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The Neuroimmune Basis of Fatigue

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The many facets of fatigue

Many definitions of fatigue have been proposed. One that is often cited refers to fatigue as "an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to carry out daily activities, including the ability to work effectively and to function at one's usual level in family or social roles" (1). There are at least two dimensions in fatigue, "I cannot do it, I am exhausted" *versus* "I do not feel like doing it, it is not worth it". The first dimension is relatively easy to characterize as it is usually associated with obvious physical signs. The second dimension is more difficult to characterize and is usually referred to as central fatigue or "the failure to initiate and/or sustain attentional tasks and physical activities requiring self motivation" (2). Central fatigue rarely occurs alone, it is often associated with sleep disorders, pain, and affective and cognitive alterations.

Fatigue is highly prevalent in the general population, with rates around 20% (3). Approximately one third of patients' complaints in medical general practice relate to fatigue (4). The prevalence of fatigue increases dramatically, up to and above 50%, in a number of medical conditions that involve dysregulation of the immune system, such as cancer, chronic infection, autoimmune diseases and neurological diseases (5). Fatigue in the physically ill patient is one of the most common and earliest non-specific symptoms of disease and can persist long after the medical condition has resolved.

In practice fatigue is self-reported. Because subjective fatigue correlate very poorly with objective measures of physical activity and performance (6), several questionnaires have been developed to measure the overall severity of fatigue and in some cases its dimensions. However, what is often forgotten while processing these scores is that fatigue is a product of the patients' representation of their condition and is part of the perceptions patients form about their illness. These perceptions vary according to time and depend on the way patients can mobilize their resources and cope with this particular threat to their integrity that their illness represents (7, 8). Patients do not remain passive but are always forming expectations

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about possible futures and actions. This aspect is captured by the concept of self-efficacy, a cognitive construct implicating one's self-perception about one's performance ability. Fatigued patients with a history of breast cancer or multiple sclerosis have a poor self-efficacy that accounts for their inability to engage in physical exercise despite its potential benefits (9).

In view of the large body of data that is available on the relationship between fatigue and inflammation and the negative impact of inflammation on motivated behavior, we propose that fatigue in subjects with inflammation is a feeling that relates to the lack of motivation to deploy resources and engage in high effort performance to cope with their situation. This is in contrast to depression that has a helplessness component together with self-depreciation, sadness, and anhedonia.

Inflammation, sickness, incentive motivation, and fatigue

The conceptualization of inflammation-induced fatigue requires an evolutionary perspective. In a seminal paper, Hart suggested the behavior of sick animals is not a maladaptive response or the effect of debilitation but an organized, evolved strategy to facilitate the role of fever in combating viral and bacterial infections (10). Subsequent studies have focused on the mechanistic aspect of inflammation-induced sickness and demonstrated that it is triggered by activation of a limited set of innate immune receptors known as toll-like receptors and common to plants and animals by evolutionary conserved structures of pathogens (11). The interaction of toll-like receptors with their ligands results in the *de novo* production of proinflammatory cytokines. In addition to their local role in coordinating the mounting and regulation of an immune response, proinflammatory cytokines produced by activated innate immune cells signal the brain via a number of immune-to-brain communication pathways. In response, the brain forms a cellular and molecular image of the peripheral inflammatory response that organizes behavior and metabolism. In essence, activation of the immune-to-brain communication pathways ultimately allows caring for the ill body to impose new behavioral priorities.

In motivational terms the motivation of sickness competes with other internally or externally driven motivational states (e.g., hunger, exploration, sex) and takes precedence unless competing motivational stimuli become more important for survival. Motivational competition between sickness and other motivational states can be demonstrated by varying the intensity of the triggering stimuli. For instance lactating mice injected with lipopolysaccharide stayed curled in a corner of the cage and failed to display typical maternal care behavior such as upright crouched nursing posture in response to solicitations from their pups (12). However, if the maternal motivation of lipopolysaccharide-treated dams was challenged by removing the pups from the nest and dispersing them in the cage, they overcame their lethargy and engaged in pup retrieving although they were slower in doing so than saline-injected dams. When tested at thermoneutral environmental temperatures lipopolysaccharide-treated dams did not engage in nest building when the nest was removed and replaced by cotton wool. However, they built a near perfect nest when exposed to a 6°C environment.

The reluctance of sick individuals to engage in motivated behaviors that are unrelated to sickness has been studied mainly in the context of food motivation. In general animals that are made sick by administration of lipopolysaccharide or proinflammatory cytokines are less likely to consume food if effort is required to obtain it than if the food is freely available. The greater the necessary effort the more sensitive to disruption their behavior is. For example intraperitoneal administration of interleukin-1(IL-1)β decreased home cage consumption of sweetened milk to a greater extent in *ad libitum* fed mice than in food-

restricted mice (13). Similarly, IL-1β-treated mice that had to repeatedly nose poke to get a small amount of sweetened milk stopped responding earlier when more nose pokes were required.. Finally, rats that had to deploy effort to obtain highly preferred carbohydrate food pellets in a concurrent performance task with laboratory chow freely available decreased responding when treated with IL-1β while simultaneously increasing chow consumption (14). These results indicate that inflammation reduces incentive motivation.

This approach to fatigue is characteristic of the prevailing strategy in biological psychiatry which aims to specify more quantifiable behaviors and neurobiological measures as an alternative to the current clinically-based classifications of mental disorders (15). Although fatigue is not a mental disorder it is a symptom complex that still requires deconstruction its full range of variation. Of the research domain criteria proposed by NIH, the most relevant to fatigue would be the behavioral function “sustained responsiveness to reward” (15). As discussed below, this behavioral function has the advantage of being a validated construct with a specifiable neural circuit.

Inflammation and fatigue: Clinical findings

At the clinical level there has been little attempt thus far at deconstructing fatigue when studying its relationship with inflammation, with the sole exception a preliminary study in which inflammation was more related to physical than to mental fatigue in patients with advanced cancer (16). Most of what we know about the role of proinflammatory cytokines in the development and severity of fatigue comes from cross-sectional clinical studies in physically ill patients suffering from fatigue although causality studies are now emerging.

Associations between fatigue and inflammatory markers (primarily IL-6, tumor necrosis factor-alpha (TNFα) and C-reactive protein, an acute phase protein) have been documented in various medical conditions, including cancer, viral infections, chronic inflammation, autoimmunity, neurological diseases, and mood disorders (17–19). Fatigue develops in a large proportion of cancer patients receiving chemotherapy and/or radiation therapy. Fatigued cancer patients have elevated circulating levels of biomarkers of inflammation although this association is more consistently observed in longitudinal than in cross-sectional studies (20).

The measurement of circulating concentrations of cytokines represents the main limitation of the present studies on fatigue and inflammation. As cytokines are autocrine and paracrine communication factors, their circulating levels have little functional value and represent mostly spillover from the site of cytokine production and action. Alternative strategies are available. They are based on *in vitro* measurements of cytokines produced by peripheral blood mononuclear cells or specific immune cell populations in response to well identified immune stimuli (21). They often include an assessment of glucocorticoid receptor function as cortisol is the main endogenous brake on the production of proinflammatory cytokines (22). However, these assays require equipment and expertise that are not easily accessible for most clinical researchers.

Compelling evidence for a causal link between inflammation and fatigue comes from studies conducted in individuals receiving cytokine inducers such as lipopolysaccharide in an experimental setting or recombinant cytokines such as interferon-alpha (IFNα) for the treatment of hepatitis C virus infection, malignant melanoma, or kidney cancer. For example, moderate to severe fatigue develops in up to 80% of cancer patients treated chronically with IFNα, as early as the first week of treatment (23). Further evidence for a causal relationship between immune activation and fatigue comes from studies in which

treatment with an antagonist of TNFα significantly reduced fatigue in patients with rheumatoid arthritis or psoriasis (24, 25).

In IFN-α-treated cancer patients, physical fatigue appears earlier than central fatigue, which is concomitant to the occurrence of mood and cognitive symptoms (23). The various dimensions of fatigue do not respond in the same way to treatment. For instance, preventive administration of paroxetine, a selective serotonin reuptake inhibitor, does not block the development of IFNα-induced fatigue (23). In contrast, this treatment is effective in preventing depressed mood and the related symptom of lassitude in the same population as well as in depressed patients. Similarly, data obtained in fatigued patients with Parkinson disease indicate that central fatigue and physical fatigue are independent symptoms that require separate treatment interventions (26).

Neural basis of inflammation-induced fatigue

There have been only a limited number of studies on the neural mechanisms of inflammation-induced fatigue, in contrast to a large number on inflammation-induced sickness and depression (11, 27). Peripheral cytokines can affect central neurotransmition indirectly by modulating the bioavailability of amino acid precursors of neurotransmitters (Fig. 1). In addition, peripherally released cytokines activate immune-to-brain communication pathways, enabling the brain to be informed about immune events even in the absence of blood-brain-barrier disturbances (Box 1). Specifically, peripheral cytokines induce the production and release of inflammatory mediators including prostaglandins and cytokines by endothelial cells, macrophages and microglia in the central nervous system. These inflammatory mediators can influence neurons directly or indirectly by modifying astrocyte, oligodendrocyte, and endothelial cell functions (Fig. 1).

Box 1

Immune-to-Brain Communication Pathways

Several communication pathways are involved in the transmission of the peripheral inflammatory message to the brain, including: a *humoral pathway* by which circulating pathogen-associated molecular patterns such as lipopolysaccharide engage Toll-like receptors on macrophage-like cells in the circumventricular organs, which results in the local production of cytokines that propagate from the blood side to the brain side of the blood-brain barrier (54–56); *saturable transport systems* allowing the passage of cytokines across the blood-brain barrier (57); and a *neural pathway* that bypasses the blood-brain barrier (55). In this last case, peripheral inflammatory mediators activate sensory nerves that innervate the site of inflammation and relay the immune message to their sites of primary and secondary projection in the brain.

The role of *brain endothelial cells* and *perivascular macrophages* in the transmission of the peripheral immune message to the central nervous system has received much attention, as they are the primary sites where activation of arachidonic cascades takes place (58). However, most of the cytokines that are expressed in the brain in response to systemic immune stimuli are produced by microglia. Adriano Fontana was the first to show that interleukin (IL)-1 is produced in the brain in response to endotoxin and to propose that it could mediate the pyrogenic action of endotoxin (59). The synthesis of IL-1β and other cytokines in the brain in response to non-septic doses of intra-peritoneal lipopolysaccharide was subsequently demonstrated at the mRNA level by reverse transcriptase polymerase chain reaction (60, 61). Receptors for IL-1 and other proinflammatory cytokines were also identified in the brain and pituitary using autoradiography, RT-PCR, and immunohistochemistry. Furthermore, light and electron

microscopic analysis of the brains of endotoxin-treated rats revealed the presence of IL-1β-producing cells in the brain in the form of macrophages in the meninges and choroid plexus and microglia (62). Involvement of microglia in the response to systemic lipopolysaccharide has since been confirmed by various approaches. Parenchymal microglia, for instance, express the inhibitory factor kappaB alpha, a proxy for activation of the nuclear factor kappa B signaling pathway, in response to systemic lipopolysaccharide (63). More recently, *ex vivo* isolation of microglial cells from the brain of adult animals has been used to assess the ability of these cells to produce inflammatory mediators in response to systemic lipopolysaccharide (e.g., (64)).

The possibility that cytokines expressed in the brain in response to systemic inflammation mediate the many facets of the host response to immune stimulation has been investigated at length. There is ample evidence from pharmacological studies with cytokine antagonists administered into the brain and from genetic studies using cytokine or cytokine receptor knock-out mice that cytokines produced *in situ* underlie the brain response to systemic inflammation (11, 65, 66).

The evidence for an impact of inflammation on dopamine, norepinephrine and serotonin neurotransmission is summarized in Box 2. There is already a vast literature on the participation of the fronto-striatal dopaminergic neurocircuitry in reward-based decision making (28, 29). Dysfunction of this network is responsible for the reduced anticipation and motivation that are at the core of anhedonia in major depressive disorders. As mentioned above, fatigue is associated with alterations in sustained response to reward. This implies that the neural circuit involved in fatigue overlaps with the neuronal network that underlies reward-based decision making. The basic elements of the fronto-striatal network including the basal ganglia and frontal cortex have been found to be the targets of inflammatory mediators (30–33) as well as the site of significant alterations in activity and function in chronic inflammatory conditions (e.g., multiple sclerosis and Parkinson's disease) (34–36).

Box 2

The neurochemical basis of fatigue

Most of the studies of the effects of inflammation on brain neurotransmitters focus on dopamine, norepinephrine and serotonin. Dopaminergic neurotransmission is very sensitive to inflammation. At the periphery, the production of neopterin and nitric oxide during inflammation consumes tetrahydrobiopterin to the detriment of the hydroxylase enzymes that use this compound as a cofactor (67). This results in the decreased bioavailability of dihydroxyphenylalanine and tyrosine for the synthesis of dopamine. In the brain, microglia activation negatively affects dopaminergic neurotransmission and sensitizes dopaminergic neurons to neurotoxins (30, 68). Inflammatory mediators can also inhibit D2 dopaminergic receptor activation indirectly by activating striatal adenosine A_{2A} receptors (14, 69). In addition, cytokines can enhance dopamine transporter activity, resulting in decreasing synaptic availability of dopamine. Most of these studies have been done in condition of acute inflammation so that the generalization to chronic inflammation is not possible. Chronic administration of IFN-α to rhesus monkeys has been found to decrease D2 binding and striatal dopamine release in association with reduced sucrose consumption (70).

Fatigue and decreased vigilance are directly linked to impaired brain norepinephrine transmission (71). In addition to the peripheral effect of inflammation on the bioavailability of norepinephrine precursors noted above, there is evidence from discrete lesion studies in rats injected with the cytokine inducer lipopolysaccharide that the inflammation-induced reduction in exploratory behavior is mediated by

catecholaminergic projections from the ventrolateral medulla and nucleus tractus solitarius to the ventral tegmental area, hypothalamus, dorsal striatum and hippocampus (72).

Serotoninergic neurotransmission can be impaired during inflammation because of cytokine-induced increase in serotonin transporter activity and increased metabolism of tryptophan to kynurenine in response to activation of indoleamine 2,3 dioxygenase (11, 73, 74). This last reaction is ultimately responsible for the formation of neurotoxic kynurenine metabolites such as 3-hydroxy kynurenine and quinolinic acid. There is evidence that kynurenine metabolites are responsible for the development of inflammation-induced depression (75). Association studies also support a role for these compounds in fatigue in cancer patients (76) and elderly subjects (77) but the causality has not yet been tested.

Finally, the development of lipopolysaccharide-induced lethargy has been attributed to a GABA-mediated inhibition of orexin containing neurons in the perifornical lateral hypothalamic area (78, 79). The involvement of orexin in fatigue appears to have some degree of specificity, as centrally administered orexin counteracted lipopolysaccharide-induced lethargy but not anorexia in rats (79).

Consistent with this model, the increase in depressed mood that is caused by the administration of a low dose of endotoxin to healthy volunteers was associated with decreased ventral striatum reactivity to monetary reward cues (37). Using functional magnetic resonance imaging (fMRI), the ventral striatum response to hedonic reward was also found to be reduced in hepatitis C patients treated with IFNα and this effect was correlated with scores of fatigue and depression (38). Although these results are strongly suggestive of an association between inflammation and decreased sensitivity to reward, it is still necessary to qualify the precise nature of this deficit. It should be possible to measure inflammation-induced impairment in motivation and reward-based decision making in fatigued patients using the Effort Expenditure for Rewards Task, a translational measure of reward motivation (39) developed as a human analog of the concurrent performance task used in rodents (Fig. 2) (14).

The ventral striatum plays a key role in mediating the rewarding aspects of stimuli through its dopaminergic innervation (40, 41). It allows the learning of goal-directed responses as the selection of appropriate actions requires the assessment of the incentive value of response outcomes. Once fully learned, goal-directed responses normally become habits. Behavior is then driven by contextual cues through stimulus-response associations rather than by response outcomes. The predominance of stimulus-response over response-outcome associations is made possible by a switch from the ventral to the dorsal striatum in rodents (caudate to putamen in humans) (41). Prefrontal cortical regions are required for the updating of response-outcome associations necessary for formation of new habits (42). Formation and maintenance of habits have primarily been studied in the context of drug addiction because of the compulsive nature of drug seeking. However, these findings can be fruitfully applied to fatigue. We propose here that inflammation-induced impairment in fronto-striatal circuits impairs the formation of habits and therefore render even simple everyday activities effortful for fatigued patients (Fig. 2). This would account for the cognitive fatigability of fatigued patients. This hypothesis could be tested by comparing the ability of fatigued and non-fatigued subjects to perform a conditional associative learning task in which there is normally a gradual transition from goal-directed actions to habitual responses (43). The emergence of habitual responses should be more vulnerable to fatigue than the early phase dominated by goal-directed actions.

As noted above, fatigue refers not only to the diminished capacity to engage in self-motivated behavior but is also a feeling. Awareness of fatigue is triggered by interoceptive stimuli arising from the activation of visceral afferents that monitor the condition of tissues of the body (Fig. 2). As proposed by Craig (44, 45), this interoceptive system in primates is composed of autonomic afferent fibers that project to lamina I neurons and the nucleus tractus solitarius, relay in the parabrachial nucleus and ventromedial and mediodorsal nucleus of the primate thalamus, and ultimately terminate in the limbic sensory (insula) and motor (cingulate) cortices. In other mammals including rodents interoceptive inputs do not project to the thalamus. Input-output loops operating at different levels of organization of the interoceptive sensation system are at the origin of somato-autonomic reflexes. According to this view, awareness of fatigue would take place in the insula while its motivational dimension would be dependent on the anterior cingulate cortex via its output to the basal ganglia (Fig. 2).

This mode of representation of internal feelings matches the results of functional imaging studies. For example, Harrison and colleagues studied the interaction between systemic inflammation produced by typhoid vaccination (as measured by increased circulating IL-6) and the enhanced cognitive demands of a Stroop task that required processing of incongruent versus congruent stimuli (46). Typhoid vaccination activated afferent interoceptive fibers within the vagus nerve and spinal lamina I pathway. This information reached the cingulate and prefrontal cortex via the right medial thalamus, and also the dorsal mid/posterior insula. Inflammation-associated fatigue, as measured by the Profile of Mood States questionnaire, was correlated positively with activity changes in the mid/posterior insula bilaterally. Of note, activation of the insula was not due to efferent autonomic changes as it remained significant after accounting for changes in blood pressure.

An alternative explanation for this pattern of results is that in these experiments subjects had to make a choice while their default bias would have been to opt for doing nothing (47). The default attitude of status quo would normally decrease activity in the anterior insula and avoid the generation of anticipatory somatic markers of risky, aversive events as a result of the activation of the insula (48, 49). In this context, activation of the insula would be the consequence of switching away from the default and running into the risk of trying to do something that would be inappropriate, with potential risk proportional to fatigue severity. This would explain why activation of the insula was also correlated with mental confusion in subjects who had received typhoid vaccination (46). As the insula is also involved in processing information about risk and uncertainty (50), the decreased ability to rely on habitual behavior to respond to environmental demands could add to contextual complexity and ambiguity and further enhance insula activation (Fig. 2).

Conclusion and perspectives

There is a wide consensus that inflammation plays a key role in the development and persistence of fatigue in patients suffering from physical illness. We have seen that this hypothesis is supported by a number of clinical studies demonstrating associations between fatigue and biomarkers of inflammation and by preclinical studies in which animals exposed to inflammatory stimuli behave in a way reminiscent of fatigue, i.e., they display reduced motor activity and incentive motivation. Among the interventions that are proposed to alleviate fatigue there are several treatments aimedat counteracting inflammation. However, their clinical efficacy remains dubious (Box#3). The subjective, patient-reported nature of fatigue has made it difficult to identify mechanisms and targets for treatment. This is not to say that patient-reported outcomes are useless. Provided their psychometric properties have been carefully validated, symptom assessment scales represent valuable tools for describing symptom trajectories and capturing the impact of treatments on patient functioning and well-

being (51, 52). This information can be used to inform clinical decisions and lower treatment burden (thus increasing compliance rates for prescribed treatments), develop more tolerable drugs, and test and approve new treatment methods. However, here we have tried to show that a better understanding of fatigue requires more than consideration of patient-reported outcomes. Specifically, this will necessitate deconstructing fatigue in a number of objectively defined constructs or endophenotypes that correspond to “changes in well-defined behavioral or cognitive processes associated with discrete deficits in defined neural systems” (53). Such a task is at hand as we already have an etiological factor for inducing fatigue, in the form of inflammation. It is now important to establish and validate basic neurobehavioral units of fatigue in order to be able to draw fruitful parallels between animal and human studies of fatigue.

Box 3

In search of a cure for fatigue

Despite all the claims that are made, there is no effective cure for fatigue. Numerous strategies have been put forward to ameliorate symptoms of fatigue, but with mitigated success. Clinicaltrials.gov lists nearly 2,000 clinical trials for fatigue, with most for cancer-related fatigue, arthritis, and multiple sclerosis. In view of the key role of inflammation in the onset of fatigue, several pharmacological and nutritional strategies can be proposed to limit inflammation and its effect on the brain.

Targeting proinflammatory cytokines with anti-cytokine strategies, particularly TNFα, improves quality of life and relieves symptoms of fatigue. Most of the studies using anti-cytokine strategies have been carried out in patients with rheumatoid arthritis, as taming the inflammatory process is the primary outcome. Alternative approaches based on modulation of inflammation by dietary supplements targeting NF-kappaB activation or oxidative stress have achieved impressive positive results in animal models (80, 81). However, controlled clinical trials are very difficult to run and the low bioavailability of these supplements represents a major obstacle. The second-generation tetracycline minocycline has the advantage of targeting inflammation both at the periphery and in the brain, where it down-regulates microglia activation (82), but its possible anti-fatigue efficacy is not yet documented.

The possibility of inhibiting the consequences of activation of indoleamine 2,3 dioxygenase and guanosine triphosphate (GTP)-cyclo hydrolase 1 on the generation of kynurenine and the relative deficit of tetrahydrobiopterin is worth considering. However, clinical trials of 1-methyl tryptophan, a competitive inhibitor of indoleamine 2,3 dioxygenase, are still at a very early stage where the emphasis is on tolerability and side effects. Tetrahydrobiopterin supplementation is currently being considered only in the context of cardiac dysfunction.

In terms of neurotransmission, serotoninergic neurotransmission could be targeted via specific serotonin reuptake inhibitors (SSRIs), especially in view of the upregulation of the serotonin transporter by inflammation. However, SSRIs do not alleviate the symptoms of fatigue in depressed patients, and the same applies to cytokine-induced fatigue in somatic patients. Targeting dopamine with the norepinephrine-dopamine reuptake inhibitor bupropion is more effective, although the usefulness of this drug in non-depressed patients remains to be assessed. Psychostimulants such as methylphenidate can provide some short-term relief for fatigue. The efficacy of modafinil or its R-enantiomer armodafinil requires further investigation since most of the available results have been obtained in non-controlled studies. Amantadine is a non-competitive antagonist of NMDA receptors with a weak dopaminergic activity that is widely used for the treatment of fatigue in multiple sclerosis and Parkinson’s disease although its efficacy

is still debated. It was initially developed as an anti-viral drug and has some inhibitory effects on microglial activation.

Holistic approaches (exercise, acupuncture, yoga, tai-chi, meditation) are often advocated for the treatment of fatigue. Besides its direct action on muscle physiology and cardiovascular function, physical exercise induces brain neurotrophic factors, which could account for its positive effects on fatigue and depression (83–85). Cognitive behavioral therapy has been claimed to improve the symptoms of fatigue in patients with chronic fatigue syndrome and fibromyalgia. Fatigued patients view themselves as fatigued and unable to engage in any physical activity, which contributes to the perpetuation of their feelings of fatigue (86). This can be aggravated by negative thoughts of anxiety and helplessness.

In most of the studies that have been conducted on the treatment of fatigue, there has been no attempt to dissociate those components of fatigue that respond to therapy from those that are unaffected. Further studies are needed to investigate the effects of therapies targeting specific pathophysiological pathways to ultimately impact the specific dimensions of fatigue.

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Highlights

- Despite its prevalence the pathophysiology of fatigue remains elusive
- We focus on the etiology of fatigue in chronic inflammatory diseases, cancer or neuropathologies
- Fatigue can be decomposed into mental and physical aspects
- Convergent data from many disciplines point to the importance of inflammation in the pathophysiology of fatigue
- Peripheral inflammation can ultimately disrupt monoaminergic neurotranmission
- Resulting alteration in fronto-striatal/insular networks underlies aspects of fatigue

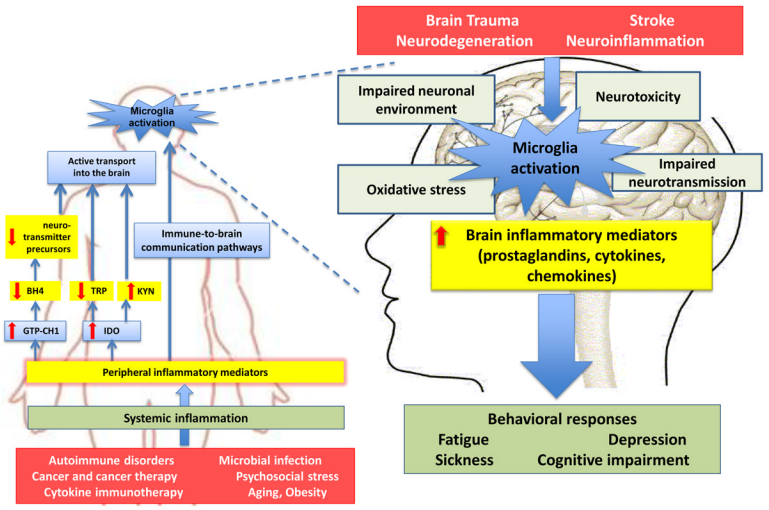

Fig. 1. Peripheral and central mechanisms of inflammation-associated central fatigue

Systemic inflammation, which can be caused by a number of factors, involves both innate immune cells and T lymphocytes. The proinflammatory cytokines that are produced *de novo* by these cells affect the bioavailability of amino acid precursors of neurotransmitters. Specifically, peripheral proinflammatory cytokines activate guanosine-triphosphate cyclohydrolase-1 (GTP-CH1), which mediates synthesis of neopterin by macrophages. This results in a relative deficit in tetrahydrobiopterin (BH4), an essential cofactor of aromatic amino acid hydroxylase enzymes used in the synthesis of dopamine, norepinephrine and serotonin. BH4 is also a co-factor for the synthesis of nitric oxide by inducible nitric oxide synthase. Proinflammatory cytokines also activate indoleamine 2,3 dioxygenase (IDO) in macrophages and dendritic cells, which degrades tryptophan (TRP) along the kynurenine (KYN) pathway. Kynurenine competes with tryptophan for entry into the brain. Kynurenine is further metabolized by activated microglia into 3-hydroxy kynurenine and quinolinic acid, which are both potent radical donors. Quinolinic acid acts also as an agonist of N-methyl-D-aspartic acid (NMDA) receptors and promotes neurotoxicity. The conversion of kynurenine into kynurenic acid, which acts as an antagonist of NMDA receptors, takes place in astrocytes. However, in conditions of inflammation this potentially neuroprotective pathway is less effective than the pathway leading to quinolinic acid.

Peripheral inflammatory mediators activate immune-to-brain communication pathways including afferent nerves. This leads to the local synthesis of inflammatory mediators that affect neuronal function and structure directly or via impairment of the neuronal environment, reduction of the synthesis of neurotrophic factors, and oxidative stress. These effects are rarely sufficient to cause neurotoxicity but they can easily potentiate the neurotoxic activity of a number of other factors. Activation of the pituitary-adrenal axis by proinflammatory cytokines under the combined effect of corticotrophin-releasing hormone and vasopressin (not shown in the graph) should normally contribute to down-regulation of the inflammatory response both at the periphery and in the central nervous system via the production of cortisol and the anti-inflammatory properties of vasopressin. However, this effect can be compromised by the development of cortisol resistance during inflammation. Adverse behavioral responses are the ultimate consequence of activation of these pathways. Red arrows signify the direction of change in a specific inflammatory mediator, enzyme or molecule following systemic inflammation, processes at similar levels, (e.g. both peripheral and central causes of inflammation) highlighted with a common color.

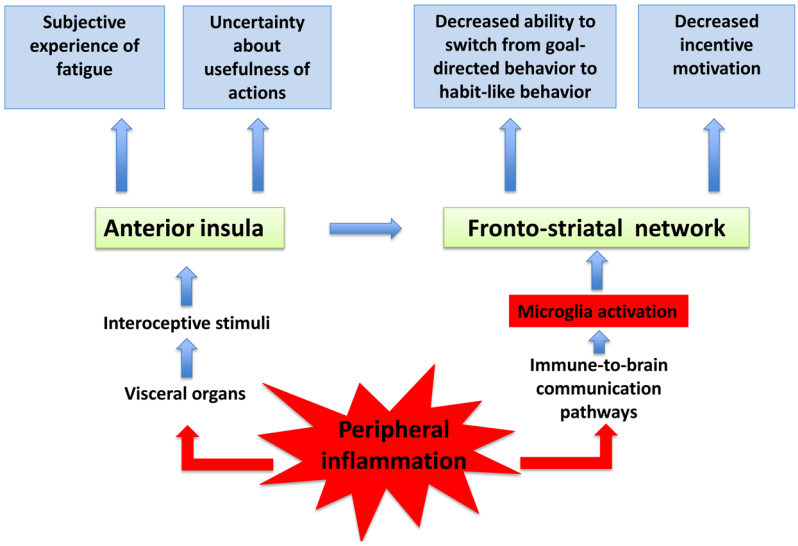

Fig. 2.

A model for deconstructing fatigue in neurobehavioral units associated with dysfunction of the fronto-striatal network in response to microglia activation and activation of the anterior insula by interoceptive visceral afferents. Note that the connection from the insula to the ventral striatum involves the anterior cingulate cortex (not shown).