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Fatigue in inflammatory rheumatic disorders: pathophysiological mechanisms

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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

Rheumatology key messages

- Inflammation can produce different forms of fatigue in chronic inflammatory diseases (CIDs).
- In CIDs, inflammation negatively affects neurotransmitter functioning in various areas in the CNS.
- Inflammation in CIDs alters the brain, leading to an overlap in fatigue, pain and depression.

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

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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.

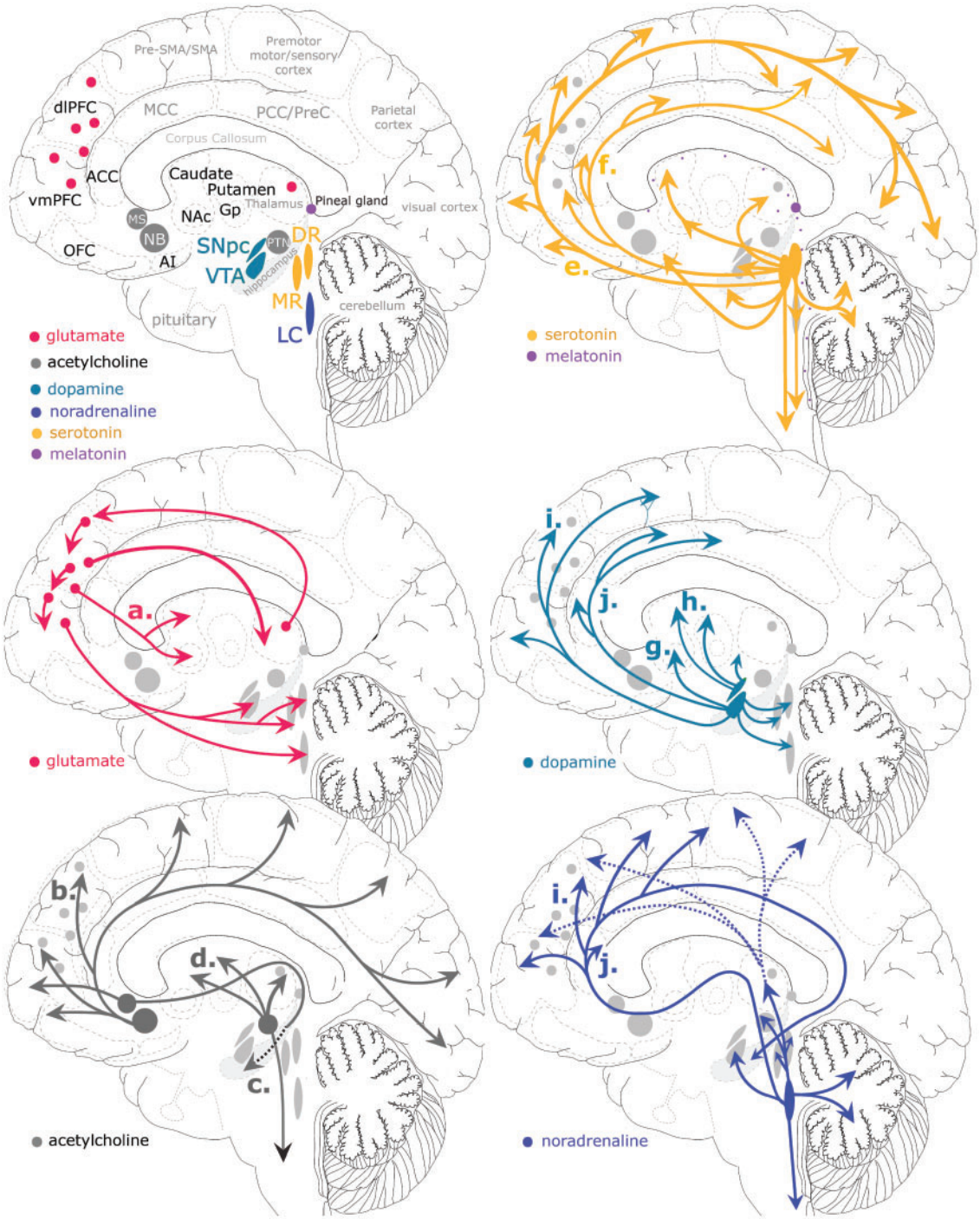
Relevant brain regions and pathways

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



Red: glutamate neurons in dlPFC, vmPFC. Grey: acetylcholine neurons in the MS, NB, PTN. Green-blue: dopamine neurons in VTA, SNpc. Yellow: serotonin neurons in DR, MR. Purple: melatonin pinealocyte in the pineal gland. Blue: noradrenaline neurons, LC. (**a**) Corticostriatal glutamatergic projection. (**b, c**) Cholinergic projections to prefrontal cortex/hippocampus. (**d**) Cholinergic projection to dorsal striatum. (**e, f**) Serotonergic projections to prefrontal cortex, OFC, ACC. (**g**) Dopaminergic projection from VTA to nucleus accumbens (mesolimbic pathway). (**h**) Dopaminergic projection from SNpc to dorsal striatum (nigrostriatal pathway). (**i, j**) (green-blue) Dopaminergic projection from VTA to cortex (mesocortical pathway). (**i, j**) (blue) Noradrenergic projection from LC to dlPFC and ACC. dlPFC: dorsolateral prefrontal cortex; vmPFC: ventromedial prefrontal cortex; MS: medial septal nucleus; NB: nucleus basalis of Meynert; PTN: pontomesencephalotegmental nuclei; VTA: ventral tegmental area; SNpc: substantia nigra pars compacta; DR: dorsal raphe nucleus; MR: median raphe nucleus; LC: locus coeruleus; OFC: orbitofrontal cortex; ACC: anterior cingulate cortex.

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

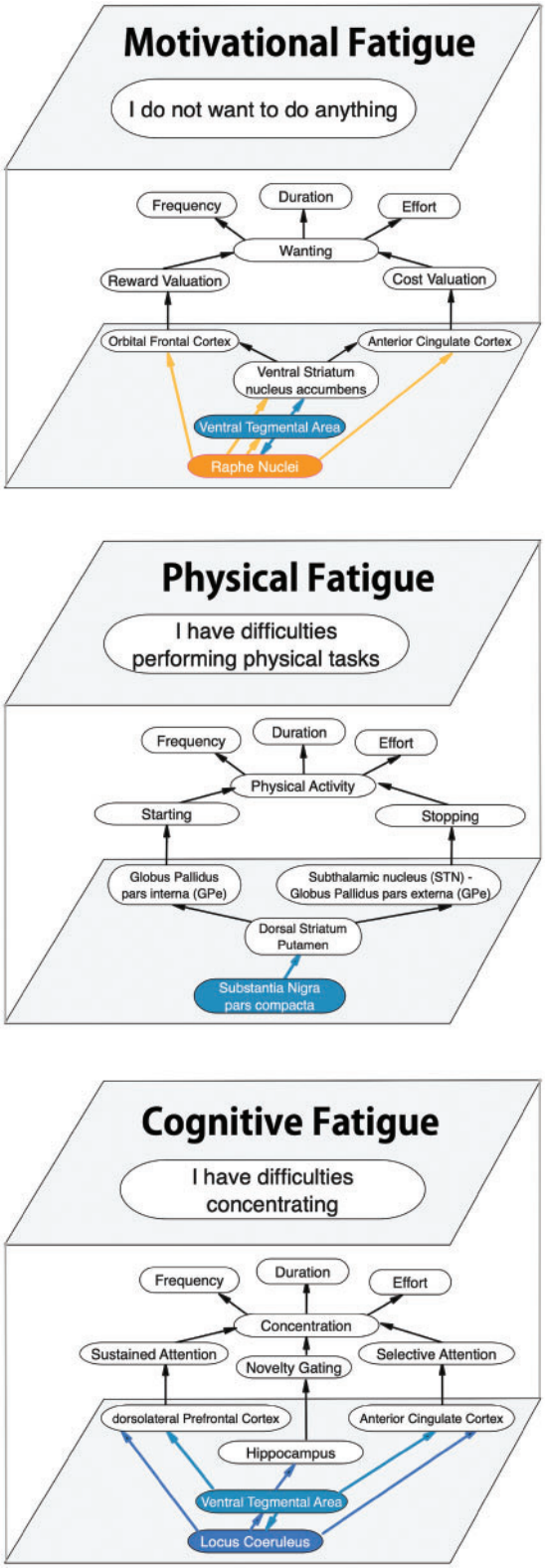
Patients express this feeling of fatigue as 'I have difficulties concentrating' [56]. Often a failure to focus and/or sustain in attentional tasks is observed, that is associated with impaired cognitive performance [70]. Therefore, we call it cognitive fatigue, formerly also known as mental fatigue [56]. 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.

FIG. 2 The different types of fatigue in chronic inflammation



Brain monoamines (orange: serotonin neurons in raphe nuclei; green-blue: dopamine neurons in ventral tegmental 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.

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

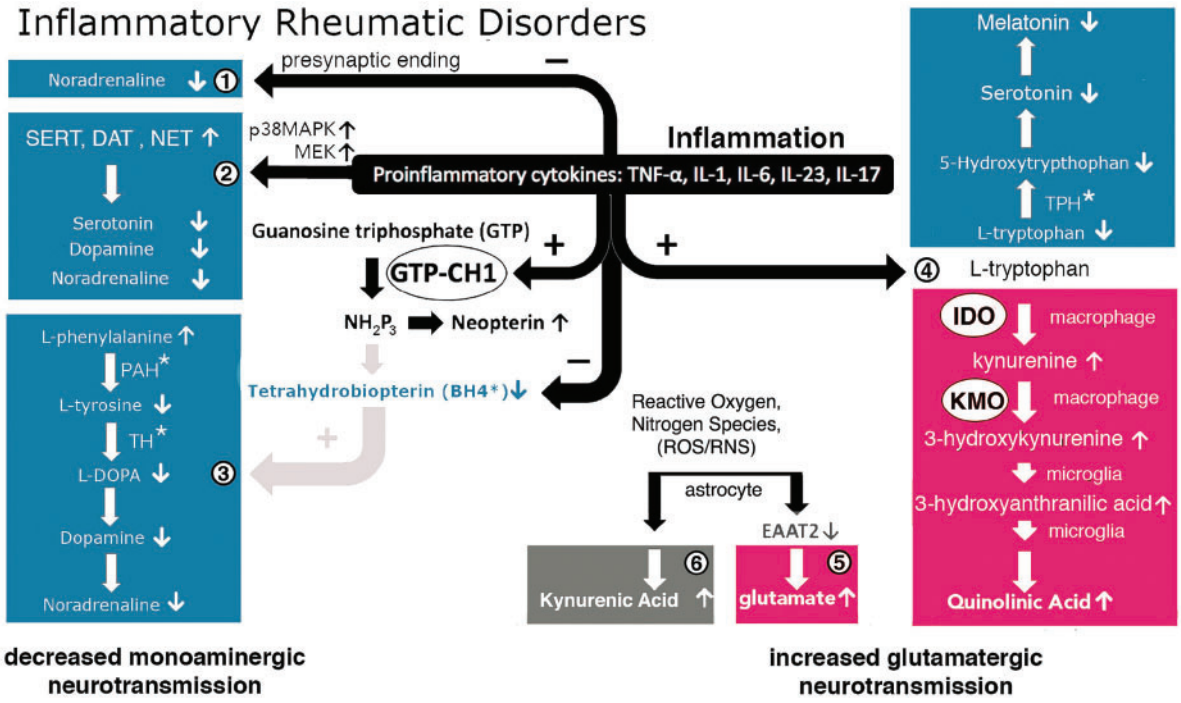
Inflammatory rheumatic disorders have an increased expression of several proinflammatory cytokines, such as IL-1, IL-6, TNF-α, IL-23 and IL-17 [89]. Inflammation or proinflammatory cytokines can lower serotonin, noradrenaline and dopamine via increase of monoamine transporter (i.e. serotonin, noradrenaline, 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 monooxygenases. 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

FIG. 3 Pathophysiological mechanisms how inflammation changes brain chemistry



(1) Inhibition of noradrenaline release by cytokines. **(2)** Increased uptake of monamines into the nerve ending reduces neurotransmitters in the synaptic cleft. Monamine transporters are activated by cytokines. **(3)** Changes in phenylalanine hydroxylase and tyrosine hydroxylase (TH) reduce catecholamine synthesis. **(4)** Changes in tryptophan metabolism lead to reduced serotonin through inhibition of TPH, through activation of IDO, and through activation of KMO. **(5)** Reactive oxygen and nitrogen species inhibit glutamate transporters, especially EAAT2 on astrocytes. Consequently, glutamate increases in the synaptic cleft. **(6)** Reactive oxygen/nitrogen species also increase kynurenic acid from astrocytes. Finally, cytokines stimulate activity of GTP-CH1 to increase neopterin but to decrease BH4. Because BH4 is important for generation of monamines, the lack of BH4 supports fatigue and depression. SERT: serotonin transporter; DAT: dopamine transporter; NET: noradrenaline transporter; TPH: tryptophan hydroxylase; IDO: indoleamine-2, 3-dioxygenase; KMO: kynurenine-3-monooxygenase; EAAT2: excitatory amino acid transporter 2; GTP-CH1: guanosine triphosphate cyclohydrolase I; BH4: tetrahydrobiopterin.

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).

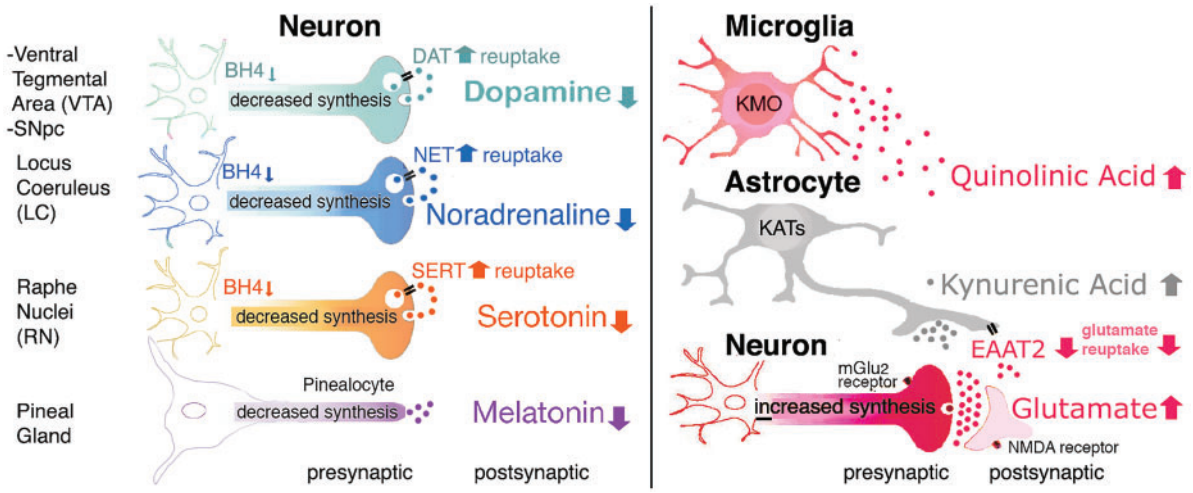
Inflammation forces tryptophan into the kynurenine route

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-dioxygenase 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.

FIG. 4 Inflammation-induced changes in neurotransmission in different areas and different cell types



mGlu2 receptor, metabotropic glutamate receptor 2 (autoreceptor for glutamate, that upon activation, inhibits the emptying of vesicular contents at the presynaptic terminal of glutamatergic neurons). SERT: serotonin transporter; DAT: dopamine transporter; NET: noradrenaline transporter.

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 corticostriatal 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 favour 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 dysfunction 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, 126]. 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 infliximab 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 spondyloarthritis (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

dysfunction [167]. In addition, TNF inhibitor therapy decreased MRI bold activity in thalamus, in primary and secondary somatosensory cortices that were involved in pain, but also decreased MRI activity in cingulate and insular cortex that were responsible for affective-motivational fatigue [168]. We cannot exclude, however, that fatigue−associated structures are also influenced by inflammation-induced phenomena such as sleep disturbance, depression, loss of mobility, or others, which reflects the complexity of fatigue research [169].

Psoriatic arthritis patients suffer from different disease symptoms such as obesity (BMI $>$ 30) in 33.6% and depression 27.7% [170]. Remarkably, TNF inhibiting therapy in psoriasis and psoriatic arthritis patients was associated with a significant reduction in serotonin transporter availability [171]. This may explain the higher incidence of depression in psoriatic arthritis.

In SpA patients treated with TNF inhibitor therapy, 60% of the SpA patients had significant relief of pain, whereas only 22% of patients had significant relief of both pain and fatigue [159]. Functional MRI clearly showed the involvement of different brain areas in pain reduction and fatigue reduction. Pain intensity reduction was associated with cortical thinning of the secondary somatosensory cortex [159]. In contrast, fatigue reduction correlated with cortical thinning of the insula, primary sensory cortex and inferior parietal sulcus, and superior temporal polysensory areas. These findings indicate different brain mechanisms in pain and fatigue [159].

Another study of the same investigators showed that individual fatigue scores were negatively correlated with the amount of grey matter in areas of the dorsal and ventral attention network, the somatosensory cortices and the caudate nucleus, but were positively correlated with grey matter within the executive control network and putamen (Fig. 1) [172]. Moreover, in patients with high fatigue scores, the functional MRI data indicated decreased white matter tract integrity in the tracts connecting the different networks [172].

This indicates that fatigue in SpA involves sensory salience and attention brain networks and TNF inhibitor therapy produces changes in brain areas implicated in motor, affective/motivational, and cognitive functions. It seems that salience networks or the underlying white matter tracts produce symptoms associated with fatigue, such as lack of motivation but also distractibility, while the cortical thinning in somatosensory areas may lead to the pathogenesis of cognitive fatigue [172].

The above-described effects of chronic inflammation on the brain are in agreement with the earlier reported brain regions affected by acute inflammation, suggesting the involvement of intrinsic brain networks that play a role in motivational, cognitive and physical fatigue.

Difference between depression and fatigue

From a practitioner's perspective it is important to make a difference between depression and fatigue, because depression can be a life-threatening disorder and medical treatment is often possible and necessary, whereas severe fatigue in itself is not life-threatening; however, it greatly lowers the quality of life. Remarkably, fatigue can be a symptom of a depression. Unfortunately, there are no proven effective therapies to combat severe fatigue. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is often used to make a diagnosis of major depressive disorder, including severe depression [173]. Accordingly, a depressed individual must be experiencing at least one of the symptoms, either feeling sad or having a depressed mood, or loss of interest or pleasure (i.e. anhedonia) in all, or almost all activities once enjoyed, both are experienced most of the day, nearly every day and during at least a 2-week period. In addition, people with depression must have five or more other symptoms in the same period, such as: fatigue or loss of energy; difficulty thinking, concentrating or making decisions; a slowing down of thought; a reduction of physical movements (observable by others) or restlessness; sleeping more or less; a change in appetite or weight loss or gain unrelated to dieting; feelings of worthlessness or excessive or inappropriate guilt; recurrent thoughts of death or suicide, or suicide attempt.

The strength and main purpose of the DSM-5 is that can be used to make the correct diagnosis of mental disorders, the weakness of the DSM-5 is that it is not based on differences in pathophysiological mechanisms. Here it is hypothesized that there is an overlap between the mechanisms underlying some of the symptoms of depression and the different forms of fatigue: e.g. anhedonia:motivational fatigue; difficulty thinking and concentrating: cognitive fatigue; and reduction of physical movements: physical fatigue. This does not come as a surprise because there is increasing evidence that a significant proportion of people with depression also have increased levels of inflammation [171, 174] and vice versa, that proinflammatory cytokines can cause depression [175]. It is therefore not surprising that in people with rheumatic inflammatory diseases there is an increased risk of getting a depression ([176, 177], and depressive symptoms may significantly improve by anti-cytokine [178]. Previously, it has been shown that inflammation 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.

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