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REVIEW

# Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis

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## ABSTRACT

Fatigue is one of the most common symptoms in multiple sclerosis (MS), with a major impact on patients' quality of life. Currently, treatment proceeds by trial and error with limited success, probably due to the presence of multiple different underlying mechanisms. Recent neuroscientific advances offer the potential to develop tools for differentiating these mechanisms in individual patients and ultimately provide a principled basis for treatment selection. However, development of these tools for differential diagnosis will require guidance by pathophysiological and cognitive theories that propose mechanisms which can be assessed in individual patients. This article provides an overview of contemporary pathophysiological theories of fatigue in MS and discusses how the mechanisms they propose may become measurable with emerging technologies and thus lay a foundation for future personalised treatments.

## INTRODUCTION

Multiple sclerosis (MS) is the most common neurological disease that causes disability in young adults (for recent reviews, see<sup>1–3</sup>). With an estimated prevalence of up to 83%, fatigue is one of the most common symptoms in MS<sup>4–6</sup> and exerts the greatest impact on patients' quality of life.<sup>4,7</sup> Fatigue therefore represents one of the most pressing clinical problems in the management of MS. Beyond MS, fatigue represents a relevant symptom in numerous disorders from internal medicine, neurology and psychiatry.<sup>7–9</sup> In general practice, 20% of patients complain of fatigue; this increases up to 50% in diseases involving the dysregulation of the immune system such as chronic infections, cancer or autoimmune diseases.<sup>10</sup> It is also a frequently reported feature of psychiatric diseases and represents a core diagnostic criterion of depression in DSM-5.

As for other neuropsychiatric symptoms, fatigue likely results from different underlying causes.<sup>7,10</sup> At present, diagnostic tools are missing which differentiate, in individual patients, between alternative potential causes of fatigue. As a consequence, we lack a principled basis for treatment selection: while several pharmacological and physical therapies are used in practice—for example, drugs like amantadine<sup>11</sup> or modafinil<sup>12</sup> that affect glutamatergic and dopaminergic transmission and reuptake of monoaminergic transmitters, respectively—treatment selection proceeds by trial and error and under

consideration of side effects, rather than by assessment of individual pathophysiological mechanisms. The current absence of objective clinical tests for differentiating alternative disease mechanisms constitutes a critical barrier to improving individual treatment decisions.

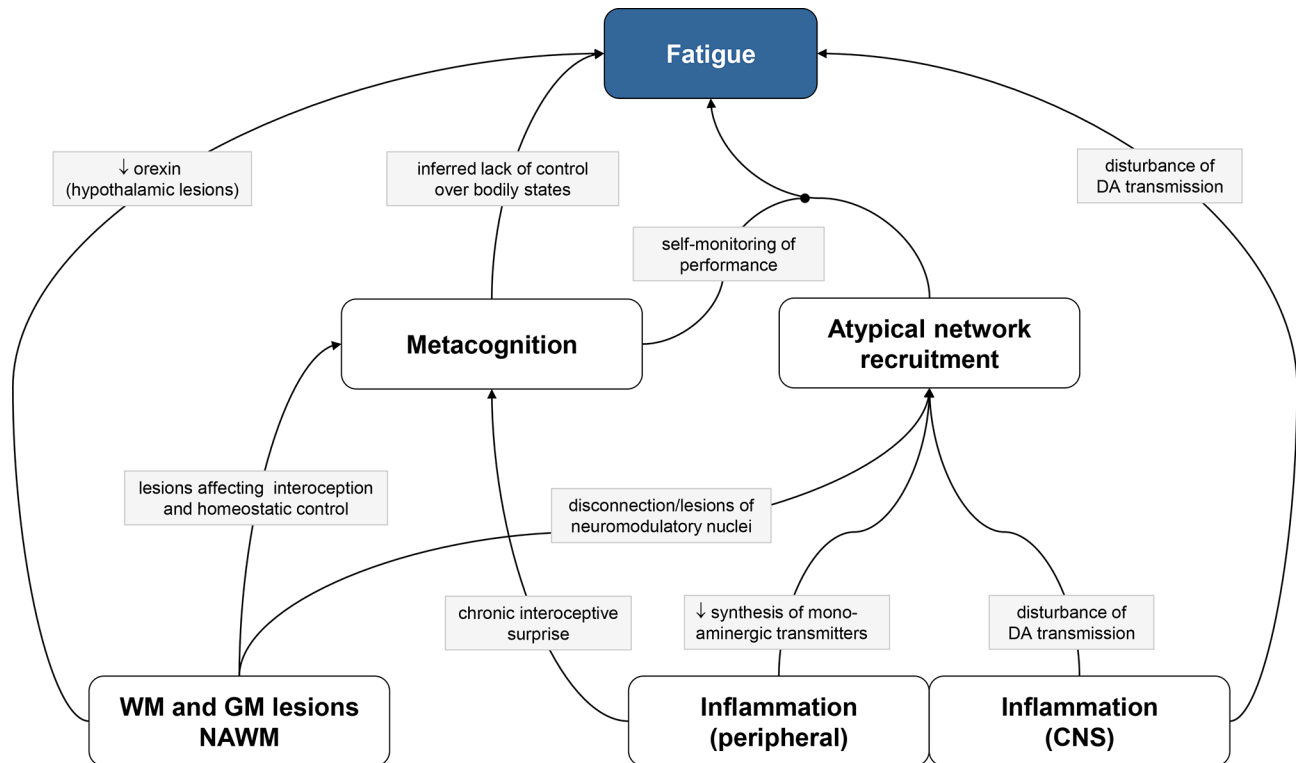
Developing tools for differential diagnosis of fatigue in MS requires pathophysiological theories that propose mechanisms which can, in principle, be assessed in individual patients. Previous review articles (eg,<sup>10</sup>) have mostly treated fatigue as a clinical symptom across disorders. In this paper, we concentrate on MS and discuss possible pathophysiological mechanisms. Our review article provides an overview of contemporary theories of fatigue in MS and discusses how the mechanisms they propose may become measurable with emerging technologies, potentially leading to differential diagnosis and treatment predictions in the future.

Initially, we briefly revisit the definition of fatigue and standard diagnostic procedures. This serves as a reminder that 'fatigue' is not a well-defined concept. This is not a trivial issue: one reason for the heterogeneity of the literature on fatigue is that past studies have assessed different constructs of fatigue, for example, not always distinguishing between the subjective perception of fatigue and externally observable fatigability of cognitive or motor functions.

## Heterogeneous concepts of 'fatigue'

Concepts of fatigue vary remarkably in the literature. For example, fatigue has been described as 'a feeling arising from difficulty in initiation of or sustaining voluntary effort',<sup>8</sup> 'an overwhelming sense of tiredness that is out of proportion (in relation to the performed activity)',<sup>13</sup> or as a 'feeling that relates to the lack of motivation to deploy resources and engage in high effort performance to cope with their situation'.<sup>10</sup>

In an attempt towards standardisation, a recent taxonomy distinguishes two major dimensions of fatigue: perception of fatigue and performance fatigability.<sup>5</sup> The latter refers to objectively measurable aspects of fatigue, for example, the observable decrease in performance during a cognitive or motor task. By contrast, the perceptual dimension is inherently subjective and cannot be assessed directly by an external observer. From a pathomechanistic perspective, these two dimensions are distinct: explanations of fatigability can, in



**Figure 1** Pathophysiological mechanisms of fatigue discussed in this article. White and grey boxes represent classes of mechanisms and specific mechanisms, respectively; directed arrows and circle-ended arrows represent direct and mediating effects, respectively. Due to space limitations, only one mechanism per arrow is shown; see main text for other mechanisms. CNS, central nervous system; DA, dopamine; GM, grey matter; NAWM, normally appearing white matter; WM, white matter.

principle, be derived from physiological and biochemical principles. By contrast, understanding the subjective perception of fatigue requires a cognitive perspective, in particular, concepts of interoception and metacognition.<sup>14–16</sup>

For clinical practice, operationalised definitions of fatigue are provided by various fatigue questionnaires; see<sup>7 17</sup> for overview. Some questionnaires were specifically designed for MS.<sup>18</sup> Again, these questionnaires show notable differences in how they operationalise fatigue, which represents an important source of heterogeneity in pathophysiological studies of fatigue.<sup>17</sup>

### Pathophysiological concepts of fatigue

This article focuses on four main classes of potential pathophysiological mechanisms of fatigue in MS (figure 1):

1. Structural damage of white matter (WM) and grey matter (GM),
2. Inflammatory processes (within or outside the central nervous system, CNS),
3. Maladaptive network recruitment due to distributed lesions or inflammation,
4. Metacognition (self-monitoring) of interoception of dyshomeostatic states.

### Structural brain damage

MS is characterised by lesions in the CNS that are disseminated in space (eg, in the cerebrum, brainstem, spinal cord) and time (dynamic changes in lesion load). A key pathological feature of MS are WM lesions with demyelination and inflammation that lead to axonal damage and progressive degeneration.<sup>1</sup> Additionally, GM lesions are present, resulting from cortical demyelination due to subpial inflammation, retrograde neuronal degeneration

following axonal transection and degenerative mechanisms due to oxidative injury.<sup>19</sup> Beyond demarcated lesions, the above processes induce diffuse damage of WM and GM that may lead to regional and whole-brain atrophy. Morphometric studies reported mixed results on the potential link between global measures of brain atrophy and fatigue<sup>20–22</sup> and between local measures of WM/GM atrophy and fatigue,<sup>23–27</sup> respectively. In the following, we discuss how different forms of WM and GM damage may play a role for the experience of fatigue.

### WM lesions

A general idea is that fatigue may result from global impairment of brain function due to distributed WM lesions.<sup>28 29</sup> Several studies have used structural MRI and morphometric analyses of WM lesion load to test this idea. Across studies, the overall results are mixed: while some studies found a correlation between fatigue and global structural damage of WM,<sup>20 21 23 30</sup> other studies failed to do so.<sup>31–34</sup> This inconsistency may partially result from differences in methodology, for example, quantifying structural brain damage with different morphometric methods.<sup>35</sup> An alternative explanation for variability across studies is that individual degrees of fatigue may be determined more by the locations of WM lesions than by global lesion load.<sup>24 36</sup> Individual differences in normal-appearing white matter might additionally contribute to this variability.<sup>24 29</sup> As a final factor of variability, there is an ongoing debate whether individual disease trajectories of MS may be driven differentially by inflammation and neurodegeneration<sup>37 38</sup>; such differences in disease mechanisms could also relate to differences in fatigue.

Assuming a correlation between WM damage and fatigue can be ascertained, what exactly mediates this link? One explanation

concerns fatigability (cognitive or motor): this might originate from reduced activation of the central or peripheral targets of synaptic connexions due to diminished speed and reliability of axonal transmission. In particular, demyelination is known to result in the slowing of conduction speed.<sup>39 40</sup> Additionally, activity-dependent conduction block may contribute to fatigability.<sup>41</sup> Therapeutically, fampridine (4-aminopyridine) is thought to improve the conduction of action potentials in demyelinated nerves by blocking voltage-gated potassium channels.<sup>42</sup> Clinical studies on the efficacy of fampridine for treating fatigue in MS have obtained mixed results so far.<sup>43 44</sup>

A second explanation refers to structural disconnection, specifically disruption of communication between brain regions with functions of relevance for fatigue, such as motor planning and execution.<sup>45 46</sup> Diffusion-weighted imaging studies demonstrated that WM changes are correlated with fatigue, particularly in the anterior internal capsule and anterior thalamic tract.<sup>23 24 28 29 47 48</sup> Alternatively, WM damage could disconnect areas of importance for arousal and motivation.<sup>46</sup> This is less well investigated, but a tractography study reported altered connectivity between posterior hypothalamus and mesencephalon,<sup>49</sup> a tract thought to contain wakefulness-promoting ascending monoaminergic connexions.

### GM lesions

GM lesions were long hypothesised to be part of the disease.<sup>50 51</sup> However, it was not until the beginning of the 21st century that improved immunohistochemical techniques, high-resolution structural MRI and quantitative morphometry techniques provided clear evidence for GM lesions in MS. GM lesions in MS are discussed by several recent reviews.<sup>52–54</sup>

The spatial distribution of GM lesions in MS is diffuse.<sup>55</sup> Recent neuropathological probability maps of lesions in both WM and GM<sup>19</sup> emphasised the occurrence of GM lesions in regions with deep invaginations, such as insular and anterior cingulate cortex (ACC); notably, these are areas of central relevance for interoception, a topic discussed below. Furthermore, this study suggested two different degenerative mechanisms in cortex, that is, inflammation-induced oxidative injury of neurons and retrograde neurodegeneration due to axonal transection.<sup>19</sup> In subcortical regions, frequent sites of GM lesions include the thalamus, basal ganglia, amygdala, substantia nigra and hypothalamus.<sup>56</sup>

How might GM lesions cause fatigue? First, similarly to WM lesions, GM lesions could disturb coordinated activity and connectivity in large-scale networks that mediate motor and cognitive processes, leading to compensatory activity in additional nodes and reducing the scope of adaptive changes.<sup>57</sup> This change in network function might be detected by metacognitive mechanisms (see below and [figure 1](#)). Empirical investigations of cerebral networks in fatigue patients by neuroimaging demonstrated altered functional connectivity of the basal ganglia,<sup>58</sup> among sensorimotor regions,<sup>59</sup> or of the default mode network.<sup>60</sup>

Second, some of the commonly found deep GM lesions affect structures that are directly involved in vigilance, arousal and motivation. One prominent example is the hypothalamus, which neuropathological studies identified as a frequent lesion site in MS<sup>61–64</sup> and which is critical for homeostatic regulation (see below). Moreover, the lateral hypothalamus hosts neurons producing orexin, a neuropeptide of fundamental importance for arousal and vigilance. In narcolepsy, a disease with dramatically reduced vigilance, autoimmunological reactions against orexin-producing neurons strongly decrease orexin levels.<sup>65</sup>

This led to the hypothesis that less pronounced reductions of orexin might produce fatigue in MS. For example, hypothalamic lesions in MS could lead to partial depletion of orexin; alternatively, immunological processes could affect the synthesis and/or postsynaptic efficacy of orexin. So far, studies correlating orexin levels in the cerebrospinal fluid (CSF) and fatigue scores have provided conflicting results.<sup>66 67</sup>

A third possibility of how GM lesions may cause fatigue refers to the frequent involvement of the brainstem in MS. Specifically, lesions of dopaminergic, serotonergic or noradrenergic nuclei in the brainstem and the consequent reduction of monoaminergic transmitter supply to cortex and basal ganglia could explain the reduction in motivation, mood and arousal that characterise fatigue.

Finally, GM lesions in hypothalamus or brainstem nuclei could disturb the hypothalamus–pituitary–adrenal axis and descending neural control of the autonomic nervous system leading to persistent endocrine and autonomic disturbances, respectively.<sup>62 68</sup> This could cause fatigue directly, for example, due to diminished energy supply or hypotension; additionally, perception of prolonged dyshomeostasis has been postulated to underlie subjective experience of fatigue by metacognitive theories that are described below.<sup>14 16</sup>

### Immunological and inflammatory processes

The immune system plays a key role in aetiology and progression of MS.<sup>2 3 69</sup> In general, immunological processes in the CNS and the body can interact through multiple pathways.<sup>70 71</sup> In MS, the relative contributions of central and peripheral immunological events during the induction and early inflammatory phase of MS are not fully understood. In particular, it remains to be clarified whether a primary immunological process takes place in the brain and spreads to the periphery or whether immune activation begins peripherally before being transferred to the initially unaffected CNS (for review, see<sup>69</sup>). The latter possibility is supported by the fact that highly effective immunomodulatory treatments for MS (eg, fingolimod, rituximab) have peripheral targets. Regardless of where the initial immune response occurred, myelin damage in the CNS is thought to lead to the release of antigens to the periphery.<sup>2</sup> This, in turn, primes immune responses in lymphoid tissue and triggers the invasion of lymphocytes into the CNS.<sup>2</sup> While peripheral immune responses may be the driving force at the early stage of MS, evidence suggests that later in the disease, the immune response is shifted and compartmentalised to the CNS in lymphoid-like follicles in the meninges that maintain chronic inflammation.<sup>72</sup>

Peripheral immunological and inflammatory processes are likely to play a central role for fatigue, in general,<sup>10</sup> and in the specific context of MS.<sup>73 74</sup> This is illustrated by ‘sickness behaviour’, a syndrome of fatigue, social withdrawal and lowered mood during common infections that trigger the production of proinflammatory cytokines.<sup>75</sup> Furthermore, fatigue can be induced by immunomodulatory drugs like interferon- $\alpha$ <sup>76 77</sup> or vaccinations that trigger production of proinflammatory cytokines.<sup>78</sup> These findings raise the question of how peripheral immunological and inflammatory processes could affect the CNS in MS and impact the experience of fatigue. Several direct and indirect immune-to-brain pathways have been unearthed in the past few decades, including humoral, cellular and neuronal interfaces.<sup>10 70 71</sup>

Humoral links are established via circumventricular organs where inflammatory cytokines can cross the blood–brain barrier and bind to neurons with specific receptors; furthermore,

cytokines such as IL-6 can exert direct actions on brain endothelial cells to produce inflammatory factors such as prostaglandin E2. These processes can trigger both central (eg, microglia activation, projections to the hypothalamus and nucleus of the solitary tract, NTS) and peripheral (eg, fever) processes. Peripheral immune states can also be signalled to the brain by trafficking of immune cells, such as monocytes; this constitutes a cellular pathway. Finally, neural immune-to-brain pathways consist of visceral (especially vagal) afferents that are activated by proinflammatory mediators such as interleukin-1.<sup>79</sup> Anatomically, afferent vagal projections are relayed via the NTS and ventromedial posterior thalamus to posterior and mid-insula.<sup>80 81</sup> Insular responses to peripheral inflammatory processes have been documented in humans, for example, using functional neuroimaging after induction of acute inflammation by typhoid vaccination<sup>80 82</sup> or after injection of endotoxins.<sup>83</sup> This interoceptive pathway is an important immune-to-brain link in sickness behaviour and plays a central role in metacognitive hypotheses of fatigue (see below). It also represents the afferent part of a reflex arc that regulates, through NTS projections to the vagal dorsal motor nucleus and nucleus ambiguus, peripheral immunological processes via hypothalamus–pituitary axis activation and anti-inflammatory cholinergic pathways.<sup>84</sup>

Additionally, several indirect pathways exist how peripheral inflammation can affect the CNS. One notable upstream consequence of peripheral inflammation is a reduction in synthesis of monoaminergic neurotransmitters such as dopamine, norepinephrine and serotonin.<sup>10 71</sup> In brief, peripheral inflammation leads to a deficit of tetrahydrobiopterin, an essential cofactor of aromatic amino acid hydroxylase enzymes which are critical for the synthesis of monoamines. This is a potentially highly relevant mechanism for fatigue: given the well-documented involvement of these neuromodulatory transmitters in motivation (dopamine), arousal (norepinephrine) and mood (serotonin), it is conceivable that a general reduction in their synthesis could produce the clinical picture of fatigue. This idea has been investigated experimentally in relation to dopamine. For example, decreased activity of the dopaminergic midbrain was recently demonstrated using functional MRI (fMRI) following typhoid vaccination as a model of systemic inflammation.<sup>80 85</sup> Similarly, <sup>18</sup>F-dopa PET in patients undergoing therapy with interferon- $\alpha$  showed significant changes in presynaptic striatal dopamine function, consistent with a decrease in synthesis of dopamine.<sup>77</sup>

A further indirect mechanism of how peripheral inflammation affects the CNS is provided by the kynurenine pathway. This pathway is involved in the metabolism of tryptophan, an essential precursor for monoamine synthesis. In brief, inflammatory mediators activate indoleamine-2,3-dioxygenase which degrades tryptophan along the kynurenine pathway and thus limits monoamine synthesis. Inside the CNS, kynurenine is further metabolised to neurotoxic metabolites such as quinolinic acid, an NMDA receptor agonist which may trigger excitotoxicity and cerebral inflammation.<sup>86</sup> Kynurenine has been studied in animal models of relapsing–remitting MS, such as experimental autoimmune encephalomyelitis, as well as in MS in humans (see<sup>87</sup> for a review of empirical evidence for altered kynurenine pathway activity in MS). While the exact contribution of kynurenines to fatigue remains to be established, a recent study in mice demonstrated that physical exercise activates molecular pathways in muscle that accelerate conversion of kynurenine (which can pass the blood–brain barrier) into kynurenic acid (which cannot), and that this mechanism protects against depressinogenic effects of both direct kynurenine administration and chronic stress.<sup>88</sup> In humans, the volume of the striatum, which is of relevance for

reward and motivational processes, is inversely associated with activation of the kynurenine pathway.<sup>89</sup>

Following this brief overview of how peripheral inflammation may relate to the experience of fatigue, the question remains how inflammation *inside* the CNS might lead to fatigue. One possibility relates to dopamine: CNS inflammation triggers activation of microglia, and the ensuing production of cytokines *in situ* negatively affects dopaminergic transmission, for example, through direct effects on dopamine transporters and receptor function (for review, see<sup>10</sup>). This has motivated a view of fatigue as resulting from altered connectivity between striatum and prefrontal cortex.<sup>8 90</sup> The efficacy of this connexion depends on dopaminergic meso-prefrontal afferents and has been implicated in reward-oriented learning and motivation.<sup>91</sup> In brief, from this view, fatigue is conceptualised as a variation of altered response to reward and the ensuing decrease in motivation.

An alternative mechanism for how inflammation within the CNS could produce fatigue rests on orexin, a neuropeptide produced by neurons in the lateral hypothalamus.<sup>65</sup> In addition to its critical role for vigilance and arousal (as visible in narcolepsy, see above), orexin is involved in the sleep–wake cycle, reward processing and food intake. Animal studies found that inflammation-induced lethargy is mediated by suppression of orexin neuron activity by interleukin-1 $\beta$  and TNF- $\alpha$ <sup>92</sup> and that orexin levels correlate with diminished vigilance and exploratory behaviour.<sup>93</sup> Concerning MS, the role of orexin for fatigue has not yet been firmly established: studies on the correlation between fatigue and CSF orexin levels have provided contradictory results.<sup>66 67</sup>

### Maladaptive network recruitment during task performance

Functional imaging studies have demonstrated that patients with MS affected by fatigue, compared with patients with MS without fatigue and healthy controls, frequently show an increase of distributed brain activity during the performance of tasks.<sup>45 47 94 95</sup> In the spinal cord, patients with MS with fatigue, despite smaller WM lesion load, show higher functional recruitment of the cervical cord than patients with MS without fatigue<sup>96</sup> (for discussion, see<sup>97</sup>). Moreover, patients with MS with fatigue often fail to show physiological adaptation of brain activity during tasks<sup>57</sup> (but see<sup>98</sup>). This may differ across disease stages and brain regions.<sup>99 100</sup>

One possible explanation for altered cortical activity in MS is that networks mediating specific cognitive operations are perturbed by one of the mechanisms described above, that is, WM/GM lesions or functional impairments due to inflammatory processes. In order to maintain cognitive performance despite lesion-induced or inflammation-induced loss of network function, compensatory recruitment of neuronal tissue may be needed, either in terms of additional regions not usually contributing to a particular task and/or in terms of unusually high levels of activation. Analogous findings have been obtained in other diseases with discrete lesions, such as stroke.<sup>101</sup> Whatever the cause of altered cortical activity, the question remains how aberrant activity levels are linked to subjective experience of fatigue. One possibility is that the activation of ‘atypical’ and the compensatory (non-adapting) activation of ‘typical’ regions might be detected by self-monitoring mechanisms, a metacognitive perspective we discuss below.

An alternative possibility is that impairment of neuromodulatory projections from the brainstem—by lesions or by inflammation-induced decrease of transmitter synthesis<sup>102</sup>—could lead to a functional reorganisation of cortical networks. This is because

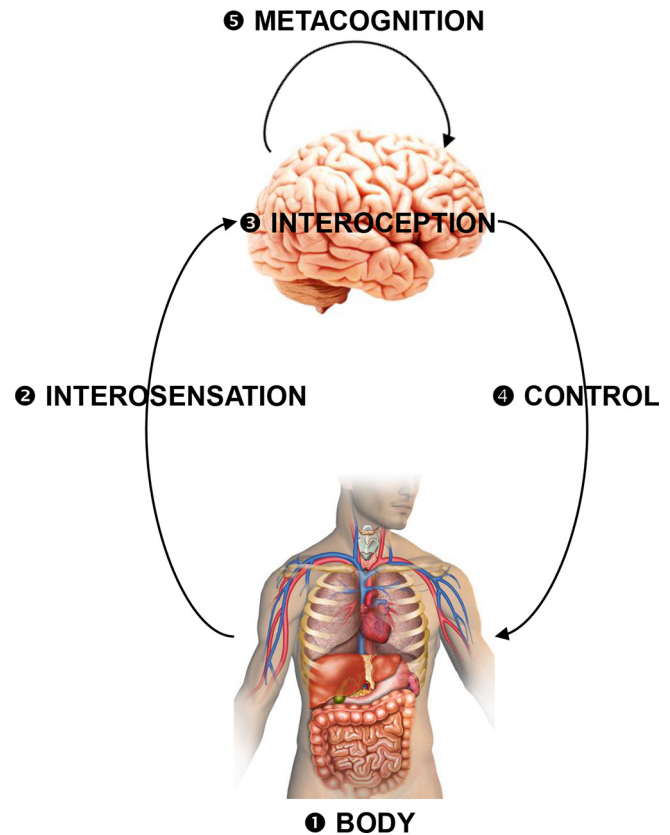


neuromodulatory transmitters profoundly influence activity and connectivity in cortex, by two major mechanisms. First, they regulate neuronal gain and excitability via slow afterhyperpolarisation currents mediated by calcium-dependent potassium channels<sup>103</sup>; second, they alter both short-term and long-term synaptic plasticity by modulating NMDA receptors.<sup>104</sup> Rapid functional reorganisation of cortical networks in response to manipulations of neuromodulatory transmitters was demonstrated in human and animal studies,<sup>105 106</sup> and it is conceivable that similar effects could arise from brainstem lesions in MS or through effects of inflammation on monoamine synthesis.<sup>102</sup>

### Metacognitive perspective on fatigue

The disease theories discussed so far offer potential physiological mechanisms but do not explain how the subjective experience of fatigue might arise. A metacognitive perspective may provide a crucial bridge here. Metacognition corresponds to cognition about cognition, such as judging the accuracy of a perceptual decision.<sup>107</sup> In cybernetic theories of brain function, metacognition is understood as ‘self-monitoring of one’s level of mastery in acting on the world... and can be seen as a high-level form of inference about one’s capacity for control’<sup>16</sup> (figure 2). Three metacognitive mechanisms of fatigue have been proposed—with emphasis on (1) interoception, that is, the perception of bodily states, (2) network-level function and (3) perceived effort of movements, respectively.

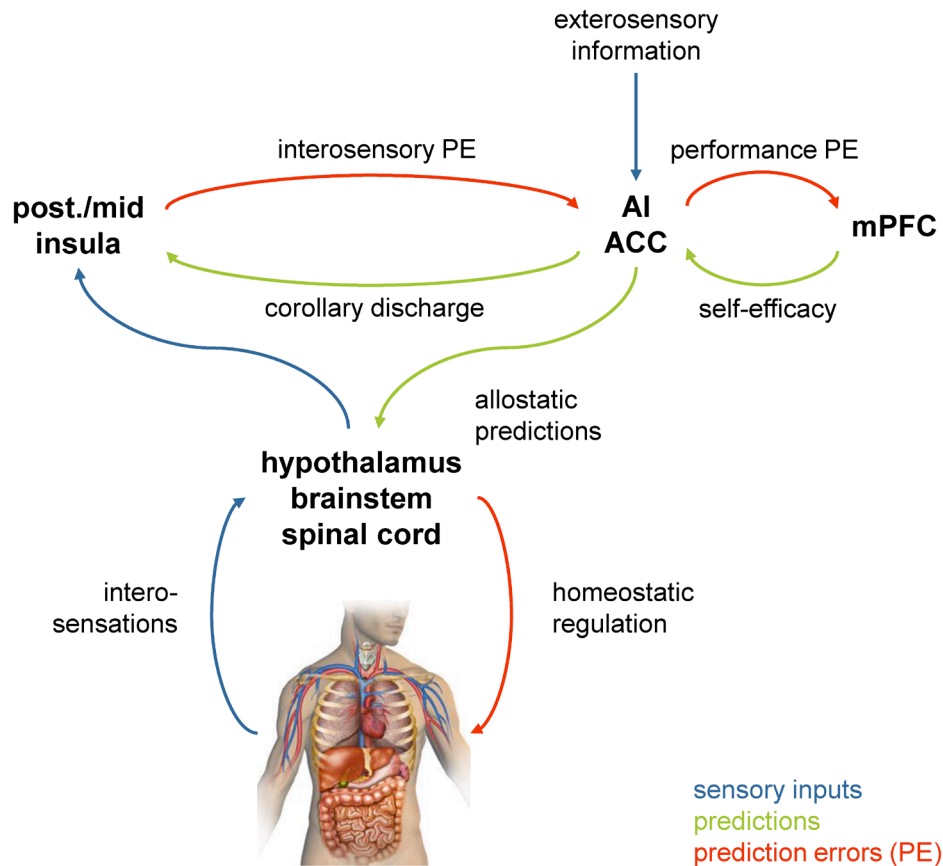
First, interoception—the perception of the physiological state of the body, including blood oxygenation, acidity and osmolality; heart rate; plasma concentration of glucose, hormones, cytokines and so on—is disturbed in MS<sup>108</sup> and is increasingly recognised as an important factor for the experience of fatigue.<sup>70 109</sup> The interoception-related metacognitive theory views fatigue as resulting from the brain’s inference about its capacity for control.<sup>14</sup> Specifically, it postulates that fatigue reflects the metacognitive diagnosis that the brain is failing to exert control over bodily states and does not have any action at its disposal to overcome a state of dyshomeostasis. Given this inferred helplessness or low ‘allostatic self-efficacy’, fatigue would correspond to a feeling state that signals the futility of any further actions. A central notion of this theory is that the brain’s capacity to regulate bodily states is represented by a compact information-theoretic quantity (ie, interoceptive surprise) that can be accessed by metacognitive areas. Neuronally, interoceptive surprise can be computed from prediction error signals that index the mismatch between expected and actual bodily states (figure 3). These prediction errors are thought to be signalled by pyramidal cells in supragranular layers of interoceptive areas (eg, insula, ACC) and to require ionotropic glutamatergic receptors, particularly NMDA receptors.<sup>14 110 111</sup> While this exact mechanism remains to be demonstrated experimentally, the general theory is supported by empirical evidence from different investigations, including the correlation of activity in insula and ACC with subjectively perceived fatigue during experimentally controlled states of dyshomeostasis, such as induced inflammation.<sup>80 82</sup> Moreover, the theory explains why fatigue is a frequent symptom of any disease that involves chronic dyshomeostatic states, including immunological, metabolic, endocrine, cardiovascular, hepatic and renal diseases.<sup>9 10</sup> Notably, recent neuroimaging investigations of patients with MS demonstrated that electrophysiological markers of interoception are altered; at the same time, insula and ACC were found to show structural atrophy and abnormal functional connectivity.<sup>108</sup>



**Figure 2** A coarse schematic overview of the inference–control–metacognition loop for bodily regulation (for details, see<sup>16</sup>). Interoceptive surprise as a possible computational substrate of fatigue can arise from perturbations of any components of this loop: (1) actual perturbations of bodily state that evade cerebral attempts of correction (eg, chronic inflammation, cancer); (2) altered interoceptions (due to pathologies of interoceptors or afferent pathways); (3) disturbances of interoception (eg, inflammatory lesions of insula); (4) disturbances of interoactions (neuronally or endocrinologically mediated cerebral influences on bodily functions), for example, inflammatory lesions of ACC, brainstem, hypothalamus or their projections; (5) altered metacognitive processes (eg, changes in expected performance levels). The multiple failure loci offer a potential explanation for the clinical heterogeneity of fatigue and speaks to the necessity of developing tools for differential diagnostics at the circuit level.

A clinically important corollary of this theory is that fatigue necessarily has very different causes. This is because interoceptive surprise can arise from disturbances of any component of the closed-loop relation between interoception, bodily regulation and metacognition<sup>16</sup> (see figure 2). Notably, interoceptive surprise can result from merely perceived dyshomeostasis. This could occur when the cortical areas that infer bodily states are perturbed, for example, due to inflammatory lesions of the insula which are frequent in MS.<sup>19</sup> The ensuing ‘illusion’ of dyshomeostasis would elicit misinformed interoactions, creating dyshomeostatic bodily states that reify the initially spurious interoceptive surprise and render it chronic. Similarly, primary disturbances of interoactions—for example, due to inflammatory lesions of visceromotor areas like ACC,<sup>19</sup> hypothalamus<sup>62</sup> or brainstem nuclei—would produce lasting perturbations of bodily states.

Second, fatigue might also arise from other forms of prediction error or surprise that the brain finds itself unable to reduce.<sup>14 109</sup>



**Figure 3** Neuroanatomically specific circuit model of interoception that plays a central role in theories of fatigue from computational psychiatry.<sup>14</sup> The regions are based on anatomical investigations of interoceptive circuitry<sup>81</sup>; the network they form is thought to instantiate a predictive model of bodily states.<sup>111</sup> In this hierarchical network, predictions are sent from higher to lower areas, while prediction errors (PE; the difference between actual and predicted states) are signalled in the opposite direction and used to update predictions ('predictive coding'<sup>110</sup>). Specifically, hierarchically higher visceromotor areas, such as the anterior insula (AI) and anterior cingulate cortex (ACC), are thought to tune homeostatic reflex arcs by means of allostatic predictions computed from bodily and environmental information. In turn, AI/ACC inform hierarchically lower areas, such as posterior and mid-insula, about the expected interosensory consequences (corollary discharge). The latter areas compare these predictions against actual interosensory input and return PE that serve to update the predictions by AI/ACC. At the top of the hierarchy, metacognitive areas (possibly medial prefrontal cortex, mPFC) monitor the level of PE and compute interoceptive surprise. The better the predicted bodily states can be achieved through regulatory action, the smaller PE and interoceptive surprise. Importantly, because of the closed-loop nature of brain–body interactions (figure 2), impairments of any part of the network can lead to chronic interoceptive surprise. This may lead to the metacognitive diagnosis of helplessness or low allostatic self-efficacy (lack of control over bodily states) and has been posited as the substrate for fatigue as a feeling state.<sup>14</sup>

The brain's self-monitoring of performance is not restricted to interoception and its associated circuitry; instead, expectations are held about any domain of cognition, and domain-independent mechanisms of metacognition exist<sup>112</sup> which might 'read out' error signals from domain-specific functional networks.<sup>16</sup> In MS, lesions outside interoceptive pathways impair performance levels of many cognitive and motor acts, as reflected by progressive changes in functional networks.<sup>113</sup> Similar to fatigue resulting from bodily dyshomeostasis, this might lead to fatigue as a metacognitive diagnosis of network function: the brain's interpretation of its own state as a chronic mismatch between actual and expected performance levels that is not amenable to actions.<sup>14</sup>

Finally, a third proposed metacognitive mechanism of fatigue focuses exclusively on the sensorimotor system.<sup>15</sup> This concept assumes that diminished sensory attenuation during the execution of movements would lead to proprioceptive prediction errors, requiring the brain to conclude that movements require more effort than predicted. Thus, here the emphasis is on fatigue

as a direct consequence of unexpectedly high perceived effort during movements (proprioceptive surprise) as a cognitive cause of fatigue.

### Towards differential diagnosis and targeted treatment of fatigue

Treatment of fatigue in MS involves the initial exclusion of MS-unrelated causes, for example, anaemia, hypothyroidism or sleep disturbances such as obstructive sleep apnoea. Subsequently, the choice of disease-modifying drugs could be oriented towards drugs with potentially beneficial effects on fatigue. For example, glatiramer acetate might reduce fatigue more effectively than  $\beta$ -interferon.<sup>114</sup> Some studies demonstrated that natalizumab may decrease fatigue in patients with MS,<sup>115 116</sup> although this might result from a primary effect of natalizumab on depression.<sup>117</sup>

A central question for this review is how fatigue-specific treatments could be personalised, given that fatigue in MS likely

arises through multiple mechanisms (figure 1). In clinical practice, we are presently unable to differentiate between alternative causes of fatigue in individual patients. As a consequence, current treatment of fatigue is driven by trial and error and consideration of side effects. Treatment strategies for fatigue in MS include both pharmacological approaches (eg, the NMDA receptor antagonist amantadine, stimulants such as modafinil, or antidepressants) and non-pharmacological strategies (eg, mindfulness-based cognitive therapy (MBCT), cognitive-behavioural therapy or exercise) (for recent reviews, see<sup>118 119</sup>). Additionally, social factors, cognitive profiles and psychological traits modulate fatigue<sup>120 121</sup>; these may offer additional entry points for therapeutic interventions.

In order to select treatments in a rational and predictive manner, novel clinical tests are needed. Importantly, these need to go beyond detecting fatigue; instead, they should inform the choice of patient-specific treatment—by enabling differential diagnosis of alternative mechanisms and/or predicting individual therapeutic response. Some of the candidate mechanisms discussed above map onto existing treatment approaches; others suggest novel treatment strategies. How could these be identified, in individual patients, with existing or emerging techniques?

As all of the pathophysiological mechanisms discussed above eventually lead to changes in network function, measures of brain connectivity are of central importance. In the domain of fMRI, methodological developments have enabled a transition from simple estimates of undirected coupling (functional connectivity) to model-based measures of directed influences between neuronal populations (effective connectivity). The latter have become increasingly sophisticated—with an ability to resolve neuronal versus haemodynamic contributions to layer-wise fMRI signals and characterising transient modulatory influences<sup>122</sup>—and are increasingly used in translational neuroimaging.<sup>123</sup> Furthermore, recent developments allow for computationally efficient whole-brain estimates of effective connectivity,<sup>124</sup> which is important for diseases with distributed pathology as MS.

In conjunction with high-resolution fMRI, models of effective connectivity could probe specific candidate mechanisms of fatigue in individual patients, with implications for treatment choice. For example, occult dysfunction of specific nuclei—say through inflammation-induced reduction of monoaminergic transmitter synthesis in brainstem nuclei or of orexin in lateral hypothalamus—could be inferred by assessing efferent connexion strengths of the corresponding nuclei to known target regions (or across the whole brain). For assays of monoaminergic nuclei, this approach could be further enhanced by computational models of transmitter release, respectively.<sup>125</sup> If abnormal connectivity of specific nuclei can be established (eg, in comparison with reference distributions), this may predict beneficial therapeutic effects of stimulants (modafinil) or selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors.

Similarly, estimates of effective connectivity between areas involved in interoception, homeostatic control and metacognition could help identify patients in whom fatigue results from a metacognitive diagnosis of helplessness with regard to overcoming dyshomeostasis (compare figure 3). This could be combined with inflammation-sensitive MRI sequences<sup>82</sup> and designed perturbations of interoceptive and homeostatic processes<sup>16</sup> to detect abnormalities in key circuit components frequently affected by inflammation and lesions in MS.<sup>19 62</sup> If investigations of this sort point to a metacognitive/interoceptive origin of fatigue, this may predict therapeutic efficacy of

MBCT<sup>126</sup> or related forms of contemplative training with a focus on interoception.

Moving from MRI to electrophysiological techniques, several approaches could contribute to differential diagnosis and prognosis of fatigue in MS.<sup>127 128</sup> For example, multimodal (visual, auditory, somatosensory, motor) evoked potentials (EPs) measured by electroencephalography (EEG) and transcranial magnetic stimulation (TMS), respectively, have predictive value with regard to future disability status in general.<sup>129 130</sup> By contrast, there are hardly any prospective EP studies with a specific focus on predicting fatigue. One such study highlighting the potential use of EPs suggested that the auditory P300 potential may predict treatment response to modafinil, although with moderate sensitivity and specificity.<sup>131</sup>

Recently developed computational methods might enhance the use of EEG data for differential diagnosis of fatigue and treatment prediction. For example, biophysical models of EEG data have shown promising potential for detecting pathologies at the synaptic level, including dysfunction of the NMDA receptor.<sup>132</sup> Models of this kind might help inform individual application of amantadine, one of the few agents featuring in official guidelines (National Institute for Health and Care Excellence, UK), but with only weak efficacy in non-selected patients.<sup>118</sup> Similar models of magnetoencephalography data from patients with monogenetic channelopathies have demonstrated that it may be possible to identify selective alterations of specific ion channels, such as voltage-gated potassium channels.<sup>133</sup> This approach could help in identifying those fatigue patients who might benefit from treatment with fampridine. This question might also be addressed by TMS: a prospective study using motor EPs in patients with MS fatigue prior to therapy with fampridine showed that increased central motor conduction time might predict individual treatment response.<sup>134</sup>

## CONCLUSIONS AND OUTLOOK

Despite its frequency and pronounced impact on the lives of patients with MS, techniques for differential diagnosis of fatigue and mechanism-guided treatment selection in individual patients do not exist. A critical basis for developing such methods are pathophysiological theories about the mechanisms of fatigue. This paper has reviewed contemporary theories about four major classes of disease mechanisms leading to fatigue: structural damage of WM/GM, inflammatory processes, maladaptive network recruitment during task performance and metacognitive interpretations of brain states that suggest ‘helplessness’. We anticipate that these theories together with recent advances in high-resolution functional neuroimaging and computational modelling will guide the development of tools for differential diagnosis. Similar to ongoing efforts in psychiatry,<sup>123</sup> computational neuroimaging tools may provide indices of different causes of fatigue that support treatment decisions in individual patients. This represents an exciting and promising endeavour, but will require prospective patient studies for validating the clinical use of candidate tools.

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