Anti-cytokine agents for anhedonia: targeting inflammation and the immune system to treat dimensional disturbances in depression

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Abstract: The etiology of mood disorders is mechanistically heterogeneous, underscoring the need for a dimensional approach to identify and develop targeted treatments in psychiatry. Accumulating evidence implicates inflammation as an important contributor to the pathophysiology of depression and presents the immune system as a viable therapeutic target that may be more proximate to the pathogenic nexus of brain-based disorders in specific subpopulations. Anhedonia is a transdiagnostic (e.g. Parkinson's disease, diabetes mellitus, rheumatic diseases), yet specific, and clinically relevant symptom dimension subserved by well-characterized neurobiological and neurophysiological substrates of the positive valence systems (PVS). Brain circuits, nodes, and networks, as well as cellular and molecular pathways (e.g. dopaminergic transmission; excitotoxicity; synaptic plasticity), subserving anhedonia are preferentially affected by inflammatory processes. To our knowledge, no published randomized, controlled clinical trial in populations with mood disorders has, to date, primarily sought to determine the effects of an anti-inflammatory agent on PVS functions or pathophysiology. Three ongoing clinical trials aim to investigate the effects of anti-TNF-alpha biologic infliximab on measures of anhedonia [ClinicalTrials.gov identifier: NCT02363738], motivational behavior and circuitry [ClinicalTrials.gov identifier: NCT03006393], and glutamatergic changes in the basal ganglia [ClinicalTrials.gov identifier: NCT03004443] in clinical populations with unipolar or bipolar depression. Positive results would further instantiate the relevance of inflammatory processes and the immune system in the pathophysiology of mood disorders and provide the impetus to develop scalable treatments targeting inflammation and the immune system to mitigate transdiagnostic, dimensional disturbances in brain-based disorders.

Keywords: anhedonia; anti-inflammatory agents; inflammation; infliximab; Major Depressive Disorder; Bipolar Depression

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Introduction

In 2017, the World Health Organization identified depression as the leading cause of disability worldwide, affecting approximately 4.4% of the total global population and increasing annually in prevalence.[1] Hitherto, no curative treatments have been identified or developed for the treatment of depression. While available treatments have established symptom-mitigating efficacy in clinical populations, approximately one-third of patients fail to respond to conventional antidepressant therapies and continue to experience clinically significant, recurrent, and progressive deficits in psychosocial, cognitive, and general functioning.[2] All pharmacological agents currently approved for depression by the US Food and Drug Administration (FDA) target monoaminergic systems, underscoring the need for novel

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conceptual frameworks that better characterize the mechanistically heterogeneous etiology of depression to develop targeted and disease-modifying treatments in mood disorders. Herein, we outline accumulating data implicating disturbances in the immune system as an important contributor to the pathophysiology of depression and a possible target for treating domain-based pathologies in depression.

Inflammation and its relevance to the phenomenology, etiology, and pathophysiology of depression

In replicated preclinical and clinical studies, transient sickness behavior and depressive symptoms (or depressive-like behaviors) are observed with immune activation.[3–7] For example, the administration of bacterial lipopolysaccharide (LPS) in rodents induces the expression of pro-inflammatory cytokines [e.g. tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta] and transient behavioral changes (e.g. decreased locomotor activity and feeding, greater social withdrawal, and increased slow-wave sleep and pain sensitivity) that peak within 2–6 h of LPS administration.[8,9] While transient sickness behaviors resolve gradually, depressive-like behaviors, such as anhedonia (e.g. reduced sucrose preference) and helplessness (e.g. greater immobility on the forced swim and tail suspension tests), peak 24 h after LPS administration after feeding and locomotor activity have normalized.[8–10] Similarly, individuals receiving pro-inflammatory immunotherapy for malignant melanoma or hepatitis C exhibit acute flu-like neurovegetative and somatic symptoms (e.g. lethargy, loss of appetite, myalgia), which emerge within 6–8 h and typically resolve within 1–3 weeks; neuropsychiatric symptoms (e.g. cognitive impairment, irritability, apathy) develop after a few weeks of treatment.[4,11–14] Up to half of patients receiving chronic interferon (IFN)-alpha therapy meet diagnostic criteria for major depressive disorder (MDD).[14–17]

Epidemiologically, chronic immune dysregulation is associated with higher depression incidence. For example, a recent population-based, case-control study (n = 103,307) reported a dose-dependent relationship between the frequency and severity of influenza infections and depression incidence.[18] Approximately 15–22% of individuals with chronic inflammatory conditions (e.g. rheumatoid arthritis, systemic lupus erythematosus) present with clinically significant depressive symptoms.[19,20] Similarly, individuals with mood disorders are more likely to have or develop metabolic and inflammatory comorbidities (e.g. diabetes mellitus, metabolic syndrome, central obesity, hypertension, cardiovascular disease, autoimmune disorders) when compared with the general population.[21–25] Diabetes mellitus and mood disorders are bidirectionally associated with a synergy index of 2.2.[26] Populations with an immune-mediated disease (e.g. inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis) also have a higher incidence of major depressive, anxiety, and bipolar disorders.[25] Chronic, aberrant activation of the immune system (e.g. increased natural killer cytotoxicity, pro-inflammatory cytokine expression) with psychological stressors has also been hypothesized to subserve the elevated risk for coronary artery disease in populations with mood disorders.[27] Moreover, the recognition of mood disorders as an independent risk factor for cardiovascular disease, commensurate with the level of risk conferred by chronic inflammatory disease or human immunodeficiency virus infection, suggests a convergence in the etiology of mood disorders and cardiovascular disease and implicates alterations in inflammatory pathways and networks.[28]

However, not all patients receiving chronic immunotherapy develop clinically significant depressive symptoms and progress to declare a psychiatric illness, underscoring the need to identify relevant risk factors and vulnerable subpopulations. Among adults receiving IFN-alpha therapy for cancer or hepatitis C, treatment-related and clinical risk factors include: longer treatment duration and higher dose; greater baseline depressive symptom severity; the presence of previous psychiatric diagnoses or sleep disorders; family history of a mood disorder; low social support; and older age.[11,13,29,30] In addition, greater pituitary–adrenal axis reactivity in response to IFN-alpha, higher baseline cytokine levels [e.g. IL-6, soluble IL-6 receptor (IL-6R), IL-2R, IL-10, soluble TNF receptor (sTNFR) 1], lower baseline anti-inflammatory polyunsaturated fatty acid levels, and functional polymorphism in immune [e.g. serotonin transporter (SERT), IL-6] and apolipoprotein E genes may contribute risk.[29,30] Peripheral changes in neopterin, kynurenine (KYN), and KYN-to-tryptophan (TRP) ratio, as well as brain-derived neurotrophic factor (BDNF), correlate with the severity of emergent depressive symptoms, implicating mechanisms of neuroplasticity, oxidative stress, and inflammatory pathways.[5,31]

The cellular and molecular biosignatures of individuals with depression exhibit the cardinal features of an inflammatory response and implicate disturbances in the immune system and inflammatory pathways [e.g. nuclear factor (NF)-kappaB, caspase-1, NLRP3 inflammasome] in the pathogenesis of mood disorders.[32–35] Case-control studies, as well as prospective and longitudinal clinical staging studies of individuals with or at risk for mood disorders, have reported elevated levels of pro-inflammatory cytokines and their associated receptors [e.g. TNF-alpha, IL-1beta, IL-6, C-reactive protein (CRP), sTNFR1, sTNFR2, soluble IL-2 receptors (sIL-2R)] peripherally and in the cerebrospinal fluid.[5,33,35–39] In addition, the dysregulation of cytokines, adiponectin, and leptin in visceral adipose as part of central obesity has been implicated in the pathogenesis of the metabolic syndrome and associated with greater depressive symptom severity and unfavorable illness course in bipolar disorder, as well as depression-like behavior in animal models.[40–42]

While the directionality of the relationship between inflammation and depression is unknown, peripheral immune activation drives inflammation in the central nervous system and alters brain functions.[33,43] Cytokines can cross the blood–brain barrier (BBB) *via* the circumventricular organs or saturable transporters in the BBB, as well as modulate peripheral afferent nerve fibers (e.g. vagus nerve) with catecholaminergic efferents, resulting in microglial activation.[16,33,44] Activated microglia and astrocytes also drive CC-chemokine ligand (CCL)-2-mediated cellular trafficking of activated immune cells (e.g. monocytes) into the brain.[33,45,46] Neuroimaging studies have noted microglial activation in the prefrontal cortex, anterior cingulate cortex (ACC), and insula among individuals with depression.[47] Moreover, microglial activation can be experimentally induced in nondepressed healthy controls with peripheral administration of inflammatory stimuli (e.g. endotoxin, lipopolysaccharide).[6,48] In addition, microglial activation is associated with self-reported depressive symptoms and elevated peripheral pro-inflammatory cytokine levels in the foregoing experimental paradigms.[6,48]

Functional allelic variants and single nucleotide polymorphisms in immune and inflammatory genes [e.g. TNF-alpha, IL-1beta, cyclooxygenase (COX)-2, phospholipase A2] contribute to depression susceptibility in probands and individuals without family history of mood disorders, correlate with depressive symptom severity in clinical populations with mood disorders, and predict antidepressant response.[17,49–51] Immune reactivity, as proxied by change in serum IL-1beta levels in an experimental paradigm of social stress, has also been reported to correlate with depressive symptoms in a population of postmenopausal women.[52] Aberrant gene expression profiles in the monocytes of individuals with mood disorders have also implicated cellular signaling, trafficking, and survival genes involved in stress-related inflammatory pathways and glucocorticoid resistance [e.g. TNF, IL-1beta, CCL2, mitogen-activated protein kinase (MAPK)-6].[53–55] Genetic polymorphisms subserving immune complex clearance pathways (e.g. gamma Fc region receptor, integrin alpha M) are also associated with depressive and other neuropsychiatric symptoms in populations with chronic inflammatory conditions.[56] Taken together, the foregoing observations not only implicate inflammation and dysregulation of the immune system in the phenomenology, etiology, and pathophysiology of depression, but also present the immune system as a possible mechanistic target for developing disease-modifying treatments in mood disorders.

Dimensional disturbances in depression: targeting the positive valence systems

The role of inflammation in the pathophysiology of depression can be further atomized into specific symptom dimensions that are aligned with the Research Domain Criteria (RDoC) and observed across multiple diagnostic categories (e.g. anxiety disorders, schizophrenia). The RDoC matrix was proposed by the National Institute of Mental Health as a novel conceptual framework for brain-based disorders that integrates findings from the biological, behavioral, and cognitive sciences with clinically observed symptoms.[57,58] Within the RDoC framework, transdiagnostic clinical phenomena are operationalized as domains of the negative valence systems, positive valence systems (PVS), cognitive systems, systems of social processes, and arousal and regulatory systems. The RDoC matrix further disentangles mechanistically heterogeneous, symptom-based categories of illness into discrete, validated constructs of neurobiological and quantitative measures of pathology (i.e. 'units of analysis') that subserve the foregoing domains, providing targets that are more proximate to the etiology and underlying pathophysiology of brain-based disorders.[59]

Anhedonia is a diagnostic feature of a major depressive episode (MDE) and defined as the diminished ability to experience pleasure or enjoy previously pleasurable activities.[60] Notwithstanding its conceptualization as a cardinal depressive symptom, anhedonia is a prevalent and pervasive clinical phenomenon, observed transdiagnostically among individuals with or without current, or history of, psychiatric disorders (e.g. schizophrenia, bipolar disorder, substance use disorders).[61–65] In addition, anhedonia is an important determinant of prognosis and quality of life in psychiatric and nonpsychiatric clinical populations (e.g. schizophrenia, Parkinson's disease, diabetes mellitus, cardiovascular disease).[62,66–72] Anhedonia is also a replicated predictor of antidepressant nonresponse, as observed in the Genome-Based Therapeutic Drugs for Depression (GENDEP) and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D).[73,74]

Within the RDoC framework, anhedonia can be conceptualized as a disturbance in the PVS, which comprises constructs related to, and neurobiological substrates subserving, reward- and motivation-related behaviors. The cellular and molecular substrates subserving PVS phenomenology and function are well characterized and include monoaminergic (e.g. dopamine, serotonin) and glutamatergic circuits, nodes, and networks, primarily in the ventral tegmental area, basal ganglia, prefrontal cortex, and ACC.[75–77]

Pro-inflammatory cytokines affect cellular and molecular substrates that influence brain structures and circuits that subserve PVS pathophysiology. For example, TNF-alpha, IL-1beta, and IFNs can decrease monoaminergic transmission by increasing dopamine, serotonin, and norepinephrine transporter activity and expression *via* activation of p38 MAPK pathways; decreasing vesicular monoamine transporter-2 expression and function; decreasing enzymatic cofactor tetrahydrobiopterin availability *via* production of reactive oxygen and nitrogen species; and depleting serotonin precursor tryptophan *via* activation of indoleamine 2,3-dioxygenase (IDO), which metabolizes TRP to KYN.[32,33,78] Serum levels of KYN and neopterin, as well as KYN-to-TRP ratios, correlate with depressive symptom severity.[31] Moreover, IDO activation appears to peak synchronously with depressive-like behavior with LPS administration in murine models.[9] In addition, TNF-alpha promotes insulin resistance, *via* its effects on insulin receptor substrate, which is associated with increased monoamine turnover (e.g. dopamine) and alterations in brain circuits, nodes, and networks subserving general cognition, as well as reward- and motivation-related behaviors.[79–82]

The activation of IDO by pro-inflammatory cytokines also modulates glutamatergic transmission. Activated microglia and infiltrating monocytes and macrophages convert KYN in the brain into neurotoxin quinolinic acid, which activates presynaptic N-methyl-D-aspartate (NMDA) receptors to release glutamate and blocks astrocytic reuptake of synaptic glutamate, decreasing BDNF expression and contributing to excitotoxicity and decreased neurogenesis.[29,83] Increased glutamate levels have been noted in the basal ganglia and dorsal ACC of depressed patients with serum CRP levels of 3 mg/l or greater, relative to those with CRP $<$ 3 mg/l, and correlate with anhedonia.[84] Oxidative stress also activates astrocytes and stimulates excess glutamate release.[29,83] Pro-inflammatory cytokines also reduce neurogenesis in the dentate gyrus, synaptic plasticity, and dendritic sprouting, ultimately affecting brain structures and functions.[33,85] Physical and psychological stressors also promote glucocorticoid resistance *via* danger-associated molecular pattern signaling pathways and its effects on the NLRP3 inflammasome.[34,54]

Convergent evidence indicates that innate immune activation and inflammatory processes, *via* their effects on monoaminergic and glutamatergic transmission and metabolism (e.g. *via* the KYN pathway) preferentially affect dopaminergic circuits and networks subserving PVS phenomenology.[86–88] For example, among 50 unmedicated adults with MDD or bipolar disorder, higher serum CRP levels predicted greater glutamate levels in the basal ganglia.[89] Glutamate levels in the basal ganglia were associated with measures of anhedonia and psychomotor processing, supporting the notion that inflammatory processes preferentially affect reward circuits and dopaminergic neurons involved in reward- and motivation-, as well as motor activity-related behaviors.[86–89] Peripheral inflammatory challenges have also been associated with decreased responsiveness to monetary reward in the ventral striatum and deficits in reward-related behaviors, as well as psychomotor slowing, in nondepressed subjects, consistent with clinical observations of anhedonia and

psychomotor slowing as predominant depressive symptoms in populations with acute infections or receiving chronic IFN-alpha therapy.[86,90,91] In addition, a proof-of-concept study inclusive of 16 healthy, nondepressed participants reported that typhoid vaccinations induced peripheral IL-6 levels, activated the subgenual ACC, and decreased subgenual ACC-ventral striatum functional connectivity; in addition, IL-6 levels moderated the foregoing decrease in reward circuit connectivity.[92] Similarly, in a resting-state neuroimaging study of 48 unmedicated, depressed subjects, higher serum CRP levels were associated with functional dysconnectivity in corticostriatal reward circuitry and predicted greater anhedonic and psychomotor slowing symptoms.[87]

Observed brain correlates of anhedonia have been reported as part of a connectome-wide association analysis in 172 adults with a mood disorder, schizophrenia, or psychosis risk and 53 adults without any psychiatric conditions.[93] Dissociable patterns of hyperconnectivity within the default mode network (DMN), diminished DMN connectivity with the nucleus accumbens and cingulo-opercular network, and increased connectivity between the nucleus accumbens and the cingulo-opercular network were noted, instantiating the transdiagnostic relevance of anhedonia and a convergence in the neurobiological substrates subserving PVS pathophysiology.[93] In addition, the antisuicide effects of ketamine have been postulated to be subserved by glutamatergic modulation of brain circuits and networks involved in general cognitive and PVS.[94]

Moreover, a recent multisite study using machine learning capabilities aimed to identify clinically relevant neurophysiological subtypes informed by symptom profiles and resting-state functional neuroimaging data from 333 subjects with MDD and a current MDE and 378 age- and sex-matched subjects without any psychiatric history.[95] Clinically relevant patterns of functional dysconnectivity in limbic and frontostriatal networks accurately classified 80–93% of subjects' diagnostic labels in an independent, out-of-sample replication dataset (n = 125 MDD, n = 352 controls).[95] Of note, hyperconnectivity in thalamic and frontostriatal networks, which correlated with increased anhedonia and psychomotor retardation, emerged as the most robust subtype, implicating anhedonia as a transdiagnostic clinical phenotype with discrete, yet convergent, neurophysiological correlates.

The immune system as a viable therapeutic target in depression

Accumulating evidence indicates that anti-inflammatory agents may be effective for the treatment of depression, at least for a significant proportion of patients presenting with baseline inflammatory activation.[96] However, available data are limited by heterogeneity in study design, such as the use of different anti-inflammatory agents with various off-target effects [e.g. non-steroidal anti-inflammatories (NSAIDs) also modulate prostaglandin production, which may be pro-inflammatory in chronic disease states]; the measurement of depressive symptom severity broadly rather than dimensionally, with symptom-specific outcomes (e.g. anhedonia); and the inclusion of patients solely on the basis of clinical diagnoses without study population enrichment for relevant neurobiological or neurophysiological substrates, or evidence of target engagement.[97–100] In contrast, preliminary evidence suggests that biologics (e.g. monoclonal antibodies) that specifically target individual cytokines (e.g. TNF-alpha) are effective in reducing depressive symptoms without off-target effects. For example, a recent meta-analysis (n = 2370) of seven randomized, controlled trials of anticytokine agents (e.g. adalimumab, etanercept, tocilizumab, infliximab) in chronic inflammatory conditions (e.g. rheumatoid arthritis) reported significant antidepressant efficacy of moderate effect size [standardized mean difference (SMD) = 0.40, 95% confidence interval (CI) = 0.22, 0.59].[100]

Greater baseline inflammatory activation has been observed among patients exhibiting poorer response to conventional antidepressant therapy.[101–103] The foregoing observation highlights the opportunity to use immune system substrates as biomarkers to identify patients who are likely to be treatment resistant and may benefit from novel therapeutic strategies.[96] For example, baseline plasma adipokine abnormalities predict antidepressant response to ketamine in unipolar or bipolar depression and are postulated to contribute to the antidepressant effects of ketamine.[104] In addition, baseline measures and changes in composite inflammatory biomarkers [i.e. body mass index $\geqslant$ 30 k/m^2, IL-6, IL-8, high sensitivity (hs)-CRP, TNF-alpha, and leptin] predicted

and correlated with antidepressant response to L-methylfolate calcium in MDD.[105] Similarly, composite markers of baseline inflammatory activation predicted greater depressive symptom improvement with eicosapentaenoic acid (EPA), and reduced responsiveness to placebo, when compared to subjects with low baseline inflammatory activation.[106] A corollary of the stratification of treatment response by inflammatory biomarkers is the presence of a U-shaped relationship between inflammation and depression.[107] Only a subpopulation of individuals with depression with baseline inflammatory activation may benefit from anti-inflammatory treatment, underscoring the importance of identifying, screening for, and targeting specific subpopulations that are most likely to benefit from an intervention, as well as highlighting the opportunity to use immune substrates as biomarkers to personalize care and improve outcomes in psychiatry.[107]

To our knowledge, the antidepressant efficacy of only one anticytokine agent–infliximab–has been investigated as part of a randomized, controlled clinical trial and published as a primary outcome among adults with mood disorders; etanercept has also been investigated as part of an open-label clinical trial.[107,108] Infliximab is a chimeric monoclonal antibody that targets TNF-alpha, is administered intravenously, and is approved by the FDA and Health Canada for the treatment of several rheumatic disorders (e.g. rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, and ulcerative colitis).[109] In a randomized, double-blinded, placebo-controlled trial of infliximab in depressed subjects meeting diagnostic criteria for a current MDE as part of treatment-resistant MDD ($n = 51$) or bipolar disorder ($n = 9$), Raison and colleagues reported that infliximab significantly improved depressive symptoms in subjects with baseline inflammatory activation (i.e. hs-CRP levels of >5 mg/l), but not in subjects without baseline inflammatory activation (i.e. hs-CRP $\leqslant 5$ mg/l); in fact, subjects without baseline inflammatory activation were more likely to benefit from placebo than active treatment.[107] A case report of antidepressant efficacy of TNF-alpha inhibitor etanercept in two geriatric patients with treatment resistant depression reported mixed findings, but did not assay baseline inflammation.[108]

Three randomized, double-blinded, placebo-controlled clinical trials investigating the efficacy of infliximab on a measure of anhedonia are currently ongoing (Table 1). One 12-week trial in adults ($n = 60$) with bipolar I/II depression exhibiting baseline inflammatory activation includes an assessment of the Snaith-Hamilton Pleasure Scale (SHAPS) with three infusions of inflixmab or placebo and is expected to complete in April 2018 [ClinicalTrials.gov identifier: NCT02363738]. Two 2-week trials include adults currently experiencing clinically significant depressive symptoms as part of bipolar or MDD with baseline CRP > 3 mg/l and a single infusion of infliximab or placebo and are expected to complete in March 2021. One study ($n = 80$) primarily aims to assess the effects of infliximab on motivational circuits and behavior as assessed using an functional magnetic-resonance-imaging-adapted Behavioral Effort-Expenditure for Rewards Task (behEEfRT) [ClinicalTrials.gov identifier: NCT03006393]. A separate study ($n = 60$) primarily aims to investigate the effects of infliximab on glutamate levels in the basal ganglia as measured by magnetic resonance spectroscopy and additionally includes cerebrospinal fluid biomarkers [ClinicalTrials.gov identifier: NCT03004443]. All three clinical trials include measures of cognition, overall depressive symptom severity, and peripheral biomarkers, among others (Table 1).

Conclusion

Taken together, the etiology of mood disorders is mechanistically heterogeneous, underscoring the need for a dimensional approach to identify and develop disease-modifying and potentially curative treatments in psychiatry. Accumulating evidence implicates inflammation as an important contributor to the pathophysiology of depression and presents the immune system as a viable therapeutic target that may be more proximate to the pathogenic nexus of brain-based disorders in specific subpopulations. Cellular and molecular inflammatory and innate immune substrates are valuable biomarkers that can be used in conjunction with specific symptom dimensions to demonstrate target engagement with novel or repurposed therapeutic agents and to differentiate patient populations who are most likely benefit from these treatments.

Anhedonia is a transdiagnostic, yet specific, and clinically relevant symptom dimension subserved by well-characterized neurobiological and neurophysiological substrates that are preferentially affected by inflammatory processes and their

Table 1. Summary of ongoing clinical trials investigating the efficacy of anti-tumor necrosis factor alpha biologic infliximab on a measure of anhedonia.

Study location [ClinicalTrials.gov identifier]	Recruitment status (estimated study completion date)	Study design	Intervention	Participants	Primary outcome measure	Secondary outcome measures
Toronto Western Hospital, University Health Network, Toronto, Canada; VA Palo Alto Health Care System, Stanford University, Palo Alto, USA [NCT02363738]	Completed (April 2018)	Phase II, 12-week randomized, placebo-controlled clinical trial with masking of participant, investigator, outcomes assessor, and care provider	Three infusions of adjunctive infliximab (5 mg/kg) *versus* saline at weeks 0, 2, 6 (parallel assignment)	Adults ($n = 60$) ages 18–65 with current MDE as part of BD-I/II exhibiting baseline inflammatory activation (obesity and hypertension/dyslipidemia, diabetes mellitus, inflammatory bowel disorder, rheumatoid arthritis, psoriasis, daily cigarette smoking, or baseline CRP $\geqslant$ 5 mg/l)	MADRS total score (change from baseline to up to week 12)	Anhedonia (SHAPS), plasma cytokine levels, cognitive function (DSST, RAVLT, PDQ-D-20), structural MRI and MRS, quality of life (SF-36), functional disability (SDS, EWPS), suicide risk (CSSRS)
Emory University, Atlanta, USA [NCT03006393]	Recruiting (November 2021)	Phase I, 2-week, randomized, placebo-controlled clinical trial with masking of participant and investigator	Single infusion of infliximab (5 mg/kg) *versus* saline (parallel assignment)	Adults ($n = 80$) ages 25–60 with current MDE as part of MDD or BD with baseline CRP $>$ 3 mg/l	fMRI-adapted behEEfRT with two task difficulty level choices (change from baseline to week 2)	Anhedonia (SHAPS, MAP), fatigue (MFI, FSS), overall depressive symptom severity (IDS-SR), emotional states (PANAS-X), suicide risk (CSSRS), cognition (Go/No-Go, RTT, DSST), motor control (FTT), plasma biomarkers (CRP, TNF-alpha, sTNFR1, sTNFR2, IL-1, IL-1RA, IL-6, sIL-6R)
Emory University, Atlanta, USA [NCT03004443]	Recruiting (March 2021)	Phase IV, 2-week, randomized, placebo-controlled clinical trial with masking of participant, investigator, and outcomes assessor	Single infusion of infliximab (5 mg/kg) *versus* saline (parallel assignment)	Adults ($n = 60$) ages 25–60 with current MDE as part of MDD or BD with baseline CRP $>$ 3 mg/l	Basal ganglia glutamate, assessed by MRS (change from baseline to day 3 to 14)	Anhedonia (SHAPS, MAP), motivation (EEfRT), motor control (FTT), cognition (RTT, DSST, TMT-A), psychomotor retardation (RSS), fatigue (MFI), overall depressive symptom severity (IDS-SR), plasma and CSF inflammatory markers (CRP, TNF, TNFR2, IL-1RA, IL-6, sIL-6R, IL-10, MCP-1, mRNA)

BD: bipolar disorder; behEEfRT: behavioral EEfRT; CRP: C-reactive protein; CSF: cerebrospinal fluid; CSSRS: Columbia Suicide Severity Rating Scale; DSST: Digit Symbol Substitution Test; EEfRT: Effort-Expenditure for Rewards Task; EWPS: Endicott Workplace Productivity Scale; FSS: Fatigue Severity Scale; IDS-SR: Inventory of Depressive Symptoms Self-Report; IL: interleukin; IL-1RA: IL-1 receptor agonist; MADRS: Montgomery-Asberg Depression Rating Scale; MAP: Mood and Pleasure Scale; MCP: monocyte chemoattractant protein; MDD: major depressive disorder; MDE: major depressive episode; MFI: Multidimensional Fatigue Inventory; MRI: magnetic resonance imaging; mRNA, messenger ribonucleic acid; MRS: magnetic resonance spectroscopy; PANAS-X: Positive Affect/Negative Affect Scale: now; PDQ-D-20: Perceived Deficits Questionnaire: Depression, 20-item; RAVLT: Rey Auditory Verbal Learning Test; SDS: Sheehan Disability Scale; SF-36: 36-item Short Form health survey; RTT: Reaction Time Task; SHAPS: Snaith-Hamilton Pleasure Scale; sIL-6R: soluble IL-6 receptor; TMT: Trail-Making Test; TNF: tumor necrosis factor; TNFR: TNF receptor; VA, Veterans Affairs.

effects on cellular and molecular pathways (e.g. dopaminergic transmission; excitotoxicity; synaptic plasticity), as well as brain circuits, nodes, and networks that subserve PVS phenomenology. To our knowledge, no published randomized, controlled clinical trial in populations with mood disorders has hitherto primarily sought to determine the effects of an anti-inflammatory agent on PVS functions and pathophysiology. Notwithstanding, three ongoing clinical trials aim to investigate the effects of anti-TNF-alpha biologic infliximab on measures of anhedonia [ClinicalTrials.gov identifier: NCT02363738], motivational behavior and circuitry [ClinicalTrials.gov identifier: NCT03006393], and glutamatergic changes in the basal ganglia [ClinicalTrials.gov identifier: NCT03004443] in clinical populations with unipolar or bipolar depression. Positive results would further instantiate the relevance of inflammatory processes and the immune system in the phenomenology and etiology of mood disorders and provide the impetus to develop scalable treatments targeting inflammation and the immune system to mitigate transdiagnostic, dimensional disturbances in brain-based disorders.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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