Title
Inflammation and Core Processes of Depression

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Publication Date
2017

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Inflammation and Core Processes of Depression

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Psychology

by

Larissa Noelle Dooley

2017

ABSTRACT OF THE DISSERTATION

Inflammation and Core Processes of Depression

by

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Doctor of Philosophy in Psychology

University of California, Los Angeles, 2017

Professor Julienne Elizabeth Bower, Chair

Depression is a leading cause of disability worldwide. A strong empirical literature has identified a role for inflammation in the pathophysiology of depression, yet evidence suggests that the precise nature of this relationship is complex and still largely undefined. It has been suggested that a barrier to understanding the role of inflammation in depression is the tendency to conceptualize and measure depression as a homogeneous, unitary construct. Instead, an approach that "deconstructs the construct" of depression and examines how inflammation impacts core processes or endophenotypes of depression may lead to new insights into the nature of the inflammation-depression link.

The first part of this dissertation consists of an integrative review of the literature linking inflammation and core processes of depression. The purpose of the review is to bring together the depression, endophenotype, and inflammation literatures in order to identify core processes of depression likely to be impacted by inflammation, which can be targets of investigation in

future work. The review first identifies key endophenotypes of depression that have been evaluated in at least preliminary work within the context of inflammation; then, the evidence examining a potential role for inflammation in each of these core processes of depression is reviewed and evaluated. Overall, existing evidence supports a role of inflammation in modulating several key domains relevant to depression, including cognitive biases, reward processing, and somatic symptoms.

The second section of this dissertation presents an empirical study aimed at testing several of the inflammation-depression endophenotype links identified in the review paper. In this study, an influenza vaccine was used to elicit increases in circulating inflammation, and resulting effects on multiple processes relevant to depression were examined, including mood, fatigue, reward processing, cognitive functioning, and attentional bias. Findings indicated that increases in inflammation were associated with attentional avoidance of positive stimuli, as well as improvements in working memory and reward learning. These findings suggest a novel mechanism by which inflammation may contribute to depression (attentional bias), as well as provide insight into the effects of low-grade inflammation on aspects of memory and reward processing.

The dissertation of Larissa Noelle Dooley is approved.

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2017

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Moderate life stress is associated with psychological resilience in breast cancer survivors. *Stress and Health.*

Dooley, L.N., Ganz, P.A., Cole, S.W., Bower, J.E. (2016). Val66Met BDNF polymorphism as a vulnerability factor for inflammation-associated depressive symptoms in women with breast cancer. *Journal of Affective Disorders.* doi: doi:10.1016/j.jad.2016.02.059

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The Role of Inflammation in Core Processes of Depression:

An Endophenotype Approach

Abstract

A wealth of evidence has implicated inflammation in the development of depression. However, inflammation is neither necessary nor sufficient to cause depression; thus, the precise nature of the inflammation-depression link remains unclear. We suggest that this relationship may be clarified by focusing on connections between inflammation and underlying endophenotypes of depression, rather than depression sum scores or clinical thresholds. In this integrative review, we draw on the depression, endophenotype, and inflammation literatures to identify several core processes that are both relevant to depression and have been empirically linked to inflammation. The endophenotypes identified are negative cognitive bias (biased attention, increased responsivity to negative information), altered reward reactivity, cognitive impairment (executive functioning and memory deficits), and somatic syndrome (fatigue, psychomotor slowing, sleep changes). For each endophenotype, we first provide a brief overview of its relevance to depression and neurobiological underpinnings, and then – in the bulk of the paper – review evidence investigating a potential role of inflammation. We focus primarily on experimental evidence from each of the three key models of exogeneously-induced inflammation: IFN-α treatment, endotoxin, and typhoid vaccination. Overall, existing evidence suggests that inflammation likely plays a role in negative cognitive bias (particularly for increased responsivity to negative information, with preliminary evidence for biased attention), altered reward reactivity, and somatic symptoms. In contrast, evidence has generally not supported an effect of inflammation on cognitive impairment, particularly for executive functioning, with more mixed findings for memory. We conclude that our understanding of the role of inflammation in depression can be advanced by research that (1) deconstructs depression to examine how inflammation impacts core processes of depression; (2) carefully considers the

potentially distinct effects of different magnitudes and durations of inflammation exposure; (3) examines potential interactions between inflammation and pre-existing risk factors, and (4) moves towards conceptual and analytic approaches that model the web of relationships between variables at multiple levels of analysis, as they play out over time.

The Role of Inflammation in Core Processes of Depression: An Endophenotype Approach

Depression is a prevalent psychiatric condition that merits urgent national and global attention. Among U.S. adults, an estimated 23% of women and 15% of men will experience a major depressive episode in their lifetime (Kessler et al., 2010). Moreover, only about half of affected individuals achieve remission under available treatments (Nemeroff, 2007). Indeed, depression remains the leading global cause of disability (World Health Organization, 2016), and, according to a recent federal report, suicide rates in the United States have risen to the highest levels in nearly 30 years (Curtin, Warner, & Hedegaard, 2016). Thus, major depression is a highly prevalent and costly disorder that is often not adequately treated. Identifying biological and behavioral processes underlying depression—and the links among them—that can be targeted by intervention is a global health priority, and a major focus of current national research.

One of the more promising research areas in this vein—integrating psychopathology, brain, and biology—involves inflammation. Substantial evidence across various populations and study designs has implicated inflammation in the etiology of depression. However, this literature has also shown that inflammation is neither necessary nor sufficient to cause depression (Raison & Miller, 2011), as not all depressed individuals exhibit elevations in inflammatory markers, and individuals who experience even robust elevations in inflammation do not necessarily develop depression. Moreover, inflammation is not specific to depression, as immune alteration has also been found in other psychiatric conditions including posttraumatic stress disorder and schizophrenia (Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Spitzer et al., 2010). This reflects challenges in current psychiatric diagnostic classification systems, in which multiple

diagnoses often share overlapping symptoms as well as biological and psychosocial vulnerability factors.

A complementary issue for psychopathology research is that a single diagnostic category can represent multiple combinations of a diverse array of symptoms, complicating our understanding of causes, characteristics, and processes. Depression is perhaps the chief example of this. It has been calculated that there are a possible 16,400 unique symptom profiles that would qualify for a diagnosis with major depressive disorder (MDD); furthermore, two individuals who both meet MDD criteria may not have a single symptom in common (Fried & Nesse, 2015). Given this marked heterogeneity, the conceptualization and measurement of depression as a homogeneous construct based on current diagnostic categories has been suggested as a major barrier to understanding the etiology of depression, as well as the potential role of inflammation in depressogenesis (Young, Bruno, & Pomara, 2014). Thus, as proposed by the National Institute of Mental Health's Research Domain Criteria (RDoC), research on the pathogenesis of depression and the role of inflammation will benefit from a biologically-informed and dimensional taxonomy of functioning that includes behavior, neuroscience, and genetics (Cuthbert & Insel, 2010; Insel et al., 2010). This dimensional or endophenotype approach to depression may help identify elementary neural and behavioral processes that both drive the onset and maintenance of depression, and are triggered or exaggerated by inflammation. As such, the endophenotype perspective holds promise for revealing links between inflammation and depressive psychopathology, which we argue have been partially obscured by emphasizing diagnostic category.

Accordingly, the aim of the present review is to identify empirically-based endophenotypes of depression which have also been shown to be impacted by inflammation.

First, we briefly review the evidence suggesting a role of inflammation in depression, and introduce the endophenotype approach to psychopathology. Next, we identify and define several key endophenotypes for depression: negative cognitive bias, altered reward processing, cognitive impairment, and somatic syndrome. For each endophenotype, we review evidence supporting its relevance for depression and its neurobiological correlates, and then examine evidence suggesting that inflammation modulates the processes represented by the endophenotype. Evidence informing the role of inflammation in each endophenotype is drawn primarily from studies employing one of the three key models of inflammation-induced depression: the IFN-α, endotoxin, and typhoid vaccine models. Finally, we propose future research directions aimed at understanding the role of inflammation in the pathogenesis of depression.

Inflammation and depression

Inflammation is a key component of the innate immune system's ability to clear infection and repair injured tissue. Characterized by redness, heat, pain, and swelling, inflammation results from the release of pro-inflammatory cytokines from innate immune cells. Cytokines can additionally communicate with the brain via various routes and result in a host of emotional, cognitive, and behavioral changes collectively termed "sickness behaviors" (Dantzer, Connor, Freund, Johnson, & Kelley, 2008). These sickness behaviors, including fatigue, loss of appetite, and social withdrawal, are considered an adaptive response intended to reduce the spread of infection and promote healing. However, when inflammation persists, as when the inflammatory response is maintained by ongoing psychosocial stress rather than physical injury, prolonged inflammatory signaling can have detrimental effects (Miller, Maletic, & Raison, 2009; Slavich & Irwin, 2014). Inflammation has been implicated in a host of chronic diseases including

cardiovascular disease, diabetes, and cancer. Accumulating evidence also suggests that inflammation plays a significant role in psychiatric disorders, including major depression.

One early indication that inflammation could play a role in depression came from the observation that inflammatory medical conditions, including asthma, rheumatoid arthritis, inflammatory bowel disease, metabolic syndrome, and coronary heart disease, frequently co-occur with depression (Goodwin, Fergusson, & Horwood, 2004; Graff, Walker, & Bernstein, 2009; Pan et al., 2012; Whooley, 2006). For example, convergent evidence has indicated that individuals with rheumatoid arthritis and inflammatory bowel disease are 2-3 times more likely to experience major depression compared with the general population (Graff et al., 2009; Katz & Yelin, 1993; Regier et al., 1988).

If the high co-occurrence of these physical disorders with depression can be explained by common underlying inflammatory processes, then inflammatory markers should be elevated among individuals with depression. Indeed, meta-analyses have concluded that depressed individuals, on average, exhibit higher levels of the proinflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), as well as inflammatory markers including IL-1 receptor antagonist (IL-1ra; a marker of IL-1 activity) and C-reactive protein (CRP; a downstream marker of IL-6 activity and a marker of systemic inflammation), compared to nondepressed individuals (Hiles, Baker, de Malmanche, & Attia, 2012; Howren, Lamkin, & Suls, 2009). However, these mean group differences are likely driven by a subpopulation of depressed individuals with elevated inflammation (Raison & Miller, 2011). Raison and Miller (2011) have suggested that elevated inflammatory markers are seen in approximately one third of individuals with depression. A study using data from the National Health and Nutrition Examination Survey provided a somewhat higher estimate of the prevalence of heightened

inflammation among depressed individuals, reporting that 47% of those with clinically significant depressive symptoms had a CRP level >= 3.0 mg/L, and 29% had a CRP level >= 5.0 mg/L (Rethorst, Bernstein, & Trivedi, 2014). Thus, depression is associated with elevated inflammation in a subpopulation of individuals with depression.

Longitudinal studies have attempted to decipher the directionality of this association between elevated inflammatory markers and depressive symptoms. Findings from these studies have shown that baseline IL-6 and CRP predict subsequent increases in depressive symptoms (Gimeno et al., 2009; Valkanova, Ebmeier, & Allan, 2013; van den Biggelaar et al., 2007; Wium-Andersen, Ørsted, Nielsen, & Nordestgaard, 2013), suggesting that elevated inflammation precedes depression. Similarly, recent data from a study of twin pairs—which holds constant shared genetic and early environmental factors—showed that the twin who had higher CRP levels at baseline was more likely to develop depression five years later (Su, 2016). It should be noted that there is also evidence that depressive symptoms predict increases in inflammation (Stewart, Rand, Muldoon, & Kamarck, 2009; cf. Su, 2016), indicating probable bidirectional effects (Matthews et al., 2010).

Beyond this correlational evidence, evidence that inflammation is a causal factor in depression comes from both animal and human studies. From the animal literature, a robust body of work shows that activation of the innate immune system and resulting inflammation lead to depressive-like behaviors (for reviews, see Anisman & Matheson, 2005; De La Garza, 2005; Dunn, Swiergiel, & De Beaurepaire, 2005; Pecchi, Dallaporta, Jean, Thirion, & Troadec, 2009). For example, numerous studies have shown that intraperiotoneal administration of endotoxin, a component of gram-negative bacteria that leads to the robust release of proinflammatory cytokines, results in a host of behaviors similar to depression in humans, including anhedonia

(e.g., reduced sucrose consumption); decreases in exploratory, novelty-seeking and social behaviors; reduced food intake; and sleep disturbance (Larson & Dunn, 2001).

This preclinical work has also elucidated the mechanisms by which peripheral inflammation can access the brain and lead to depressive symptoms. Pro-inflammatory cytokines can communicate with the brain through various routes, including 1) a "humoral" pathway in which circulating cytokines gain passage to the brain through leaky regions in the blood-brain barrier, or are actively conveyed into brain parenchyma by saturable transporters; 2) a neural pathway involving activation of cytokine receptors located on afferent nerve fibers, which in turn transmit inflammatory signals to the brain; and 3) a cellular pathway in which microglia, the resident innate immune cells of the brain, release chemokines that attract activated peripheral immune cells to the meninges and parenchyma of the brain (Dantzer et al., 2008; Miller, Haroon, Raison, & Felger, 2013). Once they have gained access to the brain, cytokines can have wide-ranging impacts on neurotransmitter metabolism, neuroendocrine function, and neuroplasticity (Haroon, Raison, & Miller, 2012), resulting in sickness behaviors including fatigue, loss of appetite, anhedonia, depressed mood, and cognitive impairment (Dantzer et al., 2008). In the context of acute illness, these symptoms are believed to represent an adaptive and temporary response that prioritizes an individual's energy resources towards healing processes and minimizes the potential for the spread of infection to others (Raison & Miller, 2013; Miller & Raison, 2016). However, when immune activation in ongoing, as is commonly seen in the context of chronic disease or chronic stress, prolonged inflammatory signaling to the brain can lead to more consequential and debilitating cognitive and behavioral changes, including the development of clinical or subclinical depressive symptoms (Dantzer et al., 2008).

Causal evidence in humans supporting a role for inflammation comes from studies administering an inflammatory challenge and examining subsequent changes in cognitive and behavioral functioning. To date, three primary models have been used to this end: the IFN-α model, the endotoxin model, and the typhoid vaccination model. 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 suggesting a link between inflammation and depression came from clinical observations of patients with Hepatitis C or cancer, who commonly develop clinically significant levels of depression after the initiation of interferon-α (IFN-α) therapy (Capuron & Miller, 2004; Raison, Demetrashvili, Capuron, & Miller, 2005). IFN-α is a cytokine released by the innate immune system, and stimulates the release of other proinflammatory cytokines such as IL-6 (Capuron et al., 2003; Taylor & 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, Brouwer, van der Mast, & Schalm, 1994; Lotrich, Rabinovitz, Gironda, & Pollock, 2007). IFN-α has been estimated to causes symptoms sufficient for a major depression diagnosis in up to 50% of patients (Musselman et al., 2001).

As dosing schedules for IFN-α therapy typically involve multiple treatments per week over a period of months, a key feature of the IFN-α model is that it reflects the effects of chronic inflammatory stimulation. Additionally, IFN-α treatment results in moderate to robust increases in inflammatory markers, depending on the disease being treated and associated dosing schedule. Hepatitis C patients typically receive a relatively mild dose of IFN-α several days a 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 a higher dose and 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 the IL-6 response to injection had declined to approximately 7 pg/mL, or a 233% increase (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. A key benefit of this paradigm is that modeling chronic inflammatory exposure allows for the examination of how different symptoms manifest temporally across time, and the relationships between symptoms or symptom clusters. Of note, one limitation of this model is the examination of inflammation in the context of chronic disease (hepatitis C, cancer), which can limit the generalizability of findings.

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 highly potent 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 & Hannestad, 2010; Eisenberger, Inagaki, Mashal, & Irwin, 2010; Reichenberg et al., 2001). Additionally, mood and anxiety effects of endotoxin appear to manifest in a dose-dependent manner, with higher doses associated with greater declines in mood and increases in anxiety (Grigoleit et al., 2011). Endotoxin results in an extremely robust but short-term inflammatory response – for example, a study by Grigoleit and colleagues (2011) reported an IL-6 increase of

approximately 140 pg/mL (a 28000% increase) two hours after a 0.4 ng/kg dose, and an IL-6 increase of approximately 190 pg/mL (a 38000% increase) two hours after a 0.8 ng/kg dose. IL-6 increases following both doses resolved within six hours of administration. Thus, the endotoxin model can inform our understanding of the acute effects of exposure to high levels of inflammation. A strength of this model is that it is typically carried out among medically healthy individuals, allowing for the generalizability of the effects of inflammation to the general population.

A third model for studying the effects of inflammation on depression has involved 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, Strike, Brydon, & Steptoe, 2005). Typhoid vaccination leads to a modest, short-term inflammatory response – for example, Wright et al. (2005) found an average increase of .82 pg/mL (a 106% increase) in IL-6 at 3 hours post-vaccination; increases in inflammation resolve within 24 hours following typhoid vaccination (Paine, Ring, Bosch, Drayson, & Veldhuijzen van Zanten, 2013). Thus, typhoid vaccine studies model the effects of mild, acute elevations 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 & Miller, 2011). Additionally, unlike IFN-α treatment or endotoxin, typhoid vaccine does not typically lead to fever, nausea, or other physical illness symptoms, suggesting that any effects on mood and cognition are not attributable simply to illness symptoms, but rather to more direct effects of cytokines on the brain.

Another approach to examining the causal relationship between inflammation and depression is to block inflammation and examine resulting effects on depressive symptoms. Antidepressants exert anti-inflammatory effects, which are in turn associated with symptom reduction, though not all studies have supported this effect (Miller et al., 2009). More compelling is evidence from studies examining the effects of targeted anti-inflammatory treatments (including nonsteroidal anti-inflammatory drugs and cytokine inhibitors) on depressive symptoms. Overall, these studies have supported the efficacy of anti-inflammatory treatments in depression reduction, particularly for individuals with elevated baseline inflammation (Kiecolt-Glaser, Derry, & Fagundes, 2015; Köhler et al., 2014).

In sum, there is substantial experimental evidence—from both human and animal models—indicating that inflammation plays a causal role in many of the symptoms comprising the depressive syndrome. Moreover, there is suggestive cross-sectional and longitudinal research linking inflammation with clinical depression and subclinical levels of depressive symptoms. Research on the role of inflammation in depression has burgeoned in recent years, but, as previously mentioned, inflammation shows limited sensitivity and specificity as a driver of depression, and its influence on fundamental processes in depressive psychopathology—including both behavioral and neural processes—remain unclear. We suggest that this influence may be best understood by focusing on effects of inflammation on underlying endophenotypes of depression.

Endophenotype Approach

The concept of endophenotypes was introduced into the psychopathology literature by Irving Gottesman and James Shields in their writings on genetic theories of schizophrenia (1972, 1973), adapting the term from biological research (John & Lewis, 1966). Gottesman and Shields

defined endophenotypes as internal biological or behavioral features "only knowable after aid to the naked eye" (1972, 1973, p. 19), as contrasted with a phenotype (or, exophenotype) as an observable manifestation of genetics. Gottesman and Gould expanded on this definition, characterizing endophenotypes as measurable, intermediate components—neurophysiological, biochemical, endocrine, neuroanatomical, cognitive, or neuropsychological—that exist "along the pathway between disease and distal genotype" (2003, p. 636; Gould & Gottesman, 2006). Endophenotypes were initially aimed at providing a more fruitful approach to gene identification; because endophenotypes are conceptualized to represent more elementary psychological and biological processes existing closer to the level of gene action, it follows that they may be informed by fewer (and thus ostensibly easier to identify) genes than broader and more complex diagnostic categories (Gottesman & Gould, 2003; Gould & Gottesman, 2006). However, in recent years, the endophenotype approach has outgrown this initial aim to identify genetic inputs, as researchers have realized that focusing on elementary depressogenic processes (rather than traditional diagnostic categories) can help identify not just genetic vulnerability factors but myriad other biological, psychological, and environmental contributors (Miller & Rockstroh, 2013). Thus, in the last decade, the endophenotype concept has fueled a substantial body of research identifying and evaluating potential endophenotypes, and attempting to leverage these endophenotypes to understand the origins of mental disorder (Miller & Rockstroh, 2013).

Importantly, the endophenotype concept also informed the National Institute of Mental Health's Research Domain Criteria (RDoC) initiative (Cuthbert & Insel, 2010; Sanislow et al., 2010), which emphasizes a focus on intermediate phenomena and their links upstream to genetic, molecular, and cellular factors, and downstream to clinically relevant behavior (Insel et al.,

2010). A central assumption of RDoC is that disorders reflect disturbances in key functional domains (e.g., affect, cognition, social), which can be shared (e.g., lower motivation in both depression and schizophrenia) or distinctive (e.g., dampened positive affect in depression, but not generalized anxiety disorder) across disorders. This approach aims to organize and explain psychopathology phenotypes across levels in a way that mirrors the endophenotype approach. Reflecting the congruence between the endophenotype and RDoC approaches, researchers at the helm of both have urged a movement away from traditional diagnostic classifications and towards more continuous or dimensional conceptualizations of clinical disorders (e.g., Hasler, Drevets, Manji, & Charney, 2004).

We propose that an endophenotype perspective may help to clarify the complex relationship between inflammation and depression, as examining effects of inflammation on more proximal behavioral and neural processes may yield more robust and uniform relationships. A substantial amount of research has focused on identifying, evaluating, and leveraging endophenotypes for major depression. Putative endophenotypes have included behavioral, biological, and neural processes (Goldstein & Klein, 2014; Hasler, Drevets, Gould, Gottesman, & Manji, 2006; Hasler et al., 2004). Given this wealth of research, the endophenotype literature provides a useful tool for identifying candidate dimensions of depression that may be influenced by inflammation.

The current review integrates the depression endophenotype and inflammation literatures, with the dual aims of (1) identifying core processes of depression that may plausibly be impacted by inflammation, and (2) reviewing and evaluating existing evidence for the impact of inflammation on these components of depression. We focus exclusively on cognitive and behavioral endophenotypes of depression that have been shown in empirical work to be impacted

by inflammation. Although numerous candidate endophenotypes for major depression have been proposed, we have excluded a number of them from this review – such as neuroticism and EEG frontal asymmetry (Goldstein & Klein, 2014) —due to a lack of studies evaluating these mechanisms in the context of inflammation. Additionally, while a number of biological endophenotypes have been proposed, such as HPA axis dysfunction (Goldstein & Klein, 2014; Hasler et al., 2004), these are beyond the scope of the current review, which focuses on cognitive and behavioral endophenotypes. Thus, we emphasize four endophenotypes as particular candidates implicated by extant research on inflammation and depression: negative cognitive bias; altered reward processing; cognitive impairment; and somatic syndrome. We first review both behavioral and neurobiological features of each endophenotype, then consider the evidence for links with inflammation. Figure 1 summarizes these potential endophenotypes, including the constellation of processes reviewed as components of each endophenotype. When considering the evidence linking inflammation and a given endophenotype, we focus on human studies situated within the three inflammatory challenge models: the IFN-α, typhoid vaccination, and endotoxin models. Given that these paradigms involve manipulating levels of inflammation (rather than simply examining correlations between inflammatory markers and outcomes), studies within these paradigms should provide the strongest tests of our hypotheses.

Endophenotypes of depression impacted by inflammation

Endophenotype #1: Negative Cognitive Bias

According to Beck's cognitive model of depression, negative early life experiences, in combination with genetic and personality factors, lead to the development of negative cognitive schemas – that is, cognitive structures that organize memory and other cognition, including fundamentally dysfunctional beliefs or attitudes about oneself, the world, and the future (Beck,

1967, 1987, 2008). These latent schemas can be activated later in life by internal or external events, such as stressful life experiences, and help explain why such events trigger depression for some people only, whereas for others—those with more adaptive schemas—such events do not. According to Beck, once activated, these negative schemas—like schemas in general—act as lenses or filters, skewing information processing, including how incoming information is attended to, perceived, interpreted, and stored (Beck, 1967, 1987, 2008). The result is a systematic negative cognitive bias, characterized by biased attention towards negative information, overly negative interpretations of incoming information, and the inhibition of positive information in attention and memory (Beck, 1967, 1987, 2008).

According to Beck, this bias explains many of the common manifestations of depression, including feelings of negative mood, hopelessness, self-criticism, and suicidal wishes. In turn, these symptoms are subjected to further negative interpretations (e.g., "my poor functioning is a burden on my family"), initiating a feedback loop between symptoms and negative cognitions that fuels the maintenance of depression (Beck, 2008). Beck's model has provided a framework for empirical work on cognitive factors that contribute to the onset and maintenance of depression. Importantly, the cognitive model is also the foundation of cognitive and cognitive-behavioral therapy, a widely used and effective treatment for depression and other disorders (Dobson, 1989).

Biased attention in depression. Attentional biases toward negative information have been consistently demonstrated in individuals with depression, and have been proposed as a key depression endophenotype (Goldstein & Klein, 2014). Among nondepressed individuals, attention is generally biased towards positive stimuli (Gotlib, Krasnoperova, Neubauer Yue, & Joormann, 2004). In contrast, depressed individuals show decreased attention for positive stimuli

and increased attention towards negative stimuli (Gotlib et al., 2004; Kellough, Beevers, Ellis, & Wells, 2008). Biased attention towards negative stimuli have been demonstrated in never-disorders daughters of depressed mothers (a sample considered at high risk for depression), implicating negative bias in the etiology of depression (e.g., Joormann, Talbot, & Gotlib, 2007). Negatively biased attention may not be due to a rapid orienting toward negative stimuli, but rather with difficulty disengaging with negative information (Mogg & Bradley, 2005). In empirical studies, negatively biased attention has been assessed using various paradigms, which typically measure reaction time or time spent looking at emotionally valenced stimuli. Attentional biases towards negative information and away from positive stimuli among depressed individuals versus nondepressed controls have been shown in meta-analyses of studies using the emotional Stroop (Epp, Dobson, Dozois, & Frewen, 2012), dot probe (Peckham, McHugh, & Otto, 2010), and eye-tracking tasks (Armstrong & Olatunji, 2012). These biases are increasingly seen as central cognitive processes underlying key mood disturbances and emotion regulation deficits in depression (Gotlib & Joormann, 2010).

Neuroimaging studies have begun to elucidate the neural pathways involved in this attentional bias. In healthy adults, brain regions that are associated with attention include the intraparietal sulcus, precentral sulcus, superior temporal sulcus and prefrontal cortex (PFC) (Corbetta et al., 1998). When two competing stimuli are present in the environment, these cortical regions coordinate to select and direct attention towards one stimulus, and this selective attention simultaneously suppresses attention towards other competing stimuli (Kastner, De Weerd, Desimone, & Ungerleider, 1998). The act of switching attention from one stimulus to another requires the engagement of higher order cortical areas, including the ventrolateral prefrontal cortex (VLPFC), which is specifically involved in selection between competing

stimuli; dorsolateral prefrontal cortex (DLPFC), which is specifically involved in inhibition of attention; and the superior parietal cortex, involved in gaze shifting (Beevers, Wells, & Mcgeary, 2010; Fales et al., 2008; Passarotti, Sweeney, & Pavuluri, 2009). In individuals with depression, these regions (the right VLPFC, right DLPFC, and right superior parietal cortex) are not activated as strongly when attempting to shift attention away from negative stimuli, compared with nondepressed controls (Beevers et al., 2010; Fales et al., 2008). Reduced activity in these regions may thus underlie depressed individuals' difficulty in disengaging with negative stimuli, thereby increasing exposure to negative and decreasing exposure to positive information in the environment (Beevers et al., 2010; Disner, Beevers, Haigh, & Beck, 2011; Fales et al., 2008; Gotlib & Hamilton, 2008; Koster, De Raedt, Goeleven, Franck, & Crombez, 2005).

Biased attention and inflammation. There is evidence from at least one study suggesting a role of inflammation in negative attentional bias (Boyle, Ganz, Van Dyk, & Bower, 2017). In a sample of early-stage breast cancer survivors, a dot probe task was administered to assess bias towards emotional (sad, angry, and happy) versus neutral faces. Findings indicated that circulating concentrations of CRP were positively associated with negative attentional bias, such that women with higher CRP exhibited greater attention towards sad faces (Boyle et al., 2017). This study provides encouraging but preliminary evidence for an association between circulating inflammatory markers and attentional bias towards negative information. It is plausible that inflammation may increase the salience of negative emotional information, and that this may be one mechanism by which inflammation can lead to risk for depression. Future work is needed to replicate these findings and determine the directionality of these effects. Additionally, no published studies have investigated the neural mechanisms that may underlie the potential effects of inflammation on attentional bias; future work might investigate whether

the same cortical regions described above as being implicated in negative attentional bias in depression underlie the effects of inflammation on attentional bias.

Increased reactivity to negative information in depression. As previously described, individuals with depression exhibit negative attentional biases, which are thought to reflect difficulties disengaging with negative information; this greater engagement with negative stimuli is also thought to explain why individuals with depression exhibit increased reactivity to negative information (Gotlib & Joormann, 2010). Evidence supports altered reactivity to negative or stressful information among depressed individuals. For example, compared to nondepressed controls, individuals with depression exhibit more negative facial expressions in response to unpleasant images (Sloan, Strauss, Quirk, & Sajatovic, 1997), report greater perceived stress in response to a laboratory stress tasks (de Rooij, Schene, Phillips, & Roseboom, 2010), and display greater increases in negative affect in response to daily stressors (Myin-Germeys et al., 2003). Depressed individuals also display altered physiological responses to laboratory stress tasks, including increased norepinephrine and epinephrine (Weinstein et al., 2010), atypical cortisol patterns (Burke, Davis, Otte, & Mohr, 2005; Weinstein et al., 2010), and increased inflammatory reactivity (Fagundes, Glaser, Hwang, Malarkey, & Kiecolt-Glaser, 2013; Miller, Rohleder, Stetler, & Kirschbaum, 2005; Pace et al., 2006; Weinstein et al., 2010).

In addition to increased behavioral, affective, and physiological reactivity in depression, research has also demonstrated altered neural reactivity to negative emotional information among depressed individuals. Studies using event-related potentials (ERPs) to examine levels of neural activity to emotional stimuli have shown that, while healthy individuals exhibit greater slow-wave amplitudes to happy and neutral faces compared with sad stimuli, depressed individuals exhibit equivalent slow-wave amplitudes to sad, happy, and neutral faces (Deveney

& Deldin, 2004), consistent with behavioral findings that depressed individuals fail to engage in the normal inhibition of negative stimuli and thus engage more strongly with negative stimuli (e.g., Gotlib & Joormann, 2010). 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 (Drevets, 2001; Fu et al., 2004; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002; Stuhrmann et al., 2013; cf. Beevers et al., 2010), a region responsible for interpreting the emotional quality and salience of a given stimulus; this exaggerated amygdala reactivity normalizes after successful antidepressant treatment (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 & 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 "emotional" limbic regions and the "cognitive" prefrontal cortex, the ACC is thought to play an important role in integration of the neural circuitry dedicated to emotional processing and affect regulation, and is thus relevant in the context of depression (Stevens, Hurley, & Taber, 2011). Two regions within the ACC that may be of particular relevance to depression and inflammation are the dorsal anterior cingulate cortex (dACC) and the subgenual anterior cingulate cortex (sACC), due to their key contributions to emotional processing (Etkin, Egner, & Kalisch, 2011). The dACC has been conceptualized as 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 & Cole, 2012). The sACC has been characterized as a key region for 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, 2005; Sacher et al., 2012). Depressed individuals display exaggerated activity in the sACC which reverses with successful depression treatment (Sacher et al., 2012).

Increased reactivity to negative information and inflammation. The evidence reviewed above suggests that depression can amplify reactivity to negative and/or stressful information. Accumulating evidence suggests that inflammation may similarly exaggerate stress reactivity, as measured at behavioral, physiological, and neural levels.

Inflammation may exaggerate affective and physiological reactivity to stressors, similar to the effect seen in depression. In a study by Brydon and colleagues (2009), a group that received typhoid vaccination exhibited 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. Additionally, participants with larger vaccine-induced IL-6 responses exhibited elevated systolic blood pressure responses to the stress tasks, as well as elevated post-stress levels of 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 (Harrison et al., 2009). Findings indicated that vaccine-induced negative mood was associated with enhanced sACC activation to emotional information (Harrison et al., 2009), suggesting that inflammation may directly or indirectly act

on the sACC to elicit changes in mood and stress reactivity. This is notable given the demonstrated role for sACC hyperreactivity in depression (Sacher et al., 2012); sensitization of the sACC may be pathway by which inflammation can lead to mood changes.

Evidence also comes from endotoxin studies showing that inflammation can upregulate stress reactivity, particularly at the neural level. For example, a recent study found that although endotoxin did not increase affective reactivity to social stress (negative feedback from a confederate "evaluator" about how the participant had come across in a previously recorded interview), endotoxin did lead to exaggerated activation in threat-related neural regions to the stressor, including greater activation of the amygdala, dACC, and dorsomedial PFC (Muscatell et al., 2016). Another study similarly found that endotoxin led to exaggerated amygdala responses to threatening stimuli, but went further to show that this effect was true for *socially* threatening stimuli in particular (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012). In this study, endotoxin led to enhanced amygdala reactivity to socially threatening images (fear faces), an effect that was not seen for non-socially threatening images (e.g., guns), socially non-threatening images (happy faces), and non-social, non-threatening images (e.g., household objects). This study suggests that inflammation leads to exaggerated amygdala reactivity to socially threatening information in particular. Moreover, results indicated that this 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.

Another finding from the same study suggested that there may be gender differences in how inflammation modulates neural reactivity to social stress. In this study, participants completed an online ball-tossing game (Cyberball) in which participants were socially excluded

by other players during a neuroimaging session (Eisenberger, Inagaki, Rameson, Mashal, & Irwin, 2009). Results revealed no overall effect of endotoxin on neural reactivity to the social exclusion task. However, among female participants only, endotoxin-induced increases in IL-6 were associated with increased activation in the dACC and anterior insula (AI). Moreover, among women exposed to endotoxin, dACC and AI activation mediated the relationship between increases in IL-6 and increases in depressed mood (Eisenberger et al., 2009). Thus, these findings support the idea that inflammation may upregulate neural reactivity to social stress (particularly in the dACC, and AI), leading to negative mood, but suggests that this effect may be unique to women. An association between inflammation and enhanced dACC and AI activity was also supported by a study by Slavich et al. (2010), which found that
that individuals who demonstrated a larger inflammatory response (oral sTNF-RII; a marker of TNF-α activity) in response to social evaluative threat (the Trier Social Stress Task) also demonstrated greater dACC and AI activation to social exclusion in a subsequently administered Cyberball task (Slavich, Way, Eisenberger, & Taylor, 2010). In contrast to the just described findings by Eisenberger et al. (2009), this association was found across both men and women. However, interpretation of these findings is somewhat limited by the correlational design and measurement of inflammatory markers in oral mucosal transudate (OMT) (a method that has yet to be thoroughly validated).

In summary, the existing literature evidence supports an effect of inflammation on increased affective, physiological, and (especially) neural reactivity to stressors, suggesting that increased reactivity to negative information may be a relevant core process by which inflammation can lead to depression. The emerging picture is that pro-inflammatory cytokines can signal the brain to effectively alter the functioning of threat-related neural circuitry including

the amygdala, dPFC, dACC, sACC, and AI, 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 & 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 (Eisenberger, Moieni, Inagaki, Muscatell, & Irwin, 2016; Inagaki et al., 2012). 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).

Although all of the above cited studies testing the effect of inflammation on stress reactivity utilized stressors with a social component, the study by Inagaki and colleagues (2012) offers preliminary evidence suggesting that the effect of inflammation on stress reactivity may be unique to social stressors (see also Eisenberger et al., 2016). More work examining the effects of inflammation on reactivity to both social and non-social stressors is needed to determine if this is indeed the case. Additionally, work testing whether there are meaningful differences in the effects of inflammation on reactivity in men and women is warranted. Finally, most existing work has focused on neural reactivity to stressors; studies are needed examining whether inflammation modulates affective and behavioral reactivity to negative information.

Endophenotype #2: Altered Reward Processing

Altered reward processing and anhedonia in depression. In addition to cognitive biases toward negative information, depression is also characterized by altered reward processing and anhedonia (Beck, 2004; Nutt et al., 2007; Winer & Salem, 2015). Anhedonia, the loss of pleasure or interest in previously rewarding stimuli, is a hallmark of depression and—along with sad mood—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 & Zald, 2011). Anhedonia is not only a symptom of current depression but also a risk factor for future depression severity; for example, a number of prospective studies have shown that self-reported anhedonia (lower levels of positive emotion) is a strong predictor of subsequent increases in depression severity (Morris, Bylsma, & Rottenberg, 2009).

In non-depressed individuals, the experience and maintenance of positive emotion is related to activity in brain regions associated with reward and motivation (Nestler & Carlezon, 2006; Tremblay et al., 2005); these regions are modulated by top-down control by the PFC (Del Arco & Mora, 2008). These 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 have been shown to be involved in reward processes (Berridge & Kringelbach, 2008; Lieberman & Eisenberger, 2009).

There is evidence that depressed individuals display reduced subjective and neural reactivity to positive stimuli. Depressed individuals exhibit a diminished emotional and affective

responses to pleasant stimuli compared with non-depressed controls (Dunn, Dalgleish, Lawrence, Cusack, & Ogilvie, 2004; Sloan, Strauss, & Wisner, 2001; Sloan et al., 1997). Additionally, some studies show that depressed individuals or those with trait-like anhedonia display attenuated reactivity of the NAc to pleasurable stimuli (Harvey, Pruessner, Czechowska, & Lepage, 2007; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005), monetary rewards (Pizzagalli et al., 2009; Wacker, Dillon, & Pizzagalli, 2009), and positive words (Epstein et al., 2006). Hyporeactivity in reward-related regions has been demonstrated in never-disordered young daughters of depressed mothers (considered at high risk for depression), suggesting that alterations in reward processing precede and potentially contribute to the etiology of depression (Gotlib et al., 2010).

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 try 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). Thus, inability to sustain engagement of reward-related neural regions may underlie depressed individuals' reduced capacity to maintain positive affect (Heller et al., 2009).

Beyond simply reduced or abbreviated reactivity to positive stimuli, there is also evidence suggesting that depression is accompanied by active blockage or avoidance of positive stimuli. A recent meta-analysis of emotional Stroop and dot probe studies showed support for the

idea that individuals with depression go beyond blunted reactivity to actually demonstrate an active *avoidance* of positive/rewarding stimuli (Winer & Salem, 2015).

Altered reward processing, anhedonia, and inflammation. Growing evidence from animal models and clinical studies support a role of inflammation in altered reward processing and anhedonia (Swardfager, Rosenblat, Benlamri, & McIntyre, 2016). A number of studies in animals have shown that experimentally-induced inflammation (endotoxin or cytokine administration) increases anhedonic-like behavior, namely reduced consumption of palatable substances (e.g. sucrose pellets or sweetened milk), implicating inflammation in the disruption of basic reward behavior (De La Garza, 2005). Moreover, it appears that this disruption may involve the key neurotransmitter dopamine. Dopamine has a fundamental role in motivation and motor activity, and a study of chronic IFN-α exposure in nonhuman primates showed that anhedonic behaviors (decreases in sucrose consumption) were associated with decreased striatal dopamine release (Felger et al., 2013).

In humans, studies using various models of experimentally-induced inflammation and distinct neuroimaging platforms have shown that inflammation can impact reward processing. Capuron and colleagues (2012) demonstrated that inflammation can modulate ventral striatal response to reward outcomes. In this study, hepatitis C patients showed significantly attenuated ventral striatal activity (as measured by fMRI) to received monetary rewards in a gambling task after 4-6 weeks of IFN-α therapy, compared with hepatitis C patients not receiving IFN-α. Reduced ventral striatal activation was in turn significantly associated with more severe symptoms of anhedonia, depressed mood, and fatigue (Capuron et al., 2012).

This same research group showed that proinflammatory cytokines can alter dopamine functioning in the ventral striatum in humans (Capuron et al., 2012), identifying a molecular

mechanism by which inflammation may alter reward processing and lead to behavioral symptoms such as reduction in motivation. In a separate sample of hepatitis C patients receiving IFN-α for 4-6 weeks, positron emission tomography (PET) with radiolabeled 18-F fluorodopa (^{18}F-dopa) was employed to examine effects of IFN-α on presynaptic striatal dopamine function. ^{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 turnover/release of ^{18}F-dopa, which can be interpreted as a measure of presynaptic dopamine activity (Miller et al., 2013). Findings indicated that 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 fMRI study (Capuron et al., 2012). Moreover, changes in ^{18}F-dopa uptake and turnover were significantly associated with symptom experience, including depressed mood and fatigue (Capuron et al., 2012). These findings suggest that inflammatory cytokines influence reward processing by specifically targeting ventral striatal and dopamine function, and that these neural and molecular processes may at least partially account for increases in behavioral symptoms including depressive symptoms, anhedonia, and fatigue resulting from chronic inflammation (Capuron et al., 2012).

Inflammation has been shown not only to modulate responses to reward consumption, but also the anticipation of reward. In a study by Eisenberger and colleagues (2010), endotoxin (vs. placebo) led to greater increases in self-reported and observer-rated depressed mood, as well as attenuated activation of the left ventral striatum to reward cues. (For observer-rated depressed mood, an experimenter blind to condition made ratings of how depressed the participant seemed at baseline and 2 hours following endotoxin injection.) This 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., 2010). Thus, inflammation may impact not only consummatory but also anticipatory reward processes, again potentially leading to behavioral manifestations of depressed mood.

Building on evidence suggesting that inflammation may reduce responsivity to consumption and anticipation of monetary rewards, Harrison et al. (2015) sought to examine the effects of inflammation on responses to a different kind of rewarding stimuli: novelty. Novel stimuli are theorized to have an intrinsic reward value, thereby promoting adaptive processes such as behavioral exploration and social approach (Kakade & Dayan, 2002), and the hippocampus and substantia nigra (a basal ganglia structure) are central to novelty detection and reward evaluation of novelty (Bunzeck & Düzel, 2006; Lisman & Grace, 2005). In this study, participants were injected with typhoid vaccine or placebo, and then completed a novelty task in the scanner, which involved viewing a series of images (neutral outdoor scenes and faces) which they had either been shown before the scanning session, or not (novel items). Findings indicated that typhoid vaccination (vs. placebo) had no effect on hippocampal activation to novelty, but did lead to blunted substantia nigra reactivity to novel stimuli. Moreover, analyses of the functional connectivity between the substantia nigra and hippocampus revealed that while there was an increase in substantia nigra-hippocampus connectivity to novelty in the placebo condition, this connectivity enhancement was attenuated in the vaccine condition (Harrison, Cercignani, Voon, & Critchley, 2015). Together, these findings suggest that inflammation does not significantly impair hippocampal responses to stimulus novelty, but does attenuate the subsequent processing of this information by the substantia nigra, possibly due to reduced connectivity between the two structures (Harrison et al., 2015). Thus, this study provides evidence that inflammatory signaling can reduce basal ganglia (specifically substantia nigra) responsivity to novel stimuli, which

offers potential relevance for reductions in motivational and approach behavior seen in depression, and broadens the picture of the types of rewards and reward-related neural mechanisms impacted by inflammation.

Although there is some compelling evidence suggesting that inflammation may dampen neural reactivity to rewards, a few recent studies have suggested that the effect of inflammation on neural and behavioral reward sensitivity is more complex. For example, two recent studies found that 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). In light of these findings, it has been postulated that inflammation may lead to enhanced reactivity to social rewards, specifically, possibly due to the adaptive benefits of social connectivity (especially with close others) during times of illness or injury (Eisenberger et al., 2016).

However, findings from another recent study suggests that the potential facilitation effects of inflammation on reward may also extend to monetary rewards. Lasselin and colleagues (2016) found that 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 highest. The researchers interpreted this finding as a potential reorganization of priorities in the context of inflammation, such that inflammation leads to a more discriminating allocation of resources towards only highly likely rewards (Lasselin et al., 2016).

Future work is needed to reconcile these recent findings with the prior research suggesting an overall dampening effect of inflammation on reward reactivity, and to delineate the potentially more nuanced relationship between inflammation and reward reactivity. The

effect of inflammation on reward 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 the inflammatory dose and duration.

Most existing experimental studies on inflammation and reward in humans (such as those outlined above) have examined the effects of inflammation on neural reactivity to reward, and correlations between these neural measures with self-reported symptom experience. From this work, in conjunction with a wealth of preclinical research, we have begun to understand the neurobiological mechanisms of the effects of inflammation on reward processing, which involves alterations in corticostriatal neural circuitry (including the ventral striatum) via modulation of dopamine availability and release (Felger & Treadway, 2016). Importantly, a new body of research is just beginning to emerge using novel behavioral tasks that tap into discrete aspects of reward (e.g., Lasselin et al., 2016) – such as the EEfRT, which taps reward motivation, and the Probabilistic Reward Task, which taps implicit reward learning (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008). Results from such studies, when considered in conjunction with neuroimaging studies, can help us understand the downstream effects of inflammation-induced changes in neural reactivity, and how and when these changes may manifest into behavioral changes relevant to depression.

Endophenotype #3: Cognitive Impairment

Cognitive dysfunction is a frequent complaint among individuals with depression (Simons et al., 2009). A large number of studies have investigated the nature of cognitive

impairment in depressed individuals by comparing performance of depressed individuals and non-depressed controls on one or more neuropsychological tests. Such studies typically include tests tapping into various dimensions of cognitive functioning. Reviews of these studies have suggested that key deficits in MDD include executive functioning and memory (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Hammar & Ardal, 2009), and deficits in memory and executive functioning have been proposed as endophenotypes of depression (Hasler et al., 2004).

Of note, although it has been established that depression is also associated with overly general autobiographical memories, no published studies have examined the effect of inflammation on autobiographical memory recall; thus, this potential endophenotype is not included in this review.

Executive functioning deficits in depression. Executive functioning is generally conceptualized as higher-level cognitive processes that organize and regulate automatic, lower-level cognitive functions (such as perception or motor responses) in order to effortfully guide behavior towards a goal (Alvarez & Emory, 2006; Banich, 2009). Executive functioning includes a variety of processes including the ability to create, maintain, and switch between task goals; inhibition of prepotent (automatic) responses and distracting information; planning and decision-making; and selecting among competing options, among many others (Snyder, 2014). Neurally, these are functions thought to rely heavily on the prefrontal cortex – in particular, the dorsolateral PFC (DLPFC), ventrolateral PFC (VLPFC) and anterior cingulate cortex (ACC) – but they also recruit broader neural networks including subcortical areas (Snyder, 2014).

Efforts have been made to dismantle the concept of executive functioning into various distinct components that can then be operationalized with specific neuropsychological tasks. A

recent meta-analysis of 113 studies found significant deficits in executive functioning among depressed individuals compared to non-depressed controls, including deficits on distinct components of executive functioning including updating, shifting, inhibition, working memory, planning, and verbal fluency, with effect sizes ranging from $d = 0.32 – 0.97$ (Snyder, 2014). (Table 2 provides definitions of these executive functioning components and the tasks typically used to measure these components in the context of depression).

Research has suggested that executive functioning deficits may be a consequence rather than an etiological factor of depression. For example, a study of never-disordered children at risk for depression (due to the presence of parental MDD) found no evidence of executive functioning deficits, whereas children with current MDD did exhibit such deficits (Micco et al., 2009). Additionally, a prospective study of older adults found that executive functioning deficits did not predict depression severity a year later; in contrast, depression severity did predict poorer executive functioning at the one-year assessment (Cui, Lyness, Tu, King, & Caine, 2007), suggesting that executive functioning deficits are a symptom rather than a prodromal factor.

In the following section, we first provide a brief overview of the experimental evidence linking inflammation to self-reported cognitive functioning broadly, and then outline the evidence for the impact of inflammation on objective measures of each of the distinct executive functioning components described in Table 2.

Executive functioning deficits and inflammation. Evidence from the primary models of experimentally-induced inflammation have provided support for an effect of inflammation on self-reported cognitive impairment broadly. IFN-α treatment has been associated with self-reported cognitive deficits, such as memory disturbances and concentration difficulties (Capuron et al., 2002). Typhoid vaccination has similarly been shown to increase subjective ratings of

mental confusion and impaired concentration (Harrison et al., 2009; Brydon et al., 2009). Thus, there is some evidence to suggest that inflammation may causally elicit changes in the subjective experience of cognitive impairment. But does inflammation also affect more observable, behavioral manifestations of executive functioning specifically?

Only one study within the primary models of experimentally-induced inflammation has examined effects on updating ability. Grigoleit and colleagues (2011) examined the effects of low (0.4 ng/kg) and moderate dose (0.8 ng/kg) endotoxin on performance on the n-back task, a measure of updating ability. Findings indicated 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), suggesting that moderate levels of inflammation can facilitate updating speed, counter to the updating deficits commonly exhibited in individuals depression.

A larger number of experimental inflammation studies have examined effects on shifting ability as measured with the Trail Making Test (TMT) part B; while a few studies have supported an effect, the majority of studies have failed to find effects. An early study of leukemia patients receiving IFN-α treatment found evidence for deficits on the TMT part B (Pavol et al., 1995); similarly, a more recent study of hepatitis C patients who received 6 months of IFN-α found that treated patients performed significantly worse on the TMT part B, compared with hepatitis C patients who did not undergo IFN-α treatment (Hilsabeck, Hassanein, Ziegler, Carlson, & Perry, 2005). However, several other studies of IFN-α treated hepatitis C patients have found no significant performance deficits on the Trail Making Test part B (Amodio et al., 2005; Drozdz, Borkowska, Halota, & Rybakowski, 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 Trail Making Test part B. Thus, a role of inflammation in shifting ability impairments is largely unsupported, with the majority of studies finding no effect of inflammation on shifting ability.

A number of studies have also examined effects of inflammatory stimuli on inhibition ability, 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, suggesting that inflammation did not impair inhibition ability per se (which would have manifested as slower response times on the incongruent trials only), but rather led to an overall psychomotor slowing and/or decrease in motivation (Brydon, Harrison, Walker, Steptoe, & Critchley, 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. Reichenberg and colleagues (2001) found no significant effect of endotoxin exposure on digit span forward performance. Three other studies also failed to find significant effects of endotoxin exposure on digit span forward and backward performance (Grigoleit et al., 2010; Krabbe et al., 2005; 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 therapeutic IFN-α found no effect of treatment on digit span performance. While the digit span task taps into verbal working memory, Grigoleit and colleagues (2010) also examined the effect of endotoxin a measure of visuospatial working memory, a block span test; no significant effects of endotoxin on task performance was found. Caraceni and colleagues (1998) examined the effect of IFN-α therapy on the block span test and similarly found no significant effect. Thus, the above studies provide little evidence that inflammation impairs verbal or visuospatial working memory.

At least one study examined the effects of an inflammatory stimulus on planning ability, and failed to find effects. Majer and colleagues (2008) examined the effect of IFN-α (plus ribavirin) treatment on performance on the Stockings of Cambridge task, a task based on the Tower of London task that assesses planning and problem-solving ability. Findings indicated no effect of IFN-α treatment on performance on this planning task.

A few studies have examined effects of inflammatory stimuli on verbal fluency, but have not found significant effects. Reichenberg and colleagues (2001) found no effect of endotoxin administration on performance on a verbal fluency task. Findings from IFN-α studies are mixed. At least one study found a significant reduction in verbal fluency task performance after three months of IFN-α treatment, which notably did not correlate with depressive symptoms (Lieb et al., 2006); in contrast, several studies have found no effect of IFN-α treatment on verbal fluency tests (Amodio et al., 2005; Fontana et al., 2007; Pavol et al., 1995).

In summary, across categories of executive functioning, with few exceptions, evidence has largely failed to support an effect of inflammation, despite a significant amount of empirical attention. Studies that have examined effects of an inflammatory stimulus on various

components of executive functioning including updating, inhibition, working memory, and planning have found either no effect, or a facilitation effect. There was more mixed evidence for the effects of inflammation on shifting ability and verbal fluency, yet even in these cases the number of studies with null findings outweighs the number of studies finding significant effects. Thus, existing empirical evidence provides little support for a role of inflammation in executive functioning deficits. It is likely, then, that inflammation simply does not impact executive functioning.

However, it remains a possibility the types of neuropsychological tasks that are 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 traditionally developed to assess cognitive deficits following major insults or neurological disease, such as traumatic brain injury or neurogenerative disease. Thus, they may simply be too blunt of instruments to pick up on the potentially more subtle changes elicited by inflammation – changes that could nevertheless could lead to significant daily impairment. Additionally, it should be noted that neuroimaging studies have not be done to examine whether inflammation impacts neural correlates of executive functioning, such as the PFC. Without such investigations, it remains possible that individuals experiencing heightened inflammation may experience alterations on a neural level that may not be evidenced behaviorally. For example, it is possible that, under inflammatory conditions, individuals are required to work harder – perhaps engaging relevant neural regions such as the PFC more avidly – in order to achieve the same level of functioning (equal performance on neuropsychological tasks) as someone not under inflammatory conditions. Future work might consider examining such possibilities.

Memory deficits in depression. Memory capacity in depression is typically assessed using standard neuropsychological tasks that test memory for a series of stimuli (verbal or visuospatial) after a delay, typically 20-25 minutes. Verbal memory tests typically examine recall of stories or word lists. Examples of tests commonly used to assess verbal memory using story recall include the Wechsler Memory Scale-Revised (WMS-R) Logical Memory subtest (Wechsler, 1987); common tasks using word recall include the Rey Auditory Verbal Learning Test (Delayed Recall trial) (Schmidt, 1996) and the California Verbal Learning Test (Long Delayed Free Recall trial) (Delis, Kramer, Kaplan, & Ober, 1987). Visuospatial memory is often tested by examining delayed recall for a series of geometric figures, such as with the Rey-Osterrieth Complex Figure Test (Osterrieth, 1944; Rey, 1941) and WMS-R Visual Reproduction subtest (Wechsler, 1987). Studies examining performance on such tasks in patients with MDD versus non-depressed controls have provided evidence for both verbal and visual memory deficits in depression (Clark, Chamberlain, & Sahakian, 2009; Hammar & Ardal, 2009), and the magnitude of memory impairments is positively associated with the severity and chronicity of the depression (Castaneda et al., 2008; Gorwood, Corruble, Falissard, & Goodwin, 2008).

These depression-associated memory deficits are likely related to hippocampal abnormalities; depression is accompanied by reduced hippocampal volumes (Campbell & MacQueen, 2004; Lorenzetti, Allen, Fornito, & Yücel, 2009; Videbech & Ravnkilde, 2004), as well as functional deficits during memory encoding (Bremner, Vythilingam, Vermetten, Vaccarino, & Charney, 2004). Preclinical evidence has suggested that these hippocampal abnormalities may be attributable to elevated glucocorticoid levels associated with depression, which can negatively impact neurogenesis, lead to excitotoxic damage, and/or the reduction of key neurotrophins. This is supported by the fact that antidepressant medications exert their

effects at least in part by increasing hippocampal neurogenesis (for review, see Campbell & MacQueen, 2004).

Evidence has suggested that memory-related hippocampal abnormalities may be a risk factor for depression, but are also potentially exacerbated by depression. For example, a review of studies on hippocampal volumes and MDD concluded that subjects at risk for MDD have reduced hippocampal volumes that predate the onset of illness, but also that repeated episodes of illness contribute to further loss of hippocampal volume (MacQueen & Frodl, 2011).

Memory deficits and inflammation. Under quiescent conditions, immune mechanisms are necessary for normal learning and memory processes, particularly hippocampal-dependent memory consolidation (Yirmiya & Goshen, 2011). Just as the immune system is responsible for tissue remodeling throughout the rest of the body (e.g., wound healing), it also coordinates the neuroplastic structural changes in the brain that underlie learning and memory, such as axonal pruning necessary for synaptic efficiency and neurogenesis (Yirmiya & Goshen, 2011). However, when the immune system is strongly activated, as is the case in infection, injury, or stress, the resulting elevations in proinflammatory cytokines have been shown to have detrimental effects on memory consolidation, neural plasticity, and neurogenesis in the hippocampus (Yirmiya & Goshen, 2011). Much of the evidence for the role of proinflammatory cytokines in cognitive dysfunction comes from work in animal models. Endotoxin-induced inflammation impairs learning and memory in rodents, particularly hippocampal-dependent spatial memory (Pugh et al., 1998; Wu et al., 2007). Moreover, peripheral endotoxin administration leads to a loss of neurons in the hippocampus and prefrontal cortex (Semmler et al., 2007) and disrupts hippocampal neurogenesis (Wu et al., 2007), which is necessary for normal memory functioning (Yirmiya & Goshen, 2011). Systematic animal studies have begun

to elucidate the mechanisms for these effects: peripheral inflammatory cytokines activate immune cells in the brain (microglia), increasing concentrations of TNF-α and IL-1, which, in the hippocampus, inhibit neural plasticity and neurogenesis (Barrientos et al., 2003; Ben Menachem-Zidon et al., 2008; Goshen et al., 2007; Koo & Duman, 2008).

However, findings linking inflammation to memory impairments in humans are more mixed. A few studies have examined memory performance among IFN-α treated patients. In a study of IFN-α treated leukemia patients, Pavol and colleagues (1995) found below normative performance on a task assessing delayed verbal memory, but found no deficits in non-verbal memory. In contrast, two studies found no deficits following IFN-α therapy on both verbal and visual memory tasks (Amodio et al., 2005; Fontana et al., 2007). Additionally, a number of studies have examined memory performance following endotoxin administration, with variable results. Endotoxin exposure was shown in at least two studies to impair story recall (Grigoleit et al., 2011; Reichenberg et al., 2001) and in at least one study to impair figure recall (Reichenberg et al., 2001). In contrast, a study by Grigoleit and colleagues (2010) found no effects of endotoxin on recall of figures, numbers, or stories. A study by Krabbe and colleagues (2005) similarly examined the effects of endotoxin on word list recall, and found no significant group differences in performance. However secondary analyses within the endotoxin group revealed that endotoxin-induced changes in plasma IL-6 and sTNF-R were both negatively correlated with changes in word-list recall, such that subjects with more robust inflammatory responses to endotoxin exhibited declines in verbal recall (Krabbe et al., 2005). This finding was based on a small sample size (N=12), yet they nevertheless raise the possibility that individual differences in the inflammatory response may help account for the mixed findings regarding the effect of endotoxin on memory.

A recent study examining the effects of typhoid vaccine-induced inflammation on memory used a novel memory task paired with neuroimaging and found support for an effect. Using a novel virtual reality task to assess spatial memory (a task developed to be analogous to the Morris water maze used in rodent models to demonstrate inflammation-induced spatial memory deficits), Harrison and colleagues (2014) found that typhoid vaccination compromised spatial memory performance on this task, an effect that was found to be independent of motivation or psychomotor speed. Moreover, effects of inflammation on spatial memory were mediated by reduced parahippocampal glucose metabolism, as measured by positron emission tomography (PET) scan, suggesting that inflammation may impair spatial memory by reducing metabolism in this brain region (Harrison, Doeller, Voon, Burgess, & Critchley, 2014).

In summary, while animal models have clearly shown that elevations in proinflammatory cytokines can impair hippocampal-dependent memory, human studies have yielded more mixed findings, with some studies supporting a relationship between exposure to inflammatory stimuli and memory deficits, and other studies reporting null findings. The findings from Krabbe et al. (2005) which found a within-subject association between higher endotoxin-induced levels of IL-6 and sTNF-R and poorer word list recall suggest that examining individual differences in the inflammatory response to an immune stimulus (rather than group differences) may help clarify these mixed results. It is possible that pro-inflammatory cytokines only impair memory at high levels that exceed some (still undetermined) threshold; an effect that is obscured by an exclusive focus on group differences (inflammatory challenge vs. placebo) that does not account for individual variability in cytokine response.

Future work may also consider testing curvilinear relationships between inflammation and memory; it is possible that the mixed findings in this area are attributable to the exclusive

testing of linear relationships between inflammation and memory. Based on the evidence from animal models that physiological levels of proinflammatory cytokines are necessary for normal learning and memory processes, whereas high levels of cytokines disrupt such processes, it is plausible that proinflammatory cytokines may be related to learning and memory in a quadratic fashion, such that too low and too high levels of inflammation could be detrimental (Yirmiya & Goshen, 2011). Yet, curvilinear associations between inflammation and cognitive functioning in humans have been largely unexplored, and thus represent a possible path for future work in this area.

Another possibility is that, as was mentioned in the context of executive functioning, the types of neuropsychological tasks used to assess memory may not be sensitive enough to detect the potentially subtle changes due to inflammation. This possibility is supported by the fact that Harrison and colleagues (2014), when using a novel virtual reality task to assess spatial memory in conjunction with neuroimaging, did find a significant effect of typhoid vaccination on recall and neurobiological correlates. Novel measurement approaches such as these – which also, as mentioned, were based on the tasks found to be impaired by inflammation in animal studies – may be needed in order to further our understanding of the relationship between inflammation and memory. More studies utilizing neuroimaging techniques are also helpful for understanding the neurobiological mechanisms that may underlie these potential effects.

Thus, findings for an effect on memory have overall been highly mixed. It may be that inflammation does not impact verbal and/or visual memory in humans, or it may be that different analyses, tasks, and modeling approaches are needed in order to detect effects.

Endophenotype #4: Somatic Syndrome

Somatic symptoms commonly experienced by individuals with depression and included in the *DSM-5* criteria for major depression include increased or decreased weight or appetite, insomnia or hypersomnia, psychomotor agitation and retardation, and fatigue or loss of energy (American Psychiatric Association, 2013). This cluster of somatic symptoms has been proposed as an endophenotype for depression (Hasler et al., 2004). While depression can be characterized by either psychomotor agitation or retardation, there is only evidence linking inflammation to decreases in psychomotor speed. Thus, the symptoms focused on here are fatigue, psychomotor retardation, and sleep changes (insomnia or hypersomnia).

Fatigue in depression. Fatigue is a prevalent presenting symptom of major depressive disorder (Demyttenaere, De Fruyt, & Stahl, 2005). Although there are various approaches for defining and assessing fatigue, symptoms of physical fatigue can include feelings of tiredness, low energy, reduced activity, decreased physical endurance, increased effort to do physical tasks, general weakness, heaviness, and slowness or sluggishness (Arnold, 2008). A large epidemiological study of more than 1800 patients who had consulted a healthcare professional about their depression found that 73% of patients reported feeling tired, and that this was the second most commonly endorsed symptom, after low mood (Tylee, Gastpar, Lépine, & Mendlewicz, 1999). Non-depressed individuals with fatigue are at a higher risk for developing MDD later in life compared with individuals without fatigue (Addington, Gallo, Ford, & Eaton, 2001; Kroenke & Price, 1993; Walker, Katon, & Jemelka, 1993), suggesting that fatigue may play a role in the etiology of depression. Additionally, fatigue often persists among individuals on antidepressants who have achieved remission of their affective symptoms (Fava et al., 2006; Targum & Fava, 2011). 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 & Fava, 2011).

Fatigue and inflammation. Inflammation has been associated with fatigue in both animal and human models. Research in rodents has shown that exogeneous injection or induction of proinflammatory cytokines cause behavioral signs of fatigue, including reductions in burrowing behavior (Teeling et al., 2007), voluntary wheel-running (Harden et al., 2011), social interaction (Konsman et al., 2008) and general locomotor activity (Anisman, Gibb, & Hayley, 2008).

In humans, studies have shown positive associations between inflammation and fatigue among cancer patients (Bower, 2014), individuals with rheumatoid arthritis (Davis et al., 2008), and, more equivocally, among patients with multiple sclerosis (Flachenecker et al., 2004; Giovannoni, Thompson, Miller, & Thompson, 2001). Inflammatory markers have also been shown in some studies to be higher in patients with chronic fatigue syndrome compared to controls (Buchwald, Wener, Pearlman, & Kith, 1997; Moss, Mercandetti, & Vojdani, 1999; cf., Gaab et al., 2005; ter Wolbeek et al., 2007). Such patterns are suggestive of a role of inflammation in fatigue.

The relationship between inflammation and fatigue has also been demonstrated in large-scale prospective studies. Using longitudinal data from 4847 initially non-fatigued participants in the Whitehall II study, Cho and colleagues (2013) showed that participants with high CRP and IL-6 were significantly more likely to have developed fatigue at the subsequent assessment several years later (mean follow-up time was 3.1 years). Similarly, in 2983 African American and white adults from the Coronary Artery Risk Development in Young Adults (CARDIA) study, plasma CRP concentrations predicted fatigue five years later; this relationship persisted

even in the subgroup of medically healthy participants (Cho, Seeman, Bower, Kiefe, & Irwin, 2009).

Studies across the endotoxin, typhoid vaccination, and IFN-α paradigms have consistently shown that stimulation of proinflammatory cytokines leads to reports of increased fatigue (Brydon, Harrison, Walker, Steptoe, & Critchley, 2008; Capuron et al., 2002; Dowell et al., 2016; Grigoleit et al., 2011; Harrison et al., 2009) 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 items assessing depression (Brydon et al., 2008; Brydon et al., 2009; Harrison et al., 2009).

Studies have begun to elucidate neurobiological mechanisms of inflammation-induced fatigue. A study by Capuron and colleagues (2007) found that IFN-α therapy led to reports of fatigue in a sample of patients with malignant melanoma; fatigue severity was positively correlated with increased glucose metabolism in the basal ganglia (the left putamen and left NAc) as assessed with PET neuroimaging with fluorine-18-labeled fluorodeoxyglucose (Capuron et al., 2007). The idea that inflammation-induced fatigue may involve alterations in basal ganglia functioning was also supported by a more recent IFN-α study within a sample of hepatitis C patients. Dowell and colleagues (2016) showed that IFN-α treatment elicited the onset of fatigue that began 4 hours after patients' initial IFN-α injection, and continued to persist throughout the 6-month treatment period, peaking between 4-12 weeks. They also observed

changes in ventral striatal microstructure within 4 hours post-injection, and these microstructure changes prospectively predicted fatigue experience at 4 weeks (Dowell et al., 2016). These findings suggest that structures of the basal ganglia are highly sensitive to fluctuations in peripheral cytokines, and changes basal ganglia functioning likely underlie inflammation-induced fatigue.

In summary, the evidence strongly supports a role of inflammation in fatigue. Indeed, fatigue is likely the most common and reliably reported consequence of inflammation. Neuroimaging evidence has suggested that inflammation-induced fatigue may be mediated by alterations within the basal ganglia.

Psychomotor slowing in depression. Psychomotor retardation, defined as a slowing of motor activity and difficulty responding quickly and spontaneously to environmental cues, is a symptom exhibited in some patients with 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.

Evidence from various lines of research suggests that psychomotor slowing involves disruptions in dopamine functioning and the basal ganglia circuit. Psychomotor slowing in depression is similar to that seen in Parkinson's disease, suggesting that dopaminergic abnormalities underlie the psychomotor slowing seen in depression as they do in Parkinson's disease (Rogers, Lees, Smith, Trimble, & Stern, 1987). 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 & Korf, 1971). More recently, a study using magnetic resonance imaging (MRI) and PET with ^{18}F-dopa found

decreased presynaptic dopamine function in the left caudate of depressed patients with clinically assessed psychomotor retardation (Martinot et al., 2001), implicating blunted dopamine transmission in psychomotor slowing in depression.

There is also evidence linking reduced dopamine functioning to behavioral measures of psychomotor processing speed. In a sample of depressed patients, decreased D2 binding was significantly correlated with reduced verbal fluency (FAS-Verbal Fluency test) and reduced speed of movement on a reaction time task (Shah, Ogilvie, Goodwin, & Ebmeier, 1997). This study suggests that verbal fluency and psychomotor speed may be depend upon dopamine levels in the striatum.

However, dopamine dysfunction in psychomotor slowing may not be confined to the striatum. Studies have indicated that 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, Friston, Brown, Frackowiak, & Dolan, 1993; Videbech et al., 2002). Taken together, this work suggests that depressed individuals with psychomotor retardation may have a dopaminergic abnormality within the frontal-subcortical network that involves the basal ganglia and PFC.

Psychomotor slowing and inflammation. Among nonhuman primates, IFN-α treatment has been associated with reduced locomotor activity, among dominant animals only (Felger et al., 2007). Studies in humans have also demonstrated motor slowing during IFN-α treatment, using standardized neuropsychological tasks. In a study of patients with hepatitis C, IFN-α (plus ribavirin) treatment led to significant decreases in motor speed as measured using a reaction time task and a rapid visual information processing task; decreased motor speed was in turn associated with increased symptoms of depression and fatigue (Majer et al., 2008). Similarly, a study of

cancer patients found that IFN-α treatment was associated with an increase in response latencies on a reaction time task, especially when the cytokine was administered intravenously and when the task involved higher attentional resources (Capuron, Ravaud, & Dantzer, 2001). A study using typhoid vaccination to stimulate inflammation showed an association between IL-6 levels following vaccination and slower response time on all trials of a color-word Stroop task (both congruent and incongruent trials); increases in IL-6 and decreases in motor speed were both in turn associated with altered activation patterns (enhanced activation) in the substantia nigra (a structure of the basal ganglia) as assessed by fMRI (Brydon et al., 2008). These findings are consistent with the role of basal ganglia in motor activity. Taken together, these data suggest that proinflammatory cytokines may target the basal ganglia nuclei, leading to psychomotor slowing.

Sleep changes in depression. Sleep disturbance is highly prevalent among individuals with depression. An estimated 50-90% of individuals with diagnosed depression complain of poor sleep quality (Casper et al., 1985; Hetta, Rimón, & Almqvist, 1985; Kupfer, Harrow, & Detre, 1969; Riemann, Berger, & Voderholzer, 2001). Common sleep alterations in depression include difficulty initiating sleep, frequent nocturnal awakenings, and early morning awakenings. Sleep research using polysomnography in depressed subjects has shown 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 (typically measured as the number of eye movements during the REM period) (Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013; Riemann et al., 2001). Consistent with a role for increased REM sleep in depression, research has shown that antidepressants suppress REM sleep (Palagini et al., 2013; Riemann et al., 2001). Hypersomnia can also accompany depression, though it is somewhat less common (Garvey, Mungas, & Tollefson, 1984).

Sleep changes and inflammation. Research in animals and humans has indicated that proinflammatory cytokines are involved in normal regulation of sleep-wake cycles and the homeostatic drive for sleep. The proinflammatory cytokines IL-1, TNF-α, and IL-6 display a circadian pattern of secretion with peak levels correlating with somnolence and sleep onset (Imeri & Opp, 2009; Vgontzas et al., 2005). Proinflammatory cytokines can have an active role in modulating sleeping and wakefulness; basic research has shown that 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 regulate sleep, it follows that disturbances in cytokine levels would be associated with sleep dysregulation. Indeed, a recent meta-analysis examining data from 72 studies (N > 50,000) that characterized sleep duration/quality or performed experimental sleep deprivation concluded that sleep disturbances, as well as both short (<7 hrs/night) and long (>8 hrs/night) sleep duration, were associated with elevations in circulating inflammatory markers (Irwin, Olmstead, & Carroll, 2015).

In a recent study, Prather and colleagues (2009) followed a group of hepatitis C patients through four months of IFN-α treatment. Findings from time-lagged analyses indicated that higher IL-6 levels at any given month predicted poorer self-reported sleep quality the following month; moreover, poorer sleep quality in turn predicted higher depressive symptoms at the subsequent assessment (Prather, Rabinovitz, Pollock, & Lotrich, 2009). Notably, these associations were uni-directional: pre-treatment sleep quality did not predict IL-6 levels over time, and depressive symptoms did not predict subsequent sleep quality (Prather et al., 2009). These findings suggest a temporal relationship in which inflammation may elicit sleep changes, and sleep changes may lead to depressive symptoms.

A subsequent IFN-α study in hepatitis C patients went beyond self-report sleep measures to show that inflammation can also alter objective measures of sleep, and began to identify the specific components of sleep disrupted by inflammation (Raison et al., 2010). This study examined nighttime polysomnography and daytime sleep latency testing at baseline and 12 weeks later in hepatitis C patients receiving IFN-α treatment (vs. hepatitis C patients not receiving treatment). Findings indicated that 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 (Raison et al., 2010). These findings highlight the specific components of sleep that may be impacted by inflammation.

Endotoxin studies have provided further causal evidence in humans suggesting that cytokines can lead to sleep changes; interestingly, these studies have found that inflammation promotes sleep up to a certain threshold, after which the effect reverses to induce sleep disruption. For example, in studies comparing effects of different doses of endotoxin administration in healthy humans, very low doses of endotoxin (0.2 ng/kg) promote sleep, whereas moderate doses (0.8 ng/kg) reduce total sleep time and increase sleep onset latency (Korth, Mullington, Schreiber, & Pollmächer, 1996; Hermann et al., 1998; Mullington et al., 2000). Further analysis of these dosage effects on different components of sleep indicate that low-level immune activation leads to increased nonrapid eye movement (NREM) sleep, while decreasing or having no effect on REM sleep; in contrast, more robust immune activation decreases both NREM and REM sleep (Mullington et al., 2000). Thus, inflammation influences sleep, but the nature of the effect depends on the degree of immune activation. The reduction in NREM sleep following moderate-dose endotoxin parallels the pattern seen in depression, which is also typically associated with reductions in NREM, particularly slow wave sleep (Palagini et

al., 2013; Riemann et al., 2001). However, while increases in REM sleep have typically been documented in the MDD literature, inflammation at both low and moderate doses can lead to decreases in REM sleep, suggesting a disconnect between processes seen in depression and those seen following immune activation.

The association between inflammation and sleep disturbance has also specifically been examined within the context of depression. A laboratory sleep study that obtained all-night polysomnography for a sample of individuals diagnosed with major depressive disorder and controls found that depressed patients experienced shorter total sleep time, increased sleep latency, decreased stage 2 (NREM) duration, and marginally higher REM duration compared to controls (Motivala, Sarfatti, Olmos, & Irwin, 2005). Importantly, depressed patients exhibited significantly higher nocturnal levels of serum IL-6 compared to controls, and IL-6 levels were associated with increased sleep latency and increased REM density (Motivala et al., 2005). (Although note that REM density was not a significant group difference between individuals with MDD and controls in this study.) This study provides evidence that inflammatory cytokines may play a role in the disruption of at least some components of sleep relevant for depression.

In addition to the effects of inflammation on sleep, a bidirectional relationship may exist such that sleep disturbance can also lead to elevations in inflammation (Irwin et al., 2015). There is also evidence that sleep disturbance may act as a vulnerability factor for inflammation-associated depression. A recent endotoxin study found that women with pre-existing sleep disturbance exhibited a stronger association between endotoxin-induced increases in proinflammatory cytokines and depressed mood compared to women without sleep disturbance (Cho, Eisenberger, Olmstead, Breen, & Irwin, 2016). Thus, sleep disturbance and inflammation

may act jointly in the development of depression (Cho et al., 2016; Irwin, Olmstead, Ganz, & Haque, 2013).

Taken together, these lines of evidence suggest that heightened inflammation can disrupt sleep. Additionally, sleep disturbances may lead to further increases in inflammation, and/or act in conjunction with inflammation in the development of depression. The few studies that have examined effects of exogeneously-induced inflammation on components of sleep have suggested that the pattern of effects may depend on the level of immune activation. Patients with major depression reliably exhibit reductions in non-REM sleep; similarly, studies of moderate-dose (but not very low dose) endotoxin and IFN-α treatment found resulting reductions in NREM sleep (Mullington et al., 2000; Raison et al., 2010), consistent with the pattern typically displayed in MDD. However, the effects of inflammation on REM sleep was not as uniformly consistent with the typical pattern seen in MDD. Individuals with depression typically display increased indices of REM sleep (decreased REM latency, protracted REM period, increased REM density); in contrast, exogeneously-induced inflammation using both endotoxin and IFN-α generally led to a suppression of REM sleep. Thus, the effects of inflammation on NREM sleep specifically may be most relevant to depression. Neuroimaging studies are lacking in this area; thus, the neurobiological mechanisms by which heightened inflammation effect sleep and its components are relatively unexplored, and represents a possible avenue for future work.

Discussion

The current review identified key endophenotypes of depression that have been linked to inflammation, and reviewed the empirical literature examining the impact of inflammation on each endophenotype. In summary, empirical evidence suggests that inflammation likely plays a role in negative cognitive bias (particularly for exaggerated reactivity to negative information,

with preliminary evidence for biased attention), altered reward reactivity, and somatic symptoms. In contrast, evidence has generally not supported an effect of inflammation on cognitive impairment, particularly executive functioning, with mixed support for memory.

Why would inflammation modulate the processes evidenced in this review – attention and reactivity, reward responsivity, energy – and how might alterations in these dimensions lead to the development of depression? When illness or injury befalls an organism, proinflammatory cytokines signal the central nervous system, triggering a constellation of behavioral changes ("sickness behaviors") that are thought to represent an adaptive motivational response aimed at facilitating healing and recovery. The classic example of these adaptive behavioral changes is fatigue, which can promote recovery by driving the organism to rest and thereby allowing 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.

Yet what is adaptive for the organism in the short-term can become maladaptive in the long-term – indeed, chronic IFN-α treatment can lead to major depression including suicidality in a significant portion of patients (Capuron et al., 2002; Capuron & Miller, 2004). How might prolonged inflammatory exposure go on to cause depression for some individuals, while others

are largely unaffected? When inflammatory signaling becomes prolonged (e.g., due to chronic disease or chronic stress), the associated cognitive and behavioral changes are presumably also sustained (e.g., fatigue, negative cognitive bias, altered reward reactivity). Over time, the effects of these alterations may begin to accumulate, and interact with pre-existing vulnerabilities to lead to depression.

For example, if inflammation leads to biased attention towards negative information and reduced responsivity to positive/rewarding information, over time this skewed processing could lead to an accumulation of negative and a dearth of positive information in an individual's mental representation of the self and the environment. For some individuals – perhaps those with pre-existing negative self-schemas (drawing from cognitive models of depression) - this aggregation of negative information could activate and reaffirm pre-existing dysfunctional beliefs about oneself and the world, leading to depressive cognitions and potentially clinically significant depression.

As another example, we might consider how chronic fatigue due to sustained inflammatory signaling could lead to depression. Although temporary fatigue may be easily accommodated, chronic fatigue can significantly impair an individual from fulfilling their work, family, and social duties. For some individuals, this impairment may be negatively construed or catastrophized (e.g., "I can't accomplish anything and am thus a failure"), thereby giving rise to common manifestations of depression (feelings of worthlessness, guilt, etc.). Support for this idea can be drawn from IFN-α studies, which show that although the large majority of patients rapidly develop somatic symptoms (e.g., fatigue), a smaller percentage of patients go on to develop cognitive depressive symptoms (e.g., feelings of guilt, suicidality), which become severe enough to merit a major depression diagnosis in some patients (Capuron et al., 2002; Capuron &

Miller, 2004; Musselman et al., 2001). Moreover, major depression is more likely to develop in individuals with pre-existing, subclinical cognitive disturbance (pessimistic thoughts) prior to the initiation of treatment (Capuron, Ravaud, Miller, & Dantzer, 2004), in line with the idea that inflammation and associated behavioral changes may interact with pre-existing dysfunctional schemas to lead to depression.

The magnitude and duration of cytokine exposure matter for symptom development

The present review examined evidence from three distinct paradigms of the inflammation-depression link. While the IFN-α paradigm models the effects of chronic exposure to mild-to-moderate levels of inflammation, endotoxin and typhoid model the effects of acute exposure at high and low levels, respectively (Table 1). Taken together, findings from these paradigms have suggested that different magnitudes and durations of cytokine exposure may have distinct effects. Certain processes relevant to depression may be vulnerable to even low and/or acute increases in cytokines, whereas other processes may not be impacted (at least at detectable levels) until cytokine exposure is high and/or chronic.

For example, the evidence reviewed suggests that mild, short-term increases in inflammation are sufficient to cause somatic symptoms, particularly fatigue and psychomotor retardation. This is exemplified by typhoid vaccine studies which despite eliciting only mild, acute increases in inflammation can lead to increases in fatigue and psychomotor retardation without 2-3 hours (Brydon et al., 2008). Similarly, patients receiving (low-dose) IFN-α treatment for Hepatitis C exhibit increases in fatigue and decreases in vigor within four hours of initial injection (Dowell et al., 2016), supporting the idea that somatic changes are rapidly elicited by even modest perturbations in cytokine levels. Notably, however, although acute inflammation was sufficient to elicit immediate increase in fatigue in the above-cited study, initial fatigue

levels doubled on average by eight weeks into treatment, suggesting that although acute inflammatory stimulation may be sufficient, chronic stimulation does maintain and amplify effects (Dowell et al., 2016).

In contrast, the development of cognitive/affective symptoms of depression may not be sensitive to mild/acute elevations in inflammation, but rather require more chronic and/or robust exposure, as well as the potential presence of pre-existing vulnerability factors. IFN-α studies have shown that, in contrast to the rapidly developing somatic symptoms, cognitive/affective symptoms (including depressed mood, anhedonia, suicidal thoughts, feelings of guilt, tension/irritability, anxious mood, fear, loss of concentration, and memory disturbances) do not manifest until 4-12 weeks into treatment, suggesting that chronic inflammatory exposure may be necessary to elicit cognitive/affective symptoms (Capuron et al., 2002; Dowell et al., 2016). Alternatively, it may be that early onset of somatic symptoms may cause the eventual development of cognitive/affective symptoms, as suggested by other IFN-α studies showing that the appearance and severity of somatic symptoms predict the later development of depressive symptoms and diagnosis (Robaeys et al., 2007; Wichers, Koek, Robaeys, Praamstra, & Maes, 2005; cf., Dowell et al., 2016). Additionally, Capuron et al. (2002) showed that although IFN-α led to the rapid onset of somatic symptoms in nearly all patients, the later onset of cognitive/affective symptoms only affected a narrower subset of patients, suggesting that the inflammatory stimulus may interact with pre-existing vulnerability factors to determine mood outcomes.

However, endotoxin studies (which elicit much higher levels of proinflammatory cytokines) have been shown to acutely elicit depressed mood and somatic symptoms simultaneously (Eisenberger et al., 2009; Eisenberger et al., 2010; Moieni et al., 2015;

Reichenberg et al., 2001), suggesting that chronic exposure may not be necessary if increases in inflammation are very robust, as in the case of endotoxin. Very high levels of inflammation may be sufficient to elicit immediate increases in depressed mood; whereas, at lower levels of inflammation, chronic exposure may be necessary to elicit depressed mood.

What does the evidence suggest about the magnitude/duration necessary to elicit changes in the other components of depression evidenced to be impacted by inflammation, such as heightened reactivity to negative information and altered reward processing? Currently only preliminary evidence exists showing that mild increases in inflammation (as elicited by typhoid vaccination) may upregulate reactivity to negative/stressful information (Brydon et al., 2009). Thus, it is possible that mild increases in inflammation are sufficient to elicit heightened reactivity to negative input but replication and examination across different types of stressors is needed. Multiple endotoxin studies have provided evidence for exaggerated reactivity to negative information (particularly at a neural level), suggesting that higher levels of inflammation can upregulate reactivity (Muscatell et al., 2016; Inagaki et al., 2012; Eisenberger et al., 2009; Slavich et al., 2010). Given a dearth of IFN-α studies on reactivity to negative information, effects of chronic inflammatory exposure on this process is yet to be examined.

As for alterations in reward processing, again only preliminary evidence exists suggesting that mild, acute increases in inflammation as stimulated by typhoid vaccination can modulate responsivity to rewards, specifically novel stimuli (Harrison et al., 2015); more research is needed to confirm sensitivity of reward processing to acute and mild inflammation and to examine effects across different types of reward. Endotoxin and IFN-α studies have shown that higher and more chronic elevations in inflammation do modulate reward processes at neural and behavioral levels (Capuron et al., 2012; Eisenberger et al., 2010), with potentially different

effects depending on properties of the reward (Inagaki et al., 2015; Lasselin et al., 2016; Muscatell et al., 2016), as previously discussed.

Overall, an understanding of the impact of inflammation on processes of depression requires consideration of the magnitude and duration of inflammatory exposure. Certain processes may be sensitive to acute and mild increases while others may not develop until magnitude and chronicity reach a certain threshold. Examining data from the different paradigms of inflammation induction can provide insight into the relative sensitivity of different processes/symptoms and their underlying neural circuitry.

Directions for Future Research

Building on existing—and in many cases quite recent— research, this endophenotype perspective can profitably guide future research on the inflammation-depression link. Most broadly, rather than conducting studies examining the link between inflammatory markers and depression as a diagnostic construct (as measured by clinical interview or a sum score on a self-report measure), future work might use the empirical research reviewed herein as a springboard to formulate and test hypotheses about how inflammation influences specific cognitive, affective, and behavioral processes that are both proximally affected by inflammation and closely associated with depression.

Specifically, a key gap identified in this review is the dearth of studies examining the impact of inflammation on negative attentional bias. The only known study to have examined this relationship showed a correlation between CRP levels and attentional bias towards negative faces in a dot-probe task administered to breast cancer survivors (Boyle et al., 2017). This represents provocative preliminary evidence that proinflammatory cytokines affect this key feature of depressive cognition, but replication is needed. Experimental studies that induce

inflammation can offer more causal evidence of the impact of inflammation on attentional biases; neuroimaging studies can examine whether the same neural mechanisms thought to underlie attentional biases in depression are involved in inflammation-induced attentional biases; and studies across various populations can increase our knowledge of the generalizability of this effect.

In contrast to the limited work on inflammation and attentional biases, a more substantial literature shows that inflammation impacts processing of and reactivity to negative information. Much of this work has focused on the impact of endotoxin-induced inflammation on reactivity to social threats (social evaluation, social exclusion, images of fearful faces). Thus, it remains unclear whether inflammation specifically upregulates reactivity to social stressors, or if reactivity to other types of negative information is also increased. Relatedly, while evidence has indicated that depressed individuals not only attend selectively to negative information, but also interpret ambiguous information more negatively (Butler & Mathews, 1983; Dearing & Gotlib, 2009; Lawson, MacLeod, & Hammond, 2002; Rude, Wenzlaff, Gibbs, Vane, & Whitney, 2002), few if any studies have examined whether inflammation leads to similar interpretive biases.

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 recent findings indicating that inflammation can lead to heightened VS reactivity to social rewards (Muscatell et al., 2016; Inagaki et al., 2015), future work should explicitly test whether the effect of inflammation on reward reactivity is specific to reward type. This could be done by directly comparing responsivity to different types of reward (e.g., social vs. monetary vs. primary rewards such as sugary snacks) 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.

A substantial amount of work has been dedicated to examining the impact of inflammation on executive functioning, but studies across various inflammatory paradigms and neuropsychological tasks provide scant support for a detrimental effect of inflammation on executive functioning. Thus, future work may instead choose to allocate resources towards clarifying the relationship between inflammation and memory impairments, which has yielded limited but somewhat more promising results. Additionally, going beyond between-group comparisons to examine the within-subject relationship between increases in proinflammatory cytokines and memory performance may yield more power to detect relationships between inflammation and memory. Additionally, based on evidence from animal models that moderate levels of inflammation promote learning and memory while high levels disrupt these processes (Yirmiya & Goshen, 2011), future research examining the relationship between inflammation and memory may benefit from exploring potential quadratic relationships.

We also reviewed the literature linking inflammation to the somatic syndrome endophenotype of depression, including fatigue, psychomotor slowing, and sleep changes. Evidence supports the hypothesis that inflammation is associated with sleep changes, which are commonly present in depression. However, whereas individuals with idiopathic depression tend to exhibit increases in REM sleep, inflammation-induced sleep disruption is characterized by decreases in REM. Thus the relevance of these inflammation-induced sleep changes for depression remains unclear, and is a subject for future research. By contrast, solid evidence

indicates that proinflammatory cytokines can cause fatigue and psychomotor slowing. Current work focused on the neurobiological underpinnings of these somatic symptoms, with a focus on dopaminergic pathways, shows promise in elucidating the mechanisms by which inflammation can rise to these symptoms. An interesting area of future work may be to elucidate the relationship between fatigue and depressed mood; in the context of inflammation, does depressed mood arise due to impairments associated with fatigue and other somatic symptoms? Or do increases in depressed mood arise independent of fatigue?

Researchers conducting studies on inflammation and depression should also consider assessing demonstrated vulnerability factors, and including them in analytic models. 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) 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, Ganz, Cole, Crespi, & Bower, 2016). Another potentially important vulnerability factor to consider is gender. Despite the fact that depression is more prevalent among women than men (e.g., Kuehner, 2003), a preponderance of studies examining the effects of inflammation on depressed mood have been conducted with solely male participants (e.g., Brydon et al., 2008; Brydon et al., 2009; Harrison et al., 2009; Harrison et al., 2014; Krabbe et al., 2005; Reichenberg et al., 2001; Wright et al., 2005). Studies that have included both male and female participants have revealed prominent gender differences in the psychological response to an inflammatory stimulus. For example, females exhibit greater increases in depressed mood and feelings of social disconnection following endotoxin exposure compared to males (Eisenberger et al., 2010; Eisenberger et al., 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, these findings suggest that females may more sensitive to the negative psychological effects of inflammation due to increased activation of threat circuitry. These gender differences deserve further investigation, as they may help to elucidate the mechanisms underlying the greater burden of depression among women. Future studies examining the relationship between inflammation and depression should aim to include both males and females in order to allow for the investigation of gender differences in the psychological response to inflammation.

A Network Perspective

Our review signals a clear benefit of deconstructing depression to examine links between inflammation and core endophenotypes of depression, 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 & Rockstroh, 2013). The notion of endophenotypes was originally put forth with the hope of identifying single major genes to account for mental disorders. However, it has become clear that this type of simple linear causal model (genotype -> endophenotype-> phenotype) is not sufficient to account for the multiplicity of factors and their interactions that ultimately give rise to psychopathology (Miller & Rockstroh, 2013). Genetic factors interact with psychological, environmental, and other biological factors and exert their influences at multiple points throughout etiology and

course of disorders; thus, simple serial models that begin with genes are reductionistic (Miller & Rockstroh, 2013). 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 & Rockstroh, 2013; 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. Traditionally, a construct like depression has been viewed as a latent factor that is the common cause of symptoms that are themselves independent of one another (e.g., fatigue and feelings of worthlessness are related only because they share a common latent cause of depression). In contrast, network models account for the clustering of symptoms by conceptualizing depression as a dynamic system of causal relations between processes/symptoms themselves over time (e.g., fatigue -> feelings of worthlessness) (Schmittmann et al., 2011). This perspective allows for the fact that symptoms can trigger other symptoms, and offers an alternative to the simple linear causal model in which symptoms are the behavioral manifestation of a genetic disorder (Fried & Nesse, 2015). This approach can model relationships not only among symptoms, but also among variables at multiple levels of analysis (e.g., interactions between symptoms, endophenotypic processes, genetic influences, environmental stressors, and time).

As an example of how this network perspective can shift our understanding of and approach to the relationship between inflammation and depression, recall the previously mentioned study of IFN-α treated cancer patients by Capuron and colleagues (2002). In this

study, it was reported that IFN-α treatment 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). Whereas the researchers interpreted these findings as indicating that IFN-α led to the development of two distinct syndromes (somatic vs. cognitive/affective), a researcher operating from a network perspective would allow for the possibility that the earlier appearing somatic symptoms could causally give rise to the later-appearing affective/cognitive symptoms (e.g., fatigue -> mood symptoms), which would reveal a different pathway from inflammation, with potentially different implications for intervention. Studies on the effects of IFN-α have already begun to examine predictive relationships between symptoms (e.g., Dowell et al., 2016; Robaeys et al., 2007; Wichers et al., 2005), even if these researchers did not explicitly situate their work within a network model. Importantly, bidirectional relationships among inflammation, inflammation-related symptoms, and other biobehavioral processes are probable. For example, inflammation may disrupt sleep, and sleep disruption may in turn trigger further inflammation (Irwin et al., 2015).

Based on our review, we argue that the endophenotype approach—focusing as it does on underlying processes—offers rich opportunities for explaining the role of inflammation in depression. The burgeoning research on the biology of inflammation, the interactions captured in psychoneuroimmunology, and the increased emphasis on mechanistic understanding in psychopathology research have begun to converge fairly recently. Moreover, as this review suggests, research on inflammation in some of these depressive endophenotypes is modest in amount and limited in conclusiveness (e.g., inflammation and attentional biases relevant to

depression). Thus, we believe this review recommends further research from an endophenotype perspective, but also an eye toward a complementary network approach.

Conclusions

The current body of evidence indicates that inflammation is linked—in many cases causally—to alterations in endophenotypic processes posited to directly underlie the phenotype of depression. In particular, inflammation appears related to core affective and cognitive disturbances (e.g., anhedonia; biased information processing) strongly implicated in current models of the etiology and treatment of depression. Moreover, inflammation somewhat consistently affects neurobiological systems implicated in depression. As such, we argue that the role of inflammation may be best understood as affecting these complex neurobiological, cognitive, and affective processes, rather than as affecting the broad depressive syndrome directly.

In summary, our understanding of the role of inflammation in depression can be advanced by research that (1) deconstructs depression to examine how inflammation impacts core processes of depression, rather than continuing to examine effects on depression sum scores or clinical thresholds; (2) considers the potentially distinct effects of different magnitudes and durations of inflammation exposure; (3) examines potential moderators (e.g., female gender, other risk factors) of the effects of inflammation, and (4) utilizes a network perspective that begins to build a model of the web of relationships between variables at multiple levels of analysis, as they play out over time. While a rich body of work clearly indicates that inflammation plays an important role in depression, research in this area has stalled in recent years, as it has become increasingly clear that the nature of the inflammation-depression relationship is more complex and nuanced than previously imagined. Unraveling this relationship

may require a more sophisticated approach to the conceptualization and measurement of depression, greater specificity in our evaluation of the effects of inflammation, the incorporation of individual difference factors into our models, and more advanced statistical approaches to modeling the complex web of factors that may give rise to the depression. Research studies that incorporate such advances hold the potential to elucidate the etiology of depression in its various iterations, and thus to speed our progress towards alleviating the substantial suffering and burden that depression brings to bear on individuals, families, and societies.

Table 1

The three primary models used to examine the link between inflammation and depression, and their key features

Paradigm	Citation	Dosing schedule	Mean IL-6 increase (% increase)	Time of IL-6 assessment	Duration of increase	Strengths	Limitations
IFN-α						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.
Hepatitis C (3 MU/m^2 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		
Malignant melanoma (20 / 10 MU/m^2 dose)	Capuron et al., 2003	20 MU/m^2 5 days/wk, for 1 month / then 10 MU/m^2 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)		
Endotoxin						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.
0.4 ng/kg dose	Grigoleit et al., 2011	1x	140 pg/mL (28000%)[a]	2 hrs post-injection	Resolves within 6 hrs		
0.8 ng/kg dose	Grigoleit et al., 2011	1x	190 pg/mL (38000%)[a]	2 hrs post-injection	Resolves within 6 hrs		
Typhoid vaccination	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. Used in medically healthy samples. Does not typically cause illness symptoms.	May not be sufficient to elicit increases in depressed mood.

[a]Values are approximate, based on graphs.
[b]Hingorani et al., 2000.

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.

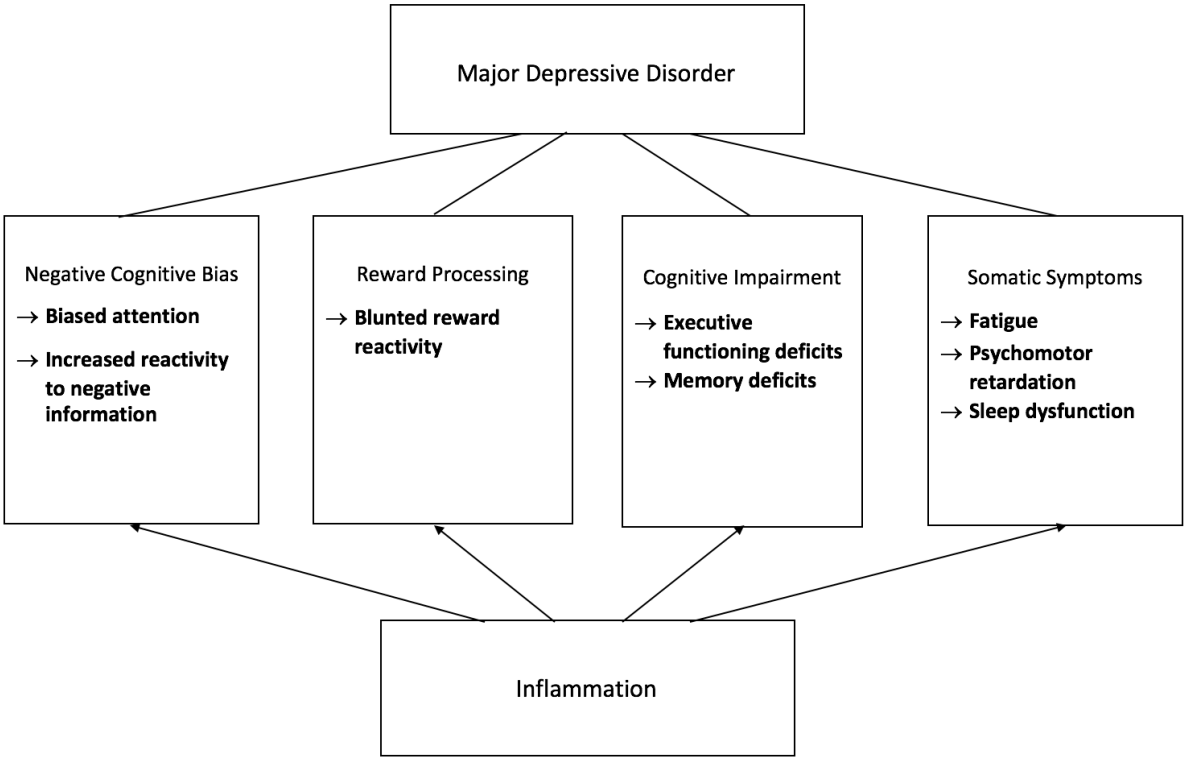

Figure 1. Core processes of depression that may be influenced by inflammation.

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Inflammation Following Influenza Vaccination and Core Processes of Depression:

An Empirical Study

Abstract

Inflammation has been implicated in the development of depression, yet the nature of this association is evidently complex. Examining links between inflammation and core processes of depression may clarify this relationship. The present study used a novel paradigm—influenza vaccination—to elicit increases in inflammation in a sample of healthy young adults ($N = 43$), and examined potential effects on multiple depression-related processes, including changes in mood, energy, reward processing, cognitive functioning, and attentional bias. Both before and one day after receiving the vaccine, participants provided blood samples for the measurement of interleukin-6 (IL-6) and all outcome measures. Outcomes included self-reported depressed mood, fatigue, and vigor (Profile of Mood States-15); behavioral measures of two aspects of reward processing: implicit reward learning (Probabilistic Reward Task) and reward motivation (Effort Expenditure for Rewards Task); three aspects of cognitive functioning: visuospatial memory (The Brief Visuospatial Memory Test - Revised), verbal memory (Rey Auditory Verbal Learning Test), and executive functioning (color-word Stroop); and attentional bias (emotional dot probe task). Results indicated that influenza vaccination led to a small but significant increase in IL-6 ($p = .008$). Primary analyses used linear regression to probe the association between within-subject changes in IL-6 from pre- to post-vaccination and within-subject changes in outcome measures. Findings indicated that increases in IL-6 were associated with increases in attentional avoidance of happy faces ($p = .001$), but were not associated with attentional bias for sad or angry faces. Unexpectedly, increases in IL-6 were associated with *improvements* in visuospatial working memory ($p = .032$) and reward learning ($p = .041$). Similarly, overall higher levels of IL-6 were also associated with improvements in verbal working memory ($p = .016$). Findings indicated no significant associations between changes in IL-6 and changes in depressed

mood, fatigue, vigor, executive functioning, or reward motivation. Mild increases in circulating inflammatory markers may not have potent effects on mood, energy, or executive functioning, but is associated with changes in attentional bias, working memory, and reward.

Inflammation Following Influenza Vaccination and Core Processes of Depression: An Empirical Study

Depression is a common and often recurring disorder that causes serious suffering, impaired functioning, and diminished quality of life (Spijker et al., 2004; Ustün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). Globally, an estimated 11 - 15% individuals experience at least one major depressive episode in their lifetime, and roughly 6% have experienced a depressive episode in the past year, with females twice as likely to experience depression as males (Kessler & Bromet, 2013). Despite treatment advances, available therapies are still only estimated to lead to full remission for roughly half of adults (Nemeroff, 2007; Shim, Baltrus, Ye, & Rust, 2011), leaving a large portion of the disease burden unmitigated. A more sophisticated understanding of the psychological, biological, and behavioral factors driving the pathogenesis of depression can illuminate new and potentially more effective targets for intervention.

Inflammation has been implicated as a key contributor to the pathophysiology of depression (Dantzer, Connor, Freund, Johnson, & Kelley, 2008; Irwin, 2002; Slavich & Irwin, 2014). The behavioral effects of inflammation have been well characterized in animal models and include changes in locomotor activity, social behavior, cognitive ability, and anhedonic behaviors (Kubera, Obuchowicz, Goehler, Brzeszcz, & Maes, 2011; Wohleb, McKim, Sheridan, & Godbout, 2015; Yirmiya & Goshen, 2011). Notably, these changes are similar to behavioral symptoms exhibited in humans with clinical depression. Meta-analyses have indicated that individuals with depression tend to exhibit elevated inflammatory markers compared to non-depressed controls (Hiles, Baker, de Malmanche, & Attia, 2012; Howren, Lamkin, & Suls, 2009), and levels of inflammation prospectively predict increases in depressive symptoms in

longitudinal studies (Gimeno et al., 2009; Valkanova, Ebmeier, & Allan, 2013; van den Biggelaar et al., 2007; Wium-Andersen, Ørsted, Nielsen, & Nordestgaard, 2013).

Moreover, causal evidence that inflammation can give rise to depressive symptoms in humans has come from studies that have administered an inflammatory stimulus and examined subsequent affective, behavioral, and neural changes. One such model involves the systematic examination of individuals with Hepatitis C or cancer undergoing IFN-α therapy, an immunotherapy that stimulates the production and release of proinflammatory cytokines. As IFN-α therapy involves multiple treatments per week over a period of months, resulting in mild to moderate elevations in inflammation (e.g., average IL-6 increases of 2.18 – 46 pg/mL, depending on the indication and dosing schedule), these studies provide insight into the effects of chronic exposure to mild/moderate levels of inflammation (Capuron et al., 2003; Dowell et al., 2016). These studies have revealed that patients receiving IFN-α therapy commonly develop a constellation of symptoms markedly similar to depression, including fatigue and appetite changes (developing within two weeks of treatment initiation) and depressed mood, anhedonia, cognitive impairment, and even suicidal ideation (developing within 4-12 weeks) (Capuron & Miller, 2004; Dowell et al., 2016; Raison, Demetrashvili, Capuron, & Miller, 2005; Raison & Miller, 2011). These symptoms are serious enough to merit a diagnosis of major depression in up to 50% of patients (Musselman et al., 2001).

More recently, models using endotoxin or typhoid vaccination to experimentally elicit inflammation have provided converging evidence that even short-term increases in inflammation (lasting a matter of hours) can cause affective and neurobehavioral changes consistent with depression among medically healthy individuals. Lipopolysaccharide (LPS) endotoxin is a component of gram-negative bacteria that strongly stimulates proinflammatory cytokine

production, resulting in robust increases in inflammation (e.g., average IL-6 increases of 190 pg/mL following a 0.8 ng/kg dose) that resolve within six hours (Grigoleit et al., 2011). Thus, endotoxin studies model effects of exposure to robust, short-term increases in proinflammatory cytokines. Findings have indicated that endotoxin exposure (versus placebo) can lead to symptoms of depression including negative mood, anhedonia, cognitive impairment, fatigue, reduced food intake, altered sleep, and feelings of social disconnection (DellaGioia & Hannestad, 2010; Eisenberger, Inagaki, Mashal, & Irwin, 2010; Eisenberger, Inagaki, Rameson, Mashal, & Irwin, 2009; Moieni et al., 2015; Reichenberg et al., 2001). Compared to endotoxin, typhoid vaccination leads to much more mild increases in inflammation (e.g., average IL-6 increases of 0.82 pg/mL) which resolve within 24 hours of administration (Wright, Strike, Brydon, & Steptoe, 2005). Studies using the typhoid vaccine paradigm have shown that even this mild and acute inflammatory challenge can lead to symptoms relevant to depression, particularly fatigue, confusion, and changes in mood (Brydon, Harrison, Walker, Steptoe, & Critchley, 2008; Brydon et al., 2009; Harrison et al., 2009; Strike, Wardle, & Steptoe, 2004; Wright et al., 2005).

Thus, substantial evidence across various samples and study designs supports a key role for inflammation in depression pathology. Yet, this literature has also revealed substantial variability in the relationship between inflammation and depression. Individuals with depression do not uniformly exhibit elevated inflammation, and not all individuals who experience heightened inflammation develop depressive symptoms. Furthermore, inflammation is not specific to depression; elevated inflammatory markers have also been shown among individuals suffering from other psychiatric disorders, including schizophrenia and posttraumatic stress disorder (Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Spitzer et al., 2010). Thus,

although a robust literature points to inflammation as a key contributor to depression, much work remains to be done to fully characterize what is evidently a complex and nuanced relationship.

It has been suggested that our understanding of the relationship between inflammation and depression has stalled due to the tendency in this area of research to measure depression as a unitary construct (e.g., a sum of depressive symptoms, or a depression diagnosis), despite the known heterogeneity in the manifestation and presentation of depression (Young, Bruno, & Pomara, 2014). It is possible that inflammation only influences certain biobehavioral processes thought to underlie depression (e.g., at a neural level, inflammation could impact reward-related circuitry, but not the prefrontal cortex), and thus may only be associated with certain components of depression (e.g., anhedonia, but not executive functioning deficits). Thus, examining links between inflammation and core components of depression should yield a more precise understanding of the relationship between inflammation and depression. This is in line with the National Institute of Mental Health Research Domain Criteria (RDoC) initiative, which states that focusing on core processes in depression may help clarify its associated biobehavioral underpinnings (in this case, the role of inflammation) (Insel et al., 2010).

In the present study, we induced changes in inflammation using the influenza vaccine, and examined how resulting changes in circulating levels of the proinflammatory cytokine interleukin-6 (IL-6) related to changes in core processes of depression. The core depressive processes we focused on were changes in depressed mood, fatigue, reward processing, cognitive functioning, and attentional bias. These specific processes were chosen by identifying endophenotypes of depression that, at least in preliminary work, have been suggested to be impacted by inflammation.

Depressed mood

Depressed mood is a cardinal symptom of depression and a core diagnostic criteria. Findings from IFN-α and endotoxin studies have indicated that inflammatory activation can lead to increases in ratings of depressed mood (Capuron et al., 2002; DellaGioia & Hannestad, 2010; Eisenberger, Inagaki, Mashal, & Irwin, 2010; Grigoleit et al., 2011; Janssen, Brouwer, van der Mast, & Schalm, 1994; Lotrich, Rabinovitz, Gironda, & Pollock, 2007; Reichenberg et al., 2001), suggesting that inflammation can impact this key feature of depression.

Fatigue

Fatigue is a commonly reported somatic symptom of depression. A study of more than 1,800 patients who had consulted a healthcare professional about their depression found that 73% of patients reported feelings of fatigue, and that this was the most commonly endorsed symptom after depressed mood (Tylee, Gastpar, Lépine, & Mendlewicz, 1999). Moreover, fatigue has been shown to prospectively predict major depression onset (Addington, Gallo, Ford, & Eaton, 2001; Kroenke & Price, 1993; Walker, Katon, & Jemelka, 1993).

There is strong evidence that inflammation plays a key role in fatigue. Studies have shown significant associations between inflammatory markers and fatigue among cancer patients (Bower, 2014), individuals with rheumatoid arthritis (Davis et al., 2008), and patients with multiple sclerosis (Flachenecker et al., 2004; Giovannoni, Thompson, Miller, & Thompson, 2001). Inflammatory markers have been shown to prospectively predict the development of fatigue in large-scale longitudinal studies (Cho, Kivimäki, Bower, & Irwin, 2013; Cho, Seeman, Bower, Kiefe, & Irwin, 2009). Additionally, IFN-α, endotoxin, and typhoid vaccination models have shown that exposure to these inflammatory challenges can lead to increased fatigue (Brydon, Harrison, Walker, Steptoe, & Critchley, 2008; Capuron et al., 2002; Grigoleit et al., 2011; Harrison et al., 2009) as well as decreased vigor (Wright et al., 2005). It should be noted

that studies experimentally stimulating inflammation have not typically examined associations between within-subject changes in inflammatory markers and within-subjects changes in fatigue specifically.

Reward processing

Anhedonia, the loss of pleasure or interest in previously rewarding stimuli, is a hallmark of depression and—along with high negative mood—is one of the core diagnostic criteria for major depression. Evidence from animal and human studies suggest that inflammation may impact reward-related processing. In animals, experimentally-induced inflammation (endotoxin or cytokine administration) increases anhedonic-like behavior (e.g., reduced consumption of palatable substances) (De La Garza, 2005). In humans, exogeneously-induced inflammation has been shown to elicit symptoms of anhedonia as well as changes in reward-related neurobiology. For example, in a study by Capuron and colleagues (2012), IFN-α treatment was associated with reduced ventral striatal activity to a monetary reward task, and this attenuated activation was in turn associated with anhedonic and depressive symptoms. Similarly, endotoxin exposure has been shown to reduce ventral striatum activity to monetary reward cues (Eisenberger et al., 2010). IFN-α treatment has also been associated with alterations in dopaminergic activity in the ventral striatum (Capuron et al., 2012). These findings suggest that proinflammatory cytokines may give rise to anhedonia by targeting neural regions and neurotransmitters central to reward processing. However, recent studies have suggested that inflammation can also upregulate reward-related neural activity to socially rewarding stimuli (Inagaki et al., 2015; Muscatell et al., 2016), suggesting that the effect of inflammation may depend on the type of reward (Eisenberger et al., 2016).

Although existing studies have examined the effects of inflammation on self-reported anhedonia and the neural mechanisms underlying this association, the effects of inflammation on behavioral measures of reward processing remains largely unexamined.

Current conceptualizations of anhedonia define it as a multifaceted construct encompassing an array of potential deficits in reward processing; these include deficits in the desire to engage in rewarding activities (anticipatory anhedonia), in the drive to exert effort to obtain rewards (motivational anhedonia), and in the subjective experience of pleasure (consummatory anhedonia) (Der-Avakian & Markou, 2013). An additional component of reward processing is the propensity to modulate behavior as a function of reward (reward-related learning) (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008). The use of behavioral reward tasks allow researchers to tap into these unique components of reward processing; examples include the Probabilistic Reward Task (Pizzagalli et al., 2008; Pizzagalli, Jahn, & O'Shea, 2005), which is designed to measure reward-related learning, and the Effort Expenditure for Rewards Task (EEfRT) (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009), which taps motivation for rewards. These behavioral tasks are now commonly used in depression/anhedonia research; however, this approach is only beginning to make its way into the inflammation-depression literature, and few studies have examined the effects of inflammation on components of reward processing via behavioral tasks. No published work has examined the relationship between inflammation and reward learning using the PRT. One recent study was the first to examine the effect of an inflammatory stimulus (endotoxin) on reward learning using the EEfRT task (Lasselin et al., 2016); findings indicated that endotoxin did not decrease reward motivation, as expected, but rather increased motivation only when the probability to win was high. The authors interpreted this as that inflammation may not lead to a general decrease in motivation but rather

trigger a reorganization of priorities, leading individuals to only spend resources pursuing rewards that are likely to pan out (Lasselin et al., 2016). Yet, given that this is the only available study examining the impact of inflammation on a behavioral measure of incentive motivation in humans, more research is needed to clarify the role of inflammation in this key aspect of reward processing.

Cognitive functioning

Individuals with depression commonly report impairments in cognitive functioning (Simons et al., 2009), and studies have shown that depressed individuals perform more poorly on objective neuropsychological tests of executive functioning and memory ability compared to non-depressed controls (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lonnqvist, 2008; Hammar & Ardal, 2009). These include significant deficits on executive functioning tests such as the Stroop color-word task (Snyder, 2014), and tests of visuospatial and verbal long-term memory (Hammar & Ardal, 2009), although findings have been mixed as to the exact nature and pattern of memory impairments exhibited in depression (Hammar & Ardal, 2009).

Much of the evidence linking inflammation and cognitive functioning comes from animal models. Findings from these studies have revealed that, under normative conditions, immune mechanisms actually promote a number of learning and memory processes, particularly hippocampal-dependent memory consolidation (Yirmiya & Goshen, 2011). However, when the immune system is strongly activated, such as due to infection, injury, or extreme stress, the resulting high levels of proinflammatory cytokines can disrupt learning, memory, and neural plasticity (Yirmiya & Goshen, 2011).

Studies in humans have examined the effects of elevated inflammation due to

typhoid vaccine, IL-6 administration, and IFN-α treatment on cognitive functioning. These studies have shown that these immune challenges often result in subjective reports of impaired cognitive functioning (Capuron et al., 2002; Harrison et al., 2009; Späth-Schwalbe et al., 1998). However, the effects of elevated inflammation on objective, behavioral measures of cognitive functioning are less clear.

Two studies compared executive functioning as measured by the Stroop in a group that received endotoxin versus controls, and found no significant differences in performance (Grigoleit et al., 2010; van den Boogaard et al., 2010). A study by Brydon and colleagues (2008) examined Stroop performance following typhoid vaccination versus placebo, and similarly found no significant group differences. However, within the vaccine condition, increases in IL-6 (baseline to post-vaccine) strongly predicted reaction times to incongruent Stroop trials, indicating that participants with a larger IL-6 response to the vaccine had significantly longer reaction times (Brydon et al., 2008). Notably, larger increases in IL-6 were also associated with longer response times to Stroop congruent trials, suggesting that the effect of inflammation on Stroop performance may have been driven by slower psychomotor speed generally, rather than (or in addition to) specific impairments in executive functioning. More work is thus needed examining the association betweeen changes in inflammatory markers and Stroop performance in order to clarify the precise nature of the deficits captured by this task.

A handful of human studies have examined effects of experimentally-induced inflammation on behavioral measures of visuospatial memory (as assessed with figure recall tasks), with one study finding negative effects on visuospatial memory (Reichenberg et al., 2001), and others have found no effects (Amodio et al., 2005; Fontana et al., 2007; Grigoleit et al., 2010). Using the typhoid vaccine model, Harrison and colleagues (2014) found that the

typhoid vaccine exposed group exhibited poorer spatial memory versus controls (assessed using a virtual reality task developed to be analogous to the Morris water maze used in rodent models), and that this effect was mediated by reduced parahippocampal glucose metabolism, a region critical for spatial memory.

Additionally, of the studies examining effects of experimentally-induced inflammation on verbal memory (as assessed with word list or story recall tasks), one study found significant negative effects (Reichenberg et al., 2001) while others have found no effects (Amodio et al., 2005; Fontana et al., 2007; Grigoleit et al., 2010). Krabbe and colleagues (2005) similarly examined the effects endotoxin on word list recall, and found no significant group differences in performance. However secondary analyses within the endotoxin group revealed that plasma IL-6 and soluble tumor necrosis factor-receptors (sTNF-R) were both negatively correlated with word-list recall, such that subjects with greater increases in IL-6 and sTNF-R exhibited poorer verbal memory (Krabbe et al., 2005).

For both executive functioning and verbal memory, studies that examined group differences in cognitive functioning between a condition that received an immune challenge versus controls revealed mixed findings. However, the few studies that moved beyond group differences to examine associations between within-subject changes in an inflammatory marker and changes in cognitive functioning have shown clearer associations between inflammation and cognitive functioning deficits (Brydon et al., 2008; Krabbe, et al. 2008), suggesting that it may be critical to account for individual differences in the inflammatory response to a given immune stimulus.

Attentional bias

Attentional bias plays a critical role in cognitive theories of depression. Selective attention towards and difficulty disengaging from negative stimuli is theorized to contribute to the onset and maintenance of depression (Kircanski, Joormann, & Gotlib, 2012). Individuals with depression or elevated depressive symptoms exhibit biases towards negative emotional information and away from positive information (Peckham, McHugh, & Otto, 2010; Winer & Salem, 2015). Negative attentional bias is also evident among women with remitted major depression, and the magnitude of this bias predicts depression recurrence (Woody, Owens, Burkhouse, & Gibb, 2016). Moreover, training individuals to reduce negative attentional bias reduces depressive symptoms (Browning, Holmes, Charles, Cowen, & Harmer, 2012), implicating attentional bias in the etiology of depression.

To date, only one study has examined the relationship between inflammation and attentional bias (Boyle, Ganz, Van Dyk & Bower, 2017). In a sample of 91 early-stage breast cancer survivors, circulating concentrations of C-reactive protein (CRP) were positively associated with attentional bias towards sad faces in a dot probe task, such that women with higher CRP demonstrated greater attention towards sad faces (Boyle et al., 2017). This study provides intriguing but preliminary evidence for an association between circulating inflammatory markers and attentional bias. No studies have experimentally manipulated levels of inflammation and examined the relationship between changes in inflammation and changes in attentional bias.

The present study

The aim of the present study was to refine our understanding of the relationship between inflammation and depression. To do so, we tested whether changes in inflammation following an inflammatory challenge led to changes in core processes of depression, including alterations in

mood, fatigue, reward processing, cognitive functioning, and attentional bias, in a sample of healthy young adults.

In order to induce changes in circulating inflammation, we administered the influenza vaccine, which has been shown in prior work to elicit an inflammatory response (Carty et al., 2006; Christian, Iams, Porter, & Glaser, 2011; McDade, Borja, Kuzawa, Perez, & Adair, 2015; Posthouwer, Voorbij, Grobbee, Numans, & Van Der Bom, 2004; Tsai et al., 2005), including an increase in circulating levels of IL-6 (e.g., an average increase of 0.7 pg/mL; Tsai et al., 2005) that peak approximately 1 day post-vaccination (Christian et al., 2013; Tsai et al., 2005). An advantage of the influenza vaccine model is that it elicits a more mild inflammatory response compared to existing models, including IFN-α, endotoxin and typhoid vaccination paradigms. This more modest inflammatory response may confer notable benefits. First, unlike IFN-α treatment or endotoxin, the flu vaccine does not typically lead to physical illness symptoms (fever, headaches, etc.), suggesting that any potential effects on mood and cognition are not attributable simply to illness symptoms, but rather to more direct effects of cytokines on the brain. Additionally, the magnitude of the inflammatory response to influenza vaccination approximates the modest elevations exhibited in groups of medically healthy individuals with MDD (Dowlati et al., 2010; Raison & Miller, 2011), as well as the inflammatory response to psychosocial stress (Carpenter et al., 2010; Edwards, Burns, Ring, & Carroll, 2006; Steptoe, Owen, Kunz-Ebrecht, & Mohamed-Ali, 2002), which is deeply implicated in the etiology of depression (Hammen, 2005; Slavich & Irwin, 2014). Psychosocial stressors can trigger the release of proinflammatory ctyokines, which in turn can elicit changes in behavior including sad mood, anhedonia, and fatigue; it has thus been hypothesized that stress-induced inflammation contributes to the onset and maintenance of depression (Slavich & Irwin, 2014). Given that the

influenza vaccine elicits levels of proinflammatory ctyokines similar to those seen following psychosocial stress, this model may inform our understanding of the effects of stress-induced inflammation on depression pathology.

The present study examines associations between within-subject changes in IL-6 following influenza vaccination and within-subject changes in core processes of depression, including changes in mood, fatigue, reward processing, cognitive functioning, and attentional bias. Mood and fatigue were assessed with self-report questionnaires, and reward processing, attentional bias, and cognitive functioning were assessed with behavioral tasks. Each outcome was assessed both pre- and post-vaccination, to allow for the examination of within-subject change. As noted above, prior work has suggested that moving beyond group differences to focus on within-subject effects often yields more power to detect effects. This is likely because examining group differences assumes a general homogeneity in the inflammatory response to a given immune stimulus; in actuality, there are pronounced individual differences in the inflammatory response. Thus, looking at within-subject changes in inflammation, which accounts for such individual differences in cytokine response, may yield a more sensitive test of the effects of proinflammatory cytokines on our outcomes of interest.

Hypothesis 1: **Mood.** Increases in IL-6 from pre- to 24-hours-post-vaccine will be associated with increases in self-reported depressed mood. This hypothesis is consistent with previous work showing that administration of an inflammatory stimulus can lead to depressed mood, which peaks in parallel with the peak in proinflammatory cytokines (Eisenberger et al., 2009; Eisenberger et al., 2010; Moieni et al., 2015; Reichenberg et al., 2001).

Hypothesis 2: Fatigue. Increases in IL-6 from pre- to post-vaccine will be associated with increases in fatigue, and decreases in self-reported vigor. This is consistent with studies

demonstrating inflammation-induced increases in fatigue and decreases in vigor (Brydon et al., 2008; Eisenberger et al., 2010; Wright et al., 2005; cf. Harrison et al., 2009).

Hypothesis 3: Reward processing. Increases in IL-6 from pre- to post-vaccine will be associated with reductions in reward learning and motivation, as indexed with behavioral reward tasks (see Measures). This hypothesis is based on prior studies demonstrating associations between heightened inflammation and altered reward processing (Brydon et al., 2009; Eisenberger, Berkman, et al., 2010; Harrison, Cercignani, Voon, & Critchley, 2015).

Hypothesis 4: **Cognitive functioning**. Increases in IL-6 from pre- to post-vaccine will be associated with declines in visuospatial learning and memory, verbal learning and memory, and executive functioning, as indexed with neuropsychological tasks (see Measures). This hypothesis is based on studies showing deficits in these aspects of cognitive functioning following an immune challenge (Harrison et al., 2014; Krabbe et al., 2005; Reichenberg et al., 2001), though findings have been mixed (Amodio et al., 2005; Fontana et al., 2007; Grigoleit et al., 2011).

Hypothesis 5: Attentional bias. Increases in IL-6 from pre- to post-vaccine will be associated with changes in performance on the emotional dot probe task. Specifically, we hypothesize that increases in IL-6 will be associated with increases in attentional bias towards both sad and angry faces and away from happy faces. This is based on work showing the depression is characterized by attentional allocation towards negative stimuli and away from positive stimuli (Winer & Salem, 2015; Woody et al., 2016), as well as recent preliminary work showing that circulating inflammation was positively correlated with attention towards sad faces in a sample of breast cancer survivors (Boyle et al., 2017).

Method

Participants

Participants were recruited by posting study fliers on the University of California, Los Angeles (UCLA) campus in areas trafficked by underclassmen during Fall 2015 and Fall 2016. Individuals interested in participating completed a phone interview to determine their eligibility to participate in the study. Participants were deemed eligible if they were 18-19 years old and had not yet received the current year's influenza vaccine. Participants were excluded if they were allergic to eggs (as influenza vaccines contain small amounts of egg protein), had any influenza or upper respiratory symptoms, used tobacco products, were currently diagnosed with and/or being treated for depression, anxiety, any major medical condition (e.g., diabetes, asthma), or were currently using any medications known to affect mood or the immune system (e.g., antidepressants, anti-anxiety medications, hormone medications). Participants were compensated $150 for full completion of the study. The research was approved by the University of California, Los Angeles Institutional Review Board, and participants provided written informed consent.

Procedure

Data collection occurred in two waves, in Fall 2015 and Fall 2016. Figure 1 is a diagram of the study design. Each subject participated in three laboratory visits. At the baseline assessment (Day 1), two neuropsychological tests assessing visuospatial and verbal learning and memory were administered by trained research staff. During the delay period for these tests, participants completed a series of baseline questionnaires assessing demographic factors, baseline depression and anxiety symptoms, and other background characteristics. The questionnaires were administered on a computer via SurveyMonkey. Participants then completed a series of computer tasks assessing reward-related processing and executive functioning. In Fall

2016, a computerized task assessing attentional bias was also administered. All computer tasks were administered using Inquisit 2.0.6 software on a laptop computer.

One week later (Day 8), participants completed a brief questionnaire, and weight, height, and oral temperature measurements were collected. Participants then provided a pre-vaccine blood sample, which was obtained by a licensed medical assistant. Following the blood draw, research staff escorted each participant to the campus student health center where they received the current year's influenza vaccine. The 2015/2016 vaccine was trivalent and included A/California/7/2009 (H1N1) pdm09-like virus, A/Switzerland/9715293/2013 (H3N2)-like virus, and B/Phuket/3073/2013. The 2016/2017 influenza vaccine was also trivalent and consisted of A/California/7/2009 (H1N1) pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, and B/Brisbane/60/2008-like virus (B/Victoria lineage).

Approximately 24 hours later (post-vaccination assessment, Day 9), oral temperature and a post-vaccine blood sample were collected by a licensed medical assistant. Participants then completed questionnaires, and repeated the cognitive and behavioral tasks they had completed at the baseline (Day 1) assessment, using alternate forms of the tasks when appropriate (see Measures). The post-vaccination assessment was conducted approximately 24-hours after vaccination, as this was when we expected IL-6 levels to peak, based on prior work assessing inflammatory markers at multiple timepoints following the influenza vaccination (Christian, Porter, Karlsson, Schultz-Cherry, & Iams, 2013; Tsai et al., 2005).

In addition to these three laboratory visits, participants were instructed to complete a brief, online daily diary (via Surveymonkey) every night for 14 nights, beginning with the evening of Day 1. The daily diaries prompted participants to report their experiences of depressed mood, fatigue, and vigor, as well as physical symptoms experienced that day. A link to

the daily diary was emailed to each participant at 8pm each night throughout the course of the study, and participants were instructed to complete the diary before they went to bed each night. Each diary took 2-5 minutes to complete. The present study will only examine data from two select daily diaries; the diary from the day before vaccination and the diary from the day following vaccination (see Measures, Depressed Mood subsection). After completion of the final daily diary, participants were compensated $150 and debriefed.

Measures

Inflammation. Levels of inflammation were assessed by measuring circulating levels of the proinflammatory cytokine interleukin-6 **(**IL-6) in plasma. Although the influenza virus has been shown to lead to increases in multiple markers of inflammation including IL-6, tumor necrosis factor-α (TNF-α), CRP, macrophage migration inhibitory factor (MIF), and serum amyloid-a (SAA) (Carty et al., 2006; Christian et al., 2011, 2013; Posthouwer et al., 2004), we chose to focus on IL-6 based on prior work showing that vaccine-induced increases in IL-6 (but not other markers) are associated with increases in self-reported negative mood, mental confusion, and fatigue (Harrison et al., 2009; Wright et al., 2005), suggesting that IL-6 activity may be especially relevant for depressive processes.

All blood samples were collected by a licensed medical assistant in the morning (before 1pm) in order to minimize variance due to the diurnal rhythm of IL-6. Samples were collected by venipuncture into EDTA tubes, placed on ice, centrifuged for acquisition of plasma, and stored at -80° C for batch testing. Samples were assayed in duplicate using a high sensitivity ELISA (R&D Systems, Minneapolis, Minnesota) at the UCLA Inflammatory Biology Core on a single plate, and the reported inter- and intra-assay coefficient of variation for all assays was <9%.

Baseline depression and anxiety symptoms. Baseline depressive symptoms were assessed using the 8-item Personal Health Questionnaire Depression Scale (PHQ-8), which has demonstrated validity as a measure of depressive symptoms in the general population (Kroenke et al., 2009). Baseline anxiety symptoms were measured using the 7-item Generalized Anxiety Disorder Scale (GAD-7; Spitzer et al., 2006), a reliable and valid measure of anxiety symptoms in the general population (Löwe et al., 2008).

Subjective symptoms. Changes in the subjective experience of depressed mood, fatigue and vigor, and sickness symptoms were drawn from daily diaries. Participants completed daily diary questionnaires each night before bed, reporting on mood and symptom experienced over the course of that day. Pre-vaccine mood/symptom experience was drawn from the daily diary completed the day before influenza vaccination (Day 7); post-vaccine mood/symptom experience was drawn from the daily diary completed the day after vaccination (Day 9) (Figure 1). Pre- to post-vaccine changes in depressed mood, fatigue and vigor, and sickness symptoms were each calculated by subtracting the pre-vaccine score from the post-vaccine score (e.g., post-vaccine daily dairy depressed mood score minus pre-vaccine daily diary depressed mood score).

Depressed mood. Depressed mood was measured using the three-item depressed mood subscale of the Profile of Mood States-15 (POMS-15; Cranford et al., 2006), a shortened version of the POMS (McNair, Lorr, & Droppleman, 1971) that has demonstrated reliability in detecting within-person changes in mood over time in daily diary research (Cranford et al., 2006). The POMS-15 was administered as part of the daily diary questionnaires. Participants were asked to rate how accurately each of the adjectives (sad, hopeless, discouraged) described their mood that day using a 5-point Likert scale, from 0 = “Not at all” to 4 = “Extremely”; a mean of these scores was taken to create an index of depressed mood (Cranford et al., 2006).

Fatigue and Vigor. Fatigue was measured using the three-item fatigue subscale from the POMS-15 (fatigued, worn out, exhausted) (Cranford et al., 2006). Vigor was assessed using the three-item vigor subscale from the POMS-15 (vigorous, cheerful, lively) (Cranford et al., 2006). These subscales have demonstrated reliability in detecting daily within-person changes in fatigue and vigor (Cranford et al., 2006). For each item, participants were asked to rate how accurately each of the adjectives described their mood that day using a 5-point Likert scale, from 0 = "Not at all" to 4 = "Extremely."

Sickness symptoms. To examine whether the vaccine elicited sickness symptoms, participants were asked on each daily diary to report their experience of the following symptoms: feeling "sick", headaches, chills, fever, and muscle/joint aches or pains. For each symptom, participants were asked to indicate their symptom experience on a Likert scale from 0 = "Not at all to 3 = "Severe". Additionally, on post-vaccination daily dairies only, participants were asked to report the level of arm soreness they experienced using the same Likert scale.

Reward processing. Two tasks were used to measure distinct aspects reward processing, including reward learning and reward motivation.

Reward learning. Participants completed two reward tasks. The Probabilistic Reward Task (PRT) (Pizzagalli et al., 2005) is a validated measure of reward-related learning (Bogdan & Pizzagalli, 2006; Pizzagalli et al., 2008). Reward-related learning is the capacity to shape one's behavior as a function of reward history (Pizzagalli et al., 2008); individuals with elevated depressive symptoms demonstrate blunted reward-learning in both instrumental (Gradin et al., 2011) and Pavlovian (Kumar et al., 2008) learning tasks.

In the PRT, participants are presented with a simple cartoon drawing of a face on a computer screen. The face initially has no mouth; subsequently, a mouth (depicted as a straight

horizontal line) briefly flashes on the screen. The participant's task is to indicate whether the mouth is "short" or "long" using a keyboard press; the actual difference in the length of the mouth is negligible and intentionally difficult to decipher. The dependent variable of interest is response bias, an index of the participants' systematic preference for the response more frequently rewarded. To elicit a response bias, the task uses an asymmetrical reinforcement ratio, such that one response is rewarded three times more frequently than the other (e.g., correctly identifying the short mouth results in a reward 30 times, whereas correctly identifying the long mouth results in a reward only 10 times), while both mouth lengths are presented an equal number of times. The reward consists of positive feedback, presented on the screen following a rewarded trial, indicating that the participant has earned a monetary award *(*e.g., *"Congratulations! You just won $1.00!")*. As the task progresses, non-depressed individuals will develop a response bias; having implicitly learned that one response is more rewarding, they will choose it more often. In contrast, individuals with depression do not develop this response bias, suggesting that reward-learning from reinforcement history is impaired in depression (Pizzagalli et al., 2008; Vrieze et al., 2013). Moreover, this blunted response bias correlates with self-reported anhedonia, further attesting to the validity of the task (Pizzagalli et al., 2008).

In the present study, the task consisted of a total of 240 trials divided in three blocks of 80 trials each, with a 30-second break between blocks. Each trial commenced with the presentation of a fixation point (asterisk) in the middle of the screen (for 500 ms), followed by the presentation of a mouthless cartoon face (for 500ms). The mouth was then flashed onto the face for 100 ms. The "short" mouth was 11.5mm and the "long" mouth was 13mm. The participant then used the keyboard to indicate whether the mouth presented was short or long. For each block, the long and short mouths were presented equally often in a pseudorandomized

sequence (no more than three of the same stimulus presented consecutively). For each block, 40% of correct response trials were followed by reward feedback, and one response was three times more likely to be rewarded than the other. If the participant was inaccurate, or accurate on a non-rewarded trial, a blank screen was displayed. Participants were informed prior to the start of the task that for each dollar they earned on the tasks, one raffle ticket in their name would be added to a raffle for one of two $50 gift cards. The participant also completed 10 practice trials prior to commencing the task. The task including practice trials took approximately 15 minutes to complete.

Four different configurations of the task were created to counterbalance the response more frequently rewarded and the two response keys paired with the two potential responses, and participants were randomly assigned to one of the four configurations for the Day 1 assessment. At the Day 9 assessment, participants completed an alternate form of the task, in which the object was to judge whether the length of a nose, rather than a mouth, was short or long, following from prior work (Bogdan, Perlis, Fagerness, & Pizzagalli, 2010). Participants were randomly assigned to one of four counterbalanced configurations for the alternate nose task at Day 9, as they had been at Day 1.

The dependent variable from this task was a response bias score, an index of overall reward learning across the three blocks. This score is derived from signal detection theory and was calculated in accordance with standard scoring procedures for this task (Pizzagalli et al., 2008). Change in reward learning was calculated as the response bias score from the post-vaccine visit minus the response bias score from the pre-vaccine visit.

Reward motivation. The Effort Expenditure for Rewards Task (EEfRT) (Treadway et al., 2009) is a measure of motivation for rewards and effort-based decision making. In this task,

reduced motivation is operationalized as a decreased willingness to exert greater effort for greater rewards, particularly when rewards are uncertain. Prior work has shown that individuals with depression demonstrate decreased motivation to expend effort for monetary rewards on this task compared to controls (Yang et al., 2014).

The EEfRT is administered on a computer, and requires participants to complete a series of trials in which they choose either an "easy" or a "hard" task in order to win money. All trials require the participant to make repeated manual button presses within a limited period of time; each button press raises the level of a virtual "bar" presented on the computer screen. The easy task consists of making 30 button presses using the index finger within 7 seconds; the hard task consists of making 100 button presses using the pinky finger within 21 seconds. While subjects are eligible to win $1 for completing an easy trial, the amount that a participant is eligible to win for completing a hard trial varies, ranging from $1.20 - $4.00. Thus, the reward magnitude varies across trials. Additionally, participants are told that completion of the task alone does not guarantee a monetary reward; some trials are more likely to result in a reward upon completion than others. The probability that a given trial will result in a reward is presented on the screen prior to the trial, and can be 88%, 50%, or 12%. Thus, the probability of reward also varies across trials. In summary, for each trial, a participant is prompted to choose either an easy (low-effort/low-reward) or a hard (high-effort/high-reward) task. The relative amounts they are eligible to win for the easy and hard task, as well as the probability of winning money upon completion of the task, is presented on the screen for them to consider as they make their decision. Thus, the reward magnitude and probability of reward are manipulated to examine the conditions under which a person will exert greater efforts for a reward. In the present study, participants played for a total of 10 minutes. Participants were informed prior to the start of the

task that for each dollar they earned on the tasks, one raffle ticket in their name would be added to a raffle for one of two $50 gift cards.

The dependent variable from this task is the number of hard (high-effort) trials choices made by the participant, representing the level of effort that participants were willing to expend in order to obtain a higher reward (i.e., reward motivation). The effects of reward magnitude and probability in predicting hard trial choices were also examined, as well as their interaction with IL-6, given previous work showing that the effect of inflammation on EEfRT performance was moderated by probability (Lasselin et al., 2016).

Cognitive Functioning. Three tasks were used to measure distinct aspects cognitive functioning, including visuospatial learning and memory, verbal learning and memory, and executive functioning.

Visuospatial learning and memory. The Brief Visuospatial Memory Test - Revised (BVMT-R) is a valid and reliable neuropsychological task measuring visuospatial memory (Benedict & Groninger, 1995; Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996). Participants are shown a display of six abstract geometric figures for 10 seconds. The display is then removed, and participants are asked to render the figures from memory on a blank sheet of paper, drawing them as accurately as possible and in their correct location on the page. This procedure is repeated twice more, each time allowing the examinee 10 seconds of exposure to the original display and requiring him or her to attempt to recreate it on a blank sheet of paper. Following a 25-minute delay in which examinees are not exposed to any potentially interfering stimuli (e.g., geometric shapes), participants are asked to again draw the display from memory (delayed free recall trial). Examinees are then shown 12 shapes, one at a time, and asked to indicate whether each was present on the original display (recognition memory trial).

In the present study, the test was administered by a trained graduate student under the supervision of a clinical neuropsychologist. Alternate forms of the test have been validated in order to minimize practice effects in the context of multiple administrations (Benedict & Groninger, 1998); using these alternate forms, each participant completed a different form of the test on Day 1 and Day 9 laboratory assessments. Participants were randomly assigned to which form of the test they would receive first. The task took approximately 5 minutes to administer for learning trials, and 2 minutes for recall trials. Participants completed questionnaires and the learning trials of the verbal memory task during the delay period.

The dependent variables of interest for the current study were Trial 1 (T1) scores (the accuracy with which the figures are reproduced after only having seen the display once for 10 seconds; reflects working visuospatial memory and attention), and Delayed Recall (DR) scores (accuracy of figure reproduction after a 25 minute delay; reflects long-term visuospatial memory capacity). Change scores for T1 performance were computed as the post-vaccine T1 score minus the pre-vaccine T1 score; change scores for DR were computed similarly.

Verbal learning and memory. The Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996) is a reliable and valid neuropsychological task assessing verbal learning and memory (de Paula et al., 2012; Schoenberg et al., 2006). Individuals with depression demonstrate impairments on this test (Günther, Holtkamp, Jolles, Herpertz-Dahlmann, & Konrad, 2004), and RAVLT performance has been shown to be impaired following endotoxin exposure (Reichenberg et al., 2001).

In the RAVLT, participants are read a list of 15 unrelated words (List A), and subsequently asked to repeat back as many words as they can remember, in any order. This procedure is repeated for four more trials. Then, a different list of 15 unrelated words is read

(List B), and the participant is asked to recite back whatever words they remember from the new list (interference trial). After doing so, the participant is asked to recite any words that they can recall from List A. After a 20-minute delay, the participant is asked to again recite as many words as they remember from List A. The experimenter then presents the participant with a list of 50 words on paper, and the participant is asked to circle any word that they recognize as having been read to them, and to indicate whether the word was from List A or List B. As with the BVMT-R, the test was administered by a trained graduate student, and alternate validated forms of the test were used at Day 1 and Day 9. Again, participants were randomly assigned to which form of the test they would receive first. The test took approximately 10 minutes to complete for learning trials, and 5 minutes for recall trials. Participants completed questionnaires and the delayed recall trials of the visuospatial memory task during the delay period.

Dependent variables of interest for this task were Trial 1 (T1) scores (total number of List A items correctly recalled after hearing the list the first time; an index of visuospatial working memory) and Delayed Recall (DR) scores (the recall of List A after the 20 minute delay; an index of long-term memory). Change scores for each dependent variable were computed by subtracting the pre-vaccine score from the post-vaccine score.

Executive functioning. The color-word Stroop task (Strauss, Sherman, & Spreen, 2006; Stroop, 1935) is an index of response inhibition, a component of executive functioning defined as the ability to suppress a prepotent response in favor of making a more effortful, task-relevant response (Miyake et al., 2000). In this task, color words are presented in incongruously colored ink (e.g., the word ‘blue’ printed in red ink). Participants are required to name, as quickly as possible, the color in which each word is presented, while attempting to suppress the meaning of the word. Response time to these incongruent trials is compared to response time to control trials

in which participants name the ink color in the absence of conflicting color information. Studies have consistently shown that individuals with major depression exhibit longer response latencies to incongruent trials, larger interference effects (a measure of the difference in response latency to incongruent and congruent trials), and lower accuracy on this task (Snyder, 2014).

In the present study, a computerized version of the color-word Stroop was administered, in which participants indicated the ink color by pressing a corresponding key on the keyboard. The present task included three conditions: (1) incongruent condition, in which the word meaning and ink color conflicted; (2) congruent condition, in which the word meaning and ink color matched; and (3) neutral condition, in which colored rectangles were presented (nonlexical stimuli). Each of the four colors (red, green, blue, and black) were presented in each of the three conditions; these were repeated seven times to equal 84 total trials. The trials presented for each participant were randomly sampled from this pool of 84 possible trials. Before beginning the task, participants completed 10 practice trials with neutral stimuli prior to the start of the task in order to become familiar with the keyboard responding. For both the practice and actual trials, an "X" was flashed on the screen to indicate an erroneous response.

Dependent variables from this task were an interference score (calculated as latency to incongruent trials minus latency to congruent trials). Change in interference from pre- to post-vaccine will be calculated by subtracting the interference score from the pre-vaccine visit from the interference score from the post-vaccine visit.

Attentional Bias. Attentional bias was assessed using a dot probe task with emotional faces (Mathews & MacLeod, 1986). The dot probe task was added to the present study in Fall 2016. In this task, a neutral face and an emotional face are presented simultaneously, side-by-side on a computer screen for a brief, predetermined span of time. A dot then appears on the

screen, in the place where one of the stimuli was previously presented. The participant's task is to use the keyboard to indicate which side of the screen the dot has appeared on. An attentional bias score is calculated as the difference between average response latency when the dot appears behind the neutral image minus average response latency when the dot appears behind an emotional image; positive scores indicate greater attention towards the emotional faces. A unique attentional bias score for each type of emotional stimuli included in the task (e.g., angry, sad) can be calculated to examine biases towards or away from particular emotional valences. Prior work utilizing the dot probe has demonstrated that although never-depressed individuals show an attentional bias towards positive stimuli (e.g., happy faces), individuals with depressive symptoms do not, and can even exhibit a bias *away* from positive stimuli, suggesting an avoidance of positive information (Winer & Salem, 2015). Additionally, depressed individuals have been shown to exhibit a greater attentional bias towards depression-related stimuli (sad faces) compared to nondepressed controls (Peckham et al., 2010). Moreover, recent evidence has suggested that depression may also be characterized by an attentional bias towards threatening stimuli (angry faces) (Sears et al., 2011; Woody et al., 2016).

The dot probe task in the present study consisted of 80 trials. In each trial, the fixation cross was presented for 500 ms, followed by the emotional-neutral face pair (presented for 1000 ms), followed by the probe (presented for 1000 ms). The emotional stimuli consisted of angry, sad, high arousal happy, and low arousal happy faces. Stimuli was drawn from the NimStim database (Tottenham et al., 2009). Prior to the task, participants completed 10 practice trials consisting of neutral-neutral face pairs to acclimate them to the task and keyboard responding. The task took approximately 5 minutes to complete. Attentional bias scores were calculated for each emotion category (sad, angry, happy high arousal, and happy low arousal) by subtracting

the average response time to probes that replaced emotional faces from the average response time to probes that replaced neutral faces. Change scores were computed as attentional bias score for a given emotion at post-vaccine minus the attentional bias score for that emotion at pre-vaccine.

Statistical Analyses

The general analytic approach involved examining associations between within-subject changes in IL-6 and changes in indices of mood, fatigue and vigor, reward processing, cognitive functioning, and attentional bias. Although our initial analytic plan involved examination of Pearson correlations between these change variables, diagnostics revealed evidence of mild violations in the assumptions inherent to Pearson correlation analyses (outliers, normality of variables). Thus, associations between change scores were examined in regression models with robust standard errors, which can adjust the size of standard errors in order to help correct for mild assumption violations.

The exception to this approach was the analysis of the EEfRT data, which requires a multilevel modeling approach due to the trial-by-trial nature of the data (trials within individuals, with each trial associated with a different level of reward and probability. To determine if change in IL-6 was associated with changes in reward motivation as measured with the EEfRT, we used multilevel mixed-effects logistic regression with hard trial choice (yes/no) as the binary dependent variable. A random intercept was included to account for clustering of trials within individuals. To model the effect of the within-subject change in IL-6 from pre- to post-vaccine on within-subject change in hard trial choices, we used person-centered IL-6 (which represents within-subject variability on this variable) as a predictor variable. Our model examined the effect of person-centered IL-6 and its interaction with expected value (hard trial reward magnitude x

probability). Both IL-6 and expected value were continuous variables. The model also included the lower-order main effects of IL-6 and expected value, as well as trial number (continuous variable), which was included as a covariate to control for potential fatigue effects over the course of the task.

Sample size. The study was designed to provide 80% power to detect the effect of within-subject changes in IL-6 on within-subject changes in core processes of depression within the context of influenza vaccination. Sample size estimates were derived based on available effect sizes from prior work, in particular, the effect of the influenza vaccine on IL-6 levels (Tsai et al., 2005), the effect of changes in inflammation on changes in self-reported mood, fatigue, and mental confusion (Wright et al., 2005; Harrison et al., 2009), and the effect of changes in inflammation on changes in neuropsychological test performance (Brydon et al., 2008). No prior work had examined associations between within-subject changes in inflammation and changes in behavioral measures of reward processing or attentional bias, and thus could not inform our power analyses. Sample size estimates were computed using G*Power 3.1.9.2. The results of these analyses suggested that a target sample size of 42 participants should be sufficient to detect significant within-subject associations between changes in IL-6 induced by influenza and changes in depression-related processes.

Results

Sample characteristics

Potential participants were recruited during Fall 2015 and Fall 2016 via study fliers posted around campus and word of mouth. Ninety-three individuals contacted us to express interest in participating in the study. Of these, five were unable to be reached for screening, and 88 were successfully screened. Of the 88 individuals screened, 29 were deemed ineligible (seven were

outside the age range; eight had already received the flu shot; six reported having a chronic health condition; one reported using tobacco; and seven reported currently experiencing symptoms of a cold or flu), and 59 were deemed eligible. Of these eligible individuals, 46 were successfully scheduled and consented (nine were unable to be reached for scheduling; three participants were scheduled but did not show up for their first visit; and one participant was no longer interested after attempting to schedule). Of the 46 individuals consented, three participants withdrew or were excluded after having completed at least one study visit due to having developed an acute illness. Thus, the final sample size consisted of 43 participants. Two further participants were unable to provide blood due to difficulties during the blood draw procedure (inability to access a vein); IL-6 data was thus available for 41 participants.

Detailed information on sample characteristics is provided in Table 1. The sample was 74.4% female and 62% Asian. Participants were on average 18 years old, of normal BMI, and reported minimal symptoms of depression (PHQ-8) and anxiety (GAD-7) at baseline, consistent with the fact that we excluded participants with known depression or anxiety. The majority of participants (79%) reported having received the influenza vaccine in their lifetime, but only 39.5% reported having received the vaccine the prior year.

IL-6 and symptom response to the influenza vaccine

Descriptive statistics of IL-6 are presented in Table 2. A paired sample t-test revealed a significant increase in IL-6 levels from baseline to post-vaccination, $t(41) = -2.77$, $p = .008$, suggesting that influenza vaccination led to a small but significant increase in circulating inflammation (Table 2). The average percentage change in IL-6 from baseline was 41%. Pre- and post-vaccine levels of IL-6 were correlated at $r = .79$. One-way ANOVAs revealed that there was no significant difference in IL-6 levels (baseline, post-vaccine, or IL-6 change) between

individuals who reported having received (n = 17), not received (n = 20), or did not recall whether they had received (n = 4) the influenza vaccine the previous year (ps > .19). Additionally, given the known association between BMI and circulating pro-inflammatory cytokines (Khaodhiar et al., 2004), we examined whether IL-6 was associated with BMI. Indeed, Pearson correlations indicated that BMI was significantly, positively associated with pre-vaccine IL-6, r = .47, p < .05, and post-vaccine IL-6, r = .35, p < .05, but not with the IL-6 change index, r = -.01, *ns*.

There was one participant who exhibited a particularly robust change in IL-6 following vaccination (a 4.2 pg/mL increase). Close examination of this participant's data did not reveal any irregularities or extraneous factors that would account for this increase (e.g., development of an acute illness or infection, or change in lifestyle factors such as major sleep changes, alcohol consumption, or medication taken). Thus, given that an aim of the study was to induce variability in IL-6 in order to be able to understand the effects of IL-6 at varying levels, we did not see a clear justification for removing this individual from our dataset. Still, given that this data point is high on the predictor variable (IL-6) and thus will likely will be a point of high leverage, we will present our primary findings with this datapoint both included and excluded.

To examine whether the vaccine elicited sickness symptoms, we examined the change in symptoms (feeling "sick", headaches, chills, fever, and muscle/joint aches or pains) reported on daily diaries from the day before and day after vaccination. Results of paired sample t-tests indicated that there was no significant change in any of these symptoms following the vaccine (ps>.3), except for muscle/joint aches or pains which exhibited a marginally significant increase (pre-vaccine M = .21, SD = .56; post-vaccine M = .37; SD=.58; t(41) = -1.86, p = .07). Yet, even for muscle/joint aches or pains, the average at post-vaccine was still indicative of a minimal

symptom experience. Additionally, there were no significant associations between change in any of these symptoms and change in IL-6 (*p*s>.3). Finally, we examined reports of arm soreness post-vaccination. The mean arm soreness at post-vaccine was 1.6 (*SD* = .7), suggesting an average level of soreness between "a little sore" and "moderately sore". The post-vaccine level of arm soreness was not significantly related to post-vaccine IL-6 levels ($p = .3$). Thus, overall participants experienced minimal levels of muscle/join aches or pains and arm soreness following the vaccine, and this symptom experienced was not related to level of IL-6 response.

Depressed mood

Descriptive statistics on depressed mood are presented in Table 2. One participant did not complete their post-vaccine daily diary and thus depressed mood scores (as well as other POMS-15 subscale scores) were available for 42 participants. Average levels of depressed mood were low at both timepoints, and a paired samples t-test revealed that there was no significant change in average depressed mood from pre- to post-vaccination, $t(41) = -0.32$, $p = .7$ (Table 2).

To investigate whether there was an association between within-subject change in IL-6 and change in self-reported depressed mood following the vaccine, a regression model was run using robust standard errors. Results revealed that there was no significant association between change in IL-6 and change in depressed mood, $b = .17$, $t(38) = 1.57$, $p = .12$, $R^2 = .02$.

Given prior work showing that endotoxin-induced increases in IL-6 were associated with increases in depressed mood in women only (Eisenberger et al., 2009), in exploratory analyses we examined the association between IL-6 change and change in depressed mood exclusively in female participants ($n = 30$); findings revealed no significant association, $p = .9$.

Fatigue and Vigor

Descriptive statistics on fatigue and vigor are also presented in Table 2. A paired samples t-test revealed that there was no significant change in average self-reported fatigue (POMS-15 fatigue subscale score) from pre-vaccine to post-vaccine, $t(42) = 0.14$, $p = .89$. Similarly, there was not a significant difference in mean vigor from pre-vaccine to post-vaccine; $t(42) = 0.26$, $p = .79$ (Table 2).

The associations between change in fatigue and vigor with change in IL-6 were then examined in regression. Results indicated that there were no significant associations between pre-to-post vaccine change in IL-6 and change in fatigue ($b = -.07$, $t(38) = -.3$, $p = .77$, $R^2 = .002$), or change in IL-6 and change in vigor ($b = -.04$, $t(38) = -.3$, $p=.78$, $R^2 = .001$).

Reward processing

See Table 2 for descriptive statistics of reward processing indices.

Reward learning (PRT). First, to examine whether participants did on average exhibit implicit reward learning over the course of the PRT (developing a response bias towards the more frequently rewarded cue), we examined whether the average response bias in the third (final) block of the task was significantly greater than the average response bias score in the first block. Indeed, paired samples t-tests indicated that the average response bias was greater at block 3 versus block 1 at the baseline visit ($t(40) = 1.9$, $p = .06$; marginally significant) and post-vaccination ($t(40) = 2.6$, $p = .01$; statistically significant). Next, a paired samples t-test was used to test whether there was a significant change in average reward learning (as indexed by change in response bias on the PRT), from pre- to post-vaccine. Results indicated no significant change in average response bias from pre-vaccine to post-vaccine, $t(40) = .74$, $p = .47$ (Table 2).

We then examined whether the within-subject change in IL-6 following the vaccine was associated with the within-subject change in reward learning. Indeed, change in IL-6 was

significantly associated with change in response bias (b = .11, $t(39)$ = 2.11, p = .041, R^2 = .08), such that individuals with a greater increase in IL-6 exhibited a greater increase in reward learning from pre- to post-vaccine (Figure 4). After excluding a high leverage data point, the relationship remained but fell to marginal significance (b = .22, $t(38)$ = 1.79, p = .082, R^2 = .12).

Reward motivation (EEfRT). Descriptive statistics for the average number of hard trials choices made at baseline and post-vaccination are presented in Table 2. To examine whether hard trial choices depended on trial number and expected value (probability*reward value) of the trial, we ran a mixed-effects logistic regression with hard trial choice as the outcome as trial number and expected value as predictors. We also included time (pre/post) as a predictor to examine whether there was a significant change in average reward motivation from pre- to post-vaccine, after accounting for trial number and expected value. As expected, trial number was significantly negatively associated with hard trial choices (b = -.02, z = -3.58, p < .001) such that individuals were less likely to choose hard trials the longer the task went on, suggestive of fatigue effects. Also, expected value was significantly positively associated with hard trial choices (b = 2.09, z = 23.95, p < .001), such that hard trials with a higher expected value were more likely to compel participants to choose to do the hard trial. However, the time variable (pre/post) was not significantly associated with hard trial choices (b = -.15, z = -1.36, p = .17), indicating that there was no significant change in average reward motivation from pre- to post-vaccination.

Next, analyses were run to examine if the within-subject change in hard trial choices from pre- to post-vaccination was predicted by the within-subject change in IL-6 and its interaction with expected value. Results of these analyses are shown in Table 3. Model 1 included trial number, expected value, person-centered IL-6, and an interaction term representing

expected value x IL-6. There was no significant effect of IL-6*expected value on hard trial choices, b = -.07, z = -.35, p = .73. We then dropped the interaction term from the model to examine if there was a main effect of IL-6 (Model 2). There was no significant main effect of change in IL-6 on change in hard trial choices, b = -.12, z = -1.0, p = .32, indicating that within-subject change in IL-6 was not associated with change in hard trial choices on the EEfRT from pre- to post-vaccination.

Cognitive functioning

See Table 2 for descriptive statistics of cognitive functioning indices.

Visuospatial memory (BVMT-R). One participant was excluded from analyses of the BVMT-R due to an administration error. To examine whether average BVMT-R T1 and DR scores changed significantly from pre- to post-vaccine, we ran paired sample t-tests. Findings indicated that there was no significant change in average T1 recall from pre- to post-vaccination; $t(41)$ = -0.9, p = .37. Similarly, there was no significant change in average DR from pre- to post-vaccination, $t(41)$ = -0.65, p = .51 (Table 2).

The association between change in BVMT-R T1 score and change in IL-6 was examined in regression. Results indicated that there was a significant positive association between change in IL-6 and change in T1 score, b = 1.2, $t(38)$ = 2.22 , p = .032, R^2 = .11, suggesting that individuals with larger IL-6 responses following the vaccine exhibited greater improvement in T1 recall from pre- to post-vaccine (Figure 2, left panel). As previously mentioned, one participant exhibited a particularly large change in IL-6 following the vaccine, and thus was identified as a point with high leverage. The regression model was thus re-run excluding this individual, and the relationship remained significant (b = 2.4, $t(37)$ = 2.36, p = .024, R^2 = .14).

The association between change in BVMT-R DR score and change in IL-6 was then examined in regression. Results indicated that there was no significant association between BVMT-R DR score and change in IL-6, $b = .23$, $t(38) = .89$, $p = .38$, $R^2 = .02$.

Verbal memory (RAVLT). There was no significant change in the average RAVLT T1 score from pre-vaccine to post-vaccine, $t(41) = -1.04$, $p = .31$. Similarly, there was no significant pre-to-post change in RAVLT DR scores, $t(41) = -.33$, $p = .74$) (Table 2). Additionally, there were no significant associations between change in IL-6 and change in RAVLT T1 scores ($b = .22$, $t(38) = .79$, $p=.44$, $R^2 = .006$), or change in IL-6 and change in RAVLT DR scores ($b = .04$, $t(38) = .13$, $p = .9$, $R^2 = .0003$).

Given the above described association between change in IL-6 and change in visuospatial working memory (BVMT-R T1 scores), in exploratory analyses we probed whether there was any association between IL-6 levels and verbal working memory (RAVLT Trial 1 scores). In addition to potential effects of within-subject changes in IL-6, it is also possible that overall levels of IL-6 might be associated with memory. To test this, exploratory analyses were run testing if mean IL-6 (average of pre-vaccination and post-vaccination IL-6 levels) predicted change in RAVLT T1 scores. This approach effectively models the between-subject (rather than within-subject) effect of IL-6 on the outcome. These analyses revealed a significant relationship between IL-6 mean and change in RAVLT T1 performance ($b = .62$, $t(38) = 2.52$, $p = .016$, $R^2 = .09$), such that higher levels of IL-6 across the two timepoints was associated with greater improvements in RAVLT T1 scores from pre- to post-vaccination (Figure 2, right panel). There were no data points with unusually high leverage in these analyses.

Executive functioning (Color-word Stroop). One participant had a number of abnormally high latencies and was thus excluded during data cleaning. As a manipulation check,

we examined whether latencies to incongruent trials were longer than latencies to congruent trials; indeed, incongruent trials yielded significantly longer latencies than congruent trials (e.g., at pre-vaccine, congruent trials M = 828 ms, SD = 123 ms; incongruent trials M = 1032 ms, SD = 207 ms; $t(39) = -8.6$, $p < .001$). Participants got significantly faster in their responses to congruent trials from pre-vaccine (M = 829 ms, SD = 123 ms) to post-vaccine (M = 753 ms, SD = 111 ms); $t(39) = 4.8$, $p<.001$, as well as in their responses to incongruent trials from pre-vaccine (M = 1036 ms, SD = 207 ms) to post-vaccine (M = 933 ms, SD = 136 ms); $t(39) = 4.02$, $p < .001$, likely due to practice effects. However, there was no significant change from pre- to post-vaccine on interference scores (latency to incongruent minus latency to congruent trials, an index of inhibition ability), $t(39) = 1.2$, $p = .25$ (Table 2). Thus, although participants got faster on the task overall, they did not exhibit improvements in inhibition ability.

The association between change in IL-6 and change in Stroop interference score was then examined in regression. Results indicated that there was no significant association between Stroop interference change and IL-6 change (b = -10.3, $t(38) = -.78$, $p = .44$, $R^2 = .003$).

Attentional bias

The emotional dot probe task was added to the study in Fall 2016, so data from this task was available for 24 participants. Table 2 provides descriptive statistics for this task. First, we examined whether there were significant attentional biases towards any of the emotional faces (sad, angry, high arousal happy, low arousal happy) at baseline. To do so, we used a t-test to examine whether each attentional bias score was significantly different from zero at baseline. There were no significant attentional biases for sad, happy high arousal, or happy low arousal faces (ps >.3), but the attentional bias score for angry faces was marginally significantly different from zero (M = - 10.02, p = .08), suggesting a marginal attentional bias away from angry faces at

baseline. Next, we examined whether there was a significant change in attentional bias towards any of the emotional faces from pre- to post-vaccine using paired sample t-tests with pre-vaccine and post-vaccine attentional bias scores for each emotion. Results indicated that there was no significant change in average attentional bias for any of the four emotions (*p*s > .3) (Table 2).

Finally, we examined the association between within-subject change in IL-6 and change in attentional bias for each emotion. There was no significant association between IL-6 change and change in attentional bias scores for either angry or sad faces (*p*s >.3). However, there was a significant association between change in IL-6 and change in attentional bias away from happy high arousal faces (b = - 17.4, $t(22) = -3.68$, $p = .001$, $R^2 = .11$), such that individuals with a greater increase in IL-6 following the vaccine exhibited greater avoidance of happy high arousal faces (Figure 3). The scatterplot of this relationship suggested a possible high leverage data point; removing this individual led to the result to fall to non-significance (b = - 30.3, $t(21) = -1.57$, $p = .13$, $R^2 = .06$).

Similarly, there was a marginally significant association between change in IL-6 and change in attentional bias away from happy low arousal faces ($b = -11.7$, $t(22) = -2.04$, $p = .054$, $R^2 = .04$), such that individuals with a greater IL-6 response showed greater avoidance of happy low arousal faces. However, removal of the high leverage case led the results to fall to non-significance ($b = 4.3$, $t(21) = .16$, $p = .88$, $R^2 = .0009$), suggesting that the initially marginally significant finding was reliant on this single data point.

Discussion

The aim of this study was to examine the potential impact of inflammation on core components of depression, including depressed mood, fatigue, reward processing, cognitive functioning, and attentional bias. In a sample of healthy undergraduates, we used a novel

paradigm involving administration of the influenza vaccine to elicit an increase in circulating levels of proinflammatory cytokines (as indexed by IL-6) and examine subsequent changes in mood and behavior.

As expected, participants exhibited a mild but significant increase in circulating levels of IL-6 following influenza vaccination. The magnitude of the IL-6 increase was similar to prior findings (Tsai et al., 2005). The vaccine did not elicit significant physical sickness symptoms (e.g., feeling "sick", headaches), except for a marginally significant increase in reported muscle/joint aches or pains, indicating that participants experienced minimal physical discomfort following vaccination.

Vaccine associated increases in IL-6 were associated with attentional avoidance of happy faces, consistent with hypotheses (but not an attentional bias towards sad or angry faces). Additionally, changes in IL-6 were associated with changes in visuospatial working memory and reward learning, but in the opposite direction as hypothesized, such that increases in IL-6 were associated with improvements in visuospatial working memory and reward learning. Overall higher levels of IL-6 (but not change in IL-6) were also associated with improvements in verbal working memory. Findings indicated no significant associations between changes in IL-6 and changes in depressed mood, fatigue, vigor, executive functioning, or reward motivation.

Attentional bias

Individuals with more robust increases in IL-6 exhibited greater avoidance of positive information, as indexed by attentional biases away from happy faces in the dot probe task. This finding is in line with findings from the depression literature, which have documented avoidance of positive stimuli in dot probe tasks among individuals with depression compared to controls (Winer & Salem, 2015). According to Beck's cognitive model of depression, attentional biases

play a prominent role in depression etiology (Beck, 1967, 1987, 2008). Thus, if mild elevations in inflammation can bias attention away from positive information, this may suggest a key process by which inflammation can contribute to the development of depression.

Why would inflammatory signaling lead to an attentional avoidance of positive information? In the context of acute illness or injury, an organism's priorities are to eliminate pathogens, coordinate healing and recovery processes, and protect itself from further insults or injury while in an already compromised state (Raison & Miller, 2013). Given this agenda, positive information may not be salient, and could even distract an organism from potentially more relevant information in the environment. Additionally, it may be that participants were looking more at the neutral faces versus the happy high arousal faces due to the neutral faces being perceived as more ambiguous and thus requiring more vigilance.

It is unclear however why we found an association between IL-6 response and attentional bias away from happy faces, but not towards sad or angry faces. If a priority of a compromised organism is to protect itself against further environmental threats while in an already vulnerable state, we might have expected to see an attentional bias towards angry faces in the dot probe task. It is possible we did not find an association with angry faces because of the stimulus exposure time used in the dot probe task – we used a stimulus exposure time of 1000 ms, while attentional biases towards angry faces have been shown in some studies to be detectable only at shorter exposure durations (e.g., 500 ms), which are thought to capture the initial orienting response, while longer durations may reflect disengagement processes (Gotlib, Krasnoperova, Neubauer, & Joormann, 2004). We elected to use the longer duration time in our study given that attentional biases towards sad faces have typically been detected at longer durations (Gotlib et al., 2004). However, we did not see an association with attentional biases towards sad faces in

our study, either. We had hypothesized an association between IL-6 and attentional bias towards sad faces based on the only prior study to examine the relationship between inflammatory markers and attentional bias, which found that CRP was cross-sectionally associated with greater attentional bias towards sad faces in a sample of breast cancer survivors (Boyle et al., 2017). Given that ours is the first study to examine an association between exogeneously-induced inflammation and attentional biases, more work is needed to begin to understand the relationship between inflammation and attentional biases. It is possible that we did not find attentional biases towards sad faces due to the level or acute nature of our inflammatory stimulus; studies examining attentional biases following endotoxin and IFN-α could test whether higher and longer-lasting exposure to inflammation would elicit biases towards negative stimuli. Additionally, given that we only had dot probe data for half the sample, we may not have had sufficient power to detect any potentially subtle effects.

Cognitive functioning

We also probed associations between changes in IL-6 and changes in aspects of cognitive functioning, including visuospatial working and long-term memory (as indexed by BVMT-R Trial 1 and delayed recall scores, respectively), verbal working and long-term memory (as indexed by RAVLT Trial 1 and delayed recall scores, respectively), and executive functioning (as indexed by Stroop interference scores). We had hypothesized that increases in IL-6 would be associated with decrements in these aspects of cognitive functioning. However, findings instead indicated that individuals with more robust IL-6 responses exhibited greater *improvements* in visuospatial learning/working memory, as indexed by changes in BVMT-R Trial 1 scores (participants' immediate recall of a display of geometric figures and their spatial location after seeing the display only once for ten seconds). A similar effect was found for verbal

learning/working memory: although we found no association between change in IL-6 and change in RAVLT Trial 1 scores, there was a significant relationship between higher mean IL-6 and higher RAVLT Trial 1 scores, suggesting that increases in IL-6 were associated with *improvements* in verbal learning/working memory. Thus, findings across measures of visuospatial and verbal learning and working memory suggested that greater increases in IL-6 were associated with improvements in learning/]working memory.

A beneficial effect of mild levels of inflammation on learning and memory processes is consistent with findings from animal studies, which have shown that physiological levels of proinflammatory cytokines are necessary for normal learning and memory processes, and that it is only when the magnitude of the inflammatory response passes a high threshold that cytokines may begin to have a detrimental effect on these processes (Yirmiya & Goshen, 2011). Learning and memory processes involve neuroplastic remodeling within the brain; just as the immune system is responsible for tissue remodeling throughout the rest of the body (e.g., wound healing), plasticity-related structural changes in the brain are also facilitated by immune mechanisms, such as axonal pruning processes necessary for synaptic efficiency and neurogenesis (Yirmiya & Goshen, 2011). Thus, when the presence of circulating IL-6 and other immune molecules are increased (to a mild degree), these neuroplastic processes may be executed with more efficiency, thus potentially explaining the improvements in learning and memory found in the present study.

In contrast, we did not find an association between change in IL-6 and change in our indices of visuospatial or verbal long-term memory (BVMT-R delayed recall and RAVLT delayed recall scores, respectively). These null findings were likely due to ceiling effects attributable to the delayed recall trials being too easy for a healthy population of college undergraduate students. Indeed, BVMT-R and RAVLT delayed recall scores at both pre- and

post-vaccination were quite high and with little variability and thus left little room for improvement (see Table 2). The high performance of participants on these tasks suggests that more challenging, innovative tasks may need to be used in order to detect possible effects of mild increases in inflammation on delayed recall in young, healthy samples. For example, while many studies across the endotoxin, IFN-α, and typhoid vaccine paradigms have failed to find effects on standard neuropsychological tests (such as the BVMT-R), Harrison et al. (2014) found that the typhoid vaccine led to significantly poorer spatial memory as assessed using a novel virtual reality task developed as an analog to the Morris water maze used in rodent models; moreover, this effect was mediated by reduced parahippocampal glucose metabolism, a region critical for spatial memory. Thus, future work examining effects of inflammation on long-term memory in healthy populations should look beyond standard neuropsychological tasks (many of which were originally developed to assess cognitive deficits following major insults or neurological disease), and instead consider using novel measures sensitive enough to detect more subtle perturbations in long-term memory ability due to inflammation among neurologically intact individuals.

The association between increases in IL-6 and changes in executive functioning (specifically, inhibition ability) was also examined, as measured by interference scores on the Stroop color-word task. No association was found between change in IL-6 and inhibition ability. This is consistent with previous findings that IFN-α treatment, endotoxin, and typhoid vaccine do not impair inhibition ability as measured with the color-word Stroop (Grigoleit et al., 2010; van den Boogaard et al., 2010; Amodio et al., 2005; Brydon et al., 2008). Despite this preponderance of null findings in the literature, we had persisted in investigating this domain in order to examine if the null findings were the result of failing to examine within-subject associations

(rather than group effects). However, this was not the case, and these null findings – taken together with prior work using the different models of inflammation – suggest that inflammation at varying levels (from the low levels elicited by influenza and typhoid vaccination, to the higher levels elicited by IFN-α and endotoxin), and across acute (as modeled by influenza vaccination, typhoid vaccination, and endotoxin models) and chronic (as modeled by IFN-α) forms, does not impact inhibition ability. It is possible that inflammation may only contribute to executive functioning impairments when coupled with pre-existing depression. This is supported by a study by Drozdz et al. (2008), which found that inhibition ability declined following IFN-α therapy only among individuals who had pre-existing depression, while participants without pre-existing depression improved on the task following IFN-α therapy (Drozdz, Borkowska, Halota & Rybakowski, 2008). Thus, inflammation may not impact inhibition ability directly but rather indirectly but exacerbating pre-existing vulnerabilities. We were not able to examine this possibility in the current study, as we excluded individuals with pre-existing depression. However, future work could examine how inflammation may exacerbate pre-existing depressive processes to contribute to inhibition impairments, and the neurobiological mechanisms for such effects.

Reward processing

Associations between vaccine-associated IL-6 responses and two aspects of reward processing were examined: reward learning (as indexed by PRT response bias scores) and reward motivation (as indexed by EEfRT hard trial choices). For reward learning, contrary to hypotheses, results indicated a positive association between change in IL-6 and change in PRT response bias from pre- to post-vaccination, such that individuals with greater increases in IL-6 exhibited greater increases in reward learning. Given the previously discussed findings that

larger IL-6 responses facilitated learning on the BVMT-R and RAVLT tasks, the finding that changes in IL-6 were positively associated with changes in reward learning may reflect a facilitation effect of IL-6 on basic learning or attention processes, which generalizes across various domains (visuospatial, verbal, and reward learning). Alternatively (or in addition to beneficial effects on general learning processes), the association between IL-6 response and PRT performance could reflect an upregulation of reward processes more specifically. More work is needed to confirm this, as no prior studies have examined the effect of inflammation on behavioral indices of reward learning. Two recent studies found that inflammation exposure led to increased neural responsivity to rewards, supporting the possibility that inflammation can increase reward sensitivity, but this heightened neural reactivity was to social rewards (positive social feedback and viewing images of close others) (Muscatell et al., 2016; Inagaki et al., 2015), rather that the monetary rewards used in the current study. Another recent study found that exposure to influenza vaccination was associated with a sizeable increase in the number of social interactions participants engaged in, suggesting that influenza vaccination may have upregulated social reward seeking behavior (Reiber et al., 2010). The two prior studies that have examined the effects of inflammation on neural responsivity to monetary rewards (received and anticipated) found that inflammation led to attenuated neural responsivity (Capuron et al., 2012; Eisenberger et al., 2010); but these studies were examining the effects of much higher and/or chronic cytokine exposure. One study examined effects of mild inflammatory activation (typhoid vaccination) on reward-related neural activity and found reduced substantia nigra activation, but the reward in this study was novel stimuli (Harrison et al., 2015). Thus, it seems clear from our study and other work that inflammation modulates reward processes, but that the relationship is complex and likely depends on the magnitude and duration of inflammation, the type of reward

(monetary, social, novel), the domain of reward processing (anticipation, motivation, consumption, and learning), and the level of analysis (neural vs. behavioral responsiveness).

No significant association was found between change in IL-6 and change in reward motivation, as indexed by performance on the EEfRT task. Only one prior published study has examined the effect of inflammation on EEfRT performance; this study found that endotoxin exposure led to increased reward motivation, but only when the probability of winning was highest (Lasselin et al., 2016). Given that only one study (using a much stronger inflammatory stimulus, endotoxin) has been published, more studies are needed across the different models of inflammation in order to understand whether or not inflammation modulates reward motivation, and potential moderators of this effect.

Depressed mood

There was no significant change in depressed mood from pre- to post-vaccination, and mean values of depressed mood were low at both timepoints. Contrary to hypotheses, there was no significant association between change in IL-6 and change in depressed mood. It is possible that depressed mood is not elicited by an inflammatory response as mild as the one triggered by influenza vaccination. Endotoxin exposure, which results in an extremely robust inflammatory response, has been shown to elicit depressed mood (Reichenberg et al., 2001; Eisenberger, et al., 2009; Eisenberger, et al., 2010; Moieni et al., 2015). IFN-α treatment also results in a significant increase in depressed mood, but only after weeks of chronic administration, and only in a subset (approximately 60%) of patients, suggesting that inflammation may only elicit depressed mood in the presence of other vulnerability factors (Capuron et al., 2002; Capuron & Miller, 2004; Dowell et al., 2016). Typhoid vaccination—which triggers a much milder, shorter-term inflammatory response—has not been shown to elicit increases in depressed mood. For example,

Strike and colleagues (2004) did not find that typhoid vaccine led to increases in negative mood, but rather that mood improved in the placebo control condition, while staying the same in the typhoid vaccination condition; thus, typhoid vaccination led to attenuated improvements in mood, rather than increases in negative mood. Similarly, Brydon et al. (2009) found that typhoid vaccination only led to negative mood when participants also underwent stress tasks (vaccine x stress led to higher levels of IL-6 compared to the vaccine-only condition); additionally, these increases in negative mood were driven by the confusion and fatigue subscales of the POMS, not the depression-dejection items. Thus, given that depressed mood is reliably seen following immune challenges that stimulate very high and/or chronic elevations in proinflammatory cytokines (endotoxin and IFN-α), but more equivocally exhibited following a more modest inflammatory stimulus (typhoid vaccination), it follows that influenza vaccination (which elicits an even milder inflammatory response relative to typhoid vaccination) may not lead to elevations in inflammation that are robust enough and/or chronic enough to trigger significant changes in depressed mood. It is possible that the level of circulating proinflammatory cytokines may need to surpass some threshold level in order impact neurobiological processes involved in depressed mood. There is evidence that IL-6 may lead to depressed mood by upregulating neural activity in the dorsal anterior cingulate cortex and anterior insula, regions theorized to be part of a 'neural alarm system' that detects threat and elicits responses to impending danger or harm (Eisenberger et al., 2009; Eisenberger & Cole, 2012). It may be adaptive to only set off such an "alarm" in the context of very high and/or persistent elevations in inflammation, when the vulnerability of the organism is a real possibility, in order to avoid the costs associated with overresponsiveness to minimal threats as signaled by minor, short-term bumps in inflammation.

Fatigue and Vigor

Our findings also indicated that there was no significant change in self-reported fatigue or vigor from pre- to post-vaccination, and, contrary to hypotheses, changes in IL-6 were not associated with changes in fatigue or vigor. As with depressed mood, it may be that changes in fatigue and vigor may not result from the modest, short-term elevations in inflammation elicited by influenza vaccination. Although findings from IFN-α and endotoxin studies have reliably shown strong effects of increased fatigue (Capuron et al., 2002; Capuron & Miller, 2004; Capuron et al., 2007; DellaGioia & Hannestad, 2010; Eisenberger et al., 2010), effects due to more mild elevations in inflammation as elicited by typhoid vaccination (while more promising than findings for depressed mood from this model) are mixed. Many of the typhoid vaccine studies measured mood using a composite measure that included items assessing fatigue and vigor, but did not report on the effects of the typhoid vaccine on fatigue and/or vigor separately (Brydon et al., 2008; Brydon et al., 2009; Strike et al., 2004; Wright et al., 2005). Of the studies that have reported on fatigue, two studies found significant increases in fatigue (Brydon et al., 2008; Harrison et al., 2009), but one study only found effects on fatigue when typhoid vaccination was also paired with stress tasks (Brydon et al., 2009). Of the two studies that reported uniquely on vigor, one study found a significant decrease in vigor following typhoid vaccination (Wright et al., 2005), but another study found no effect on vigor (Harrison et al., 2009). Thus, the magnitude of the inflammatory response to vaccination (typhoid or influenza) may not be sufficiently high and/or persistent to trigger the subjective experience of increased fatigue and attenuated vigor.

Strengths and Limitations

The current study has several limitations. First, the study did not include a control group. Without a control group, we cannot say that influenza vaccination caused the increases in IL-6 or

the changes in our outcomes measures. However, given that prior studies have consistently shown increases in inflammatory markers following influenza vaccination (Carty et al., 2006; Christian et al., 2011; Christian et al., 2013; Glaser et al., 2003; McDade et al., 2015; Posthouwer et al., 2004; Tsai et al., 2005) it is reasonable to assume that influenza vaccination indeed elicited the changes in IL-6. Additionally, without a control group, we cannot definitively say that any changes in outcome measures were not the result of non-specific time effects; however, it seems unlikely that time alone (or another third variable) would account for the found associations between within-subject changes in a biological measure and within-subject changes in task performance. Moreover, a strength of our within-subject design was that it allowed us to assess how changes in inflammation may affect changes in depression-related processes directly, instead of comparing the effects of influenza vaccination versus placebo, as in a between-group design.

Future studies in this area may also consider incorporating a measure of stress in the study design. It would have been informative to measure levels of perceived stress at regular intervals in the current study, which would have allowed us to examine how fluctuations in perceived stress (e.g., due to midterms, etc.) might influence the inflammatory response to the vaccine and/or behavioral outcomes. Given prior findings that typhoid vaccination only led to depressed mood when participants also had to undergo laboratory stress tasks (Brydon et al., 2009), inflammation and stress may act synergistically to influence mood and depression relevant processes.

Future work might also benefit from examining the effects of influenza vaccination on mood and behavior within a sample of participants that are currently healthy but with risk factors for depression (e.g., having a history of depression, early life stress, or others). Given that only

up to 50% of participants develop depression even under the most chronic inflammatory conditions - as demonstrated by studies of patients undergoing chronic IFN-α therapy - it is plausible that inflammation may only lead to depression for individuals with pre-existing vulnerability factors (Musselman et al., 2001; Raison & Miller, 2011). Thus, future work that examines the effects of influenza vaccination in samples with one or more risk factors may be more fruitful in informing the inflammation-depression link.

The study also has several conceptual and methodological strengths. We used a multi-faceted assessment of core processes of depression, drawing from the depression literature to identify behavioral tasks that are altered in depressed individuals and may be influenced by inflammation. Thus, the study bridges the depression and inflammation literatures in a novel way. In contrast to prior work which has typically examined effects of inflammation on self-reported symptoms and neural processes, we focused primarily on effects at the behavioral level of analysis, using tasks that assess implicit behavioral and cognitive processes (attentional bias, cognitive functioning, reward processing). This is the first study to examine the potential effects of an inflammatory stimulus on attentional bias and behavioral reward learning, and among the first to examine potential effects on behavioral reward motivation, and thus offers novel contributions to the inflammation literature.

Conclusions

The present study provides evidence for a previously unexplored mechanism—attentional bias—by which inflammatory activity may contribute to the development of depression. The mild increases in IL-6 exhibited following influenza vaccination were associated with an increase in avoidance of positive stimuli; a behavioral pattern theoretically and empirically linked to the onset of depression. Attentional bias thus may be a fruitful path for future work

aimed at understanding the specific depressive processes impacted by inflammation. Additionally, the findings that mild, acute increases in inflammation were not related to impairments but rather improvements in working memory and reward processes (and were not related to depressed mood or fatigue) suggest that inflammation may have very distinct effects at different levels and durations of exposure; levels may need to be very high and/or chronic in duration before beginning to have negative effects on mood, energy, reward and memory processes.

The present study used a novel paradigm – that of influenza vaccination – with the aim of probing the relationship between inflammation and depression-related processes. Although we found novel evidence for a relationship between inflammation and attentional bias, we failed to find associations with many of the other depression-related processes, including processes that have been strongly linked to inflammation in prior work, such as fatigue. Thus, it is possible that influenza vaccination results in elevations in inflammation that are too mild and/or short-term to influence key processes of depression, and thus may not be the most informative model for interrogating the depression-inflammation link. However, this model may still illuminate how more subtle changes in immune activity influence mood and behavior. The present study suggests that mild alterations in circulating inflammatory markers may not have potent effects on mood, energy, or executive functioning, but may be associated with negative changes in attentional bias and the facilitation of some aspects of memory and reward. Thus, this paradigm may be useful for understanding the subtle effects of inflammation on attentional and cognitive processes, and thus provide insight into how attention and cognitive functioning may be altered in the context of acute illness or injury, or psychological stress. Further, this model might also be used to investigate risk factors that upregulate the inflammatory response and/or sensitize an

individual to the effects of inflammation on mood and behavioral processes, with potential implications for understanding inflammation-induced depression.

Table 1

Sample characteristics (N = 43)

Characteristic	***M***	***SD***	***Range***	***n***	***%***
Age	18.5	.74	18 - 22		
Female				32	74.4
Ethnicity					
Non-Hispanic White				7	16.3
Hispanic				9	20.9
Asian				27	62.8
BMI	23.8	3.9	18.5 - 41.3		
PHQ-8	3.79	3.02	0 - 11		
GAD-7	3.59	3.54	0 - 16		
Flu vaccine - lifetime					
Yes				34	79
No				3	7
Unsure				6	14
Flu vaccine - prior year					
Yes				17	39.5
No				21	48.8
Unsure				5	11.6

Table 2

Descriptive statistics of IL-6 and outcome variables at baseline and post-vaccination, as well as change scores

	Baseline			Post-vaccination			Contrast	Change score		
Variable	***M***	***SD***	***Range***	***M***	***SD***	***Range***	**p value[h]**	***M***	***SD***	***Range***
IL-6 (pg/mL)	1.14	.95	.35 – 4.3	1.47	1.2	.46 – 6.3	.008*	.32	.75	-1.4 – 4.2
Depressed mood[a]	.46	.84	0 - 4	.51	.79	0 – 3.33	.75	.05	.95	-3 – 3.3
Fatigue[a]	1.30	1.2	0 – 4	1.28	1.2	0 – 4	.89	-.02	1.1	-2.3 – 3
Vigor[a]	1.62	.90	0 – 3.3	1.59	.94	0 – 3	.79	-.03	.80	-1.7 – 1.7
BVMT-R[b]										
Trial 1	6.9	2.1	2 - 11	7.3	2.4	3 - 12	.37	.45	2.8	-5 – 8
Delayed recall	10.7	1.2	9 – 12	10.9	1.4	7 - 12	.51	.15	1.4	-3 – 3
RAVLT[c]										
Trial 1	8.3	1.8	5 – 12	8.6	2.3	5 - 14	.31	.35	2.1	-4 – 4
Delayed recall	12.8	2.6	4 – 15	13.0	2.1	8 - 15	.74	.2	1.8	-5 – 4
Stroop interference (ms)[d]	204	150	-72 - 631	178	93	8.6 - 357	.25	-27	146	-332 - 328
Dot Probe (Attentional bias scores)[e]										
Happy High (ms)	-3.4	31.7	-47 - 109	.62	35.9	-85 - 63	.67	4.0	45.1	-110 - 76
Happy Low (ms)	1.2	27.6	-42 - 56	12.0	32.8	-72 - 70	.30	10.7	50	-113 - 92
Sad (ms)	7.5	36.8	-58 – 128	5.3	40.2	-80 – 92	.80	-2.2	43	-96 - 70
Angry (ms)	-10	27.1	-63 – 43	-11.9	38.9	-97 – 63	.83	-1.9	43.3	-81 - 79
PRT response bias[f]	.22	.14	-.14 - .58	.19	.22	-.10 - .88	.47	-.03	.28	-.53 – 1.0
EEfRT hard trial choices[g]	18.6	5.1	6 – 28	18.2	4.9	7 - 27	.35	-.44	3.1	-10 - 8

Note. BVMT-R = Brief Visuospatial Memory Test – Revised; RAVLT = Rey Auditory Verbal Learning Test; PRT = Probabilistic Reward Task; EEfRT = Effort Expenditure for Rewards Task. Change scores for all variables were calculated as the post-vaccination value minus the baseline (pre-vaccination) value.

[a]Depressed mood, fatigue, and vigor were assessed with the mean of items from the POMS-15 depressed mood, fatigue, and vigor subscales, respectively. [b]Total possible points for BVMT-R trial 1 and delayed recall trials is 12. [c]Total possible points for RAVLT trial 1 and delayed recall trials is 15. [d]Stroop interference scores were calculated as the average latency (in milliseconds) to incongruent trials minus the average latency to congruent trials. [e]Dot probe scores include attentional bias scores for faces depicting four emotions: happy high arousal, happy low arousal, sad, and angry. Attentional bias scores for each emotion were calculated as the difference between average response latency (in milliseconds) when the dot appears behind the neutral image minus average response latency when the dot appears behind an emotional image; positive scores indicate greater attentional bias towards the emotion depicted. [f]PRT response bias scores are derived from based on signal detection theory in accordance with task guidelines (Pizzagalli et al., 2008). [g]In the EEfRT task, participants can choose to work harder for higher rewards or work less for lower rewards. Hard trial choice scores reflect the average number of hard trial choices made by participants. [h]p value for the contrast between baseline and post-vaccination values (as tested with a paired samples t-test).

*$p < .01$

Table 3

Effect of IL-6 on high-effort task choices in the EEfRT task

Predictor variables	**Model 1**				**Model 2**			
	B	***SE***	***z***	***P***	***B***	***SE***	***z***	***P***
Trial number	-.02	.005	-3.6	<.001	-.02	.005	-3.6	<.001
Expected value	2.09	.09	23.95	<.001	2.09	.09	23.95	<.001
IL-6	-.07	.23	-.24	0.81	-.12	.12	-1.0	.32
IL-6 x expected value	-.07	.20	-.35	.73	---	---	---	---

Results of two mixed-effects logistic regression models using with hard trial choice (no/yes) as the outcome variable. **Model 1** assessed the effect of IL-6 and its interaction with expected value (calculated as trial probability*reward value) on hard trial choices. Results from this model revealed no significant effect of IL-6*expected value on hard trial choices. **Model 2** assessed the main effect of IL-6 on hard trial choices. Results from this model revealed no significant main effect of IL-6 on hard trial choices, indicating that within-subject change in IL-6 was not associated with change in hard trial choices on the EEfRT from pre- to post-vaccination.

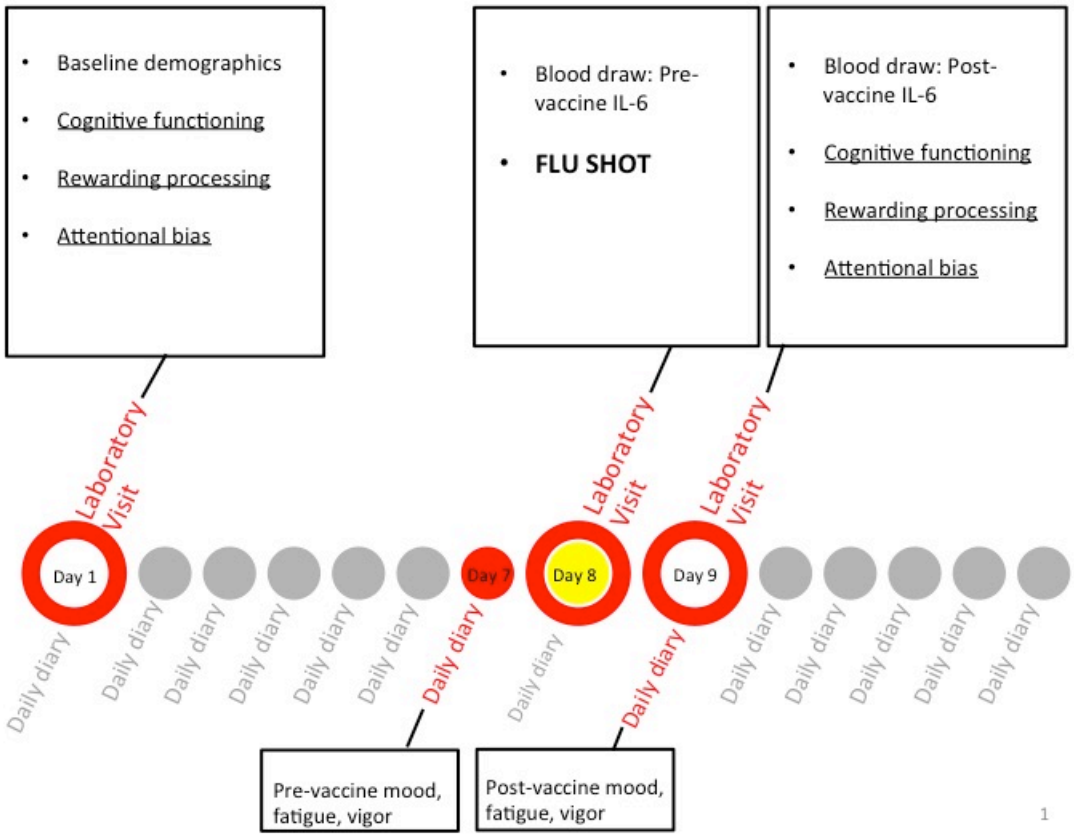

Figure 1. Study design.

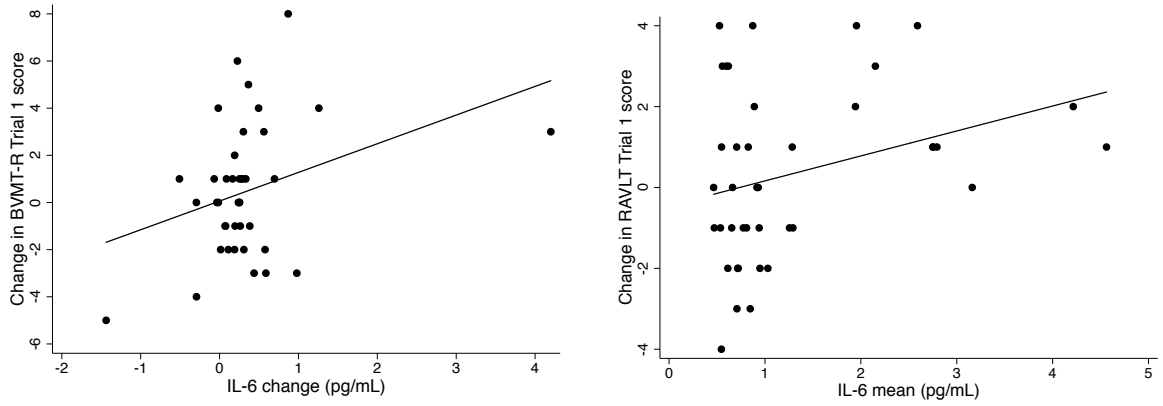

Figure 2. Left panel: Positive linear relationship between change in IL-6 and change in BVMT-R T1 scores, such that individuals with larger vaccine-associated IL-6 responses exhibited greater improvements in visuospatial working memory (p=.032). IL-6 increases may facilitate immediate visuospatial recall. The findings were robust to the removal of a high leverage data point seen to the far right of the graph (without this data point, p=.024). Right panel: Significant positive association between mean IL-6 (average of baseline and post-vaccination IL-6 levels) and change in RAVLT T1 scores, such that individuals with larger vaccine-associated IL-6 responses exhibited greater improvements in verbal working memory (p = .016). Results suggest that higher overall levels of IL-6 may facilitate immediate verbal recall.

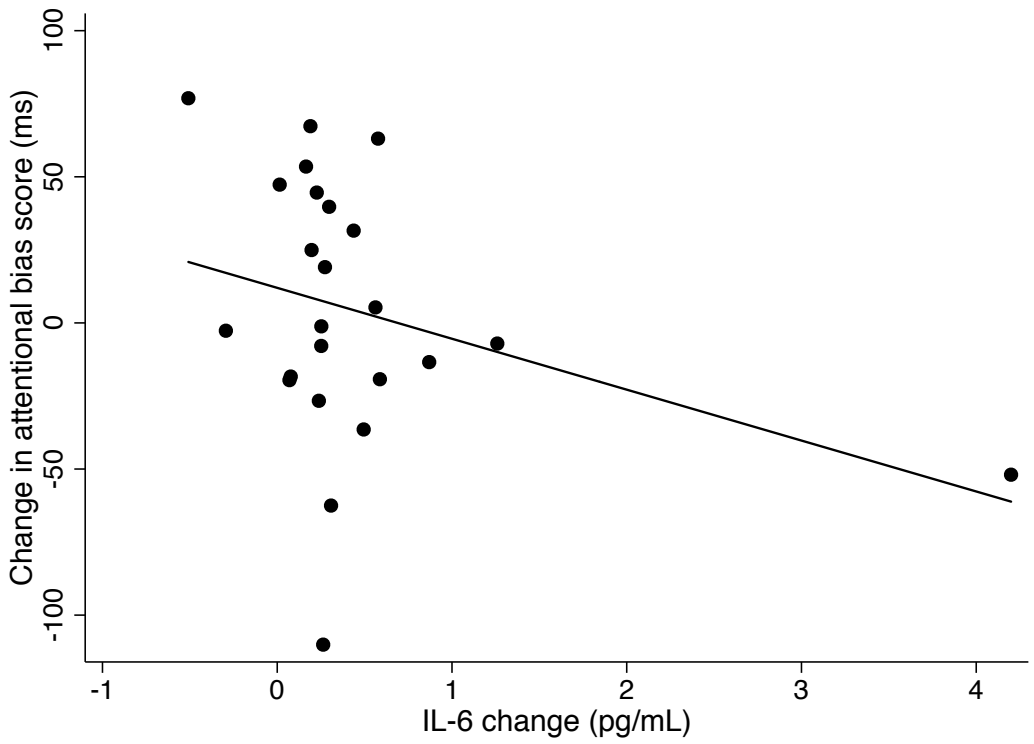

Figure 3. Negative linear relationship between change in IL-6 and change in attentional bias for happy high arousal faces in the dot probe task, suggesting that individuals with larger IL-6 responses to the vaccine exhibited greater change in attention away from happy high arousal stimuli (p = .001). After deleting a high leverage data point (far right on graph), the result fell to non-significance (p = .13).

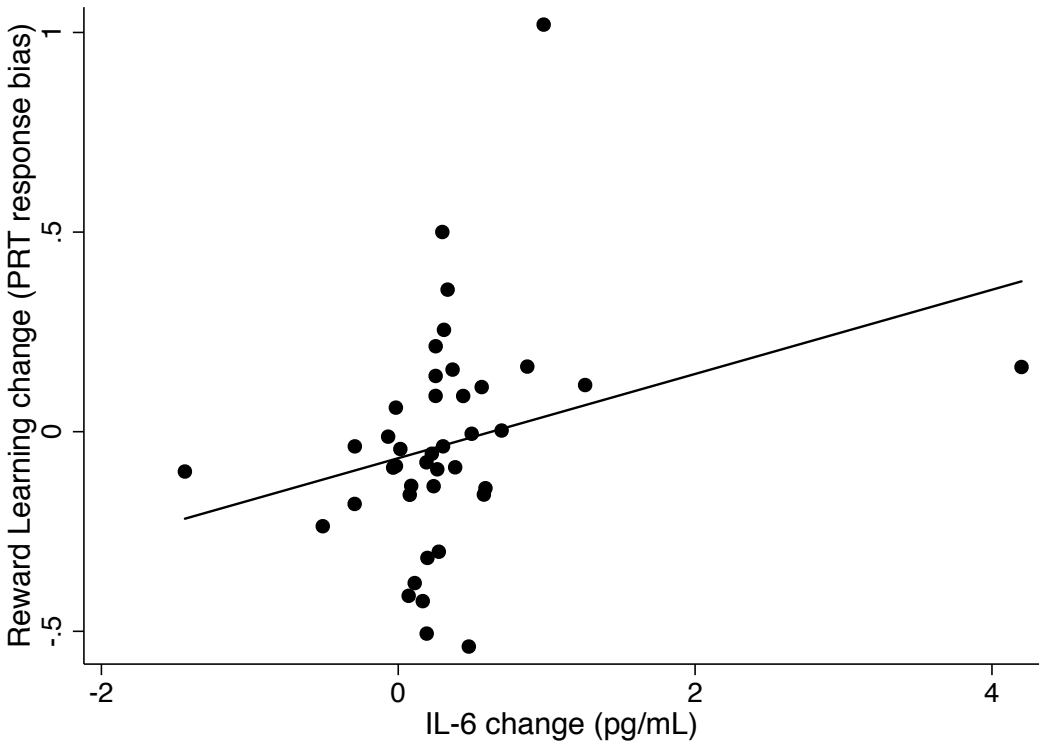

Figure 4. Positive linear relationship between IL-6 change and change in reward learning, as indexed by PRT response bias score (p = .041). The result suggests that individuals with greater increases in IL-6 exhibited a greater increase in reward learning from pre- to post-vaccine. After excluding a high leverage data point the relationship was marginally significant (p=.08).

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