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Inflammation-induced motivational changes: Perspective gained by evaluating positive and negative valence systems

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Abstract

Inflammation can profoundly impact motivated behavior, as is the case with inflammation-induced depression. By evaluating objectively measurable basic neurobehavioral processes involved in motivation, recent research indicates that inflammation generally reduces approach motivation and enhances avoidance motivation. Increased effort valuation largely mediates the effects of inflammation on approach motivation. Changes in reward valuation are not uniformly observed in approach motivation. However, inflammation increases the averseness of negative stimuli. Within the context of both approach and avoidance motivation, inflammation appears to enhance the contrast between concurrently presented stimuli. While changes in both approach and avoidance motivation appear to be mediated by midbrain dopaminergic neurotransmission to the ventral striatum, it is unclear if the enhanced contrast is mediated by the same system.

Keywords

motivation; depression; fatigue; inflammation; positive valence systems; negative valence systems

Introduction

Motivation can be defined as a central state that organizes perception and behavior. In particular it arouses, directs, and maintains behavior. While many factors are capable of affecting motivation, inflammation is the one of interest for the present review [1,2]. Inflammation-induced sickness behavior is one example of inflammation altering motivational states [3]. In response to an infection detected by innate immune cells, the host presents drastic behavioral changes that favor the development of fever and result in environmental withdrawal. However, inflammation is not necessarily associated with reduced motivation. Instead, inflammation reorganizes priorities of the sick individual. As a

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typical example, rats treated with endotoxin display reduced lever pressing for rewards (e.g., food, water, intracranial self-stimulation) but engage in increased lever pressing in order to get periods of rest when forced to exercise in a running wheel [4]. Further support for inflammation-induced motivational reorganization comes from a study of lactating mice treated with lipopolysaccharide (LPS) [5]. LPS-treated mother mice do not respond to their pups' solicitations. However, when their pups are dispersed in the home cage and the nest is replaced by cotton wool, they engage in elements of maternal behavior that vary according to ambient temperature (Fig. 1). At normal ambient temperature they move around to retrieve their pups to the cotton wool but do not build a nest. In the cold, they engage in both pup retrieval and nest building. More recently this principle has been illustrated in the context of adaptive cold-seeking behavior in a rat following a high dose of LPS [6].

While short-term alterations in motivated behavior, as in the context of sickness, are often seen as adaptive, chronic alterations in motivational states are generally considered maladaptive, as would be the case with the motivational deficits that are associated with major depressive disorder (MDD). Inflammation can induce depression [7,8]. This depression is mainly apparent in the form of decreased activity, anergia or fatigue, and decreased response to rewards [9,10]. These symptoms are relatively resistant to antidepressant treatment compared to the affective and cognitive dimensions of depression [11–13].

Understanding the relationship between inflammation and motivation may shed light onto the mechanisms that mediate these effects and lead to new interventions for chronically altered motivational states. Within this brief review we will highlight the literature exploring the components of motivation affected by inflammation and then briefly consider mechanisms. We will do this by focusing on the basic neurobehavioral processes that are involved in motivation and that can be measured objectively in mice and/or humans. This approach, advocated by the NIH Research Domain Criteria (RDoC) framework, places motivational processes primarily within two domains: positive valence systems and negative valence systems [14,15]. Positive valence systems generally govern approach motivation, or motivation guided by a reward. Negative valence systems govern response to aversive stimuli and, therefore, generally guide motivation to avoid discomfort, threat, or loss.

Positive Valence Systems: Approach Motivation

Approach motivation requires action based on integration of information concerning reward valuation and effort valuation. Valuation of the reward involves the assignment of incentive salience to the reward. The assignment of lesser value to an expected reward results in anhedonia, a common feature of MDD. However, reward valuation is insufficient to maintain behavior. Motivation also involves valuation of effort required to obtain the reward. In general individuals make decisions based on the attractiveness of the reward and the cost necessary to obtain it. A reduction in willingness to exert effort is an important component of fatigue, considered as an entity or as a symptom of depression. Apathy, a disorder of motivation that is operationalized as diminished goal oriented behavior and cognition [16], also manifests as reduced willingness to exert effort when rewards are small [17].

It is well accepted that inflammation can reduce approach motivation. Specifically, it has been demonstrated that LPS administration can decrease reward expectancy as measured by a reduction in food-related anticipatory activity [18]. Reduction in reward anticipation also appears to be an important component of the motivational deficits observed in MDD [19,20]. Further, preclinical studies in rodents and monkeys have shown that administration of inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, or interferon-alpha (IFN-α), reduces willingness to work for highly palatable rewards without reducing willingness to eat freely available, less palatable food [21–23]. Similar effects manifest as self-reported fatigue in patients with cancer or hepatitis C who are undergoing treatment with IFN-α or IL-2 [12,24,25] and in patients with MDD [20,26,27]. These studies suggest that effort valuation is impacted by inflammation but not reward sensitivity. In agreement with this interpretation is a human study in which LPS- or placebo-treated volunteers were repeatedly asked to choose whether or not to participate in an effort task after being provided information concerning the required effort level and reward level [28]. LPS treatment reduced selection of high effort tasks (i.e., increased effort valuation) with no significant effect on reward valuation.

However, in another set of studies in which both high and low effort options were available simultaneously, a different pattern of results emerged. Mice subjected to inflammation, in the form of LPS 24 hours prior to testing, showed a reduction in overall effort in a concurrent choice task that contrasts high effort/high reward and low effort/low reward options [29]. This aligns with the previously mentioned studies showing an increase in effort valuation. However, a change in reward sensitivity also emerged. Rather than showing a uniform reduction in reward value, an enhancement in contrast between rewards of different magnitudes was observed such that responding to the less preferred reward was more dramatically suppressed than responding to the more preferred reward, despite the higher work criteria. This enhanced contrast effect generalizes to human participants as demonstrated in a study of volunteers treated with LPS tested in the Effort Expenditure for Rewards Task (EEfRT) [30]. The EEfRT task was developed to assess reward and effort valuation in human subjects [27]. LPS treatment shifted participants toward increased selection of the high effort/high reward trials as opposed to low effort/low reward trials. These findings indicate that if effort is to be expended in an inflamed state, it will be directed toward stimuli that are judged to be “worth the effort”. This is in contrast to the effect observed in patients with MDD, where an overall decrease in effort has been observed [20,27]. This difference is likely due to the fact that inflammation does not induce any anhedonia.

The literature concerning motivation toward social support also helps with understanding the idea of increased motivation in the context of inflammation. Administration of endotoxin to healthy participants leads to enhanced desire for support figures and greater ventral striatum activity in response to images of support figures [31]. This effect appears to be specific to social support figures, which would be adaptive in an inflamed state, as this does not necessarily translate to all social rewards. Another report shows that depression is associated with reduced motivation to work for social feedback yet increases effort toward food rewards [32].

This body of work aligns well with the concept that inflammation shifts motivational priorities rather than blunts all reward cues. As such, inflammation-induced reductions in approach motivation appear to be a result of increased effort valuation, however, it does not necessarily result in a reduction in reward sensitivity [33]. In fact, inflammation can increase the sensitivity of contrast between rewards of differing value.

Negative Valence Systems: Motivation to Avoid

The effects of inflammation on negative valence systems are much less studied than their effects on positive valence systems. Inflammation by itself is aversive. This can be experimentally demonstrated using a conditioned taste aversion procedure or a conditioned place avoidance test; even a low dose of LPS or IL-1β is able to induce avoidance behavior in mice [34–38]. Not only is inflammation inherently aversive, it also appears to increase the averseness of negative motivational stimuli. For example, treatment with endotoxin enhances brain reactivity to negative feedback concerning social appraisal in several threat-related regions (amygdala, dorsal anterior cingulate cortex) as well as mentalizing-related regions (dorsomedial PFC) [39]. Further, this effect appears to be more pronounced when the negative stimuli are presented concomitantly with positive motivational stimuli. For instance, in a taste-reactivity task, LPS-treated rats responded normally to brief intra-oral infusions of sucrose or quinine solutions. However, they were more sensitive to the aversive component of the mixed sweet/bitter taste of a saccharin solution [40]. This inflammation-induced enhanced contrast has also been noted in human studies. For example, in a human probabilistic instrumental task in which participants learned to select high probability reward and avoid high probability loss, typhoid vaccination enhanced the averseness to loss while simultaneously making rewards less attractive [41]. The enhanced salience of loss rather than reward was also demonstrated in a study of depressed patients who showed higher connectivity between the ventral striatum and midline cortical regions during loss as compared to reward trials [42].

Mechanisms

Dopaminergic neurons terminating in the ventral striatum appear to play a key role in motivated behavior. Dopaminergic agonists, but not classical antidepressants, abrogate inflammation-induced deficits in incentive motivation [43]. A recent study elegantly demonstrated the importance of the type 2 dopamine receptor (D2) within the ventrolateral striatum in mediating motivated behavior [44]. Conditionally knocking out this receptor resulted in a chronic reduction in breakpoint on a progressive ratio task while optogenetic inhibition of these neurons caused transient reduction in breakpoint. Further, there is research indicating that the type 3 dopamine receptor within the striatum may also be involved in motivated behavior [45]. Clinical imaging studies evaluating experimental induced inflammation or natural variations in inflammation also point to the importance of the ventral striatum in mediating these findings [46–50]. For example, increased inflammation in either patients treated with IFN-α or in those with depression show increased glutamate levels in the basal ganglia [51,52], while mean diffusivity imaging reveals that only the motivational symptoms of depression show changes related to the dopaminergic system [53].

Inflammation-induced aversion also appears to be modulated by the nigro-striatal dopaminergic system. Recent experiments carried out in mice have helped to define the cellular network responsible for inflammation-induced conditioned place aversion. Peripheral upregulation of interferon signaling activates brain endothelial cells to cause the release of prostaglandin (PGE_2), via a MyD88 dependent process [34,35]. PGE_2 act on the dopaminergic system to induce aversion. Further, while imaging studies of IFN-α treated patients revealed broad impacts on functional brain connectivity networks, changes within nodes of the ventral striatum and thalamus were specifically associated with motivationally oriented symptoms, including negative mood [50]. Further, the neural representation of both reward and punishment prediction errors was located within the ventral striatum and anterior insula [41]. Therefore, we can provisionally propose that the neurobiological underpinnings of inflammation-induced motivational changes involve a dual role of midbrain dopamine neurons in modulating both motivational approach and avoidance behaviors.

Further work is needed to confirm the role of the dopaminergic system in inflammation-induced changes in motivational contrast. Additionally, while the role of the dopaminergic system is well established, the data is still unclear concerning the mechanism by which inflammation alters its function. The work that has been done in this area is primarily in the context of Parkinson's disease. This literature indicates that non-neuronal cells, such as microglia and astrocytes, play a pivotal role in neuroinflammation, leading to oxidative stress and mitochondrial damage that result in neurodegeneration of dopaminergic neurons [54,55]. However, the severity of these effects is modulated by genetic mutations (e.g., parkin, DJ-1 and α-synuclein) that are probably absent in inflammation-induced motivational changes. Therefore, much work is still needed to understand the mechanisms by which neuroinflammation negatively impacts the functionality of dopaminergic neurons projecting to the ventral striatum.

A variety of pathways have been proposed to mediate the effects of inflammation on dopaminergic activity. Brain cytokines can have direct effects on neural function, such as through oxidative stress induced mitochondrial damage or upregulation of dopamine reuptake transporter. They can also have indirect effects, such as via activation of indoleamine 2,3-dioxygenase (IDO1). IDO1 activity in the brain results in the generation of neurotoxic kynurenine metabolites and/or interference with the metabolism of extracellular glutamate [1]. Recent data indicate that activation of the kynurenine pathway is not required for inflammation-induced effect on positive valence systems [18], therefore, future work focusing on the impact of inflammation on oxidative stress, antioxidant response, and mitochondria may be warranted.

Conclusion

Inflammation is able to exert a profound effect on motivated behaviors (Table 1). These alterations can express themselves in the form of fatigue, depression, and other symptoms. Understanding how inflammation alters motivation is critical to identifying treatments. A look at the currently available literature indicates that inflammation generally reduces approach motivation and enhances avoidance motivation via midbrain dopaminergic neurotransmission to the ventral striatum. The reduction in approach motivation is largely

mediated by increased effort valuation resulting in a reduced willingness to work for rewards. Rather than uniformly impacting reward valuation, inflammation appears to enhance the contrast between rewarding stimuli of the same hedonic valence (making the less rewarding stimuli much less attractive) or of different hedonic value (increasing the averseness of negative stimuli compared to positive stimuli). Future work in this area would benefit from exploring the mechanisms by which inflammation affects dopaminergic neurotransmission, with a possible emphasis on oxidative stress and mitochondrial damage, as well as to determine whether the enhanced contrast noted above is also mediated by alterations in dopaminergic neurotransmission.

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Highlights

- Inflammation is associated with a reorganization of motivational priorities
- Reduced approach motivation is associated primarily with increased effort valuation
- Alterations in reward valuation largely depend on the nature of the reward
- Negative stimuli are perceived as more aversive
- The contrast between concurrently presented stimuli is enhanced

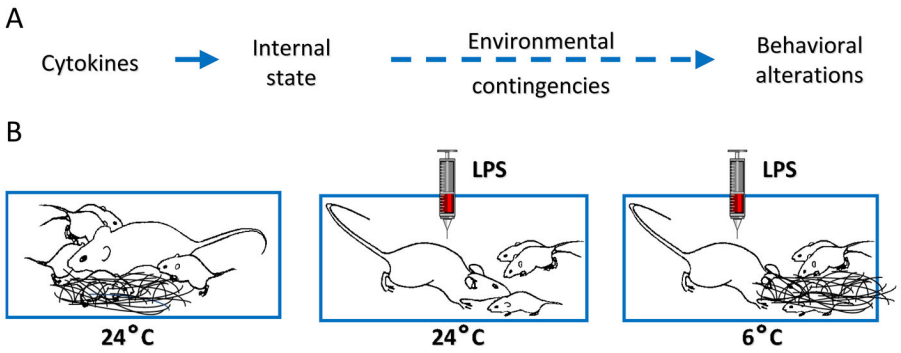

Figure 1. Motivational interpretation of sickness behavior

In a situation of motivational competition, the resulting behavior depends on the relative strength of the incentives for each motivated behavior (A). For example, sickness behavior vs. maternal behavior in different temperature contingencies (B). Note that the higher the environmental contingencies for maternal behavior (6 vs. 24°C) the lower the behavioral manifestations of sickness. At 6°C sick lactating mice engage in fast pup retrieval and nest building while at 24°C they only engage in pup retrieval.

Table 1

Summary of effects of inflammation on components of motivated behavior.

	Effects of Inflammation
Reward Evaluation	↑ ↓
Effort Evaluation	↑
Reward Expectancy	↓
Loss Evaluation	↑
Reward Contrast	↑

↑ =increase; ↓ = decrease