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Can't or won't? Immunometabolic constraints on dopaminergic drive

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Abstract

Inflammatory cytokines have been shown to have a direct effect on mesolimbic dopamine (DA) that is associated with a reduced willingness to expend effort for reward. To date, however, the broader implications of this communication between inflammation and mesolimbic DA have yet to be explored. Here, we suggest that the metabolic demands of chronic, low-grade inflammation induce a reduction of striatal DA that in turn leads to a steeper effort discounting curve because of reduced perceived ability (can't) versus preference (won't) for reward. This theoretical framework can inform how the mesolimbic DA system responds to increased immunometabolic demands during chronic inflammation, ultimately contributing to motivational impairments in psychiatric and other medical disorders.

Keywords

Dopamine; Effort; Inflammation; Cytokines; Immunometabolism

Dopamine, Effort and the Inflammatory Response

The efficient utilization of energy resources for goal-directed behaviors is believed to have been a driving force in the evolutionary development of the central nervous system (CNS) and its response to the environment [1]. Over the past several decades, our understanding of the neurobiological mechanisms that govern exploratory behavior and goal pursuit has expanded exponentially. This work has revealed a central role for mesolimbic signaling of the phylogenetically conserved neurotransmitter dopamine (DA) in shaping the willingness to expend energy [2–5], forage [6–8], and the drive to overcome obstacles [9, 10] in pursuit

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DISCLOSURES

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of rewards. To date, however, the majority of studies have focused on the behavioral consequences of mesolimbic DA signaling within the striatal, limbic, and cortical areas that mediate various aspects of normal and abnormal reward-seeking behavior. In contrast, a smaller body of work has focused on inputs to the mesolimbic DAergic system from sources outside the CNS that communicate relevant bodily states in order to influence the responsivity of DAergic neurons and the calculus of effort-based decision-making.

One emerging source of this external regulation is inflammation. There is growing appreciation that many of the behavioral sequelae associated with infection and the related inflammatory response, including alterations in reward seeking behavior (as occurs in so-called “sickness behavior”), are a direct consequence of the impact of inflammatory cytokines on mesolimbic DA signaling [11, 12]. To date, however, the broader implications of this mesolimbic DA–immune axis have yet to be fully explored. Herein, we propose that inflammatory signaling molecules play a critical role in communicating information relevant to shifts in immunometabolism that impact available energy resources in the body; a prerequisite for the mesolimbic DA system to generate accurate estimates of expected value of reward and guide effort allocation and energy expenditure. This function may have originated during evolution as a means of suppressing exploratory behavior and shifting energy resources to the immune system for fighting infection and healing wounds in an ancestral environment rife with pathogens and predators [13, 14]. Nevertheless, we suggest that in the modern world, communication between the immune system and DA may be crucial for shaping effort allocation as a function of peripheral immunometabolic states characterized by the increased energy demands of chronic low-grade (non-resolving) inflammation. Such states include chronic stress, obesity, the metabolic syndrome, aging, dysbiosis, and a variety of medical illnesses and their treatments [15, 16].

The overarching goals of this review are: first, to summarize the extant body of research describing the impact of inflammatory mediators on mesolimbic DA signaling; next, to review the metabolic consequences of chronic inflammation; and finally, to integrate these two literatures into a comprehensive framework to account for the effects of inflammation and its attendant immunometabolic costs on effort discounting. As part of this framework, we adapt an established computational model of effort discounting to incorporate the effects of chronic inflammation on energy availability. This model provides the basis for indexing and calculating the effects of chronic inflammation and associated immunometabolic states on effort-based decision-making. We also touch on the implications of this mesolimbic DA–immune axis for understanding impairments in motivated behavior in psychiatric disorders, such as depression and schizophrenia, along with potential translational implications.

Inflammation and Dopaminergic Drive

Overwhelming evidence suggests that a primary function of the mesolimbic DA system is to determine motivational drive – i.e., the value of investing effort in the pursuit of rewards [9, 17–19]. In animal models, this has been demonstrated convincingly via experimental manipulations including pharmacological blockade of DA transmission [9, 17] and optogenetic manipulation of DA neurons [19] as well as correlative studies showing that striatal DA release exhibits a “ramping” signal that approximates reward availability [20,

21]. Effort-based decision-making paradigms that operationalize motivation by assessing an individual's willingness to invest greater effort in order to obtain larger or preferred rewards have repeatedly demonstrated that DA is both necessary and sufficient for motivated behavior [9, 22]. In addition, potentiation or attenuation of DA signaling can increase or decrease effort expenditure for rewards in both rodents [3, 4, 23] and humans [5, 24]. Of note, these actions of the DA system are somewhat distinct from reward prediction error (RPE) encoding [25, 26], a discussion of which is beyond the scope of this review (see [18, 27] for reviews). Nevertheless, data suggest that striatal DA release may be distinct from midbrain DAergic neuron firing rates [20], and serves primarily to signal the need for action [19, 28, 29], consistent with the interpretation that striatal DA reflects the expected value of work [18, 19].

Based on the role of mesolimbic DA in effort expenditure for reward and reward valuation, inputs to the DA system from the peripheral body are essential to accurately estimate prevailing needs and energy resources for effort expenditure. While there are several mechanisms that have been studied relevant to peripheral inputs including those related to hunger and thirst (see Box 1), growing attention is being paid to the impact of inflammation on DA signaling and its potential implications for reward seeking behavior. Indeed, inflammatory cytokines have been shown to disrupt DA neurotransmission including DA synthesis, release, and reuptake in multiple experimental systems including laboratory animals and humans [30–34] (see Table 1).

Some of the first data supporting the notion that inflammation may influence DA pathways came from studies using positron emission tomography (PET) to examine glucose metabolism in the brain of patients receiving the inflammatory cytokine interferon (IFN)-alpha for either malignant melanoma or hepatitis C [35, 36]. These studies revealed evidence of increased glucose metabolism in subcortical regions consistent with changes observed in Parkinson's disease (PD). Further supporting the idea that inflammation may be targeting DA signaling, administration of IFN-alpha to humans has been associated with blunted ventral striatal responses to reward anticipation using functional magnetic resonance imaging (fMRI) [37]. In addition, IFN-alpha treatment of patients with hepatitis C has been shown to decrease DA release within the striatum as measured by [¹⁸F]Dopa binding using PET [37]. Other inflammatory stimuli including endotoxin and typhoid vaccination administered to healthy volunteers also have been associated with decreased neural processing in the DA-rich striatum and regions of medial prefrontal cortex (mPFC) in response to rewarding stimuli using fMRI [38–40]. Similar results have been found in depressed patients where increased inflammation as indexed by c-reactive protein (CRP) was associated with decreased connectivity between ventral striatum and mPFC, which in turn correlated with reduced motivation reflected by symptoms of anhedonia [41].

Consistent with these neuroimaging findings, studies using in vivo microdialysis in ventral striatal brain regions have demonstrated that administration of IFN-alpha to non-human primates is associated with significant decreases in extracellular DA both at baseline and following stimulation with potassium or amphetamine [42, 43]. Decreases in extracellular DA were also found in rodents administered interleukin (IL)-6 and sampling from the nucleus accumbens core [44]. An open question is the specific cellular and molecular

mechanisms by which cytokines alter striatal DA. One possibility is that inflammation may lead to decreased DA synthesis via depletion of tetrahydrobiopterin (BH4) [45]. BH4 is an essential enzyme co-factor for the synthesis of DA, supporting the activity of phenylalanine hydroxylase, which converts phenylalanine to tyrosine, and tyrosine hydroxylase which converts tyrosine to L-Dopa [46]. Increased cerebrospinal fluid (CSF) concentrations of IL-6 were found to be associated with decreased CSF BH4 [45]. Consistent with disrupted synthesis is the observation that IFN- α -induced deficits in striatal DA release were restored by administration of L-Dopa via reverse microdialysis [47]. In addition to effects on synthesis capacity, more recent data suggests the presence of a fast-acting pathway mediated by IL-6. Intraperitoneal injection of IL-6 in rodents led to a 40% reduction in striatal DA within 30 minutes of administration [48], a change that is likely too large and too rapid to be mediated by disrupted DA synthesis alone. Such rapid effects could be secondary to the activation of inflammatory signaling pathways including mitogen activated protein kinases, which have been shown to stimulate DA reuptake by increasing the maximum rate (V_{max}) of the DA transporter [49]. In addition to direct effects of cytokines such as IL-6 on DA neurons, it is also possible that cytokines or other inflammatory stimuli might activate immune cells in the brain, e.g. microglia, which in turn can produce a variety of factors that might influence the function of DAergic neurons [50]. For example, production of reactive oxygen species by activated microglia can lead to mitochondrial dysfunction and DAergic dysregulation as seen in disorders such as Parkinson's disease [51]. Mitochondrial dysfunction, which has been reported in depression [52], can also exacerbate and/or activate inflammatory responses in microglia, indicating potential bidirectional interactions between mitochondrial dysfunction in neurons and immunometabolic changes in microglia [52]. Of note, there is an overrepresentation of microglia in DAergic midbrain pathways relative to other brain regions, which may account for the special sensitivity of DA to immunologic influences [53]. These latter findings raise the question of whether the signaling of immunometabolic demands arises centrally (in the brain) or originates in the periphery. Although beyond the scope of this review, recent data suggest that signals originating from the periphery likely play a role given findings that peripheral inflammatory cytokines such as IL-6 may have direct access to striatal brain regions including the nucleus accumbens related to stress-induced decreases in Claudin-5, a protein that plays a pivotal role in blood-brain-barrier (BBB) integrity and permeability [54]. Other pathways by which peripheral inflammatory signals can be transmitted to the brain include cell trafficking to the brain, cytokine passage through leaky regions of the BBB and signaling through afferent fibers of the vagus nerve [55].

In keeping with the above noted effects of inflammation on striatal neural activity and DA neurotransmission, inflammation also produces concomitant effects on behaviors relevant to effort expenditure for reward and reward valuation. Using a concurrent choice paradigm in rodents, acute administration of IL-1 β or IL-6 was associated with a shift away from preferred foods that required effort in favor of less desirable food that was freely available [48, 56]. Consistent with the idea that cytokines may promote energy conservation, an endotoxin challenge in rodents reduced overall energy expenditure but increased the relative proportion of effort for more calorie-rich rewards, indicating that inflammation was decreasing overall effort expenditure but not sensitivity to reward [57]. Similar effects of

cytokine or endotoxin administration on effortful behavior have been observed in non-human primates [42] and humans [58], where sensitivity to reward remained intact but effort expenditure for reward was reduced.

Taken together, these data suggest that inflammation may primarily reduce effort expenditure for rewards by increasing the perceived cost of effort as opposed to reducing the value of the reward itself (though the precise role of DA in signaling regarding effort vs. reward remains a topic of some debate [9, 59]). What remains unclear, however, is the adaptive function of this communication pathway between DA and the immune system. In the following two sections, we suggest that this may result from the metabolic demands of immune activation, and the need to integrate a subsequent reduction of available energy into future effort-discounting decisions.

Metabolic Consequences of Chronic Inflammation

During significant infection or wounding and the concomitant inflammatory response, energy expenditures of the immune system can increase by up to 60%, dominating the overall daily energy expenditure of the body [16]. This metabolic reprogramming, which requires rapid mobilization of glucose, is necessary to fuel a robust protective response against perceived hostile external or internal environmental factors and represents a shift in the body's programs of maintenance from dormancy to defense, ultimately leading to divestment in growth and reproduction as well as the behaviors that support these processes [60]. Although exposure to endotoxin reflects an extreme case of inflammation—resembling that of severe infection or wounding—chronic low-grade inflammation as is seen in the case of chronic stress, metabolic disorders (e.g. obesity and metabolic syndrome), dysbiosis, and medical illnesses (e.g. cardiovascular disease, diabetes, cancer, chronic infectious diseases, and autoimmune and inflammatory disorders) also has attendant energy costs that can increase the overall daily energy expenditure by as much as 30% [16]. Moreover, as indicated above, data demonstrate that even low levels of chronic inflammation can be associated with reduced extracellular DA, disrupted reward circuitry and decreased effort expenditure for reward in humans and laboratory animals [11]. Thus, it is reasonable to consider that inflammatory cytokines may function in part to communicate to the brain shifts in bodily metabolism that warrant attendant shifts in motivation and decision-making processes relative to effort expenditure. A pivotal aspect of this communication pathway is the ability of the immune system to recognize molecules derived from both microbial and non-microbial processes that impact metabolic demands by driving chronic low-grade inflammation. Receptors that provide cells of the innate immune system with the capacity to recognize these molecules are called pattern recognition receptors (PRRs).

There are two types of PRRs including those associated with microbial threats as reflected by microbe-associated molecular patterns (MAMPs) and those associated with danger-associated molecular patterns (DAMPs), which represent non-infectious stimuli that signal cellular distress (as can occur during tissue damage or destruction), leading to so-called “sterile inflammation” [61, 62]. While MAMPs are associated with microbes (e.g. viruses and bacteria) that are typically pathogenic to the host, they also represent commensal/symbiotic microbes including bacteria and bacterial products associated with the

microbiome. Indeed, circulating MAMPS secondary to dysregulation of the gut microbiome and a leaky gut (dysbiosis) signal the consequences of poor dietary habits, hyperglycemia, psychological or physical stressors, and gastrointestinal disease by activating PRRs and the inflammatory response [63, 64]. DAMPs on the other hand are associated with molecules more directly related to cellular stress including those associated with psychosocial stress (e.g. heat shock proteins, high mobility group box 1) as well as obesity and the metabolic syndrome (e.g. free fatty acids, ATP, uric acid, markers of mitochondrial dysfunction) [65, 66]. DAMPs also reflect the tissue damage and destruction that accompanies multiple medical illnesses and their treatments (e.g. surgery chemotherapy and radiation for cancer), which along with MAMPS (especially in infectious diseases) contribute to the chronic inflammation that characterizes these disorders. Of note, chronic inflammation, in turn contributes to the progression of many of these conditions, thus leading to a vicious cycle of inflammation and disease.

Binding of MAMPS and DAMPs to PRRs leads to activation of inflammatory signaling pathways including nuclear factor kappa B (NFkB) and the inflammasome, a protein complex that together with NFkB leads to the production of multiple inflammatory mediators including the inflammatory cytokines IL-1, IL-6 and TNF [55, 62]. In the context of immune activation, immune cells also undergo a process of metabolic reprogramming that involves a relative shift from oxidative phosphorylation to glycolysis (see Figure 1) [67]. Although much more energy (more molecules of ATP per molecule of glucose) can be generated by oxidative phosphorylation, the shift to glycolysis allows rapid production of ATP, compared to the ramping up of oxidative phosphorylation which requires an increased production of mitochondria, where oxidative phosphorylation occurs [67]. Moreover, glycolysis generates a series of intermediate metabolites that contribute to fatty acid and amino acid synthesis via the pentose phosphate pathway, ultimately supporting rapid cell growth and proliferation. Of note, many of the intermediates of glycolysis further stimulate production of inflammatory cytokines through activation of the inflammasome along with fatty acid synthesis that can promote the development and function of multiple inflammatory cell types including M1 macrophages and T helper Th1 and Th17 cells, which produce a variety of inflammatory mediators including inflammatory cytokines. Indeed, glycolysis can be considered one of the metabolic hallmarks of the inflammatory phenotype [67].

Importantly, the shift in metabolism from oxidative phosphorylation to the more energy inefficient glycolysis during immune activation is a primary driver of the excessive energy demands that characterize the inflammatory response and consequently chronic low-grade inflammation [67, 68]. It is not surprising therefore that data suggest that the molecules derived from activated immune cells (e.g. inflammatory cytokines) influence mesolimbic DA systems to support the metabolic needs of managing perceived threats to body integrity signaled by MAMPS and DAMPs.

Can't or Won't: A Computational Framework for Immunometabolic Effects on Effort Discounting

Given the impact of peripheral inflammatory mediators on mesolimbic DA described above, biologically-plausible models of effort discounting should be updated to reflect the effects of inflammation on the perception of effort. Specifically, we suggest that immune signaling may suppress the DAergic system's estimate of value, subsequently adapting what is "worth the effort" to the body's current metabolic capacity (Figure 2).

To date, most theoretical models of effort perception have focused on cognitive effort and the experience of mental fatigue [69–71]. These models have generally conceptualized the phenomenological experience of mental effort in terms of a cost-benefit comparison, balancing the benefit (i.e. expected utility) against the metabolic, temporal, and opportunity costs associated with computing that solution [70, 72]. Moreover, these models have generally focused on situations with a very high likelihood of success such that input signals related to changes in individual ability are often not explicitly considered. In our proposed framework, we seek to incorporate peripheral markers of inflammation as a decision input variable that may better capture variability in decision making behavior (i.e. effort expenditure) that reflect changes in perceived ability as a function of metabolic state. In this way, the role of inflammation may be less related to effort expenditure as a matter of preference (will I/won't I?), and more related to perceived ability (can I/can't I?). We note that this is likely a distinct process from classical probabilistic discounting, as the estimate of ability is derived from peripheral signals encoding metabolic resources and thus transient changes in individual ability, rather than a Bayesian estimate based primarily on prior history or trial-wise measures of probability of reward receipt.

Prior discounting models have generally not distinguished between preference and ability [73–75], and have instead simply modeled effort as a single cost to which individuals exhibit greater or less sensitivity, which can be formally expressed by one or more free parameters. The discounting or cost functions used to integrate these quantities are defined by the model and can take a variety of shapes with differing interpretations. For example, the cost function may be linear, suggesting that single unit increases in required effort have similar effects on subjective value across effort levels. Alternately, discounting functions may be described by more complex shapes (i.e. hyperbolic, quadratic, sigmoidal) where unit increases in required effort will differentially affect subjective value at different levels of effort. These cost functions can then be used to generate trial-wise estimates of subjective value for use as parametric modulators in neuroimaging analysis, allowing for analysis of the neurocomputational mechanisms involved in decisions regarding effort expenditure [73, 76].

In the top panel of Figure 2, we present a commonly used flexible power function that has been found to provide a good fit for data from effort discounting tasks [73, 77]. In Equation 1, individual variation in sensitivity to effort is represented by the constants (free parameters) k and p that are adjusted to fit the behavior of individual agents. The value of parameter p determines the curvature of the cost function, with $p < 1$ indicating convex discounting and $p > 1$ indicating concave discounting, while parameter k additionally affects the rate at which rewards are discounted by required effort.

Interestingly, research examining the rate at which rewards are discounted by required effort has found that effort discounting is better described by parabolic or concave discounting functions [73–75, 77], as opposed to the convex discounting curves (i.e. hyperbolic) that have long characterized inter-temporal discounting [78]. The interpretation of these results is that a similar increase in effort has a smaller effect on value at low levels of effort than at higher levels of effort. We would suggest that this acceleration of discounting that occurs as effort continues to increase likely reflects a shift from a pure matter of preference to increased perception that a particular goal may be unattainable [79].

While some work has incorporated effects of task-based fatigue into subjective value calculations (e.g. [80]), the impact of peripheral immunometabolic demands have received little attention. Based on the data summarized above regarding the effects of immune signaling on striatal DA and effortful behavior, we suggest a new model where the subjective value for an action is scaled according to estimates of the current immunometabolic state as indexed by markers of inflammation (Figure 2, Equation II). The amount of effort at which the subjective value of an available reward approaches zero (and turns negative) changes in response to the amount of available resources. Immunometabolic state is represented by the quantity B , $0 < B < 1$, where 1 represents optimal resource availability. An additional consideration is that individuals may be differentially sensitive to internal changes in metabolism. The model accounts for this variability by including free parameter s that quantifies individual sensitivity to immunometabolic changes. An individual who is completely insensitive to metabolic state would act as though subjective values were independent of relevant inputs, while individuals sensitive to metabolic state would modify their behavior in response to perceived reductions in available resources. For example, our model would assume that the value for B at a given timepoint may be best approximated by the overall level of circulating inflammatory markers. Mechanisms associated with individual differences for example in the access or impact of peripheral inflammatory signals would be reflected in our proposed model as an increase in parameter s , suggesting a greater sensitivity to the effects of increased immunometabolic signaling.

Our model emphasizes the effects of immunometabolism on effort sensitivity, rather than perceived reward value, a supposition that has been supported by several empirical studies using inflammatory challenges in humans and animals [57, 58, 81]. Under this model, the addition of time-series sampling of peripheral inflammatory markers should improve model fit for effort discounting behavior during an immunometabolic state-shift (e.g., effort discounting over the course of an experimental inflammatory challenge) as compared to standard effort discounting models. That said, it should be acknowledged that the proposed model is only one possible computational mechanism by which effort allocation may be affected by immunometabolic demands. For example, it is possible that alterations in immunometabolism could primarily affect the curvature of the discounting function. Nevertheless, these details, and whether the cost function may be better represented by other shapes (e.g. sigmoidal) will require empirical testing.

An additional limitation of our model as presented here is that it focuses primarily on the actions of a unidirectional pathway; namely, peripheral cytokines $\rightarrow$ CNS DA. We should acknowledge that there many other pathways linking DA and inflammatory signaling, the

functional significance of which have not been fully elucidated. For example, it has been shown that DA can suppress immune activity in the CNS [82], while catecholamine release in response to stress can activate immune responses in the periphery [83]. Additionally, inflammatory cells are capable of synthesizing and releasing DA as a mechanism of self-regulation [84]. These complex relationships belie a linear model for describing DA-immune interactions. That said, we believe our proposed model provides an important step towards formalizing testable hypotheses for studying the effects of inflammation on DA-linked approach behavior.

Translational Implications

Given the impact of inflammation on fundamental aspects of reward processing, a logical consideration of the findings above is that inflammation may play a role in core symptoms of psychiatric disorders related to effort expenditure for reward including anhedonia in depression, anxiety disorders, and post-traumatic stress disorder as well as negative symptoms in schizophrenia. All of these psychiatric conditions have been reliably associated with increased peripheral blood inflammatory markers [55], and in many cases, the concentration of inflammatory markers have been directly associated with symptoms of impaired motivation [41, 55]. Moreover, alterations in effort expenditure for reward have been demonstrated in patients with depression and schizophrenia [85, 86], although no study to our knowledge has linked inflammatory markers to these findings. Based on the work described above, inflammation would be expected to have specific inhibitory effects on effort expenditure for reward as opposed to sensitivity to reward; a hypothesis that warrants further exploration in psychiatric populations.

Regarding the treatment of inflammation-induced impairments in motivation in psychiatric patients, probably the most obvious strategy would be to block inflammation itself. Unfortunately, only a few clinical trials have used anti-inflammatory drugs to treat psychiatric disease [87], and in only one study were individual symptoms examined [88]. In this trial of the TNF antagonist infliximab for treatment resistant depression (TRD), the item related to anhedonia on the 17-item Hamilton Depression Rating Scale was the most improved of all symptoms in TRD patients with high inflammation as indexed by a CRP >5mg/L [88]. Treatment response to infliximab in this study was also predicted by gene transcripts in peripheral blood immune cells related to glucose (glycolysis) and lipid metabolism [89], suggesting that immunometabolic shifts that drive inflammatory responses may also serve as a target for future therapies of motivational anhedonia. Indeed, the reprogramming of metabolic pathways including glycolysis in immune cells is already being considered as a novel therapeutic strategy in inflammatory disorders [90]. Aside from treatments that directly target inflammation or immunometabolism, the effects of inflammation on DA pathways probably represent the most immediately achievable method for addressing inflammation-associated motivational deficits. Indeed, a recent clinical trial in depressed patients found that individuals with increased inflammation (CRP >1mg/L) showed a much higher response to a combination of a selective serotonin reuptake inhibitor (SSRI) plus the dopamine reuptake inhibitor bupropion than the SSRI alone [91]. Further information on the molecular mechanisms by which inflammation inhibits DA signaling will greatly facilitate drug discovery in this area as well as clinical trials using inflammatory

biomarkers to guide therapies and measures of effort-based decision making and ventral striatal reward circuitry as targets of response. Regarding psychotherapeutic interventions, the data suggest that inflammation-induced effects on motivation, which spare reward sensitivity, may be especially responsive to cognitive behavioral therapies that incentivize effort expenditure including behavioral activation treatments [92]. Finally, lifestyle changes may also be relevant for supplementing pharmacologic or behavioral treatments and prevention; exercise and diet (i.e. Mediterranean) [93, 94], as well as meditation and yoga [95, 96], have been shown to reduce peripheral inflammatory markers.

Concluding Remarks and Future Directions

The goal of this review was to explore the purpose and implications of the mesolimbic DA–immune axis. We have proposed a new framework in which immunometabolic demands of chronic, low-grade inflammation may induce a transient reduction of striatal DA as a means of shifting effort discounting behavior. While this mechanism may have been adaptive in ancestral times, the increased prevalence of chronic inflammation as a function of multiple factors including poor diet, limited exercise and increased stress in Western societies may contribute to rising rates of depression and other disorders associated with motivational impairments. Future research will be needed to test our computational model, as well as determine the extent to which the effects of immune stimulation on striatal DA and effort expenditure are dependent on immunometabolism. Future research will also be needed to better clarify the precise mechanisms by which increased inflammation alters DA availability. Elucidation of these mechanisms will both enhance our understanding of how the mesolimbic DA incorporates information regarding energy availability into effort discounting and help identify new therapeutic approaches for motivational impairments.

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REFERENCES

1. Wolpert DM et al. (2003) A unifying computational framework for motor control and social interaction. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 358 (1431), 593–602. [PubMed: 12689384]
2. Salamone JD et al. (2016) Activational and effort-related aspects of motivation: neural mechanisms and implications for psychopathology. *Brain* 139 (5), 1325–1347. [PubMed: 27189581]
3. Salamone JD et al. (2007) Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology (Berl)* 191 (3), 461–82. [PubMed: 17225164]
4. Floresco SB et al. (2008) Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. *Neuropsychopharmacology* 33 (8), 1966–79. [PubMed: 17805307]
5. Wardle MC et al. (2011) Amping Up Effort: Effects of d-Amphetamine on Human Effort-Based Decision-Making. *J Neurosci* 31 (46), 16597–16602. [PubMed: 22090487]
6. Floresco SB et al. (1996) A selective role for dopamine in the nucleus accumbens of the rat in random foraging but not delayed spatial win-shift-based foraging. *Behav Brain Res* 80 (1–2), 161–168. [PubMed: 8905139]

7. Salamone JD et al. (1991) Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food choice procedure. *Psychopharmacology (Berl)* 104 (4), 515–521. [PubMed: 1780422]
8. Rutledge RB et al. (2009) Dopaminergic drugs modulate learning rates and perseveration in Parkinson's patients in a dynamic foraging task. *J Neurosci* 29 (48), 15104–15114. [PubMed: 19955362]
9. Salamone JD and Correa M (2012) The mysterious motivational functions of mesolimbic dopamine. *Neuron* 76 (3), 470–85. [PubMed: 23141060]
10. Cousins MS et al. (1996) Nucleus accumbens dopamine depletions alter relative response allocation in a T-maze cost/benefit task. *Behav Brain Res* 74 (1–2), 189–97. [PubMed: 8851929]
11. Felger JC and Treadway MT (2017) Inflammation Effects on Motivation and Motor Activity: Role of Dopamine. *Neuropsychopharmacology* 42 (1), 216–241. [PubMed: 27480574]
12. Felger JC and Miller AH (2014) Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. *Front Neuroendocrinol*
13. Raison CL and Miller AH (2013) The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). *Mol Psychiatry* 18 (1), 15–37. [PubMed: 22290120]
14. Miller AH and Raison CL (2016) The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature Reviews Immunology* 16 (1), 22–34.
15. Nathan C and Ding A (2010) Nonresolving inflammation. *Cell* 140 (6), 871–82. [PubMed: 20303877]
16. Straub RH (2017) The brain and immune system prompt energy shortage in chronic inflammation and ageing. *Nat Rev Rheumatol* 13 (12), 743–751. [PubMed: 29021568]
17. Salamone JD et al. (2001) Nucleus accumbens dopamine depletions make animals highly sensitive to high fixed ratio requirements but do not impair primary food reinforcement. *Neuroscience* 105 (4), 863–70. [PubMed: 11530224]
18. Berke JD (2018) What does dopamine mean? *Nat Neurosci*, 1.
19. Hamid AA et al. (2016) Mesolimbic dopamine signals the value of work. *Nat Neurosci* 19 (1), 117–126. [PubMed: 26595651]
20. Mohebi A et al. (2018) Forebrain dopamine value signals arise independently from midbrain dopamine cell firing. *bioRxiv*, 334060.
21. Howe MW et al. (2013) Prolonged dopamine signalling in striatum signals proximity and value of distant rewards. *Nature* 500 (7464), 575–579. [PubMed: 23913271]
22. Treadway MT and Zald DH (2013) Parsing Anhedonia Translational Models of Reward-Processing Deficits in Psychopathology. *Current Directions in Psychological Science* 22 (3), 244–249. [PubMed: 24748727]
23. Bardgett ME et al. (2009) Dopamine modulates effort-based decision making in rats. *Behav Neurosci* 123 (2), 242–51. [PubMed: 19331447]
24. Venugopalan VV et al. (2011) Acute Phenylalanine/Tyrosine Depletion Reduces Motivation to Smoke Cigarettes Across Stages of Addiction. *Neuropsychopharmacology*
25. Schultz W DP, Montague PR (1997) A neural substrate of prediction and reward. *Science* 275 (5306), 1593–9. [PubMed: 9054347]
26. Schultz W (2007) Multiple dopamine functions at different time courses. *Annu Rev Neurosci* 30, 259–88. [PubMed: 17600522]
27. Schultz W (2015) Neuronal reward and decision signals: from theories to data. *Physiol Rev* 95 (3), 853–951. [PubMed: 26109341]
28. Syed EC et al. (2016) Action initiation shapes mesolimbic dopamine encoding of future rewards. *Nat Neurosci* 19 (1), 34–36. [PubMed: 26642087]
29. Collins AG and Frank MJ (2016) Surprise! Dopamine signals mix action, value and error. *Nat Neurosci* 19 (1), 3–5. [PubMed: 26713740]
30. Felger JC et al. (2013) Chronic interferon- α decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in nonhuman primates. *Neuropsychopharmacology* 38 (11), 2179–2187. [PubMed: 23657438]

31. Dantzer R et al. (2012) Translational approaches to treatment-induced symptoms in cancer patients. *Nat Rev Clin Oncol* 9 (7), 414–26. [PubMed: 22641361]
32. Miller AH et al. (2009) Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry* 65 (9), 732–41. [PubMed: 19150053]
33. Qin L et al. (2007) Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia* 55 (5), 453–62. [PubMed: 17203472]
34. Felger JC et al. (2007) Effects of interferon-alpha on rhesus monkeys: a nonhuman primate model of cytokine-induced depression. *Biol Psychiatry* 62 (11), 1324–1333. [PubMed: 17678633]
35. Capuron L et al. (2007) Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. *Neuropsychopharmacology* 32 (11), 2384–92. [PubMed: 17327884]
36. Juengling FD et al. (2000) Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. *Psychopharmacology (Berl)* 152 (4), 383–9. [PubMed: 11140330]
37. Capuron L et al. (2012) Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Arch Gen Psychiatry* 69 (10), 1044–53. [PubMed: 23026954]
38. Harrison NA et al. (2016) A Neurocomputational Account of How Inflammation Enhances Sensitivity to Punishments Versus Rewards. *Biol Psychiatry* 80 (1), 73–81. [PubMed: 26359113]
39. Eisenberger NI et al. (2010) Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. *Biol Psychiatry* 68 (8), 748–54. [PubMed: 20719303]
40. Harrison NA et al. (2009) Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol Psychiatry* 66 (5), 407–14. [PubMed: 19423079]
41. Felger JC et al. (2016) Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. *Mol Psychiatry* 21 (10), 1358–65. [PubMed: 26552591]
42. Felger JC et al. (2013) Chronic interferon-alpha decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in nonhuman primates. *Neuropsychopharmacology* 38 (11), 2179–87. [PubMed: 23657438]
43. Felger JC et al. (2007) Effects of interferon-alpha on rhesus monkeys: a nonhuman primate model of cytokine-induced depression. *Biol Psychiatry* 62 (11), 1324–33. [PubMed: 17678633]
44. Yohn SE et al. (2016) Effort-related motivational effects of the pro-inflammatory cytokine interleukin-6: pharmacological and neurochemical characterization. *Psychopharmacology (Berl)* 233 (19–20), 3575–86. [PubMed: 27497935]
45. Felger JC et al. (2013) Tyrosine metabolism during interferon-alpha administration: association with fatigue and CSF dopamine concentrations. *Brain Behav Immun* 31, 153–60. [PubMed: 23072726]
46. Haroon E et al. (2012) Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology* 37 (1), 137–62. [PubMed: 21918508]
47. Felger JC et al. (2015) Levodopa Reverses Cytokine-Induced Reductions in Striatal Dopamine Release. *Int J Neuropsychopharmacol*, pyu084.
48. Yohn SE et al. (2016) Effort-related motivational effects of the pro-inflammatory cytokine interleukin-6: pharmacological and neurochemical characterization. *Psychopharmacology (Berl)* 233 (19–20), 3575–3586. [PubMed: 27497935]
49. Moron JA et al. (2003) Mitogen-activated protein kinase regulates dopamine transporter surface expression and dopamine transport capacity. *J Neurosci* 23 (24), 8480–8. [PubMed: 13679416]
50. Block ML et al. (2007) Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neurosci* 8 (1), 57–69. [PubMed: 17180163]
51. Puspita L et al. (2017) Oxidative stress and cellular pathologies in Parkinson's disease. *Mol Brain* 10 (1), 53. [PubMed: 29183391]
52. Culmsee C et al. (2018) Mitochondria, Microglia, and the Immune System-How Are They Linked in Affective Disorders? *Front Psychiatry* 9, 739. [PubMed: 30687139]

53. Kim WG et al. (2000) Regional difference in susceptibility to lipopolysaccharide-induced neurotoxicity in the rat brain: role of microglia. *J Neurosci* 20 (16), 6309–16. [PubMed: 10934283]
54. Menard C et al. (2017) Social stress induces neurovascular pathology promoting depression. *Nat Neurosci* 20 (12), 1752. [PubMed: 29184215]
55. Miller AH and Raison CL (2016) The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 16 (1), 22–34. [PubMed: 26711676]
56. Nunes EJ et al. (2013) Effort-related motivational effects of the pro-inflammatory cytokine interleukin 1-beta: studies with the concurrent fixed ratio 5/chow feeding choice task. *Psychopharmacology (Berl)*, 1–10.
57. Vichaya EG et al. (2014) Lipopolysaccharide Reduces Incentive Motivation While Boosting Preference for High Reward in Mice. *Neuropsychopharmacology*
58. Lasselin J et al. (2017) Lipopolysaccharide Alters Motivated Behavior in a Monetary Reward Task: a Randomized Trial. *Neuropsychopharmacology* 42 (4), 801–810. [PubMed: 27620550]
59. Walton ME and Bouret S (2019) What Is the Relationship between Dopamine and Effort? *Trends Neurosci* 42, 79–91. [PubMed: 30391016]
60. Wang A et al. (2019) An evolutionary perspective on immunometabolism. *Science* 363 (6423).
61. Takeuchi O and Akira S (2010) Pattern recognition receptors and inflammation. *Cell* 140 (6), 805–20. [PubMed: 20303872]
62. Fleshner M (2013) Stress-evoked sterile inflammation, danger associated molecular patterns (DAMPs), microbial associated molecular patterns (MAMPs) and the inflammasome. *Brain Behav Immun* 27 (1), 1–7. [PubMed: 22964544]
63. Thaiss CA et al. (2018) Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. *Science* 359 (6382), 1376–1383. [PubMed: 29519916]
64. Maslanik T et al. (2012) Commensal bacteria and MAMPs are necessary for stress-induced increases in IL-1beta and IL-18 but not IL-6, IL-10 or MCP-1. *PLoS One* 7 (12), e50636. [PubMed: 23236381]
65. Schaefer L (2014) Complexity of danger: the diverse nature of damage-associated molecular patterns. *J Biol Chem* 289 (51), 35237–45. [PubMed: 25391648]
66. Fleshner M et al. (2017) Danger Signals and Inflammasomes: Stress-Evoked Sterile Inflammation in Mood Disorders. *Neuropsychopharmacology* 42 (1), 36–45. [PubMed: 27412959]
67. O'Neill LA et al. (2016) A guide to immunometabolism for immunologists. *Nat Rev Immunol* 16 (9), 553–65. [PubMed: 27396447]
68. Lacourt TE et al. (2018) The High Costs of Low-Grade Inflammation: Persistent Fatigue as a Consequence of Reduced Cellular-Energy Availability and Non-adaptive Energy Expenditure. *Front Behav Neurosci* 12, 78. [PubMed: 29755330]
69. Kurzban R (2016) The sense of effort. *Current Opinion in Psychology* 7, 67–70.
70. Shenhav A et al. (2017) Toward a rational and mechanistic account of mental effort. *Annu Rev Neurosci* 40, 99–124. [PubMed: 28375769]
71. Kurzban R et al. (2013) An opportunity cost model of subjective effort and task performance. *Behav Brain Sci* 36 (6), 661–679. [PubMed: 24304775]
72. Gershman S and Wilson R, The neural costs of optimal control, *Advances in neural information processing systems*, 2010, pp. 712–720.
73. Arulpragasam AR et al. (2018) Corticoinsular circuits encode subjective value expectation and violation for effortful goal-directed behavior. *Proceedings of the National Academy of Sciences*, 201800444.
74. Bialaszek W et al. (2017) Physical and cognitive effort discounting across different reward magnitudes: Tests of discounting models. *PLoS One* 12 (7), e0182353. [PubMed: 28759631]
75. Hartmann MN et al. (2013) Parabolic discounting of monetary rewards by physical effort. *Behav Processes* 100, 192–196. [PubMed: 24140077]
76. Klein-Flugge MC et al. (2016) Neural Signatures of Value Comparison in Human Cingulate Cortex during Decisions Requiring an Effort-Reward Trade-off. *J Neurosci* 36 (39), 10002–15. [PubMed: 27683898]

77. Klein-Flügge MC et al. (2015) Behavioral modeling of human choices reveals dissociable effects of physical effort and temporal delay on reward devaluation. *PLoS Comput Biol* 11 (3), e1004116. [PubMed: 25816114]
78. Frederick S et al. (2002) Time discounting and time preference: A critical review. *Journal of economic literature* 40 (2), 351–401.
79. Richter M et al. (2016) Three decades of research on motivational intensity theory: What we have learned about effort and what we still don't know. In *Advances in motivation science*, pp. 149–186, Elsevier.
80. Pessiglione M et al. (2017) Why not try harder? Computational approach to motivation deficits in neuro-psychiatric diseases. *Brain* 141 (3), 629–650.
81. Draper A et al. (2018) Effort but not reward sensitivity is altered by acute sickness induced by experimental endotoxemia in humans. *Neuropsychopharmacology* 43 (5), 1107. [PubMed: 28948979]
82. Shao W et al. (2013) Suppression of neuroinflammation by astrocytic dopamine D2 receptors via [agr] B-crystallin. *Nature* 494 (7435), 90–94. [PubMed: 23242137]
83. Bierhaus A et al. (2003) A mechanism converting psychosocial stress into mononuclear cell activation 100 (4), 1920–1925.
84. Kawano M et al. (2018) Dopamine regulates cytokine secretion during innate and adaptive immune responses 30 (12), 591–606.
85. Treadway MT et al. (2012) Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *J Abnorm Psychol* 121 (3), 553–8. [PubMed: 22775583]
86. Treadway MT et al. (2015) Impaired effort allocation in patients with schizophrenia. *Schizophr Res* 161 (2–3), 382–5. [PubMed: 25487699]
87. Kohler O et al. (2014) Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 71 (12), 1381–91. [PubMed: 25322082]
88. Raison CL et al. (2013) A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* 70 (1), 31–41. [PubMed: 22945416]
89. Mehta D et al. (2013) Transcriptional signatures related to glucose and lipid metabolism predict treatment response to the tumor necrosis factor antagonist infliximab in patients with treatment-resistant depression. *Brain Behav Immun* 31, 205–15. [PubMed: 23624296]
90. Palsson-McDermott EM and O'Neill LA (2013) The Warburg effect then and now: from cancer to inflammatory diseases. *Bioessays* 35 (11), 965–73. [PubMed: 24115022]
91. Jha MK et al. (2017) Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. *Psychoneuroendocrinology* 78, 105–113. [PubMed: 28187400]
92. Farchione TJ et al. (2017) Behavioral activation strategies for major depression in transdiagnostic cognitive-behavioral therapy: An evidence-based case study. *Psychotherapy (Chic)* 54 (3), 225–230. [PubMed: 28922002]
93. O'Connor MF and Irwin MR (2010) Links between behavioral factors and inflammation. *Clin Pharmacol Ther* 87 (4), 479–82. [PubMed: 20130566]
94. Dai J et al. (2008) Adherence to the mediterranean diet is inversely associated with circulating interleukin-6 among middle-aged men: a twin study. *Circulation* 117 (2), 169–75. [PubMed: 18086924]
95. Pace TW et al. (2009) Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. *Psychoneuroendocrinology* 34 (1), 87–98. [PubMed: 18835662]
96. Kiecolt-Glaser JK et al. (2014) Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: a randomized controlled trial. *J Clin Oncol* 32 (10), 1040–9. [PubMed: 24470004]
97. Krügel U et al. (2003) Basal and feeding-evoked dopamine release in the rat nucleus accumbens is depressed by leptin. *Eur J Pharmacol* 482 (1–3), 185–187. [PubMed: 14660021]

98. Fulton S et al. (2006) Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron* 51 (6), 811–822. [PubMed: 16982425]
99. Hommel JD et al. (2006) Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron* 51 (6), 801–810. [PubMed: 16982424]
100. Hsu TM et al. (2018) Blurred lines: the integration of homeostatic signals by mesolimbic dopamine neurons. *Frontiers in psychiatry* 9, 410. [PubMed: 30233430]
101. Abizaid A et al. (2006) Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. *The Journal of clinical investigation* 116 (12), 3229–3239. [PubMed: 17060947]
102. Sztainert T et al. (2018) Hungry to gamble? Ghrelin as a predictor of persistent gambling in the face of loss. *Biol Psychol*
103. Symmonds M et al. (2010) Metabolic state alters economic decision making under risk in humans. *PLoS ONE* 5 (6), e11090. [PubMed: 20585383]
104. Stouffer MA et al. (2015) Insulin enhances striatal dopamine release by activating cholinergic interneurons and thereby signals reward. *Nature communications* 6, 8543.
105. Ter Horst KW et al. (2018) Striatal dopamine regulates systemic glucose metabolism in humans and mice. *Science Translational Medicine* 10 (442), eaar3752.
106. Hryhorczuk C et al. (2018) Oleic acid in the ventral tegmental area inhibits feeding, food reward, and dopamine tone. *Neuropsychopharmacology* 43 (3), 607. [PubMed: 28857071]
107. Morón JA et al. (2003) Mitogen-activated protein kinase regulates dopamine transporter surface expression and dopamine transport capacity. *J Neurosci* 23 (24), 8480–8488. [PubMed: 13679416]
108. Petrulli JR et al. (2017) Systemic inflammation enhances stimulant-induced striatal dopamine elevation. *Translational psychiatry* 7 (3), e1076. [PubMed: 28350401]
109. Capuron L et al. (2012) Dopaminergic mechanisms of reduced Basal Ganglia responses to hedonic reward during interferon alfa administration. *Arch Gen Psychiatry* 69 (10), 1044–53. [PubMed: 23026954]
110. Harrison NA et al. (2015) A neurocomputational account of how inflammation enhances sensitivity to punishments versus rewards. *Biol Psychiatry*
111. Treadway MT et al. (2017) Association Between Interleukin-6 and Striatal Prediction-Error Signals Following Acute Stress in Healthy Female Participants. *Biol Psychiatry*
112. Eisenberger NI et al. (2010) Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. *Biol Psychiatry* 68 (8), 748–54. [PubMed: 20719303]
113. Boyle CC et al. (2018) Inflammation and Dimensions of Reward Processing Following Exposure to the Influenza Vaccine. *Psychoneuroendocrinology*

Highlights

- Converging evidence suggests that the mesolimbic dopamine (DA) system is directly impacted by increases in inflammatory cytokines associated with chronic, low-grade inflammation.
- The reasons for this immune-DA communication are unclear, but one novel hypothesis is that inflammatory cytokines signal immunometabolic shifts that may impact valuation of future actions as a function of available energy resources.
- Future work on effort-based discounting models should incorporate variables related to inflammation and immunometabolic state.

Box 1:**Peripheral signaling and the mesolimbic DA system**

A key tenant of our proposed model is that the DA system should be sensitive to peripheral signals related to metabolic state, including hunger and thirst. Consistent with this notion, prior studies have revealed DAergic sensitivity to peripheral hormones and peptides related to hunger, satiety, and glucose consumption, including:

- **Leptin:** a peptide signaling satiety. DA neurons express leptin receptors and stimulation of DA neurons by leptin inhibits DA release in response to food cues as well as feeding behavior [97–99]
- **Ghrelin:** A stomach-derived hormone that induces feeding behavior. VTA DA neurons have been shown to express Ghrelin receptors, and Ghrelin stimulation of the VTA increases phasic burst firing and DA turnover [100, 101] as well as increased gambling behavior in humans [102, 103]
- **Insulin:** A peptide hormone critical for anabolic metabolism. Recent work has found bi-directional regulation of insulin and striatal DA. Insulin stimulation of cholinergic interneurons in the striatum has been shown to increase DA release to guide food choices [104]. Conversely, stimulation or depletion of striatal DA in both rodents and humans has been shown to influence peripheral energy utilization by potentiating or attenuating insulin sensitivity [105].
- **Fatty-Acids** – Fatty-Acids play multiple roles in the body, from acting as an energy source to regulating inflammation via prostaglandins. VTA DA neurons have recently been shown to contain genes associated with processing fatty-acids, and direct administration of fatty acid oleate has been found to suppress activity of DA neurons, as well as sucrose feeding [106].

Taken together, this line of work provides clear anatomical, pharmacological, functional and behavioral evidence that the mesolimbic DA system integrates peripheral signals related to metabolic states to guide reward-related decision-making.

Figure 1.

Causes and Consequences of the Immunometabolic Shift During Inflammation. Several well-established lifestyle and medical factors lead to the release of microbe-associated molecular patterns (MAMPs) and danger-associated molecular patterns (DAMPs), which bind to pattern recognition receptors on immune cells including Toll-like receptors (TLRs) that in turn activate nuclear factor kappa B (NF-κB) and the NACHT, LRR, and PYD domain-containing 3 (NLRP3) inflammasome. Activation of NF-κB and the protein components of the NLRP3 inflammasome including procaspase, caspase, and a caspase activation and recruitment domain (ASC) lead to immune cell activation and a metabolic shift from the more efficient oxidative phosphorylation (OX PHOS) to glycolysis to support rapid cell growth and proliferation, albeit at the cost of increased energy expenditure. Cellular activation also leads to the production and release of inflammatory cytokines that can access mesolimbic dopamine (DA) neurons and immune cells (microglia) in key brain

regions including the striatum through stress- and potentially inflammation-induced disruptions in the blood–brain barrier, ultimately contributing to disruptions in DA synthesis, release, and reuptake. Activation of microglia can also lead to the release of reactive oxygen species (ROS), which can disrupt mitochondrial and ultimately neuronal function while also exacerbating inflammatory responses. These effects on mesolimbic DA lead to decreased effort allocation for reward and motivational anhedonia due to reductions in perceived ability (can't) but not preference (won't). Abbreviations: AA, amino acid; DAR, dopamine receptor; DAT, dopamine transporter; FA, fatty acid; HSP, heat shock proteins; HMGB-1, high-mobility group box-1; IL, interleukin; LPS, lipopolysaccharide; TNF, tumor necrosis factor.

Figure 2. Computational model of effort discounting and metabolic state.

A) Sample discounting curves from flexible power model (Equation I) at varying values of parameters k and p . B) Equations representing the flexible power model (I) and model adapted to include immunometabolic state (II). R is reward, E is effort, B is immunometabolic state ($0 < B \leq 1$), and s , k , and p are free parameters. C) Sample discounting curves from Equation II showing effects of metabolic state (B ; 0.1 – 1.0) at three levels of individual sensitivity: $s = 0.1$ (left); 1.5 (middle); 3 (right). For individuals who are sensitive to metabolic state ($s > 0$), the level of effort at which a reward is steeply devalued changes in response to B , as though the ability to exert effort has changed. For curves shown parameter $p=6$ and parameter $k=5$.

Table 1.**Preclinical and Clinical Studies of Inflammation on DA and Effort**

Model system	Manipulation	Mesolimbic measure	Mesolimbic effect	Behavioral measure	Behavioral effect	Refs
<i>In vitro</i> cell culture	Stimulation of MAPK kinase	DA reuptake	DA reuptake ↑ ^a	–	–	[47]
Rat	Acute IP injection of IL-1β	–	–	FR5 concurrent choice paradigm	Effort ↓	[54]
Rat	Acute IP injection of IL-6	Microdialysis	Striatal DA ↓	FR5 concurrent choice paradigm	Effort ↓	[43]
Mouse	Acute LPS	–	–	Nose-poke paradigm	Effort ↓ Effort conservation ↑	[55]
Rhesus macaque	Chronic IFN-α	Microdialysis Raclopride PET	K ⁺ /Amph-evoked striatal DA ↓ D2 BP _{ND} ↑	Puzzle feeder	Effort ↓	[30]
Rhesus macaque	Chronic IFN-α	Microdialysis	K ⁺ /Amph-evoked striatal DA ↓	–	–	[46]
Human	Acute LPS ^b	DA receptor PET	MP-evoked striatal DA ↑	–	–	[105]
Human	Chronic IFN-α treatment	PET/fMRI	DA turnover ↓ Striatal BOLD during reward feedback ↓	Self-reported fatigue	Fatigue ↑	[106]
Human	Acute typhoid vaccine	fMRI	Striatal BOLD during RPE ↓	Learning-rate sensitivity to gain/loss information	Gain sensitivity ↓ Loss sensitivity ↑	[107]
Human	Acute stressor	fMRI	Striatal BOLD during RPE ↓	–	–	[108]
Human	Acute LPS	fMRI	Striatal BOLD during reward anticipation ↓	–	–	[109]
Human	Acute LPS	–	–	EEfRT	Effort – Effort conservation ↑	[56]
Human	Acute LPS	–	–	Effort/reward sensitivity task	Reward sensitivity – Effort sensitivity ↑	[79]
Human	Acute influenza vaccine	–	–	Effort/reward sensitivity task	Reward sensitivity – Effort ↓	[110]

^a↓, Decrease; ↑, increase; –, no change.

^b Abbreviations: Amph, *d*-amphetamine; D2 BP_{ND}, dopamine D2-like receptor non-displaceable binding potential; EEfRT, Effort Expenditure for Rewards Task; LPS, lipopolysaccharide; MP, methylphenidate.