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Brick by brick: building a transdiagnostic understanding of inflammation in psychiatry

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Abstract

Inflammatory phenomena are found in many psychiatric disorders, notably depression, schizophrenia, and posttraumatic stress disorder. Inflammation has been linked to severity and treatment resistance and may both contribute to as well as result from the pathophysiology of some psychiatric illnesses. Emerging research now suggests that inflammation may contribute to symptom domains of reward, motor processing, and threat reactivity across different psychiatric diagnoses. Reward processing deficits contribute to motivational impairments in depression and schizophrenia, and motor processing deficits contribute to psychomotor slowing in depression as well as in schizophrenia. A number of experimental models and clinical trials suggest that inflammation produces deficits in reward and motor processing through common pathways connecting the cortex and the striatum, which includes the nucleus accumbens, the caudate nucleus, and the putamen.

The observed effects of inflammation on psychiatric disorders may cut across traditional conceptualizations of psychiatric diagnoses, and further study may lead to targeted immunomodulating treatments that address difficult-to-treat symptoms in a number of psychiatric disorders. In this review, we use a Research Domain Criteria framework to discuss proposed mechanisms for inflammation and its effects on the domains of reward processing, psychomotor slowing, and threat reactivity. Furthermore, we discuss data supporting contributing roles of metabolic dysregulation and sex differences on the behavioral outcomes of inflammation. Finally, we discuss ways that future studies can help disentangle this complex topic to yield fruitful results that will help advance the field of psychoneuroimmunology.

Keywords

inflammation; cytokine; C reactive protein; mental disorders/physiopathology; immunomodulation

Introduction

There is a robust body of literature that now allows us to articulate pathways between peripheral inflammation, disruption of neural circuits, and specific symptom domains of psychiatric disorders: reward processing, psychomotor slowing, and to a lesser extent,

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threat reactivity. Early support for this relationship stemmed from administration of inflammatory stimuli in animal models and was later reinforced when symptoms of depression emerged in individuals receiving cytokines as therapy for cancer or chronic viral infection.[1–4] Continued work in this area has shown that a subset of individuals with depression exhibit persistent inflammation that has both direct and indirect effects on the functioning of brain circuits that mediate core aspects of depression and represent an important source of treatment resistance.[5–9] With depression serving as the blueprint for this relationship, data has emerged showing similar relationships for psychomotor deficits in schizophrenia and reward processing deficits in schizophrenia and PTSD.[5,10,11] Furthermore, inflammation has been associated with alterations to threat reactivity in both depression and posttraumatic stress disorder (PTSD).[12,13] We are now confronted with mounting evidence that inflammation may produce strikingly similar outcomes psychiatric illness, including depression, schizophrenia, and PTSD, which suggests that the impact that inflammation has on psychiatric symptomology may be relatively conserved across different psychiatric diagnoses and may occur through similar pathways.[5,14–18] This realization could have profound implications for our understanding of the role between inflammation and human behavior and the ways that we conceptualize and treat psychiatric illnesses.

Meta-analyses measuring circulating cytokines in depression, schizophrenia, and PTSD demonstrate dysregulation in a substantial proportion of individuals when compared with healthy controls.[19–22] Inflammation has been linked to worse treatment outcomes in both depression as well as in first-episode psychosis.[8,23,24] Recent evidence indicates that increased concentrations of C-Reactive Protein (CRP) and inflammatory markers, such as cytokines, are associated with acute illness in patients with schizophrenia, bipolar disorder, and major depressive disorder and improves with treatment. Importantly, a number of markers remain significantly elevated in patients with chronic symptoms of these disorders, which suggests the possibility that some inflammatory markers may represent state and trait markers of psychiatric illness.[19,25] Trait markers, which suggest risk for, or presence of illness, can be helpful for understanding pathophysiology or developing preventive treatments. State markers may change dynamically with severity and phase of illness and can be useful for monitoring treatment response. Studying inflammatory dysregulation in psychiatric disorders therefore presents an opportunity to “carve nature at its joints” to understand patterns that manifest in ways are not adequately reflected in current psychiatric nosology.

At the present moment, there is limited evidence implicating specific inflammatory markers with specific psychiatric disorders. Given that there is evidence for increased peripheral inflammation in patients with psychiatric disorders, it is plausible that inflammation and different inflammatory markers may play a specific role in individual psychiatric disorders. Alternatively, it is also plausible to consider that inflammation may impact the brain and behavior in a transdiagnostic fashion. In this narrative review, we consider this latter approach and use the Research Domain Criteria as a unifying framework to suggest that chronic low-grade inflammation may produce similar deficits in reward processing, motor processing, and threat reactivity independent of psychiatric diagnosis (Table 1). We consider these deficits at not only the level of symptoms, but also at the level of the brain through the impact of inflammatory cytokines on brain regions and circuits that have been shown to

drive these associated behaviors. Finally, we also discuss the interdependent relationship between metabolic dysregulation and inflammation in psychiatric disorders as well as research hinting at sex differences in the behavioral outcomes of inflammation, and then conclude with suggestions for future work.

Using the Research Domain Criteria framework to understand the role of inflammation in psychiatric disorders

The diagnostic classification system provided by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) provides a helpful construct for the clinical approach to mental disorders, but the heterogeneity present in many of these diagnoses creates artificial barriers that impede research into understanding why certain behavioral phenotypes arise and how to best treat them.[26–28] For example, if a DSM-defined psychiatric illness were to occur due to multiple pathophysiological pathways, a medication that only targets one of these pathways could appear to fail in a clinical trial that enrolls individuals with that diagnosis irrespective of the underlying biology. Furthermore, the diagnostic overlap occurring with some DSM-5 diagnoses may in fact represent distinct entities that occur due to common neurobiological pathways, which could help explain why certain treatments such as antipsychotic medications have indications for schizophrenia, bipolar disorder, and as augmentation for major depression.[29,30] In order to address these types of dilemmas, the National Institute of Mental Health created an initiative to establish a more biologically-oriented nosology of mental illness through the Research Domain Criteria (RDoC) project, which aims to characterize domains of human functioning using different units of analysis, such as genes, brain circuits, or neurotransmitters. In alignment with this initiative, we aim to present the hypothesis that inflammation produces several specific patterns of disruptions to neurocircuitry that produce similar behavioral outcomes in a cross-cutting manner. In order to minimize bias in this narrative selective review, a structured search of PubMed was performed to ensure that relevant studies were included using the following search strategy: (INFLAMMATION or CYTOKINE) and (NEUROIMAGING or MRI or NEUROCIRCUITRY or BRAIN CIRCUIT or NEURAL CIRCUIT) and (DEPRESSION or SCHIZOPHRENIA or POSTTRAUMATIC STRESS DISORDER). Results from this search strategy were used to identify articles with data that emphasized multiple units of analysis from the Research Domain Criteria framework (i.e. genes, molecules, cells, circuits, physiology, behavior) for inclusion. Studies that did not assess the effect of inflammation using at least two units of analysis for a specific topic were excluded.

Inflammation: from cytokines to circuits to behavior

Peripheral inflammation can exert effects on the central nervous system (CNS) through a number of mechanisms that challenge conventional notions that the CNS is immunologically privileged: autonomic nervous tone, cytokine transporters located within the blood-brain barrier, volume diffusion of cytokines produced in circumventricular organs and the choroid plexus, and activity of immune cells and cytokine receptors in areas adjacent to the brain.[31] Postmortem and neuroimaging studies suggest that blood-brain barrier integrity may frequently be compromised in schizophrenia; postmortem data indicates that this may be the case in affective disorders as well.[32] Furthermore, receptors for cytokines are expressed

throughout the CNS.[33] Cytokines act through these routes to facilitate neuroplastic changes in brain circuits, notably by modulating the synthesis, reuptake, and release of neurotransmitters, including serotonin, dopamine, norepinephrine, and glutamate.[34]

Studies administering cytokines and other inflammatory stimuli to human subjects have provided robust evidence of the relationship between cytokines, neurocircuitry, and specific behavioral domains of depression.[1,31] Perhaps the most well-studied of these models is the antiviral cytokine interferon-α (IFN- α), which provokes a syndrome characterized by symptoms of depressed mood, fatigue, anxiety, amotivation, and motor slowing.[1] Other commonly used models include the T-cell-stimulating cytokine interleukin-2 (IL-2) as well as typhoid vaccination and endotoxin administration, which both elicit acute inflammation.[31,35,36] These agents have been used in a number of experimental approaches to characterize neurocircuitry changes that occur as a result of inflammation. Reward deficits induced by inflammation have been linked to disruption in the dopamine-mediated mesolimbic pathway, which is composed of the ventral tegmental area and its projections to the ventral striatum, which contains the nucleus accumbens, as well as in corticostriatal pathways between the ventral striatum and ventromedial prefrontal cortex.[5,6,34] Motor processing deficits occurring due to inflammation have been principally associated with disruption to dopamine-mediated corticostriatal signaling between the dorsal striatum (which consists of the putamen and caudate), and the ventromedial prefrontal cortex, which is involved in emotional regulation and decision-making.[5,34,37] In contrast, alterations to threat reactivity in the setting of inflammation are associated with functional changes to structures involved in fear processing: the amygdala, anterior cingulate gyrus, and insula.[38–41] As will be discussed in further detail below, disruption to the mesolimbic pathway has been associated with reward processing deficits occurring due to inflammation in depression, schizophrenia, and PTSD, while disruption to corticostriatal signaling has been associated with reward processing and motor slowing due to inflammation in depression and schizophrenia.[5,11,12,34] Alterations to brain structures related to fear processing have been associated with changes in threat reactivity occurring in the setting of inflammation in both PTSD and depression.[12,42]

It is important to note that sustained inflammation also produces considerable metabolic dysregulation. In addition to its neuropsychiatric consequences, inflammation has been strongly linked to other diseases such as obesity, diabetes, and cardiovascular disease.[43–45] Obesity contributes to systemic inflammation through accumulation and activation of macrophages in adipose tissue, which then release cytokines into the circulation.[46,47] The pro-inflammatory cytokines released through this process exert substantial effects on insulin resistance and metabolic regulation.[48–50] It is increasingly apparent that the immune system, metabolism, and mental health can affect each other in a complex, closely interlinked manner.[51,52] Obesity is associated with an increased risk of depression and vice versa, and depressed individuals with metabolic dysregulation may represent a treatment-resistant group.[51,53] Surgical intervention for obesity is associated with reductions in both inflammation and depression.[54,55] In addition, inflammation has been hypothesized to play a role in the metabolic dysfunction that occurs widely in schizophrenia independent of the effects of antipsychotic medication.[56–58] Kappelman et al. analyzed genome-wide association study data and found a relationship between CRP, body mass index, and

neurovegetative symptoms of depression, supporting the role of triadic relationship between inflammation, metabolic dysregulation, and depression.[59] In a similar approach, Perry et al. found that inflammation may drive both insulin resistance and schizophrenia risk.[60] The interplay of inflammation and metabolic disruption has important implications for understanding the effects of inflammation on psychiatric illnesses and will be discussed briefly throughout this paper; this topic has been reviewed more extensively elsewhere.[52,61]

An evolutionary link between inflammation and mental health: sickness behavior

Continued research into the connection between cytokines and behavior suggests that there may be an adaptive component to the influence of inflammation on mental health. Sickness behavior, or behavior that occurs during periods of acute infection, is postulated to have an evolutionary origin: the fatigue, amotivation, social avoidance, and anhedonia experienced during illness may encourage individuals to conserve energy needed for healing and isolation, thereby preventing the spread of pathogens.[6] Tumor necrosis factor-α (TNF) and interleukin-1β, which both act as initiators of inflammation, appear to play major roles in sickness behavior and are commonly produced by inflammatory stimuli such as endotoxins.[6,31,62] These behavioral symptoms that are subsequent to acute inflammation are thought to be evolutionarily conserved and drive the hypothesis that the behavioral manifestations of chronic, low grade inflammation in psychiatric illness stems from brain regions and circuits that have been shown to be sensitive to the effects of inflammation. In order words, the chronic inflammation associated with a subset of cases of depression, schizophrenia, and PTSD may represent a maladaptive consequence of sickness behavior. Sustained low-grade inflammation in a portion of individuals with these disorders likely contributes to motivational deficits, psychomotor slowing, and altered threat reactivity in a diagnosis-independent manner.

The far-reaching role of inflammation in psychiatric disorders

Acute inflammation serves important roles in responding to infection and injury, but when it fails to resolve, the ensuing imbalance in immune, metabolic, and neuroendocrine systems contributes to a wide array of human diseases, including mental illness.[63,64] In the setting of chronic inflammation, cytokine production becomes dysregulated, leading to diverse consequences in a myriad of tissue types, including the central nervous system, adipose tissue, and the cardiovascular system.[64] Cytokines are immune signaling peptides produced by both immune and non-immune cells that can have both pro-inflammatory and anti-inflammatory effects. Cytokines can influence the production, release, and reuptake of neurotransmitters, leading to functional changes to brain circuitry that produce specific patterns of psychiatric symptoms.[34]

The systemic marker of inflammation, C-reactive protein (CRP), may be useful to quantify the degree of inflammatory burden in psychiatric illness. CRP is an acute phase reactant synthesized by the liver in response to cytokines such as interleukin-6 (IL-6). Though not thought to be an inflammatory cytokine, CRP can be considered a marker of systemic inflammation. Though there are other biomarkers that are useful to characterize systemic inflammation, CRP remains widely used in clinical settings because of the ability to be easily assayed in Clinical Laboratory Improvement Amendments (CLIA)-certified

laboratories. Moreover, CRP can be used to stratify individuals into groups with low inflammation (<1 mg/L), medium inflammation (1 to 3 mg/L), or high inflammation (>3mg/L), which are thresholds based on guidelines for evaluating cardiovascular risk due to inflammation that were developed by the Centers for Disease Control and Prevention and the American Heart Association.[65–67] A meta-analysis assessing inflammatory burden in depression showed that 60% of patients with depression exhibit low-grade inflammation as indicated by a C-reactive protein (CRP) concentration above 1 mg/L, while 30% exhibit high inflammation as measured by a CRP greater than 3 mg/L.[68] Markers of inflammation in healthy individuals are associated with an increased likelihood of later developing major depression, and for individuals with depression, inflammatory markers correlate with treatment resistance.[9,69] In bipolar disorder, CRP concentrations are elevated in all phases of the illness but appear to be worst during mania.[70] A number of inflammatory phenomena have been described in schizophrenia, including elevated systemic inflammation (including CRP as well as a number of inflammatory cytokines – most commonly interleukin 6 and tumor necrosis factor), dysregulation of microglial cells, and excess complement activity.[19,71–74] In addition, persistent low-grade inflammation has been consistently described in PTSD (e.g. CRP, IL-6, TNF, IL-1beta, and interferon-gamma).[20] Of note, inflammation has been linked to other psychiatric disorders, including anxiety and eating disorders, but these will not be included in this review due to limited availability of research analyzing the role of inflammation across multiple levels of analysis.[12,75,76]

Although individual cytokines have been shown to be increased in individual psychiatric illnesses relative to healthy controls, it is premature to suggest that individual markers may be implicated in specific disorders, or in psychiatric illness in general. The findings in the literature, for example, may be skewed by individual markers that are more commonly assayed. It should be noted that various groups have used data-driven approaches to parse the heterogeneity of the various inflammatory markers that have been implicated in the literature. These data-driven approaches that include using principle component analysis and other clustering approaches, may help identify groups of cytokines that may be implicated in psychiatric disorders in addition to behavior and brain function.[77–79]

These findings spur a host of intriguing questions: where does inflammation come from in psychiatric disorders? Does inflammation lead to psychiatric illness, or is the inverse true? Is there is a bidirectional relationship between illness and inflammation, or is the presence of inflammation purely an epiphenomenon? A number of common factors predispose to inflammation and likely play a role in perpetuating immune dysregulation in these disorders, including childhood mistreatment, stress, poor sleep, dietary factors and obesity, the gut-brain axis, and physical inactivity.[80–82] Early childhood trauma and socioeconomic adversity appear to modulate inflammation that influences the risk of developing subsequent PTSD.[81] Less well understood are the underlying cellular and molecular processes that mediate the inflammation that is present in a subset of individuals with psychiatric illness. In depression, substantial attention has been directed at the relationship between stress, the hypothalamic-pituitary axis, and the sympathetic nervous system.[83] Stress and adverse childhood experiences can modulate the hypothalamic-pituitary-adrenal (HPA) axis; glucocorticoids produced in response to stress can promote inflammation and alter immune functioning.[34,83] Glucocorticoids reduce levels of pro-inflammatory cytokines and

increase levels of anti-inflammatory cytokines, which can then act on neurocircuitry to produce behavioral changes.[34,83] More recently, production of protein complexes in cells from myeloid lineages have been shown to drive inflammation in depression (so-called inflammasomes).[84] In schizophrenia, maternal immune activation and prenatal infection may spur immune dysregulation that mediates the risk of developing schizophrenia.[85] Large-scale genome-wide association study findings showing enrichment of enhancer elements for immune cell lineages and epidemiological data showing increasing comorbidity of autoimmune disorders and increased proportions of circulating autoantibodies also point to a possible contribution from B cells in the pathogenesis of schizophrenia.[86–88] Pathological microglial activation has been hypothesized to play an important role in both bipolar disorder and schizophrenia.[72,89] Microglial cells play an important role in maintaining immune homeostasis in the central nervous system, and overactivation could lead to excessive synaptic pruning that may explain the reduced synaptic density noted in postmortem analysis of brain samples from deceased individuals with schizophrenia.[90–92] In summary, inflammation seen in these psychiatric disorders occur due to different sources of immune dysregulation that vary widely not only between different diagnoses but also within the same DSM-5 diagnosis.

Accumulating evidence suggests that inflammation likely plays a bidirectional role in the development of some psychiatric disorders. Despite substantial heterogeneity in the underlying pathogenesis of depression, bipolar disorder, and schizophrenia, longitudinal data and results from clinical trials with immunomodulating agents support the hypothesis that immune dysregulation likely plays a bidirectional role in at least a subset of cases.[6,7,18,73] Early research hints at bidirectionality in PTSD as well. Though further research is needed to dissect this relationship, current research suggests that inflammation both increases risk of developing PTSD and ensues from it.[81,93,94] Inflammation in the immediate period after a trauma may also influence the likelihood of developing chronic PTSD.[95–97]

It is unclear whether specific types of inflammation confer risk for certain psychiatric disorders, or whether inflammation generally increases the risk of developing multiple psychiatric disorders. Using a prospective birth cohort of about 4500 individuals, researchers from the Avon Longitudinal Study of Parents and Children found that levels of IL-6 and CRP at age 9 were associated with risk of developing psychosis (unadjusted odds ratios of 1.34 and 1.21 for IL-6 and CRP, respectively) and depression (unadjusted odds ratios of 1.27 and 1.13 for IL-6 and CRP, respectively) in early adulthood.[98] Interestingly, the timing of stress during development may differentially effect circuitry that can predispose to either depression or psychosis. Using inescapable footshocks and restraints in a rat model, Gomes et al. found that stress in adolescent rats resulted in circuit deficits and behaviors that resembled those of humans with psychosis, while stress in adult rats instead led to circuit changes and behaviors that mimicked those of depression.[99] These are intriguing findings, though future research will need to disentangle the effects of environmental factors and genetic risk on the development of psychiatric illness as it relates to inflammation. This dilemma is readily apparent with schizophrenia in the emerging hypothesis that dysregulated complement activation occurring due to genetic and environmental factors may influence microglial activity that leads to excessive synaptic pruning during critical periods of neurodevelopment.[71,91,100–102] Peripheral complement proteins, which are important

proteins in the innate immune system, have recently been studied as potential biomarkers in patients with psychosis and depression.[103–105] Moreover, there is a growing literature on the use of positron emission tomography (PET) imaging with ligands to the translocator protein (TSPO), thought to reflect activated microglia in the brain, in individuals with psychiatric illness.[106–108] It should be noted that there are a number of limitations to this literature that are beyond the scope of this paper, that have been reviewed elsewhere.[109–111]

Positive valence systems in the RDoC framework: the effects of inflammation on reward processing in depression, schizophrenia, and PTSD

The RDoC domain for positive valence systems includes biological pathways that motivate and reinforce the production of actions and behaviors. Reward processing has multiple constructs within the RDoC framework for positive valence systems, including reward responsiveness, reward learning, and reward anticipation. Reward processing determines how motivated an individual will be to perform a given behavior based on how eagerly they desire the reward from that behavior. Reward processing deficits occur commonly in schizophrenia, depression, and PTSD, and often create major life limitations: poor motivation can lead to worsened performance at work that culminates in termination, while reduced reward-seeking could lead to social isolation.[112–114]

In depression, inflammation has been linked to deficits in reward processing via the mesolimbic system[115] as well as corticostriatal circuitry that has also been implicated in inflammation-mediated deficits to reward processing.[115] Inflammation may play a role in the altered calculation of effort and reward observed in depression, creating a preference for low effort/low reward strategies over those that are more rewarding but more effortful.[116–118] Early research using neuroimaging in PTSD has also linked inflammation with abnormalities in the mesolimbic system.[11] Anhedonia and motivational deficits commonly seen in schizophrenia have been linked to dysregulated inflammation in a number of studies, but data integrating these finding across multiple levels of analysis are not yet available.[10]

Inflammation affects reward processing through mesolimbic and corticostrial circuits

Immune challenge with inflammatory stimuli has been shown to alter reward processing via the mesolimbic and corticostriatal pathways, which suggests that inflammation may act broadly in psychiatric illness to produce deficits in reward.[6] Administration of endotoxin in humans correlated with deficits to reward anticipation and reward responsiveness in several clinical studies by the Eisenberger group.[119,120] One study assessing the effects of endotoxin challenge or placebo in 39 participants without a history of mental illness showed a relationship between inflammatory markers, depressive symptoms, and anhedonia.[35] Endotoxin provoked depressive symptoms that were associated with increased serum levels of the pro-inflammatory cytokines IL-6 and TNF. Though reward learning was unaffected as measured by performance on the monetary incentive delay task, the authors observed a reduction in ventral striatum activity in anticipation of reward in the endotoxin group.

Mediation analysis indicated that left ventral striatal activity mediated the relationship between endotoxin administration and mood.

The ventral striatum and its projections to the cortex serve core functions in modulating effort and reward.[121] To study the effects of IFN-α on reward pathways, Capuron et al. compared individuals receiving IFN-α for treatment of chronic hepatitis C with those who were waitlisted for the drug.[122] They found that IFN-α caused reduced activation of the bilateral ventral striatum in response to a gambling task and linked this reduced activity to anhedonia. Felger et al. used IFN-α in a nonhuman primate model to ascertain changes in striatal dopamine signaling.[123] IFN-α administration led to reduced dopamine release in the striatum, and the timing of this change correlated with anhedonia-like behavior.

Inflammation alters corticostriatal and mesolimbic circuitry in depression and PTSD

Research studying the connection between inflammation and reward processing in psychiatric disorders points to a possible mediating role of corticostriatal and mesolimbic neurocircuitry. In a study of individuals with major depression and bipolar depression, Felger et al. demonstrated that levels of CRP in individuals mediated anhedonia via connectivity between the left inferior ventral striatum and the ventromedial prefrontal cortex, which aids in decision-making and emotional regulation.[124] In a study using a cohort of 56 trauma-exposed women, Mehta et al. found that higher peripheral plasma CRP negatively correlated with bilateral ventral striatum-ventromedial prefrontal cortex functional connectivity, and a separate analysis using an inflammatory composite score indicated that mesolimbic connectivity was specifically altered in women with worse PTSD symptoms and prior major trauma.[11] Left ventral striatum-ventromedial prefrontal cortex functional connectivity also correlated with higher anhedonia scores in subscales from the Beck Depression Inventory and the PTSD Symptom Scale when comparing groups after stratifying for high inflammation/low inflammation.

A number of studies have also linked immunometabolic dysregulation to specific neurocircuitry changes in depression, primarily in dopaminergic corticostriatal circuits.[52] In an fMRI study of 42 individuals with depression, metabolic markers and CRP interacted together to influence functional connectivity in reward and motor circuits.[125] Exploratory transcriptional analysis showed that enrichment for inflammatory and metabolic pathways correlated with these functional changes. Since inflammation, mental health, and metabolism are highly interrelated, treatment of individuals with psychiatric illness that have a high inflammatory burden may also need to account for the role of metabolism in the pursuit of more effective therapies. Research on the use of the tumor necrosis factor (TNF)-α antagonist infliximab in depression showed that gene transcription of biomarkers related to lipid and glucose metabolism helped predict its antidepressant response.[126,127]

Inflammation influences reward processing in schizophrenia

Deficits in reward processing and motivation are core negative symptoms of schizophrenia and represent a difficult-to-treat aspect of the illness.[10] Unfortunately, much of the research in this area does not consider reward processing separately from negative symptoms as a whole, though recent evidence supports a role for separate domains of negative symptoms

including deficits in motivated behaviors and deficits in expressivity.[128–131] A number of studies have linked inflammation to these symptoms and though no studies to date have directly linked inflammation to reward processing at the level of the brain or behavior, there is a growing literature on the association between inflammation and negative symptoms of schizophrenia, spurring intriguing hypothesis-driven questions as to whether inflammation may impact similar reward circuits in the brain in patients with schizophrenia. In the largest study on this topic, Liemburg at al. found that CRP correlated with the negative symptoms on the Positive and Negative Syndrome Scale in sample of 2,132 individuals with psychotic disorders.[132] Individuals with deficit schizophrenia, marked by prominent and persistent negative symptoms, have been shown to have higher concentrations of TNF and IL-6 compared to both healthy controls and individuals with non-deficit schizophrenia; increased TNF and IL-6 were associated with worse negative symptom severity.[133] Inflammation may also be predictive of the development of negative symptoms in individuals at risk for developing a psychotic disorder. Data from the North American Longitudinal Prodromal Study showed that increased concentrations of TNF predicted later development of negative symptoms, even after controlling for depressive symptoms.[134] Neuroimaging studies in psychotic disorders have frequently linked abnormalities in the ventral striatal to reward processing deficits in schizophrenia, but research is not yet available examining the possible mediating role of inflammation for this circuit for schizophrenia.[135–137] Future work in this area could benefit from reorganizing negative symptoms into discrete RDoC constructs such as reward processing and deficits in expressivity in order to help disentangle how inflammation influences each individual component.

As it relates to the interplay of inflammation and metabolic dysfunction, increased inflammatory and cholesterol markers have been shown to predict worse clinical outcomes after one year of treatment in individuals with first episode psychosis, even after controlling for the effects of antipsychotic medication on glucose metabolism.[23] Moreover, the interactive effect of inflammation and lipid biomarkers were shown to be associated with worse negative symptom severity in patients with schizophrenia.[138] Further work should seek to investigate these interactions as there appears to be evidence for their impact within this RDoC positive valence system and could represent novel and important treatment targets.

Sensorimotor systems in the RDoC framework: the effects of inflammation on psychomotor speed and motor planning in depression and schizophrenia

The RDoC framework for sensorimotor systems encapsulates biological pathways that plan, produce, and refine movement. Constructs and subconstructs from sensorimotor systems that are relevant to inflammation include motor processing and planning, deficits to which are commonly observed in depression and schizophrenia.[37,139,140] Conversely, this relationship has not been shown in PTSD, and for unclear reasons, individuals with PTSD that go on to develop depression may actually be less likely to exhibit psychomotor slowing.[141] Psychomotor slowing associated with inflammation represents a marker of treatment-resistant depression, which hints at the inability of currently-available treatments

to address the inflammation underlying this phenotype.[142–144] Similarly, psychomotor slowing in schizophrenia does not respond well to usual treatment with antipsychotic medication.[140]

Inflammation affects motor processing through corticostriatal circuitry

IFN-α helped provide early evidence of the connection between inflammation, depression, and psychomotor slowing. Administration of IFN-α frequently produces a depressive syndrome with prominent neurovegetative symptoms, including fatigue and motor slowing.[1] In a clinical trial studying depressive symptoms induced by IFN-α in the treatment of chronic hepatitis C, participants experienced reduced motor speed and worsened reaction times, and these deficits were worst in individuals meeting criteria for a major depressive episode.[2] Further experiments to understand the downstream effects of IFN-α have helped elucidate the impact this cytokine has on brain networks and neurotransmitter signaling. Psychomotor slowing induced by IFN-α appears to be mediated by activity in the corticostriatal network, including basal ganglia structures and the prefrontal cortex.[145,146] In vivo data using nonhuman primates showed that chronic administration of IFN-α reduced dopamine release in the striatum.[123] In another experimental model, stimulated release of cytokines via typhoid vaccination in humans provokes psychomotor slowing that is linked to activity in another basal ganglia structure, the substantia nigra.[36]

Inflammation affects motor processing via corticostriatal circuitry in depression

The impact that administration of IFN-α has on brain circuitry resembles the phenotype of psychomotor slowing that is seen in depressed individuals with high levels of inflammation. One study assessing inflammation in 93 participants with major depression and bipolar depression showed that elevated inflammatory markers correlated with worsened performance on a battery of psychomotor tasks. In multiple regression analyses, the cytokine IL-6 was identified as a significant predictor of psychomotor performance.[77] Accumulating evidence indicates that naturalistically-occurring inflammation may influence motor activity through modulation of dopaminergic corticostriatal circuitry. In a neuroimaging study of 48 participants with major depression and bipolar depression, mediation analysis showed that connectivity between the right dorsal caudal putamen and the ventromedial prefrontal cortex mediated psychomotor slowing in participants with elevated CRP (as measured with Finger Tapping Test in the dominant hand).[124] New data further supports a relationship between immunometabolic pathways and psychomotor slowing in depression.[147] Using a sample of unmedicated patients with major depression, motor speed and motor processing deficits were associated with transcriptional enrichment of immunometabolic genes in monocytes, plasmacytoid dendritic cells, and natural killer cells.

Inflammation influences motor processing in schizophrenia

Corticostriatal circuit dysfunction has been consistently linked to psychomotor slowing in schizophrenia and may represent an important phenotype of the disorder that occurs independently of antipsychotic medication side effects.[148,149] Early evidence now suggests that psychomotor processing in schizophrenia may also be influenced by inflammation. A 2020 study assessed the relationship between peripheral immune markers and psychomotor slowing in 43 participants with schizophrenia and 29 healthy controls. After correction for

multiple testing, a number of inflammatory cytokines were associated with psychomotor performance among participants with schizophrenia but not healthy controls, most consistently tumor necrosis factor, IL-6 soluble receptor, and the anti-inflammatory cytokine IL-10.[150] It is unclear at this point whether inflammation serves as a mediating factor in the relationship between corticostriatal circuit abnormalities and psychomotor slowing in schizophrenia, and this area merits further study.

Negative valence systems in the RDoC framework: the effect of inflammation on threat reactivity

In the RDoC framework, reactivity to potential threat (anxiety), acute threat (fear), and sustained threat are negative valence systems. Symptoms of PTSD that are mediated by negative valence systems include threat vigilance and avoidance. Inflammation appears to correlate with threat sensitivity, which contributes to impairment in PTSD.[12] In a study of 735 individuals with current PTSD, higher levels of CRP correlated with higher threat reactivity.[151] Another large study of 2,698 individuals showed that CRP correlated with threat reactivity as measured by a fear-potentiated startle paradigm.[152] Inflammatory stimuli can modulate neurocircuitry involved in emotional processing and threat response, particularly the amygdala, dorsal anterior cingulate cortex, and insula.[38–41] Similarly, the amygdala, dorsal anterior cingulate cortex, and related structures exhibit functional alterations in PTSD in response to threat.[12,153] There are few studies that specifically evaluate the mediating role of inflammation with paradigms that measure threat reactivity in psychiatric illness. Preliminary evidence has linked inflammation to disruption in threat-related circuitry in depression. In an fMRI study of 48 participants with major depression or bipolar depression, higher peripheral plasma CRP correlated with reduced (right) amygdala-ventromedial prefrontal cortex connectivity.[42]

Sex differences in the effects of inflammation on behavior

Despite the important role that sex plays in biological functioning, sex has been historically overlooked as a biological variable in everything from preclinical cell culture data to human clinical trials.[154] Researchers studying the effects of inflammation on mental health are placing increased emphasis on integrating sex as a biological variable into study design.[155,156] Sex differences in the prevalence of mental illnesses discussed in this paper have been well documented: women appear to be nearly twice as likely to develop depression as men, are twice as likely to develop PTSD after a traumatic event, and though are somewhat less likely to develop schizophrenia, they are often diagnosed at a later age.[157–159] Sex differences in immune functioning may help explain these epidemiological puzzles.[160–162] A large body of research indicates that immune functioning differs between men and women (reviewed extensively by Klein and Flanagan[163]), and emerging data indicate that these differences can influence behavioral outcomes. Women may appear more likely to experience increases in inflammatory cytokines after a psychosocial stressor, and this inflammatory state seems to persist longer for women.[164–166] Women may be more susceptible to inflammation-mediated depressive symptoms after receiving an inflammatory stimulus.[167,168] Inflammatory markers may better correlate with reward processing deficits

and psychomotor slowing in depressed women,[67,169,170] though this effect is not always replicated.[35,171] There also appear to be sex differences in complement gene expression that may help explain the reduced vulnerability to schizophrenia in women.[172]

Sex hormones help modulate the immune response independent of the effects of gender, and their interactions with the immune and neuroendocrine systems during critical periods of neurodevelopment likely contribute to differences in inflammation and depression susceptibility between males and females.[161,163] Sex differences appear particularly prominent in microglia: research in rodent models has demonstrated that estradiol exposure modulates microglial functioning in select regions of the rodent brain, leading to changes in dendritic spine density and ultimately to behavior.[160,173] Sex differences in the relationship between inflammation and human behavior are substantive enough that many researchers are now urging the field to explicitly evaluate sex as a biological variable in future research.[157,158,160,168,174]

Data explicitly examining the role of sex in the relationship between inflammation, neurocircuitry, and the three RDoC components examined in this paper (reward processing, motor processing, and threat reactivity) are currently sparse, but a few preliminary observations can be posited. First, there may be sex differences in the relationship between reward processing and inflammation that are mediated by corticostriatal circuitry. In a clinical trial conducted by the Eisenberger group, an endotoxin stimulus or placebo was given to a group of 115 participants to ascertain sex-based differences in reward sensitivity. Female participants showed reduced ventral striatal activity in response to reward cues after administration of endotoxin, while male participants did not.[155] Secondly, sex differences may contribute to the impact of inflammation on threat reactivity. In a study of a sample of 172 undergraduate students, higher levels of CRP correlated with increased amygdala activity in response to threat paradigms in men but not women.[175] The possible underlying processes in these sex differences and their potential impact in the setting of mental illness are unclear and merit further study.

Discussion

Inflammation appears to produce similar effects in multiple different psychiatric disorders, particularly in positive valence systems and sensorimotor systems as described by the RDoC framework. Moreover, individuals with high inflammation may exhibit similar phenotypes that are characterized by disruptions to common neurocircuitry pathways, particularly in mesolimbic and corticostriatal circuits. Further research in this area could inform the development of targeted immunomodulating therapy that may improve treatment for subsets of patients with depression, schizophrenia, and PTSD, particularly those for whom traditional therapies have not worked well due to the mediating role of inflammation.

Approaches to mitigating the impact of inflammation

There is a possibility that a marker such as peripheral plasma CRP could someday be used to help identify and treat subsets of psychiatrically ill individuals whose symptoms occur in part due to a high inflammatory burden. In two different studies of depression that stratified using a CRP threshold of 1, individuals below the threshold had a better response

to selective serotonin reuptake inhibitor (SSRI) medications, while those above the threshold had a better response with an alternative therapy: bupropion-SSRI combination in one study, and nortriptyline in the other.[176,177] The ability of these drugs to modulate norepinephrine and its downstream effects on the immune system has been proposed as a reason for their greater effectiveness in inflammation-mediated depression.[177,178] An alternate possibility is through norepinephrine-mediated modulation of dopamine signaling,[179,180] which could also explain the greater effectiveness of these agents given the impact of inflammation on dopaminergic neurocircuitry. In a proof-of-concept study, Raison et al. performed a clinical trial to assess the differential effects of the TNF-α antagonist infliximab on patients with treatment-resistant depression across varying levels of CRP.[142] Though TNF antagonism did not result in generalized improvement in depression, participants with a CRP greater than 5 experienced a clinically-meaningful improvement in the Hamilton Scale for Depression, with scores specifically improving for symptoms linked to inflammation: anhedonia, psychomotor retardation, and psychic anxiety.

Suggestions for future work in this area

Clinical trials that stratify patients based on the degree of inflammation may be able to lead to the development of novel treatments that address inflammation-mediated symptom burden. A common issue in this area is stratifying results in a post hoc manner, which limits the conclusions that can be drawn.[61,181] It is especially important to enrich for inflammation, as positive results in a high-inflammation subgroup could be lost in a heterogeneous sample. Longitudinal research assessing how inflammation and psychiatric symptomatology evolve over time could be especially useful, particularly in the case of bipolar disorder: inflammation-mediated psychomotor slowing and motivational deficits have been noted in bipolar depression, but it remains unclear how manic episodes fit into this narrative, as they are also associated with inflammation but present instead with psychomotor agitation.[70] Additionally, it is important to recognize that though there is a strong link between inflammation and some symptoms of psychiatric disorders, this is not the only way that these symptoms occur. Finally, sex is a critical biological variable that should be more consistently and explicitly assessed in future work in this area.

In summary, inflammation appears to exert similar behavioral phenotypes that are mediated by mesolimbic and corticostriatial circuitry across different psychiatric disorders, most notably depression, schizophrenia, and PTSD. Future research should emphasize a dimensional approach to identify common inflammatory pathways between different psychiatric disorders. It remains to be seen whether inflammation-mediated phenotypes across different psychiatric diagnoses respond similarly to immunomodulating treatment. As an example, a study by Nettis et al. using adjunctive minocycline in depression showed a benefit for individuals with an elevated CRP.[182] However, a separate study by Deakin et al. did not find any benefit from minocycline for negative symptoms of schizophrenia, even when stratifying for inflammation.[183] One possibility for these discrepant findings could be due to the off-target effects of many anti-inflammatory drugs, including minocycline. Similarly, it is important that anti-inflammatory trials demonstrate that they actually engage the system that is being targeted; otherwise the interpretation of negative findings are especially challenging.[61,184] For example, demonstrating evidence that an anti-inflammatory

medication decreases inflammation is imperative, since only those individuals with increased inflammation would be expected to respond to an anti-inflammatory medication. Moreover, given the evidence that inflammation targets specific neurocircuitry to lead to specific symptoms, anti-inflammatory trials should focus on hypothesized changes at the level of brain and behavior; for example, improvements in connectivity in brain reward circuits should correlate with improvement in symptoms of anhedonia.

Given the broad role that inflammation can play in psychiatric illness, a more granular understanding of the specific pathways involved could enable a new understanding of how certain phenotypes of mental illness arise and lead to targeted immunomodulating treatments that address their underlying inflammation. Careful attention should be paid to the role of immunometabolism and sex differences that contribute to the complex relationship between inflammation and mental health, and accounting for these factors could lead to novel treatments that can address the overlap between inflammation, neuropsychiatric impairment, and metabolic dysregulation in a multipronged fashion. Integrating a dimensional study of inflammation into traditional conceptualizations of psychiatric illness will help explain the considerable overlap in some features of psychiatric disorders while respecting the different components of psychopathology and neurobiology that underlie each.

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Table 1.

Inflammation produces similar behavioral outcomes in different psychiatric illnesses through common pathways

RDoC Domain*	RDoC Construct*	Behavioral outcome of inflammation			Neurocircuitry affected by inflammation
		DEP	SCZ	PTSD	
Positive Valence	Reward	Amotivation	Amotivation	Anhedonia	Mesolimbic† Corticostriatal‡
Sensorimotor	Motor	Psychomotor slowing	Psychomotor slowing	No data	Corticostriatal‡
Negative Valence	Threat	Threat sensitivity	No data	Threat sensitivity	Limbic§

*RDoC: The Research Domain Criteria is a framework proposed by the National Institute of Mental Health to help reorganize psychiatric symptomatology into biologically-aligned categories. The Research Domain Criteria are divided into six domains of human functioning, which are further categorized into different components called constructs and subconstructs. As an example, the RDoC domain for positive valence includes a construct for reward responsiveness, which is further divided into subconstructs for reward anticipation, initial response to reward, and reward satiation.

DEP: depression, SCZ: schizophrenia, PTSD: posttraumatic stress disorder

†Mesolimbic: This pathway plays a central role in reward processing. It connects the ventral tegmental area with the ventral striatum, which contains the nucleus accumbens.

‡Corticostratial: This pathway connects the ventromedial prefrontal cortex and striatum. The ventral striatum is implicated in reward processing, while the dorsal striatum, which contains the putamen and caudate, is implicated in motor processing.

§Limbic: This pathway connects the amygdala, dorsal anterior cingulate cortex, and insula, all of which are involved in threat processing.