Fatigue in inflammatory rheumatic disorders: pathophysiological mechanisms

S. Mechiel Korte¹,² and Rainer H. Straub³

Abstract

Today, inflammatory rheumatic disorders are effectively treated, but many patients still suffer from residual fatigue. This work presents pathophysiological mechanisms of fatigue. First, cytokines can interfere with neurotransmitter release at the preterminal ending. Second, a long-term increase in serum concentrations of proinflammatory cytokines increase the uptake and breakdown of monoamines (serotonin, noradrenaline and dopamine). Third, chronic inflammation can also decrease monoaminergic neurotransmission via oxidative stress (oxidation of tetrahydrobiopterin [BH4]). Fourth, proinflammatory cytokines increase the level of enzyme indoleamine-2, 3-dioxygenase activity and shunt tryptophan away from the serotonin pathway. Fifth, oxidative stress stimulates astrocytes to inhibit excitatory amino acid transporters. Sixth, astrocytes produce kynurenic acid that acts as an antagonist on the α7-nicotinic acetylcholine receptor to inhibit dopamine release. Jointly, these actions result in increased glutamatergic and decreased monoaminergic neurotransmission. The above-described pathophysiological mechanisms negatively affect brain functioning in areas that are involved in fatigue.

Key words: fatigue, rheumatic disorders, inflammation, pathophysiology, mechanisms

Introduction

Inflammatory rheumatic disorders, by definition, all produce chronic inflammation in joints and/or in other tissues. Severe fatigue is present in patients with spondyloarthritis, psoriatic arthritis, RA, Sjögren syndrome, SLE, scleroderma, osteoarthritis and fibromyalgia [1–3]. All these disorders are linked to sickness behaviour that is associated with fatigue [4], disturbed sleep [1, 2], cognitive deficits [5], anxiety [6], pain, and depression-like symptoms [1, 7–9]. The pathophysiological mechanisms underlying these different symptoms have a huge overlap and often occur together, making it difficult to determine whether they are dependent or independent of each other [1, 10]. Another factor that increases the complexity of fatigue is the fact that it is a subjective feeling [11]. Severe inflammation-induced fatigue is strongly associated with a much poorer quality of life [12, 13]. Severe fatigue is detrimental to the patient, family and friends, and society. Thus, unravelling of the underlying pathophysiological mechanisms of fatigue and developing effective treatments is a top priority in rheumatologic research. Here, we will focus on how the activated immune system can change neural chemistry and brain functioning to produce central fatigue. Coming from studying fatigue in different research fields, e.g. rheumatology, neuroscience, psychology, immunology, and pharmacology, elements that were previously considered to be domains of one discipline are now discovered in the other. There is a rapidly growing amount of evidence demonstrating a strong bi-directional signalling between the immune system and the brain that plays a role in the development of severe fatigue [14, 15]. To find an effective treatment of fatigue in inflammatory rheumatic disorders we need a
multidisciplinary approach, in which rheumatologists are indispensable.

But first, we will discuss the evolutionary aspects of inflammation-induced sickness, including fatigue. Furthermore, a conceptual framework is provided to enable rheumatologists to better understand how the activation of the immune system can produce different forms of fatigue during different infectious challenges and diseases.

Evolutionary aspects of inflammation-induced sickness behaviour

In 1975, Matthew Kluger and coworkers were the first to demonstrate that fever as part of sickness behaviour increases host survival, rather than being a simple byproduct of infection [16]. In 1988, Benjamin Hart was the first to suggest that sickness behaviour is an adaptive response that ensures vertebrates increase clearance of pathogens by directing energy to immune responses, instead of spending energy on behaviour that is not of immediate vital importance, such as foraging, territorial defence, mating or parental care [17].

Today, it is generally accepted that proinflammatory cytokines, such as IL-1β, TNF-α and IL-6, are responsible for producing sickness behaviour, including fatigue, lethargy, malaise, numbness, fever and feeling ‘cold’, hyperalgesia, loss of appetite, more sleep but often fragmented, changes in cognition, decreased libido, changes in motivation, anhedonia (loss of pleasure), depressive mood, social withdrawal, isolation, and confinement to a safe place, as part of an adaptive program positively selected for to increase survival [17–26].

Recently, it became clear in wild mice that sickness behaviour not only had positive effects on host survival. There is also limitation of disease spread because of reduced social connections due to behavioural withdrawal and isolation after infection. Consequently, the disease is contained to very few individuals [27]. In contrast, it has long been known that immune defences have high costs in terms of calories and proteins [28], slow growth [29], reduced reproductive output [30–32], and higher susceptibility to predation or further parasitism due to sickness behaviour [33]. Thus, from an evolutionary perspective, there is a trade-off between benefits and costs of strong and/or long immune defences and associated sickness behaviour, that is controlled and orchestrated by a complex network connecting immune system, endocrine system and nervous system [14, 15, 19, 34, 35].

More recently, we suggested that sickness behaviour becomes maladaptive in systemic chronic inflammatory diseases when not adequately treated, partly because of long-term changes in energy availability of single cells and energy distribution between organs in the body [20, 22, 23, 26]. In summary, sickness behaviour is not an accident of chronic inflammatory diseases but an adaptive program used during immune activation. Unfortunately, this program is switched-on considerably too long, during chronic conditions, sometimes lifelong [25]. In such cases, like chronic inflammatory rheumatic disorders, symptoms of severe fatigue, anhedonia and depression are more frequently observed.

Immune system meets brain

Early reviews demonstrated classical cytokine pathways from the peripherally active immune system to the brain [36, 37]. Cytokines can enter the brain via several pathways: the blood brain barrier is not an iron wall. Besides pathways through the bloodstream, we recognize pathways through sensory afferent nerve fibres. Early experiments showed that the vagus nerve provides a track from the periphery to the brain [38, 39].

Others showed a pathway through the glossopharyngeal nerve that innervates the pharynx [40]. In the gastrointestinal tract, sensory afferents in many parts of the gut are key to the gut-brain axis that also transfers inflammatory signals to the brain [41]. Newer work shows that sensory afferents from joints through spinal pathways transmit peripheral inflammation to the central nervous system [42]. These afferents are one anatomical substrate for joint inflammation-driven changes of brain function.

The platform for signal transmission through afferent nerve fibres is a wonderfully equipped afferent nerve terminal with many receptors that signal inflammation [43]. There are receptors for lipopolysaccharides from bacterial cell walls, for other toll-like receptor ligands, for cytokines, bradykinin, protons (hypoxia produces protons through lactate), neuropeptides such as substance P, neurotrophic growth factors, higher tissue temperature, purines released from dying cells, histamines, prostaglandins, and others [43, 44]. Again, we realize an evolutionarily positively selected program that allows transmission of inflammation and pain to the brain in order to start a ‘take care program’ for the affected tissue.

We can summarize that immune activation can be easily transmitted to the brain. Importantly, peripheral immune activation starts microglia activation in the brain [45], and this phenomenon can be the forerunner of sickness behaviour, including fatigue.

Relevant brain regions and pathways

The localization of the brain areas with different neurotransmitters involved in fatigue and the relevant pathways are shown in Fig. 1 [46–49].

From sensing inflammation to feelings

The awareness of the internal state of the body (i.e. interoception) is central to survival. Peripheral inflammation is sensed, and the immune signals are relayed from the body to specific sub-regions in the brain [50, 51]. For instance, afferent immune signals from the vagus nerve project to the nucleus tractus solitarius and parabrachial nucleus [52]. Then, the signal is relayed to the ventromedial basal nucleus of the thalamus. Then, it goes to...
FIG. 1 The localization of the brain areas with different neurotransmitters involved in fatigue and the relevant pathways.
the posterior insula for primary interoceptive representation. Form here, it goes to the mid-insula for integration of homeostatic conditions (hypothalamus and amygdala) and hedonic conditions (nucleus accumbens and orbitofrontal cortex). Now, it runs to the anterior insula for integration of motivational, social and cognitive conditions (anterior cingulate cortex, ventromedial and dorsolateral prefrontal cortex, subgenual cortex (Fig. 1 shows some locations) [50, 51].

Thus, the insular cortex is an integration hub that receives sensory inputs from all modalities from inside and outside the body, via cortical and subcortical brain areas, serving sensory, emotional, motivational and cognitive functions [53–55]. The anterior insular cortex and anterior cingulate cortex get often jointly activated, suggesting close cooperation. In this teamwork, the anterior insular cortex is the probable site for awareness based on its afferent representation of the ‘feelings from the body’. The anterior cingulate cortex is the probable site for the initiation of behaviours [52]. Remarkably, the insular cortex receives strong neuromodulator input in the form of cholinergic afferents from the basal nucleus, dopaminergic input from the ventral tegmental area, serotonergic input from the raphe nuclei, and noradrenergic input from the locus coeruleus, all related to different forms of fatigue (see next section) [53].

Different types of fatigue and locations in the brain

Central fatigue can be divided into motivational, physical and cognitive fatigue [14, 56]. Different brain areas are involved in the three types of fatigue, that will be explained below (Fig. 2).

Motivational fatigue

Patients express this feeling of fatigue as ‘I do not want to do anything’ fatigue [56]. This fatigue is dominated by decreased wanting or decreased motivation [57, 58], and therefore, it is coined as motivational fatigue [59].

Central in this neural network is the mesolimbic pathway (Fig. 2), consisting of dopamine neurons in the ventral tegmental area projecting to the nucleus accumbens located in the ventral striatum [60, 61]. Under normal conditions, this circuit controls behavioural responses to natural rewards, such as food, sex and social interactions, and is therefore an important determinant of incentive drive [47].

The ventral striatum projects to both orbitofrontal cortex and anterior cingulate cortex, enabling reward and cost valuation [62–64] (Fig. 2). Also, serotonin neurons in the raphe nuclei innervate the same cortical areas [65]. A cost-benefit analysis is made depending on the incoming internal and external environmental stimuli that affects wanting and its frequency, duration and effort [66] (Fig. 2).

Physical fatigue

Patients express this feeling of fatigue as ‘I have difficulties doing physical tasks’ [56]. Therefore, it is coined as physical fatigue [56]. Central in this neural network is the nigrostriatal pathway (Figs 1 and 2), consisting of dopamine neurons in the substantia nigra pars compacta projecting to the putamen located in the dorsal striatum [67]. Under normal conditions, this circuit controls physical activity: the dorsal striatum projects to both globus pallidus pars interna and the subthalamic nucleus, globus pallidus pars externa, enabling respectively ‘GO’ and ‘STOP’ of motor activity [68] (Fig. 2). To what degree the frequency, duration and effort of motor activity is affected depends on the incoming internal and external environmental stimuli [69].

Cognitive fatigue

Patients express this feeling of fatigue as ‘I have difficulties concentrating’ [56]. Often a failure to focus and/or sustain in attentional tasks is observed, that is associated with impaired cognitive performance [70]. Therefore, we call it cognitive fatigue, formerly also known as mental fatigue [56]. Central in this neural network is the mesocortical pathway (Figs 1 and 2), consisting of dopamine neurons located in the ventral tegmental area projecting to the dorsolateral prefrontal cortex [71] and anterior cingulate cortex [72]. Also, noradrenaline neurons located in the locus coeruleus innervate the same cortical areas [73] and the hippocampus [74] (Fig. 2). The hippocampus is needed for novelty gating to detect the change in environmental contextual representation between two perceptions (short-term memory) [74]. The dorsolateral prefrontal cortex is involved in sustained attention, while the anterior cingulate cortex is involved in selective attention [48]. Furthermore, dopamine can reduce the signal-to-noise ratio, whereas noradrenaline can increase signal strength in the processing of sensory stimuli [48, 75]. Depending on the incoming internal stimuli, the ability to concentrate (frequency, duration, effort) is affected by the noradrenergic and dopaminergic system [48, 73, 76].

Pathophysiological mechanisms of inflammation-induced changes in neural chemistry

Inflammation-induced interference with neurotransmitter release

Cytokines like TNF can interfere with secretion of noradrenaline (Fig. 3) from neonatal rat superior cervical ganglia [77]. TNF blocks noradrenaline release under certain experimental conditions [77]. Similarly, TNF can alter cellular functions of sympathetic neurons via modulating ionic conductance, e.g. calcium currents [78]. Others have shown that IL-1β and IL-2 can inhibit noradrenaline release from spleen sympathetic nerve fibres [79, 80]. The influence of cytokines on noradrenaline release was obvious in myenteric plexus or myenteric nerve varicosities in the jejunum. Here, IL-1β together with IL-6 suppressed noradrenaline release [81]. Another inflammatory molecule, nitric oxide, can similarly interfere with noradrenaline release [82]. The question remains whether or not there are similar cytokine influences on neurotransmitter release in the brain.
For example, IL-2 can inhibit dopamine release from rat cultured mesencephalic neurons at high concentrations but potentiate its release at low concentrations [83]. Others have shown IL-2 inhibition of noradrenaline release from hypothalamic tissue slices of rats [84]. A pro-secretory function of IL-2 was discovered for dopamine release in the rat striatum [85]. Moreover, TNF can inhibit noradrenaline release from the isolated rat median eminence [86], and this can be responsible for a diminished release of noradrenaline-dependent corticotropin releasing hormone (CRH) secretion. TNF inhibits noradrenaline release from rat hippocampal brain slices [87]. Furthermore, TNF and other cytokines can directly interfere with pituitary hormone release [88].

**Inflammation-induced increased uptake and breakdown of monoamines in brain**

Inflammatory rheumatic disorders have an increased expression of several proinflammatory cytokines, such as IL-1, IL-6, TNF-α, IL-23 and IL-17 [89]. Inflammation or proinflammatory cytokines can lower serotonin, noradrenaline and dopamine via increase of monoamine transporter (i.e. serotonin, noradrenaline, dopamine transporters) trafficking and function via, among others, p38MAPK- and MEK (MAP-Erk-kinase)-dependent mechanisms [90–94] (Fig. 3). Moreover, another mechanism has been described that can inhibit dopamine release. Inflammation increases kynurenic acid production in astrocytes that can inhibit dopamine release by antagonizing the α7-nicotinic acetylcholine receptor [95].

**Inflammation-induced inhibition of tetrahydrobiopterin (BH4)**

Inflammation can also decrease monoaminergic neurotransmission via the reduction of tetrahydrobiopterin (BH4) (Fig. 3) [96]. This enzymatic cofactor is necessary for some important rate-limiting amino acid monoxygenases. These are phenylalanine hydroxylase, L-tyrosine hydroxylase (TH), and tryptophan hydroxylase that are needed for the conversion of amino acids such as L-phenylalanine to L-tyrosine, L-tyrosine to L-DOPA (levodopa), and L-tryptophan to 5-hydroxytryptophan. L-DOPA and 5-hydroxytryptophan are the forerunner molecules for anti-depressive catecholamines and serotonin, respectively [96–98]. Due to inflammatory and oxidative/nitrosative stress, the cofactor BH4 decreases. In macrophages, IFN-γ triggers high output of reactive oxygen species, which can destroy the oxidation-labile BH4 [97, 98].

Activated T-helper lymphocytes that produce IFN-γ or TNF strongly stimulate the activity of guanosine triphosphate cyclohydrolase I (GTP-CH1) [96]. GTP-CH1 is the rate-limiting enzyme of BH4 biosynthesis from guanosine area or substantia nigra pars compacta; and blue: noradrenaline neurons in locus coeruleus play an important modulatory role in (i) motivational fatigue; (ii) physical fatigue; (iii) cognitive fatigue. The anatomical relations are given in figure1.
triphosphate and the intermediate 7, 8-dihydroneopterin-triphosphate (Fig. 3). In humans, however, IFN-γ stimulates GTP/CH1 enzyme activity in monocyte-derived macrophages, dendritic cells and astrocytes to increase neopterin production at the expense of BH4 formation (Fig. 3) [99, 100]. Thus, inflammation lowers BH4 activity that will ultimately result in decreased levels of noradrenaline, dopamine and serotonin (and melatonin) in the brain (Fig. 3). The above-mentioned changes are very important for the development of all three types of fatigue (Fig. 2).

Inflammation forces tryptophan into the kynurenine route
Proinflammatory cytokines increase both tryptophan 2, 3-dioxygenase in hepatocytes and indoleamine-2, 3-dioxygenase (IDO) activity and shunt tryptophan away from the serotonin route into the kynurenine route (Figs 3 and 4) [101, 102]. Kynurenine, via different routes, is metabolized into either 3-hydroxykynurenine and quinolinic acid in microglia or kynurenic acid in astrocytes [103, 104]. Interestingly, quinolinic acid is an N-Methyl-D-aspartate (NMDA) receptor agonist [104], whereas kynurenic acid is an antagonist at NMDA and α7-nicotinic acetylcholine receptors [104] (Figs 3 and 4). Both 3-hydroxykynurenine and quinolinic acid activate oxidative pathways, which cause mitochondrial dysfunctions and neuroexcitatory/neurodegenerative effects [105, 106]. Remarkably, it has been shown that stress (read glucocorticoids) can enhance tryptophan 2, 3-dioxynase function [105].

Inflammation and glucocorticoids
Glucocorticoid resistance may be the result of impaired glucocorticoid receptor function secondary to chronic exposure to inflammatory cytokines as may occur during chronic medical illness or chronic stress [105, 107]. Long-term glucocorticoid resistance produces allostatic load and may be responsible for cognitive disturbances, but also depression-like symptoms due to a decrease in neuroplasticity [21, 108]. The above-mentioned changes are very important for the development of both cognitive fatigue and motivational fatigue.
Inflammation increases glutamatergic instability in the brain

Oxidative stress may stimulate astrocytes to inhibit glutamate transporters, especially excitatory amino acid transporter 2 located on astrocytes [109–111]. Consequently, an accumulation of glutamate appears based on higher release and reduced reuptake from the synaptic cleft (Fig. 4) [112]. Such increased glutamatergic neurotransmission and increased glutamatergic instability may decrease brain-derived growth factor concentrations and neuroplasticity [113]. The above-mentioned changes are also very important for the development of cognitive fatigue and the decrease in neuroplasticity involved in motivational fatigue.

Acute experimental inflammation and different forms of fatigue

There is a large body of literature describing the effects of an activated immune system on the brain. Much of this evidence originates from studies in healthy volunteers acutely administered with immune stimuli like lipopolysaccharide or vaccination against Salmonella typhi (typhoid vaccination) (see meta-analysis [114]). Some studies in patients showed that IFN-α used as therapy for some cancers and infectious diseases like hepatitis C increase the plasma levels of CRP and proinflammatory cytokines [15, 115–117]. These experiments show specific effects on motivational, physical and/or cognitive fatigue.

A recent meta-analysis of 24 human neuroimaging studies of brain regions and networks associated with this type of acute peripheral inflammation show overlap with known intrinsic brain networks, such as the limbic network, default mode network and ventral attention network, as well as corticostrriatal loops implicated in sensory, emotional, physical, motivational and cognitive functions (Figs 1 and 2) [114].

Although most studies describe the effects of acute inflammation, it clearly shows that inflammation alters brain functioning that facilitates the reorganization of priorities [118]. In motivational terms, inflammation affects internally or externally driven motivational states (for example, maternity care, exploration, food intake, sex) in favor of survival [119]. For instance, lipopolysaccharide-treated lactating mice did not engage in nest building in a 22°C environment, but they built a near perfect nest when exposed to a 6°C environment [119].

Motivational fatigue

In humans, IFN-α therapy reduced motivation and increased anhedonia (loss of pleasure) and fatigue [120–122]. In the first two weeks of therapy especially fatigue, anorexia and pain are prevalent, whereas symptoms of depressed mood, anxiety and cognitive dysfunctions appear later. Inflammation affects neural representations of reward and so-called punishment prediction errors using the ventral striatum and anterior insula. Consequently, potential rewards are less attractive and it may lead to decreased approach motivation, while potential punishments become aversive and may increase avoidance motivation [58, 123, 124].

From an evolutionary point of view this motivational shift, due to lower phasic activity in dopaminergic striatal system [125], may be beneficial in the context of infection when metabolic resources are re-distributed to overcome infection. During chronic inflammation, however, this motivational shift may predispose to developing chronic motivational fatigue similar to major depression [120]. Indeed, inflammation leads to avoidance and to social withdrawal in general. This can be explained by the fact that IFN-α...
therapy reduced the activity of the basal ganglia, and decreased dopamine synthesis/release and ventral striatal responses to reward [121, 128]. Inflammation-induced changes in neuroplasticity may also be involved. IFN-α therapy stimulated motivational fatigue that was predicted by earlier changes in striatal microstructure [127].

Typhoid vaccination increases inflammation that was associated with higher insula activity and fatigue [128]. Furthermore, typhoid vaccination enhanced punishment sensitivity but not reward sensitivity, through distinct actions within the ventral striatum and anterior insula [124, 129].

Physical fatigue
In rodents, inflammation alters the packing, release and reuptake of dopamine in the nigrostriatal system (Fig. 1), that is associated with motor retardation or psychomotor slowing [130]. In particular, animal models of Parkinson’s disease have shown that inflammation affects dopamine neurons in the nigrostriatal pathway and impair motor control [131]. In agreement, peripheral administration of both IL-1 and IL-6 suppressed motor activity [132–134].

In rhesus monkeys, IFN-α administration reduces dopaminergic activity in basal ganglia, including dorsal striatum, which also correlated with decreased locomotor activity [116, 135]. In humans, typhoid vaccination impaired the motor response to stimuli in different specific motor tasks, whereas there was no correlation between subjective ratings of mood or illness symptoms [117]. Furthermore, typhoid vaccination strongly increased circulating IL-6 that was associated with attenuated bilateral reactivity of substantia nigra to stimulus novelty [136].

Cognitive fatigue
In rodents, a growing body of evidence suggests that proinflammatory cytokines IL-1, IL-6 and TNF are involved in the molecular and cellular mechanisms underlying cognition deficits [137–139]. It is a hypothesis that an inflammation-induced decrease in brain-derived growth factor in the hippocampus causes these cognitive deficits. Treatment with the TNF inhibitor infiximab prevented the cognitive impairments and the reduction of hippocampal brain-derived growth factor [140]. Another route that may be involved in inflammation-induced cognitive deficits is the stimulation of the kynurenine pathway that increases the levels of kynurenic acid (Figs 3 and 4). This molecule can also act as α7-nicotinic acetylcholine receptor antagonist and, thereby, produce spatial working memory deficits [141].

In humans, cognitive fatigue or ‘brain fog’ appears in patients suffering from chronic inflammatory diseases characterized by a diminished ability to concentrate, learn and remember [142]. In a recent review, authors presented effects of bacterial endotoxin and hepatitis B vaccination on cognitive function [143]. Acute experimental inflammation caused mixed changes in attention, executive functioning and memory. Disturbed cognitive function was especially related to increased social disconnectedness, reduced perception of emotions, increased avoidance of punishment or loss experiences and increased social disconnectedness [143]. It cannot be excluded that the effects of acute inflammation on cognition are less pronounced in humans because of the relative short duration of inflammation.

Chronic inflammation in rheumatic disorders and fatigue
Unfortunately, in most clinical studies, different forms of fatigue were not always labelled as such, but recent studies suggest that the various forms of fatigue do exist in inflammatory rheumatic disorders: for example, for cognitive fatigue: ‘I have difficulties concentrating’ ([144–148]); physical fatigue: ‘I have difficulties doing physical tasks’ [148–154]; motivational fatigue: ‘I do not want to do anything’ [148, 155–158].

Chronic inflammation in rheumatic disorders does not only affect fatigue but also other symptoms of sickness behaviour. Remarkably, immunosuppressants do not always equally affect these different symptoms. In spondyloarthritic (SpA) patients, TNF inhibitor therapy had a much stronger effect on pain than on fatigue [159]. This is in agreement with findings in psoriatic arthritis patients, where biological disease modifying drugs (certolizumab pegol, secukinumab, ustekinumab) and apremilast had a small effect on fatigue, but a much stronger effect on pain [160]. Similarly, in RA patients both anti-TNF and non-anti TNF biologic treatments led to a small to moderate reduction of fatigue [161].

In rodents with adjuvant-induced arthritis, decreased brain-derived growth factor levels were observed in the hippocampus (–50%) and in the prefrontal cortex (–60%) [162]. In the same animal model, enrichment of microglia in the hippocampus and aberrant insulin-growth factor signalling has been observed that was associated with reduced hippocampal neurogenesis and a smaller hippocampus [163].

In children with juvenile arthritis suffering from chronic inflammation and fatigue, an increased activity of both IDO and GTP-CH1 pathways and a decreased BH4 efficacy were observed (see also Fig. 3) [164]. This can affect neurotransmitter concentrations of serotonin, dopamine and noradrenaline and increased levels of glutamate and quinolinic acid (NMDA-receptor agonist) (Figs 3 and 4) [164]. Similar changes in activity of IDO and GTP-CH1 pathways have been observed in low-grade inflammation in the elderly that was associated with general fatigue and reduced motivation, sleep alterations, reduced appetite and digestive symptoms [165].

In RA patients, functional MRI showed an increase in grey matter content in the basal ganglia, mainly in the nucleus accumbens and caudate nucleus [166]. Others showed that high levels of peripheral inflammation in RA patients were associated with more positive connections between the inferior parietal lobule, medial prefrontal cortex and multiple brain networks, as well as reduced inferior parietal lobule grey matter, and these patterns of connectivity predicted fatigue, pain and cognitive...
Involvement of intrinsic brain networks that play a role in regions affected by acute inflammation, suggesting the brain are in agreement with the earlier reported brain pathogenesis of cognitive fatigue [172]. Tactile thinning in somatosensory areas may lead to the lack of motivation but also distractibility, while the cortical thinning of the secondary somatosensory cortex is associated with decreased functional connectivity both within ventral corticostriatal circuitry (between ventral striatum and ventromedial prefrontal cortex) [179], and within subgenual cingulate cortex and mesolimbic circuitry, that are known for their role in depressive mood and anhedonia [180]. Recently, it has been suggested that, in depression, prolonged dysregulation in tonic dopamine signalling can lead to striatal dysfunction and motivational anhedonia [181].

**Fatigue can persist even after successful treatment of inflammation**

Paradoxically, there is evidence that inflammation is involved in the onset of fatigue, while fatigue can persist even after successful treatment of inflammation in...
rheumatic disorders. Here it is speculated that this difference is caused by an inflammation-induced decline in nerve growth factors (e.g. brain-derived neurotrophic factor [BDNF]), that produce long-term changes in brain morphology, functional connectivity in different neuronal networks and sensitization. Indeed, several studies show that peripheral inflammation lower the concentrations of BDNF, that consequently decreased neuroplasticity [182]. In agreement, in a rat model of adjuvant-induced arthritis, BDNF is significantly reduced in both cortical and hippocampal brain areas [162]. Also, in humans, chronic inflammation or proinflammatory cytokines are known to change striatal microstructure that predicted fatigue [183]. Interestingly, recently it was shown that fatigue was predicted by central sensitization, independently of the presence of pain [184]. Previously, it has also been suggested that altered BDNF levels in fibromyalgia are involved in neuronal plasticity and the central sensitization process [185]. Despite these interesting findings, more research is needed to further investigate the causal role of nerve growth factors (e.g. BDNF) in relation to neuroplasticity, brain morphology, sensitization and functional connectivity in different neuronal networks and fatigue.

**Fibromyalgia and inflammatory rheumatic disorders share similarities in symptoms, including fatigue**

Fibromyalgia is a heterogeneous disorder that more likely develops in women than in men, that is characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory and mood disturbances (e.g. anxiety and/or depression) [186]. Here it is hypothesized that in some patients with fibromyalgia, including fatigue, peripheral inflammation is the driving force, because a diagnosis of endometriosis, RA or IBD (such as Crohn’s disease and ulcerative colitis) are associated with later onset of fibromyalgia [187, 188]. Furthermore, increased levels of proinflammatory cytokines have been observed in patients with endometriosis, RA or IBD [126, 189, 190]. Due to the fundamental differences in the immune systems of females and males, females have a higher prevalence of a number of autoimmune diseases (e.g. RA, IBD), suggesting that gonadal hormones may have a role in this higher prevalence of autoimmunity in women [191]. Indeed, in RA patients, it has been shown that women experience both higher disease activity and more fatigue [192]. In agreement, it has been shown that co-occurrence of endometriosis and fibromyalgia (including fatigue) in women is associated with a high burden of autoimmune disease, anxiety and/or depression, and healthcare resource utilization. The above suggests that it is important to take into account the female factor in the development of fatigue.

**Conclusions**

Together, the present review provides evidence that inflammation distorts neural chemistry, brain function and functional connectivity across a broad range of brain networks. Future studies will need to disentangle how local or global changes in network function, probably due to a widespread disturbed monoamine/glutamate balance in the brains of patients with inflammatory rheumatic disorders contribute to different forms of fatigue.

**Acknowledgements**

S.M.K. was financially supported by The Dutch Arthritis Society (ReumaNederland project 17–1–101).

**Funding:** This study was supported by the following institutions: Utrecht University, Ruhr-Universität Bochum, University Hospital Regensburg. This supplement is supported by a grant from Gilead Sciences, Inc.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**

1. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996;23:1407–17.
2. Jones SD, Koh WH, Steiner A, Garrett SL, Calin A. Fatigue in ankylosing spondylitis: its prevalence and relationship to disease activity, sleep, and other factors. J Rheumatol 1996;23:487–90.
3. Overman CL, Kool MB, Da Silva JA, Geenen R. The prevalence of severe fatigue in rheumatic diseases: an international study. Clin Rheumatol 2016;35:409–15.
4. Lorton D, Lubahn CL, Zutrau AJ, Bellinger DL. Proinflammatory cytokines and sickness behavior in rheumatic diseases. Curr Pharm Des 2008;14:1242–60.
5. Carbotte RM, Denburg SD, Denburg JA. Cognitive deficit associated with rheumatic diseases: neuropsychological perspectives. Arthritis Rheum 1995;38:1363–74.
6. Geenen R, Newman S, Bossema ER, Vriezeolk J, Boelen PA. Psychological interventions for patients with rheumatic diseases and anxiety or depression. Best Pract Res Clin Rheumatol 2012;26:305–19.
7. Edwards RR, Cahalan C, Cahalan C et al. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol 2011;7:216–24.
8. Nerurkar L, Siebert S, McIntees IB, Cavanagh J. Rheumatoid arthritis and depression: an inflammatory perspective. Lancet Psychiatry 2019;6:164–73.
9. Haroon E, Chen X, Li Z. Increased inflammation and brain glutamate define a subtype of depression with decreased regional homogeneity, impaired network integrity, and anhedonia. Transl Psychiatry 2018;8:189.
10. Huyser BA, Parker JC, Thoreson R et al. Predictors of subjective fatigue among individuals with rheumatoid arthritis. Arthritis Rheum 1998;41:2230–7.
11. Primdahl J, Hegelund A, Lorenzen AG et al. The experience of people with rheumatoid arthritis living with fatigue: a qualitative metasynthesis. BMJ Open 2019;9:e024338.
12 Sokoll KB, Hellwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. J Rheumatol 2001;28:1842–6.

13 Stebbings SM, Trehanuj GM, Jenks K, Highton J. Fatigue in patients with spondyloarthropathy associates with disease activity, quality of life and inflammatory bowel symptoms. Clin Rheumatol 2014;33:1467–74.

14 Dantzer R, Heijnen CJ, Kavelaars A, Laye S, Capuron L. The neuroimmune basis of fatigue. Trends Neurosci 2014;37:39–46.

15 Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci 2002;25:154–9.

16 Kluger MJ, Ringler DH, Anver MR. Fever and survival. Science 1975;188:166–8.

17 Hart BL. Biological basis of the behavior of sick animals. Neurosci Biobehav Rev 1988;12:123–37.

18 Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 2007;21:153–60.

19 Dantzer R, O’Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46–56.

20 Straub RH, Besedovsky HO. Integrated evolutionary, immunological, and neuroendocrine framework for the pathogenesis of chronic disabling inflammatory diseases. FASEB J 2003;17:2176–83.

21 Korte SM, Koolhaas JM, Wingfield JC, McEwen BS. The Darwinian concept of stress: benefits of allostatic load and costs of allostatic load and the trade-offs in health and disease. Neurosci Biobehav Rev 2005;29:3–38.

22 Straub RH, Cutolo M, Buttgeriet F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. J Intern Med 2010;267:543–60.

23 Spies CM, Straub RH, Buttgeriet F. Energy metabolism and rheumatic diseases: from cell to organism. Arthritis Res Ther 2012;14:216.

24 Shattuck EC, Muehlenbein MP. Human sickness behavior: ultimate and proximate explanations. Am J Phys Anthropol 2015;157:1–18.

25 Straub RH, Schradin C. Chronic inflammatory systemic diseases: an evolutionary trade-off between acutely beneficial but chronically harmful programs. Evol Med Public Health 2016;2016:37–51.

26 Straub RH. The brain and immune system prompt energy shortage in chronic inflammation and ageing. Nat Rev Rheumatol 2017;13:743–51.

27 Lopes PC, Block P, Konig B. Infection-induced behavioural changes reduce connectivity and the potential for disease spread in wild mice contact networks. Sci Rep 2016;6:31790.

28 Lochmiller RL, Deerenberg C. Trade-offs in evolutionary immunology: just what is the cost of immunity? Oikos 2000;88:87–98.

29 McErlane F, Carrasco R, Kearsley-Fleet L et al. Growth patterns in early juvenile idiopathic arthritis: results from the Childhood Arthritis Prospective Study (CAPS). Semin Arthritis Rheum 2018;48:53–60.

30 Adelman JS, Martin LB. Vertebrate sickness behaviors: adaptive and integrated neuroendocrine immune responses. Integr Comp Biol 2009;49:202–14.

31 Schmid-Hempel P. Variation in immune defence as a question of evolutionary ecology. Proc Biol Sci 2003;270:357–66.

32 Martin LB, Coon CA. Immunology. Infection protection and natural selection. Science 2010;330:602–3.

33 Day JF, Edman JD. The importance of disease induced changes in mammalian body temperature to mosquito blood feeding. Comp Biochem Physiol A Comp Physiol 1984;77:447–52.

34 Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 2016;16:22–34.

35 Dhabhar FS, Malarkey WB, Neri E, McEwen BS. Stress-induced redistribution of immune cells—from barracks to battlefields: a tale of three hormones—Curt Richter Award winner. Psychoneuroendocrinology 2012;37:1345–68.

36 Watkins LR, Maier SF, Goehler LE. Cytokine-to-brain communication: a review & analysis of alternative mechanisms. Life Sci 1995;57:101–26.

37 Besedovsky HO, del Rey A. Immune-neuro-endocrine interactions: facts and hypotheses. Endocr Rev 1996;17:84–102.

38 Bluthe RM, Walter V, Parnet P. Lipopolysaccharide induces sickness behaviour in rats by a vagal mediated mechanism. C R Acad Sci III 1994;317:499–503.

39 Fleshner M, Goehler LE, Hermann J et al. Interleukin-1 beta induced corticosterone elevation and hypothalamic NE depletion is vagally mediated. Brain Res Bull 1995;37:805–10.

40 Romeo HE, Tio DL, Rahman SU, Chiappelli F, Taylor AN. The glossopharyngeal nerve as a novel pathway in immune-to-brain communication: relevance to neuroimmune surveillance of the oral cavity. J Neuroimmunol 2001;115:91–100.

41 Abdel-Haq R, Schlachetzki JCM, Glass CK, Mazmanian SK. Microbiome-microglia connections via the gut-brain axis. J Exp Med 2019;216:41–59.

42 Schaible HG. Noiceptive neurons detect cytokines in arthritis. Arthritis Res Ther 2014;16:470.

43 Schaible HG, Ebersberger A, Natura G. Update on peripheral mechanisms of pain: beyond prostaglandins and cytokines. Arthritis Res Ther 2011;13:210.

44 Pongratz G, Straub RH. Role of peripheral nerve fibres in acute and chronic inflammation in arthritis. Nat Rev Rheumatol 2013;9:117–26.

45 McCusker RH, Kelley KW. Immune-neural connections: how the immune system’s response to infectious agents influences behavior. J Exp Biol 2013;216:84–98.

46 Stahl SM. Stahl’s essential psychopharmacology: neuroscientific basis and practical application. 4th edn. Cambridge, New York: Cambridge University Press, 2013.

47 Schwartz TL, Sachdeva S, Stahl SM. Glutamate neurocircuity: theoretical underpinnings in schizophrenia. Front Pharmacol 2012;3:195.
48 Stahl SM. The prefrontal cortex is out of tune in attention-deficit/hyperactivity disorder. J Clin Psychiatry 2009;70:950–1.
49 Stahl SM. Norepinephrine and dopamine regulate signals and noise in the prefrontal cortex. J Clin Psychiatry 2009;70:617–8.
50 Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 2002;3:655–66.
51 Harshaw C. Interoceptive dysfunction: toward an integrated framework for understanding somatic and affective disturbance in depression. Psychol Bull 2015;141:311–63.
52 Goehler LE, Gaykema RP, Hansen MK et al. Vagal immune-to-brain communication: a visceral chemosensory pathway. Auton Neurosci 2000;85:49–59.
53 Gogolla N. The insular cortex. Curr Biol 2017;27:R580–R6.
54 Castro DC, Berridge KC. Opioid and orexin hedonic hotspots in rat orbitofrontal cortex and insula. Proc Natl Acad Sci USA 2011;108:9821–6.
55 Critchley HD, Harrison NA. Visceral influences on brain and behavior. Neuroimage 2013;77:624–38.
56 Karshikoff B, Sundelin T, Lasselin J. Role of inflammation in human fatigue: relevance of multidimensional assessments and potential neuronal mechanisms. Front Immunol 2017;8:21.
57 Salamone JD, Correa M. Motivational views of reinforcement: implications for understanding the behavioral functions of nucleus accumbens dopamine. Behav Brain Res 2002;137:3–25.
58 Berridge KC. Evolving concepts of emotion and motivation. Front Psychol 2018;9:1647.
59 Muller T, Apps M. Motivational fatigue: a neurocognitive framework for the impact of effortful exertion on subsequent motivation. Neuropsychologia 2019;123:141–51.
60 Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 1998;28:309–69.
61 Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 2016;3:760–73.
62 Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev 2011;35:1219–36.
63 Castro DC, Berridge KC. Opioid and orexin hedonic hotspots in rat orbitofrontal cortex and insula. Proc Natl Acad Sci USA 2011;114:E9125–E34.
64 Walton ME, Bannerman DM, Alterscru K, Rushworth MF. Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. J Neurosci 2003;23:8475–9.
65 Chandler DJ, Lamperski CS, Waterhouse BD. Identification and distribution of projections from monoaminergic and cholinergic nuclei to functionally differentiated subregions of prefrontal cortex. Brain Res 2013;1522:38–58.
66 Kim SI. Neuroscientific model of motivational process. Front Psychol 2013;4:98.
67 Presna L, Giménez-Amaya JM, Parent A, Bernácer J, Cebrián C. The nigrostriatal pathway: axonal collateralization and compartmental specificity. J Neural Transm Suppl 2009;73:49–58.
68 Frank MJ, Seeberger LC, O’Reilly RC. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 2004;306:1940–3.
69 Bubic A, von Cramon DY, Schubotz RI. Motor foundations of higher cognition: similarities and differences in processing regular and violated perceptual sequences of different specificity. Eur J Neurosci 2009;30:2407–14.
70 Holtzer R, Shuman M, Mahoney JR, Lipton R, Vergheese J. Cognitive fatigue defined in the context of attention networks. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2010;18:108–28.
71 Arnsten AF, Wang M, Paspalas CD. Dopamine’s actions in primate prefrontal cortex: challenges for treating cognitive disorders. Pharmacol Rev 2015;67:681–96.
72 Kohler S, Bar KJ, Wagner G. Differential involvement of brainstem noradrenergic and midbrain dopaminergic nuclei in cognitive control. Hum Brain Mapp 2016;37:2305–18.
73 Aston-Jones G, Cohen JD. An integrative theory of locus coerulescent-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 2005;28:403–50.
74 Kitchigina V, Vankov A, Harley C, Sara SJ. Novelty-elicited, noradrenaline-dependent enhancement of excitability in the dentate gyrus. Eur J Neurosci 1997;9:41–7.
75 Ramos BP, Arnsten AF. Adrenergic pharmacology and cognition: focus on the prefrontal cortex. Pharmacol Ther 2007;113:523–36.
76 Bourgeois J, Chelazzi L, Vuilleumier P. How motivation and reward learning modulate selective attention. Prog Brain Res 2016;229:325–42.
77 Soliven B, Albert J. Tumor necrosis factor modulates the inactivation of catecholamine secretion in cultured sympathetic neurons. J Neurochem 1992;58:1073–8.
78 Soliven B, Albert J. Tumor necrosis factor modulates Ca2+ currents in cultured sympathetic neurons. J Neurosci 1992;12:2665–71.
79 Bognar IT, Albrecht SA, Farasaty M et al. Effects of human recombinant interleukins on stimulation-evoked noradrenaline overflow from the rat perfused spleen. Naunyn Schmiedebergs Arch Pharmacol 1994;349:497–502.
80 Bognar IT, Albrecht SA, Farasaty M, Fuder H. Inhibition by interleukin-1 beta of noradrenaline release in rat spleen: involvement of lymphocytes, NO and opioid receptors. Naunyn Schmiedebergs Arch Pharmacol 1995;351:433–8.
81 Ruhl A, Hurst S, Collins SM. Synergism between interleukin-1 beta and 6 on noradrenergic nerves in rat myenteric plexus. Gastroenterology 1994;107:993–1001.
82 Ruhl A, Collins SM. Role of nitric oxide in norepinephrine release from myenteric plexus in vitro and in Trichinella spirals-infected rats. Neurogastroenterol Motil 1997:9:33–9.
83 Alonso R, Chaudieu I, Diorio J et al. Interleukin-2 modulates evoked release of [3H]dopamine in rat cultured mesencephalic cells. J Neurochem 1993;61:1284–90.
84 Lapchak PA, Araujo DM. Interleukin-2 regulates monoamine and opioid peptide release from the hypothalamus. Neuroreport 1993;4:303–6.
Fatigue in inflammatory rheumatic disorders

85 Lapchak PA. A role for interleukin-2 in the regulation of striatal dopaminergic function. Neuroreport 1992;3:165–8.
86 Elenkov IJ, Kovacs K, Duda E, Stark E, Vizi ES. Presynaptic inhibitory effect of TNF-alpha on the release of noradrenaline in isolated median eminence. J Neuroimmunol 1992;41:117–20.
87 Reynolds JL, Ignatowski TA, Gallant S, Spengler RN. Elevation of cortical serotonin: immunologic and neuropsychiatric aspects. Curr Med Chem 2003;10:1581
88 Gaillard RC, Turnill D, Sappino P, Muller AF. Tumor necrosis factor-alpha regulation of norepinephrine release in the brain. Brain Res 2004;1023:112–20.
89 Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokine-induced 1-beta and tumor necrosis factor-alpha activate serotonin transporters. Neuropsychopharmacology 2006;31:2121–31.
90 van Heesch F, Prins J, Konsman JP et al. Lipopolysaccharide increases degradation of central monoamines: an in vivo microdialysis study in the nucleus accumbens and medial prefrontal cortex of mice. Eur J Pharmacol 2014;725:55–63.
91 Korste-Bouw G, van Heesch F, Westphal KGC et al. Bacterial lipopolysaccharide increases serotonin metabolism in both medial prefrontal cortex and nucleus accumbens in male wild type rats, but not in serotonin transporter knockout rats. Pharmaceuticals 2018;11:66.
92 Moron JA, Zakharova I, Ferrer JV et al. Mitogen-activated protein kinase regulates dopamine transporter surface expression and dopamine transport capacity. J Neurosci 2003;23:8480–8.
93 Okuno A, Fukuwatari T, Shibata K. High tryptophan diet reduces extracellular dopamine release via kynurenic acid production in rat striatum. J Neurochem 2011;118:796–805.
94 Werner ER, Werner-Felmayer G, Wachter H. Tetrahydrobiopterin and cytokines. Proc Soc Exp Biol Med 1993;203:1–12.
95 Wirzullte B, Neurauter G, Schorschandek K, Frick B, Fuchs D. Interferon-gamma-induced conversion of tryptophan: immunologic and neuropsychiatric aspects. Curr Med Chem 2003;10:1581–91.
96 Neurauter G, Schorschandek K, Scholl-Burgi S et al. Chronic immune stimulation correlates with reduced phenylalanine turnover. Curr Drug Metab 2008;9:622–7.
97 Schoeden G, Troppmair J, Adolf G, Huber C, Niedervieser A. Interferon-gamma enhances biosynthesis of preproins in peripheral blood mononuclear cells by induction of GTP-cyclohydrolase I activity. J Interferon Res 1986;6:697–703.
100 Fuchs D, Avanzas P, Arroyo-Espiguero R et al. The role of neopterin in atherogenesis and cardiovascular risk assessment. Curr Med Chem 2009;16:4644–53.
101 Badawy AA. The functions and regulation of tryptophan pyrrolase. Life Sci 1977;21:755–68.
102 Taylor MW, Feng GS. Relationship between interferon-gamma, indoleamine 2, 3-dioxygenase, and tryptophan catabolism. FASEB J 2014;19:2516–22.
103 Eddleman M, Mucke L. Molecular profile of reactive astrocytes—implications for their role in neurologic disease. Neuroscience 1993;54:15–36.
104 Schwartz R, Pelliciari R. Manipulation of brain kynurenines: gial targets, neuronal effects, and clinical opportunities. J Pharmocol Exp Ther 2002;303:1–10.
105 Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new ‘5-HT’ hypothesis of depression: cell-mediated immune activation induces indoleamine 2, 3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan metabolites (TRYCATs), both of which contribute to the onset of depression. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:702–21.
106 Sas K, Robotka H, Toldi J, Vecsei L. Mitochondria, metabolic disturbances, oxidative stress and the kynurenine system, with focus on neurodegenerative disorders. J Neurol Sci 2007;257:221–39.
107 Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. Brain Behav Immun 2007:21:9–19.
108 McEwen BS, Wingfield JC. The concept of allostatics in biology and biomedicine. Horm Behav 2003:43:2–15.
109 Okuda S, Nishiyama N, Saito H, Katsuki H. 3-Hydroxykynurenine, an endogenous oxidative stress generator, causes neuronal cell death with apoptotic features and region selectivity. J Neurochem 1998;70:299–307.
110 Anderson CM, Swanson RA. Astrocyte glutamate transport: review of properties, regulation, and physiological functions. Glia 2000;32:1–14.
111 Danbolt NC. Glutamate uptake. Prog Neurobiol 2001;65:1–105.
112 Volterra A, Trotti D, Tromba C, Floridi S, Racagni G. Glutamate uptake inhibition by oxygen free radicals in rat cortical astrocytes. J Neurosci 1994;14:2924–32.
113 McEwen BS, Bowles NP, Gray JD et al. Mechanisms of stress in the brain. Nat Neurosci 2015;18:1353–63.
114 Kraynak TE, Marsland AL, Wager TD, Gianaro PJ. Functional neuroanatomy of peripheral inflammatory physiology: a meta-analysis of human neuroimaging studies. Neuronci Biobehav Rev 2018;94:76–92.
115 Capuron L, Raison CL, Musselman DL et al. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. Am J Psychiatry 2003;160:1342–5.
116 Felger JC, Alagie O, Hu F et al. Effects of interferon-alpha on rhesus monkeys: a nonhuman primate model of cytokine-induced depression. Biol Psychiatry 2007;62:1324–33.
S. Mechiel Korte and Rainer H. Straub

117 Brydon L, Harrison NA, Walker C, Steptoe A, Critchley HD. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. Biol Psychiatry 2008;63:1022–9.

118 Larson SJ. Behavioral and motivational effects of immune-system activation. J Gen Psychol 2002;129:401–14.

119 Aubert A, Goodall G, Dantzer R, Gheusi G. Differential effects of lipopolysaccharide on pup retrieving and nest building in lactating mice. Brain Behav Immun 1997;11:107–18.

120 Capuron L, Gumnick JF, Musselman DL et al. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 2002;26:643–52.

121 Capuron L, Pagnoni G, Drake DF et al. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. Arch Gen Psychiatry 2012;69:1044–53.

122 Felger JC, Li L, Marvar PJ et al. Tyrosine metabolism during interferon-alpha administration: association with fatigue and CSF dopamine concentrations. Brain Behav Immun 2013;31:153–60.

123 Vichaya EG, Dantzer R. Inflammation-induced motivational changes: perspective gained by evaluating positive and negative valence systems. Curr Opin Behav Sci 2018;22:90–5.

124 Harrison NA, Voon V, Cercignani M et al. A neurocomputational account of how inflammation enhances sensitivity to punishments versus rewards. Biol Psychiatry 2016;80:73–81.

125 Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol 1998;80:1–27.

126 Eisenberger NI, Berkman ET, Inagaki TK et al. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol Psychiatry 2010;68:748–54.

127 Dowell NG, Cooper EA, Tibble J et al. Acute changes in striatal microstructure predict the development of interferon-alpha induced fatigue. Biol Psychiatry 2016;79:320–8.

128 Harrison NA, Cooper E, Dowell NG et al. Quantitative magnetization transfer imaging as a biomarker for effects of systemic inflammation on the brain. Biol Psychiatry 2015;78:49–57.

129 Felger JC. The role of dopamine in inflammation-associated depression: mechanisms and therapeutic implications. Curr Top Behav Neurosci 2017;31:199–219.

130 Felger JC, Treadway MT. Inflammation effects on motivation and motor activity: role of dopamine. Neuropsychopharmacology 2017;42:216–41.

131 Duty S, Jenner P. Animal models of Parkinson’s disease: a source of novel treatments and clues to the cause of the disease. Br J Pharmacol 2011;164:1357–91.

132 Bonsall DR, Kim H, Tocci C et al. Suppression of locomotor activity in female C57Bl/6J mice treated with interleukin-1beta: investigating a method for the study of fatigue in laboratory animals. PLoS One 2015;10:e0140678.

133 Harden LM, du Plessis I, Poole S, Laburn HP. Interleukin-6 and leptin mediate lipopolysaccharide-induced fever and sickness behavior. Physiol Behav 2006;89:146–55.

134 Bluthé RM, Michaud B, Poli V, Dantzer R. Role of IL-6 in cytokine-induced sickness behavior: a study with IL-6 deficient mice. Physiol Behav 2000;70:367–73.

135 Felger JC, Miller AH. Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. Front Neuroendocrinol 2012;33:315–27.

136 Harrison NA, Cercignani M, Voon V, Critchley HD. Effects of inflammation on hippocampus and substantia nigra responses to novelty in healthy human participants. Neuropsychopharmacology 2015;40:831–8.

137 Pickering M, O’Connor JJ. Pro-inflammatory cytokines and their effects in the dentate gyrus. Prog Brain Res 2007;163:339–54.

138 Viviani B, Gardoni F, Marinovich M. Cytokines and neuronal ion channels in health and disease. Int Rev Neurobiol 2007;82:247–63.

139 McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. Neurosci Biobehav Rev 2009;33:355–66.

140 Şahin TD, Karson A, Balci F et al. TNF-alpha inhibition prevents cognitive decline and maintains hippocampal BDNF levels in the unpredictable chronic mild stress rat model of depression. Behav Brain Res 2015;292:233–40.

141 Chess AC, Simoni MK, Alling TE, Bucci DJ. Elevations of endogenous kynurenic acid produce spatial working memory deficits. Schizophr Bull 2007;33:797–804.

142 Theoharides TC, Stewart JM, Hatzigelaki E, Kolaitis G. Brain “fog,” inflammation and obesity: key aspects of neuropsychiatric disorders improved by luteolin. Front Neurosci 2015;9:225.

143 Bollen J, Trick L, Llewellyn D, Dickens C. The effects of acute inflammation on cognitive functioning and emotional processing in humans: a systematic review of experimental studies. J Psychosom Res 2017;94:47–55.

144 Duzova A, Bakkaloglu A. Central nervous system involvement in pediatric rheumatic diseases: current concepts in treatment. Curr Pharm Des 2008;14:1295–301.

145 Dima A, Groseanu L, Balanescu A et al. Cognitive dysfunctions in connective tissue diseases. Ann Rheum Dis 2017;76:THU0606.

146 Petersen LE, Baptista TSA, Molina JK et al. Cognitive impairment in rheumatoid arthritis: role of lymphocyte subsets, cytokines and neurotrophic factors. Clin Rheumatol 2018;37:1171–81.

147 Katchamart W, Narongroeknawin P, Phutthinart N et al. Disease activity is associated with cognitive impairment in patients with rheumatoid arthritis. Clin Rheumatol 2019;38:1851–6.

148 Hartkamp A, Geenens R, Bijl M et al. Serum cytokine levels related to multiple dimensions of fatigue in patients with primary Sjogren’s syndrome. Ann Rheum Dis 2004;63:1335–7.

149 Godaert GL, Hartkamp A, Geenens R et al. Fatigue in daily life in patients with primary Sjogren’s syndrome and
Fatigue in inflammatory rheumatic disorders

systemic lupus erythematosus. Ann N Y Acad Sci 2002;966:320–6.
150 Al Dhanhani AM, Gignac MA, Beaton DE, Su J, Fortin PR. Work factors are associated with workplace activity limitations in systemic lupus erythematosus. Rheumatology 2014;53:2044–52.
151 Dailey DL, Keffala VJ, Stuka KA. Do cognitive and physical fatigue tasks enhance pain, cognitive fatigue, and physical fatigue in people with fibromyalgia? Arthritis Care Res 2015;67:288–96.
152 Hammer NM, Midtgaaard J, Hetland ML, Krogh NS, Esbensen BA. Physical activity behaviour in men with inflammatory joint disease: a cross-sectional register-based study. Rheumatology 2018;57:803–12.
153 Gok K, Erol K, Cengiz G, Özgöçmen S. Comparison of level of fatigue and disease correlates in patients with rheumatoid arthritis and systemic sclerosis. Arch Rheumatol 2018;33:316–21.
154 Suh CH, Jung JY, Oh H, Boo S. Evaluation of factors affecting the levels of physical activity in patients with rheumatoid arthritis: a cross-sectional study. Clin Rheumatol 2019;38:2483–91.
155 Sturgeon JA, Finan PH, Zautra AJ. Affective disturbance in rheumatoid arthritis: psychological and disease-related pathways. Nat Rev Rheumatol 2016;12:532–42.
156 Kiltz U, Essers I, Hiligsmann M et al. Which aspects of health are most important for patients with spondyloarthritis? A Best Worst Scaling based on the ASAS Health Index. Rheumatology 2016;55:1771–6.
157 Sun Y, Wang D, Salvador G et al. The effects of interleukin-6 neutralizing antibodies on symptoms of depressed mood and anhedonia in patients with rheumatoid arthritis and multicentric Castleman’s disease. Brain Behav Immun 2017;66:156–64.
158 Lee Y, Subramaniampillai M, Brietzke E et al. Anti-cytokine agents for anhedonia: targeting inflammation and the immune system to treat dimensional disturbances in depression. Ther Adv Psychopharmacol 2018;8:397–44.
159 Wu Q, Inman RD, Davis KD. Tumor necrosis factor inhibitor therapy in ankylosing spondylitis: differential effects on pain and fatigue and brain correlates. Pain 2015;156:297–304.
160 Reygaerts T, Mitrovic S, Fautrel B, Gossec L. Effect of biologics on fatigue in psoriatic arthritis: a systematic literature review with meta-analysis. Joint Bone Spine 2018;85:405–10.
161 Almeida C, Choy EH, Hewlett S et al. Biologic interventions for fatigue in rheumatoid arthritis. Cochrane Database Syst Rev 2016;6:CD008334.
162 Pedard M, Demougeot C, Prati C, Marie C. Brain-derived neurotrophic factor in adjuvant-induced arthritis in rats. Relationship with inflammation and endothelial dysfunction. Prog Neuropsychopharmacol Biol Psychiatry 2018;82:249–54.
163 Andersson KME, Wasen C, Juzokaitė L et al. Inflammation in the hippocampus affects IGF1 receptor signaling and contributes to neurological sequelae in rheumatoid arthritis. Proc Natl Acad Sci USA 2018;115:E12063–E72.
164 Korte-Bouws GAH, Albers E, Voskamp M et al. Juvenile arthritis patients suffering from chronic inflammation have increased activity of both IDO and GTP-CH1 pathways but decreased BH4 efficacy: implications for well-being, including fatigue, cognitive impairment, anxiety, and depression. Pharmaceuticals 2019;12:9.
165 Capuron L, Schroecksnadel S, Feart C et al. Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. Biol Psychiatry 2011;70:175–82.
166 Wartolowska K, Hough MG, Jenkinson M et al. Structural changes of the brain in rheumatoid arthritis. Arthritis Rheum 2012;64:371–9.
167 Schrepf A, Kaplan CM, Ichesco E et al. A multi-modal MRI study of the central response to inflammation in rheumatoid arthritis. Nat Commun 2018;9:2243.
168 Sergeeva M, Rech J, Schett G, Hess A. Response to peripheral immune stimulation within the brain: magnetic resonance imaging perspective of treatment success. Arthritis Res Ther 2015;17:268.
169 Irwin MR, Olmstead R, Carrillo C et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep 2012;35:537–43.
170 Kavanaugh A, Hellwell P, Ritchlin CT. Psoriatic arthritis and burden of disease: patient perspectives from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) Survey. Rheumatol Ther 2016;3:91–102.
171 Krishnadass R, Nicol A, Sassarini J et al. Circulating tumour necrosis factor is highly correlated with brainstem serotonin transporter availability in humans. Brain Behav Immun 2016;51:29–38.
172 Wu Q, Inman RD, Davis KD. Fatigue in ankylosing spondylitis is associated with the brain networks of sensory salience and attention. Arthritis Rheumatol 2014;66:295–303.
173 Tolentino JC, Schmidt SL. DSM-5 criteria and depression severity: implications for clinical practice. Front Psychiatry 2018;9:450.
174 Strawbridge R, Arnone D, Danese A et al. Inflammation and clinical response to treatment in depression: a meta-analysis. Eur Neuropsychopharmacol 2015;25:1532–43.
175 Majer M, Welberg LA, Capuron L et al. IFN-alpha-induced motor slowing is associated with increased depression and fatigue in patients with chronic hepatitis C. Brain Behav Immun 2008;22:870–80.
176 Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology 2013;52:2136–48.
177 Varan Ö, Babaoglu H, Göker B. Associations between depressive disorders and inflammatory rheumatic diseases. Curr Top Med Chem 2018;18:1395–401.
178 Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol Psychiatry 2018;23:335–43.
179 Felger JC, Li Z, Haroon E et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol Psychiatry 2016;21:1358–65.

180 Harrison NA, Brydon L, Walker C et al. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry 2009;66:407–14.

181 Szczypinski JJ, Gola M. Dopamine dysregulation hypothesis: the common basis for motivational anhedonia in major depressive disorder and schizophrenia? Rev Neurosci 2018;29:727–44.

182 Calabrese F, Rossetti AC, Racagni G et al. Brain-derived neurotrophic factor: a bridge between inflammation and neuroplasticity. Front Cell Neurosci 2014;8:430.

183 Dowell NG, Bouyagoub S, Tibble J et al. Interferon-alpha-induced changes in NODDI predispose to the development of fatigue. Neuroscience 2019;403:111–7.

184 Druce KL, McBeth J. Central sensitization predicts greater fatigue independently of musculoskeletal pain. Rheumatology 2019.

185 Nugraha B, Karst M, Engeli S, Gutenbrunner C. Brain-derived neurotrophic factor and exercise in fibromyalgia syndrome patients: a mini review. Rheumatol Int 2012;32:2593–9.

186 Clauw DJ. Fibromyalgia and related conditions. Mayo Clin Proc 2015;90:680–92.

187 Larrosa Pardo F, Bondesson E, Schelin MEC, Jöud A. A diagnosis of rheumatoid arthritis, endometriosis or IBD is associated with later onset of fibromyalgia and chronic widespread pain. Eur J Pain 2019;23:1563–73.

188 Wolfe F, Hauser W, Hassett AL, Katz RS, Walitt BT. The development of fibromyalgia-I: examination of rates and predictors in patients with rheumatoid arthritis (RA). Pain 2011;152:291–9.

189 Eisenberg VH, Zolli M, Soriano D. Is there an association between autoimmunity and endometriosis? Autoimmun Rev 2012;11:806–14.

190 Beutler BA. The role of tumor necrosis factor in health and disease. J Rheumatol Suppl 1999;57:16–21.

191 Straub RH. The complex role of estrogens in inflammation. Endocr Rev 2007;28:521–74.

192 Sokka T, Toloza S, Cutolo M et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther 2009;11:R7.