

Brain Structures Implicated in Inflammation-Associated Depression

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Abstract Systemic inflammation rapidly impairs mood, motivation, and cognition inducing a stereotyped cluster of symptoms collectively known as “sickness behaviors.” When inflammation is severe or chronic, these behavioral changes can appear indistinguishable from major depressive disorder (MDD). Human and rodent neuroimaging combined with experimental inflammatory challenges has clarified the neural circuitry associated with many of the key features of inflammation-induced-sickness behavior, and in so doing revealed often-remarkable commonalities with circuit abnormalities observed in MDD. This review aims to provide the first synthesis of this work illustrating areas of convergence and divergence with the MDD literature as well as highlighting areas for future study.

Keywords Amygdala • Cytokine • Depression • fMRI • Inflammation • Insula • Interferon • Microglia • MRI • PET • Ventral striatum

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1 Introduction

Human and animal studies implicate systemic inflammation in the pathogenesis of depression [1]. In healthy mammals, systemic infection triggers profound behavioral changes, including cognitive and mood symptoms (e.g., memory impairment, social withdrawal, anxiety, and depression), change in motivation (anorexia, adipsia, and anhedonia), and neurovegetative symptoms (sleep disturbance, fatigue, and psychomotor slowing) [2–4] known as sickness behaviors. Clinical and pre-clinical studies suggest that inflammatory cytokines play a central role in mediating these sickness-related behaviors by communicating peripheral inflammation to the brain. These cytokine-induced sickness behaviors show striking similarity to symptoms of major depression [1] supporting a role for immune–brain interactions in the etiology of at least some patients with major depressive disorder (MDD).

In rodents, systemic administration of interleukin (IL)-1 β or bacterial lipopolysaccharide (LPS), a potent stimulant of cytokine release, can rapidly elicit a depression-like syndrome characterized by a reduction in positively motivated approach behaviors such as exploration, social interaction, and operant behaviors for food reward [5–7]. Similarly, experimental induction of inflammation in healthy human participants using either LPS [8, 9] or typhoid vaccination [10–12] induces symptoms of fatigue, psychomotor slowing, mild cognitive confusion, memory impairment, social withdrawal, anxiety, and deterioration in mood that mirror features of depression. However, arguably, the most powerful empirical support for an etiological role for inflammation in depression comes from studies of patients with chronic Hepatitis-C infection treated with interferon-alpha (IFN- α)-based therapies, up to 50% of whom develop major depressive episodes [13]. Moreover, in patients with MDD, the presence of high levels of pro-inflammatory cytokines (in particular IL-6) [14] and acute phase proteins [15] suggest that inflammatory mediators might contribute to the pathophysiology of depression even in the absence of medical illness.

Far from being a unitary construct, depression is recognized to be a multi-componential disorder involving changes in motivation, cognition, attention, memory, and mood; as well as features such as disturbed appetite, sleep, and sexual dysfunction and physiological changes including cardiovascular and metabolic change. In studies of MDD, patients are typically recruited when symptoms are well established across each of these domains. However, following chronic IFN- α administration, individual features of clinical depression evolve with characteristic time-courses allowing a unique opportunity to investigate the temporal evolution of

individual symptom domains. For example, changes in mood, motivation, and fatigue (and in some cases feelings of social connection and spatial memory) can be readily observed within hours of IFN- α administration [16] and/or other experimental inflammatory challenges such as typhoid vaccination [11, 12, 17, 18] and LPS injection [8, 9, 19]. Changes in physiology, including altered central autonomic regulation of heart rate variability (similar to that observed in MDD) also occur acutely [20]. However in contrast, subjective reports of depressed mood, anxiety, and irritability assessed with clinical depression scales typically develop later, between the first and third months of IFN- α therapy [21].

This differential evolution of individual features of inflammation-associated clinical depression also provides a unique opportunity to characterize the neural circuitry underpinning specific components of inflammation-induced depression. To date, rodent and human brain imaging studies have successfully identified a discrete set of cortical and sub-cortical structures that appear particularly sensitive to changes in peripheral inflammation. These include the amygdala, striatum (particularly ventral regions), substantia nigra, insula, sub-genual and dorsal anterior cingulate, orbitofrontal cortex, and hippocampus/parahippocampus. Some of these structures appear to play relatively specific roles in particular aspects of inflammation-associated behavioral change. For example, actions on the ventral striatum [8, 22, 23] are associated with impaired reward sensitivity and hippocampus/parahippocampus acute memory impairment [4, 20] whereas other regions such as the insula, anterior and sub-genual cingulate, and amygdala appear to play broader less circumscribed roles [11, 16]. Common to many of these regions is that they form part of the extended limbic circuitry critical to complex motivational behavior, emotion, learning, and memory and the integration of behavioral and physiological allostatic responses to infection [24, 25].

Together, these studies are beginning to clarify how changes in peripheral inflammation are communicated to the brain. As discussed in more detail in the following sections they are also beginning to identify how actions of inflammation on discrete neural circuits induce individual components of this coordinated behavioral reorientation, which when chronic may evolve to MDD.

2 Communicating Inflammation to the Brain

In rodents, both the early central communication of peripheral inflammatory signals [26] and the subsequent motivational reorientation appear dependent upon the integrity of interoceptive visceral afferents traveling in the vagus nerve, visceral terminals of which express cytokine binding sites [27]. Early in the inflammatory response, antigen-presenting cells cluster in the vicinity of vagus nerve afferents and act as immune chemosensory elements signaling to vagal neurons via cytokine-dependent [28] and -independent mechanisms [29].

Immunohistochemical studies using the immediate early gene c-Fos to index neural activation confirm that peripheral inflammation and specifically binding of

pro-inflammatory cytokines to vagus nerve receptors activate a network of brain structures implicated in homeostasis and the representation of internal bodily state (interoception) [26]. This afferent signaling is rapid; in the rat peripheral inflammation induces c-Fos expression in the primary projection nucleus of the vagus nerve (nucleus tractus solitarius – NTS) and secondary projection regions (including parabrachial, paraventricular and supraoptic hypothalamic nuclei, central amygdala, and bed nucleus of the stria terminalis) within an hour of peripheral inflammatory challenge [26].

In addition to signaling via the vagus nerve, central signaling of peripheral inflammation may also occur via interoceptive information conveyed via the spinal cord. For example, information traveling through spinal lamina I is predominantly tuned to motivationally salient sensations, including pain [30, 31], temperature [32], itch [33], and sensual touch [34], and converges with afferents traveling in the vagus nerve within the brainstem and thalamus [35]. In humans, cortical projections of convergent vagus and spinal interoceptive pathways to the posterior then mid/anterior insula cortex have been proposed to support a consciously accessible representation of physical wellbeing [36] and provide a neural substrate for subjective emotional feelings [30, 36].

We have previously demonstrated that this human interoceptive pathway is also activated by mild systemic inflammation [12]. Specifically, we demonstrated increased activity on fMRI within bilateral thalamic (basal (VMb) and posterior (VMpo) ventromedial nuclei) and dorsal mid and anterior insula components of this interoceptive pathway within 3 h of typhoid vaccine induced inflammation. The location of these activations is noteworthy as both the VMb (which receives predominantly vagal fibers) and VMpo (predominantly sympathetic inputs) project to dorsal mid/posterior insula in a rostrocaudal topographic manner (with vagal projections extending more rostrally) [30]. Following inflammation activations occurred in more rostral regions of interoceptive insula cortex than those reported for thermal sensation [32], noxious pain, and itch (non-vagal) but close to the region previously reported to be activated by antigen-induced airways inflammation in asthmatic patients [37].

Insula (and cingulate cortices) also played a key role in mediating subjective responses to inflammation, particularly fatigue (Fig. 1). For example, inflammation but not placebo-associated fatigue was predicted by activity changes within bilateral mid/posterior insula and right anterior cingulate (pACC/aMCC). These findings highlight a degree of specificity of the neural mechanisms underlying inflammation-associated fatigue that is not seen in more general placebo-associated fatigue (which might result from more heterogeneous mechanisms).

Previous studies showing insula responses to subjective experience of graded cooling [32], itch [38], and intensity of dynamic exercise [39] support the hypothesis that the subjective experience of inflammation-associated fatigue results from an insula-based interoceptive mechanism. This hypothesis has also been reinforced by three more recent studies. The first, using typhoid vaccine induced inflammation and fluorodeoxyglucose PET (FDG-PET) imaging, which replicated associations between changes in mid insula activity (in this case glucose metabolism) and the

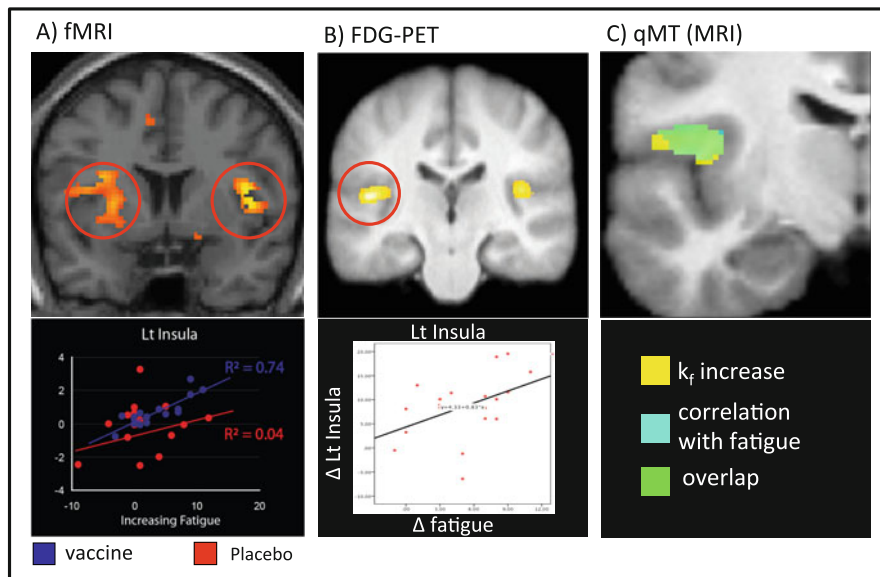


Fig. 1 Inflammation-induced insula activity predicts subjective fatigue. (a) Increase in bilateral insula activity on fMRI during performance of a color word Stroop task after inflammation compared to placebo. *Lower panel* shows that left insula cortex activity predicted experience of inflammation-induced fatigue (*blue*) but not fatigue associated with placebo (*red*). Data from Harrison et al. [12]. (b) Increase in bilateral resting glucose metabolism (FDG-PET) after typhoid vaccine induced inflammation compared to placebo. *Lower panel* shows correlation between change in left insula glucose uptake and subjective fatigue. Data from Harrison et al. [23]. (c) Left insula region showing an increase in magnetization transfer constant k_f after typhoid vaccine induced inflammation compared to placebo (*yellow*), correlation with fatigue (*blue*), and overlap of these regions (*green*). Data from Harrison et al. [23]

subjective experience of inflammation-induced fatigue [23]. The two other studies used a more potent model of inflammation (0.8–0.6 ng/kg LPS) and either FDG-PET or resting state fMRI which is a powerful technique for identifying functionally connected brain networks [40]. The first demonstrated an increase in right anterior insula glucose metabolism that correlated with loss of social interest (but not fatigue) [41] while the latter demonstrated correlations between subjective feelings of both inflammation-induced malaise and discomfort and heightened functional connectivity between the left anterior insula and mid-cingulate cortex [42]. Together, these studies highlight the importance of this interoceptive pathway projecting to insula in the central communication of inflammation induced using experimental models of bacterial infection. They also emphasize the likely importance of the insula in translating these interoceptive signals into negative subjective experiences of inflammation-induced fatigue and malaise (and possibly social disconnect) that develop early after the onset of inflammation.

Interestingly, patients with left or right insular strokes describe significantly greater subjective anergia with under activity and tiredness than patients with

strokes sparing the insula region [43]. Furthermore, increased insula metabolism and altered interoceptive processing have also emerged as key features of MDD [44, 45]. Increases in insula (particularly anterior insula) glucose metabolism occur following sadness induction with a converse reduction in insula glucose metabolism observed following successful depression remission [44]. Insula functional connectivity [46] and regional homogeneity (ReHo) (a measure of the temporal homogeneity of neural activity within this region) are also impaired in MDD with the later correlating with retardation components of depression [47]. These findings have been interpreted as consonant with neurovegetative features of MDD (such as fatigue) and associated changes in autonomic function [44].

In addition to this neurally mediated pathway, LPS-induced peripheral inflammation also results in a rapid (within 3 h) and diffuse increase in the central nervous system (CNS) expression of translocator protein (TSPO) [48]. In the CNS, TSPO is predominantly expressed in activated microglial cells suggesting that systemic inflammation may be translated into a central microglial inflammatory signal through diffuse actions at the cerebrovascular endothelium. However to date, relatively few participants have undergone TSPO imaging post-LPS and no association has been identified between regionally specific increases in TSPO uptake and subjective experiences of inflammation-induced fatigue.

Curiously, activation of interoceptive projections to insula appears less critical in mediating subjective responses to inflammation induced using mimics of viral infection such as IFN- α . Indeed, IFN- α does not appear to be associated with substantial changes in insula microstructure or glucose metabolism either acutely [16] or when chronically administered [49] suggesting that visceral afferents may not be the principle pathway mediating IFN- α -induced fatigue. Why such marked differences exist between models of bacterial and virally induced infection is currently unclear though may be usefully informed by the pre-clinical rodent and non-human primate literature. For example, though IFN- α injection results in a rapid increase in circulating and cerebrospinal fluid (CSF) concentrations of type-I interferon [50] other pro-inflammatory cytokines such as IL-6, TNF-alpha, and IL-1 are only modestly elevated [16]. Furthermore, in rodents profound CNS induction of IFN-inducible genes is observed within hours of intraperitoneal IFN injection [51], indicating that IFN- α likely gains rapid access to the CNS where its actions may be more directly transduced.

To summarize, the dorsal insula represents the ultimate projection of interoceptive pathways and is believed to provide a cortical representation of all aspects of bodily physiology including changes in peripheral inflammation [24]. Progressive posterior to anterior projections are proposed to integrate and translate this information into experiential feeling states such as feelings of warmth, malaise, or fatigue. Experimental models of bacterially induced inflammation result in rapid structural and functional changes in posterior, mid, and anterior insula cortices that correlate with concomitant increases in subjective fatigue and malaise. Similar changes in insula function are also well described in MDD where they correlate with neurovegetative symptoms of depression including fatigue illustrating striking

commonalities between inflammation-induced fatigue/malaise and neurovegetative symptoms of depression.

3 Motivational Change

Impairment in reward-related behavior is a core feature of the motivational reorientation characteristic of both inflammation-induced sickness behavior [2] and idiopathic depression [52]. In the context of sickness, this motivational shift is proposed to efficiently prioritize whole organism responses to clearing the infecting agent. However when inflammation is severe or prolonged this persistent motivational reorientation may predispose to the development of MDD [1].

A wealth of human and rodent studies have identified the ventral striatum as a critical structure for mammalian reward-related processing and appetitive motivation [53]. Single cell recordings demonstrate that a subgroup of dopaminergic cells within the midbrain encode a reward prediction error, increasing (or decreasing) firing rate if a reward is higher (or lower) than predicted [54]. Dopaminergic projections from the midbrain to the ventral striatum serve to update estimates of the value of different available options and bias behavioral choice so that long-term future reward is maximized. Reinforcement learning algorithms such as temporal difference models [55] have provided a powerful framework for modeling this dopaminergic prediction error signal that is proposed to mediate learning of associations between stimuli, responses, and outcomes [56]. They also allow interrogation of brain imaging data to identify brain regions whose activity correlates with these reward prediction error signals [57]. Dopamine firing may also contribute to “incentive salience,” the process by which a stimulus grasps attention and motivates goal-directed behavior by its association with reinforcing events [58].

Interestingly, both MDD patients [59] and previously healthy participants given an inflammatory challenge show a reduction in ventral striatal responses to reward outcomes [22, 60]. Inflammation has also been linked to acute reductions in ventral striatal reactivity to cues predicting rewards [19], though this is less convincingly reported in MDD [60]. In the context of inflammation, reduced ventral striatal responses to both reward cues and reward outcomes also correlate with induced anhedonia [19, 22]. Patients with MDD have also been shown to exhibit reduced reward prediction error encoding in the striatum and midbrain [59]. This change also correlated with the severity of anhedonia symptoms suggesting that abnormal encoding of prediction errors in MDD could result in anhedonia by altering the learning and salience of rewarding events [59].

Using a similar probabilistic instrumental learning task we have recently demonstrated that mild inflammatory challenge (induced with typhoid vaccination) also results in a relative impairment in sensitivity to rewards compared to punishments [61]. Furthermore, this motivational reorientation was associated with opposing actions on ventral striatal reward (and right anterior insula punishment) prediction error encoding [61]. Similar to patients with MDD, inflammation was associated

with reduced striatal reward prediction error encoding. Behaviorally, after inflammation participants in this study also showed a reduced propensity to choose rewarded options but enhanced avoidance of punished ones. This behavioral change was captured computationally as a significant condition (gain, loss) by inflammation (vaccine, placebo) interaction for the subjective value of rewards compared with punishments.

Though dopamine activity was not measured in this (or Eisenberger's study demonstrating effects of inflammation on reward cues), a similar reduction in striatal reward prediction error magnitude (and propensity to choose the most rewarded action) has been reported on this task after haloperidol (a dopamine receptor-2 antagonist) [57]. This suggests that effects of inflammation on striatal prediction errors were likely mediated by actions on dopamine release. Supporting this, inflammation has been linked to altered nucleus accumbens dopamine efflux in rodents [62] and disrupted presynaptic dopamine synthesis/release in humans [22]. After LPS challenge monkeys also exhibit significantly lower cerebrospinal fluid concentrations of the dopamine metabolite homovanillic acid [50].

However, exactly how inflammation modulates dopamine function is currently unclear. Cytokines such as interferon-alpha have been shown to inhibit dopamine synthesis by reducing CNS tetrahydrobiopterin, an essential cofactor for tyrosine hydroxylase, the rate-limiting step in dopamine synthesis [63]. Inflammation can also decrease synaptic dopamine by increasing expression of the monoamine reuptake transporter [63–66]. Inflammation may further influence dopamine neurotransmission via activation of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase and resultant formation of neurotoxic kynurenine metabolites [1].

To date most studies investigating the basis of the motivational reorientation associated with inflammation have focused on reward-related processing. However, in our recent study we also showed that inflammation significantly enhances sensitivity to punishment. This was captured in the data modeling as a significant increase in the subjective (negative) value of punishment; i.e., the magnitude of the potential punishment was experienced as being greater after inflammation [61]. This behavioral change was also associated with greater encoding of negative punishment prediction error in the right anterior insula.

Increasing punishment prediction error is one way to increase the subjective value of punishment and may serve as the computational mechanism by which the anterior insula drives this improvement in avoidance behavior. This interpretation is in keeping with theories proposing that brain areas like the insula involved with somatic affective representations (as discussed above) are causally involved in choice behaviors [24, 30, 57]; particularly in the context of potential losses [67]. This association between punishment sensitivity and insula activity also complements an earlier study showing impaired punishment sensitivity in patients with selective insula lesions [68] and suggests that relative sensitivity to reward versus punishment is a state rather than a trait-dependent attitude; flexibly enhancing loss minimization in the context of a serious threat (such as an infection) yet maximizing responses to gains when in good health.

As predicted by models of learned helplessness, dysfunctional responses to negative feedback were some of the earliest cognitive changes described in depression [69]. More recently, meta-analysis of computationally modeled reinforcement learning tasks in patients with current or past history of MDD has reported a selective reduction in subjective reward value (rather than reward learning rate) [52] similar to what has been observed in the context of inflammation. Relatively selective actions on reward/punishment magnitude have also been reported following dopamine manipulation and insular damage [57, 68]. This rapid cognitive adaptation following inflammation serves to heighten relative sensitivity to punishment versus reward raising the intriguing possibility that while this may be beneficial in the context of an infective challenge when metabolic resources are diverted to fighting the infecting organism, when chronic, it may predispose to developing the maladaptive changes in motivation observed in depression. Evidence for common neural mechanisms mediating motivational change and anhedonia in MDD and inflammation have been further strengthened by a recent paper in unmedicated MDD patients showing that decreased connectivity between the ventral striatum and ventromedial prefrontal cortex (vmPFC) also mediates observed associations between raised CRP and anhedonia [70].

4 Psychomotor Retardation

Psychomotor retardation, defined as a slowing-down of thought and physical movements, is a core feature of depression [71] and readily induced following systemic administration of pro-inflammatory cytokines or other experimental models of inflammation [72].

In rodents, systemic administration of bacterial LPS or inflammatory cytokines (notably IL-1 β) consistently suppresses locomotor and motivational behaviors, resulting in increased periods of immobility [73]. These depressant effects of peripheral IL-1 β on behavior are potentiated by IL-6 [74] and motor-suppressing effects of inflammatory challenge are reduced by antibodies against IL-6 [75, 76] and attenuated in IL-6 knockout mice [77]. Psychomotor retardation expressed as prolonged motor reaction times is also a feature of human sickness behaviors [78, 79], and is observed even after relatively mild inflammatory challenges [10].

In the first study to directly investigate the neural mechanisms underlying the psychomotor consequences of peripheral inflammation Brydon et al. [10] recorded whole brain responses to performance of a simple motor task (button press). They demonstrated that low-level inflammation (induced using typhoid vaccine) selectively modulated substantia nigra reactivity to performance of a button press task during both a low-level visual stimulation (flashing checkerboard) task and a more demanding cognitive (color word Stroop) task. They also observed a striking correlation between peripheral IL-6 responses and motor response time on the Stroop task for both low level (congruent) and attentionally demanding (incongruent) trials suggesting an action on low-level pre-cognitive processes. Supporting

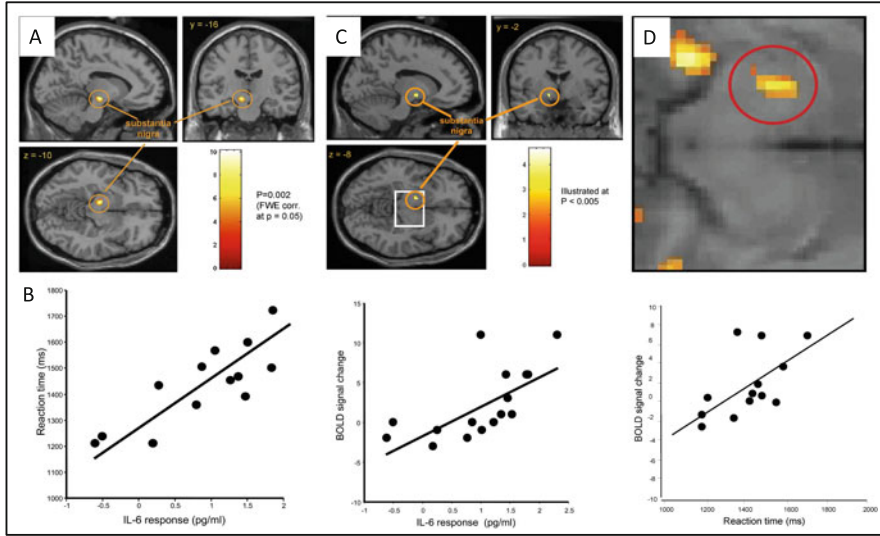


Fig. 2 Inflammation induces psychomotor slowing through actions on substantia nigra. (a) Effect of inflammation on substantia nigra reactivity during a low-grade visual stimulation task (flashing checkerboard). (b) Correlation between IL-6 response to typhoid vaccination and reaction time on a color word Stroop task. (c) Correlation between IL-6 response to typhoid vaccine and increase in left substantia nigra activity during Stroop task performance. (d) Correlation between mean Stroop reaction time and left substantia nigra reactivity following inflammation. Reproduced from Brydon et al. [10] with permission

this, both peripheral IL-6 responses and changes in left substantia nigra reactivity predicted inter-individual differences in sensitivity to the motor impairing effects of inflammation (Fig. 2).

Located in the midbrain, the substantia nigra is the major source of dopamine in the brain with striatal projections playing a pivotal role in the facilitation of movement [80]. Nigral dopaminergic projections within striatal target regions also modulate sensorimotor processing in response to stimulus salience [81] and have been linked to the reduction in novelty salience observed during inflammation [17]. Agonists that potentiate dopaminergic neurotransmission improve the speed of motor responses in animals, whereas striatal dopamine depletion and selective blockade of dopamine D1 or D2 receptors have been shown to significantly impair performance on reaction time tasks [82, 83]. Similar to effects of inflammation, impaired task performance following inhibition of dopamine is due to lengthened response latencies rather than deficits in the accuracy of responses [83]. Lower levels of striatal dopamine transporter have also been associated with slower motor reactions in healthy elderly humans [84]. Brydon's results extend these observations and provide empirical evidence for involvement of the dopamine system in behavioral consequences of peripheral inflammation, highlighting a role for IL-6 and substantia nigra neural activity in infection-related psychomotor impairments.

As discussed in the previous section, brain dopamine levels are modulated by peripheral administration of IFN- α and other inflammatory cytokines in rodents [66]. Human patients receiving IFN- α -based immunotherapy also experience marked psychomotor slowing [72] which has been shown to correlate with abnormalities in left dorsal striatal glucose metabolism [49]. These patients also demonstrate bilateral reductions in striatal 18F-DOPA turnover on PET imaging suggesting decreased presynaptic dopamine synthesis or release, though associations with psychomotor responses were not reported in this study [22]. Interestingly, elevated circulating IL-6 and altered striatal dopaminergic neurotransmission are also associated with psychomotor slowing in people with MDD [85, 86]. However, these studies have tended to focus on changes within striatal projection regions (rather than the substantia nigra) that are typically easier to image in human functional imaging studies. Interestingly, a recent study has shown that older individuals appear particularly susceptible to the psychomotor effects of IFN- α treatment. In this study, increased choice movement time correlated with changes in both peripherally induced TNF and left basal ganglia glutamate (reflected by glutamate/creatine ratio (Glu/Cr)), the other major neurochemical input to the striatum [87].

Correspondingly, decreased left striatal presynaptic dopamine function has been described in depressed patients presenting with marked psychomotor retardation [86]. Left dorsal striatum (caudate) lesions are also associated with a higher frequency and severity of post-stroke depression [88]. In their study using 18F-DOPA PET Martinot et al. [86] demonstrated a reduction in left caudate tracer uptake in MDD patients with psychomotor retardation but not MDD patients with high impulsivity or comparison control participants, providing direct evidence of a link between striatal dopamine hypofunction and psychomotor retardation. The importance of the left dorsal striatum to psychomotor retardation associated with MDD and inflammation has been further strengthened by a recent paper demonstrating a link between plasma and CSF levels of C-reactive protein (CRP), left basal ganglia glutamate, and psychomotor slowing in untreated depressed patients [89].

Together, these data support a central role for bottom-up dopaminergic (substantia nigra) and top-down glutaminergic inputs into the dorsal striatum in both inflammation- and MDD-associated psychomotor retardation. Curiously, most of these studies also report strikingly left lateralized effects. Though robustly reported this finding is currently poorly understood and will require further investigation in future studies. During an infection, psychomotor slowing may serve to minimize energy expenditure and conserve heat, thereby enhancing immune function. Convergent findings in inflammation and MDD-associated psychomotor retardation suggest that chronic activation of these mechanisms may differentiate MDD patients presenting with predominant psychomotor retardation or impulsivity/anxiety symptoms. Whether this difference in presentation also relates to differences in peripheral inflammatory markers is the focus of ongoing studies.

5 Autonomic Responses

Physiological changes including hyperactivity of the hypothalamic-pituitary-adrenal axis [90] and disturbance in the autonomic control of the heart and vasculature [91] are another feature of MDD, with the later proposed to mediate the relationship between MDD and risk for cardiovascular disease. Inflammation is also increasingly implicated in cardiovascular disease and has been highlighted as a potentially modifiable risk factor by the American Heart Association (AHA) and Centers for Disease Control (CDC) [92]. In this context it is therefore noteworthy that, in addition to impairing mood, experimentally induced inflammation can also perturb both local cardiovascular reactivity [93] and the central autonomic control of the vasculature [20].

One of the most consistent physiological changes reported in MDD is a change in heart rate variability (HRV) which provides an index of beat-to-beat changes in heart rate [91]. Briefly, high frequency (HF) variation in heart rate is mediated by parasympathetic tone and is believed to maintain cardiac stability and protect against myocardial infarction and heart failure. In contrast low frequency (LF) variation tends to reflect sympathetic tone which is associated with an increased risk of malignant arrhythmias and sudden cardiac death. The ratio of these measures (LF/HF) provides a composite measure of HRV with lower values reflecting healthy cardiac function [94]. Meta-analysis demonstrates a significantly higher LF/HF ratio in MDD patients, suggesting an increase in sympathetic and reciprocal decrease in parasympathetic activity [91] that may underlie the association with increased cardiovascular risk.

A similar acute increase in LF/HF ratio has also been observed following induction of mild inflammation using typhoid vaccination [20] and shown to mediate associated changes in blood pressure. Within the brain, inflammation-induced shifts in LF/HF balance are associated with changes in glucose metabolism (FDG-PET) within three discrete regions: dorsal anterior cingulate, posterior cingulate, and pons. Each of these regions is implicated in regulating stressor-evoked blood pressure reactivity. Their recruitment following inflammation and role in mediating effects on blood pressure further illustrates how central effects of inflammation can also contribute to peripheral physiological changes. Together, these findings demonstrate that commonalities between MDD and inflammation extend beyond mood and motivational changes to include changes in physiological function and highlight the brain mechanisms that bind psychological and physiological wellbeing in these conditions.

6 Attention and Executive Function

Cognitive alterations are a prominent feature of sickness behaviors and manifest predominantly as disturbances in attention, memory, and higher-level executive function [4, 95]. Following experimentally induced influenza infection performance is impaired on oddball type tasks that demand sustained attention, though hand-eye coordination and logical reasoning are unaffected [95]. Similar impairments on attentionally demanding tasks are also observed after acute [96] and chronic administration of interferon-alpha [78]. Patients receiving chronic interferon-alpha also show impaired performance on tests of cognitive speed, verbal memory, and executive functions indicating likely impairment of frontal-sub-cortical brain function [97]. This interpretation is supported by EEG which shows focal changes in frontal lobe regions after acute IFN-alpha administration [98].

Cognitive impairments are an important feature of MDD with deficits particularly prominent in measures of sustained attention, memory, and executive function [99, 100]. Deficits in executive function appear wide-ranging and include impairments in inhibition, set shifting, updating, working memory, and planning indicating frontal-sub-cortical dysfunction [100]. Focusing on inhibition, which has been most closely investigated in inflammation, meta-analysis of color word Stroop studies (where target words are presented in congruent or incongruent font colors) shows a relatively selective impairment on incongruent trials that demand inhibition of pre-potent lexical responses [100]. Studies investigating this effect using neuroimaging suggest that MDD patients show greater interference because they fail to adequately recruit left dorsolateral prefrontal cortex (DLPFC) [101] or require greater left DLPFC activation to achieve performance levels observed in controls [102]. Interestingly, mid-DLPFC is implicated in selecting and biasing attention to the most task-relevant representation indicating a potential circumscribed cognitive deficit in MDD patients [100].

In the first neuroimaging study of inflammation and cognition Capuron et al. [103] used a variation of the CANTAB response time (RT) task to investigate effects of IFN- α on visuospatial attention. Interferon-alpha did not impair task performance or recruitment of the parieto-occipital attention network. However, IFN- α treated patients did recruit an additional dorsal anterior cingulate cortex (ACC) region that was not observed in controls. ACC is implicated in conflict monitoring and its activation is proposed to reflect the degree of intentional effort or willed control needed to perform a task [104]. ACC activation in IFN-treated patients therefore potentially reflects a need to exert greater cognitive control to maintain normal levels of task performance in the face of inflammation.

Interestingly, a similar pattern of behavioral and neuroimaging changes also emerged in a study using the color word Stroop task to investigate effects on mild inflammation (typhoid vaccination) on cognitive inhibition [12]. Again, inflammation was not associated with any significant change in task performance. However, it did have a striking impact on the network of brain regions recruited during

attentionally demanding incongruent trials (that require inhibition of pre-potent responses) including DLPFC and mid-cingulate (aMCC/pMCC) cortices. Because participants showed no performance differences, these effects likely represent a need for additional neural resources to maintain task performance under inflammation. As mentioned above, activity within both DLPFC and dorsal ACC is typically enhanced with increasing cognitive demands. Both regions also show an increase in activity during performance of a cognitively demanding visual task in the face of cross-modal auditory distracters [105]. Their concurrent activation in states of inflammation therefore suggests that interdependent cognitive/attentional [106] and somatic (autonomic) [107] mechanisms may be invoked to maintain performance in the face of increased conflict from interoceptive processing.

In sum, these studies indicate the need to recruit additional neural resources, notably DLPFC and ACC to maintain cognitive performance in the face of systemic inflammation. Similar to findings observed in MDD, this is particularly marked in tasks with high attentional demand or requiring inhibition of pre-potent responses. Exactly how closely the cognitive deficits induced by inflammation relate to those observed in MDD is yet to be fully determined. Future research will need to further clarify the origin of impairments in executive function observed in MDD and dissect the neurobiological and cognitive mechanisms underlying the broad cognitive deficits reported in both MDD and inflammation. Neurobiological differences including changes in inflammatory state and its impact on neurotransmitters such as serotonin or kynurenine breakdown products are one possible cause for these changes and recent studies are now beginning to characterize this [108].

7 Memory

Work in rodents has demonstrated that inflammatory cytokines modulate a number of neuronal processes including long-term potentiation (LTP) [109, 110], synaptic plasticity [111], and neurogenesis [112] that are critical to learning and memory. In health, immune mechanisms play a role in each of these processes and contribute to the remodeling of neural circuits that promote learning and memory [4, 111]. However, during systemic infection this positive regulatory function is disrupted resulting in acute memory impairments [113]. When inflammation is severe, cognitive impairment may also become persistent [114] and when it is chronic typical age-related impairments in cognition are accelerated [115].

Medial temporal lobe (MTL) structures appear to be particularly sensitive to the effects of inflammation. This may reflect their relatively high receptor and messenger RNA expression for pro-inflammatory cytokines [116, 117] and their connectivity to regions such as the insula [118] that support cortical representations of peripheral inflammatory states [24]. Rodent studies have particularly emphasized the role of the hippocampus in inflammation-associated memory impairments. For example, IL-1 administration into the hippocampus selectively impairs spatial and contextual memory processes and contextual, but not (hippocampus independent)

auditory-cued, fear conditioning [4, 119, 120]. Similarly, over-expression of IL-1 mRNA within the hippocampus has been associated with delayed acquisition of spatial memory [120]. LTP is arguably the key neuronal mechanism for synaptic plasticity that underlies memory encoding and recall. It is therefore noteworthy that IL-1 compromises both hippocampal and dentate gyrus LTP [109, 121, 122]. Peripheral inflammatory challenges also induce IL-1 expression within brain regions, including the MTL [123] and can replicate many of the direct actions of inflammatory cytokines on MTL-dependent memory [124, 125].

In humans, individuals suffering from acute flu-like symptoms have been shown to exhibit impaired memory on tests of immediate and delayed verbal (and delayed picture) recall [126]. However, retrieval of semantic information consolidated in long-term store is unimpaired [126]. Similarly, inflammation induced experimentally with LPS impairs both verbal and nonverbal, declarative memory [9]. Importantly, these memory impairments remain prominent even when mood normalizes suggesting an effect induced by inflammation rather than being secondary to associated changes in mood [9]. Impaired verbal memory is also reported following IFN- α [97]. These studies, which have focused on declarative memory, broadly support the MTL sensitivity to inflammation observed in rodents. However, marked differences in the memory testing paradigms used in rodents and humans limit finer-grained translational inferences.

This difficulty has been partially mitigated (in the context of spatial memory) by the recent translation of the Morris water maze, used extensively to assess rodent spatial memory, for human use [127]. This task requires participants to remember the identity and spatial location of objects in a virtual arena and has been recently used to demonstrate that low-level inflammation also selectively impairs human spatial memory [18]. In particular, inflammation was associated with a selective impairment in remembering object location but not object identity. Furthermore, inflammation did not impair motor skill learning (indexed by performance on a mirror tracing task), a form of procedural memory that relies on a separate dorsal striatum-based memory system independent of the MTL [127]. Interestingly, inflammation was also associated with bilateral reductions in MTL resting glucose metabolism (measured using FDG-PET) with changes in the right parahippocampus significantly mediating the inflammation-induced impairment in spatial memory [18] (Fig. 3). The location of this effect is noteworthy as studies in rodents associate similar spatial memory impairments with changes localized to the hippocampus not the parahippocampus [4].

Why these inter-species differences exist may be usefully informed by human lesion studies, that show that human performance on Morris water maze type tasks and direct tests of object-location memory can be more strongly dependent on right parahippocampal than hippocampal integrity [128, 129]. Right parahippocampal activity during object-location encoding has also been shown to predict subsequent retrieval success with a spatial cue [130]. Furthermore one-trial memory for object-place associations also appears to be critically dependent on posterior parahippocampus rather than the hippocampus in monkeys [131].

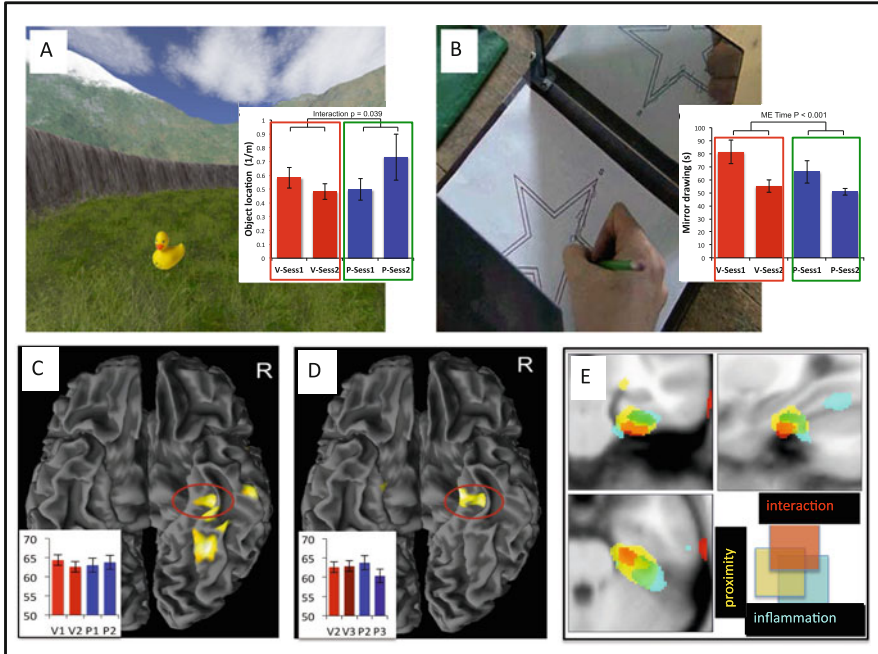


Fig. 3 Inflammation impairs spatial memory via actions on medial temporal lobe glucose metabolism. **(a)** Virtual reality object-location task. *Inset* shows that object-location accuracy (y axis) improves after placebo (*red*) but deteriorates after typhoid vaccine induced inflammation (*blue*). **(b)** Control mirror tracing task. *Inset* shows equivalent improvement in performance after both placebo (*red*) and vaccine (*blue*). **(c)** Decrease in medial temporal lobe (MTL) fluorodeoxyglucose (FDG) uptake in participants given typhoid vaccine after scan 1 (V1 to V2 *red*) compared to controls (*blue*). **(d)** Similar reduction in MTL FDG uptake in participants given typhoid vaccine after scan 2 (P2 to P3 *blue*). Note participants given typhoid vaccine after scan 1 (*red*) show a sustained reduction in FDG uptake at scans 2 and 3 (V2 to V3). **(e)** Reduction in MTL FDG uptake after typhoid vaccination (*blue*), correlation between object-location accuracy and FDG uptake (*yellow*), and area correlating with interaction between task performance and inflammation illustrated in *a* (*red*). Data from Harrison et al. [18]

Episodic memory is also one of the cognitive functions most susceptible to depression suggesting a relatively selective impairment in MTL function [132, 133]. Supporting this, meta-analyses of structural MRI studies have shown an 8–10% reduction in hippocampal volume in MDD [134, 135]. Similar to participants receiving LPS or experiencing flu-like symptoms, studies conducted on large populations of MDD patients (>8,000) report impaired performance on the delayed paragraph recall test of verbal declarative memory [136]. MDD patients have also been shown to perform significantly worse on a virtual reality measure of spatial memory [137]. Though to date most studies investigating memory function in MDD have focused on the hippocampus, evidence suggests that MDD may also be associated with abnormalities in broader MTL structures [138]. Future studies characterizing the specific pattern of memory deficits associated with MDD and

inflammation and their underlying neural substrates will be essential to furthering our understanding of how inflammatory processes contribute to the memory deficits observed in MDD.

8 Social Responses

Another feature of sickness behaviors is social withdrawal and social disconnection [139]. Feelings of social disconnection (experienced as loneliness) contribute to the development and maintenance of depression [140]. The observation that inflammation-induced social withdrawal can be reversed by antidepressant treatment [141] has motivated a number of recent human studies seeking to understand how inflammation leads to social disconnection as a way of potentially understanding the mechanistic relationship between inflammation and depression.

In an early study, Eisenberger et al. [8] showed that inflammation increases feelings of social disconnection and furthermore that this change mediated the relationship between inflammatory activity and depressed mood. The questionnaire used to assess feelings of social disconnection in this study included items reflecting both a desire to withdraw socially and items that reflected a feeling of being socially isolated or disconnected from others. Both types of items were altered following LPS suggesting potentially dissociable effects on motivational processes (“I want to be alone”) as well as processes involved in social cognition and social perception. Addressing this, Moieni et al. have recently demonstrated that LPS induced inflammation impairs performance on the “Reading the Mind in the Eyes” test of theory of mind [142]. This task evaluates how accurately participants can identify another’s emotional state by looking only at their eyes [143] and suggests that in addition to effects on motivation, inflammation can additionally alter social processes central to our ability to correctly infer others mental and emotional states.

Another important feature of MDD is that it is twice as common in women as men. One factor proposed to mediate womens’ increased vulnerability is their greater exposure and reactivity to interpersonal stressors [144]. It is therefore noteworthy that though women do not show convincingly greater pro-inflammatory cytokine responses to LPS they do report greater increases in feelings of social disconnection and depressed mood suggesting that inflammation may play a role in mediating sex differences in rates of MDD [145]. This is supported by another study that combined LPS and the Cyberball task during fMRI to investigate effects of inflammation on social exclusion [146]. In this study, LPS-induced increases in IL-6 correlated with increased activity within a matrix of brain regions including dorsomedial prefrontal cortex (PFC), posterior superior temporal sulcus (STS), dorsal anterior cingulate (dACC), and insula that are implicated in social processing. However, though this relationship was observed across all participants only in women did it significantly mediate associations between inflammation and depressed mood.

Brain regions such as the posterior superior temporal sulcus (pSTS) and medial prefrontal cortex are strongly implicated in tasks of social cognition that involve extracting socially meaningful information and inferring another's mental state [147]. It is therefore noteworthy that each of these regions showed heightened activity in proportion to induced inflammation [146]. This interpretation is also in keeping with reported impairments in performance on the "Mind in the Eyes" test on theory of mind [142]. Supporting these findings, inflammation has also been shown to disrupt the functional connectivity of both the pSTS and medial prefrontal cortex to sub-genual cingulate (sACC) (a region central to integrating social, emotional, and physiological responses) during an implicit emotional face processing task [11]. Together, these studies demonstrate effects of inflammation on social processing including increased feelings of social disconnection and impaired theory of mind. Accumulating evidence suggests that in some participants, particularly women, these changes may mediate associated impairments in mood and illustrate a potential mechanism linking inflammation to depression.

9 Network Connectivity

The preceding sections have focused on dissecting effects of inflammation and MDD on discrete emotional, cognitive, behavioral, and physiological changes and relating this to regional changes in brain function. However, a small number of recent studies have begun to look at the effects of inflammation on network connectivity, driven by the recognition that even the simplest cognitive functions involve highly distributed processing [148]. The first such study used a simple psychophysiological interaction (PPI)-based approach to investigate the effects of systemic inflammation on connectivity of the sub-genual cingulate (sACC) [11]. In so doing, this study showed that inflammation-associated changes in total mood modulated not just sACC activity but also its functional connectivity to the nucleus accumbens, amygdala and superior temporal sulcus, regions central to the processing of reward, and emotionally and socially salient information, respectively. Furthermore, inflammation-induced reductions in the effective connectivity of the sACC to each of these regions predicted the associated deterioration in total mood.

This study is noteworthy as the sACC is recognized as a key node in functional and anatomical models of mood regulation [149] and the coordination of emotional processing. It is also strongly implicated in the pathophysiology of MDD [44]. Increased sACC activity seen in depression has also been shown to reverse with successful depression treatment with a selective serotonin reuptake inhibitor [44, 150], deep brain stimulation [151] of adjacent white matter tracts, and even placebo [150]. Importantly, the sACC is a region that is strongly implicated in integrating multiple components of mood homeostasis. Its recruitment in inflammation-induced mood change suggests that inflammation-associated changes

in mood recruits a network of brain regions similar to that implicated in primary depression.

More recently three further studies have investigated the effects of inflammation on brain functional connectivity networks observed at rest. In the first using low dose LPS (0.4 ng/kg), seed-based analysis revealed a rapid and widespread reduction in the functional coupling of the amygdala, insula, and cingulate cortices to multiple brain networks involved in affective-emotional, motivational, and cognitive-modulatory processes [152]. Similar to the PPI analysis of task-related fMRI [11], LPS was associated with reduced connectivity between the amygdala and prefrontal structures, though these authors were unable to show any significant relationship to changes in mood. The second study used a slightly higher dose (0.6 ng/kg) of LPS and specifically investigated effects on connectivity between anterior and posterior insula seeds and orbitofrontal and cingulate (anterior and middle). This study identified a specific increase in left anterior insula to left mid-cingulate cortex that additionally predicted LPS associated back pain and global sickness [42]. These regions form key components of the pain matrix, and it is noteworthy that they have also been previously linked to LPS induced increases in visceral pain sensitivity [153].

The third study adopted a different approach and investigated effects of IFN- α on measures of network function derived from graph theory [154]. Briefly, graph theory provides a powerful mathematical approach for analyzing the structure of complex networks, and application to the human brain has revealed insights unavailable from conventional approaches. For example, it has shown that similar to other complex networks, the brain utilizes an efficient “small-world” connectivity architecture that serves to minimize wiring cost while maintaining robustness to random damage to individual regions (nodes) or connections (edges) [155]. Within 4 h of administration, IFN- α was associated with a striking reduction in global network connectivity and network efficiency indicating a global reduction in information transfer among nodes forming the whole brain network. Furthermore, these changes in global network connectivity and efficiency of information exchange correlated strongly with IFN- α induced changes in mood, confusion, fatigue, and tension/anxiety.

How peripherally administered IFN- α or LPS can so rapidly impair the functional connectivity of such large-scale brain networks is currently uncertain. However, the observation that these actions are effected on a global scale points towards a likely role for neuromodulators such as dopamine, norepinephrine, or serotonin that can rapidly alter diverse and widespread neuronal populations rather than a more regionally targeted effect. In support of this, inflammation has been linked to altered nucleus accumbens dopamine efflux in rodents [62], decreased striatal dopamine release in rhesus monkeys [156, 157], and reduced presynaptic dopamine synthesis or release in humans [22]. Further, monkeys showing behavioral impairment after inflammatory challenge with lipopolysaccharide exhibit significantly lower cerebrospinal fluid concentrations of the dopamine metabolite homovanillic acid [50].

Network-based analyses have also been pursued in MDD and, similar to the findings of post-LPS, have shown reduced functional connectivity within broad prefrontal-limbic-thalamic areas, particular regions sub-served by the left amygdala-ACC and the right insula-precuneus Labrenz et al. [158]. Graph theoretic analyses of MDD have also demonstrated changes in network topology including abnormal small-world organization and network efficiency [159]. Though application of advanced connectivity analyses to both MDD and inflammation remains in its relatively infancy, similar marked changes in network connectivity, particularly within prefrontal and limbic regions across conditions, support the utility of this approach as a way of characterizing the relationship between inflammation and MDD. Demonstration of often-marked correlations between global measures of network function and mood/cognition suggests a likely role for neuromodulators such as dopamine and serotonin, that are implicated in the pathophysiology of both MDD and sickness behaviors. Further characterization of these associations will require combination of network-based analyses with PET imaging of specific neuromodulators and/or metabolomic approaches.

10 Summary

Rodent and human brain imaging studies have been successful in characterizing a discrete set of cortical and sub-cortical structures sensitive to changes in peripheral inflammation and highlighted their role in many of the key components of sickness behavior. These regions show a striking similarity to the network of areas implicated in the mood, motivational, and cognitive deficits characteristic of MDD. In the context of models of bacterial infection, peripheral inflammation rapidly recruits an interoceptive pathway projecting to insula. This pathway and its terminal projection to the insula provides a central representation of all aspects of bodily physiological state and its translation into consciously accessible feeling states. Following inflammation, recruitment of the insula cortex is implicated in feelings of fatigue and malaise (and possibly social disconnection) as well as a heightened sensitivity to punishment. Bidirectional connections between the insula and the anterior and mid-cingulate cortex provide a substrate for the heightened sensitivity to visceral and pressure pain. Similar to MDD, actions of inflammation on ventral striatal reward processing and reward prediction error encoding appear to underlie shifts in reward sensitivity and motivation. Cognitive deficits (particularly impaired MTL dependent memory and performance on attentionally demanding tasks) are characteristic of both MDD and inflammation and relate to disrupted hippocampal/parahippocampal processing and DLPFC, respectively. More recent functional connectivity studies highlight the distributed nature of cognitive processes and hint at the likely importance of broadly acting neuromodulators like dopamine and serotonin in the mood, motivational, and cognitive impairments characteristic of both MDD and inflammation.

Based on these foundations, future studies combining multiple functional neuroimaging techniques with metabolomic and proteomic approaches should help us move closer to the goal of a mechanistic understanding of the relationships between peripheral inflammation, regional brain structure/function, and discrete cognitive phenotypes observed in MDD.

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