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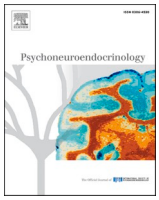

Are sick people *really* more impulsive?: Investigating inflammation-driven impulsivity

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ABSTRACT

In both animals and humans, inflammatory stimuli – especially infections and endotoxin injections – cause "sickness behaviors," including lethargy, malaise, and low mood. An emerging line of research asserts that inflammation may provoke present-focused decision making and impulsivity. The current article assesses that claim in the context of the broader literature – including preclinical models and clinical interventions. This literature presents three challenges to purported inflammation-impulsivity link that have not been addressed to date: (1) the nebulous and imprecise definition of impulsivity; (2) reverse causality; and (3) a lack of causal evidence. These challenges point to ways in which future research designs can improve upon the extant literature to further explore the ostensible relationship between inflammation and impulsivity.

1. Introduction

Inflammation's effect on behavior is well-characterized in both animals and humans. Experimentally-induced inflammation provokes fatigue, decreased appetite, social withdrawal, and low mood – a well-established constellation termed sickness behavior (Shattuck and Muehlenbein, 2016). Far more than an uncomfortable correlate of infection, one well-accepted theory is that this coordinated response conserves energy and promotes healing (Dantzer, 2001). An emerging line of research posits that the acute inflammatory response may also promote impulsivity and "present-focused" decision making (e.g., Gassen et al., 2019a, 2019b). The theoretical justification is that the inflammatory response is metabolically costly, and therefore individuals place greater weight on gathering resources for the present, rather than saving or waiting for the future. Specifically, the risk-sensitivity foraging theory posits that an organism will choose to prioritize current resources instead of waiting for better alternatives when there is a risk that resources will become unavailable or when there is a high opportunity cost associated with not having immediate access (Fawcett et al., 2012). However, serious issues plague this literature, raising key questions about the inflammation-impulsivity link, including: (1) the nebulous and imprecise definition of impulsivity; (2) reverse causality; and (3) a lack of causal evidence.

2. Reviewing the evidence

In the past, the primary biological explanations for intra- and inter-individual variation in self-regulatory failures, which may include impulsive behavior, centered on glucose depletion and cortisol rises (Gailliot and Baumeister, 2007; Shields et al., 2015). Recently, there is also an immunologic model of self-regulatory failure, which posits that inflammation promotes behaviors that impede the ability to maintain alignment with long-term and abstract goals (Shields et al., 2017). To date, most of the clinical research examining this link is cross-sectional. Among non-psychiatric participants, higher plasma levels of inflammation (IL-6, TNF-α, and IL-1β) predicted greater present-focused decision making, a construct derived from an ambiguous composite score comprising two self-report trait impulsivity scales and two laboratory tasks (Gassen et al., 2019b). The same lab also reported results from an experiment in which they provoked an inflammatory response via a variety of emotionally-charged images and found that those with higher levels of post-task inflammation chose to receive less money now rather than more money later (Gassen et al., 2019a). However, this finding is not truly causal, as there was no control group for comparison because

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inflammatory was mildly elevated following all image types; other aspects of the stress response (e.g., the neuroendocrine response) may better explain the observed effect; post-manipulation inflammation rather than change was the focal predictor; and inflammation was measured in the saliva, which captures a localized, oral immunological response. Other research among non-psychiatric samples has shown that those with hostile or angry dispositions have higher levels of inflammation (Graham et al., 2006; Ranjit et al., 2007; Suarez, 2004), but adjusting for health behaviors and biomedical risk factors like BMI may attenuate this link (Graham et al., 2006). There are also reports of impaired executive function, as well as corresponding structural alterations, among those with elevated levels of inflammation (Beydoun et al., 2019; Marsland et al., 2015; Trollor et al., 2012; Trompet et al., 2008), and although some of these changes can certainly underlie impulsive choices and behaviors, they certainly are not specific to impulsivity. For instance, higher levels of inflammation have tracked with poorer memory, verbal proficiency, learning and memory, and *slower* response times on the Stroop task (Brydon et al., 2008; Grigoleit et al., 2011; Marsland et al., 2015). Overall, findings among healthy individuals are not enough to support a causal pathway from inflammation to impulsivity.

The relevant findings among psychiatric patients are also primarily cross-sectional and non-experimental. For example, those who met diagnostic criteria for bipolar or unipolar depression and also had a history of non-suicidal self-injury (NSSI), which has impulsivity at its root, differed from those without an NSSI history; the former had higher inflammation and faster reaction times on a go-no-go test, and greater inflammation predicted more frontal theta power, which has been associated with suicidal ideation (Kim et al., 2020; Lee et al., 2017). Similarly, among those with traumatic brain injury, those with increased inflammation in the central nervous system displayed more behavioral disinhibition (Juengst et al., 2014). Some post-mortem studies have reported elevated inflammation in suicide victims' brains (Pandey et al., 2012; Steiner et al., 2008; Tonelli et al., 2008) – even after controlling for depression severity (O'Donovan et al., 2013). Although there are other reports of lower proinflammatory cytokines in suicidal individuals (Clark et al., 2016; Gabbay et al., 2009), meta-analytic evidence suggests that suicidal individuals have greater central and peripheral inflammation (Black and Miller, 2015). Additionally, intermittent explosive disorder is also characterized by aggression and impulsivity, and individuals with this disorder had higher plasma inflammatory markers than nonaggressive individuals with or without a history of an Axis I or II disorder (Coccaro et al., 2014). Also, these inflammatory markers were positively correlated with continuous measures of aggression across the entire sample (Coccaro et al., 2014). In sum, there are several lines of correlational evidence among both psychiatric patients and healthy controls that suggest a connection between inflammation and impulsivity, but they are not sufficient to support causal claims.

3. Important Considerations for Inflammation-Impulsivity Research

To further explore this link, future research in this domain should consider the following points, relevant to research design and methodology:

1) **Impulsivity is a nebulous umbrella term for many different phenomena.**

Impulsivity is a diffuse, multidimensional construct with several neurological underpinnings, including mesolimbic dopaminergic function and frontal lobe top-down inhibitory control (Congdon and Canli, 2005). There are many ways to measure impulsivity, including self-report, behavioral observation, and performance on cognitive tasks. Self-report measures are prone to response bias and are only accurate if the individual has insight into their own behavior (Cyders and Coskunpinar, 2011). Further complicating matters, impulsivity has a trait and state dimension, such that, for instance, a person with low trait impulsivity may act impulsively when under pressure. In fact, measures of trait and state impulsivity are only moderately correlated (Bagge et al., 2013). The literature also distinguishes between cognitive impulsivity, or impulsive *choices,* and behavioral impulsivity, or impulsive *acts.* For example, the widely used Barratt Impulsiveness Scale includes three factors of impulsivity: (1) non-planning; (2) motor (i.e., behavioral); and (3) cognitive or attentional (Patton et al., 1995). Whiteside and Lynam (2001) outlined a well-established model of impulsivity that is based on the Five Factor Model of personality. Based on their exploratory analysis using data from young adults, they outlined four physiologically distinct processes that lead individuals to engage in impulsive behavior: urgency, lack of premeditation, lack of perseverance, and sensation seeking (Whiteside and Lynam, 2001). Impulsivity's many dimensions foil efforts to measure it and pinpoint its neurological underpinnings, as reflected in the lack of consensus in the literature. Even so, behavioral impulsivity, or the inability to inhibit a motor response, is a core component of impulsivity and may be an endophenotype, or a subtle behavior that may not be evident to the naked eye or untrained observer but is situated on a continuum between genetic risk and onset of an impulsive disorder (Congdon and Canli, 2008, 2005).

As another definitional issue, recent publications investigating the relationship between inflammation and impulsivity have used the term "present focus" to describe the time orientation of those who presumably are more impulsive (Gassen et al., 2019a, 2019b). Granted, a preference for a smaller reward now rather than a larger reward later (i.e., delay discounting) is a common facet of impulsivity. In apparent conflict, mindfulness interventions attempt to increase present-focused awareness, thereby decreasing impulsivity among children (Vekety et al., 2021) and those with Attention-Deficit/Hyperactive Disorder but perhaps not among healthy adults (Korponay et al., 2019). There is also a growing body of evidence suggesting that mindfulness can lower inflammation (Black et al., 2019; Black and Slavich, 2016; Lindsay et al., 2021; Pascoe et al., 2017). To resolve the apparent conflict regarding present focus and its association with impulsivity and inflammation, it may be necessary to consider types of present focus. Mindfulness interventions not only foster a connection with current internal sensations and external stimuli, but they also emphasize the importance of non-judgmental acceptance of these stimuli – however unpleasant and undesirable they may be. Promoting present focus without the accompanying nonjudgmental awareness may be detrimental at worst, or at best – ineffective. Accordingly, mindfulness and acceptance theory (MAT) situates acceptance as a key ingredient of mindfulness interventions, suggesting that promoting acceptance can maximize the efficacy of mindfulness interventions (Lindsay and Creswell, 2019), in concert with evidence from randomized controlled trials (Lindsay et al., 2018a, 2018b). Further, a dispositional nonjudgmental orientation to the present moment was connected with reduced impulsivity, particularly negative urgency and higher perseverance, among college students (Peters et al., 2011). Besides nonjudgment, gratitude may be another beneficial lens through which individuals view their present-moment experience, ultimately reducing the likelihood of rash, risky behavior (Zhang et al., 2020). Whereas gratitude and nonjudgmental acceptance may foster contentment even in unpleasant circumstances (e.g., chronic pain) and thereby decrease impulsive and risky behaviors, hedonistic or fatalistic orientations to the present may boost risk propensity (Jochemczyk et al., 2017). In short, vague definitions of impulsivity-related terms hinder progress in identifying etiological factors and, in turn, effective treatments. To advance this area of research, it is critical to identify and study inflammation's relationship with specific facets of impulsivity.

2) **Reverse causality: Impulsive behavior drives heightened inflammation.**

The existing research linking inflammation and impulsivity simply *cannot* rule out the strong possibility that reverse causality may fully explain this association – the well-replicated findings that impulsivity-related health behaviors (e.g., substance abuse, smoking, poor diet, short or disturbed sleep, low levels of physical activity, and risky sexual behavior) support or provoke inflammation (Aragues et al., 2011; Emery et al., 2020; McGowan and Coogan, 2018; Miller et al., 2017a; Miller et al., 2017b; Pitts and Leventhal, 2012; Steele et al., 2021; Stevens et al., 2014; van den Berk Clark, 2021). Indeed, longitudinal data support the idea that impulsivity and related behaviors augment inflammation: In one study among over 5000 Italian community-dwelling participants aged 14–102, self-reported trait impulsivity and excitement-seeking predicted higher total white blood cell and lymphocyte counts three years later (Sutin et al., 2012). In fact, for each standard deviation increase in impulsivity, there was almost a 30% higher risk of having white blood cell counts above the risk threshold for mortality (Sutin et al., 2012). Smoking and high body mass index partially explained this association. Also, childhood internalizing and externalizing disorders foreshadowed greater inflammation two years later, but the reverse was unsubstantiated (Slopen et al., 2013). A systematic literature review described the directional pathway from time discounting to obesity and unhealthy diets, which have inflammatory correlates (Barlow et al., 2016). Also, early life stress can translate to emotion regulation difficulties and behavioral impulsivity, leading to risky behaviors that promote inflammation (Lovallo, 2013). Indeed, prior research has thoroughly paved the path from impulsive behavior to inflammation. To account for this relationship, restricting participant behavior in the days prior to study visits (e.g., asking participants to abstain from smoking, exercise, drinking alcohol, and sexual behavior as in Gassen et al., 2019b) is not sufficient to negate the effects of a lifetime of impulsive behavior.

3) **Causal paradigms do not support the inflammation-impulsivity link.**

The essential test for the impulsivity-inflammation link requires a causal paradigm in which increases in specific aspects of impulsivity follow amplified inflammation. Vigorous exercise reliably boosts inflammation, as IL-6 levels can rise 10–100 fold (Fischer, 2006), but no behavioral changes related to impulsivity or inability to delay gratification follow exercise. In fact, the opposite may be true, in that there is emerging evidence of gains in inhibitory control and selective attention following acute bouts of exercise (e.g., Grassmann et al., 2017; Sofis et al., 2017). Aging is another relevant paradigm, as aged and senescent immune and bodily cells secrete more pro-inflammatory than anti-inflammatory signaling molecules and other components, respectively (Franceschi et al., 2000; Mogilenko et al., 2021), yet, on the whole, older people are less impulsive than younger people (delay discounting: Reimers et al., 2009; resistance to distraction: Rey-Mermet et al., 2018, but not inhibiting prepotent responses: Butler and Zacks, 2006; Rey-Mermet et al., 2018). Although there are a few reports of impaired spatial memory following administration of an inflammatory stimulus (e.g., interleukin-2 cytokine immunotherapy: Capuron et al., 2001, typhoid vaccination: Harrison et al., 2014), it does not directly map on to impulsivity. Indeed, impulsive behavior is not commonly observed in a myriad of inflammation-related paradigms, including vaccination, acute infectious illness, chemotherapy, or surgery (Capuron et al., 2004; Dieperink et al., 2000; Lasselin et al., 2020; Shattuck and Muehlenbein, 2016). Null results from one double-blind randomized crossover trial are particularly noteworthy: reaction time and errors on a simple reaction time task and go/no go task did not differ three hours after an LPS injection (0.8 ng/kg body weight) compared to three hours after a placebo injection (Handke et al., 2020). As another paradigm, acute psychosocial stressors trigger a cascade of inflammation (Marsland et al., 2017) – albeit to a lesser extent than vaccines and naturalistic infections – and yet they boost inhibitory control (Chang et al., 2020; Schwabe et al., 2013). Thus, across many different paradigms, inflammation does not robustly trigger specific facets of impulsivity.

Chronic psychosocial stress may be an interesting exception, as it is related to greater systemic inflammation (Cohen et al., 2012) as well as increased motor impulsivity and aggressiveness in rodents (Couch et al., 2016) and risky behaviors in humans (Lovallo, 2013). Chronic stress exposure is not typically manipulated in humans, so it is difficult to tease out directionality. A murine model may shed light on this relationship, ultimately suggesting that other aspects of the stress response – including cortisol and glucose – may be responsible for impulsivity following chronic stress exposure. In mice, low-dose lipopolysaccharide (LPS; a component of the outer membrane of gram-negative bacteria) and chronic mild stress both increased inflammation to differing extents yet resulted in distinct behavioral phenotypes: Low-dose LPS reduced aggressive and impulsive behavior but increased anhedonia and helplessness, while chronic mild stress boosted all four (Couch et al., 2016). When low-dose LPS was administered after chronic mild stress, it augmented anhedonia and helplessness but inhibited stress-induced impulsivity and aggression (Couch et al., 2016). These findings suggest that impulsivity is not a specific effect of inflammation itself; even if both inflammation and impulsivity rise in tandem following stress, it may be a spurious relationship, as other aspects of the stress response may control both. Time course matters as well: as previously outlined, chronic stress can lead to poor health behaviors, thereby fueling inflammation (Lovallo, 2013). Granted, certain inflammatory stimuli may provoke aspects of impulsivity, but impulsivity does not appear to be a universal outcome of inflammation, as it depends on the type of inflammatory stimulus that is administered as well as the time course.

As another causal test, decreased inflammation should diminish problematic behavior. A number of different drugs and dietary supplements decrease inflammation, but behavioral changes such as less impulsive behavior are not typically or consistently observed (Ginty et al., 2017; Kiecolt-Glaser et al., 2012; Köhler et al., 2014). Emerging evidence from murine models suggests that lithium reduces motor impulsivity, perhaps due to decreased proinflammatory cytokines in the orbital frontal cortex (Adams et al., 2020), but this finding has not yet been replicated in humans. The glaring absence of causal evidence poses serious problems for the proposed impulsivity-inflammation linkage.

Even so, experimental evidence that inflammatory stimuli affect dopaminergic function and reward processing are worthy of consideration. Although other neurotransmitters and neurocircuits are involved, low tonic mesolimbic dopaminergic activity and blunted phasic dopaminergic responding during reward anticipation are key neurological underpinnings of impulsivity (Zisner and Beauchaine, 2016). Perhaps as an evolved mechanism to reduce energy expenditure when sick, an inflammatory stimulus can reduce ventral striatum responses to rewards (Eisenberger et al., 2010). Also, inflammation can decrease the synthesis and release of dopamine and alter glutamate receptor function, thereby rendering traditional antidepressants ineffective (Felger, 2016; Haroon et al., 2020; Miller et al., 2017b; Miller et al., 2017a). In short, inflammation can alter reward processing, which may manifest as anhedonia, impulsivity, or sensation seeking. Therefore, at a physiological level, there may be some overlap between mania and depression, and vulnerability to each may depend on other underlying neurocircuitry function, as neurocircuits interact to determine behavioral phenotype. For example, trait anxiety – mediated by septo-hippocampal function – may serve as a protective factor against externalizing pathology among those with poor mesolimbic dopaminergic function, but such individuals maintain a high risk for internalizing pathology (Beauchaine and Thayer, 2015). Thus, if later supported with considerably more robust evidence, a link between inflammation and impulsivity may be simply the other side of the inflammation-driven anhedonia coin.

Although experimental paradigms with an inflammatory stimulus do not provide robust support for an inflammation-fueled impulsive behavior, they have highlighted a variety of contextual factors, including individual differences and task type, that may help to determine inflammation's behavioral effect. Individuals respond differently to inflammatory stimuli (Lasselin, 2021), as demonstrated most compellingly in the original clinical observations of mood and behavioral changes among patients with cancer and hepatitis after they received proinflammatory cytokine treatments. For instance, some patients treated with interferon-α for chronic hepatitis developed mania (10%), irritable hypomania (50%), and depressive mixed states (40%) (Constant et al., 2005). Stress levels also play a role: As an example, breast cancer survivors with higher levels of psychological stress were more prone to the depressogenic-effects of inflammation (Manigault et al., 2021). Also, there are notable differences in motivation following experimental inflammation depending on the task type, difficulty, and reward (Draper et al., 2018; Lasselin et al., 2017). In essence, gradations in the behavioral phenotype following an inflammatory stimulus occur, and future trials with within-subjects designs featuring an inflammatory stimulus and placebo control can help to minimize this noise.

Factors related to the inflammatory stimulus itself also help to shape the behavioral response. For instance, the dose of the inflammatory stimulus matters: In a randomized, placebo-controlled crossover trial among healthy men, LPS administration did not affect working memory performance but a higher dose of LPS (0.8 ng/kg of body weight) facilitated improved reaction time on the n-back test while a lower dose of endotoxin (0.4 ng/kg of body weight) engendered impaired long-term memory of emotional stimuli (Grigoleit et al., 2011). Another factor is the duration of inflammation. Acute inflammation is a normal and healthy response to insult, while chronic systemic inflammation is a non-specific sign of pathology somewhere in the body. This distinction may translate to divergent behavioral and neurological outcomes. In research with potential relevance for impulsive behavior, low dopamine levels correspond to chronic systemic inflammation, while elevated dopamine levels are present in models with acute inflammation (Felger et al., 2013; Petrulli et al., 2017). Moreover, the timing of the inflammatory stimulus can shape the psychological and behavioral outcome, as inflammation impacts brain function and development differently through development. For instance, in a maternal immune activation model of schizophrenia, children of women who had a documented exposure to influenza during the first trimester of pregnancy had seven times the risk of later developing schizophrenia (Brown et al., 2004) – a disorder characterized by abnormally high levels of subcortical dopamine. In short, heightened inflammation can alter reward processing and motivation, which can manifest as several distinct psychopathologies, depending on the context.

4. Conclusion

The present paper has outlined several caveats to the emerging literature that attempts to pinpoint inflammation as an etiological factor promoting impulsive choice and action. The clinical research to date has not offered compelling, robust evidence of a causal link. Correlational findings with a single measurement of basal inflammatory markers may simply reflect chronic systemic inflammation, which is a non-specific sign of pathology somewhere in the body. Furthermore, inflammation is both a cause and consequence of human behavior. Due to inflammation's multipronged etiology and bidirectional relationships with human behavior, it is relatively easy to identify a wide variety of factors that track with inflammation, including impulsivity. Yet many of these associations may not be causal at best, and may be spurious, at worst. Moreover, in future investigations of the inflammation-impulsivity link, it is critical to measure a specific facet of impulsivity, such as ability to inhibit prepotent responses. Experimental research with a strong inflammatory stimulus and a within-subject design to account for individual differences and rule out reverse causality is the essential next step to address the question of whether inflammation fuels impulsivity.

Declaration of Competing Interest

The authors report no biomedical financial interests or potential conflicts of interest.

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