

Interoception and Inflammation in Psychiatric Disorders

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ABSTRACT

Despite a historical focus on neurally mediated interoceptive signaling mechanisms, humoral (and even cellular) signals also play an important role in communicating bodily physiological state to the brain. These signaling pathways can perturb neuronal structure, chemistry, and function, leading to discrete changes in behavior. They are also increasingly implicated in the pathophysiology of psychiatric disorders. The importance of these humoral signaling pathways is perhaps most powerfully illustrated in the context of infection and inflammation. Here we provide an overview of how interaction of immune activation of neural and humoral interoceptive mechanisms mediates discrete changes in brain and behavior and highlight how activation of these pathways at specific points in neural development may predispose to psychiatric disorder. As our mechanistic understanding of these interoceptive pathways continues to emerge, it is revealing novel therapeutic targets, potentially heralding an exciting new era of immunotherapies in psychiatry.

Keywords: Autism, Cytokine, Depression, fMRI, Imaging, Inflammation, Insula, Interoception, Schizophrenia

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Inflammation is increasingly implicated in the pathogenesis of many common psychiatric disorders. Similar to other physiological processes, interoceptive pathways play a critical role in communicating immune state to the brain. Within the body, the immune system acts as a distributed chemosensory system using diverse pattern-recognition receptors to detect the presence of pathogen-associated molecular patterns and tissue stress or damage-associated molecular patterns. On activation, immune cells release immune and inflammatory mediators, notably cytokines. Parallel neural, humoral, and cellular interoceptive pathways then communicate these changes in immune state to the brain to trigger alterations in mood and cognition, motivation, and neurovegetative processes (1–3). However, immune activity is not solely regulated in the periphery. Top-down influences from the brain can dampen peripheral inflammation via hypothalamic release of corticotropin-releasing hormone and the vagus nerve inflammatory reflex (4). Conversely, sympathetic projections to lymphoid tissue, including the bone marrow, lymph nodes, and spleen, can prime immune responses to actual or perceived environmental threats (5–7).

Typically, inflammation is short lived and these adaptive changes in behavior that serve to reprioritize behavioral responses toward the insult rapidly return to baseline (8). However, when inflammation is severe, becomes chronic (9), or occurs during critical developmental windows (10) or on a background of neurodegeneration (11) or chronic severe stress, prolonged activation of interoceptive pathways and consequent neurochemical changes can precipitate long-standing maladaptive neurobiological and behavioral changes that are implicated in the pathophysiology of many common psychiatric disorders.

Recent progress in understanding the molecular and cellular processes underlying bidirectional immune-brain interactions is revealing the complex nature of interoceptive signaling of immunity. For example, it is now recognized that during periods of severe stress, increased sympathetic outflow can result in sustained splenic enlargement and production of monocytes with enhanced migratory and proinflammatory phenotypes in rodents (7,12). Historically, only the adaptive immune system has been considered capable of retaining a memory of past events. However, these persistent immunological changes appear to provide a peripheral, bodily index of prior stress exposure that accords with recent recognition of wider innate immune system memory (13). Supporting this, subsequent stress exposure (even when subthreshold) results in significant trafficking of these proinflammatory monocytes to the brain, where they then differentiate into tissue macrophages to promote inflammatory signaling and amplify behavioral stress responses (7). Findings such as this are highlighting the importance of cellular as well as more conventional humoral and neural pathways and underscore the need to broaden our conceptualization of interoceptive signaling. As we discuss below, these developments are also beginning to reveal novel therapeutic drug targets and allow a reappraisal of how some established therapies may be exerting therapeutic efficacy.

HOW IS INFLAMMATION COMMUNICATED TO THE BRAIN?

Visceral Afferents

Similar to the signaling of other physiological processes, central communication of peripheral inflammation appears to be

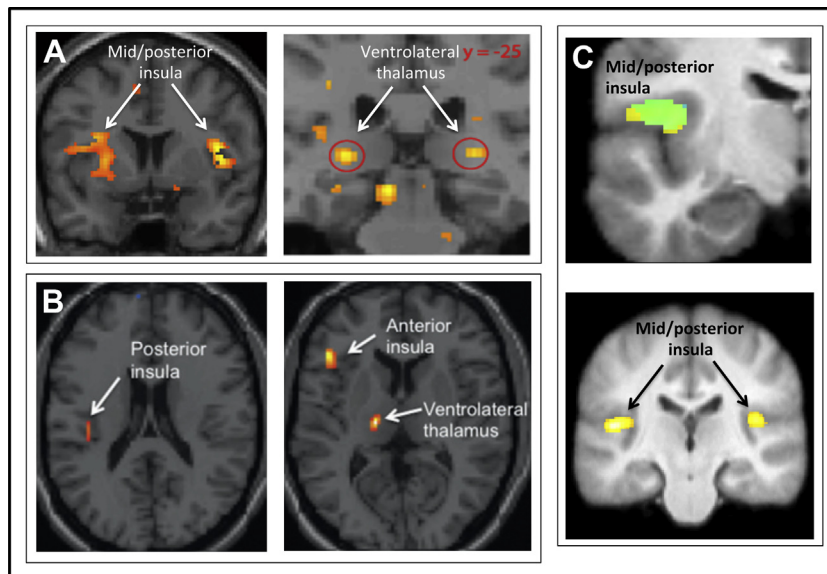


Figure 1. Convergent data from diverse imaging techniques show that peripheral inflammation activates a neurally mediated interoceptive pathway projecting to the insula. **(A)** Mild proinflammatory challenge using the typhoid vaccine model increases blood oxygen level-dependent signal within the human interoceptive brain regions, including the lateral thalamus (encompassing the basal and posterior ventromedial nuclei [basal ventromedial nucleus and posterior ventromedial nucleus]), and cortical projections to the dorsal mid/posterior and anterior insula within 3 hours of challenge. [Modified with permission from Harrison *et al.* (19).] **(B)** Lipopolysaccharide-induced peripheral inflammation increases fluorodeoxyglucose uptake with ventrolateral thalamus and posterior and anterior insula within 2 hours of inflammatory challenge. [Modified with permission from Hannestad *et al.* (18). © by the Society of Nuclear Medicine and Molecular Imaging, Inc.] **(C)** Mild inflammation (induced using typhoid vaccination) increases mid/posterior insula fluorodeoxyglucose-glucose uptake (lower figure) and magnetization transfer from molecular-bound to free water (upper figure) within 4 hours of inflammatory challenge. [Modified with permission from Harrison *et al.* (20).]

dependent on interoceptive visceral afferents traveling in the vagus and other autonomic nerves (14). These afferents express cytokine-binding sites (15). Antigen-presenting cells accumulate around sites of inflammation and then signal to visceral afferents using cytokine-dependent (16) and cytokine-independent (17) mechanisms. Signaling via this neural interoceptive pathway is rapid, inducing c-Fos expression in the solitary nucleus (the primary projection nucleus of the vagus nerve) and higher projection regions within an hour of challenge in rats (14). Human functional imaging studies demonstrate activation of a similar neurally mediated interoceptive pathway (projecting to the ventromedial posterior thalamus and then the mid/posterior insula) within 2 to 3 hours of the inflammatory challenge (18–20) (Figure 1). Projections from the solitary nucleus to the vagal dorsal motor nucleus and nucleus ambiguus initiate reflex responses including the inflammatory reflex, which regulate the magnitude of innate immune responses (4). Conversely, projections to the caudovernal and then rostroventrolateral medulla influence sympathetic outflow. Ascending projections to the hypothalamus, hippocampus, extended amygdala, striatum, cingulate, insula, and higher cortical areas underpin discrete changes in behavior (17,21) (see Figure 2 for circuit diagram). Though beyond the scope of the current review, a number of recent approaches have applied principles of hierarchical predictive coding and/or Bayesian active inference to information processing within these regions to provide a theoretical framework linking them to discrete changes in behavior and/or psychopathological features (22–24).

Humoral Pathways

Circulating inflammatory mediators also activate humoral interoceptive pathways. Some mediators can access the brain directly via the sensory circumventricular organs located in the walls of the third and fourth ventricles (25). In these regions, loops of fenestrated capillaries surrounded by large perivascular spaces facilitate a dramatic increase in surface area and permeability (26). This, together with dense

receptor expression, enables detection of large circulating molecules, including those that provide information about systemic inflammation. While the circumventricular organs are specialized for the detection of low concentrations of circulating factors, some inflammatory mediators, e.g., interleukin (IL)-6, interferon alpha (IFN α), and immune cells (e.g., stress-induced monocytes), can also enter the central nervous system (CNS) in small quantities in other regions to exert direct functional effects (7,27). Perhaps the best illustration of humoral interoception is inflammation-induced pyrexia. Here, cytokines (particularly IL-6) act directly on the brain endothelium to trigger prostaglandin E₂ release, which acts as a pyrogen at the hypothalamic median preoptic nucleus (28).

Cellular Pathways: Monocytes and Microglia

As highlighted earlier, direct monocyte trafficking also provides a cellular interoceptive pathway for communicating immune state to the brain (7). Though typically low during health, monocyte trafficking increases significantly following severe stress in rodents and appears to serve as a mechanism for amplifying behavioral stress responses given a history of previous sustained threat (7). Transduction of interoceptive signaling of inflammation also involves microglia (specialized brain macrophages with distinct phylogenetic origins) (29). In health, microglia show highly dynamic behavior, expanding and retracting branched ramifications to continuously sample neighboring cells and extracellular space (30). In this resting state they are implicated in synaptic pruning (31), a process critical for neural plasticity and learning. Like peripheral macrophages, microglia exist in multiple activated forms associated with distinct changes in morphology and secretory profile that can alter local neuronal and endothelial function (32). Within the brain, activation of microglia occurs in response to diverse danger-associated homeostatic changes, e.g., ischemia. However, it is also observed following exposure to repeated environmental stresses, which is likely mediated via

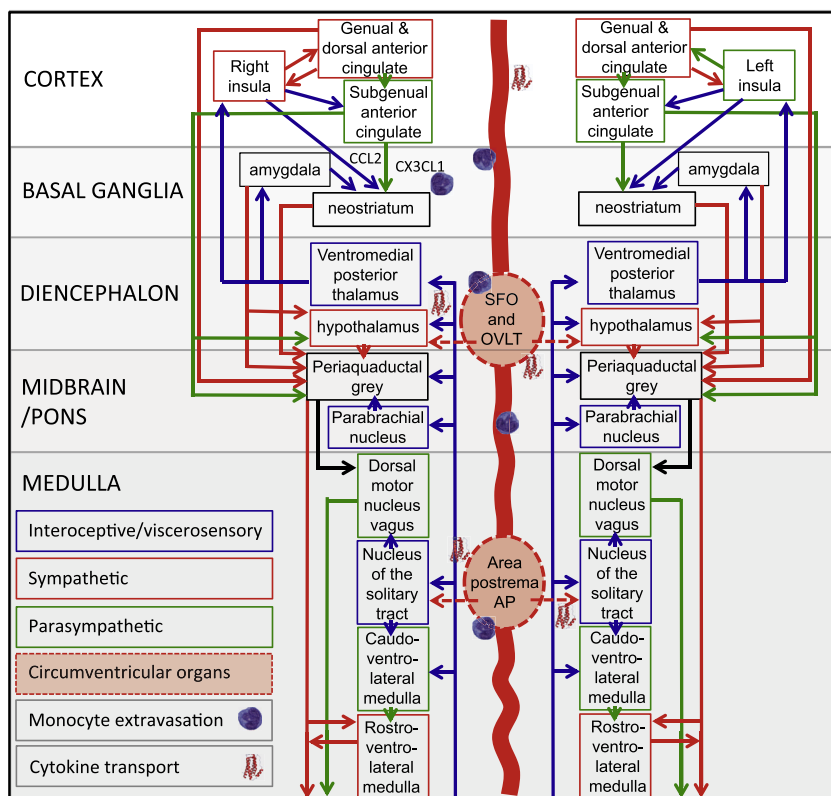


Figure 2. Circuit diagram illustrating visceral, humoral, and cellular interoceptive signaling pathways and the major points of interaction. AP, area postrema; CCL2, chemokine (C-C motif) ligand 2; CX3CL1, chemokine (C-X3-C motif) ligand 1; OVLT, organum vasculosum laminae terminalis; SFO, subfornical organ.

activity-dependent release of adenosine triphosphate in response to neuronal glutamate signaling (33).

Important to their role in interoceptive signaling, microglia are also sensitive to systemic danger signals including peripheral inflammation. In this context, microglial activation likely occurs through activation of interoceptive pathways that involve passage of cytokines across the blood-brain barrier (BBB) (34), release of prostaglandin E2 by perivascular and endothelial cells in response to intravascular inflammation (35), or entry of stress-sensitive monocytes into the CNS (33). In rodents, peripheral inflammation results in rapid activation of microglia within the circumventricular organs, leptomeninges, and choroid plexus, which release tumor necrosis factor (TNF) to trigger a cascade of microglial activation that spreads across the brain (36). Translocator protein positron emission tomography (a marker of activated microglia) has illustrated a similar pattern of widespread microglial activation following lipopolysaccharide-induced peripheral inflammation in humans (37).

Below, we describe how signaling via these pathways can result in regional disturbances in neuronal metabolism, neurotransmitter release, and brain activity associated with discrete features of psychopathology.

INTEROCEPTIVE SIGNALING OF INFLAMMATION IN PSYCHIATRIC DISORDERS

Mood Disorders

Arguably the strongest evidence implicating interoceptive signaling of inflammation to psychiatric illness is in mood

disorders. Stress, particularly in early life, is a major vulnerability factor for mood disorders and has been linked to sustained inflammation in human meta-analysis (38). Preclinical studies link this stress vulnerability to bidirectional interactions between the brain and immune system. Specifically, repeat exposure to severe social stress (using the repeated social defeat model) activates fear-associated neural circuitry. It also increases sympathetic outflow, which acts on the bone marrow and spleen to bias myeloid precursor cells (particularly monocytes) toward a glucocorticoid-resistant and primed lineage (33). Sustained glutamatergic activity within brain regions mediating fear responses also triggers local microglial priming, likely through activity-dependent adenosine triphosphate release from astrocytes binding to microglial P2X purinoceptor 7 (P2X7) receptors (7).

Interoceptive pathways link these central and peripheral immune changes and make a powerful contribution to the cumulative effects of repeated stress. For example, in addition to release of inflammatory mediators including IL-1 (which modify neuronal function and disrupt monoamine synthesis) (33,39), activated microglia also release chemokines (e.g., chemokine [C-C motif] ligand 2 [CCL2] and chemokine [C-X3-C motif] ligand 1 [CX3CL1]), which trigger the homing of monocytes primed by previous stress exposure from the circulation into stress-associated brain regions (33). Proinflammatory cytokine release from primed monocytes that have entered the CNS then further contributes to the maladaptive effects of chronic stress. This cellular interoceptive signaling pathway also appears to underlie the process of stress

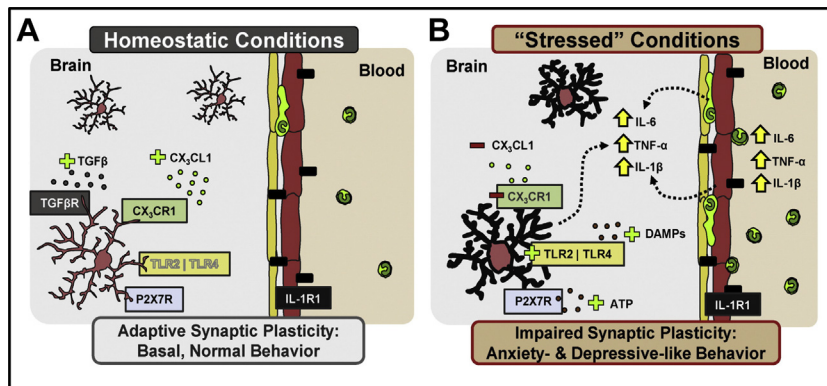


Figure 3. Role of humoral interoceptive pathways in anxiety and depressive-like behavior. **(A)** During homeostatic conditions neuron-derived regulatory factors, such as chemokine (C-X3-C motif) ligand (CX3CL1) and transforming growth factor- β (TGF β), maintain microglia in a resting state. Low levels of effector monocytes circulate in the blood, patrolling for pathogens or tissue damage, and a small number of brain macrophages reside in the perivascular space to sample the brain microenvironment. **(B)** During severe psychosocial stress microglia respond to damage-associated molecular patterns (DAMPs) and elevated adenosine triphosphate (ATP) released from neurons to adopt an activated phenotype. Simultaneous increase in sympathetic output results in an increase in circulating monocytes and consequently brain macrophages. These monocytes are

believed to traffic to stress-associated brain regions and amplify proinflammatory responses through humoral interoceptive pathways involving vascular endothelial interleukin-1 receptor type 1 (IL-1R1) signaling. Modified with permission from Wohleb and Delpech (145). CX3CR1, CX3 chemokine receptor 1; P2X7R, P2X purinoceptor 7 receptor; TGF β R, transforming growth factor- β receptor; TLR, toll-like receptor; TNF- α , tumor necrosis factor alpha.

sensitization, whereby previously stressed animals show a heightened propensity to maladaptive stress responses to later subthreshold stressors (12,40) (Figure 3).

Interoceptive signaling of inflammation also plays a role in human depression. Cumulative meta-analyses now provide convincing evidence for raised peripheral inflammatory markers, particularly IL-6 and C-reactive protein, in a subset of depressed patients (41). Gene expression analyses also implicate IL-6, TNF, and IFN α signaling pathways (42–44). This increase in peripheral inflammatory markers is linked to disturbances in brain function. For example, depressed patients with raised C-reactive protein show impairments in the functional connectivity of ventral striatum and medial prefrontal reward- and motivation-processing areas (39). Recently, depression has also been linked to CNS inflammation, with widespread increases in activated microglia observed using translocator protein positron emission tomography (45). Perhaps the most powerful evidence supporting an etiological role for inflammation comes from patients receiving prolonged IFN α therapy, up to 50% of whom develop major depressive episodes (46,47).

Here, IFN α appears to trigger depression-associated behavioral changes through activation of humoral and, to a lesser extent, neural interoceptive pathways (48). In humans, therapeutically administered IFN α is observed in the cerebrospinal fluid (CSF) (49). In rodents, peripheral IFN α rapidly upregulates interferon-sensitive gene expression within predominantly subcortical structures (50,51). Together, these studies support rapid activation of humoral interoceptive signaling pathways. Within the brain parenchyma, IFN α shows a marked predilection for subcortical structures, including the basal ganglia and hippocampus (51,52). This is reflected in imaging studies of patients receiving IFN α for the treatment of hepatitis C who show changes in striatal glucose metabolism, dopamine uptake, and glutamate (53,54) and microstructural changes in striatal water distribution (48,55). The functional significance of these striatal changes is supported by significant correlations with IFN α -induced changes in motivation and/or fatigue (53,54).

Proinflammatory cytokines also increase expression of the enzyme indoleamine 2,3-dioxygenase, which shunts

tryptophan metabolism away from serotonin synthesis into the kynurenine pathway. This results in the production of a number of neuroactive metabolites, including the neuroprotective *N*-methyl-D-aspartate receptor antagonist kynurenic acid (KynA) and the potentially neurotoxic *N*-methyl-D-aspartate receptor agonists 3-hydroxykynurenine and quinolinic acid (QA), both of which can influence glutamatergic signaling. During IFN α treatment, CSF concentrations of each of these metabolites increases, with increases in KynA and QA correlating with depressive symptoms (56). Under inflammatory conditions, brain production of QA tends to overshadow that of KynA (57), such that the ratios KynA/3-hydroxykynurenine and KynA/QA can provide a sensitive index of the competing effects of these neuroactive metabolites. Several investigators have now reported reduced KynA/QA in major depressive disorder (MDD) as well as bipolar disorder and schizoaffective disorder, which is additionally linked to altered hippocampal and medial prefrontal cortex volume/function (58–61). These studies illustrate putative mechanisms through which activation of interoceptive signaling pathways can lead to neurochemical change and shifts in behavior.

Schizophrenia and Autism Spectrum Disorder

Like mood disorders, schizophrenia and autism spectrum disorder (ASD) have been associated with raised circulating proinflammatory cytokines in cohort studies (62). However, unlike depression, emerging evidence suggests that this proinflammatory phenotype may have its origins in early development. Epidemiological work has long identified in utero infection as a risk factor for development of schizophrenia in offspring (63). Maternal exposure to infection has also been linked with autism, with a recent prospective study reporting a dosage effect, such that three or more episodes of fever during the second trimester raised the risk of having a child with ASD threefold (64).

Preclinical studies of maternal immune activation (typically modeled with the viral mimetic polyinosinic:polycytidylic acid) lend support to epidemiological studies by showing sustained abnormalities in rodent analogs of the repetitive movements and deficits in social behavior, sensory gating, and cognition that characterize autism and/or schizophrenia (65). Postmortem and animal imaging studies further show that maternal

immune activation leads to changes in synaptic connectivity and neuroplasticity that may manifest as changes in cortical thickness and brain volume (65). The mechanisms underpinning this dysregulation of neural development remain to be fully characterized, though they suggest that even before birth interoceptive-signaling pathways may play a role in human psychopathology.

As most pathogens do not directly infect the fetus, early infection is thought to impair normal brain development via activation of the maternal immune system. Preclinical models indicate that maternal cytokines are necessary for development of disease in offspring, though whether cytokines cross the placenta or act indirectly remains unclear (65). Either way, maternal immune activation appears to initiate changes in gene expression that affect neuronal migration, synaptic pruning, and myelination. Here again microglia may play a role, as these cells are involved in multiple aspects of brain development, especially synaptic pruning (66). Fetal oligodendroglia may also be impacted: in a recent study, polyinosinic: polycytidylic acid administration resulted in downregulation of genes involved in myelination in the medial prefrontal cortex and nucleus accumbens that correlated with spatial memory deficits in the offspring. Further, the viral mimetic group had a greater myelin water fraction in the cortex (including insula), hippocampus, and cerebellum, potentially indicating changes in the microstructure of the myelin sheath (67). Nonetheless, as most maternal infections do not directly lead to schizophrenia or ASD, subsequent “hits” taking the form of stress or adult-onset infections may be necessary for the manifestations of psychiatric disorders (65,68).

Analogous to what is described in chronic stress, these second hits may dysregulate an already sensitized or primed immune system, leading to the neural and behavioral abnormalities characteristic of schizophrenia and ASD. A case in point is microglia, which are known to be primed by infection (69), are increased in density in schizophrenia postmortem (70), and show a shift toward a primed morphology in ASD (71).

Linking Interoception to Discrete Behavioral Phenotypes

Most human studies addressing how interoceptive signaling of inflammation contributes to discrete dimensional psychiatric constructs have adopted an experimental medicine approach using a variety of inflammatory challenges (Table 1). Some have used vaccines (19) or inhaled antigens (72) to induce mild increases in inflammatory cytokines similar to those observed in depression; others have used low-dose lipopolysaccharide to induce more robust proinflammatory responses (18,73). Despite the variety of inflammation-induction techniques used, increases in insula activity are commonly observed, consistent with activation of a neurally mediated interoceptive pathway (Figure 1). Interestingly, many of these studies also link changes in insula activity to shifts in subjective experience (18–20), particularly fatigue, consistent with the proposed role of the insula in subjective experiential states (74).

Motivation

During infection, interoceptive signaling of inflammation rapidly reorients motivation, impairing reward-related behavior

Table 1. Human Imaging Studies Linking Inflammation to Regional Changes in Brain Structure/Function

	Publications	Participants	Technique
Neural Interoception: Insula	Rosenkranz, 2005 (72)	6 (WS)	fMRI
	Harrison, 2009 (19)	16 (WS)	fMRI
	Hannestad, 2012 (18)	9 (WS)	FDG PET
	Harrison, 2015 (20)	20 (WS)	FDG PET
	Harrison, 2015 (20)	20 (WS)	qMT
	Lekander, 2016 (141)	48 (BS)	rs-fMRI
Reward: Ventral Striatum	Eisenberger, 2010 (73)	39 (BS)	fMRI
	Capuron, 2012 (53)	28 (BS)	F-DOPA PET
	Haroon, 2014 (54)	31 (BS)	MRS
	Harrison, 2016 (77)	24 (WS)	fMRI
	Felger, 2016 (39)	48 (correlation ^a)	rs-fMRI
Memory: Medial Temporal Lobe	Marsland, 2008 (126)	76 (correlation ^a)	sMRI
	Harrison, 2014 (115)	20 (WS)	FDG PET
	Raz, 2014 (142)	80 (correlation ^a)	sMRI
	Satizabal, 2012 (143)	1841 (correlation ^a)	sMRI
	Baune, 2012 (144)	303 (correlation ^a)	sMRI
Psychomotor Slowing: Substantia Nigra	Brydon, 2008 (88)	16 (WS)	fMRI

BS, between subjects; F-DOPA, fluorodopa; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; qMT, quantitative magnetization transfer magnetic resonance imaging; rs-fMRI, resting-state functional magnetic resonance imaging; sMRI, structural magnetic resonance imaging; WS, within subjects.

^aCorrelational analysis.

and increasing sensitivity to punishments, particularly pain (8). This serves to prioritize whole-organism responses toward fighting the infecting agent; however, if sustained they may predispose to the development of MDD or chronic pain syndromes (25).

A wealth of studies have identified a critical role for the ventral striatum in mammalian reward processing and appetitive motivation [see (75) and articles cited therein]. Within the midbrain, dopaminergic cells encode a reward prediction error, with their firing rate increasing (or decreasing) if rewards are higher (or lower) than predicted (76). Projections to the ventral striatum serve to update value estimates for available options and bias behavior to maximize long-term future reward. Recent studies have started to clarify how interoceptive signaling of inflammation can disrupt these processes. For example, peripheral inflammation results in an acute reduction in ventral striatal encoding of reward prediction error signal (77). It is also linked to disrupted presynaptic dopamine synthesis in humans (53) and reduced CSF concentrations of the dopamine metabolite homovanillic acid in monkeys (78). Cytokine-associated reduction in dopamine synthesis may also be achieved by reducing CNS concentrations of tetrahydrobiopterin, an essential dopamine synthesis cofactor (79). Alternatively, dopamine neurotransmission may be reduced either by activation of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (leading to the formation of neurotoxic kynurenine metabolites) (25) or by increasing expression of reuptake transporters (79–82). Together, these implicate humoral interoceptive pathways in the reward-related motivational impairment characteristic of inflammation.

Though most studies of motivation have focused on reward, some brain areas implicated in neural interoceptive signaling (e.g., insula) are also linked to choices associated with potential losses (21,74,83,84). Specifically, the anterior insula cortex appears to encode a punishment prediction error signal linked to learning to avoid punishing outcomes (83). In patients with selective insula lesions this signal is disrupted and punishment sensitivity impaired (85). Conversely, during inflammation, when interoceptive signaling is increased, insula encoding of punishment prediction error and sensitivity to punishments are enhanced (77). This suggests that relative sensitivity to reward and punishments can be dynamically modulated as a function of interoceptive signaling of inflammation, flexibly enhancing loss minimization during threats (e.g., infection) but maximizing responses to gains during health. Though potentially beneficial during acute infections when substantial metabolic resources are diverted toward fighting infection, when inflammation is chronic this mechanism may underlie the maladaptive motivational changes observed in depression.

Psychomotor Retardation

Psychomotor retardation is defined as a slowing down of thought and physical movements. It is ubiquitous during infections (86,87) and can be readily induced by even mild inflammatory challenges (88). It is also a cardinal symptom of depression (89) and a notable feature in a subset of patients with schizophrenia. In rodents, systemic inflammation consistently suppresses locomotor activity resulting in increased periods of immobility (90). IL-6 is strongly implicated in these motor-suppressing effects, which are reduced in IL-6 knockout mice (91) and following blockade of IL-6 signaling (92,93).

In humans, low-level inflammation has been shown to selectively modulate substantia nigra reactivity during both low-level button-press and more challenging color-word Stroop tasks (88). Corroborating effects in rodents, this study also showed a tight correlation between induced changes in circulating IL-6 and motor response slowing across both congruent and incongruent Stroop trials, suggesting an action on low-level precognitive processes. Changes in IL-6 and left substantia nigra responses also predicted individual sensitivity to inflammation-induced motor slowing. This association between IL-6 and poorer performance on simple and choice movement time tasks has subsequently been replicated in MDD patients (94).

This finding is noteworthy, as the substantia nigra is the major source of dopamine within the brain. Projections to the striatum play a critical role in facilitating movement (95) and modulating motor responses to stimulus salience (96); they are also linked to inflammation-associated reductions in novelty salience (97). Lower striatal dopamine transporter activity is also linked to slower motor responses in the healthy elderly (98), and lower striatal presynaptic dopamine is reported in patients with depression and psychomotor retardation, but not with anxiety (99). Recently, psychomotor slowing in depression has also been linked to lower left basal ganglia glutamate (the other major neurochemical input to the striatum) and higher plasma and CSF C-reactive protein (100).

Together, these studies support a central role for ascending dopaminergic (substantia nigra) and descending glutamatergic inputs into the dorsal striatum in psychomotor retardation associated with both inflammation and depression. During infection, slowing of psychomotor responses likely facilitates immune function by preserving energy and conserving heat. The convergence of findings across depression and inflammation suggests that chronic activation of these mechanisms may differentiate patients presenting with predominantly psychomotor or anxiety symptoms.

Sleep

Proinflammatory cytokines (particularly IL-1 and TNF) are sleep regulatory agents that modulate slow-wave sleep (101). During neuronal activity, corelease of adenosine triphosphate, which acts on microglial P2X7 receptors to induce IL-1 and TNF release, is believed to provide a potential mechanism for enabling the brain to track prior usage history (102). During systemic inflammation, dynamic interactions between peripheral and central cytokines potentiate the effects of IL-1 and TNF on sleepiness, duration of non-rapid eye movement sleep, and slow-wave power (102). Vagotomy attenuates some of these actions in rodents, supporting a role for neural interoceptive pathways in mediating the effects of inflammation on non-rapid eye movement sleep (103). Sleepiness and disrupted sleep are common features of many human inflammatory disorders (101) and are observed following acute inflammatory challenge (104), demonstrating the importance of interoceptive signaling in regulating sleep in response to systemic inflammation. Conversely, sleep also mediates susceptibility to infection during exposure to airborne respiratory viruses, further demonstrating the bidirectional nature of immune-brain communicatory pathways (105).

Sleep disturbance is also an important risk factor for depression (106–108), conceivably because it increases inflammation (109–111), which, as discussed above, likely plays a causal role in some forms of psychiatric illness. Perhaps because the vagus nerve is involved in the processing of sleep signals (112), depressed subjects with sleep disturbance have interoceptive deficits such as reduced accuracy in their perception of their heartbeats but increased subjective perception of interoceptive sensitivity (113). Conversely, high cardiac vagal control, as evidenced by high resting heart rate variability, has been reported to be associated with better subjective and objective sleep quality in healthy women (114).

Memory

Microglia and inflammatory cytokines influence a number of processes critical to learning and memory including long-term potentiation, synaptic plasticity, and neurogenesis. In health, these immunological processes support the remodeling of neural circuits to promote learning and memory (3,31). However, during systemic inflammation, interoceptive signaling can disrupt this positive regulatory function, impairing memory. Typically, this memory impairment is mild and reversible (115); however, when inflammation is chronic or severe it can lead to accelerated age-related cognitive decline (116) or even persistent cognitive impairment (117). Medial temporal lobe

(MTL) structures appear particularly sensitive to systemic inflammation. This may reflect their higher BBB permeability (118) and proinflammatory cytokine receptor expression, leading to heightened humoral interoceptive signaling (119,120), or alternatively their connectivity to insula (121) and consequent sensitivity to neural interoceptive signaling (115).

In rodents, peripheral inflammation induces IL-1 expression within the MTL (122) and replicates many of the direct actions of inflammatory cytokines on MTL-dependent memory, including impaired spatial memory (3). In humans, naturalistic and experimental inflammatory challenges are associated with acute (reversible) impairment in spatial, verbal, and nonverbal declarative memory (115,123,124). These effects are restricted to MTL-dependent memory, i.e., they do not perturb procedural memory and appear to be mediated via actions of inflammation on MTL glucose metabolism (115). However, when inflammation is chronic it has been linked to reductions in hippocampal volume (125,126). This has important implications for psychiatry, particularly the neuropathology of depression, which is associated with both raised inflammatory markers and reduced hippocampal volume (127,128). Furthermore, MTL-dependent episodic memory impairment is one of the most commonly observed cognitive deficits in depression (129–131). Future studies will need to better understand the molecular mechanisms through which sustained interoceptive signaling of peripheral inflammation leads to persistent changes in MTL structure, determine whether modifiable factors can reverse this process, and clarify the significance of this link to the pathophysiology of inflammation-associated depression.

Treatment Implications

Above, we have highlighted the diverse interoceptive pathways recruited during the central signaling of inflammation and its subsequent impact on regional neuronal function and behavior. Identification of the molecular and cellular mechanisms that mediate these effects is revealing novel therapeutic targets and leading to a reappraisal of how some established therapies might exert therapeutic efficacy.

Perhaps the clearest example of a therapy directly targeting interoceptive mechanisms is vagus nerve stimulation, which exhibits potent predepressant properties (132). Though its mode of action is still only partially understood, it is now believed that actions on visceral afferent fibers at least partially underlie its clinical efficacy. However, vagus nerve stimulation also modulates the efferent arm of the inflammatory reflex, inhibiting peripheral TNF, IL-1, and IL-6 production in humans (133). This anti-inflammatory action results in a reduction in circulating cytokines and consequently reduces signaling via humoral interoceptive pathways. Prolonged vagus nerve stimulation also increases the firing rate of both serotonergic and noradrenergic neurons in the brainstem that are each implicated in the pathophysiology of depression (134). It remains to be clarified how many of these effects are achieved through modulation of interoceptive signaling of inflammation.

Another strategy adopted in depression is the use of pre-cytokine therapies to block cytokine signaling across interoceptive pathways. These agents (e.g., anti-TNF therapies) powerfully reduce circulating cytokine levels. Despite being

unable to cross the BBB, they also reduce depressive symptoms, suggesting an action through inhibition of interoceptive signaling (135,136). Consistent with this, predepressant effects appear limited to individuals with raised inflammatory markers, and by extension, interoceptive signaling of inflammation (135). Other approaches, e.g., the use of nonsteroidal anti-inflammatory drugs, target specific interoceptive mechanisms. During systemic inflammation, cytokines act on the brain endothelium to trigger release of lipophilic prostaglandins that readily diffuse across the BBB to exert central effect (35). By inhibiting prostaglandin production, nonsteroidal anti-inflammatory drugs block this interoceptive-signaling pathway. In the context of acute inflammation, they alleviate flu-like symptoms; meta-analyses have also suggested efficacy in patients with depression (137), though this remains controversial, with some studies even suggesting a worsening of depressive symptoms (138). This will need careful evaluation in future larger-scale clinical trials.

Another strategy is to target microglia, which appear central to transducing interoceptive signaling of peripheral inflammation into changes in neural function. One example of a microglial active agent is minocycline, a tetracycline antibiotic that readily crosses the BBB and inhibits microglial activation in rodents (77). Minocycline has demonstrated predepressant properties in preclinical studies in an open-label trial for bipolar depression (78) and in a recent randomized controlled trial of adjunctive treatment of MDD (79). It also has reported efficacy for negative symptoms in schizophrenia (80). However, minocycline has many additional actions that limit mechanistic interpretation of these studies (139). An alternative target is microglial P2X7 receptors that govern microglial IL-1 release and can modulate CNS chemokines, glutamate, and nitric oxide (140). In preclinical studies P2X7 knockout mice show a protective phenotype in models of depression. However, further human *in vivo* trials are needed to test its therapeutic effects in depression and characterize phenotypes that may be most conducive to this therapeutic approach.

SUMMARY

The immune system is a diffuse sensory organ that uses parallel neural, humoral, and cellular pathways to communicate peripheral immune signals to the brain. However, the immune system does not act in isolation. Top-down influences from the brain can dampen or even prime peripheral immune responses. In the latter case this appears to provide a form of innate immune memory for previous stress exposure, which then utilizes cellular interoceptive mechanisms to heightened behavioral responses in the face of subsequent stress. Though adaptive in the short term, when immune activation is prolonged or severe or occurs in specific neurodevelopmental contexts it can give rise to psychiatric disorders such as depression, schizophrenia, and ASD. Developing understanding of the complexity of these interacting communicatory pathways is rapidly forcing a broadening of how we conceptualize interoception. It is also motivating the development and repurposing of novel immunotherapeutic agents, potentially heralding an exciting new era of immunotherapies for use in psychiatry.

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ARTICLE INFORMATION

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