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Inflammation-related functional and structural dysconnectivity as a pathway to psychopathology

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Abstract

Findings from numerous laboratories and across neuroimaging modalities have consistently shown that exogenous administration of cytokines or inflammatory stimuli that induce cytokines disrupt circuits and networks involved in motivation and motor activity, threat detection, anxiety, interoceptive and emotional processing. While inflammatory effects on neural circuits and relevant behaviors may represent adaptive responses promoting conservation of energy and heightened vigilance during immune activation, chronically elevated inflammation may contribute to symptoms of psychiatric illnesses. Indeed, biomarkers of inflammation such as cytokines and acute phase reactants are reliably elevated in a subset of patients with unipolar or bipolar depression, anxiety-related disorders, and schizophrenia, and have been associated with differential treatment responses and poor clinical outcomes. A growing body of literature also describes higher levels of endogenous inflammatory markers and altered, typically lower functional or structural connectivity within these circuits in association with transdiagnostic symptoms like anhedonia and anxiety in psychiatric and at-risk populations. This review will present recent evidence that inflammation and its effects on the brain may serve as one molecular and cellular mechanism of dysconnectivity within anatomically and/or functionally connected cortical and subcortical regions in association with transdiagnostic symptoms. We also discuss the need to establish reproducible methods to assess inflammation-associated dysconnectivity in relation to behavior for use in translational studies or biomarker-driven clinical trials for novel pharmacological or behavioral interventions targeting inflammation or its effects on the brain.

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Keywords

inflammation; functional connectivity; fMRI; depression; anxiety; anhedonia; interoception

1. Inflammation in psychiatric disorders: sources and symptoms

1a. Mechanisms and prevalence of increased inflammation in psychiatric patients

In otherwise medically-healthy psychiatric patients, genetic predisposition may interact with environmental/lifestyle factors that contribute to low-grade inflammation including pathogens (e.g., latent infections, gut dysbiosis) and “sterile” inflammatory signals that trigger innate immune responses in the absence of pathogens (Figure 1a)(1). Many of these factors increase risk for both psychiatric and medical illnesses, suggesting shared pathophysiologic mechanisms that explain high rates of comorbidity (2). Activated innate immune cells release inflammatory cytokines like interleukins (ILs), tumor necrosis factor-alpha (TNF), and interferons (IFNs), which then induce acute phase reactants like CRP from the liver. Numerous studies and meta-analyses report higher CRP and protein or gene expression markers of circulating inflammatory cytokines (e.g., IL-1, IL-6, TNF, IFNs) in depression as well as other psychiatric disorders sharing commons symptom domains of reduced motivation, psychomotor slowing and anxiety, including bipolar disorder, schizophrenia, anxiety disorders and post-traumatic stress disorder (PTSD)(3–9). High peripheral inflammation defined as CRP >3 mg/L (i.e., high risk for cardiometabolic disease) is observed for example in ~25-40% of depressed patients (10–13), and may reflect increased activity of some but not all inflammatory cytokines. Longitudinal studies found CRP to predict depressive symptoms (14–16) even beyond prior depression severity (17). Importantly, higher CRP and inflammatory cytokines have also been associated with resistance to conventional antidepressants in depression and worse clinical outcomes in schizophrenia (18–23).

Peripheral-central immune crosstalk at the blood-brain interface.—Elevated CRP, innate/inflammatory cytokines, and peripheral white blood cells are found in CSF (11, 24), and postmortem studies show evidence of increased inflammatory cytokines and signaling pathways, activated microglia, and/or peripheral immune cell trafficking to brain parenchyma in depression, bipolar disorder and schizophrenia (25–29). However, lack of evidence of widespread BBB disruption (e.g., as indicated by CSF/circulating albumin, IgG ratios) observed in depression versus controls (n=106/group) or in relation to CRP (n=73) (11, 24) is consistent with evidence from animal models. For example, while monocyte trafficking and peripheral IL-6 are required for expression of anhedonic and depressive behaviors in chronic stress-induced depression models, the BBB remains relatively intact with region-specific decreases in integrity characterized by increased permeability to IL-6 in nucleus accumbens (NAc)(30, 31). Reduced BBB proteins (e.g., claudin 5) were also seen in NAc of susceptible mice, and postmortem NAc but not prefrontal cortex (PFC) or hippocampus of depressed patients (n=39)(30).

While peripheral immune activation is sufficient to cause depressive symptoms (see below), it is important to note that this involves bidirectional processes whereby peripheral cytokines

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and immune cells interact with endothelial cells, astrocytes, and microglia to elaborate production of cytokines and inflammatory mediators; microglia in turn release chemokines that recruit peripheral cells (Figure 1b). These bidirectional mechanisms may be particularly relevant in disorders like schizophrenia involving genetic, developmental, or autoimmune predispositions and inflammatory processes potentially initiating in the brain to engage the peripheral immune system (29). For example, and distinct from depression, in addition to CSF/serum albumin ratio and other markers of BBB disruption (n=104/group)(32), CSF evidence of complement activation and in some cases anti-neuronal antibodies are seen in psychotic disorders (32–34). Conversely, translocator protein (TSPO) positron emission tomography (PET) imaging thought to reflect microglial/macrophage activation is often reported to be increased in depression (despite not correlating with peripheral inflammatory markers) but lower in schizophrenia (35, 36), likely reflecting method limitations, e.g., off-target binding, competition from activated peripheral immune cells (37, 38), rather than a reduced inflammatory state. Nevertheless, similar patterns of innate/inflammatory cytokines and acute phase reactants in blood and CSF of patients in relation to symptom domains across disorders reflect potential common mechanisms of the effects of innate immune activation on the brain (see below), regardless of its source.

1b. Increased inflammation and transdiagnostic symptoms: cause-effect relationships

Inflammatory cytokines induce symptoms of reduced motivation, motor slowing and anxiety.—Consistent with an above-described role for inflammation in psychiatric disorders, a wealth of clinical and translational data demonstrate that administration of cytokines or inflammatory stimuli that induce cytokines affects neurotransmitters and circuits implicated in the pathophysiology of multiple disorders in association with symptoms of depression and anxiety (39–41)(Figure 1c,d). Some of the strongest clinical evidence of a potentially causal role for inflammation in psychiatric symptoms comes from patients chronically administered antiviral/antiproliferative cytokines like IFN-α for infectious diseases/cancer (42, 43). Up to 50% of IFN-α-treated patients reliably developed symptoms meeting criteria for major depression, and ~80% experienced fatigue, reduced energy, and/or psychomotor slowing (43–50). Anxiety and reduced motivation or anhedonia are also frequently reported post-IFN-α (42, 51). Indeed, instruments specifically probing anhedonia or reduced motivation yielded comparable effect sizes (r=0.47-0.49) as IFN-α-induced increase in total depression or fatigue scores (42, 52). Acute administration of inflammatory stimuli like low-dose endotoxin/vaccination, which potently induces cytokines, transiently increases depressive/anxiety symptoms (53, 54) in humans and laboratory animals and is used to study the impact of peripheral inflammation on the brain.

Endogenous inflammation, transdiagnostic symptoms, and reversal with anti-cytokine therapies.—While inflammatory effects on relevant circuits and behaviors described above may represent adaptive responses promoting conservation of energy (re. reduced motivation/anhedonia, psychomotor slowing), heightened vigilance (re. threat detection, anxiety), or social/emotional adaptations during immune activation, chronically elevated inflammation may contribute to psychiatric symptoms (40). Accordingly, relationships between biomarkers of low-grade inflammation and symptoms consistent with

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those induced by exogenous inflammatory stimuli and common to depression and other psychiatric disorders are frequently reported. For example, in medically-stable, unmedicated depressed patients, we found associations between anhedonia and both plasma CRP and clusters of inflammatory cytokines (IL-1, IL-6, TNF) and their soluble receptors in CSF (n=76)(11, 55). Results were extended by studies reporting correlations between both T and non-T cell cytokines with anhedonia (56), and longitudinal correlations between baseline TNF and 4-month anhedonia in depression (57). We also uncovered relationships between psychomotor slowing and inflammatory markers in depression (58, 59), and numerous studies report high inflammation in schizophrenia in association with negative symptoms including motivational deficits, blunted affect, and social withdrawal (60, 61). A growing literature further describes correlations between CRP/cytokines and anxiety (62–64), including longitudinally (65) and depression (66).

The TNF antagonist infliximab reduced overall depression severity only in treatment-resistant depressed (TRD) patients with higher plasma CRP (67), and anhedonia (*work and activities*) was the symptom most improved followed by motor slowing (*retardation*) and anxiety (*psychic anxiety*). Recent studies similarly found that infliximab or sirukumab (anti-IL-6) preferentially reduced anhedonia in unipolar or bipolar depressed patients with evidence of increased inflammation (68, 69). These cause-effect relationships indicating that transdiagnostic symptoms like anhedonia, motor slowing and anxiety can be both induced by inflammatory stimuli and reversed by cytokine antagonism, support specificity of inflammation effects on relevant brain regions/circuits that may serve as translational targets for development of treatments for patients with high inflammation (70, 71).

2. Impact of inflammatory stimuli on brain regions and circuits: from the clinic to the lab

As described above, chronically administered inflammatory cytokine therapies like IFN-α cause clinically-significant depressive symptoms at high rates, and this model was used in early work examining peripheral inflammation effects on the brain. Whole-brain analyses of fluorodeoxyglucose PET in patients undergoing IFN-α therapy revealed increased resting glucose metabolism in basal ganglia (consistent with low dopamine signaling in neurologic disorders) and decreased PFC metabolism (72, 73). These findings were subsequently linked to both low dopamine availability/release in caudate, putamen, and ventral striatum (VS: including NAc) by PET(42) and increased glutamate in basal ganglia and dorsal anterior cingulate cortex (dACC) by magnetic resonance spectroscopy (MRS)(74)(Figure 1d), all of which correlated with IFN-α-induced symptoms including reduced motivation and anergia. These clinical findings in patients during chronic IFN-α therapy indicating that peripheral inflammation impacts cortical and subcortical regions via effects on neurotransmitters like dopamine and glutamate have been confirmed and complemented by numerous laboratory human and animal studies using a variety of inflammatory stimuli, the neurobiological mechanisms of which are reviewed elsewhere (75–77)(see Figure 1c). Relevant to a larger body of work addressing the functional consequences of exogenous inflammatory stimuli on brain regions/circuits (78, 79), seminal fMRI studies are briefly summarized herein (Figure 1d) as they provided a foundation for a newer literature primarily using circuit and network-

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based approaches to understand relationships between endogenous low-grade inflammation and altered functional and structural connectivity in psychiatric patients (Section 3).

2a. Impact of inflammation on reward and motor regions and circuits

Complementary to the above-described effects of inflammation on dopamine availability, functional effects of peripheral inflammation on brain regions relevant to reduced motivation and psychomotor slowing have been consistently revealed by functional MRI (fMRI) in subjects administered inflammatory cytokines (e.g., IFN-α therapy) or inflammatory stimuli (e.g., endotoxin or vaccination given in the laboratory)(75). For example, chronic IFN-α treatment decreased VS neural activation to receipt of reward in association with reduced motivation (42). Similar effects on reward processing have been observed after acute endotoxin/vaccine in healthy volunteers (80, 81), and complemented by vaccine effects on task-based activity in substantia nigra that correlated with psychomotor slowing and IL-6 (82, 83). In addition to findings from region-focused task fMRI, whole-brain analysis revealed rapid (4-hour) IFN-α-induced microstructural changes in free water signal (consistent with edema) localized to left striatum that predicted subsequent fatigue (84). Importantly, evidence from acute IFN-α or vaccine suggests these neurotransmitter, structural and functional changes in discrete regions known to regulate motivation and motor activity contribute more broadly to inflammation effects on functional connectivity (FC) in key circuits including VS-ventromedial (vm)PFC, or as primary nodes within a global network that predicted depressive symptoms (85, 86).

2b. Impact of inflammation on regions and circuits for threat, anxiety, emotional and interoceptive processing

In addition to effects on reward and motor regions (per Section 2a/Figure 1d), peripheral inflammatory stimuli have been shown to increase neural activation of amygdala, dACC and insula (79), similar to findings reported in depression, anxiety disorders and PTSD. While analyses targeting amygdala showed higher right amygdala responses to emotional or socially threatening stimuli in relation to IFN-α or endotoxin-induced depressive or social disconnection symptoms (87, 88), whole-brain-analyses have revealed inflammation-by-task-related increases in dACC, mPFC and insula activation independently or in concert with each other or amygdala (89–92). For example, typhoid vaccine increased task activation of an interoceptive network including mid/posterior insula as well as amygdala and dACC (90). Given the role of insula in interoception, it is not surprising this region showed increased PET resting glucose metabolism (93) and lower seed-to-voxel resting-state (rs)FC with a number of cortical regions (94) after endotoxin. While task and seed-based analyses may bias or limit observed effects of inflammation to specific regions, a more agnostic network approach revealed reduced rsFC within a salience network (including amygdala, insula, dACC) in association with increased temporal variation of the rsFC signal only in amygdala, which in turn correlated with endotoxin-induced anxiety (95). These findings are consistent with animal studies showing rapid and behaviorally-relevant activation of amygdala by peripheral inflammatory stimuli in part via direct cytokine effects (96–98), and reinforce the importance of functionally connected regions involved in interoceptive/emotional processing, vigilance/threat detection, to contribute to relevant symptoms induced by inflammation including anxiety.

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3. Structural and functional dysconnectivity in patients with high inflammation

As discussed in Sections 1 and 2, inflammation can influence neurotransmitters and key regions and circuits thought to underlie network dysfunction observed across psychiatric diagnoses (79, 99)(Figure 1d), and may contribute to disease pathophysiology and discrete symptomologies in a subset of patients. While inflammation-associated structural and free-water changes are reported in schizophrenia (23, 100–102), studies contributing to our evolving understanding of relationships between endogenous inflammation and brain activity or FC relevant to transdiagnostic symptoms in psychiatric disorders have focused primarily on depression or bipolar disorder and taken hypothesis-driven, symptom-focused approaches to examine relationships between inflammation and frontostriatal, amygdala-prefrontal, and interoceptive circuits/networks (Table 1). Accordingly, findings are presented with a circuit/symptom focus. As relationships between inflammatory markers in psychiatric patients and low rsFC have emerged as the most consistent findings for inflammation-associated dysconnectivity, with potential for translational use as a reliable brain biomarker of inflammation, these studies are highlighted in Figure 2.

Inflammation and low rsFC in non-psychiatric populations: risk factors across the lifespan.

As our discussion focuses on endogenous inflammation and rsFC in the context of psychiatric disorders, it is worthy to mention representative studies from a similar body of work in non-psychiatric populations. Consistent with the above-described effects of peripheral inflammation on regions and circuits involved in emotion regulation (Section 2b), a composite index of CRP/inflammatory cytokines, or numbers of classical monocytes, associated with low rsFC in an emotion-regulation network in cohorts of at-risk African American (AA) youth (103). Associations between cytokines (TNF) and altered rsFC in adolescents also extended to other inflammation-sensitive regions including right amygdala and left VS (104). In adults, IL-6 partially mediated relationships between childhood abuse and lower amygdala-vmPFC rsFC (105), and an inflammatory cytokine composite related to low salience, default mode network (DMN), and central executive inter-network rsFC in association with sub-clinical PTSD symptoms in stress-exposed firefighters (106). Finally, an inflammatory cell index (neutrophil/lymphocyte ratio) in older adults negatively correlated with rsFC within regions of vmPFC in relation to geriatric depression symptoms (107). These findings, together with the impact of inflammatory stimuli on the brain (Section 2), suggest that inflammation-effects on FC within sensitive regions/circuits serve as potential brain mechanisms of the frequently reported associations between inflammatory markers and psychiatric symptoms in individuals exposed to risk factors like stress, early life adversity, and aging (2, 40), and support these pathways as mechanisms of inflammation-related dysconnectivity in psychiatric patients.

3a. Frontostriatal circuits and transdiagnostic symptoms of reduced motivation and psychomotor slowing

Inflammation and low rsFC in reward and motor circuits.—Similar to the effects of exogenous inflammatory stimuli on reward-relevant regions (Section 2a, Figure 1d), we and

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other have found relationships between endogenous inflammation in psychiatric patients and low rsFC in frontostriatal circuits including VS-vmPFC, a classic reward circuit found to be disrupted in depression and other psychiatric disorders (108, 109). For example, negative associations between plasma CRP and left VS-vmPFC rsFC were observed using both seed-to-voxel-wise and targeted seed-to-ROI approaches in medically-stable, unmedicated depressed patients (n=48), whereby lower VS-vmPFC rsFC in turn correlated with and mediated relationships between CRP and anhedonia (55). Frontostriatal rsFC also negatively associated with inflammatory cytokines and their soluble receptors (55). These relationships in depression were corroborated by parcellation-based network analyses whereby primary (vmPFC) and secondary (VS, as anterior caudate) hubs, along with multiple other edges of a 63-feature network of CRP-associated dysconnectivity, highly predicted anhedonia symptoms in support vector regression (110). Negative associations between inflammatory markers and left VS-vmPFC rsFC were replicated by Rengasamy et al. for IL-6 in TRD (111), and in our group for CRP in association with anhedonia in trauma-exposed inner-city AA women, while a composite of inflammatory cytokines and their receptors (11) only correlated with rsFC in women with significant PTSD symptoms (112). Relevant to risk factors for associations between high inflammation and low rsFC, early-life adversity modified these relationships whereby severity of childhood maltreatment predicted stronger negative cytokine-rsFC associations in both studies (111, 112).

Consistent with inflammatory stimuli effects on motor activity (75), endogenous inflammation also correlated with dysconnectivity within corticostriatal circuits involving cognitive and motor regions of dorsal striatum. For example, we found negative relationships between CRP and rsFC for dorsal caudate and dorsal caudal putamen with vmPFC and/or presupplementary motor area in association with psychomotor slowing in depression (55). These relationships along with additional rsFC features identified in network analyses highly predicted psychomotor slowing (110). Similar relationships have been seen in depressed, but not euthymic (113), bipolar disorder patients including negative correlations between IL-8 and rsFC of right precentral gyrus within a somatomotor network, as demonstrated by Tang et al. with independent component analysis (ICA)(114).

Complementary task fMRI, neurotransmitter, and structural studies.— Relationships between endogenous inflammation and low rsFC in frontostriatal reward and motor circuits in patients are complemented by a study from Burrows et al. showing decreased activation of dorsal caudate, thalamus, left insula, and left precuneus in anticipation of small wins in depression with higher CRP (>3 mg/L)(115). Costi et al. also found an endotoxin-stimulated inflammatory factor to negatively correlate with VS response to reward anticipation in association with anhedonia in depression (116). Relationships between either CRP or inflammatory cytokine factors and reward anticipation/attainment in striatal and prefrontal regions were similarly seen in adolescents with clinically-significant psychiatric symptoms (117, 118). These associations between inflammation and low activity or rsFC within frontostriatal circuits may involve its effects on neurotransmitters like dopamine and glutamate (75, 76)(Figure 1c,d). Plasma and CSF CRP in medically-stable, unmedicated depressed patients associated with left basal ganglia glutamate (using single-voxel MRS)(119), which jointly identified a larger network of low regional homogeneity

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("ReHo," concordance of oscillatory activity in neighboring MRS voxels, including a reward-related subnetwork)(120), and correlated with anhedonia and psychomotor slowing. Regarding links to dopamine, we recently reported that acute challenge with its precursor levodopa (which rapidly increases dopamine availability) improved left VS-vmPFC rsFC only in depressed patients with higher CRP (>2 mg/L) in association with higher task-FC during reward anticipation and levodopa-induced decreases in anhedonia (121). In addition to neurotransmitter influence on functional circuits/networks, inflammation may impact rsFC through effects on structural connectivity as relationships between CRP/cytokines and low white matter integrity (quantitative and fractional anisotropy) have been observed in depressed and bipolar patients in numerous important tracts including corticostriatal and thalamic radiations connecting cortical and subcortical structures (122–125).

3b. Amygdala-prefrontal circuits involved in threat detection, anxiety, and emotional processing

Inflammation and low amygdala-PFC rsFC.—In addition to effects on motivation and motor activity, inflammatory stimuli induce symptoms of anxiety in the context of heightened reactivity and low rsFC of amygdala and prefrontal regions (53, 88, 94, 95) (Section 2, Figure 1d), consistent with reports of associations between inflammation and low rsFC in this circuitry in psychiatric patients. Accordingly, we found associations between endogenous inflammatory markers, plasma CRP and inflammatory cytokines and their soluble receptors, and low right amygdala-vmPFC rsFC in medically-stable, unmedicated patients with a primary diagnosis of depression (126). Right amygdala-vmPFC rsFC in turn negatively correlated with and mediated relationships between CRP and symptoms of anxiety, and these findings were strongest in patients with co-morbid anxiety disorders or PTSD. Relationships between CRP or cytokines and rsFC between right amygdala and mPFC/vmPFC were also generalizable to trauma-exposed AA women with or without PTSD in association with anxiety (127), and to unmedicated bipolar patients (128).

Complementary task-fMRI studies.—Relationships between endogenous inflammatory markers and low rsFC with amygdala is supported by a recent report that an endotoxin-stimulated inflammatory factor associated with heighted amygdala activation to fear>happy faces, which in turn associated with symptoms of anxious arousal in depression (129). Importantly, while not all studies report similar associations between inflammation and amygdala reactivity (130), TNF-antagonism with infliximab in patients with inflammatory illness reduced depressive symptoms in association with decreased amygdala reactivity to emotional face-processing (87). Savitz and colleagues also extended findings of relationships between inflammation and amygdala reactivity to a broader network of regions activated by inflammatory stimuli in concert with amygdala (Section 3b, Figure 1d) by showing positive correlations between inflammatory genes in peripheral blood immune cells and activation of amygdala, vmPFC, and hippocampus to sad>happy faces (131). Emotional task fMRI also revealed relationships between inflammatory cytokines (IL-1beta, IL2) and PFC, insula and/or ACC activation in women with a history of suicidality or depression (132), and generally anti-inflammatory T regulatory cells inversely correlated with dorsolateral PFC activation in bipolar depression (133). Therefore, endogenous inflammation-associated increases in reactivity of amygdala, PFC and functionally-related

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regions like insula are consistent with effects of inflammatory stimuli on these regions, and may contribute to low amygdala-vmPFC rsFC seen in psychiatric patients.

3.c Interoceptive, Default Mode, and other Large-Scale Networks

Similar to findings that inflammation effects on the brain extend beyond individual regions/circuits (Section 2b), network analyses have revealed endogenous inflammation/rsFC associations within largescale networks in psychiatric patients that overlap with inflammation-sensitive regions/circuits constructed by meta-analysis (134), e.g., DMN (135, 136), ventral attention network (VAN)(137), and interoceptive pathways involving insula (138, 139). In high CRP-depressed (>3mg/L, n=33/83) versus healthy controls (n=46), Aruldass et al. reported low rsFC within VAN (insular/frontal opercular cortex) and posterior cingulate cortex (PCC) of DMN, and many features of this predefined network negatively correlated with CRP, IL-6, and neutrophils in all patients (140). While Kitzbichler et al. reported a greater proportion of negatively weighted rsFC features within DMN in depressed, particularly high CRP, patients in this same cohort along with positive correlations between CRP and proton density (PD; tissue-free water/edema) within DMN (141), analysis of all 70,500 possible pair-wise correlations between individual edges and CRP in all patients also revealed positive associations primarily with hippocampus. However, positive correlations between CRP and PD in PCC subregions mediated negative relationships between CRP and PCC-mPFC rsFC, but not positive relationships between CRP and PCC-hippocampus rsFC. Thus, inflammation-related structural changes in key regions of high CRP patients may contribute to low within-network rsFC, subsequently influencing rsFC with outside networks/regions possibly not as directly impacted by inflammation. While exclusively negative CRP-rsFC associations found using a similar strategy with less parcellations (100 versus 376) in another depressed cohort (n=44) (110) suggest that fine-grained, agnostic approaches may be necessary to reveal positive correlations. While stronger internetwork DMN-VAN rsFC was also seen in association with CRP in a small depression cohort (n=27)(142), negative seed-to-voxel rsFC correlations for insula and DMN were reported for IL-6 in unmedicated bipolar depressed and schizophrenic patients (143, 144). Thus, peripheral inflammation in psychiatric patients primarily associated with low connectivity within large-scale networks, with some evidence of increased connectivity across networks or with other brain regions.

4. Conclusions and translational implications

Herein, we discuss key findings from an emerging literature describing associations between inflammatory markers and functional dysconnectivity in both discrete circuits and broad networks relevant to transdiagnostic symptoms in depression and other disorders (Figure 2). Results are consistent with and described in the context of a wealth of data demonstrating the causal impact of clinically or experimentally administered cytokines or inflammatory stimuli on neurotransmitters and functional activity and connectivity in the same regions and circuits in association with relevant symptoms (Section 2/Figure 1). Supporting evidence of inflammation-associated alterations in neurotransmitters, task activation, structural connectivity, and edema in patients (Section 3/Table 1) further serve as potential mechanisms of functional dysconnectivity.

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Most studies reported relationships between low structural or functional connectivity and innate/inflammatory cytokines (ILs, TNF, IFNs assessed individually or as a composite) or CRP (thought to reflect activity of multiple cytokines). While a handful of studies measured more than one cytokine (but not CRP) and only reported on one marker (IL-1beta, IL-6, IL-8, TFN)(102, 111, 114, 123, 124, 128, 143), it is not clear whether this represents biologically significant cytokine-circuit associations within the context of chronic low-grade inflammation in patients, or rather inter-study/marker variability in methods/detection. As this area of research expands, relationships between connectivity and individual immune markers can be examined in large datasets, and longitudinal and experimental studies can confirm stability, neurobiological mechanisms, and causal associations/pathway specificity.

For example, in region/circuit analyses, relationships between inflammation and low rsFC in frontostriatal reward/motor-related circuits have as emerged as a consistent finding across laboratories and samples (Figure 2), and parallel findings on the impact of inflammatory stimuli on multimodal neuroimaging outcomes in these regions (Section 2)(145). Our recent report that levodopa increased VS-vmPFC rsFC only in depressed patients with higher CRP in association with improved anhedonia not only link inflammation-related reward circuit deficits to dopamine (121)(Section 3a), but also indicate rsFC as a modifiable imaging biomarker for the efficacy of interventions to reverse the impact of inflammation on the brain. Future research using this approach in patients with high inflammation will focus on other targetable substrates, e.g., glutamate or immune-modulating therapies (71, 145).

In sum, a growing field describes reliable associations between endogenous innateimmune/inflammatory markers and structural/functional dysconnectivity in regions, circuits and networks known to be sensitive to inflammatory stimuli in association with transdiagnostic symptoms in psychiatric patients. Future work will examine specificity/causality of these associations and their potential use as brain biomarkers to develop therapies targeted to patients with high inflammation (70, 71).

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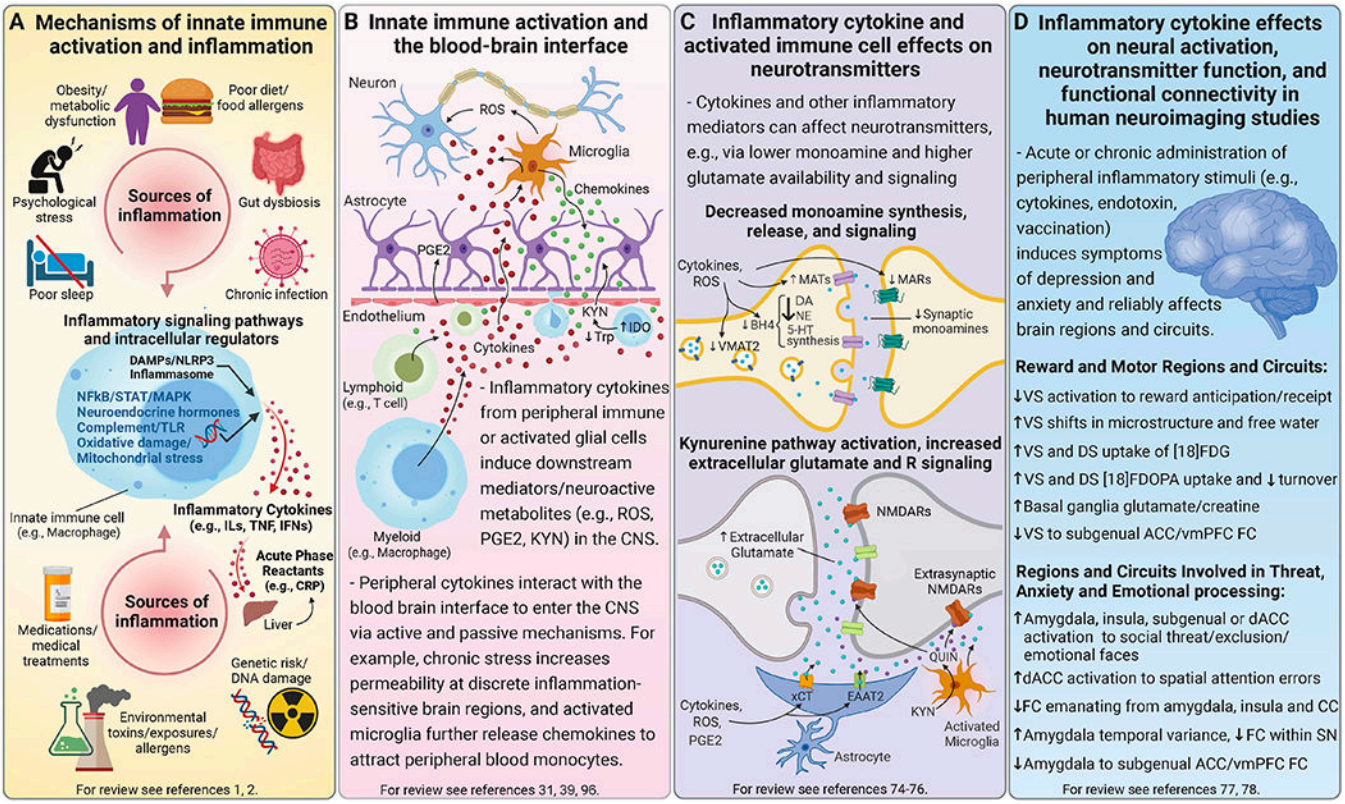

Figure 1. Sources and mechanisms of inflammation and its effects on neurotransmitters and circuits that contribute to psychiatric symptoms.

Mechanisms of innate immune activation and chronic low-grade inflammation. Panel **A**. Genetic predisposition may interact with multiple environmental and lifestyle factors that contribute to chronic low-grade inflammation, many of which are risk factors for both psychiatric disorders and major medical illnesses including psychological stress, disturbed sleep, poor diet, metabolic changes and gut dysbiosis, as well as chronic infections and environmental toxins. Innate immune cells are activated by pathogens or sterile inflammatory (e.g., DAMPs, metabolic, neuroendocrine, or oxidative stress) pathways to synthesize and release inflammatory mediators like cytokines (e.g., ILs, TNF, IFNs), which in turn induce acute phase reactants such as CRP from the liver. Acute inflammatory activity is typically resolved by homeostatic processes, but disruption of these mechanisms or prolonged immune activation can lead to chronic low-grade inflammation that impacts multiple systems including the brain. Bidirectional inflammatory processes at the blood-brain interface. Panel **B**. Activated innate immune cells interact with adaptive immune cells (e.g., lymphocytes), migrate into circulation, and traffic to organs and tissues including the brain. Circulating inflammatory cytokines and activated immune cells communicate with brain endothelial cells to induce other inflammatory mediators (e.g., PGE2). Inflammatory cytokines can enter the CNS via active transport or passively at circumventricular organs or openings in tight junctions of the BBB, while also signaling to the brain via vagal afferents (not shown). Microglia can be activated by inflammatory stimuli originating in the CNS or by these inflammatory signals from the periphery, and elaborate release of inflammatory mediators in the CNS like cytokines, ROS and nitrogen intermediates, as well

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as chemokines that further recruit peripheral inflammatory cells to perivascular regions or brain parenchyma. Inflammation also increases neuroactive metabolites from the catabolism of KYN, which is synthesized from Trp by IDO either locally in activated microglia or by macrophages followed by active transport into the brain. Inflammatory cytokines and associated oxidative molecules affect monoamine and glutamate neurotransmission. Panel **C**. Inflammatory cytokines and the associated release of ROS and nitrogen species can impact neuronal function through several ways including effects on neurotransmitters like monoamines and glutamate. For example, oxidation of BH4, a cofactor required for the synthesis of monoamine precursors, leads to decreased availability and release of monoamines - particularly DA, which requires BH4 for conversion of both Phe to Tyr and Tyr to L-DOPA. Evidence also exists that inflammatory cytokines can decrease expression or function of VMAT2, increase expression and activity of MATs especially the 5-HTT, and reduce expression of MARs like D2R. These effects together lead to a net decrease in synaptic monoamine availability and signaling. Inflammatory and oxidative factors also affect multiple aspects of glutamate transmission particularly by decreasing astrocytic buffering of glutamate by EAAT2, including reversing its efflux while promoting activity of the xCT to increase extracellular glutamate. Increased transport or local production of KYN in the brain and subsequent generation of neurotoxic metabolites like QUIN (a NMDAR agonist) further increase glutamate signaling including at extrasynaptic Rs, which lead to excitotoxicity and downstream generation of ROS (not shown). Peripherally administered acute and chronic inflammatory stimuli, which induce symptoms of depression and anxiety, reliably impact relevant brain regions and circuits in human neuroimaging studies. Panel **D**. Neuroimaging of patients chronically treated with inflammatory cytokines (e.g., IFN-α) or healthy participants administered stimuli that induce cytokines (e.g., endotoxin, vaccination) have shown that cytokines affect reward and motor-related regions and circuits, as well as those involved in threat, anxiety and emotional processing. For example, PET and MRS studies in IFN-α-treated patients reflect the impact of cytokines on neurotransmitters including reduced striatal DA availability and release as well as increased extracellular glutamate, both of which correlated with reduced motivation and low energy. Corresponding striatal microstructural as well as functional changes have included attenuated VS responses to reward anticipation/receipt and reduced FC between key regions of vmPFC and VS, after acute or chronic administration of IFN-α or other inflammatory stimuli. Inflammatory stimuli also increased neural activation of the amygdala, insula and dACC either independently or together during tasks designed to trigger emotional responses. Importantly, endotoxin also induced greater temporal variance in the amygdala at rest that correlated with lower FC within the SN as well as greater inflammation-induced anxiety. These findings on the impact of exogenous inflammatory stimuli on the brain have established a framework for the growing body of work assessing relationships between endogenous inflammatory markers and structure and function of these regions/circuits in psychiatric patients. **Abbreviations:** 5-HT - serotonin; 5-HTT - serotonin transporter; ACC - anterior cingulate cortex; BBB - blood-brain barrier; BH4 - tetrahydrobiopterin; CNS - central nervous system; CRP - C-reactive protein; D2R - dopamine 2 receptor; DA - dopamine; dACC - dorsal anterior cingulate cortex; DAMPs - danger-associated molecular patterns; DS - dorsal striatum; EAAT2 - excitatory amino-acid transporter 2; FC - functional connectivity; [18]FDG - fluorodeoxyglucose; [18]FDOPA - fluorodopa; IDO - indoleamine

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2, 3-dioxygenase; IFN - interferon; ILs - interleukins; KYN - kynurenine; L-DOPA - levodopa; MAPK- mitogen-activated protein kinase; MARs - monoamine receptors; MATs - monoamine transporters; MRS - magnetic resonance spectroscopy; NE - norepinephrine; NFkB - nuclear factor kappa B; NLRP3 - NOD- LRR- and pyrin domain-containing protein-3; NMDAR - N-methyl-D-aspartate receptor; PET - positron emission tomography; PGE2 - prostaglandin E2; Phe - phenylalanine; QUIN - quinolinic acid; ROS - reactive oxygen species; SN - salience network; TLR - toll-like receptor; STAT - signal transducer and activator of transcription; TNF - tumor necrosis factor; Trp - tryptophan; Tyr - tyrosine; VMAT2 - vesicular monoamine transporter 2; vmPFC - ventromedial prefrontal cortex; VS - ventral striatum; xCT - cystine-glutamate exchanger

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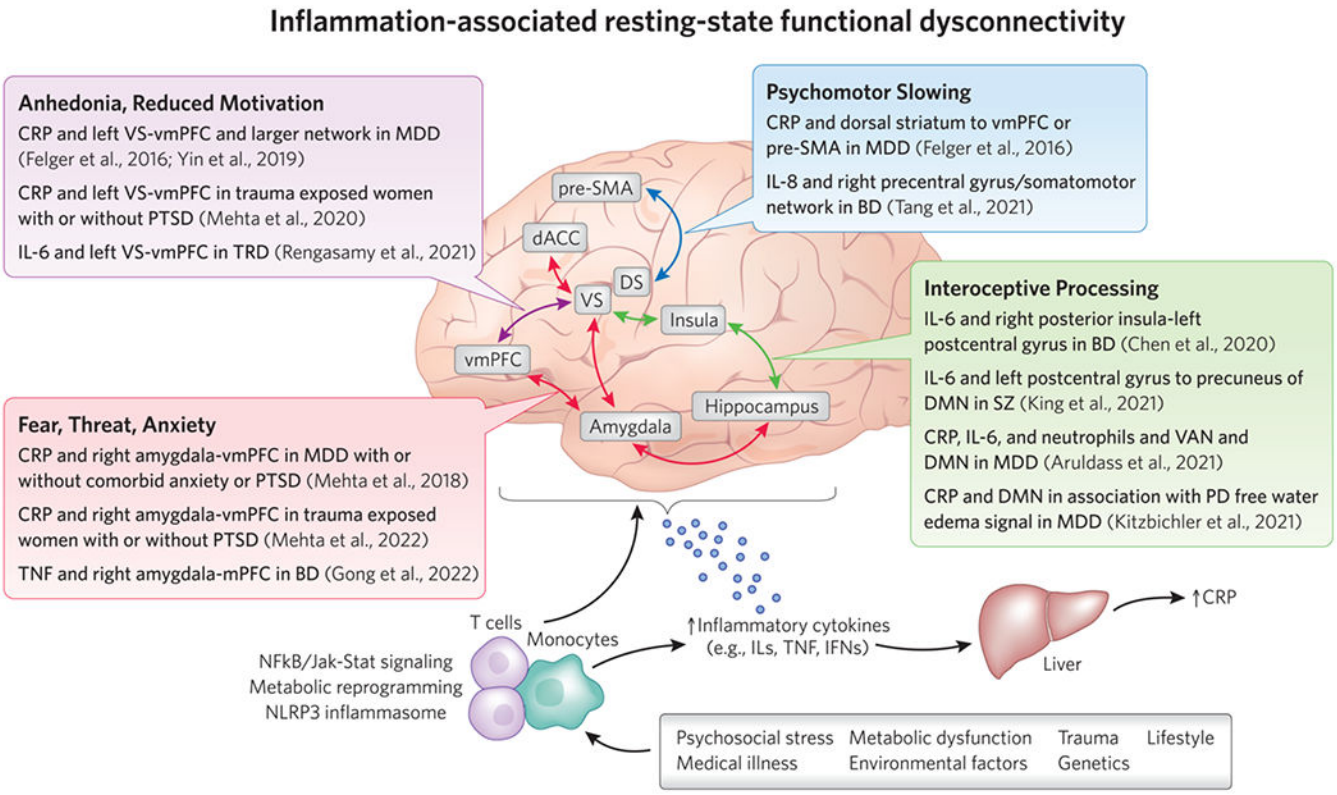

Figure 2. Inflammation-associated resting-state functional "dysconnectivity" in key circuits and networks that contribute to psychiatric disorders.

Summary of key studies from an emerging literature describing associations between circulating biomarkers of inflammation, such as inflammatory cytokines and the acute phase reactant CRP, in patients with depression or other psychiatric illnesses and low resting-state functional connectivity (rsFC) in frontostriatal circuits regulating motivation or motor activity, amygdala-prefrontal circuits involved in fear, threat and anxiety, and circuits/networks involved in interoceptive and emotional processing, all of which may contribute to transdiagnostic symptoms in patients with psychiatric disorders. A host of medical, environmental, and lifestyle factors contribute to innate immune activation in patients with depression and other psychiatric disorders. Peripheral immune cells like monocytes and T cells activate inflammatory signaling pathways and undergo a metabolic reprograming to facilitate the release of cytokines and cell trafficking to the brain. Inflammatory cytokines produced in the periphery and CNS can impact neural activation and functional connectivity within key brain regions, circuits, and networks relevant to psychiatric disorders through effects on neurotransmitters like dopamine and glutamate, or structural changes like reduced white matter integrity. **Abbreviations:** BD - bipolar disorder; CRP - C- reactive protein; DMN - default mode network; FA - fractional anisotropy; FC - functional connectivity; IFN - interferon; IL - interleukin; Jak-Stat - Janus kinase-Signal transducer and activator of transcription; MDD - major depressive disorder; MRS - magnetic resonance spectroscopy; NAc - nucleus accumbens; NFkB - nuclear factor kappa B; PCC - posterior cingulate cortex; PD - proton density; pSMA - pre-supplementary motor area; PTSD - post-traumatic stress

disorder; TNF - tumor necrosis factor; TRD - treatment-resistant depression; VAN - ventral attention network; vmPFC - ventromedial prefrontal cortex; VS - ventral striatum

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Table 1.

Summary of studies assessing relationships between endogenous inflammation and functional or structural neuroimaging outcomes in the context of significant psychiatric symptoms or diagnoses.

Study	Population	Inflammatory Markers	Outcome	Brain Region/White Matter Tract
Resting State Functional Connectivity and Supporting fMRI Studies				
Circuits and Regions Relevant to Reduced Motivation or Psychomotor Slowing				
Felger et al., 2016 (55)	MDD	CRP	↓ seed-to-voxel and seed-to-ROI, resting-state FC	(1) Left VS-vmPFC (2) Dorsal striatum and vmPFC, presupplementary motor area
Yin et al., 2019 (110)	MDD	CRP	↓ Voxel-wise GBC and PBA of 100 ROIs, resting-state FC	Network with central hubs in vmPFC followed by VS
Mehta et al., 2020 (112)	Trauma-exposed women with or without clinically significant PTSD symptoms	CRP, inflammatory cytokine composite score	↓ seed-to-ROI, resting-state FC	VS-vmPFC
Tang et al., 2021 (114)	BD (current episode depressed)	IL-8	↓ ICA, resting-state FC	Right precentral gyrus (somatomotor network)
Tseng et al., 2021 (113)	BD (euthymic)	CRP	↑ seed-to-voxel, resting-state FC	Right dorsal caudal putamen-middle orbitofrontal gyrus
Rengasamy et al, 2022 (111)	TRD	IL-6	↓ seed-to-ROI, resting-state FC	Left VS-vmPFC
Haroon et al., 2018 (120)	MDD	CRP	↓ local and network, resting-state ReHo functional integrity	Left basal ganglia and network varying by levels of CRP and MRS glutamate
Bradley et al., 2019 (118)	Adolescents presenting with clinically significant psychiatric symptoms	Inflammatory composite factors	↓ activation to reward attainment (1) and anticipation (2)	(1)Basal ganglia (ROI), angular gyrus (whole-brain) (2) Precuneus/PCC (whole-brain)
Liu et al., 2020 (117)	Adolescents presenting with clinically significant psychiatric symptoms	CRP	↑activation to reward attainment (1) ↓ activation to reward anticipation (2) ↑ activation to positive prediction error (3)	(1) Visual and dorsal attention networks (whole-brain) (2) dACC (ROI) (3) NAc (ROI)
Burrows et al., 2021 (115)	MDD	CRP	↓ activation to anticipation of small rewards	Dorsal caudate, thalamus, left insula, left precuneus (whole-brain)
Costi et al., 2021 (116)	MDD and healthy adults	Stimulated blood immune markers	↓ activation to reward anticipation	VS (ROI)
Circuits and Regions Relevant to Threat, Anxiety and Emotional Processing				
Mehta et al., 2018 (126)	MDD with or without comorbid anxiety disorders or PTSD	CRP, IL-6, IL-1ra	↓ ROI-to-voxel and ROI-to-ROI, resting-state FC	(1) Right amygdala-vmPFC (2) Right amygdala-left precentral gyrus
Gong et al., 2022 (128)	BD (>75% depressive episode)	TNF	↓ seed-to-voxel, resting-state FC	(1) Right amygdala-bilateral medial PFC (2) Left amygdala-left temporal pole
Mehta et al., 2022 (127)	Trauma-exposed women with or without clinically significant PTSD symptoms	CRP, inflammatory cytokine composite score	↓ ROI-to-ROI, resting-state FC	Right amygdala-vmPFC

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Study	Population	Inflammatory Markers	Outcome	Brain Region/White Matter Tract
Savitz et al., 2013 (131)	MDD	Expression of immune-related PBMC genes	↑ activation to sad vs happy faces	Amygdala, left hippocampus, and vmPFC (ROIs from whole-brain MDD > HC)
Mocking et al, 2017 (130)	MDD	CRP	No association with reactivity to negative faces	Bilateral amygdala (ROI)
Poletti et al., 2017 (133)	BD (current episode depressed)	T regulatory cells	↓ activation to negative vs. positive stimuli	Right dorsolateral PFC/inferior frontal gyrus (whole-brain)
Conejero et al., 2019 (132)	Women with history of MDD and/or SA and healthy controls	IL-1β, IL-2	↓ activation related to IL-1β (1) ↑ activation related to IL-2 (2) during social exclusion	(1) Right orbitofrontal cortex (2) Right orbitofrontal cortex, insula and ACC (ROI)
Boukezzi et al., 2022 (129)	MDD	Stimulated blood immune markers	↑ activation to fear vs happy faces	Amygdala (ROI)
Interoceptive, Default Mode and other Large-Scale Networks				
Chen et al., 2020 (143)	BD (current episode depressed)	IL-6	↓ seed-to-voxel, resting-state FC	Right posterior insula-left postcentral gyrus
Aruldass et al., 2021 (140)	MDD	CRP, IL-6, neutrophils, CD4+ T-cells	↓ NBS of 8 networks, resting-state FC	Within insular/frontal opercular cortex (VAN) and the posterior cingulate cortex (DMN)
Kitzbichler et al., 2021 (141)	MDD	CRP	↓↑ PBA of 360 cortical and 16 subcortical ROIs, resting-state FC	Lower within DMN, higher DMN-hippocampus, in association with PD free water edema signal
King et al., 2021 (144)	SZ	IL-6	↓ seed-to-voxel, resting-state FC	Left lateral parietal cortex-precuneus of DMN
Beckmann et al., 2022 (142)	MDD	CRP	↑ seed-based analysis of 5 networks, resting-state FC	Internetwork DMN to AN
Structural Connectivity Studies				
Prasad et al., 2015 (100)	SZ	CRP, IL-6	↓ FA, ↑ RD	Inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, forceps major (RD to IL-6 only)
Benedetti et al., 2016 (125)	BD (current episode depressed)	TNF, IL-8, IFN-γ	↓ FA ↑ RD	Corpus callosum, cingulum, superior and inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, uncinate, forceps, corona radiata, thalamic radiation, internal capsule
Sugimoto et al., 2018 (123)	MDD	IL-1β	↓ FA	Inferior fronto-occipital fasciculi, left uncinate fasciculus
Wang et al., 2020 (102)	SZ	IL-6	↓ FA	Genu and body of corpus callosum, anterior/posterior limbs of internal capsule
Lim et al., 2021 (124)	MDD	TNF	↓ FA	Genu of corpus callosum, left anterior and superior corona radiata
Thomas et al., 2021 (122)	MDD	CRP	↓ QA	Corticostriatal tracts, thalamic radiations, inferior longitudinal fasciculi, corpus callosum, cingulum, and left superior longitudinal fasciculus

AN - affective network; BD - bipolar disorder; CRP - C-reactive protein; dACC - dorsal anterior cingulate cortex; DMN - default mode network; FA - fractional anisotropy; FC - functional connectivity; GBC - global brain connectivity; HC - healthy controls; IFN - interferon; IL - interleukin; L-DOPA - levodopa; MDD - major depressive disorder; MRS - magnetic resonance spectroscopy; NAc - nucleus accumbens; NBS - network-based statistics; PBA - parcellation-based analysis; PBMC - peripheral blood mononuclear cells; PCC - posterior cingulate cortex; PD - proton density; PTSD - post-traumatic stress disorder; QA - quantitative anisotropy; ra - receptor antagonist; RD - radial diffusivity; ReHo - regional homogeneity;

SA - suicide attempt; SZ - schizophrenia; TNF - tumor necrosis factor; TRD - treatment-resistant depression; VAN - ventral attention network; vmPFC - ventromedial prefrontal cortex; VS - ventral striatum

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