation. In contrast to IFN-α, a strength of the endotoxin model is that it is typically carried out among medically healthy individuals. This reduces confounds associated with the presence of pre-existing disease; however, it can also limit the ability to generalize findings to groups of individuals with chronic diseases who are at higher risk for depression.

Inflammation can also be induced by vaccines (Carty et al., 2006;

Christian et al., 2011; Paine et al., 2013; Tsai et al., 2005). A third model for studying the effects of inflammation on depression involves administration of a typhoid vaccine to elicit increases in inflammation among healthy individuals. Results from such studies have shown that typhoid vaccination can lead to symptoms relevant to depression, including negative mood, fatigue, and confusion (Harrison et al., 2009; Wright et al., 2005). Typhoid vaccination leads to a modest, short-term inflammatory response; for example, an average increase of 0.82 pg/mL (a 106% increase) in IL-6 at 3 h post-vaccination (Wright et al., 2005) and increases in inflammation resolve within 24 h following typhoid vaccination (Paine et al., 2013). Thus, typhoid vaccine studies model the effects of mild, acute increases in inflammation. A strength of these studies is that the mild increases elicited by typhoid vaccination are comparable to the elevations in inflammation seen in some individuals with depression (Dowlati et al., 2010; Raison and Miller, 2011). Additionally, unlike IFN-α treatment or endotoxin, vaccines do not typically lead to fever, nausea, or other physical illness symptoms. Therefore, any effects on mood and cognition are not simply attributable to illness symptoms, but rather to more direct effects of cytokines on the brain. As a result of the typhoid studies, the influenza vaccine is now emerging as a useful, mild inflammatory stimulus to further interrogate these within-subject associations in a wider range of populations (Kuhlman et al., 2018).

Together, these experimental models have been instrumental in providing causal evidence for an association between inflammation and depression. Here, we use this research to examine the effects of inflammation on specific features of depression, using an endophenotype approach.

1.3. Core features of depression: an endophenotype approach

Endophenotypes are measurable, intermediate components, including neurophysiological, biochemical, endocrine, neuroanatomical, cognitive, or neuropsychological, that exist "along the pathway between disease and distal genotype" (Gottesman and Gould, 2003; Gould and Gottesman, 2006). Endophenotypes were intended to aid in identification of genes that cause diseases; because endophenotypes are conceptualized to represent more proximal psychological and biological processes to the level of gene action, it follows that they may be informed by fewer (and thus easier to identify) genes than complex diagnostic categories (Gottesman and Gould, 2003; Gould and Gottesman, 2006). As researchers have realized that elementary depressogenic processes (rather than traditional diagnostic categories) can help identify not just genetic vulnerability factors but myriad other biological, psychological, and environmental contributors, the endophenotype approach has outgrown its initial aim to identify solely genetic inputs (Miller and Rockstroh, 2013). Importantly, the endophenotype approach to understanding psychiatric disorders has informed the National Institute of Mental Health's Research Domain Criteria (RDoC) initiative (Cuthbert and Insel, 2010; Sanislow et al., 2010), which emphasizes largely transdiagnostic intermediate phenomena and their links upstream to genetic, molecular, and cellular factors, and downstream to clinically relevant behavior (Insel et al., 2010).

Putative endophenotypes for depression include behavioral, biological, and neural processes (Goldstein and Klein, 2014; Hasler et al., 2006, 2004; Webb et al., 2016). The current review characterizes our current knowledge of the role of inflammation in four established cognitive and behavioral endophenotypes of depression: exaggerated reactivity to negative information, altered reward processing, deficits in cognitive control, and somatic syndrome. These four endophenotypes were selected for this review based on two criteria: 1) identified in the depression literature as an empirically-validated phenotype; and 2) examined in relation to inflammation in human research. With respect to the first criteria, a number of published studies have aimed to establish the empirical validity of endophenotypes within depression. For

example, Hasler and colleagues (2004) identified 8 psychopathological endophenotypes: mood bias, impaired reward function, impaired learning and memory, direction of appetite change, diurnal variation, executive function, psychomotor change, and increased stress sensitivity. Among these, mood bias, increased stress sensitivity, impaired reward function, diurnal variation, and executive function were rated as having the most consistent evidence to support their role as endophenotypes. Webb and colleagues (2016) conducted a similar investigation proposing that neuroticism, blunted reward learning, and cognitive control deficits were depression endophenotypes by showing their distinct neural signature via EEG. Finally, Glahn et al. (2012) rank-ordered measures of behavioral endophenotypes and the top ranked measures included the Beck Depression Inventory II, neuroticism, working memory, facial memory, attentional control, psychomotor speed, and emotional recognition. Exaggerated reactivity to negative information, altered reward processing, deficits in cognitive control, and somatic syndrome were selected to broadly reflect the domains identified in these previous studies; importantly, these endophenotypes also meet the second criteria as they have been examined in studies of induced inflammation in humans. It should be noted that while these core features were identified from studies aimed specifically at identifying endophenotypes for depression, each of these constructs is largely transdiagnostic.

In the following sections, we review these four core features of depression in terms of their neurobiological and behavioral correlates, and the role of inflammation as determined in human studies that have used IFN-α, typhoid vaccination, and endotoxin administration to exogenously stimulate inflammatory processes.

2. Inflammation and core features of depression

2.1. Exaggerated reactivity to negative information in depression

Individuals with depression exhibit increased reactivity to negative information (Gotlib and Joormann, 2010). For example, compared to non-depressed controls, individuals with depression exhibit more negative facial expressions in response to unpleasant images (Sloan et al., 1997), report greater perceived stress in response to laboratory stress tasks (de Rooij et al., 2010), and display greater increases in negative affect in response to daily stressors (Myin-Germeys et al., 2003). Depressed individuals also display exaggerated physiological responses to laboratory stress tasks, including norepinephrine and epinephrine (Weinstein et al., 2010).

In addition to increased behavioral, affective, and physiological reactivity in depression, altered neural reactivity to negative emotional information has been observed among depressed individuals. Studies using event-related potentials (ERPs) to emotional stimuli have shown that healthy individuals exhibit greater slow-wave amplitudes to happy and neutral faces compared with sad whereas depressed individuals exhibit equivalent slow-wave amplitudes to sad, happy, and neutral faces (Deveney and Deldin, 2004). Studies using fMRI have elucidated neural regions involved in this altered responding. Among individuals with depression, processing of negative information is associated with stronger and longer lasting activation of the amygdala (Beevers et al., 2010; Drevets, 2001; Fu et al., 2004; Siegle et al., 2002; Stuhrmann et al., 2013), a region responsible for interpreting the emotional quality and salience of a given stimulus (Fu et al., 2004). Reactivity to negative information may be sustained due to deficits in left dlPFC inhibitory control over the amygdala (Disner et al., 2011; Drevets, 2001); depressed individuals tend to exhibit anatomical and functional abnormalities in the dlPFC, such as reduced gray matter volume, lower resting-state activity, and decreased activation to emotional stimuli (Gotlib and Hamilton, 2008).

Another region implicated in heightened processing of negative emotional information in depression is the anterior cingulate cortex (ACC). With ample connections to both the excitatory limbic regions

and the inhibitory prefrontal cortex, the ACC is thought to play an important role in integration of the neural circuitry dedicated to emotional processing and affect regulation (Stevens et al., 2011). Two regions within the ACC that may be of particular relevance to depression and inflammation due to their key contributions to emotional processing are the dorsal anterior cingulate cortex (dACC) and the subgenual anterior cingulate cortex (sACC), (Etkin et al., 2011). The dACC is believed to be involved in the appraisal and evaluation of threat and negative emotions (Etkin et al., 2011). Along with the amygdala, anterior insula, and periaqueductal gray, the dACC has been posited as part of a 'neural alarm system' that detects threat and elicits responses to impending danger or harm (Eisenberger and Cole, 2012). The sACC has been characterized as central to the integration and processing of emotional information from the limbic system (Disner et al., 2011), and increased activation of this region has been consistently implicated in depression (Mayberg, 2003; Mayberg et al., 1999; Sacher et al., 2012, 2012; Tremblay et al., 2005).

2.2. Inflammation and exaggerated reactivity to negative information

Inflammation may exaggerate affective and physiological reactivity to stressors, thus contributing to reactivity to negative stimuli as seen in depression. Typhoid vaccination caused greater negative mood following two stress tasks (a Stroop color-word task and a simulated public speaking exercise) compared to a placebo group; elevations in negative mood were driven by increases in fatigue and confusion (Brydon et al., 2009). Additionally, participants with larger vaccine-induced IL-6 responses exhibited elevated systolic blood pressure responses to stress tasks, as well as elevated post-stress cortisol and a marker of noradrenaline (Brydon et al., 2009). To examine the neural mechanisms by which inflammation may influence mood reactivity, a subset of participants underwent neuroimaging while completing an emotional face processing task following typhoid vaccination (Harrison et al., 2009). In this study, vaccine-induced negative mood was associated with enhanced sACC activation to emotional information (Harrison et al., 2009).

Endotoxin studies have also shown that inflammation can upregulate stress reactivity, particularly at the neural level. For example, although endotoxin did not increase self-reported affective reactivity to social stress, endotoxin did lead to exaggerated activation of threat-related neural circuits, including greater activation of the amygdala and dACC (Muscatell et al., 2016). Another study similarly found that endotoxin led to exaggerated amygdala responses to threatening stimuli, particularly *socially* threatening stimuli (e.g., fear faces versus guns) (Inagaki et al., 2012). Moreover, the exaggerated amygdala response to socially threatening images was associated with increased feelings of social disconnection (Inagaki et al., 2012); thus, inflammation may upregulate amygdala reactivity to social threats, resulting in the experience of social disconnection and withdrawal.

Overall, the existing literature, though limited in size, supports an effect of inflammation on exaggerated affective and neural reactivity to stressors. The emerging picture is that pro-inflammatory cytokines can signal the brain to effectively alter the functioning of threat-related neural circuitry leading to amplified neural responses to stressful information. Heightened neural activation in these regions may result in downstream increases in physiological arousal; indeed, regions including the dACC and amygdala modulate sympathetic nervous system and hypothalamic-pituitary axis (HPA) activity (Muscatell and Eisenberger, 2012). Given that heightened inflammation is often the result of illness or injury that leaves the organism in a vulnerable state, cytokine upregulation of threat-related neural circuitry has been postulated as an adaptive response in the service of increasing vigilance to further threats in the environment such as unfriendly strangers that could result in potential further harm (Inagaki et al., 2012; Muscatell et al., 2016; Slavich and Irwin, 2014). However, when this circuitry is chronically activated, the chronic expression of behavioral symptoms

(including negative mood, fatigue, confusion, and feelings of social disconnection) may culminate into clinically significant depression (Miller et al., 2013).

3. Inflammation and altered reward processing

3.1. Altered reward processing in depression

Anhedonia, the loss of pleasure or interest in previously rewarding stimuli, is a hallmark of depression and is one of the core diagnostic criteria for major depression (American Psychiatric Association, 2013). Anhedonia is a broad construct that includes deficits in anticipation of, motivation toward, and responsiveness to reward, as well as deficits in reward learning (ability to recall and make decisions based on past rewarding experiences) (Treadway and Zald, 2011) and is estimated to be 46% heritable in studies of monozygotic twins (Bogdan and Pizzagalli, 2009). Anhedonia is often conceptualized as the behavioral manifestation of altered reward processing in depressed patients (Beck, 2004; Nutt et al., 2007; Webb et al., 2016; Winer and Salem, 2015), and may underlie many of the profound social impairments that are central to depression (Kupferberg et al., 2016). Importantly, these alterations in reward processing precede and potentially contribute to the etiology of depression in at-risk groups (Gotlib et al., 2010), and number of prospective studies have shown that self-reported anhedonia (less frequent and intense positive affect) is a strong predictor of subsequent increases in depression severity (Morris et al., 2009).

In non-depressed individuals, the experience and maintenance of positive affect is related to activity in brain regions associated with reward and motivation (Nestler and Carlezon, 2006; Tremblay et al., 2005); these regions are modulated by top-down control by the PFC (Del Arco and Mora, 2008). Reward-related brain regions consist of neural structures receiving dopamine input from the ventral tegmental area, including the nucleus accumbens (NAc) of the ventral striatum, which plays a critical role in reward learning and the experience of pleasure. The ventromedial PFC and amygdala are also major dopaminergic targets that are involved in reward processes (Berridge and Kringelbach, 2008; Lieberman and Eisenberger, 2009).

Depressed individuals display attenuated subjective and neural reactivity to positive stimuli, including diminished emotional and affective responses to pleasant stimuli compared with non-depressed controls (Dunn et al., 2004; Sloan et al., 2001, 1997). Additionally, depressed individuals or those with trait-like anhedonia display attenuated reactivity of the NAc to pleasurable stimuli (Harvey et al., 2007; Keedwell et al., 2005), monetary rewards (Pizzagalli et al., 2009; Wacker et al., 2009), and positive words (Epstein et al., 2006).

In addition to reduced reactivity to reward, there is also evidence that individuals with depression have reduced capacity to sustain positive affect following a reward. Among individuals with depression, NAc and PFC activation has been shown to dissipate more quickly following the presentation of positive stimuli, compared to healthy controls (Epstein et al., 2006; Heller et al., 2009). In a study in which participants were explicitly asked to sustain their positive mood following the presentation of positive stimuli, depressed individuals failed to sustain NAc activation over time compared with controls; moreover, this reduced capacity was associated with lower self-reported positive affect (Heller et al., 2009).

3.2. Inflammation, altered reward processing, and anhedonia

Evidence from IFN- α, endotoxin, and typhoid research supports an effect of induced inflammation on aspects of reward. For example, after 4–6 weeks of IFN-α therapy, patients with hepatitis C showed significantly attenuated ventral striatal activity (as measured by fMRI) to receipt of monetary rewards in a gambling task when compared with hepatitis C patients not receiving IFN-α (Capuron et al., 2012). Reduced ventral striatal activation was in turn significantly associated with more

severe symptoms of anhedonia, depressed mood, and fatigue (Capuron et al., 2012). These changes may occur through the effect of proinflammatory cytokines on dopaminergic functioning in the ventral striatum (Capuron et al., 2012), as outlined in section 1.2. This possibility was investigated using positron emission tomography (PET) with radiolabeled 18-F fluorodopa (^{18}F-dopa) in patients with Hepatitis C receiving IFN-α for 4–6 weeks. ^{18}F-dopa is taken up by dopaminergic neurons and converted into dopamine, which is then stored and subsequently released. PET imaging using ^{18}F-dopa can assess the uptake and release of ^{18}F-dopa, which is likely a measure of presynaptic dopamine activity (Miller et al., 2013). Patients exhibited increased uptake and decreased turnover of ^{18}F-dopa in the same ventral striatal regions shown to be effected by IFN-α in the previously mentioned fMRI study (Capuron et al., 2012). Thus, inflammatory cytokines may influence reward processing by specifically targeting the ventral striatum via dopaminergic functioning.

Inflammation has been shown not only to modulate responses to reward consumption, but also the anticipation of reward. In one report, endotoxin (vs. placebo) led to attenuated activation of the left ventral striatum to anticipation of monetary reward (Eisenberger et al., 2010a). Further, blunted ventral striatum activity to anticipated reward mediated the relationship between endotoxin exposure and increases in observer-rated (but not self-reported) depressed mood (Eisenberger et al., 2010a). Thus, inflammation may impact not only consummatory but also anticipatory reward processes, potentially leading to behavioral manifestations of depressed mood.

The effects of inflammation have also been examined in relation to novelty, a different kind of rewarding stimuli. Novel stimuli are high in intrinsic reward value, thereby motivating adaptive behaviors such as exploration and social approach (Kakade and Dayan, 2002). The hippocampus and substantia nigra (a basal ganglia structure) are central to novelty detection and reward evaluation of novelty (Bunzeck and Düzel, 2006; Lisman and Grace, 2005). Typhoid vaccination (vs. placebo) had no effect on hippocampal activation to novelty, but led to blunted substantia nigra reactivity to novel stimuli (Harrison et al., 2015). Moreover, analyses of the functional connectivity between the substantia nigra and hippocampus revealed that substantia nigra-hippocampus connectivity to novelty was increased in the placebo condition and attenuated in the vaccine condition (Harrison et al., 2015). Thus, inflammatory signaling may reduce basal ganglia (specifically substantia nigra) responsivity to novel stimuli, which is relevant to reductions in motivational and approach behavior seen in depression, and expands our understanding of the types of rewards and reward-related neural mechanisms impacted by inflammation.

Although there is some compelling evidence that inflammation may dampen neural reactivity to rewards, a few studies present more complex findings. For example, inflammation can lead to *heightened* ventral striatal reactivity to social rewards, specifically positive social feedback (Muscatell et al., 2016) and viewing images of close others (Inagaki et al., 2015). The potential facilitation effects of inflammation on reward may also extend to monetary rewards. For example, endotoxin led to increased motivation for monetary rewards using a behavioral measure of reward motivation, the Effort Expenditure for Rewards Task (EEfRT), but only when the probability of winning was high (Lasselin et al., 2016b). These, perhaps unexpected, findings may reflect that inflammation facilitates some adaptive behaviors during acute illness or infection, such as drawing an individual closer to potential caretakers and conserving energy by selectively pursuing rewards that are highly likely and valuable (Eisenberger et al., 2016; Lasselin et al., 2016b).

In summary, all three models of induced inflammation have demonstrated effects on neural responses to reward. Much of this work has shown attenuated reward-related neural activity following an inflammatory stimulus, which is generally consistent with preclinical research on inflammation and reward (See Swardfager et al., 2016 for review). From this work, we have begun to understand the neurobiological mechanisms of the effects of inflammation on reward

processing, which may involve alterations in corticostriatal neural circuitry (including the ventral striatum) via modulation of dopamine availability and release (Felger and Treadway, 2016). However, effects of inflammation on reward are complex and may depend on the level of analysis (neural vs. behavioral responsiveness), the domain of reward processing (anticipation, motivation, consumption, and learning), the nature of the reward (social vs. monetary rewards; primary vs. secondary rewards), the level of reward value and probability of receiving the reward (for reward anticipation and motivation tasks), as well as inflammatory dose and duration. More research interrogating these possible moderators is needed. Importantly, novel behavioral tasks that tap into discrete aspects of reward are being developed, such as the EEfRT, which taps reward motivation, and the Probabilistic Reward Task, which taps implicit reward learning (Pizzagalli et al., 2008; Treadway et al., 2009). These and other tasks can help us understand how and when inflammation-induced changes in neural reactivity manifest into behavioral changes relevant to depression (e.g., Lasselin et al., 2016b), and to investigate effects on inflammation on distinct components of reward.

4. Inflammation and cognitive control

4.1. Cognitive control deficits in depression

Deficits in cognitive control are among the most frequent complaints for individuals with depression (Simons et al., 2009). Cognitive control broadly describes the ability of higher-level cognitive processes to organize and regulate automatic cognitive functions (such as perception or motor responses) in order to guide behavior towards a goal (Alvarez and Emory, 2006; Banich, 2009). Cognitive control, often operationalized as executive functioning within neuropsychology, includes the ability to create, maintain, and switch between task goals; inhibition of automatic responses and distracting information; planning and decision-making; and selecting among competing options (Snyder, 2014). Impaired cognitive control is heritable and (Friedman et al., 2008) has been proposed as an important depression endophenotype within and across several units of analysis (Castaneda et al., 2008; Hammar and Ardal, 2009; Hasler et al., 2004; Webb et al., 2016). A meta-analysis of 113 studies found significant deficits in executive functioning among depressed individuals compared to non-depressed controls, including deficits in updating, shifting, inhibition, working memory, planning, and verbal fluency, with effect sizes ranging from d = 0.32 – 0.97 (Snyder, 2014). Cognitive control relies heavily on the prefrontal cortex, particularly the dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC) and anterior cingulate cortex (ACC), but also recruits broader neural networks including subcortical areas (Snyder, 2014). See Table 2 for definitions of these cognitive control domains and the tasks typically used to measure these components in the context of depression.

4.2. Inflammation and cognitive control deficits

There is some evidence that inflammation may elicit changes in the subjective experience of cognitive control. In particular, IFN-α treatment has been associated with self-reported cognitive deficits, such as concentration difficulties (Capuron et al., 2002). Typhoid vaccination increases subjective ratings of mental confusion and impaired concentration (Brydon et al., 2009; Harrison et al., 2009).

Evidence that inflammation leads to changes in objective measures of cognitive control is decidedly more mixed. Counter to the updating deficits commonly exhibited in individuals with depression, the only published study examining the role of inflammation in performance on behavioral tasks of updating found that moderate inflammation facilitated (rather than slowed) updating speed (Grigoleit et al., 2011). In their evaluation of low (0.4 ng/kg) and moderate (0.8 ng/kg) doses of endotoxin on updating via working memory using the *n*-back task, there

was no significant effect of low-dose endotoxin on *n*-back task performance; however, the moderate-dose endotoxin group exhibited significantly *faster* reaction times on the *n*-back task compared to the placebo condition (with comparable levels of accuracy across the two groups) (Grigoleit et al., 2011).

A larger number of studies have examined effects of inflammation on shifting ability as measured with the Trail Making Test (TMT) part B. Leukemia patients receiving IFN-α treatment showed deficits on the TMT part B (Pavol et al., 1995), and hepatitis C patients who received 6 months of IFN-α performed significantly worse on the TMT part B when compared with hepatitis C patients who did not undergo IFN-α treatment (Hilsabeck et al., 2005). However, several other studies of IFN-α treated hepatitis C patients have found no significant performance deficits on the TMT part B (Amodio et al., 2005; Drozdz et al., 2008; Fontana et al., 2007), the Wisconsin Card Sorting task (Fontana et al., 2007), or on the Intradimensional/Extradimensional Shift task (Majer et al., 2008). Consistent with this, studies examining effects of both moderate- (0.8 ng/kg) (Reichenberg et al., 2001) and very low-dose (0.2 ng/kg) (Krabbe et al., 2005) endotoxin have failed to find significant effects on performance on the TMT part B. Thus, a role of inflammation in shifting ability impairments is mixed, with the majority of studies finding no effect of inflammation on shifting ability.

A number of studies have examined the effect of inflammation on inhibitory control, as assessed with the color-word Stroop task; most have found no effect. Stroop performance was not impaired after endotoxin administration at either a low dose (0.4 ng/mL) (Grigoleit et al., 2010) or high dose (2.0 ng/mL) (van den Boogaard et al., 2010). A study of hepatitis C patients found no change in Stroop performance over the course of IFN-α treatment (Amodio et al., 2005). Brydon et al. (2008) examined Stroop performance after typhoid vaccination, and found that individuals with higher vaccine-induced IL-6 levels had significantly slower reaction times across both incongruent and congruent trials. Thus, inflammation did not impair inhibitory control, but rather led to an overall psychomotor slowing and/or decrease in motivation (Brydon et al., 2008).

Various studies have examined the effect of inflammation on working memory, and have failed to support a role of inflammation in this aspect of executive functioning. Among the four studies that have been conducted, no significant effect of endotoxin exposure on digit span forward or backward performance was observed (Grigoleit et al., 2010; Krabbe et al., 2005; Reichenberg et al., 2001; van den Boogaard et al., 2010). Similarly, two studies among hepatitis C patients (Amodio et al., 2005; Fontana et al., 2007) and one study among melanoma patients (Caraceni et al., 1998) receiving IFN-α therapy found no effect of treatment on digit span performance. In addition, no significant effects of inflammation on visuospatial working memory were observed following either acute endotoxin (Grigoleit et al., 2010) nor following IFN-α therapy (Caraceni et al., 1998). Thus, the currently available data provide little evidence that inflammation impairs verbal or visuospatial working memory.

Only one study to our knowledge has examined the effects of an inflammatory stimulus on planning ability, and failed to find effects. This study used IFN-α (plus ribavirin) as an inflammatory stimulus and measured planning ability with the Stockings of Cambridge task, and no effect of inflammation on planning ability was observed (Majer et al., 2008).

The evidence is mixed with regard to the effect of inflammation on verbal fluency. Inflammation did not impact performance on a verbal fluency task following endotoxin administration (Reichenberg et al., 2001). Similarly, several studies found no effect of IFN-α treatment on verbal fluency (Amodio et al., 2005; Fontana et al., 2007; Pavol et al., 1995), although one study showed a significant reduction in verbal fluency after three months of IFN-α treatment (Lieb et al., 2006)

In summary, detrimental effects of inflammation have not been consistently observed for updating, inhibition, working memory, or planning ability, and in some cases facilitation effects have been

Table 2
Domains of executive functioning commonly disrupted in depression and the tasks typically used to measure them.

Component	Definition	Tasks and descriptions
Updating	Ability to replace no longer relevant information with new, relevant input	*N-back*: Subjects must indicate if a displayed stimulus (letter or number) matches a stimulus that was presented *n* (e.g., 4) items back. DVs: Accuracy and reaction time.
Shifting	Ability to switch between task sets or response rules	*Trail Making Test Part B*: Subjects must alternatively connect letters and numbers; results are contrasted with part A, which doesn't require shifting between letters and numbers. DV: Total time to complete task.
		Wisconsin Card Sorting Task: Subjects initially sort cards based on one characteristic (e.g., color), but must subsequently switch to sort by a different characteristic after receiving negative feedback. DVs: Number of perseverative errors (continuing to sort by old rule), successful switches achieved.
		Intradimensional/Extradimensional Shift Task: Similar to Wisconsin Card Sorting Task, but shifts are initially intra-dimensional (switching to a previously non-rewarded stimulus) and subsequently extra-dimensional (switching to a different stimulus dimension). DVs: Number of perseverative errors, successful switches achieved.
Inhibition	Ability to suppress a prepotent response and instead make a more effortful, task-relevant response	*Color-word Stroop*: Color words are presented in incongruously colored ink; subjects must name the ink color of each word while ignoring the word meaning. Performance is compared to a neutral condition in participants name the ink color in the absence of conflicting color information. DVs: An interference score that measures the difference in completion time between incongruent and control conditions; a score that represents accuracy in the incongruent condition relative to the control condition.
Working Memory	Ability to actively maintain or manipulate (verbal, visuospatial) information across a short delay	*Forward and backward digit span* (verbal working memory): Subjects hear a sequence of numbers and must repeat it back in forward or reverse order. DV: Length of longest sequence correctly repeated.
		Block span test (visuospatial working memory): Subjects watch a pattern of taps on arranged shapes and must repeat the taps in the same order. DV: Length of longest sequence correctly repeated.
Planning	Ability to identify and organize a sequence of steps towards the completion of some larger goal	*Tower of London*: Subjects must move beads from a starting position to a target position in a minimum number of moves. Obtaining the target solution is believed to require the subject to visualize the solution several moves in advance. DVs: number of moves to reach target solution; number of targets reached in the minimum number of moves.
Verbal fluency	Ability to retrieve verbal information from memory.	*Word generation tasks*: Subjects must generate as many words as possible for a given category within a specific period of time. Categories can be semantic (e.g., animals, fruits) or phonemic (e.g., words that begin with the letter *a*). DV: Number of words generated within the time limit.

observed in these domains. There is some evidence that inflammation impairs shifting ability and verbal fluency, yet even in these domains there are more studies reporting null findings than not. It is possible that the types of neuropsychological tasks typically used to assess executive functioning following an inflammatory challenge are not sensitive enough to detect the magnitude of changes triggered by inflammation. Many of the neuropsychological tasks that are commonly used and discussed in this section were developed to distinguish between normal and abnormal cognitive abilities following major insults or neurological disease and may not capture more subtle changes in executive function. Of note, inflammation has been associated with increases in *subjective* reports of cognitive difficulties, which may be more sensitive to small changes in cognitive function. Additionally, studies have not examined effects of inflammation on neural correlates of executive functioning that may not be manifest behaviorally.

5. Inflammation and somatic syndrome

Somatic symptoms in depression, often referred to as neurovegetative, include fatigue, sleep disturbance, appetite disturbance, and psychomotor changes. Up to 74% of individual differences in somatic symptoms are explained by genetic factors in twin studies (Kato et al., 2009; Kendler et al., 1992), which supports the co-occurrence of these somatic symptoms as a depression endophenotype.

5.1. Fatigue in depression

Fatigue is a prevalent presenting symptom of major depressive disorder (Demyttenaere et al., 2005). Symptoms of physical fatigue include feelings of tiredness, low energy, reduced activity, decreased physical endurance, increased effort to perform physical tasks, general weakness, heaviness, and slowness or sluggishness (Arnold, 2008). A large epidemiological study of more than 1,800 depressed patients

found that 73% reported feeling tired, and that this was the second most commonly endorsed symptom, after low mood (Tylee et al., 1999).

Fatigue may also play a role in the pathogenesis of depression. Non-depressed individuals with fatigue are at higher risk for developing MDD later in life compared with individuals without fatigue (Addington et al., 2001; Kroenke and Price, 1993; Walker et al., 1993). Persistent fatigue can lead to substantial impairment in fulfilling social, familial, and work roles, and patients with residual fatigue are more likely to experience depression recurrence despite continued prophylactic treatment (Targum and Fava, 2011). At the neural level, fatigue is associated with alterations in dopamine and associated frontostriatal regions (Dobryakova et al., 2015). In addition, conceptual models have suggested a role for the anterior insula and the dorsal ACC in fatigue, particularly in the context of inflammation (Dantzer et al., 2014; Karshikoff et al., 2017), while the basal ganglia and frontal lobes have been implicated in diseases such chronic fatigue syndrome (DeLuca et al., 2009).

5.2. Inflammation and fatigue

Studies across the endotoxin, typhoid vaccination, and IFN-α paradigms have consistently shown that exogenous stimulation of proinflammatory cytokines leads to reports of increased fatigue (Brydon et al., 2008; Capuron et al., 2002; Dowell et al., 2016; Eisenberger et al., 2010a; Grigoleit et al., 2011; Harrison et al., 2009; Moieni et al., 2015) and decreases in ratings of vigor (Dowell et al., 2016; Wright et al., 2005). Indeed, increased fatigue may be the most consistently reported symptom across these paradigms. In IFN-α models, fatigue is the most commonly reported symptom, affecting an estimated 80% of patients (Capuron et al., 2002). Studies using typhoid vaccination to elicit modest increases in inflammation have shown that increases in mood disturbance are driven by increases in items assessing fatigue (as well as

confusion), rather than increases in depressed mood (Brydon et al., 2009, 2008; Harrison et al., 2009).

Studies have begun to elucidate neurobiological mechanisms of inflammation-induced fatigue. IFN-α therapy led to reports of fatigue in a sample of patients with malignant melanoma that were positively correlated with increased glucose metabolism in the basal ganglia (the left putamen and left NAc) (Capuron et al., 2007). In another sample of hepatitis C patients, IFN-α treatment elicited increases in fatigue that began 4 h after patients' initial IFN-α injection, and continued to persist throughout the 6-month treatment period, peaking between 4–12 weeks (Dowell et al., 2016). They also observed changes in ventral striatal microstructure within 4 h post-injection, which prospectively predicted fatigue experience at 4 weeks (Dowell et al., 2016). In a typhoid vaccination study, individual differences in inflammation-associated fatigue were predicted by activity changes within bilateral mid/posterior insula and left anterior cingulate during performance of the Stroop color-word task (Harrison et al., 2009).

5.3. Psychomotor slowing in depression

Psychomotor retardation, defined as a slowing of motor activity and difficulty responding quickly and spontaneously to environmental cues, is a common symptom of depression (Taylor et al., 2006). Psychomotor speed can be assessed by self-report, clinician assessment, or behaviorally, using neuropsychological tests that assess reaction time, speech rate, motor speed, mental speed, and initiation and spontaneity of response.

Psychomotor slowing involves disruptions in dopamine functioning and the basal ganglia circuit; dopaminergic abnormalities underlie the psychomotor slowing seen in depression as they do in Parkinson's disease (Rogers et al., 1987). Depressed individuals with psychomotor retardation may have a dopaminergic abnormality within the frontal-subcortical network that involves the basal ganglia and PFC. For example, psychomotor retardation is associated with reduced activity in higher-order prefrontal regions that connect to the basal ganglia and are associated with the initiation, planning, and control of movement, including the dlPFC and orbitofrontal cortex (Bench et al., 1993; Videbech et al., 2002). Moreover, depressed patients with psychomotor slowing (as assessed by a clinician) exhibit decreased cerebrospinal fluid levels of homovanillic acid, the primary metabolite of dopamine (van Praag and Korf, 1971), and decreased presynaptic dopamine function in the left caudate (Martinot et al., 2001). Further, decreased D2 binding among depressed patients was significantly correlated with reduced speech rate (FAS-Verbal Fluency test) and reduced speed of movement on a reaction time task (Shah et al., 1997).

5.4. Inflammation and psychomotor slowing

IFN-α (plus ribavirin) therapy led to significant decreases in motor speed among patients with hepatitis C (Majer et al., 2008). Notably, decreased motor speed in this study was also associated with increased symptoms of depression and fatigue (Majer et al., 2008). Similarly, IFN-α treatment was associated with an increase in response latency on a reaction time task among cancer patients, especially when the cytokine was administered intravenously and when the task involved higher attentional resources (Capuron et al., 2001). Further, greater IL-6 following typhoid vaccination was associated with slower response times on all trials of a color-word Stroop task (both congruent and incongruent trials) (Brydon et al., 2008). Notably, increases in IL-6 and decreases in motor speed were both associated with altered activation patterns (enhanced activation) in the substantia nigra (Brydon et al., 2008).

5.5. Sleep changes in depression

An estimated 50–90% of individuals with diagnosed depression complain of poor sleep quality (Casper et al., 1985; Hetta et al., 1985; Kupfer et al., 1969; Riemann et al., 2001). Common sleep alterations in depression include difficulty initiating sleep, frequent nocturnal awakenings, and early morning awakenings. Depressed subjects also show reductions in slow wave (stage 3/4) sleep, increases in rapid eye movement (REM) sleep, including a shorter latency to REM initiation, a protraction of the REM sleep period, and increases in REM density (Palagini et al., 2013; Riemann et al., 2001; Tsuno et al., 2005). Hypersomnia can also accompany depression, though it is somewhat less common (Garvey et al., 1984; Tsuno et al., 2005). Sleep deprivation appears to cause alterations to neural processes that underlie a wide range of cognitive tasks, including attentional control, memory, reward processing, and emotion discrimination which involve multiple brain regions and the connectivity between them (Krause et al., 2017). These neural regions include, but are not limited to the dlPFC, mPFC, amygdala, intraparietal sulcus, the hippocampus, the anterior cingulate cortex, and instability within the default mode network (See Krause et al., 2017 for review).

5.6. Inflammation and sleep

Proinflammatory cytokines are involved in normal regulation of sleep-wake cycles and the homeostatic drive for sleep in both animals and humans. The proinflammatory cytokines IL-1, TNF-α, and IL-6 display a circadian pattern of secretion with peak levels correlating with feelings of sleepiness and sleep onset (Imeri and Opp, 2009; Vgontzas et al., 2005). Indeed, proinflammatory cytokines can actively inhibit wake-promoting neurons and stimulate (a subset of) sleep-promoting neurons in the preoptic area and basal forebrain (Alam et al., 2004). Given that cytokines can regulate sleep, it follows that disturbances in cytokine levels would be associated with sleep dysregulation.

An IFN-α study in patients with hepatitis C showed that inflammation alters objective measures of sleep, and began to identify the specific components of sleep disrupted by inflammation using polysomnography (Raison et al., 2010). In particular, IFN-α treatment led to increased awakenings after sleep onset, decreases in stage 3/4 sleep and sleep efficiency, increases in REM latency, and decreases in stage 2 sleep over 12 weeks (Raison et al., 2010). Endotoxin studies have also provided causal evidence that cytokines can lead to acute sleep changes, though effects depend on dose. For example, very low doses of endotoxin (0.2 ng/kg) promoted sleep, whereas moderate doses (0.8 ng/kg) reduced total sleep time and increased sleep onset latency (Hermann et al., 1998; Korth et al., 1996; Mullington et al., 2000). Specifically, low-level immune activation leads to increased non-rapid eye movement (NREM) sleep, while decreasing or having no effect on REM sleep; in contrast, more robust immune activation decreased both NREM and REM sleep (Mullington et al., 2000).

Taken together, results suggest that inflammation can disrupt sleep in ways that mirror the sleep disruptions observed in depression, including reductions in sleep quality, increases in NREM sleep, and decreases in REM sleep latency following IFN-α and moderate doses of endotoxin. However, exogenously-induced inflammation using both endotoxin and IFN-α also led to a suppression of REM sleep (Mullington et al., 2000; Raison et al., 2010), which is the opposite of changes observed in depressed patients (Palagini et al., 2013; Riemann et al., 2001; Tsuno et al., 2005). Across the few existing studies, the effects of inflammation on components of sleep may depend on the magnitude of immune activation. Neuroimaging studies are lacking in this area; thus, the neurobiological mechanisms by which heightened inflammation affects sleep and its components are relatively unexplored, and represents an important avenue for future work.

6. Discussion

The current review considered four core features of depression and

Table 3
Review of associations between exogenous immune activation and core features of depression by paradigm and level of analysis.

| Endophenotype	Paradigm	Subjective reports	Objective behavior	Neural activity
Exaggerated reactivity to negative information	Typhoid vaccination	• greater negative mood following stress tasks	• elevated systolic blood pressure, cortisol, and noradrenaline following stress tasks	• enhanced sACC activation to emotional information in subjects with negative mood • greater activation of the amygdala and dACC in subjects with greater IL-6 response
	Endotoxin	• increased feelings of social disconnection • did not increase self-reported affective reactivity to social stress	• No data available	
	IFN-α therapy	• No data available		• No data available
Altered reward processing	Typhoid vaccination	• No data available	• No data available	• blunted substantia nigra reactivity to novel stimuli • attenuated substantia nigra-hippocampus connectivity to novelty
	Endotoxin	• greater increases in self-reported and observer-rated depressed mood	• increased effort for high probability monetary rewards	• attenuated activation of the left ventral striatum to anticipation of monetary reward • heightened ventral striatal reactivity to positive social feedback and viewing images of close others
	IFN-α therapy	• more severe symptoms of anhedonia	• No data available	• attenuated ventral striatal activity to monetary rewards • increased uptake and decreased turnover of 18F-dopa in ventral striatum
Cognitive control deficits	Typhoid vaccination	• subjective ratings of mental confusion and impaired concentration	• No data available	• No data available
	Endotoxin	• No data available	• facilitated updating speed • faster reaction times on the n-back task (0.8 ng/kg dose only) • no effect on working memory or reaction time following low dose (0.4 ng/kg) • no effect on shifting ability • no effect on inhibitory control	• No data available
	IFN-α	• self-reported concentration difficulties	• deficits in shifting ability observed in 2 studies; no effect on shifting ability observed in 5 studies • no effect on working memory • no effect on planning • one study observed impaired verbal fluency, 3 studies observed no effect on verbal fluency	• No data available
Somatic symptoms: fatigue, psychomotor retardation, sleep disturbance	Typhoid vaccination	• increased self-reported fatigue	• slower reaction times	• enhanced activity in the substantia nigra
	Endotoxin	• increased self-reported fatigue • decreased vigor	• low dose endotoxin (0.2 ng/kg) promotes sleep via increased sleepiness, increased nighttime NREM sleep • moderate dose (0.8 ng/kg) reduced total sleep time (REM and NREM) and increased sleep onset latency	• No data available
	IFN-α	• increased self-reported fatigue • decreased vigor	• decreased reaction times • more frequent awakening after sleep onset, decreased stage ¾ sleep, decreased sleep efficiency, increases in REM latency, and decreases in stage 2 sleep	• increased glucose metabolism in the basal ganglia (the left putamen and left NAc) as assessed with PET neuroimaging with fluorine-18-labeled fluorodeoxyglucose • changes in ventral striatal microstructure
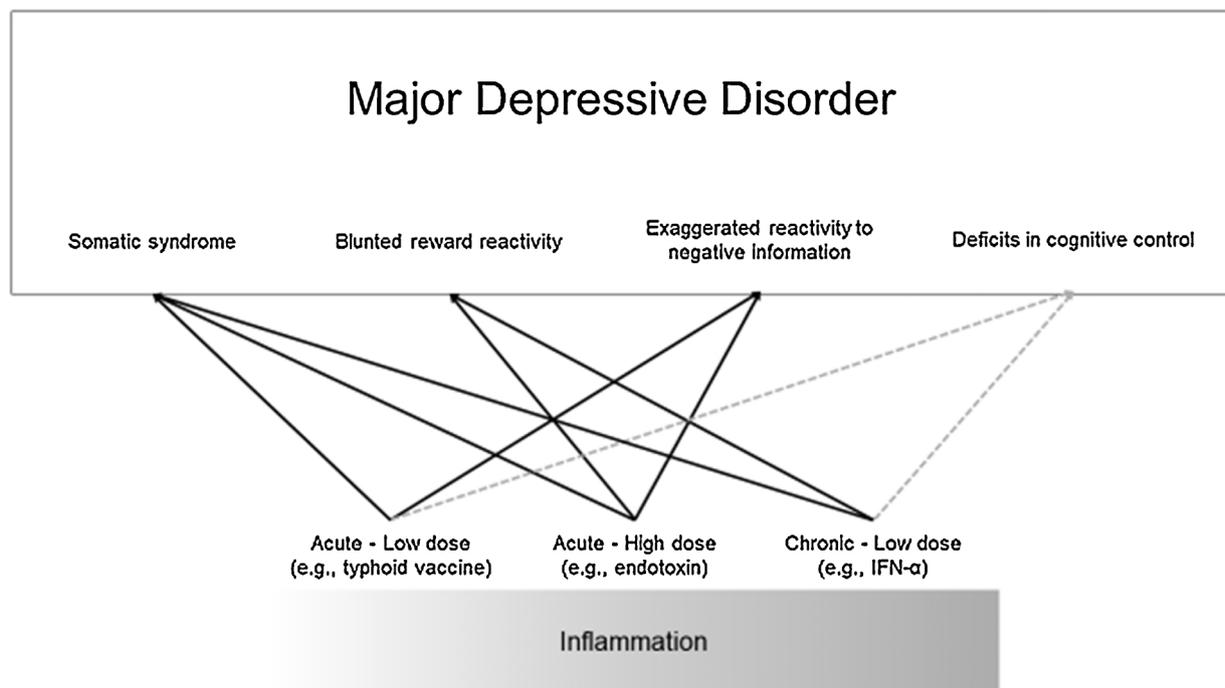
Fig. 1. Core processes of depression that are influenced by inflammation.

their links with inflammation: exaggerated reactivity to negative information, reward processes, cognitive control, and somatic symptoms. Here, we briefly summarize the results of the review, focusing on similarities and differences across the different models of cytokine induction. We then consider this body of research from a network perspective, and conclude with clinical implications and suggestions for future research.

6.1. Summary and integration across models

Effects of inflammation on core features of depression have been interrogated using different stimuli to induce peripheral inflammatory activity. While the IFN-α paradigm models the effects of chronic exposure to moderate levels of inflammation, endotoxin and typhoid vaccination model the short-term effects of acute exposure at high and low levels, respectively. One important conclusion that can be drawn from this review is that the dose and sustained exposure to inflammation induced by each of these three different paradigms may matter. Table 3 provides a summary of findings by endophenotype by paradigm and level of analysis and Fig. 1 provides a summary of results of experimental studies so far.

Overall, there is strong and consistent evidence that inflammation leads to changes in somatic symptoms of depression across paradigms. Mild, short-term increases in inflammation are sufficient to cause somatic symptoms, particularly fatigue. This is exemplified by typhoid vaccine studies which can lead to increases in fatigue within 2–3 h despite eliciting only mild, acute increases in inflammation (Brydon et al., 2008). Similar results have been observed in endotoxin studies, which document elevations in fatigue and other sickness symptoms that peak 2 h post injection (Eisenberger et al., 2010a,b; Moieni et al., 2015). Further, patients receiving (low-dose) IFN-α treatment for Hepatitis C exhibit increases in fatigue and decreases in vigor within four hours of initial injection that continue to rise across the 8 weeks of treatment (Dowell et al., 2016). Together, these findings indicate that fatigue is rapidly elicited by even modest perturbations in cytokine levels and there may be a dose response association between inflammation and the severity of somatic symptoms like fatigue (Dowell et al., 2016).

In general, research also supports an effect of inflammation on negative reactivity and reward processing, with most studies focusing on neural processes. Effects here may be more specific to the experimental paradigm. For example, only acute inflammatory challenges appear to induce increases in reactivity to the environment, whereas altered reward processing appears to only be observed in studies with high doses of inflammation regardless of their acute or chronic nature. That being said, there is no published evidence for or against the role of INF-α in reactivity to negative information, and little behavioral evidence on the role of mild inflammatory challenges in reward processing. Thus, our conclusions on this topic are limited by the studies published to date, and should be considered preliminary.

Finally, we found very little evidence that cognitive control, as assessed by validated neuropsychological measures of executive function, was affected by exogenously-induced inflammation in either the endotoxin or the IFN-α model. In some ways, this is puzzling given that inflammatory processes have been shown to regulate learning and memory (e.g., Yirmiya and Goshen, 2011) and that correlational studies have identified associations between mild elevations in inflammatory markers and both self-reported (Davis et al., 2018; Kuhlman et al., 2018) and objective (Marsland et al., 2015) measures of cognitive function. Further, IFN-α and typhoid studies have documented links between increases in inflammation and subjective cognitive complaints (Brydon et al., 2009; Capuron et al., 2002; Harrison et al., 2009). However, results from both endotoxin and IFN-α studies were fairly consistent in showing no effects across a range of tasks assessing different aspects of executive function. It is possible that these tasks may not be sensitive to acute changes in inflammation, even at the high levels elicited by endotoxin, or to more "chronic" exposures elicited by IFN-α (that are still circumscribed compared to exposures seen in midlife and older adults). Alternatively, self-reported problems with basic daily cognitive processes may reflect another domain of functioning in depression that is not captured with executive functioning tasks. For example, cognitive control in these tasks are typically measured under ideal testing conditions that remove social and other contexts from the assessment. It is possible that inflammation may interfere with an individual's sensitivity to context that makes daily cognitive tasks more effortful and distressing.

Altogether, it is important to examine different doses of inflammatory stimuli on the endophenotypes using stimuli that probe different aspects of the dimension in question (e.g., social vs. non-social reward) and that examine outcomes at several levels of analysis: neural, subjective, and behavioral. In addition, given that there are pronounced individual differences in response to a uniform inflammatory stimulus, it is important to examine how these differences influence outcomes. For this reason, studies that directly examine the effects of different doses of inflammatory stimuli (e.g., Grigoleit et al., 2011; Lasselin et al., 2016a) as well as individual differences in inflammatory responses to challenge (e.g., Kuhlman et al., 2018) on behavioral and neural outcomes are increasingly important to our understanding.

6.2. A network perspective

A network perspective of psychopathology assumes that symptoms causally influence one another over time, rather than emerge from a singular, common cause (Borkulo et al., 2015; Borsboom and Cramer, 2013). Taking a network perspective may enhance our understanding of the links between core features of depression. For example, it is possible that earlier appearing somatic symptoms may give rise to later-appearing affective symptoms (e.g., fatigue→mood symptoms), thus clarifying a biobehavioral pathway that informs interventions and their evaluation. Support for this idea derives from IFN-α studies, which show that although the large majority of patients rapidly develop somatic symptoms (e.g., fatigue), only a subgroup go on to develop other symptoms (e.g., feelings of guilt, suicidality) severe enough to qualify for a major depression diagnosis (Capuron et al., 2002; Capuron and Miller, 2004; Musselman et al., 2001). Indeed, these studies found that major depression was more likely to develop in individuals with pre-existing, subclinical cognitive disturbance (pessimistic thoughts) prior to the initiation of treatment (Capuron et al., 2004). Other IFN-α studies have begun to examine predictive relationships between symptoms (Dowell et al., 2016; Robaeys et al., 2007; Wichers et al., 2005).

This network model is also more synergistic with evolutionary conceptualizations of the role that inflammation can play in human behavior. When illness or injury befalls an organism, proinflammatory cytokines signal the central nervous system, triggering a constellation of behavioral changes ("sickness behaviors") that represent an adaptive motivational response aimed at facilitating healing and recovery (Dantzer et al., 2008). The classic example of these adaptive behavioral changes is fatigue, which can promote recovery by driving the organism to rest and thereby allow the body to devote its energy to healing. Blunted responsivity to rewards may be similarly adaptive, minimizing an organism's pursuit of rewards in favor of rest; the exception to this blunted reward responsivity could be social rewards, due to the likely benefits of having close others nearby for caretaking purposes (Eisenberger et al., 2016). Increased attention and reactivity to negative stimuli could also confer benefits; a vulnerable organism (due to illness, infection) may benefit from heightened vigilance to potential threats in the environment in order to prevent further injury while in an already compromised state. Thus, the inflammation-associated changes may be in the service of shielding the organism and promoting healing in the context of acute illness. In the short-term, these adaptations serve a clear benefit to the individual, but if sustained (such as through ongoing stress or immune dysregulation) could be iatrogenic in the long-term. Importantly, this approach also highlights the importance of contextual factors in driving the behavioral effects of inflammation. For example, heightened reactivity to negative stimuli may be beneficial when the threat is present, but not when an organism perceives safety.

One important issue to be disentangled using a network approach is whether the effect of inflammation on each of our identified endophenotypes occurs independently of the effect of inflammation on mood. There is evidence that somatic symptoms follow a different temporal course than depressed mood following inflammatory challenge and may have distinct neurobiological underpinnings. In

particular, IFN-α therapy resulted in the emergence of a cluster of somatic symptoms that appeared in the majority of patients within two weeks of treatment initiation (including symptoms of anorexia, fatigue, and pain), whereas a cluster of affective/cognitive symptoms (including symptoms of negative mood, anxiety, and cognitive dysfunction) emerged later and in a smaller proportion of patients (Capuron et al., 2002). Further, the cognitive/affective symptoms were more responsive to paroxetine than symptoms of fatigue (Capuron et al., 2002). Similar findings have been observed in cancer patients, where paroxetine led to reductions in depressed mood but not fatigue in patients undergoing chemotherapy (Morrow et al., 2003). In addition, Eisenberger et al. (2010b) found that feelings of social disconnection following endotoxin persisted for two hours after depressed mood had recovered. Based on the studies to date, we expect that the effect of inflammation on somatic symptoms, negative reactivity, and reward sensitivity are independent of the effects of inflammation on mood, although only a handful of studies have directly addressed this issue. For example, IFN-α therapy resulted in the emergence of a cluster of somatic symptoms that appeared in the majority of patients within two weeks of treatment initiation (including symptoms of anorexia, fatigue, and pain), as well as cluster of affective/cognitive symptoms that emerged in a smaller proportion of patients (including symptoms of negative mood, anxiety, and cognitive dysfunction) (Capuron et al., 2002). Indeed, the association between inflammation and both attentional bias and fatigue remain when accounting for concurrent depressed mood (Bower et al., 2009; Boyle et al., 2017). Further, see Fig. 1 of Eisenberger et al., (2010b) which illustrates that feelings of social disconnection following endotoxin persist for two hours after depressed mood has recovered. However, the majority of studies reviewed here did not control for depressed mood in their models, and therefore more careful testing of these associations is warranted to understand the independence or interdependence of depressed mood on these putative endophenotypes.

Overall, our review signals a clear benefit of deconstructing depression to examine links between inflammation and its underlying features, and provides substantial evidence supporting a relationship between inflammation and some of these key depressive processes. Moving forward, research in this area may benefit further from an updated conceptualization and modeling of endophenotypes and their position within explanatory models (Miller and Rockstroh, 2013). Genetic factors interact with psychological, environmental, and other biological factors and exert their influences at multiple points throughout the course of disorders. Instead, we might envision a network or web of influences that includes a multitude of factors and processes across multiple levels of analysis (e.g., genetic, neural, behavioral, developmental), with the recognition that none of these levels is more fundamental than any other (Miller and Rockstroh, 2013; Moore and Depue, 2016; Schmittmann et al., 2011). Network models offer the potential to develop more sophisticated and detailed models of the pathogenesis of depression, allow for the modeling of more complex (e.g., bidirectional, feedforward) associations, and are consistent with the RDoC initiative to capture pathological processes across multiple levels of analysis (e.g., interactions between symptoms, endophenotypic processes, genetic influences, environmental stressors, and time).

6.3. Clinical implications

If inflammation contributes causally to symptoms of depression, then anti-inflammatory medications would mitigate depressive symptoms. Indeed, antidepressant medications have anti-inflammatory effects on the body (Kenis and Maes, 2002), and remediate one of the sleep problems influenced by inflammation (Palagini et al., 2013; Riemann et al., 2001) while behavioral interventions that reduce somatic symptoms like fatigue also appear to work by reducing inflammatory signaling (Bower et al., 2014). There is also meta-analytic evidence that anti-inflammatory treatments can be effective means for

treating depression (Köhler et al., 2014). Based on our review of the causal role of inflammation on core features of depression, we would expect anti-inflammatory treatments to benefit patients presenting with exaggerated reactivity to negative information, altered reward processes, and somatic symptoms but not necessarily those presenting primarily with difficulties in cognitive control. However, there are some published studies showing that supplementing anti-depressant treatment with anti-inflammatory drugs only benefit individuals with high peripheral inflammation (Raison et al., 2013), that inhibiting inflammation entirely has negative implications for learning and memory (Yirmiya and Goshen, 2011), and targeting inflammatory pathways may only benefit a subset of depressed patients (Raison, 2017). We posit that the effects of inflammation on specific features of depression, rather than the entire syndrome, may explain some of the mixed findings with regard to the effectiveness of targeting inflammatory pathways as part of depression treatment.

Inflammation may only be relevant for some individuals with depression, while also being relevant to specific aspects of depression and not others. For example, only 33–47% of depressed individuals demonstrate elevated peripheral markers of inflammation (Raison and Miller, 2011; Rethorst et al., 2014). Further, although anti-inflammatory pharmacological interventions appear to improve depressive symptoms (Köhler et al., 2014), they may only be helpful for patients with elevations in peripheral inflammation (e.g., Raison et al., 2013). However, the impact of inflammation on mood and behavior occurs through inflammatory signaling in the brain or neuroinflammation, for which peripheral markers are only a proxy. Thus, it could be the case that depressed individuals have elevated neuroinflammation, but not elevated peripheral markers. What remains to be understood is whether and how acute increases in inflammation exert effects on some neural substrates but not others. It is possible that some people may be either genetically or environmentally predisposed to the effects of inflammation on specific receptors or neural substrates. For example, early life exposure to immune activation and exposure to chronic stress alter the density and morphology of microglia, particularly in regions of the brain involved in emotion and emotion regulation (Bilbo and Schwarz, 2012; Tynan et al., 2010). Thus early experiences may shape the effect that later inflammatory activation may have on behavior. Indeed, preclinical models have demonstrated that vulnerability factors like early life stress can alter the structure and function of microglia, leading to more neuroinflammation following an adult immune stimulus that their non-exposed peers (Bilbo and Schwarz, 2012), while minocycline treatment can rescue the effects of early life stress induced neuroinflammation during adulthood (Majidi et al., 2016). Further, there are health behaviors such as sleep and diet that can alter the permeability of the blood-brain barrier (He et al., 2014; Kanoski et al., 2010), thus rendering some individuals more vulnerable to the effects of peripheral inflammation on the brain. Taken together, these factors provide insight into how some individuals with depression do not exhibit elevated peripheral markers of inflammation while some individuals without depression do.

6.4. Limitations and directions for future research

Despite the conclusions that can be drawn based on the studies to date, there are several limitations to our understanding that warrant consideration and further investigation. First among these is the fact that studies of exogenously activated inflammation have been limited to either clinical samples undergoing treatment for a serious health condition (e.g., cancer, hepatitis C), or in extremely healthy, young adult samples. Thus, it remains to be seen whether populations at risk for depression or with current depression would respond to inflammatory challenges in the same way. However, paradigms that can be extended to higher risk and more vulnerable populations are emerging which will bridge our understanding of the putative role of inflammation in the development of depressive symptoms (e.g. Kuhlman

et al., 2018).

Much of the work on reactivity to negative information has focused on the impact of endotoxin-induced inflammation on negative reactivity to social threats (social evaluation, social exclusion, images of fearful faces) and sensitivity to social rewards. Thus, it remains unclear whether inflammation specifically upregulates reactivity to social stressors, or if reactivity to other types of negative information is also exaggerated. Relatedly, reactivity to negative information may be driven by cognitive biases toward negative information. Depressed individuals attend selectively to negative information (Gotlib and Joormann, 2010; Joormann and Quinn, 2014), and also interpret ambiguous information more negatively (Butler and Mathews, 1983; Dearing and Gotlib, 2009; Lawson et al., 2002; Rude et al., 2002). The only known study to have examined whether inflammation contributes to the cognitive bias toward negative information showed a correlation between CRP and attentional bias towards negative faces in a dot-probe task administered to breast cancer survivors (Boyle et al., 2017); this is an important area for future research.

Further, the accumulating evidence that elevated inflammation leads to blunted behavioral and neural reward reactivity, key elements of dampened positive affect and motivation in depression, in most cases comes from studies using monetary reward tasks. However, given the pronounced social deficits observed in depressed patients (Kupferberg et al., 2016), and the recent findings indicating that inflammation can lead to heightened VS reactivity specifically to social rewards (Inagaki et al., 2015; Muscatell et al., 2016), future work should explicitly test whether the effect of inflammation on reward reactivity is more pronounced for social compared to monetary rewards. This could be tested by directly comparing responsivity to different types of reward (e.g., social vs. monetary vs. primary rewards) under inflammatory conditions. Additionally, future work would benefit from examining the influence of inflammation on distinct domains of reward processing, including effects on reward anticipation (i.e., wanting), the consummatory reward response (i.e., liking), reward motivation, and reward-related learning, in order to understand more precisely the reward mechanisms affected by inflammation. Finally, research that incorporates subjective reports of cognitive function, current methods for assessing executive function (e.g., Snyder, Miyake, Hankin, 2015), and neuroimaging approaches are important to clarify effects of inflammation on cognitive control processes.

Researchers conducting studies on inflammation and depression should also consider assessing demonstrated vulnerability factors. Given that depressive symptoms only arise in a subset of individuals even under chronic inflammatory conditions, inflammation must interact with pre-existing host factors to determine mood outcomes. Potential risk factors include early life stress (Danese et al., 2008; Kuhlman et al., 2017) and certain genetic factors, such as the BDNF Met allele, which has been shown to moderate the association between CRP and cognitive depressive symptoms (Dooley et al., 2016). Another potentially important vulnerability factor to consider is sex. Despite the fact that depression is more prevalent among women than men (Kuehner, 2003; Nolen-Hoeksema, 2001, 1987), a preponderance of studies examining the effects of inflammation on mood and behavior have been conducted with solely male participants (Brydon et al., 2009, 2008; Harrison et al., 2014, 2009; Krabbe et al., 2005; Reichenberg et al., 2001; Wright et al., 2005). Studies that have included both male and female participants have revealed prominent sex differences in the psychological response to an inflammatory stimulus (See Lasselin et al., 2018 for review). For example, females exhibit greater increases in depressed mood and feelings of social disconnection following endotoxin exposure than males (Eisenberger et al., 2010a, 2009; Moieni et al., 2015). Moreover, endotoxin-induced increases in TNF-α and IL-6 were correlated with increases in social disconnection for females but not for males (Moieni et al., 2015). Additionally, among females but not males, endotoxin-induced increases in IL-6 have been associated with increased activation of threat-related neural regions (dACC, anterior

insula), which mediate the relationship between IL-6 levels and depressed mood (Eisenberger et al., 2009). Taken together, females may be more sensitive to the negative psychological effects of inflammation via increased activation of threat circuitry. Early exploration of these pathways in preclinical models suggests that males have more microglia in early life and females have more activated or primed microglia during adolescence and adulthood (Schwarz et al., 2012). Further, gene expression profiles for a large number of cytokines and chemokines are sex-dependent (Schwarz et al., 2012). These gender differences deserve further investigation, as they may help to elucidate the mechanisms underlying the greater burden of depression among women that emerges in adolescence.

7. Conclusions

Using endophenotypes as intervention targets in depression has been a beneficial approach so far. For example, targeting the neural circuit associated with cognitive control using transcranial magnetic stimulation reduces depressive symptoms by at least 55% and is particularly effective in depressed patients with comorbid substance use disorders (Dunlop et al., 2017). Further, the field is shifting toward neuroscience-driven treatments for transdiagnostic endophenotypes (Craske et al., 2016). This is fitting given that the endophenotypes reviewed here are not specific to depression alone, but relevant to a number of psychiatric disorders. Targeting the biological underpinnings of these complex cognitive and behavioral processes could have profound implications for the treatment of psychiatric diseases. Yet, there remain important gaps in our knowledge that impede the translation of these findings to practice.

The current body of evidence indicates that inflammation is linked, in many cases causally, to alterations in core affective and cognitive processes (e.g., anhedonia; negative reactivity bias) and their neural circuits that are strongly implicated in current models of the etiology and treatment of depression. As such, the role of inflammation may be best understood as affecting these complex neurobiological, cognitive, and affective processes, rather than affecting the broad depressive syndrome directly. Our understanding of the role of inflammation in depression can be advanced by research that (1) deconstructs depression to effectively account for the heterogeneity across individuals; (2) considers the potentially distinct effects of different magnitudes and durations of inflammation exposure; (3) examines potential moderators (e.g., female gender, early life stress exposure) of the effects of inflammation, and (4) utilizes a network perspective that models these interdependent psychophysiological processes at multiple levels of analysis, as they play out over time. Research studies that incorporate such advances may elucidate the etiology of depression in its various iterations, and thus speed our progress towards alleviating the substantial suffering and burden that depression has on individuals, families, and societies.

Acknowledgements

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