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TNF-alpha Antagonist Infliximab Increases Willingness to Expend Effort in Patients with Depression and High Inflammation

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An abstract of a thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Master of Arts in Psychology

2022
Abstract

TNF-alpha Antagonist Infliximab Increases Willingness to Expend Effort in Patients with Depression and High Inflammation

By Sarah Etuk

Background: Increasing evidence suggests that alterations in inflammation and immunometabolism may contribute to the pathophysiology of motivational anhedonia in major depressive disorder (MDD). To date, only a few studies have explored the impact of pharmaceuticals that target inflammation on motivational anhedonia in depressed patients. Here, we present novel results from a newly completed clinical trial (NCT03006393) aimed at identifying the mechanisms by which inflammation and immunometabolism contribute to motivational anhedonia in depressed patients.

Methods: 33 patients with CRP >3 mg/L were randomized to receive a single infusion of either the TNF-alpha antagonist Infliximab (5mg/kg) or saline solution as part of a double-blind, placebo-controlled, randomized clinical trial. Motivated behavior and peripheral inflammatory markers were assessed prior to infusion and 14 days post infusion. Motivated behavior was assessed using an effort-based decision-making (EBDM) task. A composite measure of TNF soluble receptors (TNFRII) and glucose metabolism was formed using TNFRII and five markers of glucose metabolism.

Results: Patients that received Infliximab showed an increase in effortful options chosen relative to placebo (p= 0.034). Further, post-infusion reductions in plasma TNFRII and glucose metabolism predicted decreases in effort discounting (p = 0.042). Finally, there was trend level evidence that changes in inflammation and immunometabolism mediated the relationship between treatment arm and change in effortful choices at the highest effort level (p=0.094).

Conclusion: Administration of Infliximab to patients experiencing current MDD and high inflammation increases willingness to expend effort, a hallmark of motivational anhedonia. These results highlight the potential for using inflammatory biomarkers and anti-inflammatory treatment strategies to identify and treat motivational impairments.
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**Background and Introduction**

Major Depressive Disorder (MDD) is a common and devastating psychiatric illness. It has a lifetime prevalence rate of 20.6% among adults within the United States (Hasin et al., 2018) and is a leading cause of disability worldwide (Vos et al., 2015). First line pharmacological therapies for MDD include serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors (MAOIs). Many of these pharmaceuticals target monoamine pathways, meaning that they target neurotransmitter systems such as dopamine, serotonin, and noradrenaline (Miller et al., 2009). In fact, SSRIs and SNRIs make up more than 90% of the global antidepressant market (Artigas, 2013). Despite the plethora of widely-available and empirically validated pharmacological treatments, approximately 30% of individuals with MDD fail to respond to treatment (Rush et al., 2006). This highlights the need for developing new conceptual frameworks that can aid in the identification of therapeutic targets for the treatment of MDD.

The heterogeneity of MDD has made it difficult to study its pathophysiology. As a result, there has been a shift away from research on the pathophysiological mechanisms that contribute to MDD as a whole, and a shift towards research on the pathophysiological mechanisms that contribute to its symptoms. One symptom that has gained considerable attention is anhedonia. Anhedonia, a core symptom of MDD, is clinically characterized by either reduced motivation or interest in engaging in pleasurable life activities (American Psychiatric Association, 2013). Anhedonia is considered to be a clinically significant symptom due to its association with poor treatment outcomes in depression (McMakin et al., 2012; Uher et al., 2014), suicidal ideation (Ducasse et al., 2018, 2021), and suicide attempts (Auerbach et al., 2015).
Anhedonia is a complex construct. Deficits in effort-based decision-making, hedonic responses, reward anticipation, and reinforcement learning can all contribute to its clinical presentation (Berridge & Kringelbach, 2015; Cooper et al., 2018; Treadway, Bossaller, et al., 2012; Treadway & Zald, 2011). However, these different sub-domains of anhedonia are theorized to have distinct etiopathologies (Cooper et al., 2018). For example, deficits in effort-based decision-making and reinforcement learning, herein referred to as “motivational anhedonia,” have been associated with alterations in corticostriatal reward networks (Cooper et al., 2018). Despite current knowledge of the neurobiological manifestations of motivational anhedonia, little is known about the factors that contribute to its development.

A growing literature has implicated inflammation in the pathophysiology of motivational anhedonia in MDD. The term “inflammation” denotes the coordinated response of the immune system to injury and infection. A hallmark of inflammation is the increased production and circulation of pro-inflammatory cytokines and other inflammatory markers (acute-phase reactants, chemokines, etc.) that are released by immune cells at the site of infection. In the context of mood disorders, reliably elevated pro-inflammatory cytokines include tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and interleukin-1beta (IL-1b) (Dowlati et al., 2010; Howren et al., 2009; Köhler et al., 2017; Osimo et al., 2020).

The inflammatory response is not only responsible for fighting off pathogens, but also for enhancing protective behaviors during times of illness. The constellation of reduced appetite, fatigue, and low motivation, is often referred to as “sickness behaviors,” and are protective responses that promote energy conservation. This shift towards energy conservation occurs because inflammation is metabolically expensive (Lacourt et al., 2018; O’Neill et al., 2016). It takes quite a bit of energy to sustain an immune response due to the energy costs associated with
the synthesis of pro-inflammatory cytokines among other factors (Straub, 2017). Indeed, it has been shown that energy expenditure by immune cells increases up to 30% in response to active infection (Straub et al., 2010). In fact, during states of acute infection such as sepsis, energy expenditure by immune cells has been shown to increase up to 60% (Straub, 2017).

Clinical and preclinical studies have consistently shown that pro-inflammatory stimuli can induces sickness behaviors. For example, when injected with inflammatory cytokines, animals have been shown to decrease exploration of their environment, reduce in food intake, and limit locomotor activity (Dantzer, 2001). Similarly, human participants with no prior history of mood disorders have been shown to exhibit psychomotor slowing and fatigue following treatment with the cytokine inducer Interferon-alpha (IFN-alpha) (Capuron & Miller, 2004). Of note, these sickness behaviors heavily overlap with symptoms of depression such as psychomotor slowing, reduction in appetite, anhedonia, and low mood.

Inflammation is reliably elevated in individuals with MDD. A recent meta-analysis demonstrated that CRP, IL-6, and TNF-alpha are most consistently increased in individuals with MDD (Osimo et al., 2020). Evidence of elevated inflammation in MDD can also be found across multiple levels of analysis. For example, elevated levels of TNFA1P3, a gene that encodes proteins involved in the inflammatory response, have been associated with symptoms of depression (Chen et al., 2017). Furthermore, studies have shown that patients with MDD exhibit evidence of central nervous system inflammation (Felger et al., 2020; Franzen et al., 2020). Administration of inflammatory stimuli such as vaccines and endotoxin has also been associated with behaviors consistent with depression. Separate studies found that influenza and typhoid vaccination increased depressive symptoms (Harrison et al., 2009; Kuhlman et al., 2015). Additionally, it one study it was observed that up to 50% of patients that received treatment with
INF-alpha went on to meet criteria for depression (Musselman et al., 2001). Of note, inflammation has also been associated with decreased responsiveness to treatment with conventional antidepressants (Arteaga-Henríquez et al., 2019; Lucido et al., 2021; Strawbridge et al., 2015). For example, patients with low CRP saw greater improvement in their symptoms of depression than patients with high CRP following treatment with Escitalopram (Uher et al., 2014).

It is important to emphasize that the inflammatory response is not inherently problematic. A leading cause of chronic low-grade inflammation is chronic stress (Furman et al., 2019). During ancestral times, being hunted, a chronic stressor, was associated with wounding, and thus risk of exposure to pathogens (Raison & Miller, 2013). Given that chronic stress is associated with an increase in inflammatory biomarkers, it is understandable why chronic stress in that context would be adaptive. However, in modern lifestyle environments, the threat of physical harm from being hunted has reduced, and yet, the inflammatory response to chronic stress has remained. For this reason, what was once a maladaptive response has become maladaptive outside of the context of illness.

It is also important to emphasize that MDD is not an inflammatory disorder. A recent meta-analysis found that inflammation is only elevated in approximately 30% of individuals with depression (Osimo et al., 2019). A proof-of-concept study by Raison and Colleagues (2013) found that treatment with Infliximab, an anti-inflammatory drug, primarily improved depressive symptoms in individuals with a CRP greater than 5mg/L. Similar anti-cytokine clinical trials also found that inflammation does not improve depressive symptoms across the board (Husain et al., 2020; McIntyre et al., 2019; Raison et al., 2013). Further evidence for the fact that MDD is not an inflammatory disorder is that inflammation is increased across other psychiatric disorders. For
example, meta-analyses of the literature have shown that inflammation is also elevated across bipolar disorder, generalized anxiety disorder, and posttraumatic stress disorder (Costello et al., 2019; Goldsmith et al., 2016; Yang & Jiang, 2020). For this reason, a working hypothesis within the field is that inflammation only contributes to depressive symptoms in a subset of individuals with depression (i.e., the “inflammatory subtype”).

Inflammation is believed to contribute to depressive symptoms in the inflammatory subtype by acting on the neurocircuits and neurotransmitter systems that underlie symptoms of motivation and psychomotor function, particularly the mesolimbic and mesocortical dopamine (DA) pathways. These pathways have been broadly implicated in MDD more generally; prior studies have found that depressed patients have been shown to exhibit reduced activity of the ventral striatum in response to rewards compared to control subjects (Pizzagalli et al., 2009). Furthermore, administration of endotoxin to healthy participants has also been shown to reduce activity of the ventral striatum in response to monetary reward cues (Eisenberger et al., 2010).

Endogenous inflammation is also associated with alterations in the neural circuitry associated with depression. For example, high inflammation is associated with blunted striatal responses to reward anticipation (Burrows et al., 2021). Inflammation is believed to alter reward circuitry by influencing dopamine synthesis and reuptake. In patients with hepatitis C, treatment with IFN-alpha was shown to promote increased dopamine breakdown and decreased dopamine turnover (Capuron et al., 2012). Importantly, the observed inflammation induced changes in dopamine were associated with changes in depressive symptoms.

The literature has shown that changes in dopamine are often accompanied by changes in effortful behavior (Randall et al., 2015; Salamone & Correa, 2012; Yohn et al., 2016). For example, treatment with the Bupropion, a pharmaceutical shown to increase extracellular
dopamine, resulted in the selection of more high effort options in rats (Randall et al., 2015). Furthermore, administration of amphetamine has been shown to increase high effort choices in healthy participants (Soder et al., 2021). Additionally, dopamine release in the ventral striatum has been shown to predict greater effort expenditure for rewards (Treadway, Buckholtz, et al., 2012).

Given the role of DA in effortful behavior, it has been proposed that inflammation may induce lower motivation through its actions on dopamine systems. Increases in inflammation have been associated with decreases in motivational anhedonia in healthy participants (Boyle et al., 2020; Draper et al., 2018). Preclinical studies have shown that this relationship is mediated by changes in signaling in DA pathways (Yohn et al., 2016). However, this mechanism has not been well characterized. Furthermore, the relationship between inflammation and motivational anhedonia has not been explored in depressions patients with the inflammatory subtype. This is a significant gap in the literature given that individuals in that subtype might be most sensitive to the deleterious effects of inflammation.

In sum, increasing evidence suggests that alterations in inflammation and may contribute motivational anhedonia in MDD. However, no study to date has examined the relationship between inflammation and motivational anhedonia in depression patients with the inflammatory subtype. In the present study, we examined the relationship between inflammation and motivational anhedonia in patients with MDD and high inflammation through a placebo-controlled manipulation of inflammation using the TNF-antagonist infliximab. Our primary goal was to test whether decreases in inflammation would be associated with increases effortful behavior. We believed that by targeting a sample of MDD patients enriched for MDD in the
absence of other medical conditions, we would be well positioned to detect a specific effect of a powerful anti-inflammatory on motivated behavior.

**Materials and Methods**

*Participants*

60 participants (85% female, $M_{age} = 37.91; SD_{age} = 9.82; \text{range} = 21-65$) were enrolled in the study. All participants were right-handed, met DSM-V (APA, 2013) criteria for Major Depressive Disorder (MDD), and had CRP > 3mg/L. Of the 60 participants, 37 were randomized to receive a single infusion of either the TNF-alpha antagonist Infliximab (5mg/kg) or saline solution as part of a double-blind, placebo-controlled, randomized clinical trial. Of these 37 participants, four were excluded due to inadequate task performance. Therefore, our final sample includes 33 participants (84.85% female, $M_{age} = 38.81; SD_{age} = 9.23; \text{range} = 21-65$), from which 15 were given the placebo and 18 Infliximab. Study participants were recruited via community advertisements or referral from Emory’s Behavioral Immunology Program. Inclusion criteria included a primary diagnosis of MDD or Bipolar, depressed type (as determined by Structured Clinical Interview (SCID) for DSM-5; a score of $\geq 16$ on the Quick Inventory of Depressive Symptomatology; and CRP > 3mg/L. Additionally, participants were required to be off antidepressant medications for at least 8 weeks prior to the baseline visit. Exclusion criteria included any autoimmune disorder (as confirmed through laboratory testing); a history of tuberculosis (as confirmed through medical history or detection from a chest X-ray, skin testing, or blood testing) or at high risk of tuberculosis exposure; Hepatitis B, Hepatitis C, or human immunodeficiency virus infection (as confirmed through laboratory testing); a history of fungal infection; a history of recurrent or viral bacterial infections; a history of cancer (any type); unstable cardiovascular, endocrinologic, hematologic, hepatic, renal, or neurologic diseases (as
confirmed through a physical examination and laboratory testing); a history of a non-mood-related psychotic disorder, active psychotic symptoms, substance abuse/dependence within 6 months of study entry (as confirmed by SCID); a score of $\geq 3$ on the Columbia Suicide Severity Rating Scale (C-SSR); a current eating disorder; a history of a cognitive disorder or a score $\leq 28$ on the Mini-Mental State Exam; pregnancy or lactation; not effectively and appropriately using medically accepted means of contraception for those that can become pregnant; known allergy to murine products or other biologic therapies; chronic use of non-steroidal anti-inflammatory agents (with the exception of 81mg of aspirin), medications that contain glucocorticoids or statins; and a diagnosis of co-morbid PTSD or OCD (as confirmed by SCID). The study procedures were reviewed and approved by the Emory University Institutional Review Board. Written informed consent was received by all participants. The study is registered in ClinicalTrials.gov, Identifier: NCT03006393.

**Study Procedures**

The study consisted of an initial screening visit, a baseline fMRI visit, an infusion visit, three follow up visits, and an endpoint fMRI visit. At the initial screening visit, participants were screened for exclusion and inclusion criteria. The baseline visit was scheduled after eligibility was confirmed.

At the baseline fMRI session, participants filled out a series of surveys and completed the Effort-Based Decision-Making (EBDM) task in addition to several other behavioral tasks. The current manuscript focuses only on the EBDM task. Future publications will include the additional tasks completed.
At the infusion visit, participants were administered either infliximab (5mg/kg) or the placebo saline solution through an indwelling catheter. Independent pharmacists from the Investigational Drug Services dispensed either infliximab or the placebo, after which independent nurses at the Georgia Clinical Research Centers administered the solutions from 250ml saline bag. Bags were matched in color and consistency. All study personnel involved in the study were blinded to subject group assignment. The blind key was tracked by individuals at the Investigational Drug Services.

Three post infusion follow up visits were scheduled (24 hours, 3 days, and 7 days). At these follow-up visits, participants provided blood samples and completed a series of neuropsychiatric and self-report assessments.

At the endpoint fMRI visit, participants provided a final blood sample and completed the EBDM task.

**Effort Based Decision-Making Task**

The EBDM task is an fMRI-adapted effort based decision-making task (Arulpragasam et al., 2018; Suzuki et al., 2020). It was used to measure neural responses to effort and reward magnitude. During each trial, participants were given the choice between a High Effort and Low Effort option. The High Effort option required more effort (as measured by button presses) than the Low Effort option. The reward obtained from the Low Effort option was always $1 while the reward obtained from the High Effort option varied between $1 and $5. The magnitude of effort required in the High Effort option consisted of 20%, 50%, 80%, and 100% of the participant’s max effort. The participant’s maximum effort was measured prior to the scan. A rapid event-related design with an exponential jitter between trials drawn from a Poisson distribution was
used to optimize HRF estimation. An MRI-compatible button-box was used to record task responses. To prevent motion artifacts, participants made their choices in the scanner and then completed their button presses outside of the scanner. For example, once participants were outside of the scanner, they were presented with the effortful choices that they made in the scanner (ex. $2.40 for 80% effort) and given the option to either make their effortful button presses or change their option. At the baseline fMRI scan, the participant’s chose the same option on 91 ± 12% of trials. At the endpoint fMRI scan, the participant’s chose the same option on 96 ± 7% of trials.

Blood Collection

Whole blood was collected through indwelling catheters after the participants had at least 30 minutes of rest. To isolate plasma, blood was collected by venipuncture into EDTA-containing vacutainer tubes. The plasma collected was used to quantify concentrations of cytokines, cytokine receptors, and CRP. Blood was drawn by independent phlebotomists at the Emory Medical Lab and the Emory Psychology and Interdisciplinary Sciences (PAIS) Blood Lab.

Measurement of metabolic and inflammatory markers

Customized Fluorokine MAP Multiplex Human Biomarker Panels (R&D Systems, Minneapolis, MN) were used to measure plasma IL-6, NF-kB, and IL-1B. These cytokines were selected because of their association with depression and reward pathways. All processing of samples was done in accordance with manufacturer instructions.

Plasma CRP concentrations were obtained using a high sensitivity turbidimetric assay.
Behavioral Analysis

All plasma markers were natural log (ln) transformed for parametric statistics. This is allowed for the plasma markers to take on a normal distribution and was consistent with previous literature (Felger et al., 2016; Raison et al., 2013). A composite measure of TNFRII and glucose metabolism was created using TNF soluble receptors (TNFRII) and five markers of glucose metabolism: adiponectin, resistin, leptin, glucose, and insulin. A composite measure of lipid metabolism was created using total cholesterol, low and high-density lipoprotein (LDL, HDL) cholesterol, non-HDL cholesterol, triglycerides, and non-esterified fatty acids (NEFA) (Bekhbat et al., 2018).

Multiple linear regression was used to identify baseline associations between choice data, clinical measures, and plasma markers. Multiple linear regression was also used to examine associations between change from baseline to endpoint across choice data, clinical measures, and plasma markers. Repeated measures ANOVAs were used to examine associations between choice data across levels of effort and reward magnitude. Greenhouse-Geisser corrections were used when the sphericity assumption was violated.

Subjective value models

A quadratic function was used to estimate the subjective value of the options provided to the participants during each trial. This quadratic effort discounting model has previously been described in the literature (Hartmann et al., 2013; Phillips et al., 2007; Prevost et al., 2010). The greatest percentage of individuals were fit by the quadratic model compared to other commonly used models (ex. flexible power, hyperbolic, linear). The quadratic effort discounting model has been described in previous literature. The subjective value of the participants’ choices is
calculated using a subjective value equation (Eq. 1). In this equation \( SV \) describes the subjective value, \( R \) the reward magnitude, \( E \) the effort magnitude, and \( k \) the free parameters fit for each participant. The free parameter \( k \) was used in our later analyses as a measure of the participants effort discounting. A larger \( k \) indicated greater effort discounting.

\[
SV = R - kE^2
\]  

[1]

Given that the no value option does not require any effort to be exerted, the subjective value of the no effort option is always $1. Since the effort magnitude is raised to the second power, the fit is able to take on a curved shape depending on how much the participant devalues the presented reward based on the effort required to obtain it. The models were fit to the participants data using the function “fminsearch” in MATLAB. The \( p \) obtained for each subject represented the value that optimized the likelihood of the behavior displayed while they completed the task.

The Softmax function (Eq. 2) was used to calculate the probability of selecting either the effortful or no effort option presented during each trial based on their estimated subjective value. Included in the Softmax Equation is the inverse temperature parameter \( \beta \) and estimated subjective value of each option. The inverse temperature is a free parameter that is fit for each participant for each of the discounting models (ex. linear, quadratic, flexible power, hyperbolic). The higher the inverse temperature parameter, the greater the likelihood of choosing the option with the highest subjective value.

\[
P_t(a) = \frac{e^{\beta - SV_a}}{\sum_{i=1}^{n} e^{\beta - SV_i}}
\]  

[2]
Results

Behavioral Results

At baseline a 4 (effort) x 2 (treatment) RM ANOVA indicated that effort magnitude did not guide differences in choice across the placebo and Infliximab groups [F(1.38, 45.46) = 0.46, p = 0.47] (Figure 1).

![Figure 1](image.png)

**Figure 1.** The percentage of effortful options chosen as a function of effort magnitude by participants that received Infliximab and the placebo at baseline. There was no significant difference in effortful options chosen between the Infliximab and placebo groups at each effort magnitude.

At the endpoint a 4 (effort) x 2 (treatment) x 2 (time) RM ANOVA indicated that administration of Infliximab was associated with an increase in effortful choices at endpoint [F(1.839, 57.01) = 3.70, p = 0.034] (Figure 2).
Controlling for age and sex, post infusion reductions in inflammation and immunometabolism (as indexed by negative difference scores post-pre in inflammatory and immunometabolic markers) predicted increases in effortful choices at the highest effort level \( (b=-0.11, se=0.042, p=0.011) \) (Figure 3). Similarly, after controlling for age and sex, post infusion reductions in inflammation and immunometabolism (as indexed by negative difference scores post-pre in inflammatory and immunometabolic markers) predicted decreases in effort discounting (as indexed by lower k values) \( (b=0.60, se=0.28, p=0.042) \) (Figure 4). This indicates that, as inflammation decreased, the extent to which participants devalued rewards based on the effort required to obtain them decreased as well. A bootstrapped mediation indicated that there

**Inflammatory Results**

Figure 2. The percentage of effortful options chosen as a function of reward magnitude by participants that received Infliximab and the placebo at endpoint. There was a significant difference in effortful options chosen between the Infliximab and placebo groups at 100% effort.
was a trend level mediation of treatment assignment and change in effortful behavior by change in inflammation and immunometabolism (p=0.094) (Figure 5). Decreases in inflammation and immunometabolism (as indexed by negative difference scores post-pre in inflammatory and immunometabolic markers) also predicted decreases in CRP (as indexed by negative difference scores post-pre in CRP) (p= 0.0057) and TNFRII (as indexed by negative difference scores post-pre in TNFRII) (p= 0.0000022).

Figure 3. Post infusion reductions in inflammation and immunometabolism increased effortful choices at 100% effort.

Figure 4. Post infusion reductions in inflammation and immunometabolism decreased effort discounting at 100% effort.

Figure 5. An example of the mediation model. There was trend level evidence of a mediation of treatment assignment and change in effortful choices by change in inflammation and immunometabolism.
Discussion

The goal of the present study was to examine the relationship between inflammation and motivational anhedonia in patients with MDD and high inflammation through a placebo-controlled manipulation of inflammation using the TNF-antagonist infliximab. A prior study found that Infliximab only improved depressive symptoms in patients with high CRP (Raison et al., 2013). In this study we observed that a reduction in markers of inflammation and immunometabolism were accompanied by a decrease in effort discounting and an increase in effortful options chosen. Additionally, we found trend level evidence of a mediation of the association between treatment arm and change in effortful decision-making by change in markers of inflammation and immunometabolism.

Prior studies have observed that the percentage of effortful options chosen decreases as effort magnitude increases. This is the first study to demonstrate that treatment with an anti-inflammatory can lead to a change in effortful choices made. This study is also one of the first to demonstrate that decreases in inflammation can lead to an increase in effortful behavior. This study extends prior work on factors associated with motivated behavior.

Our results might be explained by prior studies on inflammation-induced alterations in dopamine signaling and anhedonia. Inflammation is believed to preferentially act on the neurocircuits and neurotransmitter systems that underlie anhedonia. For example, treatment with the inflammatory drug IFN-alpha has been associated with increased dopamine breakdown and increased dopamine turnover in reward related brain regions. Moreover, the administration of L-Dopa, a dopamine precursor, has also been found to normalize DA function following IFN-alpha (Felger et al., 2015). These data suggest that inflammation may increase effortful behavior by increasing dopamine the availability of dopamine.
Further evidence for this comes from our bootstrapped mediation model. Although the results did not reach significance, the finding that change in inflammation mediated the relationship between treatment assignment and change in effortful behavior may offer insight to the mechanism by which treatment with an anti-inflammatory contributes to changes in effortful behavior. Emerging work suggests that administration of an amphetamine leads to an increase in effortful behavior. Future research should focus on whether these changes in effortful decision-making as a function of inflammation and immunometabolism are accompanied by changes in brain function in brain areas implicated in decision-making. This would lend further support to the idea that inflammation decreases motivated behavior by limiting the availability of dopamine in the peripheral and central nervous system.

The is one of the first studies to examine the effects of an anti-inflammatory in a group of individuals with depression and high inflammation. Furthermore, this study is one of the first to use an objective measure of behavioral effort in addition to self-report and clinician rated measures. This is significant because prior research has shown that self-report data is highly biased by the way that questions are asked as well as the participants mood state. Adding different levels of analysis provides us with a more precise understanding of how Infliximab is influencing effortful behavior.

There are some important limitations associated with this study. This study examined the effect of a single dose of Infliximab on motivational anhedonia. We may have needed more time or a greater sample to detect a mediation effect. Additionally, due to the onset of the 2020 covid pandemic, our recruitment was halted in the final year of the study. Future studies could examine the effects of multiple doses of Infliximab on facets of motivational anhedonia. This would extend prior research examining administration of an anti-inflammatory over multiple weeks. In
future studies we will also look at how our behavioral, clinical, and inflammatory markers correlate with markers of gene expression.

In conclusion, treatment with the TNF-antagonist Infliximab increased willingness to expend effort in patients with depression and high inflammation. These results highlight the potential for the combination of inflammatory biomarkers and anti-inflammatory treatment strategies to identify and treat motivational impairments.
References


Infliximab vs Placebo in the Treatment of Adults With Bipolar I/II Depression: A Randomized Clinical Trial. *JAMA Psychiatry, 76*(8), 783.

https://doi.org/10.1001/jamapsychiatry.2019.0779


https://doi.org/10.1176/appi.ajp.158.8.1252


https://doi.org/10.1038/nri.2016.70


Antagonist Infliximab for Treatment-Resistant Depression: The Role of Baseline Inflammatory Biomarkers. *JAMA Psychiatry, 70*(1), 31.

https://doi.org/10.1001/2013.jamapsychiatry.4


https://doi.org/10.1093/ijnp/pyu017


https://doi.org/10.1176/ajp.2006.163.11.1905


