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REVIEW

# Inflammation Effects on Motivation and Motor Activity: Role of Dopamine

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Motivational and motor deficits are common in patients with depression and other psychiatric disorders, and are related to symptoms of anhedonia and motor retardation. These deficits in motivation and motor function are associated with alterations in corticostriatal neurocircuitry, which may reflect abnormalities in mesolimbic and mesostriatal dopamine (DA). One pathophysiologic pathway that may drive changes in DAergic corticostriatal circuitry is inflammation. Biomarkers of inflammation such as inflammatory cytokines and acute-phase proteins are reliably elevated in a significant proportion of psychiatric patients. A variety of inflammatory stimuli have been found to preferentially target basal ganglia function to lead to impaired motivation and motor activity. Findings have included inflammation-associated reductions in ventral striatal neural responses to reward anticipation, decreased DA and DA metabolites in cerebrospinal fluid, and decreased availability, and release of striatal DA, all of which correlated with symptoms of reduced motivation and/or motor retardation. Importantly, inflammation-associated symptoms are often difficult to treat, and evidence suggests that inflammation may decrease DA synthesis and availability, thus circumventing the efficacy of standard pharmacotherapies. This review will highlight the impact of administration of inflammatory stimuli on the brain in relation to motivation and motor function. Recent data demonstrating similar relationships between increased inflammation and altered DAergic corticostriatal circuitry and behavior in patients with major depressive disorder will also be presented. Finally, we will discuss the mechanisms by which inflammation affects DA neurotransmission and relevance to novel therapeutic strategies to treat reduced motivation and motor symptoms in patients with high inflammation.

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## INTRODUCTION

Deficits in aspects of reward processing, motivation, and motor function are common in neuropsychiatric disorders, particularly in patients with major depressive disorder (MDD), bipolar disorder, and schizophrenia (Caligiuri and Ellwanger, 2000; Morrens *et al*, 2007; Pizzagalli, 2014; Treadway and Zald, 2011). These symptoms have been associated with abnormal sensitivity to reinforcement during learning or decision-making and concomitant alterations in dopaminergic corticostriatal circuitry (Hamilton *et al*, 2011; Kaiser *et al*, 2015; Treadway and Pizzagalli, 2014). These findings imply acute dysfunction within mesolimbic dopamine (DA) pathways, although the cause of such alterations is unclear.

One candidate mechanism is inflammation. A significant proportion of patients with psychiatric disorders exhibit a chronic, low-grade inflammation, as measured by increased peripheral and central inflammatory cytokines, inflammatory mediators, and acute-phase reactants (for review, see Barbosa *et al*, 2014, Felger and Lotrich, 2013b, Goldsmith *et al*, 2016b and Haroon *et al*, 2012). Findings from numerous laboratories have consistently indicated that innate immune activation and the release of inflammatory cytokines preferentially affect reward circuitry and basal ganglia DA to contribute to reduced motivation and motor slowing (Brydon *et al*, 2008; Capuron *et al*, 2007; Capuron *et al*, 2012; Eisenberger *et al*, 2010; Felger and Miller, 2012; Harrison *et al*, 2015b; Majer *et al*, 2008). In humans, this evidence stems primarily from studies in healthy volunteers acutely administered cytokine inducers such as endotoxin or typhoid vaccination (Eisenberger *et al*, 2010; Harrison *et al*, 2015b), and from patients chronically administered inflammatory cytokines (eg, interferon (IFN)-$\alpha$) as therapy for some cancers and infectious diseases (Capuron *et al*, 2007; Capuron *et al*, 2012). Preclinical data in non-human primates and rodents also suggest that the effects of inflammation on reward circuitry and motivation are mediated by cytokine-induced reductions in striatal DA (Felger *et al*, 2013c; Kitagami *et al*, 2003; Nunes *et al*, 2014).

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Symptoms related to reduced motivation and motor slowing are notoriously difficult to treat in patients with psychiatric disorders and in patients administered chronic IFN-α (Capuron *et al*, 2002a; Morrow *et al*, 2003; Raison *et al*, 2005b; Shelton and Tomarken, 2001). Furthermore, a relationship exists between high levels of inflammation and treatment resistance, particularly in depression (Cattaneo *et al*, 2013; Lanquillon *et al*, 2000; Raison *et al*, 2013a; Sluzewska *et al*, 1997). Moreover, symptoms of anhedonia and motor slowing are difficult to treat with selective serotonin reuptake inhibitors (SSRIs; Dunlop and Nemeroff, 2007; Rush, 2007; Targum and Fava, 2011; Trivedi *et al*, 2008), suggesting that other neurotransmitter systems, such as DA, may be involved in SSRI-resistant, inflammation-related symptoms (Nutt *et al*, 2007). Nevertheless, classical stimulant medications that increase DA release and/or block DA reuptake have demonstrated limited long-term efficacy in the treatment of fatigue in patients with inflammation-associated medical illnesses (Butler *et al*, 2007; Mar Fan *et al*, 2008; Moraska *et al*, 2010). Therefore, a better understanding of the mechanisms by which inflammation and cytokines may affect DA function will inform strategies to improve the treatment of symptoms related to reduced motivation and motor slowing in medically ill and medically healthy individuals.

This review will highlight the wealth of clinical and translational work demonstrating the impact of peripheral inflammation on DA, corticostriatal circuitry, motivation, and motor function following acute or chronic administration of cytokines or inflammatory stimuli. Furthermore, studies involving administration of inflammatory stimuli have informed recent work in patients with MDD, which has revealed similar relationships between increased peripheral cytokines and other inflammatory markers, alterations in DA-relevant neurocircuitry, motivational deficits, and psychomotor slowing (Felger *et al*, 2016; Goldsmith *et al*, 2016a). Although many aspects of reward-related behaviors, such as reinforcement learning, have only begun to be explored in relation to increased inflammation, these concepts may be relevant to future studies examining relationships between DA and motivated behavior in the context of increased inflammation, and are reviewed in the context of health and psychiatric illness. Mechanisms by which inflammation may affect DA and corticostriatal circuitry, as well as implications for the treatment of inflammation-related behavioral symptoms, are also discussed.

## NORMAL AND ABNORMAL DA FUNCTION IN THE CONTEXT OF MOTIVATION AND PSYCHOMOTOR FUNCTION

### Striatal DA, Motivation, and the Value of Action

DA's basic roles in approach-related behavior, including effort expenditure (Correa *et al*, 2002), reinforcement learning (Schultz, 2015), and motor control (Bernheimer *et al*, 1973; Romo and Schultz, 1990), have been thoroughly covered in the literature and will only be briefly reviewed here. Initial evidence for these functions occurred primarily through electrophysiological techniques of DA cell activity, DAergic lesions, and pharmacological manipulations at DAergic terminal field regions. This body of work has led to several widely accepted principles regarding DA's various functions. These include the idea that nigrostriatal DA neurons projecting to dorsal striatum and ventrolateral putamen are principally engaged in motor control (Guo *et al*, 2014; Puryear *et al*, 2010), whereas DA neurons within the ventral tegmental area (VTA) projecting to ventral striatum are primarily involved in reward processing. Within the VTA, it has further been suggested that phasic DA is responsible for encoding reward prediction errors (RPEs) capable of driving reward-related reinforcement learning (Schultz, 2002) via receptor subtype-dependent potentiation or depression within 'go' and 'no-go' pathways in the striatum (Frank and O'Reilly, 2006; Frank *et al*, 2004; Reynolds *et al*, 2001). In contrast, tonic DA in the striatum has been hypothesized to have a key role in motivation (including aversive motivation; Salamone and Correa, 2012; Salamone *et al*, 1997), effort (Correa *et al*, 2002), and response vigor (Niv *et al*, 2007; Phillips *et al*, 2007). In the case of DA's role in effort expenditure, a large number of studies have demonstrated that local blockade of DA signaling through either 6-hydroxy DA lesions (Salamone *et al*, 2001) or vesicular monoamine transport inhibition (Nunes *et al*, 2013) can shift an animal's preference away from preferred rewards requiring greater effort.

It is also worth highlighting the now well-established distinction between manipulations of DA on processes related to reinforcement learning and motivation as compared with hedonic reactions. As has been well documented elsewhere, DA modulation appears to selectively influence various forms of approach-related behavior in the context of reward and reward-predicting cues, whereas having little effect on hedonic reactions to reward receipt (for reviews, see Berridge, 2007 and Berridge and Kringelbach, 2013). Further, the near total absence of DA does not ablate the expression of putatively hedonic preferences, such as sucrose preference (Cannon and Palmiter, 2003), provided that behavioral effort is minimal (Salamone *et al*, 2001).

Human neuroimaging and pharmacological studies have largely corroborated this preclinical literature, with clear evidence that BOLD signal within both the DAergic midbrain (D'Ardenne *et al*, 2008) and ventral striatal terminal field regions (O'Doherty *et al*, 2004; Schönberg *et al*, 2007) exhibit fluctuations in response to rewarding outcomes consistent with RPE models, and meet necessary axiomatic requirements of a true RPE signal (Rutledge *et al*, 2010) that can be modulated by DAergic agents (Pessiglione *et al*, 2006). Also in keeping with animal studies, effort expenditure for rewards can be increased or decreased through either potentiation (Wardle *et al*, 2011) or attenuation (Venugopalan *et al*, 2011) of DA levels, and individual

differences in striatal DA release predict effort-related preferences (Treadway *et al*, 2012b).

Human studies also support an absence of DAergic effects on hedonic responses (Berridge and Kringelbach, 2008). Despite early results suggesting that DA-acting drugs such as amphetamine and cocaine could induce euphoric mood states (de Wit *et al*, 1986), and that such euphoria was correlated with amphetamine-induced DA release in the striatum (Drevets *et al*, 2001), further data suggested that these effects may result from DA stimulation of opioid-rich 'hedonic hotspots'. For example, when amphetamine is taken in conjunction with an opioid antagonist, euphoria is significantly diminished (Jayaram-Lindstrom *et al*, 2004). In contrast, subtler augmentations of DA, such as L-3,4-dihydroxyphenylalanine (L-DOPA) administration, show no effect on hedonic response, despite clear modulation of motivation and response vigor (Beierholm *et al*, 2013; Liggins *et al*, 2012; Sharot *et al*, 2012; Sharot *et al*, 2009). Further, transient reduction of DA increased subjective reports of boredom and apathy, with no effect on affective ratings (McLean *et al*, 2004; Venugopalan *et al*, 2011).

Within the past 10 years, however, new discoveries have revealed some unexpected complexities to these traditional boundaries. First, there is clear evidence from both human and primate electrophysiological studies that nigrostriatal DA neurons also exhibit many of the phasic RPE-type signals previously believed to exist primarily within the ventral striatum (Varazzani *et al*, 2015; Zaghloul *et al*, 2009), blurring the line between DA's putatively distinct roles in movement and reward. Conversely, whereas nigrostriatal DA projections are thought to primarily regulate motor function, electrophysiologic, and optogenetic studies have revealed that DAergic neurons in the VTA may also contribute to initiation of locomotor activity (Guo *et al*, 2014; Puryear *et al*, 2010), which may reflect motivational aspects of motor output. In addition, the discovery of heterogeneous populations of DA neurons within the VTA that selectively respond to either rewards or punishments and project either to ventral striatum or medial prefrontal cortex (mPFC), respectively, raises questions about the long-held view that DA neurons' primary response to negative outcomes was limited to transient 'dips' in firing (Lammel *et al*, 2011; Lammel *et al*, 2012). Even more strikingly, optogenetic induction of phasic burst firing in DA cells that project to nucleus accumbens (NAcc) during stress produced a depressive phenotype in mice, whereas the same stimulation applied to VTA DA neurons projecting to mPFC had no effect (Chaudhury *et al*, 2013), further highlighting the functional importance of these heterogeneous DA populations.

Using fast-scan voltammetry in the striatum, one critical study in recent years isolated a new 'ramping' DA signal associated with active goal pursuit (Howe *et al*, 2013). The slope of these DAergic 'ramps' appeared to encode activity-dependent proximity to a goal and seemed to confound the classic phasic/tonic dichotomy. Even more recently, a study combining reinforcement learning with both go and no-go responses found that the strength of DAergic RPE signaling in the striatum was heavily moderated by whether go or no-go responses were required to harvest a reward following a reward-predicting cue (Syed *et al*, 2016). Expanding on these results, Hamid *et al* (2016) used extended analysis of striatal DA release over repeated trials to show that DA ramps encoded an expected value of action, whereas short-term phasic bursts and dips reflected prediction error updates to these expected value estimates (Collins and Frank, 2016).

Taken together, these exciting new results further refine our understanding of DA's role in approach-related behavior as well as the implications of disruptions within DA-related circuitry. Specifically, they suggest that alterations to striatal DAergic tone as well as inappropriate firing patterns may have diverse contradictory effects on motivational states, reinforcement learning, and movement. This broad array of consequences to DAergic alterations may contribute to the challenge in identifying stable deficits both across and within clinical diagnostic groups. Indeed, one of the potential advantages of focusing on motivational impairments in the context of inflammation–DA interactions is that it may point to a more precise phenotype with greater homogeneity at the level of pathophysiology.

## Reduced Motivation and Psychomotor Function in Psychiatric Disorders—Behavioral Evidence and Clinical Correlates

As the preclinical literature has progressively refined our understanding of the specific behaviors and information processing that is affected by DA signaling, clinical researchers have been increasingly challenged to establish more precise measure of reward-related symptoms. In the diagnosis of MDD, for example, loss of interest, decreased sexual drive, fatigue, and psychomotor slowing have been viewed as distinct depressive symptoms (Feighner *et al*, 1972), whereas the single criterion of anhedonia has been defined so broadly that it can be met through demonstrated 'loss of pleasure *or* interest' (italics added) in previously enjoyed activities. This lumping of pleasure and interest/motivation echo the distinction between 'wanting' and 'liking' aspects of reward behavior, as it pertained to DA function, and is just one example of how current diagnostic criteria may be out of step with neurobiological reality (Treadway and Zald, 2011; Treadway and Zald, 2013). Similarly, the putatively distinct symptoms of reduced motivation, fatigue, and psychomotor slowing in depression may share a common mechanism in terms of inflammation effects on DA availability (as argued in the sections 'Inflammation-induced impairments in motivation and motor activity—links to striatal dopamine function' and 'Mechanisms of inflammation effects on dopamine synthesis and release' below)—at least for a subset of depressed patients (Raison and Miller, 2011).

In seeking to refine the assessment of reward-related deficits in psychiatric disorders, a number of self-report and behavioral measures have been developed in recent years that

attempt to isolate or dissociate various subconstructs of reward. This includes behavioral measures of effort expenditure (Gold *et al*, 2013; Hartmann *et al*, 2015; Hershenberg *et al*, 2016; Treadway *et al*, 2009; Wolf *et al*, 2014), affective responses to positive stimuli (Bylsma *et al*, 2008; Dichter *et al*, 2010; Gold *et al*, 2008), and reinforcement learning (Pizzagalli *et al*, 2008) as well as self-report measures that seek to dissociate aspects of anticipation, motivation and enjoyment (eg, Cooper *et al*, 2008; Gard *et al*, 2006).

Armed with these purer measures, researchers have begun to clarify the nature of reward-related deficits in psychopathology as well as evidence for DA involvement. In unipolar depression, several studies have found evidence for reduced physical effort expenditure in exchange for monetary rewards (Hershenberg *et al*, 2016; Treadway *et al*, 2012a; Yang *et al*, 2014). In a related effort paradigm using a handgrip apparatus, Clery-Melin *et al* (2011) observed that patients exerted less physical force than controls and were less responsive to monetary incentives. Within these patient samples, relationship between reported anhedonic symptoms and effortful performance has been mixed. Several studies have reported expected negative associations between effortful responses and anhedonic symptoms (Hershenberg *et al*, 2016; Treadway *et al*, 2012a; Yang *et al*, 2014), yet in several instances there was either no observed relationship (Clery-Melin *et al*, 2011) or a an unexpected positive relationship between effort and total BDI scores (Treadway *et al*, 2012a), although further analysis suggests this might be driven by a positive association between self-criticism end effortful performance (Hershenberg *et al*, 2016). Of these studies, only one study to date has also examined effort-related behavior in patients diagnosed with bipolar disorder (currently depressed), and observed a near identical pattern when compared with unipolar patients (Hershenberg *et al*, 2016).

In schizophrenia, an even greater number of studies have found evidence for effort-related abnormalities using a variety of effort-tasks (Barch *et al*, 2014; Fervaha *et al*, 2013; Gold *et al*, 2013; Hartmann *et al*, 2015; McCarthy *et al*, 2016; Reddy *et al*, 2015; Strauss *et al*, 2016). Interestingly, although some studies have detected an overall decrease in effort expenditure (Hartmann *et al*, 2015; McCarthy *et al*, 2016; Wolf *et al*, 2014), the most consistent group differences observed across studies have implicated deficits in effort allocation rather than effort expenditure (Barch *et al*, 2014; Gold *et al*, 2013; Horan *et al*, 2015; Reddy *et al*, 2015). That is, schizophrenia patients may not choose to expend less effort overall, but they appear to be significantly less sensitive to reward-related information when choosing when to expend effort. Although the precise role for DAergic alterations in these effort allocation deficits remains unknown, the aberrant salience model (Winton-Brown *et al*, 2014) would predict that failure of DA neurons to response appropriately to reward-predicting cues could result in sub-optimal effort allocation.

As with depression, the associations between performance on effort-related measures and measures of negative symptoms in schizophrenia have been mixed. Several studies reported relationships with between reduced effort and negative symptoms (Hartmann *et al*, 2015; Strauss *et al*, 2016; Wolf *et al*, 2014), whereas others found that the strongest relationships were between measures of poor effort allocation and negative symptoms (Barch *et al*, 2014; Reddy *et al*, 2015). Still other studies found that greater negative symptoms severity as assessed by clinical interview measures such as the Clinical Assessment Interview for Negative Systems (CAINS; Kring *et al*, 2013) was associated with *greater* effort expenditure (McCarthy *et al*, 2016). Although the causes of this discrepancy are not entirely clear, one possibility suggested by Strauss and Gold is that schizophrenia patients are often limited in their ability to accurately report on and forecast their motivational states (Strauss and Gold, 2012). This hypothesis has found recent support using ecological-momentary assessment (EMA) methods. One study found that patients reported engaging in significantly fewer effortful daily activities, despite reporting greater anticipation (Gard *et al*, 2014). Even more striking, a second study found that effort performance during a laboratory task was predictive of negative symptoms as assessed by EMA, but neither was correlated with negative symptoms as measured by the CAINS (Erin Moran, personal communication).

In addition to deficits in motivation, psychomotor slowing is a prominent feature of both mood disorders and schizophrenia, and has been shown to correlate with symptoms of anhedonia and amotivation (Heinz *et al*, 1998; Lemke *et al*, 1999; Stein, 2008). Motor retardation can be assessed in psychiatric patients using objective measures of psychomotor processing or reaction time and tests of fine motor speed, which have been shown to be more sensitive than self-reported symptoms and clinician ratings (Bennabi *et al*, 2013; Caligiuri and Ellwanger, 2000; Morrens *et al*, 2007). In schizophrenia, psychomotor symptoms have been shown to correlate with negative symptoms, such as apathy and amotivation, as well as with depressive symptoms, and confer significant impairments in function and increased patient burden (Ananth *et al*, 1991; Heinz *et al*, 1998; Morrens *et al*, 2007). Motor deficits are also observed in patients with bipolar II, as well as in bipolar I during the depressed phase (Bennabi *et al*, 2013; Mitchell *et al*, 2001). Interestingly, objective measures of motor function have revealed different patterns of motor deficits in patients with unipolar depression versus bipolar II disorder. Bipolar patients showed greater impairment in scaling of movement velocity in anticipation of changing target distances (similar to bradykinesia seen in patients with Parkinson's disease (PD)) and patients with unipolar depression primarily exhibited deficits in tests of psychomotor processing speed that probe more cognitive aspects of motor function (eg, digit symbol substitution and trail making tests; Caligiuri and Ellwanger, 2000). Indeed, differential performance on these tests classified unipolar and bipolar depression with a high degree of accuracy (Caligiuri and Ellwanger, 2000). Moreover, greater severity of motor impairments has been

associated with increased depression severity and with treatment outcomes (Bennabi *et al*, 2013; Caligiuri and Ellwanger, 2000). Although findings have been mixed due to differences in the definition and measurement of psychomotor symptoms, as well as the use of different drugs and variable doses within a class, evidence suggests that agents with broad pharmacologic actions (eg, tricyclics, combined serotonin–norepinephrine or norepinephrine–DA reuptake inhibitors) may be more efficacious in the treatment of psychomotor retardation than SSRIs (Buyukdura *et al*, 2011; Parker *et al*, 2010). Finally, patients with severe depression and psychomotor retardation are at increased risk for the development of neurological disorders such as PD (Leentjens *et al*, 2003; Walter *et al*, 2015), which is also thought to involve inflammation effects on DA neurons (Lotharius *et al*, 2005). Therefore, objective measures of psychomotor slowing may serve as excellent behavioral markers for the effects of inflammation on corticostriatal circuitry and DA in patients with psychiatric illness.

## Reduced Motivation and Psychomotor Function in Psychiatric Disorders—Links to Striatal DA Function

Given robust evidence that striatal DA is necessary to overcome effortful response costs, combined with repeated observations of altered motivation and psychomotor behavior in psychiatric patients with anhedonia, a growing body of work has sought to link these symptoms to alterations in DAergic circuitry. These studies have included pharmacological probes to enhance or reduce DA availability, behavioral paradigms believed to engage DAergic activity or neurochemical measures of DA-related proteins.

In the case of functional imaging, early functional magnetic resonance imaging (fMRI; and non-imaging) studies frequently focused on passive consumption of positive stimuli (eg, see Keedwell *et al*, 2005, Mitterschiffthaler *et al*, 2003 and Surguladze *et al*, 2005). These studies observed altered neural responses primarily in mPFC, an area believed to support encoding of the hedonic impact of rewarding stimuli (Berridge and Kringelbach, 2013; Hare *et al*, 2008). As researchers began to focus more specifically on DAergic mechanisms, an increasing number of functional imaging studies have turned to paradigms that assess striatal responses to reward-predicting cues or reward feedback, both of which have been linked to striatal DA (Ferenczi *et al*, 2016; Knutson and Gibbs, 2007). These latter approaches have been mostly consistent in their observation of blunted striatal responses to reward outcomes or reward-predicting cues in MDD patients (Dichter *et al*, 2009; Forbes *et al*, 2009; Gotlib *et al*, 2010; Pizzagalli *et al*, 2009), and these initial findings have been replicated in recent studies with larger patient samples. Indeed, one recent study of over 1500 adolescents found that reduced ventral striatal activity during reward anticipation was associated with clinical or subclinical depression, and that lower ventral striatal activity in non-depressed teens at the time of scanning was predictive of developing depressive symptoms over a 2-year follow-up period (Stringaris *et al*, 2015). In addition to neural responses to anticipation, a second recent study identified a failure in the expected temporal shift of striatal responses to reward cues from reward outcomes as a task was learned, a pattern that was specific to patients with greater anhedonia (Greenberg *et al*, 2015).

In schizophrenia, even greater evidence exists for altered striatal signaling during reward anticipation and RPEs. To date, the most reliable decreases in ventral striatal activity have been observed during periods of reward anticipation (for a recent meta-analysis, see Radua *et al*, 2015), which have also been linked to reduced effortful behavior in schizophrenia (Wolf *et al*, 2014). In addition, recent work has demonstrated both a blunting of neural prediction errors to contextually relevant cues (Morris *et al*, 2011) as well as behavioral evidence for enhanced prediction error learning for irrelevant stimuli (Hannestad *et al*, 2012b; Williams *et al*, 2013). These findings are consistent with predictions from the aberrant salience hypothesis, which predicts that both positive and negative symptoms are linked to irregular striatal DA systems that may fail to appropriately respond to meaningful reward incentives (Winton-Brown *et al*, 2014). Interestingly, transdiagnostic studies comparing groups of patients with schizophrenia and depression have found similar decreases relative to controls for both reward anticipation (Arrondo *et al*, 2015) and prediction error signaling (Gradin *et al*, 2011), with little evidence of clear differences between patient groups.

As a global measure of neural activity, fMRI studies demonstrating alterations of striatal activity can provide only circumstantial evidence for DAergic impairment. Studies combining functional imaging with pharmacological manipulations of DA systems can therefore provide further support for the role of DA in observed group differences. Hasler and colleagues used $\alpha$-para-methyl-tyrosine to temporarily deplete DA in patients with current MDD, and found that this produced a significant increase in glucose consumption in ventral striatum (Hasler *et al*, 2008). Further implicating some form of DAergic depletion in depression is the observation that depressed patients experience a much stronger affective response to amphetamine than controls (Tremblay *et al*, 2002; Tremblay *et al*, 2005), which is known to be linked to the magnitude of striatal DA release (Drevets *et al*, 2001). Of relevance to schizophrenia, a recent study tested the effects of methamphetamine administration on RPE signals in healthy controls and found that amphetamine significantly disrupted striatal prediction error encoding, consistent with a role for DA in prediction error abnormalities observed in schizophrenic patients (Bernacer *et al*, 2013).

To further test for DA abnormalities, additional studies have used positron emission tomography (PET) with DA-specific ligands, including measures of D1 and D2-type receptors, DA synthesis capacity, and the DA transporter (DAT). In depression, these studies have been fairly mixed, with little clear evidence supporting gross alterations in expression of DA-related proteins (for a recent review, see

Treadway and Pizzagalli, 2014). In some cases, increased striatal D2/D3 receptor binding has been shown to occur in heterogeneous depressed samples (D'Haenen and Bossuyt, 1994; Shah *et al*, 1997), whereas other studies have found no change (Hirvonen *et al*, 2008; Parsey *et al*, 2001). Importantly, null findings have occurred in unmedicated samples, with one additional small study reporting changes in D2-like binding following treatment with SSRIs (Klimke *et al*, 1999). One study reported reduced D1 availability in left middle caudate (Cannon *et al*, 2009), but this finding has not yet been replicated. In addition, only a few studies have looked at symptom-specific relationships with DA proteins. Interestingly, two such studies found evidence for reduced DA synthesis capacity in the striatum only in depressed individuals with flat affect or psychomotor slowing, but not in depressed individuals without these symptoms (Bragulat *et al*, 2007; Martinot *et al*, 2001).

In schizophrenia, PET imaging measures suggesting altered DA function have been much more robust, with significant evidence for increased striatal DA synthesis capacity and amphetamine-induced release (Abi-Dargham *et al*, 1998; Fusar-Poli and Meyer-Lindenberg, 2012). Importantly, these effects are in the opposite direction as those observed in depression or following exposure to an inflammatory stimulus (as discussed below). That said, the overwhelming evidence of blunted striatal responses to reward-related stimuli in schizophrenia—whereas not a direct measure of DA—strongly suggest that the enhanced DA synthesis capacity is likely dysregulated in the striatum, which may contribute to negative symptoms.

In sum, current conceptualizations of DA signaling suggest a critical integration of value and action. This view strongly supports the hypothesis that alterations within DA systems would produce changes in motivation and psychomotor function. A large literature now exists supporting the presence of altered reward-related behavior and associated striatal responses in clinical populations. The question remains, however, as to how these putatively DAergic abnormalities may develop, and whether they might be related to increased inflammation.

## INCREASED INFLAMMATION IN PSYCHIATRIC DISORDERS

### Peripheral and Central Cytokines, and Acute-Phase Reactants

A growing body of evidence suggests that inflammatory mediators and cytokines are increased in a number of patients with psychiatric disorders, which may contribute to DAergic dysfunction and behavioral changes in these patients. Numerous studies have reported increased circulating inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), their soluble receptors, and acute-phase reactants, such as C-reactive protein (CRP), in patients with MDD (Maes, 1999; Maes *et al*, 1992; Sluzewska, 1999). These findings have been corroborated by meta-analyses (Dowlati *et al*, 2010; Howren *et al*, 2009). Although mood disorders may have complex pathophysiology with heterogeneous etiologies, it is thought that increased inflammation may be involved in the disease process and contribute to discreet symptomologies in a subset of patients. Indeed, recent studies have indicated that high inflammation (plasma CRP concentrations $>3$ mg/l, as defined by the American Heart Association; Ridker, 2003) is consistently found in 20–40% of patients with MDD, with higher concentrations observed in patients who are resistant to standard antidepressant therapies (Felger *et al*, 2016; Haroon *et al*, 2016; Raison *et al*, 2013a; Raison *et al*, 2013b; Rapaport *et al*, 2016). Similar increases in inflammatory cytokines and acute-phase reactants have also been reported in patients with bipolar disorder and schizophrenia, including meta-analyses (Goldsmith *et al*, 2016b; Miller *et al*, 2011; Potvin *et al*, 2008). Increased inflammatory cytokine concentrations in the cerebrospinal fluid (CSF) of patients with unipolar and bipolar depression, and schizophrenia have also been observed (Garver *et al*, 2003; Levine *et al*, 1999; Schwieler *et al*, 2015; Soderlund *et al*, 2011; Soderlund *et al*, 2009). In MDD, CSF cytokines have been shown to be associated with the severity of depression or with the change in symptoms in response to successful treatment (Levine *et al*, 1999; Lindqvist *et al*, 2009; Martinez *et al*, 2012). In schizophrenia, increased cytokines have been associated with delayed treatment response (Garver *et al*, 2003), and in bipolar disorder, they are higher in patients that have had more recent manic or hypomanic episodes (Soderlund *et al*, 2011).

### Gene Expression and Genetic Predisposition

Several functional allelic variants and single-nucleotide polymorphisms of genes encoding immune and inflammatory molecules have been associated with depression and schizophrenia, including those encoding the expression of inflammatory cytokines, major histocompatibility complex proteins, B and T cells, and inflammatory mediators such as cyclo-oxygenase2 (Bamne *et al*, 2012; Bosker *et al*, 2011; Bufalino *et al*, 2012; Raison and Miller, 2013; Schizophrenia Working Group of the Psychiatric Genomics, 2014). These findings have engendered speculation as to whether alleles that promote enhanced inflammatory cytokine secretion were evolutionarily advantageous and thus conserved (Raison and Miller, 2013). Indeed, heightened inflammatory responses to environmental stimuli may have improved survival by conferring greater protection from bacterial and viral infection (Raison and Miller, 2013), and genetic priming to respond to stress and the environment with increased inflammatory and antiviral responses could contribute to the high prevalence of psychiatric disorders comorbid with medical illnesses that are associated with inflammation (eg, cardiovascular disease, metabolic disorders, and autoimmune disorders) (Evans *et al*, 1999; Pollak and Yirmiya, 2002; Raison and Miller, 2003; Shelton and Miller, 2010; Yirmiya *et al*, 2000; Yirmiya *et al*, 1999).

In addition to genetic polymorphisms, increased inflammatory gene expression in circulating immune cells has been found in patients with depression and other psychiatric disorders (Chase *et al*, 2015; Fillman *et al*, 2014; Mostafavi *et al*, 2014) and may predict treatment response. For instance, a targeted analysis of leukocyte mRNA expression of a subset of genes related to inflammation, glucocorticoid receptor signaling, and neuroplasticity revealed higher baseline mRNA levels of IL-1β, macrophage inhibitory factor, and TNF in patients with depression who failed to respond to 8 weeks of treatment with escitalopram or nortriptyline (Cattaneo *et al*, 2013). Interestingly, increased expression of a number of inflammatory markers has been observed in the brains of patients with both mood disorders and schizophrenia (Fillman *et al*, 2014; Shelton *et al*, 2011).

## Peripheral and Central Immune Cell Activation

Peripheral inflammatory cytokines may access the CNS to initiate local immune activation by several mechanisms, including (1) passage through leaky regions in the blood–brain barrier at circumventricular organs (Katsuura *et al*, 1990; Pan and Kastin, 2003), (2) active uptake mechanisms of cytokines across the blood–brain barrier (Banks and Erickson, 2010; Banks *et al*, 2002; Banks *et al*, 1995), and (3) local actions at peripheral vagal nerve afferents that relay cytokine signals to relevant brain regions, including the nucleus of the solitary tract and hypothalamus (the so-called 'neural route'; Bluthe *et al*, 1994; Ericsson *et al*, 1994; Watkins *et al*, 1995; Watkins *et al*, 1994). However, recent translational data indicate that during peripheral inflammation, activated monocytes/macrophages traffic to the brain in response to monocyte chemoattractant protein-1 (MCP-1), a chemokine produced by activated microglial cells in response to cytokine signaling in from the periphery (D'Mello *et al*, 2009; D'Mello *et al*, 2015). These monocytes/macrophages traffic primarily to perivascular and meningeal spaces, and have been shown to contribute to the behavioral changes in rodent models of stress-induced depressive and anxiety behaviors (Hodes *et al*, 2014; Wohleb *et al*, 2012; Wohleb *et al*, 2014). Interestingly, patterns of gene expression in the peripheral blood of patients with psychiatric disorders exhibit increased signatures consistent with pro-inflammatory 'M1' activation of monocyte/macrophages (Brambilla *et al*, 2014; Drago *et al*, 2015; Mostafavi *et al*, 2014). Furthermore, the recruitment of activated peripheral macrophages to perivascular spaces, as well as localized activation of microglia neighboring theses blood vessels and increased expression of MCP-1, has been observed in the dorsal ACC of post-mortem tissue from suicide patients with mood disorders (Steiner *et al*, 2011; Torres-Platas *et al*, 2014). These findings indicate that accumulation of peripheral immune cells in vascular compartments in association with restricted and/or regionally specific activation of microglia may be characteristic of patients with mood disorders who exhibit high inflammation.

## *In vivo* Imaging of CNS Immune Cell Activation in Psychiatric Disorders

With such strong evidence for increased inflammatory markers at the periphery of patients with psychiatric illness, there has been growing interest in finding ways to more directly measure activation of inflammatory processes in the brain. Despite intense efforts, however, the direct *in vivo* assessment of activation of immune cells in the CNS has remained somewhat elusive. One primary strategy has been the development of radioligands that bind to macrophage as well as activated microglia in the brain. Microglia were previously believed to exist primarily in two states: dormant or activated (Tremblay *et al*, 2011). In the latter state, microglia increase surface expression of the translocator protein (TSPO), which could therefore be used as a potential marker of activated microglia. Consistent with this, PET ligands that bind to TSPO, such as [$^{11}$C]PK 11195, show elevated non-displaceable-binding potential ($BP_{ND}$; Lockhart *et al*, 2003) and have been used to assess microglia activation in animal models of neuroinflammation (Cagnin *et al*, 2007; Venneti *et al*, 2007). Unfortunately, the specific activity of PK 11195 is too low to detect subtler inflammatory effects. More recently, second-generation TSPO ligands such as [$^{11}$C]PBR28 (Imaizumi *et al*, 2007) and [$^{18}$F]FEPPA (Wilson *et al*, 2008) have been developed that partially address this problem, and have been used to test for activated CNS immune cells in patients with depression and schizophrenia with mixed results (Bloomfield *et al*, 2015; Hannestad *et al*, 2012b; Kenk *et al*, 2015; Setiawan *et al*, 2015). In a sample of mild–moderate depression using the [$^{11}$C]PBR28, Hannestad *et al* (2012b) found no difference between patients and controls in $BP_{ND}$, though the sample was small and the depression severity was relatively low. In contrast, Setiawan *et al* (2015) used the 18F analog of [$^{11}$C]PBR28—[$^{18}$F]FEPPA—to examine the microglia activity in a more severely depressed sample, and observed significant increases in $BP_{ND}$ in the striatum, hippocampus, insula, and prefrontal areas (Setiawan *et al*, 2015). Similar inconsistencies have been observed in schizophrenia, where one study found no difference between actively psychotic patients and healthy controls (Kenk *et al*, 2015), and another found large global increases in TSPO binding in both diagnosed schizophrenia patients as well as individuals at clinical high risk (Bloomfield *et al*, 2015).

Although these studies provide some preliminary support for the tantalizing possibility of more directly visualizing activated immune cells in the CNS, several caveats are worth mentioning. First, microglia are not as 'dormant' as once believed, and are now known to have a variety of ongoing sentinel-type functions (Tremblay *et al*, 2011). Moreover, microglia exhibit a graded response of activation (Raivich *et al*, 1999), and increases in some activation markers—such as TSPO—may not indicate a true inflammatory phenotype (Marshall *et al*, 2013; Saijo and Glass, 2011). Consequently, the distinction between normally *vs* pathologically active microglia may be difficult to resolve solely on the basis of TSPO expression. In addition, within patient samples, there

has been no evidence linking TSPO $BP_{ND}$ to peripheral cytokine concentrations. This may be an artifact of the volume transmission analysis model, as TSPO $BP_{ND}$ is determined through the use of an arterial input function. Given the wide distribution of TSPO, it is possible that evidence of increased inflammation may also be associated with elevated TSPO expression outside the CNS. If this is the case, then the use of an arterial input function may obscure associations between peripheral and central inflammatory measures. That being said, two studies have established that TSPO binding is highly sensitive to an acute inflammatory challenge in both human and non-human primates (Hannestad *et al*, 2012a; Sandiego *et al*, 2015).

In sum, although PET measures of immune cell activation in the CNS in clinical samples provide some evidence that inflammation impacts DA-rich areas such as basal ganglia and ACC, as well as other cortical and subcortical structures, further studies are needed to validate the efficiency of TSPO ligands as markers of inflammation in the brain in psychiatric states as well as their relationships to peripheral measures of inflammation and clinical symptom profiles.

### Sources of Innate Immune Activation and Inflammation

Factors that may activate the innate immune system and contribute to increased inflammation in psychiatric patients who are otherwise medically stable include psychosocial stress (and particularly early life stress), sleep disturbance, inflammatory diet and gastrointestinal permeability, obesity, and other lifestyle factors such as smoking (Berk *et al*, 2013). Subjects with a history of childhood trauma exhibit elevated inflammatory biomarkers and higher rates of depression as adults (Danese *et al*, 2008; Danese *et al*, 2007), and a 'biological embedding' or imprinting of stress through inflammatory processes in childhood has been proposed (Danese *et al*, 2011; Nusslock and Miller, 2015). For instance, subjects with MDD and a history of early life stress responded to psychological stress (the Trier Social Stress Test), with exaggerated circulating IL-6 production and increased DNA binding of nuclear factor-kB in peripheral blood mononuclear cells compared with non-depressed controls (Pace *et al*, 2006). Increased IL-6 production in adolescents with histories of childhood adversity has been shown to precede subsequent development of depression 6 months later (Miller and Cole, 2012), indicating causal relationships between early life stress, increased inflammation, and depression. Sleep disturbance may be another variable that is related to inflammation (Bryant *et al*, 2004; Motivala *et al*, 2005; Opp *et al*, 2007; Suarez, 2008). Sleep deprivation results in increased circulating levels of IL-6, TNF, and CRP when compared with periods of undisturbed sleep (Meier-Ewert *et al*, 2004; Vgontzas *et al*, 1999; Vgontzas *et al*, 2004). Disturbed sleep also increase circulating IL-6, TNF, and CRP (Meier-Ewert *et al*, 2004; Vgontzas *et al*, 1999; Vgontzas *et al*, 2004), and sleep impairments in psychiatric illnesses such as depression have been associated with increased inflammation (Bryant *et al*, 2004; Motivala *et al*, 2005; Opp *et al*, 2007; Suarez, 2008).

In terms of lifestyle factors, inflammatory diets that promote gut permeability and changes in the microbiota, smoking, and increased body mass index (BMI) all contribute to increased inflammation and may interact with genetics and stress to contribute to behavioral symptoms and poor overall health outcomes in patients with psychiatric illness (Berk *et al*, 2013; Jamal *et al*, 2014). For example, obesity from consumption of a high-fat diet in rodents induces changes in the gut microbiota and increases ileal inflammation and permeability (de La Serre *et al*, 2010). Obesity and high BMI are associated with increased concentrations of IL-6 and other inflammatory markers in humans (Khaodhiar *et al*, 2004; Lim *et al*, 2005) thought to be the result of macrophage accumulation in adipose tissue, and especially visceral adiposity, which can release cytokines into portal circulation (Park *et al*, 2005; Suganami and Ogawa, 2010; Weisberg *et al*, 2003). Interestingly, adiposity has been suggested as a link between psychiatric illness, increased inflammatory markers, and increased risk of coronary heart disease (Miller *et al*, 2003; Miller *et al*, 2002).

## INFLAMMATION-INDUCED IMPAIRMENTS IN MOTIVATION AND MOTOR ACTIVITY—LINKS TO STRIATAL DA FUNCTION

A wealth of data suggests that alterations in motivation and motor function may be driven by increased inflammation via effects on reward circuitry and DA. In humans, much of this evidence stems from studies in healthy volunteers acutely administered inflammatory stimuli (eg, endotoxin or typhoid vaccination) and from patients chronically administered inflammatory cytokines (eg, IFN-$\alpha$) as therapy for some cancers and infectious diseases. Like endotoxin and vaccination, IFN-$\alpha$ administration induces release of the inflammatory cytokines IL-6, IL-1, and TNF (Capuron *et al*, 2003b; Felger *et al*, 2007; Raison *et al*, 2009; Sissolak *et al*, 1992; Taylor and Grossberg, 1998). Depending on the dose, up to 50% of patients administered IFN-$\alpha$ as treatment for hepatitis C virus (HCV) or malignant melanoma meet symptom criteria for major depression, and up to 80% experience significant fatigue, lack of energy, and motor slowing (Capuron *et al*, 2002a; Capuron *et al*, 2002b; Capuron *et al*, 2003a; Donnelly, 1998; Musselman *et al*, 2001; Raison *et al*, 2005a; Raison *et al*, 2009; Raison *et al*, 2010b). In addition, reduced motivation and anhedonia are frequently reported in IFN-α-treated patients (Capuron *et al*, 2002a; Capuron *et al*, 2012; Majer *et al*, 2008). Indeed, targeted instruments that assess aspects of anhedonia, including the Snaith–Hamilton Pleasure Scale and Reduced Motivation subscale of the Multidimensional Fatigue Inventory (MFI), have yielded comparable effect sizes (all $r = 0.47–0.49$) as for increases in self-reported depression or fatigue scores after chronic IFN-α treatment (Capuron *et al*, 2012; Majer *et al*, 2008).

Although the role of inflammation in psychiatric disorders has been studied primarily in comparison to healthy controls or as a function of overall disease severity, the few studies that have examined relationships between inflammatory markers and symptom dimensions reveal evidence of associations between increased inflammation and reduced motivation and motor function. For example, in patients from a high-risk urban setting with a history of trauma, those who carried a CRP genotype (rs1130864) that is associated with elevated CRP concentrations had higher rates of post-traumatic stress disorder and reported higher scores for the loss of interest in activities (Michopoulos *et al*, 2015). Furthermore, recent data indicate that increased plasma concentrations of CRP and inflammatory cytokines and their soluble receptors correlate with symptoms of both anhedonia and psychomotor slowing in medically stable patients with MDD (Felger *et al*, 2016; Goldsmith *et al*, 2016a; Haroon *et al*, 2016). These findings provide encouraging data that increased inflammation may be associated with symptoms of motivation and motor behavior across disorders, and may be useful for identifying subtypes of patients with psychiatric illness. Both clinical and translational evidence support the hypothesis that the impact of inflammation on motivation and motor function is driven by cytokine effects on DAergic systems, as reviewed below.

## Biochemical and Behavioral Studies in Laboratory Animals

Initial evidence that inflammation can affect brain DA originates from neurochemical and behavioral studies in rodents administered acute or subchronic IFN-$\alpha$ that measured DA and/or DA metabolites in concert with depressive behaviors and changes in locomotor activity (Kamata *et al*, 2000; Kitagami *et al*, 2003; Kumai *et al*, 2000; Sato *et al*, 2006; Shuto *et al*, 1997). Some studies reported increases (Kumai *et al*, 2000; Sato *et al*, 2006), whereas others have reported decreases (Kamata *et al*, 2000; Kitagami *et al*, 2003; Shuto *et al*, 1997) in brain DA and/or metabolites following acute or subchronic IFN-$\alpha$ administration. These discrepancies were likely due to differences in dosing, length of exposure, and, most importantly, the fact that species-specific IFN-$\alpha$ was variably used and rodents do not respond to human IFN-$\alpha$ with activation of classic type I IFN receptor signaling (Loftis *et al*, 2006a; Loftis *et al*, 2006b; Wang *et al*, 2008). Moreover, human IFN-$\alpha$ administered to rodents binds to opioid receptors, which may be responsible for some of the observed changes in brain monoamines (Blalock and Smith, 1981; Ho *et al*, 1992; Wang *et al*, 2006). Moreover, chronic (6 days to 4 weeks) peripheral administration of both human- and species-specific IFN-a administered to rodents has demonstrated only limited ability to reliably induce depressive behaviors (eg, see Fahey *et al*, 2007,Guo *et al*, 2016,Kosel *et al*, 2011,Loftis *et al*, 2006a,Loftis *et al*, 2006b,Makino *et al*, 2000a,Makino *et al*, 2000b,Orsal *et al*, 2008 and Zheng *et al*, 2014.

Rhesus monkeys exposed to chronic IFN-$\alpha$ exhibit immune, neuroendocrine, and behavioral responses similar to that of cytokine-treated patients, including decreases in psychomotor activity and increases in depressive-like huddling behavior (in ~ 50% of animals; Felger *et al*, 2007; Felger and Miller, 2012). Of note, depressive huddling behavior in non-human primates has been previously described following chronic administration of the monoamine-depleting agent reserpine, and DA receptor antagonists and partial agonists (McKinney *et al*, 1971; Rosenzweig-Lipson *et al*, 1994). Only animals that displayed depressive behavior following IFN-α administration were found to have significantly lower CSF concentrations of the DA metabolites homovanillic acid (HVA) and 3,4-dihydroxy-phenylacetic acid (DOPAC), which also correlated with decreased locomotor activity (Felger *et al*, 2007; Felger and Miller, 2012). Moreover, chronic IFN-α administration reduced effort-based but not freely available sucrose consumption by the monkeys (Felger *et al*, 2013c). Similar to the effects of IFN-$\alpha$, peripheral administration of IL-1β to rodents has been shown to decrease effortful responding for sucrose reward over freely available chow, in the absence of a decrease in preference for freely available sucrose over chow (Nunes *et al*, 2014); an effect that was reversed by lisdexamfetamine (Yohn *et al*, 2016). Interestingly, peripheral administration of IL-1$\beta$ in mice at 24 h has been shown to decrease locomotor (wheel running) activity, which was improved by methylphenidate but not modafinil (Bonsall *et al*, 2015). Furthermore, similar to IL-1$\beta$ administration, an overall decrease in responding for food reward has been reported in mice following peripheral administration of lipopolysaccharide (LPS; ie, endotoxin) with no decrease in reward sensitivity (preference for high value sucrose rewards) (Vichaya *et al*, 2014).

To further explore the effects of inflammatory cytokines on synaptic availability and release of striatal DA that may underlie inflammation effects on motivation and motor function, *in vivo* microdialysis was conducted on IFN-$\alpha$-treated monkeys (Felger *et al*, 2013c). Results indicated that stimulated DA release was indeed decreased in the striatum after chronic administration of IFN-$\alpha$, which correlated with reduced effort-based sucrose consumption (Felger *et al*, 2013c). Furthermore, IFN-$\alpha$-induced decreases in striatal DA release were reversed by the DA precursor levodopa (L-DOPA) administered via reverse *in vivo* microdialysis, indicating that cytokines may reduced DA synthesis and availability (Felger *et al*, 2015). In addition to IFN-$\alpha$ administration, models of peripheral inflammation in rodents have also been shown to decrease DA availability. For example, single injections of septic doses of LPS (5 mg/kg) cause progressive neurodegeneration of the nigrostriatal DArgic system (Qin *et al*, 2007; Reinert *et al*, 2014). It should be noted that acute systemic administration of low-dose LPS (~100 μg/kg) has been reported to either decrease tissue DA content or increase extracellular DA metabolites in the NAcc (van Heesch *et al*, 2014; Yeh *et al*, 2015). However, these studies assessed DA and 'anhedonic' behavior (sucrose

preference or responding for brain stimulation) at 2–4 h post LPS (van Heesch *et al*, 2014; van Heesch *et al*, 2013; Yeh *et al*, 2015), a time point that may be confounded due to the febrile effects of LPS and related sickness behaviors (Dinarello, 2004; Frenois *et al*, 2007; O'Connor *et al*, 2009b). These early effects of LPS may also reflect, for instance, acute activation of neuroendocrine peptides and hormones (minutes to hours), which can have stimulatory effects on turnover or release of brain catecholamines (Barrot *et al*, 2000; Lavicky and Dunn, 1993; Matsuzaki *et al*, 1989; Mekaouche *et al*, 1996), and which may occur ahead of the more chronic mechanisms by which inflammation is thought to contribute to decreased DA availability (see the section 'Mechanisms of inflammation effects on dopamine synthesis and release' below for detailed discussion). Nevertheless, both the short- and long-term effects of LPS on brain DA can be blocked by inhibition or genetic deletion of inflammatory cytokines such as TNF (Qin *et al*, 2007; Tian *et al*, 2006; van Heesch *et al*, 2014). Even localized inflammation in the hind paw following carrageenan administration has been shown to decrease DA release in the insula (Coffeen *et al*, 2010). Finally, models of inflammation-related medical illness, such as experimental tumors, are associated with decreased brain DA (Lebena *et al*, 2014; Uomoto *et al*, 1998). Together, these results from animal studies indicate that a variety of inflammatory stimuli have been consistently found to affect brain DA to lead to relevant behavioral symptoms, and have prompt further investigation into inflammation effects on DA and the basal ganglia in clinical populations.

## Neuroimaging of the DA System and Corticostriatal Reward Circuitry

Neuroimaging studies across several laboratories suggest that disruption of the basal ganglia and DA is a major contributor to inflammation-induced behavioral change (Table 1). In the first study to examine IFN-$\alpha$ effects on the brain, in addition to the decreased metabolism in PFC, increased glucose metabolism was found in the basal ganglia and particularly the DA-rich putamen (Juengling *et al*, 2000), as assessed by PET neuroimaging with fluorine-18-labeled fluorodeoxyglucose (FDG). More recently, FDG PET revealed increased basal ganglia glucose metabolism in patients receiving high-dose IFN-$\alpha$ as therapy for malignant melanoma (Capuron *et al*, 2007). Increased glucose metabolism in the left putamen and left NAcc correlated significantly with the

TABLE 1 Summary of Findings from Neuroimaging Studies Examining the Effect of Administration of Inflammatory Stimuli or Cytokines on Dopamine and/or Reward Circuitry

| Neuroimaging technique | Subjects | Inflammatory stimulus | Region | Finding | Study |
|---|---|---|---|---|---|
| *PET* | | | | | |
| [18F]FDOPA, uptake | HCV+ patients | 4–6 weeks IFN-α | VS, DS | ↑ | Capuron *et al*, 2012 |
| [18F]FDOPA, turnover | HCV+ patients | 4–6 weeks IFN-α | VS, DS | ↓ | Capuron *et al*, 2012 |
| [18F]FDG, glucose metabolism | HCV+ patients | 12 weeks IFN-α | DS | ↑ | Juengling *et al*, 2000 |
| [18F]FDG, glucose metabolism | HCV+ patients | 12 weeks IFN-α | PFC | ↓ | Juengling *et al*, 2000 |
| [18F]FDG, glucose metabolism | MM patients | 4 weeks IFN-α | VS, DS | ↑ | Capuron *et al*, 2007 |
| [18F]FDG, glucose metabolism | MM patients | 4 weeks IFN-α | PFC | ↓ | Capuron *et al*, 2007 |
| [11C]raclopride, D2R binding | Rhesus monkeys | 4 weeks IFN-α | VS, DS | ↓ | Felger *et al*, 2013c |
| [11C]raclopride, AMPH displacement | Rhesus monkeys | 4 weeks IFN-α | VS, DS | ↓ | Felger *et al*, 2013c |
| *fMRI/MRI* | | | | | |
| Activation to receipt of reward (gambling) | HCV+ patients | 4–6 weeks IFN-α | VS | ↓ | Capuron *et al*, 2012 |
| Activation to reward anticipation (MIDT) | Healthy controls | Endotoxin | VS | ↓ | Eisenberger *et al*, 2010 |
| Activation to social support figures | Healthy controls | Endotoxin | VS | ↑ | Inagaki *et al*, 2015 |
| Activation to positive social feedback | Healthy controls | Endotoxin | VS, vmPFC | ↑ | Muscatell *et al*, 2016 |
| Activation to RPEs (probabilistic learning) | Healthy controls | Vaccination | VS | ↓ | Harrison *et al*, 2015b |
| Activation to PPEs (probabilistic learning) | Healthy controls | Vaccination | AI | ↑ | Harrison *et al*, 2015b |
| Activation to cognitive Stroop | Healthy controls | Vaccination | SN | ↑ | Brydon *et al*, 2008 |
| Activation to visual stimuli | Healthy controls | Vaccination | SN | ↓ | Brydon *et al*, 2008 |
| Activation to novel stimuli | Healthy controls | Vaccination | SN | ↓ | Harrison *et al*, 2015a |
| qMT—$k_f$ | HCV+ patients | 4 h IFN-α | VS, DS | ↑ | Dowell *et al*, 2016 |
| qMT—$T_{2f}$ | HCV+ patients | 4 h IFN-α | VS, DS | ↓ | Dowell *et al*, 2016 |

Abbreviations: ↑, increased; ↓, deceased; AI, anterior insula; AMPH, amphetamine; D2R, dopamine 2 receptor; DS, dorsal striatum; FDG, fludeoxyglucose; FDOPA, fluorodopa; fMRI, functional magnet resonance imaging; HCV, hepatitis C virus; IFN, interferon; $k_f$, rate magnetization transfer from free (water) to molecular-bound protons; MIDT, monetary incentive delay task; MM, malignant melanoma; PET, positron emission tomography; PFC, prefrontal cortex; PPE, punishment prediction error; qMT, quantitative magnetization transfer; RPE, reward prediction error; SN, substantia nigra; $T_{2f}$, free water spin–spin relaxation time; vmPFC, ventromedial prefrontal cortex; VS, ventral striatum.

reports of fatigue in these patients, as assessed by the 'energy' subscale of the Visual Analog Scale of Fatigue (Capuron *et al*, 2007). This pattern of increased glucose metabolism in basal ganglia nuclei is similar to that seen in patients with PD (Eidelberg *et al*, 1994; Mentis *et al*, 2002; Spetsieris *et al*, 1995), where it is thought to reflect increased oscillatory burst activity in relevant basal ganglia nuclei secondary to the loss of inhibitory nigral DA input (Wichmann and DeLong, 1999,2003). Interestingly, this pattern of increased metabolism in striatum is also similar to the effects of transient catecholamine depletion in patients with MDD reported by Hasler *et al* (2008), which correlated with anhedonic symptoms.

fMRI conducted by Capuron and colleagues has also demonstrated decreased neural activation in the basal ganglia, including ventral striatum, to unexpected delivery of reward (winning in a gambling task (Reuter *et al*, 2005)) in HCV+ patients undergoing IFN-$\alpha$ administration, which correlated with self-reported reduced motivation (Capuron *et al*, 2012). Acute administration of IFN-$\alpha$ has also been shown to induce a change in striatal microstructure, as measured by quantitative magnetization transfer imaging, that predicted an increase in symptoms of fatigue (Dowell *et al*, 2016). Administration of the cytokine inducers endotoxin and typhoid vaccination to healthy volunteers produces similar effects on the ventral striatum in response to rewarding stimuli, suggesting that findings from IFN-$\alpha$ generalize to other inflammatory stimuli (Eisenberger *et al*, 2010; Harrison *et al*, 2015b). Indeed, Eisenberger *et al* (2010) demonstrated that endotoxin administration led to the reduced activation of ventral striatum to reward-predicting cues during a monetary incentive delay task, which was associated with increases in self-reported depressed mood as measured by the Profile of Mood States depression subscale. Similar blunting of neural responses to reward anticipation has been observed following dietary depletion of precursors for DA synthesis (Bjork *et al*, 2014). Moreover, typhoid vaccination was found to cause a shift in reward *vs* punishment sensitivity in a probabilistic instrumental learning task combined with fMRI (Harrison *et al*, 2015b). Compared with saline control, Harrison *et al*, 2015b determined that vaccination reduced behavioral attractiveness of rewards while making punishments more aversive, effects that were related to decreased neural activation of ventral striatum to RPEs, and increased activation of anterior insula to punishment prediction errors. Of relevance to potential effects of inflammation on DA and as discussed in the section 'Normal and abnormal dopamine function in the context of motivation and psychomotor function' above, the magnitude of response to prediction error signaling is fundamentally modulated by a DA-dependent striatal activity as determined by the administration of drugs that enhance (L-DOPA) or inhibit (haloperidol) DAergic function (Pessiglione *et al*, 2006). In addition, typhoid vaccination compared with saline has been shown to affect activity in the substantia nigra, including increased activation during a cognitive Stroop task and decreased activation in response to visual or novel stimuli, which correlated with both psychomotor slowing and increased peripheral blood concentrations of IL-6 (Brydon *et al*, 2008; Harrison *et al*, 2015a). Finally, it should be mentioned that neural activation in reward circuitry (ventral striatum and ventromedial PFC (vmPFC)) has also been shown to encode endotoxin-induced increased sensitivity to social rewards, including positive social feedback and increased approach to familiar others (Inagaki *et al*, 2015; Muscatell *et al*, 2016).

To further examine the role of DA in the effects of inflammation on neural activation and metabolism in reward circuitry, Capuron *et al* (2012) conducted a PET study in HCV+, IFN-$\alpha$-treated subjects using [$^{18}$F]fluorodopa (FDOPA). Like the DA precursor L-DOPA, FDOPA is taken up by DAergic neurons and converted by DA decarboxylase to DA, whereupon it is stored in vesicles for release. Interestingly, both increased uptake and decreased turnover of FDOPA in the caudate, putamen, and ventral striatum of IFN-$\alpha$-treated patients were found (Capuron *et al*, 2012). Baseline and percent change in FDOPA uptake was in turn correlated with IFN-$\alpha$-induced behavioral alterations including depression and fatigue, as measured by the Montgomery Asberg Depression Rating Scale (MADRS) and MFI, respectively (Capuron *et al*, 2012). Increased uptake and decreased turnover of FDOPA in the basal ganglia following IFN-$\alpha$ administration are in stark contrast to that observed in patients with PD, where decreased uptake and increased FDOPA turnover are seen. Decreased uptake of FDOPA in PD is believed to be a function of the loss of DAergic neurons and/or their projections throughout the basal ganglia (Kaasinen *et al*, 2001; Kumakura and Cumming, 2009; Leenders *et al*, 1986), and intact or increased turnover suggests that the surviving neurons are capable of normal release (Kumakura and Cumming, 2009; Kumakura *et al*, 2006). Increased FDOPA uptake during IFN-$\alpha$ treatment suggests intact terminals that exhibit a potential depletion of DA and increased synthetic capacity. These findings are consistent with that of the decreased striatal DA release observed in IFN-$\alpha$-treated monkeys, as measured by both [$^{11}$C]raclopride PET with amphetamine displacement (in putamen and NAcc) and *in vivo* microdialysis—which was reversed by L-DOPA administration (see above; Felger *et al*, 2015; Felger *et al*, 2013c).

Despite the abundance of reports indicating changes in basal ganglia and DA function in subjects administered cytokines and inflammatory stimuli, little work has been done to investigate similar effects of inflammation in patients who exhibit high inflammation, as a function of medical or neuropsychiatric illnesses. One study in patients with chronic fatigue syndrome, who have been frequently reported to exhibit elevated inflammatory markers including cytokines, observed decreased activation of basal ganglia structures, such as caudate and globus pallidus, in response to hedonic reward using the gambling task mentioned above (Miller *et al*, 2014). In medically stable patients with MDD, we observed a relationship between increased inflammation and decreased functional connectivity within reward-related

corticostriatal neurocircuitry (Felger *et al*, 2016). Indeed, increased inflammation (plasma concentrations of CRP as well as cytokines and their soluble receptors) was associated with decreased functional connectivity between the ventral striatum and vmPFC, and the dorsal striatum and the vmPFC and pre-supplementary motor area (pre-SMA), which correlated with self-reported symptoms of anhedonia and objective measures of psychomotor slowing, respectively (Felger *et al*, 2016). Interestingly, dorsal striatum and pre-SMA/SMA are key components of corticostriatal circuitry involved in linking motivation to motor output (Haber and Knutson, 2010; Samanez-Larkin and Knutson, 2015), and like the ventral striatum, vmPFC is part of classic reward circuitry that receives significant mesocorticolimbic DA innervation (Diekhof *et al*, 2012; Russo and Nestler, 2013). Accordingly, inflammation-related decreases in corticostriatal connectivity within reward and motor circuitry in depression may involve cytokine-induced decreases in DA, and have potential for reversal with pharmacological strategies that increase DA availability or receptor signaling (see the sections 'Mechanisms of inflammation effects on dopamine synthesis and release' and 'Potential therapeutic targets for inflammation effects on dopamine' below for further discussion; Felger and Miller, 2012).

Together, these data from humans and laboratory animals indicate that inflammation-related decreases in DA availability and release may have functional consequences on reward circuitry that are associated with fundamental alterations in motivation and motor function, to contribute to symptoms of anhedonia and psychomotor retardation (Figure 1). This work supports further consideration of the mechanisms of cytokine effects on DA synthesis, release, reuptake, or receptor signaling, which may lead to the development of novel therapeutic strategies to increase DA availability in patients with increased inflammation.

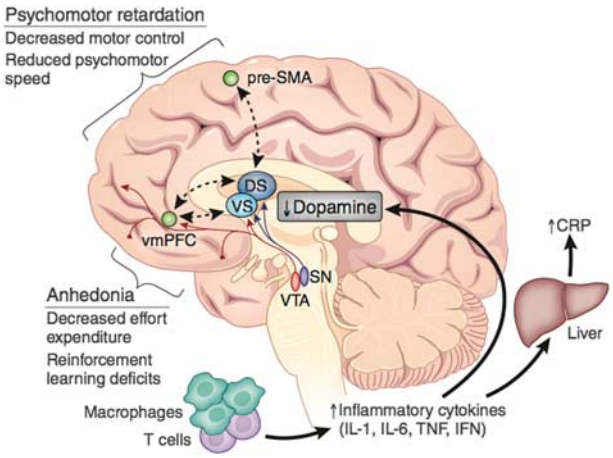


Figure 1. Inflammation-induced decreases in dopamine (DA) may affect corticostriatal reward and motor circuitry to drive symptoms of anhedonia and psychomotor retardation. Peripheral innate immune activation and the release of inflammatory cytokines, and acute-phase reactants (eg, C-reactive protein (CRP)) in patients with major depressive disorder (MDD) have been associated with decreased functional connectivity between the ventral and dorsal striatum and reward and motor-related cortical regions, ventromedial prefrontal cortex (vmPFC) and pre-supplementary motor area (SMA; Felger *et al*, 2016). Inflammation-related changes in corticostriatal connectivity correlated with symptoms of anhedonia and psychomotor retardation, and may involve deficits in DA-relevant, goal-directed behaviors such as such effort expenditure, reinforcement learning, and motor control. A wealth of knowledge from studies in humans and animals administered inflammatory stimuli or cytokines indicates that these effects on corticostriatal circuits may be related to inflammation-induced decreases in DA availability and release. CRP, C-reactive protein; DS, dorsal striatum; IFN, interferon; IL, interleukin; SMA, supplementary motor area; SN, substantia nigra; TNF, tumor necrosis factor; vmPFC, ventromedial prefrontal cortex; VS, ventral striatum; VTA, ventral tengmental area.

## MECHANISMS OF INFLAMMATION EFFECTS ON DA SYNTHESIS AND RELEASE

Inflammation and cytokines can potentially affect multiple aspects of DA function, leading to decreased synthesis, impaired packaging and release, increased reuptake, or decreased DA receptors, all of which may interact to a greater or lesser extent to reduce DA signaling in the basal ganglia (see Figure 2). Accordingly, the following section will discuss potential mechanisms by which inflammation may affect DA neurotransmission.

### DA Synthesis and Availability

DA synthesis relies on the conversion of tyrosine to L-DOPA by tyrosine hydroxylase (TH), the rate-limiting enzyme for DA synthesis. A major source of tyrosine is phenylalanine, which is converted to tyrosine by phenylalanine hydroxylase (PAH). Both of these enzymes, TH and PAH, require the enzyme cofactor tetrahydrobiopterin (BH4). Although inflammation and cytokines have been shown to induce GTP cyclohydrolase I, the enzyme necessary for BH4 synthesis, inflammation may in turn decrease BH4 availability (Neurauter *et al*, 2008). BH4 is also a cofactor for nitric oxide synthases (NOS). Inflammation-induced increases in inducible NOS activity can usurp available BH4, which results in NOS uncoupling and the generation of reactive oxygen species instead of NO (Cunnington and Channon, 2010; Xia *et al*, 1998). This increase in oxidative stress can then contribute to oxidative reduction of BH4 itself (which is highly redox sensitive) to 7,8-dihydrobiopterin (BH2), leaving even less BH4 available for DA synthesis (Figure 2) (Cunnington and Channon, 2010). Indeed, intramuscular injection of rats with IFN-$\alpha$ has been shown to decrease CNS concentrations of BH4 through stimulation of NO, and inhibition of NOS was found to reverse IFN-$\alpha$'s inhibitory effects on brain concentrations of both BH4 and DA (Kitagami *et al*, 2003). Of note, IL-6 treatment has also been shown to reduce BH4 content in sympathetic neurons (Li *et al*, 2003).

Concentrations of phenylalanine, tyrosine, BH4, and BH2 can be measured in the peripheral blood and CSF, and the BH4/BH2 and phenylalanine/tyrosine ratios have been proposed as indicators of BH4 availability and PAH activity,

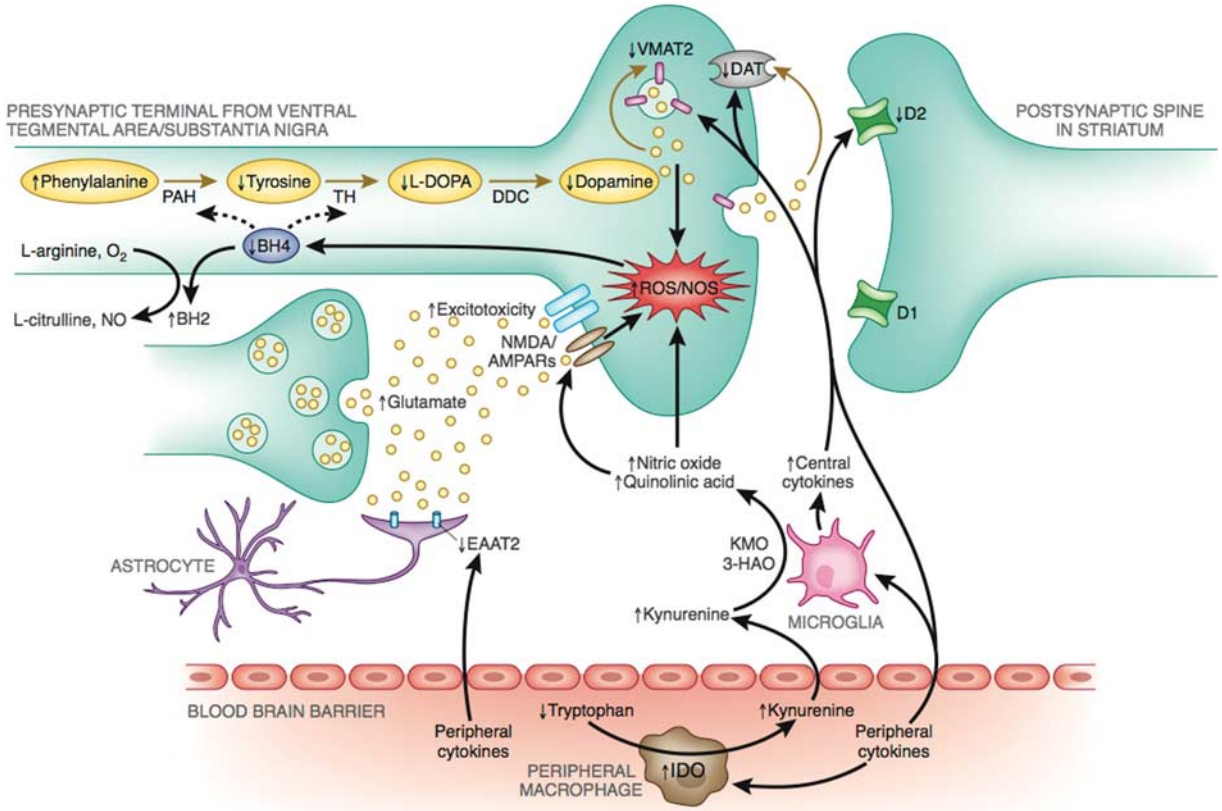


Figure 2. Potential mechanisms of inflammation effects on dopamine (DA) synthesis, release, and receptor signaling. Evidence indicates that inflammation and release of cytokines from the periphery, or those produced locally by activated microglia or infiltrating macrophages, can produce nitric oxide, as well as quinolinic acid through indoleamine 2,3-dioxygenase (IDO) and kynurenine pathways, both of which contribute to oxidative stress, and reactive oxygen species (ROS) generation. Increased ROS and inflammation-induced nitric oxide contribute to oxidation of tetrahydrobiopterin (BH4), a cofactor required for the conversion of phenylalanine to tyrosine and tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), which are necessary for the synthesis of DA. Furthermore, some evidence exists that inflammatory cytokines may decrease the expression or function of the vesicular monoamine transporter 2 (VMAT2) and/or increase expression or function of the dopamine transporter (DAT). Dysregulation of DAT and vesicular packaging mechanisms can increase cytosolic DA, leading to auto-oxidation and generation of ROS and neurotoxic quinones. In addition, inflammation-induced increased release and decreased reuptake of glutamate by glial cells, combined with quinolinic acid activation of *N*-Methyl-D-aspartic acid receptors, may lead to glutamate excitotoxicity that further contributes to oxidative stress and decreased DA availability. Finally, inflammatory cytokines may also decrease DA signaling by reducing DA D2 receptors. Figure adapted from Felger and Miller, 2012. 3-HAO, 3-hydroxyanthranilic acid oxygenase; AMPAR, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor; D1, dopamine 1 receptor 1; D2, dopamine 2 receptor; DDC, dopamine decarboxylase; KMO, kynurenine 3-monooxygenase; NMDAR, *N*-methyl-D-aspartic acid receptor; NO, nitric oxide; NOS, nitric oxide synthase; PAH, phenylalanine hydroxylase; ROS, reactive oxygen species; TH, tyrosine hydroxylase.

and may serve as indirect biomarkers of DA synthetic capacity (Candito *et al*, 1994; Capuron *et al*, 2011; Hashimoto *et al*, 2004; Neurauter *et al*, 2008; Yokoyama *et al*, 2002). For example, a number of patient populations with increased inflammation, including patients with trauma, sepsis, cancer, and HIV, have been found to exhibit increased peripheral blood concentrations of phenylalanine (Hufner *et al*, 2015; Neurauter *et al*, 2008). Furthermore, increased phenylalanine concentrations in patients with cancer have been correlated with markers and mediators of inflammation including IL-6, IL-2 receptor, and soluble TNF receptor-2, as well as peripheral blood markers of oxidative stress (Neurauter *et al*, 2008). Moreover, in a study of healthy elderly persons with low-grade inflammation, peripheral blood concentrations of phenylalanine, tyrosine, and an increased phenylalanine/tyrosine ratio were associated with neuropsychiatric symptoms including anhedonia and altered sleep (Capuron *et al*, 2011).

Evidence of reduced BH4 activity has also been observed in IFN-$\alpha$-treated patients (Felger *et al*, 2013a; Zoller *et al*, 2012). For example, IFN-$\alpha$ administration was associated with increased peripheral blood phenylalanine/tyrosine ratio, which in turn correlated with decreased CSF DA and its major metabolite HVA (Felger *et al*, 2013a). Increased CSF IL-6 was also correlated with decreased BH4 in CSF of IFN-$\alpha$-treated patients, and the phenylalanine/tyrosine ratio significantly correlated with IFN-$\alpha$-induced depressive symptoms (Felger *et al*, 2013a). These findings are consistent with decreased DA metabolites in the CSF of IFN-$\alpha$-treated patients and monkeys (Felger *et al*, 2007; Felger and Miller, 2012), and with reversal of IFN-$\alpha$-induced decreased release of DA by L-DOPA administered via reverse *in vivo*

microdialysis in monkeys (Felger *et al*, 2015). Of note, during L-DOPA administration, no change was found in DOPAC/DA, which increases when DA is not properly packaged in synaptic vesicles and is subsequently metabolized via monoamine oxidase (Caudle *et al*, 2007).

Another mechanism by which cytokines may influence the basal ganglia and DA function is through the effects on glutamate neurotransmission. For example, there has been recent interest in the impact of cytokine stimulation of indoleamine 2,3-dioxygenase (IDO) and downstream kynurenine pathway metabolites on glutamate neurotransmission in the brain (Dantzer *et al*, 2011). Immune-mediated activation of IDO catabolizes tryptophan, the primary amino-acid precursor of serotonin, to kynurenine, which is converted to QUIN in the microglia (Dantzer and Walker, 2014; Schwarcz and Pellicciari, 2002). Increased concentrations of QUIN have been found in the plasma and CSF of IFN-$\alpha$-treated patients (Bonaccorso *et al*, 2002; Capuron *et al*, 2003a; Raison *et al*, 2010a), which correlated with depressive symptoms, as measured by MADRS (Raison *et al*, 2010a). In addition to increasing oxidative stress (Behan *et al*, 1999; Santamaria *et al*, 2003), the neurotoxic metabolite QUIN can also directly activate the N-methyl-d-aspartate (NMDA) receptor (Schwarcz et al, 2002; Tavares *et al*, 2005; Tavares *et al*, 2002). In addition, inflammatory cytokines can increase extracellular glutamate by decreasing excitatory amino-acid transporters, which are responsible for glutamate reuptake, and increasing glutamate release from astrocytes and activated microglia (Dantzer and Walker, 2014; Takaki *et al*, 2012; Tilleux and Hermans, 2007). This inflammation-mediated increase in glutamate release and NMDA activation can lead to excitotoxicity in the brain (Guillemin, 2012; Guillemin *et al*, 2003), further increasing oxidative stress and potentially contributing to the effects on BH4 and DA synthesis (Felger and Miller, 2012; Najjar *et al*, 2013), as described above (Figure 2). In addition, increased xanthurenic acid, a metabolite of the kynurenine pathway upstream of QUIN, has been shown to directly attenuate BH4 biosynthesis by inhibition of sepiapterin reductase (Haruki *et al*, 2016).

Although these findings strongly suggest that inflammatory cytokines reduce DA availability through a deficiency in its precursors, some evidence exists indicating that cytokines may also target DA packaging, release, and reuptake mechanisms, as presented below.

## DA Packaging, Release, and Reuptake

Synaptic DA is dependent on the vesicular monoamine transporter 2 (VMAT2) to package cytosolic DA into vesicles for release. There is some evidence that inflammatory cytokines and inflammation may negatively affect the expression and function of VMAT2 (Figure 2). For example, the inflammatory cytokines IL-1 and TNF were found to decrease expression of VMAT2 in rat enterochromaffin-like cells, whereas transforming growth factor-β, which is immunomodulatory and anti-inflammatory, increased VMAT2 expression (Kazumori *et al*, 2004). In addition, the anti-inflammatory compound, pituitary adenylate cyclase-activating polypeptide 38, administered *in vivo* by subcutaneous minipump, was able to increase VMAT2 expression, reduce neuroinflammation, and oxidative stress, and protect against DA neurotoxicity following chronic methamphetamine exposure (Guillot *et al*, 2008).

Attention has been paid to the effects of cytokines and inflammatory signaling pathways on monoamine reuptake pumps, and particularly the serotonin transporter (Moron *et al*, 2003; Zhu *et al*, 2006; Zhu *et al*, 2005; Zhu *et al*, 2010). Both *in vitro* and *in vivo* data have established that the stimulation of p38 mitogen-activated protein kinase (MAPK), a primary signaling pathway activated by IFN-α and other cytokines, can increase the expression and function of the serotonin transporter, leading to increased serotonin reuptake (Zhu *et al*, 2006; Zhu *et al*, 2005; Zhu *et al*, 2010). MAPK pathways have also been found to influence DAT. For example, DAT-expressing cells transfected with constitutively activate MAPK kinase (MEK) show increased DA reuptake (Vmax), whereas the treatment of rat striatal synaptosomes with MEK inhibitors decreased DA reuptake in a concentration- and time-dependent manner (Moron *et al*, 2003). Furthermore, subjects with neuropsychiatric disturbances as a result of HIV infection and subsequent neuroinflammation are thought to have increased expression of DAT (Ferris *et al*, 2008; Gelman *et al*, 2006). Therefore, reduced synaptic DA following chronic exposure to inflammatory cytokines may be mediated, in part, by increased DAT expression or function (Figure 2). However, no change in DAT binding, as measured by PET with 18F-labeled FECNT, was observed in monkeys exposed to chronic IFN-α (Felger *et al*, 2013c).

## DA Receptor Expression and Function

Finally, inflammation and cytokines may affect DA signaling by reducing the expression or function of DA receptors. For instance, decreased D2 receptor binding using [$^{11}$C]raclopride PET was found in the striatum of rhesus monkey chronically administered IFN-α (Felger *et al*, 2013c). Interestingly, decreased D2 receptor binding has been observed in the striatum of patients with obesity, who also exhibit both high levels of inflammatory markers and altered reward processing (Michaelides *et al*, 2012; Shelton and Miller, 2010; Steele *et al*, 2010; Timpson *et al*, 2011; Voon *et al*, 2015). In addition, decrease D2 receptors may have a feed forward effect on inflammation given that D2 signaling on astrocytes has been shown to inhibit inflammatory responses in the CNS (Shao *et al*, 2013), and DA receptors modulate anti- and pro-inflammatory responses of immune cells in the periphery (Pacheco *et al*, 2014).

# POTENTIAL THERAPEUTIC TARGETS FOR INFLAMMATION EFFECTS ON DA

The data summarized herein demonstrate that inflammatory cytokines affect DA function and may contribute to the development of depressive symptoms relevant to reduced

TABLE 2 Pharmacological Strategies that May Reverse Inflammation Effects on Dopamine to Improve Motivation and Motor Function

| Target | Compounds | Previous in studies/trials |
|---|---|---|
| Inflammation | Cytokine antagonists | Increased motivation in MDD with high CRP (Raison *et al*, 2013b) |
| | COX inhibitors | Mixed results in psychiatric patients (Köhler *et al*, 2014; Sommer *et al*, 2012) |
| | Minocycline | Reduced negative symptoms in schizophrenia (Köhler *et al*, 2014; Sommer *et al*, 2012) |
| DA synthesis | L-DOPA | Increased motivation in PD (Czernecki *et al*, 2002) |
| | BH4 | Case reports: improves depressive/motor symptoms (Pan *et al*, 2011; Sato *et al*, 2014) |
| | SAMe | Evidence of success as adjuvant in MDD (Papakostas *et al*, 2010; Sarris *et al*, 2014; Sarris *et al*, 2015) |
| | L-Methylfolate | Evidence of success as adjuvant in MDD (Ginsberg *et al*, 2011; Godfrey *et al*, 1990; Papakostas *et al*, 2012; Shelton *et al*, 2015) |
| DA receptors | D2 agonists | Successful adjuvant in unipolar and bipolar depression (Cassano *et al*, 2004; Cusin *et al*, 2013; Fawcett *et al*, 2016; Franco-Chaves *et al*, 2013) |
| | Adenosine A2A antagonists | Reversal of IL-1β-induced decrease in effort-based motivation in rats (Nunes *et al*, 2014) |
| DA packaging (VMAT) | 7,8-dihydroxyflavone | Increased VMAT2 and neuroprotection in a rodent model of PD (Jang *et al*, 2010) |
| Oxidative stress/ | NMDA antagonists | Reversed decreased striatal DA in SIV (Meisner *et al*, 2008); depressed responders have high IL-6 (Yang *et al*, 2015) |
| excitotoxicity | IDO inhibitors | Inhibited inflammation-induced depressive behavior in mice (O'Connor *et al*, 2009b; O'Connor *et al*, 2008) |

Abbreviations: BH4, tetrahydrobiopterin; COX, cyclooxygenase; CRP, C-reactive protein; D2, dopamine 2 receptor; DA, dopamine; IDO, indoleamine 2,3-dioxygenase; L-DOPA, L-3,4-dihydroxyphenylalanine; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; SAMe, *S*-adenosyl-methionine; SIV, simian immunodeficiency virus; TrkB, tropomyosin receptor kinase B; VMAT, vesicular monoamine transporter.

motivation and motor activity in psychiatric patients with increased inflammation. Current antidepressant therapies are effective for many patients with MDD. However, up to 30% fail to achieve remission and even responders often exhibit significant residual symptoms that are consistent with those that are caused by the exposure to cytokines and inflammation, such as anhedonia, fatigue, and psychomotor retardation (Dunlop and Nemeroff, 2007; Nierenberg, 2015; Rush, 2007; Targum and Fava, 2011; Trivedi *et al*, 2008). Non-responsiveness of inflammation-related symptoms to standard antidepressant therapies has been exemplified in patients receiving IFN-$\alpha$ therapy who were treated with SSRIs. SSRIs alleviated cancer related or IFN-$\alpha$-induced anxiety and some depressive symptoms, but not those of fatigue or psychomotor retardation (Capuron *et al*, 2002a; Morrow *et al*, 2003; Raison *et al*, 2005b). In addition, patients with advanced cancer undergoing chemotherapy exhibit increased inflammation in association with fatigue that is not responsive to SSRIs (Ahles *et al*, 2002; Bower *et al*, 2002; Miller *et al*, 2008). Therefore, new conceptual frameworks are needed to treat these inflammation-associated symptoms (Capuron and Miller, 2004; Cattaneo *et al*, 2013; Raison *et al*, 2013a), which may respond to novel treatment strategies that target the DA system (Table 2).

Although classical stimulant medications that increase DA release and/or block DA reuptake increase motivation in rodent models (Randall *et al*, 2015; Yohn *et al*, 2015), they have demonstrated only limited efficacy in chronically treating fatigue and other DA-related symptoms in trials for patients with cancer and other medical illnesses that are associated with inflammation (Bruera *et al*, 2013; Butler *et al*, 2007; Escalante *et al*, 2014; Gong *et al*, 2014; Mar Fan *et al*, 2008; Moraska *et al*, 2010; Pucci *et al*, 2007; Ruddy *et al*, 2014; Stankoff *et al*, 2005; Sugawara *et al*, 2002). As stimulants act to increase DA release and block DAT function to increase synaptic levels of available DA, these drugs may not provide long-term efficacy in the context of inflammation. As described in detail in the section 'Mechanisms of inflammation effects on dopamine synthesis and release' above, although some evidence exists that inflammation may reduce DA packaging and/or release, and decrease DA receptor signaling, the primary mechanism by which inflammation may impact DA transmission is by decreasing DA synthesis, which would lend to only a limited supply of available vesicular or cytosolic DA on which stimulants may act. Consistent with this idea, dietary depletion of DA precursors has been shown to decrease stimulant-induced striatal DA release in healthy humans and laboratory animals, as measured by [11C]raclopride PET, and to decrease stimulant-induced locomotor behavior in laboratory animals (Dominic and Moore, 1969a, b,; Le Masurier *et al*, 2004; Leyton *et al*, 2004). Therefore, consideration should be given to alternative strategies such as compounds that increase DA synthesis, packaging, or receptor signaling, or those that inhibit activation of the neuroactive metabolites of the kynurenine pathway and/or glutamate, which increase oxidative stress and may contribute to effects on DA transmission during inflammation. Of course strategies that inhibit inflammation and/or inflammatory cytokines themselves should also be considered and will be discussed.

## Therapies that Block Inflammation

A number of recent studies have begun to test the potential of anti-inflammatory compounds as possible antidepressant therapies. Most studies to date have focused on compounds such as cyclooxygenase (COX) inhibitors or minocycline,

which have relatively mild anti-inflammatory effects and numerous 'off target' effects that may confound data interpretation (Miller and Raison, 2015). A recent meta-analysis found a modest antidepressant effect of anti-inflammatory agents in bipolar disorder (Rosenblat *et al*, 2016), yet trials using drugs that block oxidative stress—which may have many sources other than inflammation—were also included in this analysis. Recent meta-analyses in depression and schizophrenia have also reported modest effect sizes indicating a benefit of COX inhibitors in reducing symptom severity, but with high heterogeneity across studies and mostly small sample sizes (Köhler *et al*, 2014; Sommer *et al*, 2012). A meta-analysis of four trials in schizophrenia found that the antibiotic minocycline was superior to placebo at reducing negative but not positive symptoms (Oya *et al*, 2014). It should be noted that the majority of studies included in the meta-analyses described above have not selected patients with increased inflammation nor have they measured peripheral inflammatory markers to establish anti-inflammatory activity of the treatments. Interestingly, a recent study tested the efficacy of infliximab, a highly selective TNF antagonist, in treatment-resistant patients with MDD as a function of peripheral inflammation. Treatment with infliximab was associated with robust decreases in plasma CRP concentrations, as well as a strong antidepressant effect, but only in patients with elevated CRP at baseline (Raison *et al*, 2013b). Moreover, the greatest area of symptom improvement was related to motivation (Raison *et al*, 2013b), which is consistent with the hypothesis that blockade of inflammation may exert antidepressant properties through normalization of striatal DA function.

## Compounds that Improve DA Synthesis and Availability

Considering the strong evidence presented above, indicating that inflammation can inhibit key components of DA synthesis, pharmacologic strategies that increase DA may effectively treat inflammation-related symptoms of anhedonia, fatigue, and psychomotor slowing. For instance, there are a number of compounds than can boost BH4 availability or activity, which may facility the capacity of PAH and TH to synthesize DA. These include the administration of BH4 itself (Douglas *et al*, 2013), which is currently approved in a synthetic form to treat phenylketonuria (Burton *et al*, 2010; Trefz *et al*, 2009; Utz *et al*, 2012), and folic acid or *S*-adenosyl-methionine (SAMe), which have a role in the synthesis and/or regeneration of BH4 (Felger and Miller, 2012; Shintaku, 2002; Stahl, 2007). Although the effects of BH4 administration on depressive and motor symptoms have not been reported outside of case reports (Pan *et al*, 2011; Sato *et al*, 2014), folic acid (in the form of L-methylfolate) and SAMe have demonstrated efficacy as adjuvants in depression trials (Ginsberg *et al*, 2011; Godfrey *et al*, 1990; Papakostas *et al*, 2010; Papakostas *et al*, 2012; Shelton *et al*, 2015). Interestingly, low serum folate has been associated with the increased risk of depression, as well as non-response to antidepressant treatment and an increased likelihood of depression relapse (Fava *et al*, 1997; Gilbody *et al*, 2007a; Gilbody *et al*, 2007b; Papakostas *et al*, 2004a; Papakostas *et al*, 2004b). Administration of L-methylfolate (marketed as Deplin and Zervalx) to patients with MDD has been shown to augment the efficacy of standard antidepressant therapy in two studies (Ginsberg *et al*, 2011; Godfrey *et al*, 1990); however, mixed results were reported in two parallel-sequential trials with only one trial finding efficacy over placebo (Papakostas *et al*, 2012). Treatment with SAMe adjunctive to SSRIs led to significantly higher rates of remission and 50% or greater decreases in depressive symptoms compared with placebo (Papakostas *et al*, 2010). Although SAMe produced a significantly greater reduction in depression scores compared with escitalopram at weeks 2–6 in a recent placebo-controlled trial in patients with MDD, no significant difference in response or remission rates was observed, possibly due to the increased variability over two study sites (Sarris *et al*, 2014). However, a subgroup analysis of this trial indicated that SAMe was effective in men but not women (Sarris *et al*, 2015). Of the reports described above, only one *post hoc* analysis of the two parallel-sequential adjuvant trials of L-methylfolate in patients with MDD (Papakostas *et al*, 2012) considered inflammatory markers. It was found that BMI $>30$ as well as concentrations of TNF, IL-8, CRP, and leptin over the median, alone or in combination with each other or with IL-6, predicted greater symptom improvement (Shelton *et al*, 2015). Therefore, strategies to augment BH4 activity exhibit potential for restoring DA function and treating symptoms of depression in patients with increased inflammation, yet specific effects on motivation or motor function remain to be determined. Replacement of DA with the precursor L-DOPA is known to improve motor function, but has also been shown to increase motivation in patients with PD (Czernecki *et al*, 2002). However, peripheral and CNS side effects may complicate the use of L-DOPA as a therapy in psychiatric patients (Castro-Garcia, 1997).

Finally, inhibition of the IDO pathway or glutamate may be an important target in reversing the impact of inflammation on basal ganglia DA function. The IDO antagonist, 1-methyl tryptophan, has been shown to abrogate the impact of LPS, as well as an attenuated form of *Mycobacterium bovis*, on depressive-like behavior (O'Connor *et al*, 2009a; O'Connor *et al*, 2008). Given that the neurotoxic effects of QUIN may be mediated by excessive glutamate excitotoxicity (Schwarcz et al, 2002; Tavares *et al*, 2005; Tavares *et al*, 2002), glutamate antagonists may be useful in preventing excitotoxic and oxidative effects on the highly sensitive DA neurons. Indeed, metabotropic glutamate receptor antagonists that modulate glutamate transmission in the basal ganglia have been successful in reducing DA cell loss in an animal model of PD (Masilamoni *et al*, 2011). Antagonism of the NMDA receptor with memantine in monkeys infected with simian immunodeficiency virus (SIV) also reversed the loss of DA in the striatum (Meisner *et al*, 2008) that occurs during SIV and HIV infection secondary to immune cell

activation in the basal ganglia (Kumar *et al*, 2011; Scheller *et al*, 2005), in association with increased brain-derived neurotrophic factor (BDNF). Interestingly, inflammation-induced release of glutamate from glia cells (see above) may preferentially activate extrasynaptic NMDA receptors, which has been shown to decrease BDNF (Hardingham *et al*, 2002). Administration of the NMDA antagonist ketamine has potent antidepressant effects in depressed patients who are resistant to standard therapies and who often exhibit increased inflammation (aan het Rot *et al*, 2010; Price *et al*, 2009; Raison *et al*, 2013a). Indeed, a recent study in treatment-resistant depression found that patients who were most responsive to ketamine were those with the highest concentrations of serum IL-6 (Yang *et al*, 2015). Therefore, blockade of kynurenine pathways or modulation of glutamate neurotransmission may confer protection against inflammation and/or IDO-mediated effects on DA function to improve behavioral symptoms in patients with increased inflammation.

### Strategies to Facilitate DA Packaging and Release or DA Receptor Signaling

In terms of targeting DA packaging and release, compounds that improve VMAT2 function could be considered for the treatment of cytokine-induced depression and fatigue. For instance, VMAT2 activity can be increased with the small molecule trkB agonist, 7,8-dihydroxyflavone, which was neuroprotective in a rodent model of PD (Jang *et al*, 2010). In addition to compounds that may increase DA availability and release, adenosine (A2A) receptor antagonists, which are thought to facilitate the activation of DA D2 receptors, are efficacious in reversing decreased effort-based sucrose consumption after DA depletion with tetrabenazine (a vesicular monoamine transporter inhibitor) and after peripheral administration of IL-1β in rats (Chen *et al*, 2001; Collins *et al*, 2010; Nunes *et al*, 2014; Xie *et al*, 2009; Yohn *et al*, 2015). The DA receptor agonist, pramipexole, has been shown to block endotoxin-induced degeneration of nigrostriatal DA cells (Iravani *et al*, 2008), and has also demonstrated the efficacy in unipolar and bipolar patients with treatment-resistant depression (Cassano *et al*, 2004; Cusin *et al*, 2013; Fawcett *et al*, 2016; Franco-Chaves *et al*, 2013).

## SUMMARY AND CONCLUSIONS

In this review, we have attempted to outline the case for a molecular pathway linking precipitators of inflammation to reduced effort expenditure and impaired motor function via their effects on mesolimbic DA availability and signaling. Inflammation is increased in a significant proportion of patients with psychiatric illnesses, and has been associated with symptoms such as anhedonia, fatigue, and psychomotor retardation. Further, a large preclinical and clinical literature suggests that one of the proximal causes for these symptoms is alterations within DA-rich striatal circuitry. We have summarized ample data suggesting that disruptions of striatal DAergic tone can produce profound shifts in motivated behavior, and that increased inflammatory factors are capable of inducing such disruptions. Taken together, this suggests that inflammation may be associated with the origin of such symptoms, although this should not be taken to imply that all expressions of anhedonic symptoms are necessarily linked to inflammation. As stated by Miller and Raison (2015), 'no psychiatric disorder is an inflammatory disorder', and this may also be true at the level of specific symptoms. Rather, inflammation effects on DAergic systems may represent an etiopathophysiological subtype for reward-related symptoms that are common to multiple psychiatric disorders.

Importantly, the primary symptoms of this proposed subtype are often difficult to treat with standard therapies. Mechanistic evidence from humans and animals administered cytokines or inflammatory stimuli suggests that inflammatory cytokines may affect multiple aspects of DA neurotransmission, leading to decreased synthesis, DA receptor signaling, and/or impaired packaging or release, all of which may interact to a greater or lesser extent to reduce DA function. Multiple potential pharmacological treatment strategies exist, yet future studies are needed to identify precise targets for reversing inflammation effects on brain DA. Moving forward, studies using experimental strategies to block inflammation or reverse its effects on DA and reward circuitry will further validate the existence of an inflammatory subtype, and guide development of novel therapies to treat DA-relevant behavioral symptoms in psychiatric patients with increased inflammation.

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