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OPINION

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Central pathways causing fatigue in neuro-inflammatory and autoimmune illnesses

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Abstract

Background: The genesis of severe fatigue and disability in people following acute pathogen invasion involves the activation of Toll-like receptors followed by the upregulation of proinflammatory cytokines and the activation of microglia and astrocytes. Many patients suffering from neuroinflammatory and autoimmune diseases, such as multiple sclerosis, Parkinson's disease and systemic lupus erythematosus, also commonly suffer from severe disabling fatigue. Such patients also present with chronic peripheral immune activation and systemic inflammation in the guise of elevated proinflammatory cytokines, oxidative stress and activated Toll-like receptors. This is also true of many patients presenting with severe, apparently idiopathic, fatigue accompanied by profound levels of physical and cognitive disability often afforded the non-specific diagnosis of chronic fatigue syndrome.

Discussion: Multiple lines of evidence demonstrate a positive association between the degree of peripheral immune activation, inflammation and oxidative stress, gray matter atrophy, glucose hypometabolism and cerebral hypoperfusion in illness, such as multiple sclerosis, Parkinson's disease and chronic fatigue syndrome. Most, if not all, of these abnormalities can be explained by a reduction in the numbers and function of astrocytes secondary to peripheral immune activation and inflammation. This is also true of the widespread mitochondrial dysfunction seen in otherwise normal tissue in neuroinflammatory, neurodegenerative and autoimmune diseases and in many patients with disabling, apparently idiopathic, fatigue. Given the strong association between peripheral immune activation and neuroinflammation with the genesis of fatigue the latter group of patients should be examined using FLAIR magnetic resonance imaging (MRI) and tested for the presence of peripheral immune activation.

Summary: It is concluded that peripheral inflammation and immune activation, together with the subsequent activation of glial cells and mitochondrial damage, likely account for the severe levels of intractable fatigue and disability seen in many patients with neuroimmune and autoimmune diseases. This would also appear to be the case for many patients afforded a diagnosis of Chronic Fatigue Syndrome.

Keywords: Immune, Inflammation, Oxidative stress, Toll-like receptor, Fatigue, Mitochondria, Multiple sclerosis, Chronic fatigue syndrome, Parkinson's disease

Background

There is copious evidence establishing the causative role of peripheral immune activation and inflammation, evidenced by elevated levels of proinflammatory cytokines in the genesis of debilitating fatigue in neuro-inflammatory, autoimmune and inflammatory disorders [1,2]. Activation of pathogen recognition receptors by pathogen associated

molecular patterns leads to the production of nuclear factor NF-kappaB and subsequent production of proinflammatory cytokines by the myeloid differentiation primary response gene (88) (MYD88), which is a universal adapter protein that is used by almost all Toll-like receptors (TLRs) in dependent and independent pathways [3-5]. Systemic inflammatory stimuli, resulting from the presence of proinflammatory cytokines in the peripheral circulation, enter the brain via a number of routes [1,6] activating microglia and astrocytes inducing the production of proinflammatory cytokines and other neurotoxins leading to an environment of neuroinflammation [7,8]. This sequence of events ultimately underpins the

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genesis of fatigue and other signs and symptoms associated with acute pathogen invasion [1,9,10]. Many people suffering from a range of neuroimmune and autoimmune diseases also suffer from debilitating or intractable fatigue.

The existence of chronically activated immune and inflammatory pathways in the periphery and their causative role in the genesis of neuroinflammation has been established in a range of neuroinflammatory and neurodegenerative diseases, such as multiple sclerosis, Alzheimer's and Parkinson's disease [11-16]. Many individuals with neuroinflammatory and neurodegenerative diseases also suffer from fatigue. For example, upwards of 80% of multiple sclerosis patients suffer from fatigue [17]. A study by Beiske and Svensson reported that between 37% and 57% of patients with Parkinson's disease also experience incapacitating fatigue [18]. Fatigue is one of the characteristics of major depression [19,20]. Chronic systemic inflammation and the presence of activated microglia are also found in patients with major depression [19-22]. Chronic systemic inflammation and immune activation is also an invariant finding in many patients diagnosed with chronic fatigue syndrome (CFS) even without evidence of increased pathogen load [17].

Severe chronic fatigue is also experienced by many people with an autoimmune disease. Thus, upwards of 67% of people with Sjogren's syndrome [23], 76% of patients with systemic lupus erythematosus (SLE) [24] and 70% of people with rheumatoid arthritis [25] suffer incapacitating levels of fatigue. Peripheral systemic inflammation and immune activation, as evidenced by elevated levels of proinflammatory cytokines and other inflammatory mediators, is seen in patients with rheumatoid arthritis [26,27], SLE [28,29] and Sjogren's syndrome [30,31]. It is interesting to note that neurological sequelae are seen in up to 80% of patients with SLE and 70% of patients with primary Sjögren's syndrome [32,33]. In addition, the presence of neuroinflammation, in the shape of activated microglia, has been confirmed in patients with SLE [34]. Neurological complications are also commonplace in patients with rheumatoid arthritis [35].

The question arises as to the factors involved in creating a chronically activated immune system in these patients. While there is some evidence linking viral infections to the development of multiple sclerosis [36,37], the situation in Parkinson's disease is different, where there is considerable evidence suggesting environmental toxins in the etiopathogenesis of the illness [38]. One of the key drivers in the development of chronic immune activation in the absence of bacteria or virus infection is the development of chronic inflammation as evidenced by elevated levels of cytokines and oxidative and nitrosative stress (O and NS) and characterized by activated NF- κ B [6,39]. Indeed, the production of proinflammatory cytokines and other inflammatory molecules by macrophages

and other sentinel cells, even in the absence of pathogen invasion, and the subsequent activation of NF- κ B are early events in the genesis of chronic inflammation [40,41]. Activation of this transcription factor leads to the upregulation of cytokines and O and NS [6,42-44]. These players can engage in a feed-forward manner to maintain and amplify chronic inflammation and immune activation in a TLR radical cycle [4].

Briefly, elevated levels of proinflammatory cytokines can amplify the activity of NF- κ B by stimulating the canonical pathway leading to a cycle of mutually elevated activity [45,46]. The relation between O and NS and NF- κ B is a little more complex, but the upregulation of O and NS can directly increase the activity of NF- κ B [47]. Moreover, O and NS may damage lipids, proteins and DNA, leading to the formation of redox-derived damage-associated molecular pattern molecules (DAMPs) [48,49]. Once formed, these redox-derived DAMPs engage with TLRs further amplifying production of NF- κ B, cytokines and O and NS [4,50]. Hence, chronic inflammation and immune activation can be maintained and amplified by engagement of TLRs by DAMPs [4].

Chronically elevated levels of NF- κ B, proinflammatory cytokines and O and NS, in turn, lead to a disruption of epithelial tight junctions in the intestine allowing translocation of gram-negative bacteria, containing lipopolysaccharides, into the circulation, which can further amplify the TLR-radical cycle by acting as a pathogen-associated molecular pattern (PAMP) [1]. Translocation of bacterial lipopolysaccharides (LPS) from the gut and engagement with TLRs, due to a state of increased intestinal permeability driven by the effector molecules of chronic inflammation is another cause of chronic immune activation that may play a role in major depression, CFS, neuro-inflammatory disorders and some systemic autoimmune disorders [6,7]. For example, further evidence of chronic immune activation in these neuroimmune and autoimmune illnesses is provided by data demonstrating TLR activation and upregulation in multiple sclerosis (MS) [51] and SLE [52].

Given the established association between chronic inflammation and the genesis of incapacitating fatigue [1], the TLR-radical cycle can potentially explain the development of incapacitating fatigue in patients suffering from these and other illnesses. This association may be explained by chronically increased levels of proinflammatory cytokines and reactive oxygen and nitrogen species (ROS/RNS) produced by the TLR-radical cycle upon stimulation by PAMPs and DAMPs [4]. We have reviewed previously that some proinflammatory cytokines, including IL-1 β , TNF- α and IL-6, and increased O and NS processes may cause fatigue in some vulnerable individuals [1,4,6,7]. Mitochondrial dysfunction likely plays a major role in the progression of MS. Electron transport chain (ETC)

complex I, complex III and complex IV activity is grossly reduced in normal appearing gray matter and in normal tissue within the motor cortex in patients suffering from this illness [53,54]. There is also direct evidence of globally impaired energy production and longitudinal depletion of ATP levels leads to increased levels of physical disability [55]. Multiple lines of evidence demonstrate the existence of mitochondrial dysfunction in many, but by no means all, patients afforded a diagnosis of CFS [56]. These abnormalities include loss of mitochondrial membrane integrity and oxidative corruption of translocatory proteins [57,58]. Other findings include abnormal muscle mitochondrial morphology and defective aerobic metabolism uncharacteristic of muscle disuse [59]. Several other teams have reported significant downregulation of oxidative phosphorylation in striated muscle [60,61]. Complex I deficiency is seen in the frontal cortex and substantia nigra of Parkinson's disease patients [62], and this defect is also observed in peripheral tissues, such as skeletal muscle [63], strongly indicating a widespread reduction in complex I activity in Parkinson's disease. Impaired complex III function has also been reported in the platelets and lymphocytes of patients with this illness [64]. There is also accumulating evidence that inflammation and subsequent mitochondrial dysfunction drive the symptoms of major depression [65,66]. Localized or global mitochondrial dysfunction is also an invariant feature of autoimmune diseases. Persistent mitochondrial membrane hyperpolarization and increased O and NS production combined with depleted levels of glutathione and ATP is an invariant characteristic of T cells in SLE [67,68]. The release of DAMPS into the systemic circulation, consequent to necrosis, acts as a mechanism by which localized mitochondrial pathology can lead to self-perpetuating systemic inflammation which, in turn, amplifies mitochondrial dysfunction in a vicious feed-forward loop [56,69]. The association between chronic oxidative stress, systemic inflammation and mitochondrial dysfunction and chronic oxidative stress is also firmly established in Sjogren's syndrome [70]. There is also evidence of widespread nitric oxide (NO)-induced inhibition of complex III and V of the ETC in patients with rheumatoid arthritis [71,72]. The causative role of chronic inflammation and oxidative stress and mitochondrial dysfunction is explained by the presence of elevated levels of ROS and RNS in such environments. These entities cause damage to proteins, DNA and lipid membranes [56]. NO and peroxynitrite have the capacity to inhibit crucial enzymes within the ETC and can inactivate crucial enzymes in the tricarboxylic acid cycle leading to, often critical, reductions in the generation of ATP [7]. Peroxynitrite, in particular, also has a destructive influence on the mitochondrial membrane leading to the loss of potential difference between the outer and inner

membrane needed to manufacture ATP [7]. The products of lipid peroxidation driven by elevated levels of ROS are also toxic to mitochondrial membranes. It is noteworthy that inhibition of the ETC leads to the formation of even higher concentrations of oxygen radical species which, in turn, leads to further impairment of mitochondrial function [7]. Needless to say there are numerous studies demonstrating that the origin of severe intractable fatigue seen in people with syndromic mitochondrial diseases lies in mitochondrial pathology and depleted generation of ATP. The reader is referred to the work of [56] for further details.

In this narrative review we will review the evidence pertaining to the genesis of intractable debilitating fatigue in multiple sclerosis, Parkinson's disease, SLE, Sjogren's disease, rheumatoid arthritis, major depression and CFS with a view of forming a conclusion as to whether such evidence justifies the viewpoint that the debilitating fatigue commonly suffered by those patients diagnosed with various illnesses is immune, inflammation or O and NS-mediated either directly or indirectly by causing abnormalities such as mitochondrial dysfunctions and central, neuropathological or functional processes [56,73-75]. These specific disorders were selected as examples along a spectrum of imbalance involving various degrees of activation of immune-inflammatory and O and NS pathways, and mitochondrial and brain metabolic dysfunctions in systemic auto-immune, immune-inflammatory and neurodegenerative disorders. Figure 1 shows the underlying processes and pathways associated with secondary fatigue, which we will discuss in the following sections.

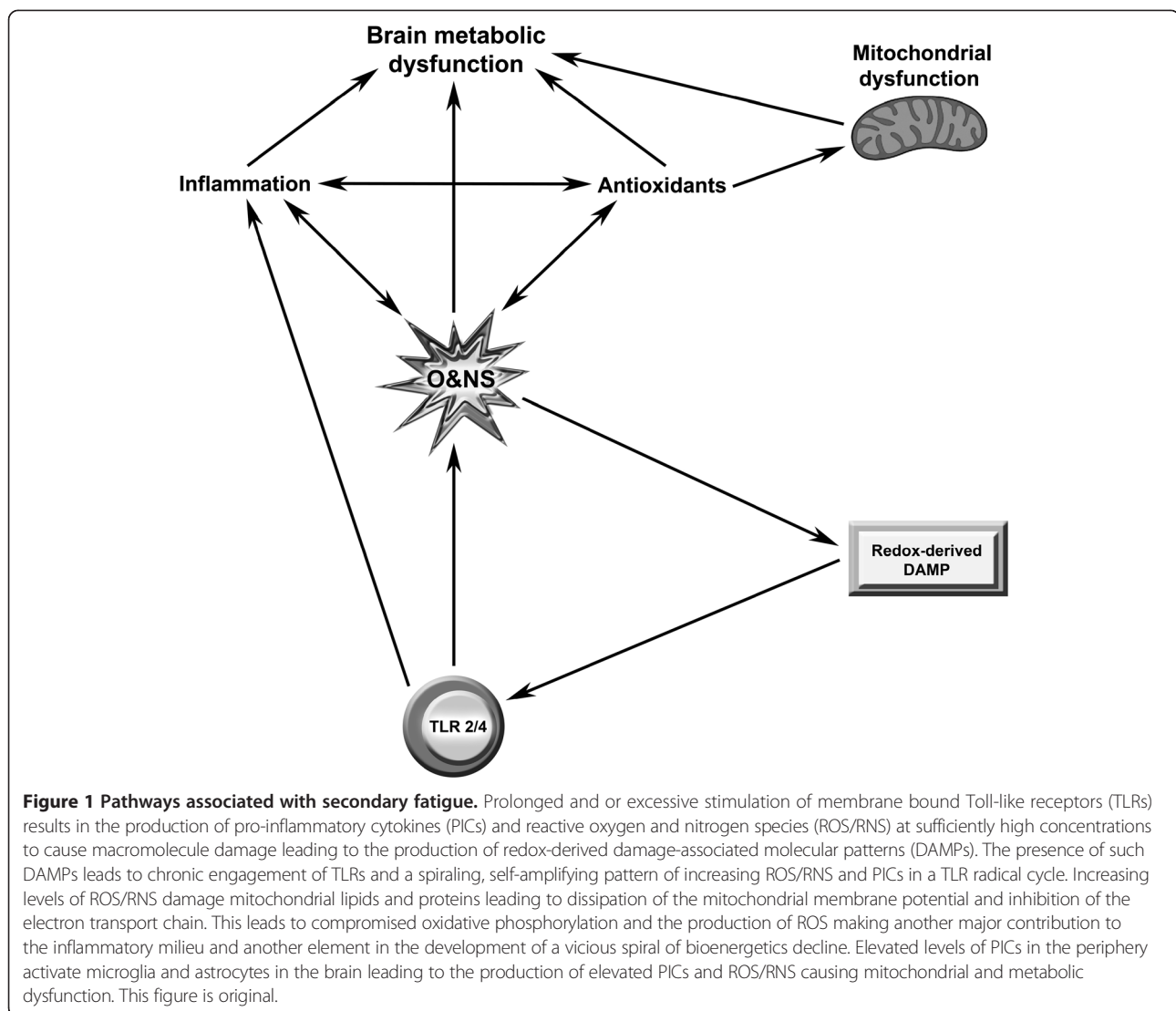
Multiple sclerosis

Fatigue in MS

Fatigue is recognized as one of the most disabling and common symptoms of MS affecting up to 80% of sufferers [17,76,77]. Numerous studies have demonstrated that the Expanded Disability Status Score (EDSS) correlates positively with patient self-reported fatigue scores using a variety of fatigue scales in patients with MS [78-81].

Immune activation, chronic inflammation and mitochondrial dysfunction

Chronic activation of the peripheral immune system is a characteristic observation in MS patients. Many studies report elevated levels of activated Th17 and Th1 T cells, and impaired function of regulatory T cells [17,82,83]. The evidence demonstrating an associative relationship between chronic activation of the immune system and the genesis of neuroinflammation is strong in MS due to the proven effectiveness of rituximab [84] and natalizumab [85], which are monoclonal antibodies which primarily target leucocytes but significantly reduce objective markers of



disease activity in the central nervous system (CNS) [86]. It is also noteworthy that increased levels of TNF- α in the periphery are often predictive of the development of active disease. Peripheral TNF- α levels are also predictive of disability levels as estimated by the EDSS [87-89]. Peripheral levels of this and other cytokines correlate positively with fatigue severity which affects the vast majority of people with this illness [17,90-92]. TLR4 receptors are also upregulated in the brain and peripheral immune system in patients with MS [93-95]. There is also copious evidence indicating that chronic systemic inflammation and oxidative stress play a causative role in the etiopathogenesis of MS [96-98]. Elevated markers of chronic inflammation and oxidative stress are found in the brain, cerebrospinal fluid (CSF) and various blood compartments [82,99]. Oxidative stress levels increase quite dramatically during relapses but drop to barely detectable levels in patients during the remission phase [100]. It is also noteworthy

that levels of chronic inflammation and oxidative stress in the CSF and blood correlate positively and significantly with disability levels as estimated by EDSS [101,102]. Finally, the extent of gadolinium-enhanced lesions appears to correlate significantly and positively with levels of oxidative stress [102].

It appears that although the genesis of pathology in early disease is mainly driven by inflammation [103], mitochondrial dysfunction likely plays a pivotal role in disease progression. Oxidative damage to mitochondrial DNA and impaired complex 1 activity is a characteristic finding in active MS lesions [104], but complex I, complex III and complex IV activity is also reduced in normal appearing gray matter and in normal tissue within the motor cortex [53,54,105].

The use of nuclear magnetic resonance (NMR) spectroscopy has found direct evidence of globally impaired energy production and increased lactate production in

the CSF [106-108]. In a longitudinal study, progressive central depletion of ATP over a three year period correlated positively and significantly with increased indices of physical disability as measured by EDSS changes, which strongly suggests a global impairment of ATP synthesis in MS [108].

Neuroimaging and neuropathology

Until recently, all studies investigating the phenomena had failed to find any significant correlation between increasing self-reported fatigue during the performance of sustained cognitive tasks and changes in brain activity using any neuroimaging modality [109]. It has been argued that this situation has arisen because self-reported fatigue is not an objective or accurate indicator of cognitive performance in the first place [109]. However, the first evidence displaying a positive relationship between cognitive fatigue and changes in brain activity during a task was provided in a recent study [109]. While the relationship between self-reported fatigue and neuroimaging changes is still a matter of considerable debate, the positive association between changes in brain activity and objective measures of cognitive fatigue is generally accepted [110,111]. The bulk of evidence demonstrates that these changes in activity occur in several areas of the brain with most studies reporting this phenomenon in the basal ganglia and the prefrontal cortex [109]. Overall, the results of these studies have been interpreted as support for the hypothesis that the origin of fatigue seen in patients with MS and other neurological diseases arises as a result of failure of integrative processes within the basal ganglia which normally coordinate inputs from the limbic system and outputs to the motor cortex [109,112]. MS was once considered to be a disease of white matter but there is now overwhelming evidence that gray matter pathology occurs early in the disease often before the advent of white matter involvement [113,114]. Conventional magnetic resonance imaging (MRI) is of limited value in revealing gray matter pathology but newer MRI approaches based on FLAIR technology and NMR spectroscopy appear to display adequate sensitivity [114,115]. Gray matter atrophy occurs in very early stages of disease and is seen in people with clinically isolated syndrome (CIS) [115-117]. Indeed, this phenomenon is detected in people with first attack MS [118]. The extent of gray matter atrophy correlates significantly and positively with the degree of physical disability and cognitive impairment seen in many patients with this illness [119,120]. It is noteworthy that reduced gray matter perfusion is seen in very early disease without any loss of volume or other visible sign of gray matter (GM) pathology [121]. Cortical inflammation and metabolic abnormalities, such as reduced choline and N-acetyl aspartamine levels, are also evident in early MS without evidence of any kind of

gray or white matter abnormalities [114,119,122]. Other studies, when viewed as a whole, have established a clear relationship between global or localized gray matter atrophy and hypoperfusion in the development of fatigue [123-126]. Other observations include an association between fatigue and glucose hypometabolism in the basal ganglia and frontal cortex [127-129] and a decreased N-acetyl aspartamine/creatine ratio in the basal ganglia, suggestive of gliosis [130].

Finally, Calabrese *et al.* reported a positive association between increased fatigue and widespread atrophy of the basal ganglia and prefrontal cortex [131]. It is tempting to speculate that these observations could arise from astrogliosis and underlying loss of astrocyte numbers and the normal regulatory functions of the surviving astrocyte population. Recent evidence indicates that reactive astrogliosis may play a major causative role in the development and progression of MS [132,133]. It is also worthy of note that astrocyte loss is a characteristic feature of this disease [134]. Protoplasmic astrocytes are primarily found in gray matter and form the vast bulk of cells located in this tissue [135]. These glial cells in particular have crucial roles in coordinating neurometabolic and neurovascular coupling and, hence, the delivery of oxygen and energy to neurons [136,137]. Given that astrocytes form the vast bulk of gray matter it seems likely that the loss of gray matter seen very early in the development of the disease is due to loss of astrocytes [138]. It is also interesting that the magnitude of gray matter loss correlates positively with severity of inflammation [138]. The presence of reactive astrogliosis would suggest that the regulatory performance of the remaining astrocytes could be compromised and, thus, would go some way to explaining the abnormalities in perfusion and glucose metabolism and the development of fatigue seen in these studies. This state of affairs could explain, in part, the regulatory dysfunction seen in the basal ganglia which seems to underpin the observations surrounding the changes in brain activity and the development of cognitive fatigue noted earlier.

Chronic fatigue syndrome

Fatigue in chronic fatigue syndrome

Pathological levels of fatigue unrelated to activity and not relieved by rest is a mandatory requirement for a diagnosis of chronic fatigue syndrome under the current internationally accepted diagnostic guidelines [139]. The original diagnostic criteria contained another mandatory element, namely a clinical picture whereby the patient's global symptoms represent a unitary illness with a single pathogenesis and pathophysiology. It is more likely that a diagnosis of CFS represents a spectrum of illnesses where different pathophysiological processes converge to produce a very similar phenotype [140]. Hence, any information regarding immune abnormalities, chronic inflammation,

mitochondrial dysfunction and neuroimaging should be viewed with these issues in mind [141].

Immune activation, chronic inflammation and mitochondrial dysfunction

Numerous research teams have reported a wide range of peripheral immune abnormalities in people afforded a diagnosis of CFS [1,142,143]. The presence of circulating activated Th1, Th2 and Th17 T cells have all been detected. Recent evidence has challenged the view that people with CFS display immune abnormalities consistent with a Th2 pattern of T cell differentiation, and now data reveal that while some patients present with a Th2 profile and a preponderance of anti-inflammatory cytokine production, others present with a Th1 or possibly Th17 profile, with the synthesis of proinflammatory cytokines being dominant [144-146]. Elevated levels of TNF- α and IL-1B are, in fact, particularly commonplace observations in patients recruited into studies using the internationally agreed [139] diagnostic guidelines [144,147-151]. We have reviewed previously that patients with CFS and Myalgic Encephalomyelitis (ME) show different cytokine profiles, for example, a Th1-like pattern, with increased levels of IFN- γ , IL-2, IL-12 and IL-2 receptor, or a Th2-like pattern, with increased levels of IL-10, IL-4 and IL-5, or combinations thereof [1]. Two recent studies reported evidence of activated TLR4 receptors [152-154]. The causative relationship between chronic inflammation and the development of fatigue is perhaps strongest in patients afforded a diagnosis of CFS, with many studies demonstrating a significant positive correlation between surrogate markers of inflammation, oxidative stress and symptom severity [17,155-159]. Miwa and Fujita (2010) demonstrated that a rapid decline in inflammation and oxidative stress of patients corresponded with a decline in severity of fatigue and amelioration of their entire symptom profile [160]. Markers of chronic inflammation and oxidative imbalance have also been detected in skeletal muscle and levels of oxidative stress in this patient population correlated positively with objective measures of muscle fatigability [161]. Numerous authors have reported abnormalities consistent with mitochondrial dysfunction in patients afforded a diagnosis of CFS [56]. These abnormalities include loss of mitochondrial membrane integrity and oxidative corruption of translocatory proteins [57,58,162]. Other findings include abnormal muscle mitochondrial morphology and defective aerobic metabolism uncharacteristic of muscle disuse [59,163]. Several other teams utilizing 31-P NMR spectroscopy have reported significant down regulation of oxidative phosphorylation [60,61,164-167]. Other studies reported the presence of abnormal lactate responses to exercise indicative of a shift to glycolytic energy generation in at least some patients with a CFS diagnosis [168]. In a recent review, Filings and others [169] conclude that

there was ample evidence of mitochondrial dysfunction and impaired bioenergetics performance in patients afforded a diagnosis of CFS, but once again it was confined to patients diagnosed according to internationally agreed criteria and not apparent in all patients [169]. Defects in oxidative phosphorylation and ATP generation have also been revealed in exercise testing with the pattern of physiological responses being characteristic of mitochondrial dysfunction [170]. Exercise performance was examined in a cohort of CFS patients and a loss in the linear relationship between heart rate and cardiac output and the dissipation of oxygen concentration gradient between venous and arterial blood characteristic of mitochondrial dysfunction was reported [171]. Finally, authors utilizing NMR spectroscopy have reported that some patients with CFS display significantly elevated ventricular lactate levels, again suggestive of a shift towards aerobic glycolysis [159,172,173].

Neuroimaging and neuropathology

There is now considerable neuroimaging evidence demonstrating impaired blood flow in the cortex and cerebellum in many patients with a diagnosis of CFS [174-176]. Other studies report loss of gray matter volume [177-179]. Interestingly, this phenomenon has also been observed in patients given a primary diagnosis of fibromyalgia which is held by many to be an overlapping illness. Kuchina *et al.* reported that patients displayed levels of gray matter loss which were some three times greater than expected for their age [180]. Another study using 3-T voxel-based morphometry MRI reported reduced occipital lobe gray and white matter volume in the CFS group [181]. Cook and fellow workers, using functional MRI (fMRI) reported a significant positive association between perceived severity of fatigue and responsiveness in the cingulate frontal, temporal and cerebellar regions [182]. Another research team demonstrated impaired fMRI activation in the dorsolateral, dorsomedial and prefrontal cortices during a fatigue provocation task [183]. Glucose hypometabolism, especially in the prefrontal cortex, has also been demonstrated [184,185]. Finally Barden *et al.* [186] once again using 3 T MRI-based morphometric analysis reported evidence of astrocyte dysfunction and failure of autoregulatory mechanisms in patients in their trial cohort [186].

Parkinson's disease

Fatigue in Parkinson's disease

Pathological fatigue, often described as a state of overwhelming exhaustion not necessarily related to physical effort, is recognized as a major, and possibly the most common, non-motor symptom of Parkinson's disease [187,188] and often presents an insurmountable problem for patients and their caregivers [189,190]. Profound fatigue is experienced by some 82% of patients with

advanced (HY stage 5) disease and the prevalence of fatigue increases with disease severity [191]. Although fatigue has been clearly established as an independent non-motor symptom of Parkinson's disease, it is often confused with depression or excessive daytime sleepiness in clinical practice [189]. Some authors have actually adduced evidence indicating that fatigue could even be a pre-motor feature of Parkinson's disease [192,193]. Schifitto *et al.* reported the presence of fatigue in just over a third of untreated non-depressed patients [194]. Furthermore, several other authors have reported that pathological levels of fatigue occur in non-depressed patients who are also untroubled by sleep problems [187,189].

Immune activation, inflammation and mitochondrial dysfunction

Numerous authors have reported that the serum and CSF of Parkinson's disease patients contain elevated levels of activated CD4 and CD8 T cells and IL-1 β , TNF- α , and IL-2 [195-199]. Increased frequencies of activated CD4⁺ T cells expressing the programmed death receptor Fas [198] and increased numbers of IFN- γ -producing Th1 cells, decreased numbers of IL-4-producing Th2 cells, and an overall decrease in CD4⁺CD25⁺ T cells have been found in the peripheral blood compartment of patients with this illness [200]. Studies have demonstrated that elevated peripheral cytokine production influences the progression of this illness. Parkinson patients display increased serum levels of TNF- α and TNF- α receptor 1 when compared to healthy control subjects, which makes an independent contribution to the pathogenesis of this illness [197,201,202]. It is also noteworthy that elevated plasma IL-6 concentrations significantly and positively correlate with increased risk of developing the illness [203].

Neuropathy and functional central processes

The increased frequencies of activated peripheral and memory T-cell subsets and activated T cells in the substantia nigra indicate the putative roles of T cells in the progression of Parkinson's disease. There is also evidence that the balance of regulatory or effector T lymphocytes at inflammatory foci can either attenuate or exacerbate neuroinflammation and, hence, the subsequent development of neurodegeneration [13].

The intimate association between Parkinson's disease and chronic inflammation has been revealed in different studies [204-208]. It is now recognized that chronic systemic inflammation plays a major role in the pathophysiology of Parkinson's disease [209,210]. Nitrated proteins, DNA damage and lipid peroxidation bear testimony to the presence of elevated oxidative and nitrosative species [211,212]. The detection of extracellular HMGB1 and corrupted protein, DNA and lipid derived entities suggests substantial DAMP activity [213]. The weight of evidence indicates that the

engagement of high-mobility group protein B1 (HMGB1) and alpha synuclein plays a major part in exacerbating the pathology of Parkinson's disease [214,215]. Due to its modified conformation alpha synuclein behaves as a DAMP by activating TLR4 receptors on microglia resulting in the release of a plethora of neurotoxic entities, toxic molecules, including O and NS and proinflammatory cytokines and prostaglandin E2 (PGE2), thereby exacerbating neuro-inflammation [216,217].

Mitochondrial dysfunction in Parkinson's disease in the shape of Complex I (CI) impairment has been suggested to be one of the fundamental causes of the illness [218,219]. This complex I deficiency is seen in the frontal cortex and substantia nigra in the patients [62], and in peripheral tissues, such skeletal muscle [220-222] and platelets [63,223,224], strongly indicating a widespread reduction in complex I activity in Parkinson's disease. This defect is likely due to oxidative damage to complex I and possibly mis-assembly, as this latter phenomenon has been observed in isolated Parkinson's disease brain mitochondria [225]. This complex I inhibition can induce the degeneration of neurons via a number of different mechanisms, such as excitotoxicity and increased oxidative stress [226]. A decrease in complex III function has also been reported in the platelets and lymphocytes of patients with this illness [64,223]. An association between the level of impairment of mitochondrial complex III assembly leading to a subsequent increase in ROS production and the development of Parkinson's disease has also been reported [227]. This elevation in free radical production and release likely stems from the increased leakage of electrons from complex III. An alternative, but not mutually exclusive, explanation is that the inhibition of complex III assembly results in a severe reduction in the levels of functional complex I in mitochondria [228], again leading to an increase in ROS production via complex I deficiency. It is also noteworthy that the complex I and II electron acceptor ubiquinone is also reduced in the mitochondria of patients with Parkinson's disease [229].

Neuroimaging and neuropathology

An almost bewildering array of neuroimaging abnormalities have been observed in patients with Parkinson's disease and overall it is now clear that the various manifestations of the disease cannot be attributed to basal ganglia dysfunction alone [230,231]. Numerous studies employing voxel based morphometry have revealed a global pattern of gray matter loss and conformational abnormalities in Parkinson patients [232,233]. These gray matter changes are associated with cognitive and memory impairments which are seen in patients with very early disease [234,235]. Nagano-Saito and others reported that gray matter density displayed a positive and significant correlation in the dorsolateral prefrontal cortex and parahippocampal gyrus [236]. Loss

of gray matter volume is apparent in treatment naïve patients, once again bearing testimony to the existence of these abnormalities at the earliest stages of the disease [237]. The use of NMR spectroscopy has revealed neurometabolic abnormalities particularly a decrease in N-acetyl aspartate levels [238]. Finally, the use of the same technique has revealed the existence of widespread mitochondrial dysfunction in the brains of people with Parkinson's disease even in the absence of any overt clinical manifestations [239]. Treatment naïve patients also display glucose hypometabolism in the dorsal pons, putamen and ventral thalamus [240-242]. Positron emission tomography (PET) imaging has revealed cortical hypometabolism in Parkinson's disease. The severity and topography of glucose hypometabolism in the frontal and occipital cortex seen even in prodromal patients [243] intensifies and involves the lateral parietal and prefrontal cortices [242,244,245] and may also include the medial frontal and occipital regions [243,246] in patients with mild cognitive impairment (MCI). The severity and location of this hypometabolism may reflect the degree and extent of cognitive dysfunction [243,245,247,248]. The widespread cortical hypo-perfusion reported by many authors is also apparent at very early stages of disease and also appears to be related to the development of cognitive dysfunction [246,249,250].

Major depressive disorder

Fatigue in depression

Fatigue of variable severity occurs in practically 100% of people with a diagnosis of depression [251,252]. It is worthy of note, however, that a systematic review reported that almost 80% of patients still experienced chronic debilitating levels of exhaustion following treatment of their depression [253]. This is perhaps to be expected given that several studies have now demonstrated that antidepressants have no positive modulatory effects on fatigue [254-257].

Immune activation, inflammation and mitochondrial dysfunction

The existence of increased levels of circulatory proinflammatory cytokines in these patients is now a textbook truism [20]. The picture regarding patterns of cytokine imbalance is complex with elevated levels of anti-inflammatory cytokines often reported [258]. There is copious evidence of chronically activated T cells with Th1, Th2 and Th17 patterns of differentiation [20,259,260]. It is worthy of note, however, that T cells appear to be dysfunctional, displaying an overall pattern of abnormalities consistent with a state of anergy [261]. Until recently, evidence of TLR activation in depression was limited to an animal model [262] but recently a study reported elevated levels of TLR4 in the brains of depressed patients displaying

suicidal ideation [263]. Chronic systemic inflammation and oxidative stress play a major role in the etiology of depression [19,20]. Elevated levels of redox-damaged DAMPs, including oxidized low density lipoprotein, oxidized phospholipids, and malondialdehyde (MDA)-adducts are also consistently found in patients suffering from this illness [48]. Compromised epithelial barrier integrity is also a finding in depression and the resulting bacterial translocation into the systemic circulation is intimately involved in the pathogenesis of the disease [20,155]. Mitochondrial dysfunction affects neuronal function, synaptic plasticity, energy metabolism and neurotransmitter release and, hence, it is not surprising that there is increasing evidence that mitochondrial dysfunction and inflammation drive the symptoms of major depression [65,66]. Gardner and Boles highlighted the fact that research has failed to confirm a consistent relationship between serotonin levels and depression and that compromised bioenergetics should become a focus of research into the pathogenesis of the illness [264].

Neuroimaging and neuropathology

Hamilton and fellow workers reported the results of their meta-analysis of studies utilizing various modalities of functional neuroimaging in patients with depression [265]. These authors concluded that a synthesis of the studies revealed a pattern of higher baseline neural activity in the pulvinar nucleus [265]. They further reported that studies utilizing negative stimuli demonstrated a significantly greater neural response in certain areas of the brain, such as the amygdala, and lower responses in other regions, such as the prefrontal cortex, possibly indicating impaired contextual processing and reappraisal of visceral inputs [265]. In another meta-analysis, Kempton and others reported that patients with a diagnosis of depression and bipolar disorder displayed increased rates of hyperintensities in subcortical gray matter and increased volume of the lateral ventricles compared to healthy controls [266]. Interestingly, this meta-analysis also revealed distinct differences in neuroimaging abnormalities between depression and bipolar disorder, with the former having reduced rates of hyper-intensities in white matter and smaller basal ganglia and hippocampi compared to bipolar patients [266]. There is evidence that patients in a state of depression display reduced gray matter volume in the hippocampus compared to healthy controls or patients in remission [267]. Other investigators analyzing studies involving voxel based morphometric analysis have reported more widespread loss of gray matter in many different areas of the brain, especially in the prefrontal cortex [268-270]. It is noteworthy that gray matter reduction is evident in patients with first episode depression [271]. Impaired perfusion in frontotemporal regions has been reported [272] and a recent study has reported global cerebral

hypoperfusion [273]. Interestingly, the degree of hypoperfusion in the prefrontal cortex correlates positively with the severity of depressive symptoms in patients with Alzheimers disease [274]. Another research group has recently reported that regional cerebral blood flow abnormalities in the prefrontal cortex and anterior cingulate cortices reverse during remission [275]. Glucose hypometabolism has been demonstrated in depressed patients both in the prefrontal cortex [276] and in several other regions [277]. An intriguing connection between glucose hypometabolism was proposed in a study by Hirono and others, who reported a positive significant association with the presence and severity of depressive symptoms in Alzheimer patients and decreased glucose metabolism in the frontal lobe [278]. Finally, the presence of activated microglia in patients suffering from depression has been established via the use of *in vivo* non-invasive neuroimaging [279].

Systemic lupus erythematosus

Fatigue in SLE

Fatigue is an extremely common and disabling symptom affecting some 80% of patients with SLE [280]. Fatigue severity scores are significantly higher than population norms and similar to levels seen in patients with MS and Lyme disease [281,282]. Chronic debilitating fatigue is a major cause of morbidity in patients with SLE [283], that decreases quality of life [284-286] and increases work disability [287,288]. The aerobic capacity of patients with mild SLE is comparable to that observed in patients with severe cardiopulmonary disease [289-291]. Disease activity appears to be a major factor in the genesis of fatigue although this relationship is not evident in all studies [280,283,292,293].

Immune activation, inflammation and mitochondrial dysfunction

There is extensive evidence of activated T cells in the peripheral immune system of patients with SLE [294]. Elevated levels of proinflammatory cytokines play a key role in the pathophysiology of SLE [295]. Salbry *et al.* [296] reported a significant positive correlation between levels of TNF- α and IL-6 and objective markers of disease activity [296]. The weight of evidence indicates that significantly elevated levels of proinflammatory cytokines in the systemic circulation also plays a causative role in the development of systemic inflammation [297,298]. The presence of a chronic inflammatory state in people suffering from SLE has been reported by several research teams [28,299]. Wang and colleagues reported a significant positive correlation between elevated markers of O and NS with disease activity in this illness [300]. A range of TLRs are involved in initiating and maintaining the pathology of SLE, including TLR4, TLR3, TLR9 and

TLR7 [301,302]. Impaired clearance of apoptotic cells is a pathological feature of SLE and, hence, the blebs and modified cellular contents act as autoantigens and are recognized by the immune system as DAMPS with the resultant activation of TLRs especially TLR4 [303,304]. The impaired clearance of these cells sets off a sequence of biochemical events allowing the escape of extramatrix debris once again acting as an autoantigen and recognized as a DAMP with the consequent activation of TLR4 and, indeed, a range of other TLRs as well [304]. Interestingly, polymorphisms in TLR4 (and CD14) genes are now thought to play a significant role in the etiopathogenesis of SLE. Persistent mitochondrial membrane hyperpolarization, increased O and NS production combined with depleted levels of glutathione and ATP is characteristic of T cells in SLE [67,68]. This environment sensitizes T cells towards necrotic cell death and the consequent release of DAMPS into the blood stream affords a mechanism by which localized mitochondrial pathology can lead to self-perpetuating systemic inflammation [69,305].

Neuroimaging and neurological abnormalities

Neurological symptoms in SLE are commonplace, affecting upwards of 80% of sufferers [32]. These neurological abnormalities occur even in the absence of the various systemic disease manifestations [306]. Voxel based morphometric analysis revealed widespread gray matter volume reduction in patients diagnosed with SLE [307-309]. Other studies have revealed the presence of white matter hyperintensities, whose prevalence in an individual is predictive of disease progression [309-311]. The presence and severity of fatigue in patients with SLE is associated with white matter hyperintensities [312]. These authors reported that the White Matter Hyperintensity score correlated positively and significantly with fatigue severity [312]. The pathophysiology of 'neuropsychiatric' Lupus is mediated by cytokines, complement components and autoantibodies leading to the development of neuroinflammation and, ultimately, apoptosis of neurons and glial cells [313-316]. It is perhaps no surprise that the presence of activated microglia have been confirmed in patients with SLE [34].

Sjogren's syndrome

Fatigue in Sjogren's syndrome

Fatigue and pain are, again, the most common extra-glandular symptoms of Sjogren's syndrome [317,318]. A total of 70% of patients with Sjogren's syndrome suffer from fatigue and many patients state that fatigue is one of the most disabling symptoms of their disease [319]. There are a number of studies reporting a significant positive association between the severity of fatigue experienced by patients and various surrogate markers of disease activity [320-322]. The fatigue levels are associated with higher sicca symptoms, lower salivary volume,

increased serum anti-Sjögren's syndrome A antigen, immunoglobulin G (IgG) and proinflammatory cytokine levels [323]. Further evidence suggesting cytokine involvement in the genesis of fatigue was provided by Norheim and fellow workers who reported that patients' fatigue levels were reduced by some 50% following blockade of IL-1 β [324].

Immune activation, inflammation and mitochondrial dysfunction

Predictably there is copious evidence demonstrating the existence of a chronically activated innate immune system in patients diagnosed with this illness [325]. There is a wealth of data demonstrating disturbed cytokine networks [326], with cytokines secreted by activated Th1 and Th17 T cells being commonly detected in various blood compartments [327,328]. Epithelial cell activation leading to TLR upregulation is considered by many to be a pivotal early event in the pathogenesis of Sjogren's syndrome [329,330]. A range of TLRs, including TLR2, TLR3 and TLR4, are chronically up-regulated in sufferers of this illness [329,331]. Chronic systemic inflammation is an almost invariant finding in Sjogren's syndrome patients [332]. The existence of chronically elevated O and NS and subsequent oxidative stress has also been repeatedly demonstrated in patients with this disease [70,333]. The link between mitochondrial dysfunction and chronic oxidative stress is now firmly established in Sjogren's syndrome [70].

Neuroimaging and neurological abnormalities

A wide range of abnormalities in the central and peripheral nervous system occur in up to 70% of patients with Sjogren's syndrome, which may precede diagnosis in over 90% of cases [33,334,335]. Those interested in the details of these neurological abnormalities are invited to consult an excellent review by Tobon *et al.* [33]. There is some evidence that CNS pathology is immune mediated [336] and many patients display abnormalities on MRI with increased signaling intensity in T2 weighted images being the commonly noted finding [337,338]. These white matter hyperintensities (WMH) are indicative of widespread hypoperfusion [336,339-341]. Voxel based morphometry has once again revealed a global pattern of gray matter volume loss [340,342] and very recently loss of cerebral white matter was observed for the first time [343].

Rheumatoid arthritis

Fatigue in rheumatoid arthritis

Patients with rheumatoid arthritis commonly complain of severe intractable fatigue with prevalence rates of up to 80% depending on definitions of fatigue used [344]. A study employing a fatigue measuring instrument reported that 40% of patients with rheumatoid arthritis experienced unremitting severe fatigue of the same level and pattern as fatigue experienced by patients with a diagnosis of chronic

fatigue syndrome [345]. From a patient perspective fatigue is often described as extreme, unremitting and unrelated to activity and is associated with a failure to perform routine daily activities and non-refreshing sleep which, when considered together, are more debilitating than pain [346,347]. Reducing inflammation with disease modifiers significantly reduces fatigue [348]. Considerable evidence now exists demonstrating that the severity of fatigue experienced by patients suffering from this disease correlates significantly and positively with levels of disease activity [349,350].

Immune activation, inflammation and mitochondrial dysfunction

Numerous research teams have adduced evidence of a chronically activated immune system in rheumatoid arthritis patients as evidenced by significantly increased serum Th1, Th2 and Th17 cytokines [351-353]. Blockade of Th1 and Th17 cytokines can result in significant clinical benefit in patients with rheumatoid arthritis, strongly indicating their role as causative agents in the disease [354,355]. The frequency of Th17 T cells and associated cytokines strongly correlates with a poor prognosis which again suggests that these entities play a major causative role [356]. There is also good evidence that the use of biologic agents results in significant improvements in fatigue, strongly implicating elevated levels of these species in the genesis of intractable fatigue in patients with rheumatoid arthritis [357,358]. There is also considerable evidence demonstrating the activation and upregulation of TLRs in this disease with upregulated TLR2, TLR3 and TLR4 being commonplace findings [359-361]. Rheumatoid arthritis is recognized as being a systemic inflammatory condition [359] and chronic inflammation and accompanying oxidative stress play a causative role in the illness [362,363]. Perhaps unsurprisingly then, it has been demonstrated that levels of inflammation correlate positively with measures of disease activity [364]. The positive association between inflammation and fatigue genesis is evidenced by the fact that reducing inflammation with disease modifiers significantly reduces fatigue [348]. The effector molecules of chronic inflammation and oxidative stress can induce irreversible genetic changes and one such change, mutations in p53, has been suggested as a 'turning point' in converting a state of chronic inflammation into chronic disease [365]. There is evidence of somatic mutations in the mitochondrial DNA (mtDNA) within synovocytes of rheumatoid arthritis patients which may confer immunogenicity on mtDNA derived proteins which consequently adopt the character of DAMPS and be one of such entities thought to play a major role in the etiopathogenesis of this disease [366]. A positive association has been reported in these cells between the extent of these mutations and the

expression of cyclo-oxygenase 2 (COX-2), prostaglandin (PG)E₂ and IL-8 [367]. The existence of these inflammatory markers is highly suggestive of NO-induced inhibition of complex III and V of the electron transport chain [72,368].

Neuroimaging and neuropathology

There is no direct evidence supporting the existence of chronically activated microglia and neuroinflammation in patients with rheumatoid arthritis, but neurological sequelae are commonplace and the role of chronic systemic inflammation in establishing such sequelae is accepted [35]. Wartoloska *et al.* reported widespread cortical atrophy in their patients with rheumatoid arthritis using unbiased voxel morphometric analysis and a pattern of increased gray matter density in subcortical areas notably the basal ganglia with the latter finding being suggestive of decreased dopamine levels [369]. An earlier MRI imaging study by Bekkelund and fellow workers also detected cortical atrophy in rheumatoid arthritis patients but only in those with longstanding disease [370].

Cross-talk peripheral and CNS inflammation

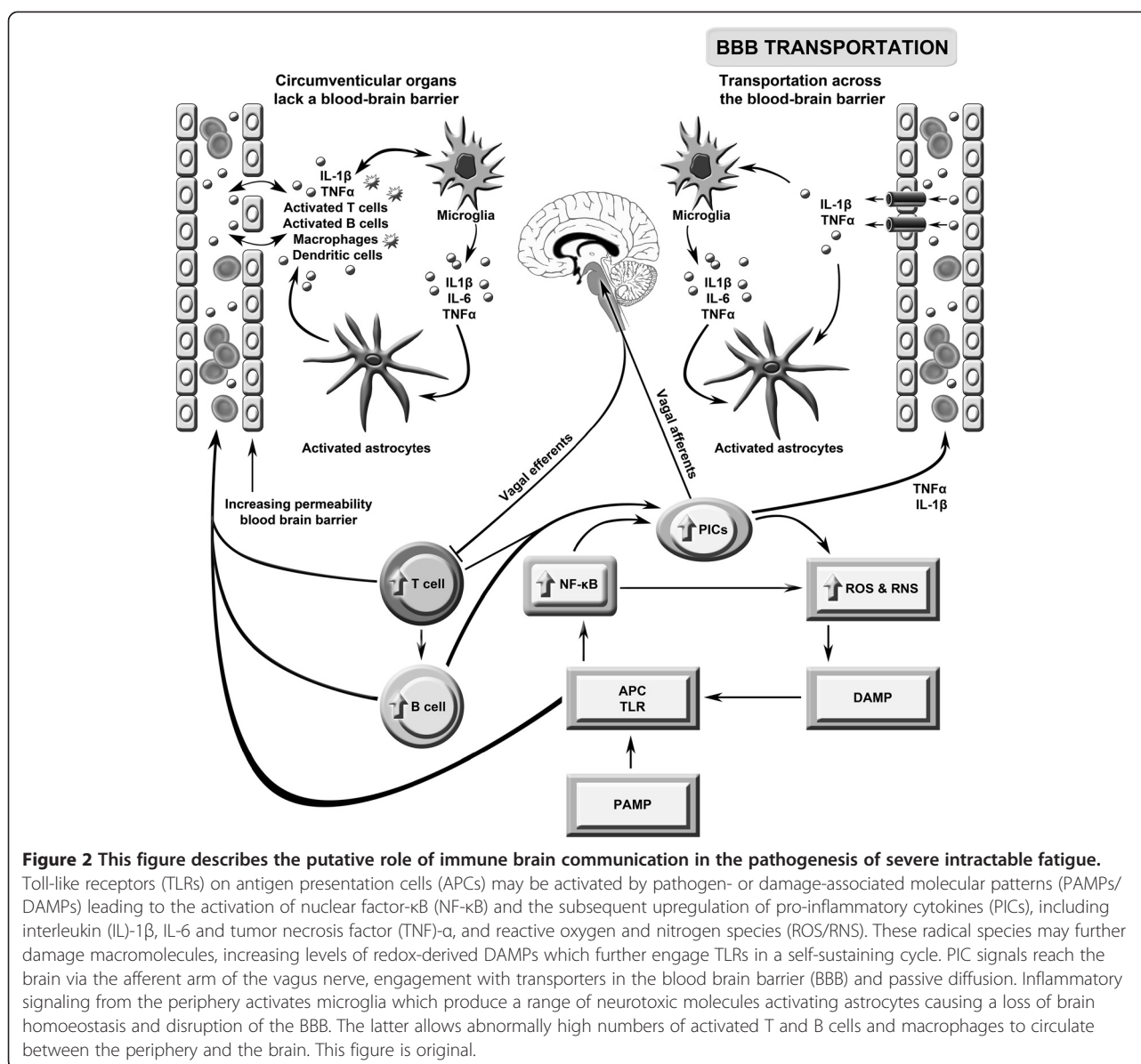
There is now copious evidence that chronic or intermittent inflammation, as observed in the abovementioned systemic disorders, can worsen or trigger neuroinflammatory or neurodegenerative processes via the induction of primed microglia [8,12]. Briefly, prolonged or intermittent peripheral inflammation and immune activation act to prime microglia which thereafter become exquisitely sensitive to future inflammatory stimuli [8]. Once microglia have achieved this sensitized status, subsequent peripheral inflammation and proinflammatory cytokine production mediated by a number of insults (for example, biotoxin exposure or pathogen invasion) provokes an exaggerated response from microglia and the production of excessive concentrations of neurotoxic molecules, such as nitric oxide, peroxynitrite, prostaglandins, cyclo-oxygenase 2 and cytokines [6,7]. The secretion of these neurotoxins and alarmins leads to the activation of astrocytes and the combined activation of these glial cells provokes dysregulation of brain homeostasis, development of chronic neuroinflammation and neurotoxicity. Both humoral and neuroendocrine routes mediate proinflammatory signaling to the brain. The neural route operates via the dorsal motor nucleus of the afferent vagus nerve [6]. The humoral route is facilitated by circulating proinflammatory cytokines that communicate their presence to the brain via direct and indirect routes. Such pathways involve engagement with specific transporters in the blood brain barrier (BBB), the activation of endothelial cells and macrophages, creating a mirror pattern of production on the adluminal side of the BBB, and passive diffusion into areas of the brain lacking a functional BBB (for

example, circumventricular organs) and thereafter into the glial limitans [1]. The cumulative effects of proinflammatory cytokines and activated astrocytes cause disruption of the BBB allowing abnormally high numbers of activated T cells and B-cells to circulate between the peripheral immune system and the brain, acting as more channels of communication between the peripheral and central immune system [13]. It should be noted that cytokines are able to diffuse from the CNS into the bloodstream as well [13]. Finally, the presence of proinflammatory cytokines in the brain activates the hypothalamus instigating the cholinergic anti-inflammatory pathway designed to terminate the immune response [1,6]. These processes are depicted in Figure 2.

ASIA syndrome and sex effects

All disorders reviewed here, except Parkinson's disorder, are more frequent in women than in men. For example, in patients with rheumatoid arthritis a four to five greater incidence is found in women than in men when less than 50 years old, whereas these differences are less pronounced in 60- to 70-year old individuals. The female predilection is also observed in depression, CFS, MS, Sjogren's syndrome and systemic lupus erythematosus [371-375]. In Parkinson's disorder the male/female incidence rate ratio is 1.6 to 1 [376]. One main difference between Parkinson's disease and the other disorders discussed here is that the autoimmune component is less pronounced in Parkinson's disease. An increased incidence rate in women is observed in most autoimmune disorders [371]. Nevertheless, also in Parkinson's disease autoantibodies are observed and they are associated with specific symptom profiles, including depression [377]. It is argued that these sex-related differences in incidence may be explained by endogenous sex-hormones.

Estrogen, progesterone and testosterone play important immunomodulatory roles and influence the quantity and pattern of cytokine secretion by antigen presentation cells and T lymphocytes and immunoglobulin production by B cells. Sex hormones also regulate the Th1/Th2 balance of the immune system, the production of regulatory T cells and the functionality of granulocytes and natural killer cells [378,379]. An interested reader is referred to an excellent review by [380] for a detailed consideration of the mechanistic effects of sex hormones on individual classes of immune cells. In the light of the discussion above, it also seems noteworthy that estrogen is neuroprotective in many animal models of neuroimmune and neurodegenerative disorders essentially by down regulating the expression of neuroinflammatory genes in glial cells, such as those coding for elements of the complement system, proinflammatory cytokines and TLRs [381]. Thus, excessive estrogens but less androgens may favor activation of B cells, a Th2-like response and increased numbers



of autoimmune cells and, thus, autoimmune responses [371]. Nevertheless, the precise effects of sex- or gender-related factors on the increased incidence of autoimmune-related disorders has remained elusive. Future research should delineate not only sex but also gender-related effects according to the gendered innovations approach [382].

These parameters and elevated number of circulating T cells seen in premenopausal women may be one reason for the powerful prolonged activation of inflammatory pathways and adverse reactions to aluminum adjuvants seen in women following administration of a range of vaccines [383,384]. The engagement of TLR receptors by aluminum, as well as the activation of the NLP3 inflammasome, could create a state of chronic inflammation

and oxidative stress in a person with functional polymorphisms in immune genes as discussed above and, hence, could be a cause of Autoimmune Inflammatory Syndrome Induced by Adjuvants (ASIA), alternatively known as Schoenfield's Syndrome [385-387]. The activation of TLR4 by silicon [388] could also explain the connection of this element with the development of ASIA and the chronic activation of TLRs can potentially explain many environmental contributions to the 'mosaic of autoimmunity' [389].

Sex effects may also determine responsivity to drug therapy as, for example, in MS. Thus, postmenopausal women are poorer responders to rituximab than men of the same age [390,391]. This might seem a little counter intuitive from the frame of reference that rituximab

exerts its effects mainly on the B cell population and that B cell levels do not appear to differ in postmenopausal women and age equivalent men to any significant extent [392]. However rituximab also exerts modulatory effects on the T cell compartment [393]. Numerous researchers have reported that the clinical benefits seen following the use of rituximab in rheumatoid arthritis and other autoimmune conditions are associated with the antibody's capacity to increase the expression of FOXP3 [394], suppress the expression of retanoic acid-like orphan receptors ultimately suppressing the production of Th17 T cells and IL-17 [395] and reducing the expression of cytokines by Th1, Th2 and Th17 T cells [396]. It is possible that the Th2 shift in the immune system seen in postmenopausal women negates the benefits of rituximab on a Th1/Th17 biased immune system [392]. The positive benefits of rituximab and natalizumab on MS [84,85] is probably most easily explained by the modulatory effects of rituximab and, likely, natalizumab on the T cell compartment as well as their well-documented effects on B cell depletion.

Summary and conclusion

Figure 3 shows a diagram illustrating the causal links being described in the above sections synthesizing the significant pathways that lead to secondary fatigue in these different neurodegenerative and systemic (auto)immune disorders. There is clear evidence of a positive relationship between fatigue severity and levels of disability in MS. It is of interest that levels of peripheral inflammation, oxidative stress and TNF- α also display a positive correlation with objective markers of disease activity and disability levels and that levels of proinflammatory cytokines correlate positively with levels of fatigue. The existence of gray matter atrophy before the advent of white matter abnormalities, and the existence of metabolic abnormalities before the advent of gray matter pathology, rather argues against the proposition that the chronic peripheral immune activation and oxidative stress seen in early disease is secondary to the release of inflammatory mediators from the CNS. These observations, coupled with data demonstrating that the severity of neuro-inflammation depends on the level of peripheral immune activation

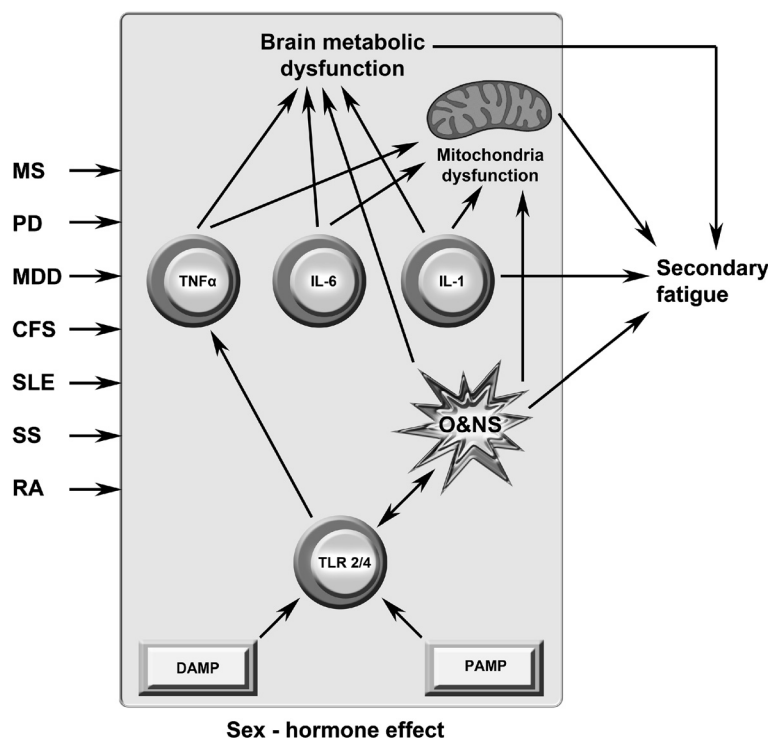


Figure 3 This figure depicts shared pathways in the illnesses described in this paper that may cause secondary fatigue. Activation of Toll-like receptors 2/4 (TLR2/4) by pathogen- and damage-associated molecular patterns (PAMPs/DAMPs) leads to the production of interleukin (IL)-1 β , tumor necrosis factor (TNF)- α and IL-6 together with elevated levels of reactive oxygen and nitrogen species (ROS/RNS). IL-1 β is a primary source of secondary fatigue and together with the other cytokines acts as a secondary source of fatigue via the inhibition of mitochondrial performance and the provocation of metabolic dysfunction in the brain via the activation of astrocytes and microglia. ROS/RNS can also be a primary cause of secondary fatigue by damaging lipids and proteins which are essential for the performance of mitochondria and inhibiting the electron transport chain. These actions lead to impaired mitochondrial performance which is also a source of fatigue in a similar manner as found in syndromic mitochondrial diseases. This figure is original.

and that inflammation drives the development of disease, emphasizes the likely causative role of peripheral pathology. The strong association between the severity of fatigue and disability and the level and geographical distribution of glucose hypometabolism and gray matter hypoperfusion strongly indicates that these elements are driven by generic rather than disease specific pathology. These kinds of generic abnormalities are also evident in Parkinson's Disease where peripheral immune activation, oxidative stress, GM atrophy and widespread glucose hypometabolism are all evidenced in the very earliest stages of disease development. It is also noteworthy that the prevalence of severe intractable fatigue increases with the degree of disease progression and that the degree of peripheral inflammation and levels of proinflammatory cytokines are predictive of disease development and severity. When viewed as a whole these observations also support the view that severe intractable fatigue results from processes which are not disease specific but involved in disease pathogenesis. The existence of chronic peripheral inflammation and immune activation together with GM atrophy and glucose hypometabolism in patients with first episode depression is now a textbook truism. Interestingly, the pattern of neuroimaging abnormalities and GM pathology appears to be quite distinct from that seen in patients with neuroimmune and autoimmune diseases for reasons which are not yet clear. This pattern of peripheral inflammation and immune activation is also found in autoimmune diseases with levels of oxidative stress and proinflammatory cytokines having a causative role in the pathophysiology of SLE and displaying positive correlations with objective markers of disease severity. This is also true of patients with Sjogren's syndrome where objective markers of disease activity are reduced by cytokine blockade. There is also evidence demonstrating that the severity of fatigue is associated with the degree of white matter hyperintensities in people with SLE and evidence that the neuropathology in Sjogren's syndrome is immune mediated. The widespread mitochondrial dysfunction seen in people with autoimmune diseases could also make a significant contribution to the development of fatigue. Widespread mitochondrial dysfunction, in otherwise normal tissue, is also seen in patients with MS, Parkinson's disease and in many patients with apparently idiopathic fatigue. Given that many such patients also display evidence of peripheral immune activation, oxidative stress, gray matter pathology, glucose hypometabolism, hypoperfusion and metabolic abnormalities in the pre-frontal cortex, basal ganglia and elsewhere, it would seem reasonable to investigate all such patients for the presence of these abnormalities. Standard MRI is unlikely to be helpful but other approaches discussed in the main body combined with serum measures of immune activation and oxidative stress may well bear fruit.

As these mechanisms are extensively inter-related, it should be underscored that without a solid prospective timeline and known systems biomedicine, it has remained difficult to distinguish causation from association. Therefore, future research should delineate: 1) the overwhelmingly complex and dynamic interactions between these different pathways and the intracellular networks that modulate them; and 2) the multifactorial triggers that cause secondary fatigue by activating the networks/pathways in those disorders, including viral and bacterial infections, bacterial translocation, psychosocial stressors, exposure to adjuvants, nicotine dependence, sex- and gender-related factors, and so on. Towards this end, a systems biomedicine approach is essential to delineate the genetic and molecular signature of fatigue in these disorders and the non-linear interactions between the many pathways, networks, and trigger and genetic factors that underpin secondary fatigue.

Multi-targeting these interlinked dysfunctions may show benefit in these diseases. For example, a number of antioxidant compounds have demonstrated efficacy in modifying pathways leading to chronic inflammation, oxidative stress and immune dysregulation at relatively high doses for a long duration [7]. N-acetyl-cysteine is an example of a multi-target therapeutic approach having the capacity to decrease the levels of ROS/RNS, increase the levels of cellular antioxidants, such as reduced glutathione, and normalize the production of proinflammatory cytokines and immune cell functions [397]. This supplement has demonstrated the capacity to improve fatigue and disease activity in SLE, CFS and major and bipolar depression [7,398]. Omega-3 polyunsaturated fatty acids (PUFAs) and zinc are also very effective antioxidants and anti-inflammatory compounds and supplementation has produced clinical benefit in patients diagnosed with depression and chronic fatigue syndrome [7,399,400]. Omega-3 PUFAs also show a clinical efficacy in SLE and rheumatoid arthritis [398,401,402]. Curcumin, another nutraceutical with anti-inflammatory and antioxidative effects, is useful in the treatment of depression and rheumatoid arthritis [403,404]. Coenzyme Q10 is another powerful antioxidant and anti-inflammatory compound which also has positive effects on mitochondrial function and which displays disease modifying effects in Parkinson's disease and produced clinical benefit in patients with a diagnosis of CFS [56]. Other approaches aimed at up-regulating antioxidant defenses include N acetylcysteine, methylfolate and dimethyl fumarate, with the latter displaying disease modifying properties in MS [140]. Methylfolate produces a similar quantum of benefit in MDD as antidepressants and can often be effective in treatment-resistant depression [140].

It is concluded that there are sufficient robust multiple lines of evidence to support the proposition that the

severe fatigue and profound disability experienced by people with the neurodegenerative, neuro-immune and autoimmune diseases discussed here is largely driven by peripheral immune activation and systemic inflammation either directly or indirectly by inducing mitochondrial damage.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

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