The Neurobiology of Motivational Deficits in Depression—An Update on Candidate Pathomechanisms

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Abstract Anhedonia has long been recognized as a central feature of major depression, yet its neurobiological underpinnings remain poorly understood. While clinical definitions of anhedonia have historically emphasized reductions in pleasure and positive emotionality, there has been growing evidence that motivation may be substantially impaired as well. Here, we review recent evidence suggesting that motivational deficits may reflect an important dimension of symptomatology that is discrete from traditional definitions of anhedonia in terms of both behavior and pathophysiology. In summarizing this work, we highlight two candidate neurobiological mechanisms—elevated inflammation and reduced synaptic plasticity—that may underlie observed reductions in motivation and reinforcement learning in depression.

Keywords Depression · Motivation · Effort-based decision-making · Reinforcement learning · Dopamine · Inflammation · Neuroplasticity

Contents

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1 Introduction

The term anhedonia—introduced to the clinical literature over 100 years ago—describes a debilitating psychological state that reflects an almost complete lack of enjoyment and positive emotionality. Activities such as meals, work, and social interaction are left devoid of the normal pleasures associated with appetite, motivation, or connection. Though anhedonia was originally intended to describe a state of severe despair and lack of pleasure (Ribot 1896), it has been used by clinicians and clinical researchers as a "catch-all" term related to patient impairments across a range of components that underlie approach behavior, including motivation, enjoyment, optimism, and positive mood states. As discussed in more detail below, this "big tent" definition for anhedonia can raise challenges when attempting to study its pathophysiology. Consequently, the current chapter uses the term anhedonia to denote a symptom domain that has a variety of possible subcomponents rather than a single construct and focuses primarily on what is known about pathomechanisms for deficits related to motivation and impaired reinforcement learning as compared to a pure loss of pleasure.

This stance is consistent with a number of recent reviews that have called for a critical reexamination of the anhedonia construct [(Foussias and Remington 2008; Barch and Dowd 2010; Treadway and Zald 2011; Strauss and Gold 2012) also see chapters in this volume by Barch et al., Reddy et al., Waltz and Gold]. A central question raised by this work has been whether anhedonia describes a primary deficit in the capacity to experience positive emotions, or does it include deficiencies in a number of reward-related domains? While there is no debate that depressive states are associated with reduced motivation for and failure to anticipate rewarding experiences, the former hypothesis assumes that these are more or less normative responses to reduced hedonic capacity. In contrast, the alternative hypothesis is that, at least for some depressed individuals, the pathophysiology of the disorder may diminish motivation directly. The answer to this question has substantial implications for the theoretical conceptualization of anhedonia and related constructs, for the assessment of psychopathology involving these symptoms, for understanding the neural substrates of psychiatric symptoms, and for the treatment or reward processing abnormalities.

As currently defined by the DSM-5, anhedonia is one of two symptoms required for diagnosis of a depressive episode. A patient is considered to meet the anhedonia criterion by reporting either the loss of pleasure in previously enjoyable activities or a loss of interest/motivation in pursuing them. If pleasure and interest are reflections of a singular process, then this reduction to a single symptom is not a problem. However, if reductions in pleasure and interest reflect different pathophysiologies, then underlying neurobiological mechanisms may differ across anhedonic patients, thereby eluding their detection in research studies that treat both manifestations of anhedonia as being equivalent (Barch and Dowd 2010; Treadway and Zald 2011). Indeed, most traditional measures of psychopathology and dimensional assessments of anhedonia fail to discriminate between these various domains of reward

processing. While such measures have had a useful place in the context of clinical assessment and care, they may mask important behavioral and biological distinctions that are critical toward understanding pathophysiology. It has long been recognized that reinforcement involves multiple subprocesses, such as anticipation, motivation, prediction, subjective pleasure, and satiety. It has only been more recently, however, that investigators have been able to clearly show that these subcomponents are neurobiologically dissociable (see Robinson et al., in this volume). That is, manipulations of distinct circuits and neurochemicals can produce isolated effects on a single dimension of reward-related behavior, such as an abolition of motivation without any change in hedonic responsiveness. This finding suggests that a reduction in reward-seeking behavior may result from impairments in one or many subcomponent processes, which in turn implies that they may have shared or unshared neurobiological origins across different individuals. Despite this new understanding of the biological divisions involved in reward and reinforcement in the preclinical literature, current clinical methods have largely continued to conceptualize anhedonic symptoms along a unitary dimension of pleasure and positive emotions (Gold et al. 2008; Treadway and Zald 2011).

It is worth highlighting that this debate has occurred against a backdrop of growing interest in the clinical significance of anhedonia. Following the publication of DSM-3, which prominently featured anhedonia in conditions of major depressive disorder (MDD) and schizophrenia (Klein 1974; Meehl 1975), empirical research devoted to the understanding and treatment of this symptom domain has grown rapidly. Further augmenting the focus on anhedonic symptoms has been the observation of comparatively poorer treatment outcomes for patients with an anhedonic presentation (Shelton and Tomarken 2001), as well as a steep rise in preclinical discoveries regarding the molecular and system-level mechanisms underlying reward processing generally [for reviews, see Salamone et al. 2007; Berridge and Kringelbach 2008; Rushworth et al. 2011 as well as chapters in this volume by Corbit and Balleine, Robinson et al., Roesch et al., and Salamone et al.]. This latter trend is of particular importance as the field of psychiatry has increasingly turned toward translational neuroscience as a means of understanding the etiopathophysiology of mental disorders (Insel et al. 2010; Insel and Cuthbert 2015).

Despite this heightened focus, many fundamental questions remain regarding the nature of anhedonic symptoms, their etiology, phenomenology, biological underpinnings, and specificity to psychiatric illness. In this chapter, we briefly review the known neural circuitry evidence supporting motivated behavior, highlight recent behavioral evidence suggesting that impairments in these processes are associated with depressive symptoms, and discuss candidate pathomechanisms that may underlie the expression and etiology of these deficits. Importantly, we believe that this work can help begin to isolate subtypes of depressive disorders that may be defined by distinct pathophysiologies rather than symptoms, which has long been a goal of psychiatric medicine.

2 Motivation, Reinforcement, and Dopamine

Over the past two decades, animal models have found robust evidence linking mesolimbic dopamine circuitry to motivated behavior. The mesolimbic DA system encompasses a specific subpopulation of DA neurons that innervate the ventral striatum (VS), an integrative hub involved in translating value-related information into motivated action (Haber and Knutson 2010; Floresco 2015). Evidence for the role of mesolimbic DA in motivation was first provided through the use of effort-based decision-making tasks in rodents (see Salamone et al., this volume). In these paradigms, animals must choose whether to exert physical effort in exchange for greater or more palatable food rewards (High Effort) or to consume freely available, but less desirable food rewards (Low Effort). Across different paradigms, healthy rats on a food-restricted diet typically show a strong preference for the High-Effort option, while attenuation or blockade of DA—especially in the VS—results in a behavioral shift toward Low-Effort options (Cousins and Salamone 1994; Salamone et al. 2007). Importantly, DA blockade does not reduce overall consumption, suggesting that these manipulations do not impair primary motivation for food, but rather selectively ablate willingness to work for larger or more preferred rewards. Additionally, potentiation of DA through drugs such as *d*-amphetamine produces the opposite effects, resulting in an increased willingness to work for preferred rewards (Bardgett et al. 2009). In contrast to this strong evidence for DA in motivation, attenuation or even complete absence of DA appears to have little effect on measures of hedonic response, including sucrose preference and hedonic facial reactions (for a review, see Berridge and Kringelbach 2008).

In humans, similar results have been observed using effort-based decision-making tasks in which participants choose how much (physical or mental) effort to invest in order to obtain a reward (typically money). Previously, our laboratory developed the effort expenditure for reward task (EEfRT, pronounced "effort"), which has been used to examine neural substrates of effort mobilization in humans. During this task, participants perform a series of trials in which they are asked to choose between completing a "High Effort" task and completing a "Low Effort" task in exchange for monetary compensation, where the required effort is in the form of speeded button presses (see Fig. 1). Other groups have developed similar tasks for physical effort using handgrip paradigms (Pessiglione et al. 2007; Hartmann et al. 2013) or cognitive effort in the form of task switching (McGuire and Botvinick 2010), attentional control (Croxson et al. 2009) or working memory (Westbrook et al. 2013).

Using these tasks, human studies have begun to map out the role of mesolimbic DA circuitry in normal and abnormal reward motivation. Mirroring the effects of DA potentiation in rats, one study found that administration of the DA agonist d-amphetamine produced a dose-dependent increase in the willingness to work for rewards as assessed by the EEfRT (Wardle et al. 2011) (see Fig. 2a). Similar effects of DA enhancement using the DA precursor L-Dopa have been observed on

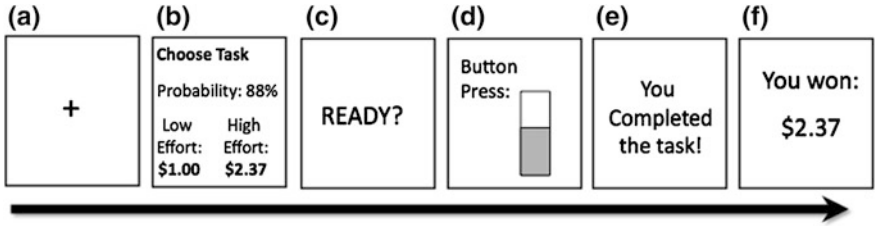

Fig. 1 Schematic diagram of a single trial of the effort expenditure for reward task (EEfRT) (Treadway et al. 2009). **a** Trial begins with a 1-s fixation cue, followed by **b** a 5-s choice period in which subjects are presented with information regarding the reward magnitude of the hard task for that trial, and the probability of receiving a reward. After making a choice, **c** a 1-s "ready" screen is displayed, after which **d** subjects make rapid button presses to complete the chosen task for 7 s (easy task) or 21 s (hard task). **e** Subjects receive feedback on whether they have completed the task. **f** Subjects receive reward feedback as to whether they received any money for that trial

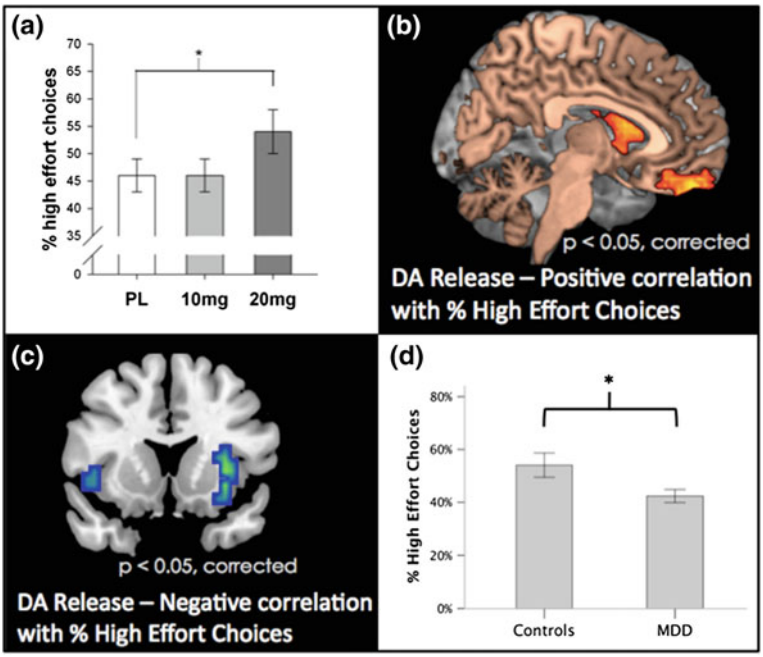

Fig. 2 Summary of recent EEfRT studies in humans (adapted from Treadway and Zald (2013)). **a** Administration of amphetamine produces a dose-dependent increase in willingness to expend greater effort for larger rewards (Wardle et al. 2011). **b** Proportion of High-Effort choices during low-probability trials shows positive associations with amphetamine-induced change in D2/D3 binding potential in striatum and vmPFC (Treadway et al. 2012). **c** Proportion of High-Effort choices is *inversely* associated with amphetamine-induced change in D2/D3 binding potential in bilateral insula. **d** Depressed patients choose fewer High-Effort options than matched controls (Treadway et al. 2012)

measures of vigorous effortful responding (Beierholm et al. 2013) as well reward anticipation (Sharot et al. 2009).

While these studies have suggested that direct manipulation of DAergic systems may alter motivated behavior in humans, they do not address the questions of whether endogenous variability in DA function may serve as a substrate for individual differences. This latter issue is particularly important if DA dysfunction is to serve as a pathomechanism for depressive symptoms. To investigate this question, a follow-up study from our group used positron emission tomography (PET) imaging to test associations between amphetamine-induced DA release (a probe of DA system reactivity) and willingness to work for rewards on during the EEfRT (Treadway 2012). Here, we found that the magnitude of DA release in dorsomedial and ventral aspects of the striatum positively predicted the proportion of High-Effort choices subjects made during low-probability trials (see Fig. 2b). Localization to this region is consistent with preclinical findings (Cousins and Salamone 1994; Salamone et al. 2007) as well as human functional neuroimaging studies (Croxson et al. 2009; Kurniawan et al. 2010; Schmidt et al. 2012, also see O'Doherty, this volume). Intriguingly, our study also found a negative relationship between percentage of High-Effort choices and DA release in the insula (see Fig. 2c). While insula DA function has not traditionally been a focus for rodent models of effort-based decision-making, recent work suggests that insula DA receptor mRNA expression is predictive of effort-related behaviors (Simon et al. 2013). Moreover, other human imaging studies have observed insula activation when participants chose not to expend effort (Prevost et al. 2010). Although further investigation is necessary, these data suggest that the insula and striatum may play somewhat antagonistic roles in determining whether an individual is willing to overcome effort costs.

In addition to the role of DA in motivation, DA signaling in the striatum–especially phasic signaling–has been heavily linked to reinforcement learning. Consistent evidence from DA cell recordings (Schultz 2007) and fast-scan cyclic voltammetry of DA projection targets in the striatum (Hart et al. 2014) support the hypothesis that phasic DA signaling in the striatum reflects the difference between expected rewards and received rewards, often referred to as a "prediction error" (Sutton and Barto 1998). In humans, corroborative results have been obtained using high-resolution fMRI of the midbrain (D'Ardenne et al. 2008), as well as pharmacologic manipulations (Pessiglione et al. 2006).

Taken together, a solid body of evidence has implicated DA signaling in the striatum in both reward motivation (effort expenditure) and reinforcement learning. Using these data as a foundation, a number of studies in depression over the last ten years have investigated whether this disorder is associated with alterations in these behaviors, possibly implicating a corticostriatal DAergic mechanism.

3 Motivation and Reinforcement in Depression—Implications for DA Dysfunction

In a relatively recent literature, studies of motivation and reinforcement in depression have been largely consistent in detecting differences as compared to healthy controls (Whitton et al. 2015). In several studies using the effort expenditure for reward task (EEfRT), patients with MDD expended less effort for rewards when compared with controls (Treadway et al. 2012; Yang et al. 2014) (see Fig. 2d). Further evidence suggests that the longer the depressive episode is, the more impaired this decision-making is (Treadway et al. 2012a), and when in remission, this deficit normalizes (Yang et al. 2014). However, a similarly designed study did not detect a main effect of depression on willingness to expend effort for rewards (Sherdell et al. 2011). It is worth noting, however, that this study utilized an EEfRT requiring significantly fewer button presses for its High-Effort condition (an average of 42 mouse clicks as compared to the EEfRT, which requires 100 button presses in 21 s with the non-dominant pinky finger); these varying levels of required effort may have influenced the sensitivity to these two tasks for detecting group differences. For reinforcement learning, Pizzagalli and colleagues have used a signal detection task that has consistently demonstrated reduced implicit reinforcement learning in depression (Pizzagalli et al. 2008; Vrieze et al. 2013). Like the EEfRT, performance on this task has similarly been linked to DA function in humans (Vrieze et al. 2011). Supporting these behavioral findings, functional neuroimaging studies have found that depression is associated with reduced prediction error signaling in the striatum during reinforcement learning (Kumar et al. 2008) as well as striatal responses to reward feedback (Pizzagalli et al. 2009).

In sum, clinical, behavioral, and a handful of imaging studies support the hypothesis that motivation and reinforcement learning are impaired in MDD and that DA function may serve as a primary substrate. Several factors complicate this hypothesis, however, as most studies focused on direct imaging of DA have produced ambiguous results (Treadway and Pizzagalli 2014). First, PET studies of DA receptor distribution—a common tool for measuring pathological alteration of DA systems—have found some mixed evidence for DA involvement in depression. An early study using single-photon emission tomography (SPECT) found that MDD patients exhibited reduced DA synthesis capacity as measured by L-Dopa uptake (Agren and Reibring 1994). In subsequent PET and SPECT studies of the DA transporter (DAT), MDD has been associated with both lower (Meyer et al. 2001) and higher (Laasonen-Balk et al. 1999; Amsterdam and Newberg 2007; Yang et al. 2008) binding potential in the striatum. These data should be taken with the caveat that all studies that observed an increase in striatal DAT binding in MDD used SPECT, which has much lower sensitivity than PET (Rahmim and Zaidi 2008), and postmortem studies also suggest a decrease, rather than increase, in DAT availability in depression (Klimek et al. 2002).

PET studies of DA receptor availability have yielded similarly mixed results. PET measures of striatal D2/D3 receptor binding potential have observed increases in several depressed samples (D'Haenen and Bossuyt 1994; Shah et al. 1997), a finding that conflicts with predictions based on some preclinical animal data (Gershon et al. 2007). It should be noted, however, that striatal D2/D3 PET ligands are unable to differentiate between pre- versus postsynaptic receptors. Given that pre- and postsynaptic D2/D3 receptors are known to exert distinct—even oppositional—effects on postsynaptic DA signaling, the inability to resolve this difference in clinical studies may limit interpretability. Other studies using medication-naïve or medication-free patients have failed to find group differences in striatal receptor binding (Parsey et al. 2001; Hirvonen et al. 2008). Interestingly, one additional small study showed variable changes in D2-like binding following treatment with SSRIs such that patients who showed increased binding exhibiting greater clinical improvement than those who did not (Klimke et al. 1999). With respect to the D1 receptor, fewer studies have examined this system given the lack of available ligands that reliably distinguish between D1 and serotonin 5-HT_{2A} receptors, especially in extrastriatal areas where the receptor density of D1 and 5-HT_{2A} is roughly equivalent. One study reported reduced D1 availability in left middle caudate (Cannon et al. 2009), but this finding has not yet been replicated. Taken together, while behavioral and clinical evidence suggests that depression affects motivational and reinforcement behaviors that are known to depend heavily on DAergic function, the evidence for a primary DAergic deficit is undeniably equivocal, particularly when compared to other DA-linked neuropsychiatric disorders, such as schizophrenia, Parkinson's disease, or substance use.

One explanation for these discrepancies is the possibility of distinct subtypes of depression, only some of which may involve alterations to DA signaling. Supporting this is the observation of slightly more consistent effects when MDD samples are selected on the basis of a particular symptom profile. For example, one study that restricted its MDD patient sample to individuals with symptoms of affective flattening as assessed by the Snaith–Hamilton Pleasure Scale reported decreased DAT binding (Sarchiapone et al. 2006). In addition, decreases in [^{18}F] Dopa binding—a marker of DA synthesis capacity—have been observed in the striatum of depressed individuals with flat affect or psychomotor slowing as measured by the Depression Retardation Scale (Martinot et al. 2001; Bragulat et al. 2007). As with behavioral studies, these data suggest that some—but not all—patients with depression may exhibit abnormalities in DA signaling, which may manifest as anhedonic symptoms. If true, however, this hypothesis begs the question as to what possible mechanisms may account for this selective effect.

4 Candidate Pathophysiological Mechanisms of Motivational and Reinforcement Deficits in Depression

In this next section, we present two candidate mechanisms that may be partially responsible for motivational and reinforcement learning impairments observed in depression.

4.1 A Role for Inflammation in Motivational Deficits in Depression

One candidate mechanism for motivation-related impairments in MDD is inflammation. An extensive literature has now shown that compared to controls, a subset of depressed patients exhibit elevated inflammatory proteins and gene expression in both peripheral tissue and cerebrospinal fluid (CSF), as well as increased peripheral blood acute-phase proteins, chemokines, and adhesion molecules (Miller et al. 2009a, b). Meta-analyses of this literature have identified that the most reliable inflammatory biomarkers in depression are increases in peripheral blood inflammatory cytokine tumor necrosis factor (TNF) and interleukin (IL)-6 as well as increases in the acute-phase protein C-reactive protein (CRP) (Howren et al. 2009; Miller et al. 2009a, b; Dowlati et al. 2010). Finally, non-depressed individuals who develop a primary immune disorder show substantially higher rates of anhedonic symptoms on commonly used symptom inventories than the general population (Pincus et al. 1996; Dickens and Creed 2001; Blume et al. 2011).

While inflammation may affect a variety of brain areas, significant data highlight the striatum as a primary site of inflammation-induced CNS dysfunction (Capuron et al. 2007; Miller et al. 2009a, b). Inflammatory cytokines are known to disrupt DA neurotransmission including DA synthesis and release in rodents and non-human primates (Felger et al. 2007; Qin et al. 2007; Miller et al. 2009a, b; Dantzer et al. 2012; Felger et al. 2013), leading to impairments in effort expenditure and anticipation.

Of note, these reductions in motivation are similar to those observed by direct DA antagonism in the striatum as described above and suggest that cytokine interference with DA synthesis capacity may be partially responsible for these effects. Moreover, the effects of inflammation on DA signaling may worsen over time; DA plays an important anti-inflammatory role in the brain (Sarkar et al. 2010; Yan et al. 2015), and decreased DA availability may further exacerbate inflammatory effects via a positive feedback loop, resulting in a chronically inflamed, hypo-dopaminergic state.

As a consequence of inflammation-mediated DA interference, corticostriatal networks may become dysfunctional. Supporting this notion, human fMRI studies have identified associations between peripheral cytokine levels and fMRI measures

of neural processing in the DA-rich striatum and regions of medial prefrontal cortex (mPFC) in healthy volunteers exposed to typhoid vaccination (Harrison et al. 2009). Additionally, administration of inflammatory cytokines [interferon (IFN) alpha] or cytokine inducers (endotoxin) is associated with blunted ventral striatal responses to reward anticipation (Eisenberger et al. 2010; Capuron et al. 2012), as well as decreased DA release within the striatum as measured by [18F] Dopa binding in humans and in vivo microdialysis in non-human primates (Capuron et al. 2012; Felger et al. 2013). These data clearly demonstrate that increasing inflammation can reduce DA availability and impair corticostriatal circuit function.

Further supporting an inflammation–dopamine subtype of depression, growing evidence suggests that inflammation may specifically induce symptoms related to motivation. In animal models of effort-based decision-making, administration of cytokines or cytokine inducers reduces willingness to work for rewards (Nunes et al. 2013; Vichaya et al. 2014), an effect which is reversible through pharmacologic stimulation of striatal pathways (Nunes et al. 2013). Motivational deficits have also been observed in rodents and non-human primates following IFN-α manipulations (Couch et al. 2013; Felger et al. 2007; Thorne et al. 2008; Felger and Miller 2014). Finally, in humans, IFN-α and cytokine inducers rapidly and robustly produce motivational complaints (apathy, lassitude) in the majority of recipients, while cognitive and affective symptoms develop later, and are often more pronounced in individuals with a predisposing diathesis, such as elevated trait neuroticism (Capuron et al. 2004; Capuron and Miller 2011).

Blockade of inflammation selectively improves motivation symptoms *only* in patients with high baseline inflammation. Recently, a randomized, placebo-controlled clinical study was conducted to determine the effects of inflammation blockade on depressive symptoms (Raison et al. 2013). Blockade was achieved using infliximab, a monoclonal antibody to TNF with minimal "off-target" effects compared to other anti-inflammatory compounds. Following a single infusion of this highly selective TNF antagonist, a robust decrease in the plasma inflammatory biomarker, high-sensitivity C-reactive protein (hs-CRP), was observed and a subsequent improvement in reported symptoms of motivation and engagement in activities. Notably, the magnitude of change in this symptom domain following infliximab was double that of any other symptoms, and this effect was only present in patients with high inflammation at baseline (CRP > 5 mg/L).

In sum, there is strong evidence that inflammation is elevated in a subset of depressed patients and that increased inflammatory signaling may deplete DA availability, reduce DA-moderated regulation of inflammation, and produce motivational impairments in animals that mirror depressed phenotypes. Moreover, stimulation of cytokines results in motivational symptoms, and these symptoms are selectively ameliorated by anti-inflammatory treatments in patients with elevated inflammatory profiles. These data suggest that inflammation-mediated decreases in DA synthesis capacity may underlie reduced motivation in a subset of depressed patients.

5 Synaptic Plasticity Alterations May Impact Motivation in Patients with Depression

Clearly, however, many patients meeting criteria for depression and apathy do not express gross alterations in immune signaling (Raison and Miller 2011). Consequently, a second candidate mechanism underlying motivational deficits in depression is impaired synaptic plasticity. Growing evidence from preclinical and computational modeling work suggests that dopamine may contribute to reinforcement in large part through altering synaptic plasticity within corticostriatal circuits; that is, DA signaling—particularly phasic DA bursts or dips—helps strengthen corticostriatal synaptic connections that link reward-related cues to rewarding outcomes (Reynolds et al. 2001; Frank et al. 2004; Wieland et al. 2015). Alterations of postsynaptic plasticity mechanisms may therefore manifest as blunting of DA-related reinforcement signals, thereby contributing to dysfunction in DAergic circuitry without reflecting a primary deficit in DA-releasing neurons per se.

A variety of data support the hypothesis that neuroplasticity is affected in MDD. Early evidence comes from structural neuroimaging studies, demonstrating diminished gray matter volume in the hippocampus (Sheline et al. 1999; MacQueen et al. 2003)—a key region involved in neurogenesis—and these findings have been confirmed and replicated in meta-analyses and subsequent large-sample studies (Kempton et al. 2011; Schmaal et al. 2015). Further evidence comes from postmortem studies, where decreases in cellular density (Cotter et al. 2001; Chana et al. 2003; Monkul et al. 2006) and reduced expression of proteins involved in neurogenesis and synaptic plasticity (Kempermann and Kronenberg 2003; Dwivedi et al. 2005; Pittenger and Duman 2007) have been observed. More recently, serum measures of brain-derived neurotrophic factor (BDNF) have been found to be significantly decreased in patients during a depressive episode (Molendijk et al. 2014; Bus et al. 2015). This latter finding is of particular interest, as BDNF is a well-characterized neurotrophin that is known to stimulate growth of new synapses and dendrites throughout the life span via stimulation of tropomyosin kinase B (Trk-B) receptors (Yoshii and Constantine-Paton 2010; Autry and Monteggia 2012).

Finally, the discovery of ketamine as an efficacious antidepressant with remarkably rapid onset (Zarate et al. 2006; Diazgranados et al. 2010; Ibrahim et al. 2011; Zarate et al. 2012; Murrough et al. 2013a, b) has suggested possible plasticity-dependent mechanisms. Administration of ketamine at therapeutic doses is believed to stimulate synaptic plasticity (Duman and Aghajanian 2012, Monteggia and Zarate 2015). Evidence for this hypothesis comes from a recent study showing that ketamine may stimulate BDNF expression via inhibition of a eukaryotic elongation factor 2 signaling pathway that ultimately results in reduced suppression of BDNF translation (Autry et al. 2011). Moreover, this study found that administration of ketamine failed to produce antidepressant effects in BDNF

knockout animals, suggesting that enhanced BDNF translation may be a necessary component for ketamine's antidepressant effects.

In sum, two plausible biological pathways are proposed that may result in disruption of DAergic corticostriatal circuitry and subsequent reductions in motivation and reinforcement learning. Both of these pathways have found significant support in preclinical and clinical studies of depression, though we note that only one involves a direct effect on DA itself, which may partially account for some of the heterogeneity observed in DA imaging studies in depression. It is worth noting that some studies have suggested that these pathways may interact, as inflammation may directly impair peripheral BDNF levels in humans (Lotrich et al. 2013), as well as disrupt neurogenesis in rodents (Monje et al. 2003). Conversely, DA is believed to play a role in synaptic plasticity via promoting long-term potentiation or depression within striatal circuits, as described above (Reynolds et al. 2001; Wieland et al. 2015). Therefore, it may be the case that inflammation and impaired plasticity represent distinct points of vulnerability within a common circuit and may act independently or in concert to produce deficits in motivation and reinforcement learning associated with depression.

6 Conclusion

Anhedonia is a complex symptom domain that may include multiple facets associated with approach behavior. Over the years, there have been various efforts to introduce new terminology to distinguish the narrow definition of anhedonia as "loss of pleasure" from the much broader connotation used in the clinical literature (Klein 1987; Salamone et al. 1994; Treadway and Zald 2011), but a new consensus has yet to emerge. This can hamper translational efforts, as studies performed at different levels may use the same terms to describe distinct processes. As described in this chapter, the various components of anhedonia are likely instantiated by distinct neural circuits, and isolating these factors biologically may require parsing this symptom domain more finely than has been achieved by many clinical measures.

In this review, we have focused primarily on possible mechanisms related to deficits in motivation and reinforcement learning, as these are two possible components of anhedonia that have received empirical support in recent years. This should not be taken to imply, however, that other aspects of anhedonic symptoms, such as loss of pleasure, are unimportant or less prevalent. Indeed, these questions have yet to be fully addressed in part because the relational structure of different components within the anhedonic symptom domain remains unknown. Rather, a possible advantage of the focus on motivation and reinforcement learning is that there is a rich preclinical literature upon which to draw. As summarized above, this approach has already begun to bear fruit, as studies linking elevated neuroinflammation, decreased dopamine signaling, and reduced motivation have begun to point to the targeted administration of anti-inflammatory treatments for individuals with

depression and high inflammation. In the not-too-distant future, one can even imagine that screening for high inflammation may become a routine part of selecting an antidepressant treatment. While more needs to be done, progress has been made in our understanding of the pathophysiology of motivational symptoms in depression.

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