Fatigue in inflammatory rheumatic diseases: current knowledge and areas for future research

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Abstract | Fatigue is a complex phenomenon and an important health concern for many people with chronic inflammatory rheumatic diseases, such as rheumatoid arthritis, psoriatic arthritis, primary Sjögren syndrome and systemic lupus erythematosus. Although some clinical trials have shown the benefits of cognitive behavioural therapy in fatigue management, the effect of this approach is relatively modest, and no curative treatment has been identified. The pathogenesis of fatigue remains unclear. Despite many challenges and limitations, a growing body of research points to roles for the immune system, the central and autonomic nervous systems and the neuroendocrine system in the induction and maintenance of fatigue in chronic diseases. New insights indicate that sleep, genetic susceptibility, metabolic disturbances and other biological and physiological mechanisms contribute to fatigue. Furthermore, understanding of the relationships between psychosocial factors and fatigue is increasing. However, the interrelationships between these diverse mechanisms and fatigue remain poorly defined. In this Review, we outline various biological, physiological and psychosocial determinants of fatigue in inflammatory rheumatic diseases, and propose mechanistic and conceptual models of fatigue to summarize current understanding, stimulate debate and develop further research ideas.

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Inflammatory rheumatic diseases are a group of multi-system, immune-mediated rheumatic conditions that include primary Sjögren syndrome (pSS), systemic lupus erythematosus (SLE), vasculitis, psoriatic arthritis and rheumatoid arthritis (RA). Although the clinical manifestations of inflammatory rheumatic diseases vary, fatigue is a prevalent and often disabling symptom in many of them[1]. An international study of over 6,000 patients found that approximately half were severely fatigued, defined by a score of ≤35 on the 36-item short-form survey (SF-36) vitality scale[2]. Fatigue represents the largest health economic burden and unmet need to patients and society. Fatigue has been identified as one of the most challenging symptoms to manage for patients with inflammatory rheumatic diseases and is associated with poor quality of life[3–5]. Fatigue is also an important independent predictor of job loss and disability in patients with RA, ankylosing spondylitis, SLE, pSS and vasculitis[6–10]. Considering the widespread personal and economic burden of fatigue, discerning the underlying mechanisms and finding effective treatment options are research priorities.

In this Review, we outline various biological, physiological and psychosocial determinants of fatigue in inflammatory rheumatic diseases. We have taken a biopsychosocial approach[11] to understanding fatigue mechanisms, systematically considering biological, physiological, psychological and social factors and their complex interactions. Owing to the vast number of published articles mentioning "fatigue", and the challenges in drawing comparisons between different research studies on fatigue, we have not performed a comprehensive, systematic literature search. Also, several excellent reviews have focused on the role of inflammation and the brain in fatigue pathogenesis[12–15]. Therefore, in this Review we discuss what we consider to be the relevant evidence in the literature and include potential contributing mechanisms of fatigue that currently do not receive much attention. We also present hypothetical mechanistic and conceptual models of fatigue to summarize current understanding, stimulate debate and support the development of further research ideas.

The challenges of fatigue research

Fatigue is a complex, multifaceted phenomenon, and the many challenges in fatigue research limit our current understanding (BOX 1). Conceptually, no consensus exists on the definition of fatigue. Most people have experienced fatigue during their everyday life, but qualitative research suggests differences between fatigue

Key points

- Fatigue is a common and disabling symptom of inflammatory rheumatic diseases.
- The mechanisms of fatigue in inflammatory rheumatic diseases are not fully understood but are likely to involve multiple biological, physiological, psychosocial and behavioural mechanisms.
- The mechanisms of fatigue in inflammatory rheumatic diseases might change over time and vary between individuals.
- Fatigue might reflect the body's resource management strategy in response to chronic stressors, favouring rationing and storage over expenditure.
- Studying fatigue has many challenges; consensus on a study framework for fatigue research and a multidisciplinary approach are essential.
- Optimal management of fatigue requires a personalized and holistic approach.

Recall period
The period over which people are asked to recall a prior event (for example, their fatigue experiences, thoughts and/or behaviours).

Sickness behaviour
Adaptive behaviours (such as social withdrawal, reduced activity and increased sleep) developed by animals and humans during an acute infection that are presumed to be beneficial for recovery and survival.

Anhedonia
Loss of interest in activities that were previously enjoyed and a decreased ability to feel pleasure.

associated with chronic diseases and 'usual' or premorbid fatigue. The most distinguishing features of fatigue associated with chronic diseases include the perception of the fatigue as having no obvious 'explanation', a lack of improvement with rest, variability in severity, unpredictability and fatigue being profound or overwhelming[16,17]. Patients often explain their fatigue in relation to the considerable impact it can have on all aspects of their daily lives[18]. Such findings suggest the involvement of different mechanistic pathways in pathological fatigue and the fatigue experienced by healthy individuals, although the mechanisms of fatigue in both settings remain poorly defined. A related consideration is whether occurrences of fatigue associated with different chronic conditions (for example, RA, fibromyalgia, inflammatory bowel disease, Parkinson disease and cancer) are similar phenomena. Studies have shown similarities in the qualities of the fatigue experienced across a range of inflammatory and non-inflammatory chronic diseases[19,20]. Studies in different diseases have also identified similar 'predictors' of fatigue[21–23] (BOX 2). Furthermore, fatigue correlates poorly with the disease activity of the underlying conditions[24–28]. These observations suggest that fatigue might be the same phenomenon across different chronic conditions. In this Review, we focus on fatigue associated with inflammatory rheumatic diseases.

Measuring fatigue accurately and reliably is challenging. Fatigue is inherently a subjective phenomenon, and its assessment relies on the use of self-reported questionnaires. Many questionnaires have been developed to measure fatigue using different approaches and each having strengths and weaknesses[29]. Factors to consider when selecting a method to measure fatigue include whether the instrument should be generic versus disease-specific, whether it should be single-item versus multi-item, and/or whether it should provide a single overall score (usually for the severity of physical fatigue) versus sub-scale scores for different facets of fatigue (for example, physical, cognitive and emotional). The number of questionnaires in use and the lack of an agreed gold standard means that comparisons across studies are difficult, as demonstrated for studies in RA[30]. Additional issues contributing to cross-study comparisons include differing recall periods, variation in wording between questionnaires and the lack of cut-off values to define cases of fatigue in most questionnaires. Moreover, these questionnaires poorly capture the variability of the fatigue. Finally, patient-reported outcomes are prone to recall bias and other psychosocial influences, increasing the subjectivity of patients' responses. Objective assessment of fatigue, if available, would overcome some of these issues, although capturing patients' perceptions is also important to aid the interpretation of the outcomes.

Box 1 | **Challenges in fatigue research**

- No consensus has been reached on a definition of fatigue.
- Difficulties exist in measuring fatigue accurately and reliably.
- Addressing potential confounders of fatigue remains a challenge.
- The premorbid state of fatigue is often poorly described.

Difficulties in fatigue research also arise from potential confounders of fatigue, such as mood disorder and pain, and a lack of information about the premorbid fatigue state. Without knowledge on the premorbid levels of fatigue, one cannot determine whether the level of fatigue changes following the onset of the inflammatory rheumatic disease, thereby making it difficult to evaluate how the inflammatory rheumatic disease contributes (if at all) to the symptom.

Putative mechanisms in fatigue

Many biological, physiological and psychosocial mechanisms have been implicated in fatigue pathogenesis, such as the central nervous system, inflammation, pain and anxiety (FIG. 1). However, the cross-sectional nature of many of the studies investigating mechanisms of fatigue makes establishing causality and directionality a challenge. Furthermore, complex interactions exist between many of these mechanisms. It is likely that multiple mechanisms promote fatigue, with the contribution of each mechanism differing between patients and potentially within patients over time. Therefore, support for fatigue should be tailored to individuals and involve exploration of possible contributing factors. A systematic review of factors associated with fatigue in RA identified a cluster of variables that should be considered as potentially maintaining fatigue, including psychological and physical functioning, pain, sleep disturbance, depression and anxiety[31].

In this section, we describe the evidence supporting each putative mechanism of fatigue in inflammatory rheumatic diseases.

Biological and physiological mechanisms

Immunological mechanisms. Inflammation is arguably the most frequently studied mechanism underlying fatigue. The sickness behaviour model describes conditions such as fatigue, anhedonia, social withdrawal and depression as immune-mediated responses by vertebrates that enhance survival from infection[32]. Energy expenditure is thereby reserved for the immune system, and social withdrawal prevents further disease spread and reduces the risk of predation[33]. The production of type I interferons and other pro-inflammatory cytokines contributes to sickness behaviour[32]. Studies in animals and humans have not only provided strong evidence

for inflammation-induced fatigue but also revealed its potential molecular basis. A large body of data demonstrates the links between inflammation and fatigue in inflammatory rheumatic diseases and is reviewed in the literature[6,12,13,34]. However, how far the acute sickness behaviour model and inflammation explain fatigue in chronic inflammatory rheumatic diseases remains unclear.

If inflammation is the only factor contributing to fatigue, one would expect a strong correlation between fatigue severity and production of pro-inflammatory cytokines and disease activity, and that fatigue should improve with immunomodulatory treatment and subside when the underlying inflammatory rheumatic disease is in remission. However, although circulating concentrations of pro-inflammatory cytokines are typically elevated in patients with inflammatory rheumatic diseases compared with healthy individuals and those with non-inflammatory rheumatic disease[35,36], higher circulating concentrations of these cytokines are not necessarily associated with worse fatigue. In RA, although fatigue often accompanies disease flare[14], no consistent relationship between fatigue and validated disease activity scores has been identified[25–27,37]. In particular, a substantial proportion of patients with inflammatory rheumatic diseases continue to experience disabling fatigue despite seemingly being in clinical and biological remission, as observed in patients with RA[37]. Conversely, as shown in pSS, a small proportion of patients do not experience fatigue despite having active disease[38,39].

In pSS, clinical trial data on the effect of immunemodulating therapies on fatigue are inconsistent. For example, out of seven trials of rituximab, a reduction in fatigue was shown in four[40–42], two studies showed a mild improvement only at certain time points[43,44] and one study showed no effect[45]. In a phase II trial, treatment with RSLV-132 (an RNase-Fc fusion protein) led to improvement of fatigue in patients with pSS, which was intriguingly accompanied by an increase in expression of selected interferon-inducible genes[46]. Several studies even revealed an inverse relationship between fatigue severity and circulating concentrations of the pro-inflammatory cytokines CXCL10 (also known as IP-10), TNF, lymphotoxin-α and IFNγ in patients with pSS, and such inverse relationships between these pro-inflammatory cytokines and fatigue, together with depression and pain, were important predictors of fatigue in a multi-regression model[35,47]. Similarly, an inverse relationship between interferon activation and fatigue was observed in patients with pSS in two separate studies[38,46]. In addition, using gene set enrichment analysis of the genome-wide transcriptomic data of 133 patients with pSS, 19 biological pathways were associated with fatigue, but none was overtly inflammation related[24]. Thus, no consistent relationship between systemic inflammation and fatigue has been demonstrated; one possible explanation is that the role of inflammation varies at different stages of the disease.

Many patients with RA continue to experience disabling fatigue despite having no demonstrable synovitis or systemic responses[37,48]. A meta-analysis of studies on interventions for RA with fatigue as a primary or secondary outcome (most of which ran for 24 weeks or less) demonstrated that both anti-TNF agents and other biologic DMARDs (including rituximab, tocilizumab, canakinumab, abatacept and anti-IFNγ) similarly reduced fatigue in patients with active RA compared with placebo[48]. Whether fatigue improvement is a direct result of reduced disease activity and inflammation, or results indirectly via another mechanism, such as reduced pain, is unclear[49]. Notably, participants in the trials included in the aforementioned meta-analysis had a high level of disease activity, fatigue was measured as a secondary outcome and little adjustment was made for confounding factors. Thus, although immunomodulatory therapies can improve fatigue in some patients with RA, whether this improvement is attributable to the reduction of inflammation remains unclear.

The relationship between fatigue and inflammation in SLE is also unclear. The BLISS-52 and BLISS-76 trials of the B cell-inhibiting biologic DMARD belimumab measured fatigue as a secondary outcome using the SF-36 Health Survey questionnaire over a study period of 52 weeks and 76 weeks, respectively[50,51]. In post hoc analysis, statistically significant improvements from baseline in SF-36 physical component score were demonstrated in the group who received 10 mg/kg belimumab compared with placebo in BLISS-52, but not in BLISS-76 (REF.[52]). In a long-term extension study of BLISS-76 in which all participants who completed the parent trial had the option to continue belimumab or switch from placebo to belimumab, improvement in fatigue scores was maintained[53]. Interestingly, fatigue levels initially rose with belimumab treatment, suggesting that sustained therapy could be needed to see improvement in fatigue.

Overall, these observations indicate a complex relationship between fatigue and disease activity in inflammatory rheumatic diseases, and that the relationships between pro-inflammatory responses and fatigue remain to be fully defined. Inflammation probably has an important function in initiating fatigue responses, particularly in the early stages of the disease and during disease flares. However, the evidence for systemic inflammation in the maintenance of fatigue in chronic disease is less clear. In some individuals, inflammation might not be an important factor, and additional or different mechanisms are the predominant promoters of fatigue. Consistent with this idea, some patients with hepatitis C treated with IFNα therapy reportedly continued to experience fatigue even 6 months after completing treatment, that is, when IFNα would no longer be present[54].

Box 2 | Common predictors of fatigue in chronic diseases[21–23]

- Pain
- Depression
- Sleep disturbances
- Reduced physical activities
- Autonomic dysfunction
- Altered hypothalamic–pituitary–adrenal axis responses

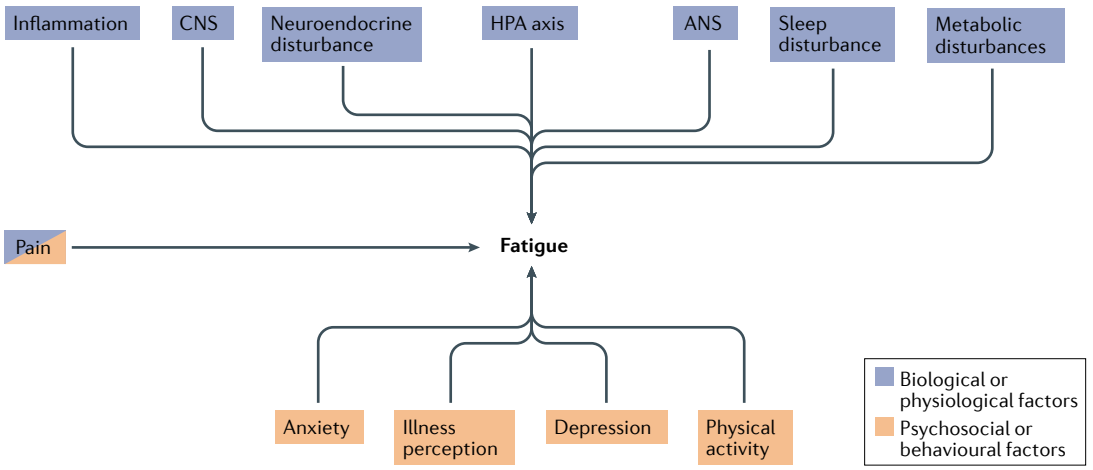


Fig. 1 | **Putative mechanisms implicated in the pathogenesis of fatigue.** Putative pathogenetic mechanisms of fatigue include biological and physiological factors (purple) as well as psychosocial or behavioural factors (orange). Pain involves the conscious interpretation of a physiological signal as 'pain' and therefore can be considered as either type of factor. All these mechanisms could contribute to fatigue pathogenesis, and might also interact with each other. ANS, autonomic nervous system; CNS, central nervous system; HPA axis, hypothalamic–pituitary–adrenal axis.

Arguably, fatigue that correlates closely with activity of the underlying disease and/or systemic inflammation is not a large clinical and scientific unmet need, as such fatigue should improve when the underlying disease is treated or when systemic inflammation is suppressed. By contrast, fatigue dissociated from disease activity or systemic inflammation is a conundrum for clinicians, scientists and the pharmaceutical industry and represents a large health-economic burden and unmet need to society and patients.

Central nervous system changes. Several characteristics of fatigue point to the potential involvement of the central nervous system (CNS). For instance, symptoms such as cognitive impairment and lack of motivation are common among patients with inflammatory rheumatic diseases experiencing fatigue[55]. Furthermore, the CNS can contribute to muscle fatigue during exercise by reducing the neural drive to the muscles[56]. As the neural drive decreases, a smaller number of motor neurons are activated, resulting in a weaker force of muscle contraction.

Potential mechanisms by which inflammation might alter neurochemistry and functional connectivity in the brain, and in turn might contribute to fatigue, have been comprehensively reviewed elsewhere[15]. Bidirectional communication between the immune system and the brain is mediated by multiple signalling pathways[32,57]. Circulating pro-inflammatory cytokines transfer directly across the blood–brain barrier via various direct mechanisms (for example, receptor-mediated transcytosis, leakage across damaged tight junctions or via circumventricular organs), or indirectly via activated vascular endothelial cells or the vagus nerve (FIG. 2a), leading to microglia activation in the brain[58]. Pro-inflammatory activity in the brain in turn results in several changes. First, the release of the neurotransmitter noradrenaline, which is important for increasing arousal, alertness and attention, is inhibited[59]. Second, the uptake and breakdown of monoamines (serotonin, dopamine and noradrenaline) is increased, reducing their availability in the synaptic cleft[15]. These monoamines play a key role in mood, motivation and arousal. Third, tryptophan-2,3-dioxygenase and indoleamine-2,3-dioxygenase 1 (IDO-1), which promotes tryptophan conversion in the kynurenine metabolic pathway, is increased. The metabolites of the kynurenine pathway further induce local inflammation in the brain. In a rat model of induced fatigue, metabolites of the kynurenine pathway were present in the presynaptic neurons of the hypothalamus, hippocampus and cerebral cortex[60]. In patients with SLE or RA, kynurenine pathway activation and elevated kynurenine to tryptophan ratios correlated with fatigue[61,62]. However, in a study of pSS, peripheral levels of *IDO1* mRNA were similar in patients with and without fatigue[63]. Furthermore, in a study of patients with hepatitis C receiving IFNα treatment (a model of inflammation-induced fatigue), although levels of kynurenine metabolites were altered, they were not associated with persistent fatigue[54]. Therefore, whether kynurenine metabolites directly mediate fatigue remains to be elucidated. Tryptophan also acts as a precursor for serotonin synthesis. Therefore, tryptophan depletion could result in decreased serotonin synthesis, which could have important consequences for mood and cognitive functioning. However, in patients with SLE, tryptophan metabolism correlated with fatigue but not with depression[61]. Increased plasma concentrations of kynurenine were associated with exhaustion in athletes and correlated with worse fatigue and depression scores in patients undergoing haemodialysis[64,65], suggesting that kynurenine metabolism could also be implicated in fatigue in other settings. Taken together, these findings support the notion that the CNS is implicated in fatigue pathogenesis in inflammatory rheumatic diseases.

Direct evidence of pro-inflammatory or metabolic changes in the CNS in patients with fatigue remains elusive. Proteomic analysis using liquid

Neural drive
The activation signals from the central nervous system delivered to the innervating motor neurons of the muscle.

chromatography-mass spectrometry and tandem mass spectrometry identified 15 proteins present in cerebrospinal fluid from patients with pSS that could discriminate those with fatigue from those without, but none of the proteins has known pro-inflammatory functions[66]. Instead, many are associated with cellular stress responses, cellular metabolism and depression. However, in another study examining the role of the IL-1 pathway in fatigue in patients with pSS, the concentration of IL-1 receptor antagonist (IL-1RA), a natural inhibitor of IL-1β, was elevated in the cerebrospinal fluid from the patients with fatigue compared with those without, and predicted severity of fatigue (alongside depression and pain)[67,68]. As IL-1RA is implicated in the IL-1β pathway via its role as an IL-1β antagonist, the detection of increased IL-1RA concentrations could indicate activation of the IL-1β pathway in the CNS in fatigue.

Neuroimaging is a promising tool for exploring the role of the CNS in fatigue. MRI can show volumetric changes in different areas of the brain, which might have implications for function, and functional MRI (fMRI) can reveal alterations in neural networks during fatiguing tasks. For instance, fMRI has provided evidence for a positive correlation between fatigue and increased functional connectivity between the dorsal attention network and right medial prefrontal cortex in patients with RA[69]. In another fMRI study, patients with granulomatosis with polyangiitis and fatigue had hyperactivity in several brain regions during a mental challenge task, as compared with those without fatigue[70]. A meta-analysis of fMRI and PET studies that involved either markers of peripheral inflammation or induced inflammation (for example, following vaccination or immunotherapy such as IFNα) showed that these studies have identified changes in brain regions and networks that are associated with peripheral inflammation[71]. Some of these brain regions and networks could provide an explanation of sickness behaviour. However, this meta-analysis did not directly explore the relationship between CNS changes and fatigue. In a systematic review of MRI studies of fatigue in chronic diseases, the brain areas implicated in fatigue were highly heterogeneous, not only between diseases, but also within the same disease[72]. Similarly, another systematic review found conflicting data regarding lesion location and post-stroke fatigue[73]. Thus, more research is needed to characterize the CNS changes relevant in fatigue.

Neuroendocrine disturbances. The neuroendocrine system controls many physiological processes, including stress response, metabolism and energy utilization; therefore, neuroendocrine disturbances may contribute to fatigue. An appropriate cortisol response is important for the body to handle stressors, which can be physical (for example, injuries), physiological (for example, hypotension), pathological (for example, infections) or emotional (for example, significant life events). Cortisol production is primarily regulated by the hypothalamic–pituitary–adrenal (HPA) axis. Interaction between the HPA axis and the immune system is complex. Pro-inflammatory cytokines (particularly gp130 cytokines, such as IL-1 and IL-6) stimulate the production of corticotropin-releasing hormone by the hypothalamus and of adrenocorticotropic hormone (ACTH) by the pituitary glands[74], resulting in increased cortisol production by the adrenal glands. Cortisol in turn suppresses pro-inflammatory responses, completing a feedback loop (FIG. 2b). With persistent inflammation, however, the response of the HPA axis could be blunted[75]. In addition to having immunomodulatory effects, cortisol is important for the regulation of metabolism. Cortisol and other glucocorticoid hormones increase the availability of energy by mobilizing the release of glucose, free fatty acids and amino acids from endogenous stores. Fatigue and lack of motivation are well-recognized features of hypoadrenalism. In clinical studies, HPA dysfunction can be demonstrated by reduced basal cortisol concentrations, relative cortisol insufficiency (for example, reduced cortisol to pro-inflammatory cytokine ratio) or suboptimal cortisol response to stimulation (for example, by exogenous ACTH and/or corticotropin-releasing hormone or by hypoglycaemic states). Blunted HPA axis response has been reported in patients with pSS[76], RA[77,78] and SLE[79] compared with healthy individuals.

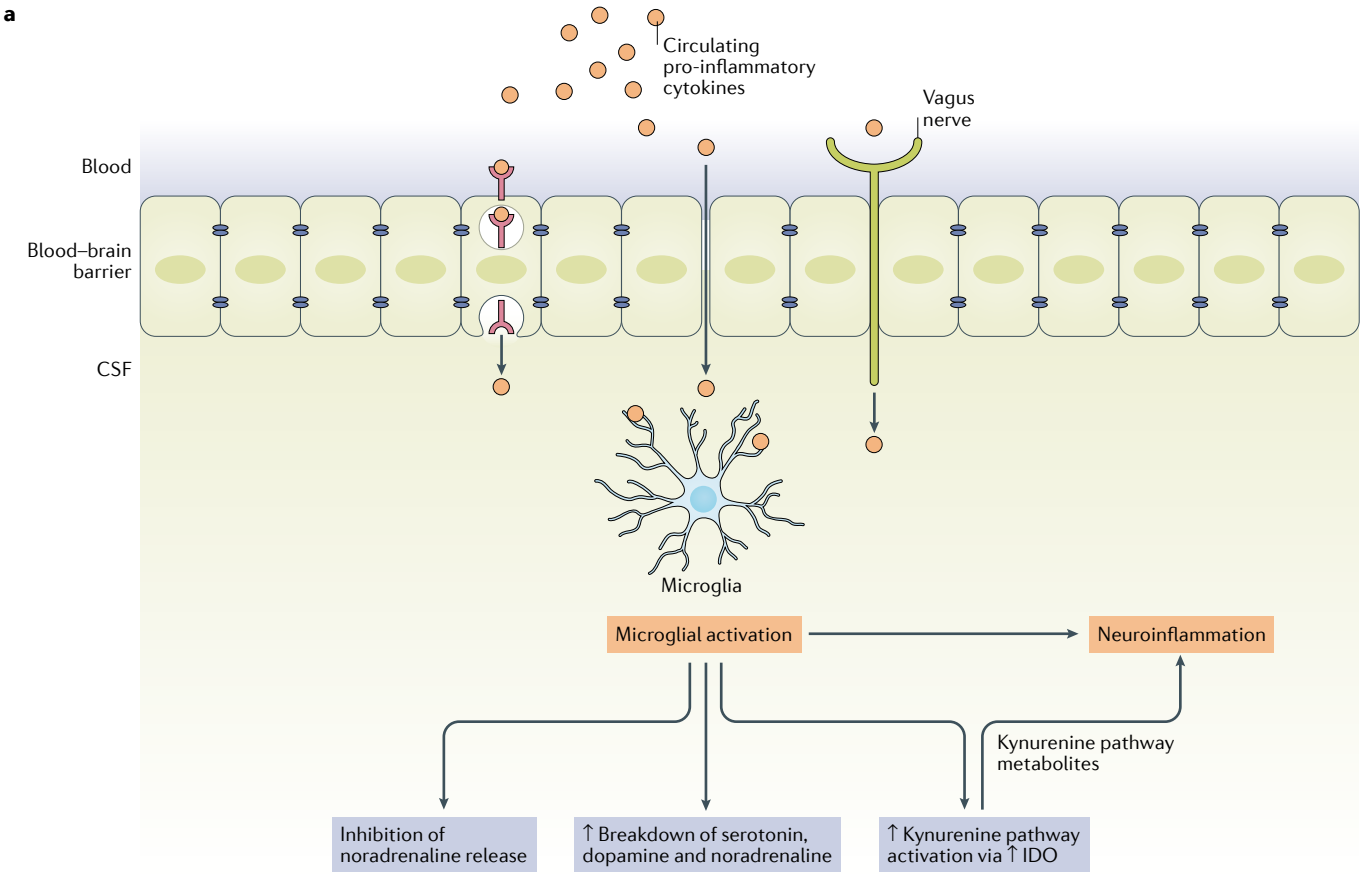
However, few studies have directly explored the link between HPA axis dysfunction and fatigue in patients with inflammatory rheumatic diseases. A longitudinal study exploring the relationships between daily stressors, worrying, the HPA axis (cortisol), pro-inflammatory cytokines, disease activity, pain and fatigue over 6 months in 80 patients with RA showed that daily stressors, IL-1β and IFNγ predicted increased fatigue 1 month later[80]. However, daily stressors, worrying, cortisol and pro-inflammatory cytokines were not included in a single model, so whether they represent independent predictors is not clear. A multivariate analysis of a cohort of patients with SLE without concomitant fibromyalgia showed that stress, depression and pain independently correlated with fatigue[28], with stress being the largest contributor to fatigue whereas disease activity did not contribute. However, another study of patients with SLE concluded that pain, social support and depression predict fatigue, but perceived stress did not[81]. Dysfunction of the hypothalamic–pituitary–gonadal axis and hypothalamic–pituitary–thyroid axis has been reported in patients with pSS, SLE and RA[82,83], although the relationship with fatigue was not examined[84]. Given that fatigue is a symptom of thyroid dysfunction and reduced sex drive is associated with fatigue, investigation into potential links between hypothalamic–pituitary–thyroid or hypothalamic–pituitary–gonadal dysfunction in fatigue is of interest.

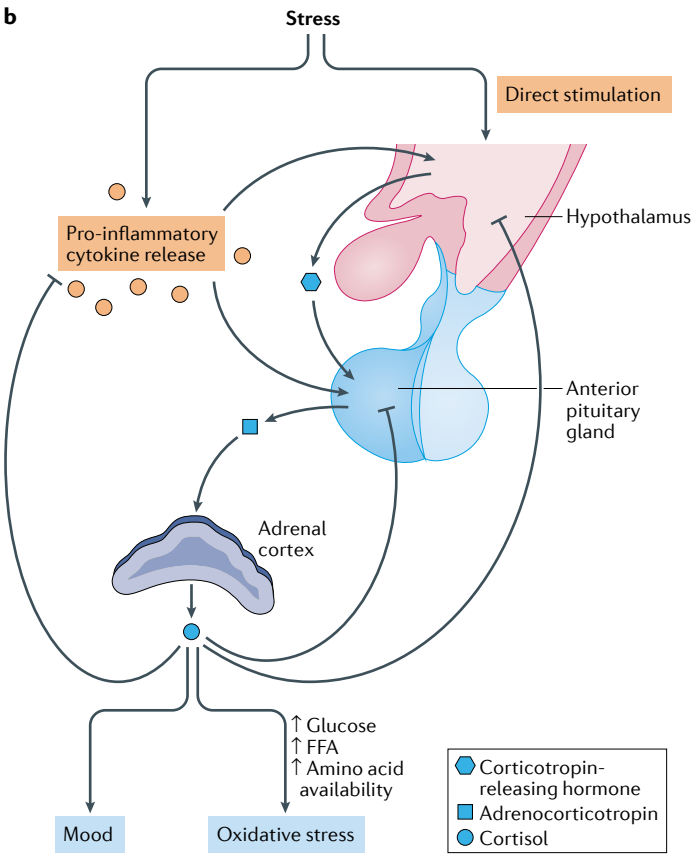
Autonomic nervous system dysfunction. The autonomic nervous system (ANS) has a vital function in responses to stressors through its ability to rapidly implement anticipatory actions. Inflammation activates pattern-recognition receptors on innate immune cells and other cells, which in turn stimulate the vagus nerve, resulting in the release of the neurotransmitter norepinephrine. In animal models, norepinephrine activates T cells that produce the neurotransmitter acetylcholine and inhibit

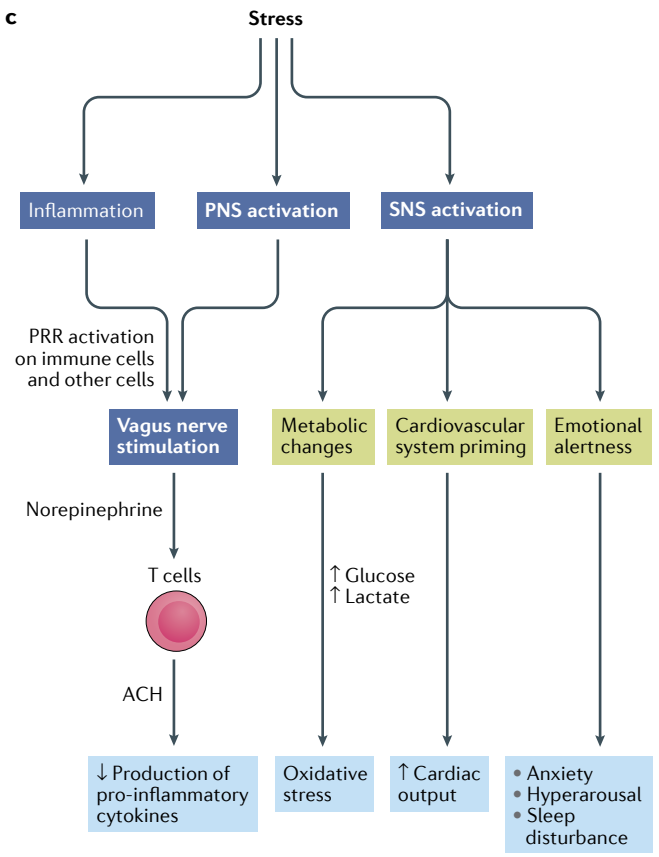
Hypothalamic–pituitary–adrenal (HPA) axis
Refers to the connections and interactions between the hypothalamus, pituitary gland and adrenal glands.

Hypothalamic–pituitary–gonadal axis
Refers to the connections and interactions between the hypothalamus, pituitary gland and the gonads.

Hypothalamic–pituitary–thyroid axis
Refers to the connections and interactions between the hypothalamus, pituitary gland and the thyroid glands.


a
Circulating pro-inflammatory cytokines
Vagus nerve
Blood
Blood–brain barrier
CSF
Microglia
Microglial activation
Neuroinflammation
Kynurenine pathway metabolites
Inhibition of noradrenaline release
↑ Breakdown of serotonin, dopamine and noradrenaline
↑ Kynurenine pathway activation via ↑ IDO


b
Stress
Direct stimulation
Pro-inflammatory cytokine release
Hypothalamus
Anterior pituitary gland
Adrenal cortex
↑ Glucose
↑ FFA
↑ Amino acid availability
Mood
Oxidative stress
Corticotropin-releasing hormone
Adrenocorticotropin
Cortisol


c
Stress
Inflammation
PNS activation
SNS activation
PRR activation on immune cells and other cells
Vagus nerve stimulation
Metabolic changes
Cardiovascular system priming
Emotional alertness
Norepinephrine
T cells
ACH
↑ Glucose
↑ Lactate
↓ Production of pro-inflammatory cytokines
Oxidative stress
↑ Cardiac output
• Anxiety
• Hyperarousal
• Sleep disturbance

◀ Fig. 2 | **The role of the nervous system in fatigue. a** | Central nervous system. Circulating pro-inflammatory cytokines transfer directly across the blood–brain barrier by receptor-mediated transcytosis, leakage across damaged tight junctions or via the circumventricular organ (not shown), or indirectly via the vagus nerve or activated vascular endothelial cells, causing brain microglial activation. Pro-inflammatory activities in the brain inhibit noradrenaline release, which is important for increasing arousal, alertness and attention, and also mediates increased uptake and breakdown of the monoamines serotonin, dopamine and noradrenaline, reducing their availability in the synaptic cleft. Additionally, inflammation increases tryptophan-2,3-dioxygenase and indoleamine-2,3-dioxygenase (IDO), which promotes tryptophan conversion in the kynurenine metabolic pathway, further promoting neuroinflammation. **b** | Hypothalamic–pituitary–adrenal axis. Stress and pro-inflammatory cytokines stimulate release of corticotropin-releasing hormone from the hypothalamus, causing release of adrenocorticotrophin-releasing hormone from the anterior pituitary gland. Adrenocorticotrophin-releasing hormone stimulates the adrenal gland to release cortisol, which affects mood, inhibits inflammation and promotes the release of amino acids, free fatty acids (FFA) and glucose into the circulation, enhancing oxidative stress. **c** | Autonomic nervous system. Stress promotes inflammation, antagonizes the parasympathetic nervous system (PNS) and primes the cardiovascular system to optimize cardiac output. Systemic nervous system (SNS) activation promotes shifts in metabolism, release of glucose and lactate, oxidative stress and emotional alertness leading to hyperarousal, anxiety and sleep disturbance. Inflammation stimulates the vagus nerve, causing acetylcholine (ACH) production by T cells and inhibiting pro-inflammatory cytokine production. The PNS limits stress reactions and restores equilibrium post-threat. Imbalances between the SNS and PNS lead to hyper-arousal, emotional changes and attenuated heart rate variability. CSF, cerebrospinal fluid; PRR, pattern-recognition receptor.

pro-inflammatory cytokine production by macrophages, completing a feedback loop[85] (FIG. 2c). The sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) are part of the ANS; the SNS triggers the 'fight or flight' response to enable rapid reactions to a threat, whereas the PNS tends to limit stress reactions and restore equilibrium once the threat has passed. Catecholamines have an important function in the regulation of energy mobilization and utility as well as cardiovascular function (which control the supply of fuel to tissues). Imbalances between the SNS and PNS can lead to hyper-arousal, emotional changes and attenuated heart rate variability[86]. Symptoms of dysautonomia, such as postural hypotension and exercise intolerance, as well as objective measures of autonomic dysfunction, are both common in patients with pSS and have been associated with fatigue[87–96]. Of note, in one cohort study >40% of patients with pSS had decreased parasympathetic activities[89]. More interestingly, non-invasive vagus nerve stimulation twice daily for 4 weeks was accompanied by improvement in fatigue in patients with pSS[97]. These observations support a role for the ANS, particularly the vagus nerve, in the modulation of fatigue. Autonomic dysfunction has also been reported in other inflammatory rheumatic diseases; however, the relationship with fatigue was not explored[98–100]. In RA, vagus nerve stimulation is associated with clinical improvement and a reduction in pro-inflammatory cytokines, although the effect of this treatment on fatigue was not measured[101,102].

These findings support a role for autonomic dysfunction in the pathogenesis of fatigue in inflammatory rheumatic disease.

Sleep disturbances. Sleep disturbances affect 40–75% of patients with rheumatic diseases and are often associated with fatigue[103]. The relationship between fatigue and sleep is not fully defined but is probably a bi-directional relationship, with poor sleep leading to fatigue and daytime fatigue resulting in sleep disturbances[104,105]. Sleep has a complex relationship with inflammation, the HPA axis, the ANS and mood disorders, and is influenced by factors such as chronicity and type of sleep disruption[104]. As described earlier in this Review, inflammation affects synthesis of neuroendocrine mediators such as monoamines, melatonin, prolactin, and growth hormone, all of which can affect sleep[106]. Sleep disturbance is associated with altered HPA activity and cortisol production, and changes in the circadian pattern of circulating concentrations of cortisol in turn regulate sleep[107]. Sleep disruption is associated with activation of the SNS. Sleep disturbances in patients with RA are characterized by worse sleep efficiency, sleep quality, sleep latency, number of awakenings and time awake after sleep compared with healthy individuals[108,109]. In patients with SLE, sleep disorders seem to be associated with disease activity alongside pain and fatigue[110]. In patients with pSS, poor sleep is prevalent and is associated with a high symptom burden, orthostatic symptoms and fatigue[111].

These findings support a role for sleep disturbance in the pathogenesis of fatigue in inflammatory rheumatic disease.

Metabolic disturbances. Metabolic disturbances, including oxidative stress, are associated with fatigue. Oxidative stress refers to an imbalance of pro-oxidants and antioxidants in favour of the former[112], whereas nitrosative stress is characterized by overproduction of nitric oxide[113]. Inflammation, a key pathological condition in inflammatory rheumatic diseases, increases oxidative and nitrosative stress by inducing the production of free radicals and reactive intermediates of oxygen and nitrogen. Measurement of F_2-isoprostanes has been used to assess oxidative stress. Increased concentrations of urine and plasma F_2-isoprostanes independently predict fatigue levels in patients with SLE[114]. The activities of the antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase and the antioxidant molecule glutathione were reduced in patients with SLE compared with healthy individuals[115], and might be responsible for the increased oxidative stress observed. The precise mechanisms by which increased oxidative or nitrosative stress results in fatigue, however, are unclear. Possible mechanisms include attenuation of aerobic metabolic capacity and reduction in muscle force production[116]. Antioxidant supplementation, which theoretically reduces oxidative stress, has been shown to improve exercise performance and reduce muscle fatigue[117,118].

Cardiopulmonary fitness, physical activity and body mass index. Reduced physical activity is a hallmark of fatigue, and cardiopulmonary fitness and BMI are predictors of physical activity. In a cross-sectional study, female patients with pSS had lower VO_{2peak}, muscle strength and function and higher levels of fatigue than healthy women matched for age and habitual physical activity levels[119]. Physical activity levels (measured using an accelerometer) were comparable in the two groups, and no statistically significant correlation between fatigue and VO_{2peak}, muscle strength and

Dysautonomia
An umbrella term used to describe conditions attributable to malfunctioning of the autonomic nervous system.

Sleep disturbances
An umbrella term used to describe the spectrum of sleep disorders, such as difficulty falling asleep, frequent wakening and sleep apnoea.

Somatic focus
Heightened attention to physical symptoms.

function or physical activity was found. However, fatigue was measured using Functional Assessment Chronic Illness Therapy (Fatigue), which may not be the most appropriate tool for analysing the relationship between fatigue and these objective measurements as it contains question items that might not be affected by physical performance or capacity. Furthermore, only bivariate correlation analysis was performed, without taking into consideration potential confounders such as mood or pain[119]. Conversely, a randomized controlled trial of supervised walking in patients with pSS found that improvement in VO_{2max} and cardiovascular fitness was associated with reductions in fatigue and depression[120]. Reduction of cardiopulmonary fitness could be a consequence of reduced physical activity due to fatigue and musculoskeletal pain. Data from 273 patients in the UK Primary Sjögren's Syndrome Registry revealed that self-reported physical activity levels at all intensity levels were reduced among patients with pSS compared with healthy individuals matched for age and sex[121]. Furthermore, reduced levels of moderate or vigorous physical activity were associated with fatigue in patients with pSS[121]. Consistently, reduced physical activity, activity avoidance and somatic focus were associated with fatigue among patients with pSS[122]. Thus, physical activity and physical capacity may contribute to fatigue and vice versa in pSS.

Poor exercise tolerance and reduced maximum aerobic capacity were also observed in patients with SLE or RA[123,124]. In a study of 443 patients with RA, Løppenthin and co-workers showed that 78% of the patients were mainly sedentary or had a low level of physical activity, which was higher than the general Danish population. Physical fatigue is the strongest predictor of reduced physical activity in RA[125]. Increased physical activity is associated with improved cardiorespiratory fitness and reduced fatigue in patients with RA[126]. In a meta-analysis and subsequent review the investigators concluded that physical activity potentially improved fatigue in patients with RA, although the effect size was described as small to moderate[127,128]. Furthermore, although physical activity intervention seemed to improve fatigue in patients with RA, the trials included in the meta-analysis were often performed over a short period of time (typically <12 weeks) without evidence of sustained improvement. In two studies in patients with SLE, home exercise interventions over longer periods (8 and 12 weeks) led to reductions in fatigue[129,130], which were sustained at 3 months if participants continued to exercise[130]. These findings suggest that in RA and SLE, physical activity may contribute to fatigue and vice versa.

Patients with fatigue often describe that their muscles feel weak and unable to sustain prolonged or vigorous activity. Reduced muscle strength and endurance are well-documented in patients with inflammatory arthritis and correlate with disease activity and reduced physical activity[131]. Sarcopenia (reduced muscle mass) and myositis (muscle inflammation) can occur in many inflammatory rheumatic diseases[132–135], which could also contribute to fatigue.

Obesity is a predictor of fatigue in patients with RA[136–138] and SLE[139,140]. The association between obesity and fatigue is interesting from the perspective of energy management because although accumulation of adipose tissues in obesity results from a surplus in energy, there is an imbalance in energy expenditure and conservation in favour of the latter, and individuals with obesity experience fatigue and decreased physical endurance, reflecting an energy-deficient state. The mechanisms linking obesity and fatigue in inflammatory rheumatic disease are unclear. However, a study using electromyography showed a greater reduction of voluntary (that is, CNS-mediated) activation of available motor units in obese participants when fatigued compared with participants who were not obese[141]. Other possible mechanisms linking obesity and fatigue include altered energy distribution or production and mitochondrial dysfunction, particularly in skeletal muscles. Obesity could also contribute to both oxidative stress and fatigue by increasing the inflammatory burden[142]. However, obesity is associated with several determinants of health including the social and economic environment, the physical environment, and the person's individual characteristics and behaviours. Therefore, the relationship between obesity and fatigue is an example of one that involves potentially interacting factors at the intra-individual, inter-individual and societal levels.

Psychosocial determinants

Mood disturbances. Depression is more prevalent in patients with inflammatory rheumatic diseases compared with the general population[143]. Many factors can contribute to the co-occurrence of depression and inflammatory rheumatic diseases, such as common genetic risk factors and shared biological pathways, as well as the influence of social, behavioural and psychological factors[144]. Depression is also strongly linked with fatigue in inflammatory rheumatic diseases[21,28,35,47,49,81,145] as well as in non-inflammatory diseases[146]. Notably, 'marked tiredness' is one of the classification criteria for depression[147]. However, although it is possible that fatigue can contribute to depression via shared mechanistic pathways and consequences of daily life, depression and fatigue are distinct phenomena[148] and many patients with fatigue do not have depression[38]. Distinguishing depression from fatigue in the clinic can be challenging. Depression is primarily psychological, and the main signs include sad mood, social isolation and negative thoughts, sometimes accompanied by physical symptoms such as headaches, cramps and stomach upsets. Fatigue is often a feature, but not the primary symptom, of depression. Patients with depression commonly experience anhedonia and become uninterested in taking part in activities, irrespective of the task or the amount of effort the task requires. By contrast, fatigue is primarily physical, and many patients report wanting to engage in activities but feel too tired to do so.

Inflammation has been implicated in the pathogenesis of depression on the basis of findings such as increased circulating concentrations of pro-inflammatory cytokines and microglial activation in the brain (as demonstrated in post-mortem and in vivo imaging studies)[149]. The extent to which inflammation mediates all depressive illness remains unclear. Notably, adverse childhood

events can result in immune activation[150], raising the possibility of a bi-directional relationship between depressive illness and inflammation. Furthermore, whether the same mechanisms by which inflammation mediates depressive symptoms also mediate fatigue is unclear. In this regard, the IL-1β pathway is a candidate mechanism linking depression and fatigue at a molecular level[151,152].

Pain. Pain occurs as a complex interplay between peripheral and central sensitization, biological influences (such as pro-inflammatory cytokines) and the psychological perception of pain[152,153]. Musculoskeletal pain is often a defining feature of many inflammatory rheumatic diseases[39,154,155] and is an important predictor of fatigue[28,35,47,49,81]. Data from clinical trials further underline a relationship between pain and fatigue. In RA, improvement in fatigue is associated with pain reduction following treatment with DMARDs[49]. However, a causal link between pain and fatigue is not proven, and fatigue potentially also enhances pain[152]. Similar to fatigue, pain constitutes a survival mechanism and is an 'alarm system' of ongoing or impending damage. Therefore, pain and fatigue could be two symptoms of a coordinated response of the body to chronic stressors with shared underlying mechanisms. It has also been suggested that pain is an activator rather than a consequence of sickness behaviour, leading to a state of hyperalgesia to enable the body to remain vigilant against an external threat. The alternative model stipulates that peripheral pain leads to the production of cytokines, specifically IL-1β, which then promotes sickness behaviour including fatigue[152].

Psychosocial factors. Adverse life events (whether in early life or adulthood), access to psychosocial support, relationship status, income and educational levels are associated with fatigue in chronic diseases[156]. Additionally, coping strategies and attitudes to illness have been linked with fatigue[157]. One example is learned helplessness, which predicts fatigue in recent-onset inflammatory polyarthritis (that is, symptom duration of ≤2 years)[158]. Tendency to catastrophize, avoidance and negative illness perception or belief are associated with fatigue in many chronic diseases[159,160]. The mechanisms linking these factors to the development or maintenance of fatigue are unclear. However, understanding which psychosocial factors are amenable to intervention and can contribute to effective self-management of fatigue is helpful in making treatment decisions[161]. Indeed, cognitive behavioural therapy has shown promising short-term and long-term benefits in fatigue management in patients with RA[3,161].

Access to data on premorbid fatigue would provide important insights into fatigue in inflammatory rheumatic diseases. Data on premorbid fatigue in patients with inflammatory rheumatic diseases are rarely available. However, premorbid fatigue is an important predictor of cancer-related fatigue[22], an observation that supports the notion that genetic or environmental factors pre-dispose individuals to fatigue.

The study of psychosocial factors in fatigue can be challenging and considered by some researchers to be less exciting or scientific or by some patients even to trivialize the seriousness of fatigue. Stigma around psychological factors can also contribute to prioritization of physical over mental aspects of health, which can influence agendas and resources in research. In care provision, the preference for treating physical over mental health issues can be enacted by both patients and clinicians (for example, in a consultation) and by health-care systems, which could prioritize the commissioning of services for physical health). However, psychological and social factors are not merely epiphenomena and emotions and feelings are no less 'real' than genes and molecules. The concept of 'self' consists of not only a 'neuro-biological self' but also a 'psychological self' that are intricately linked. For instance, a 2020 meta-analysis suggested that mindfulness is associated with the reduction of pro-inflammatory biomarkers such as IL-6 and TNF in blood and in saliva in patients with mood disorders[162]. Research into neurobiological changes associated with thoughts, emotions or feelings as potential therapeutic targets is increasing. However, such a neurobiological approach is not without potential pitfalls if the thoughts and emotions are the triggers of those neurobiological changes. As an illustration, to move one's right hand normally involves a conscious decision, leading to the activation of the left motor cortex, which sends signals to the muscles of the right hand. Electromagnetic stimulation of the left motor cortex also causes our right hand to move, but it is unlikely to cause one to 'make a conscious decision'. Therefore, critical issues in evaluating whether thoughts, emotions and feelings are amenable to therapeutic intervention include determining if they are a cause or consequence of the associated neurobiological changes. The evidence for cognitive-behavioural approaches in reducing fatigue suggests that cognitions can be helpfully re-framed using Socratic questioning to promote a change in beliefs and enhanced coping[161]. Such changed beliefs and enhanced coping lead to better knowledge of why the person thinks the way that they do and how that has been influencing their behaviours (for example, avoiding physical activity because they think it will make their fatigue worse and this thought frightens them). Such changed beliefs and enhanced coping also increase confidence and reactivation in everyday activities. The use of daily activity diaries for patients to monitor their energy expenditure and individualized goal setting lends weight to the argument that a 'personalized' and 'holistic' approach is likely to be needed to optimally manage fatigue[3]. Psychosocial factors in fatigue research deserve more attention but require a multidisciplinary and open-minded approach.

Putative models of fatigue

In this section, we present models of fatigue in inflammatory rheumatic diseases that take into consideration several important clinical observations that are among the most consistent findings (BOX 3). We first explore the 'mechanistic' model — that is, how the different mechanisms discussed in the previous sections might contribute to the pathogenesis of fatigue in inflammatory rheumatic disease. We then discuss the possible physiological and functional value of fatigue, which we term the 'conceptual' model of fatigue.

Learned helplessness
An attributional style whereby a person perceives that they have little control over the events in their life and so responds passively to the challenges that they face.

Mindfulness
The ability to be fully aware of one's thoughts, feelings and sensations without being overly reactive.

Socratic questioning
The technique of asking focused, probing, open-ended questions that encourage reflection.

Mechanistic model of fatigue

Both physical and psychological aspects are important considerations in fatigue research and have many interconnecting functional systems. Stressors elicit a coordinated response from several functional systems, even if the stressor was directed primarily to one system. For instance, a simple cut to the skin triggers responses from multiple systems: vasoconstriction and coagulation to stop blood loss, inflammatory cascades to prevent infection and nociception and SNS activation to alert and prepare the body for danger. In chronic inflammatory rheumatic diseases, multiple functional systems are affected. However, determining how these different functional systems contribute to fatigue is challenging.

As inflammation is the central pathological condition, it is probably the main initiator of fatigue through several interconnecting biological, psychological and physiological mechanisms. The relationship between inflammation and these various mechanisms is likely to be bi-directional. As the underlying inflammatory condition becomes chronic, additional mechanisms, such as neuroendocrine and psychological mechanisms, might become involved in an attempt to establish a new equilibrium. In individuals with fatigue, such maladaptive responses can perpetuate fatigue, and possibly suppress inflammation at the same time, providing a potential explanation for the observation of the inverse relationship between circulating pro-inflammatory cytokines and fatigue severity. At this chronic stage of disease, systemic inflammation might have a much lesser or even no role in the maintenance of fatigue. However, it is likely that an acute disease flare would disturb the established equilibrium, with systemic inflammation again contributing to fatigue.

As some patients experience minimal or no fatigue despite ongoing systemic inflammation[38], inflammation alone is therefore unlikely to be sufficient to cause fatigue. Furthermore, fatigue is prevalent in many chronic conditions in which evidence of an inflammatory basis is weak, and yet very similar predictors of fatigue have been identified, such as pain, depression, autonomic dysfunction, neuroendocrine disturbances and sleep disturbances[22,163]. Moreover, a study of fatigue across five chronic conditions (RA, heart failure, multiple sclerosis, chronic kidney disease and chronic obstructive pulmonary disease) found that the qualitative experience of fatigue is similar across these conditions[20]. In addition, the unpredictability and variability of fatigue experienced by many patients within short timeframes is also difficult to explain with a mechanistic model centred solely on inflammation. We hypothesize that inflammation is one of the many interconnecting mechanisms that contribute to the development of fatigue in response to external or internal stressors to the body (FIG. 1). Consistent with this model, circulating levels of the stress protein HSP-90α are elevated in patients with pSS and fatigue compared with patients with pSS without fatigue[149]. Furthermore, together with depression, plasma concentration of HSP-90α was an independent predictor of fatigue in patients with pSS in multi-regression analysis[149].

The ANS, the HPA axis and the immune system have important functions in the body's response to biological, physiological and psychosocial stressors and are probably the systems mainly involved in the initiation of a complex network of responses that contribute to fatigue. For instance, the ANS is adept at prompting rapid reactions to a threat and engaging the body in anticipatory actions, and therefore is likely to be an important contributor in the day-to-day (even hour-to-hour) variability of fatigue severity. By contrast, the HPA axis and aspects of the immune system are less flexible than the ANS[164], and therefore might contribute to other facets of fatigue.

Different subtypes of fatigue have been proposed, such as 'physical', 'mental' and 'motivational'. However, no formal definition for such fatigue subtypes exists. Furthermore, studies using fatigue questionnaires including different subscales to assess different facets of fatigue that are similar to the proposed fatigue subtypes (for example, the Multidimensional Fatigue Inventory, which has five subscales: general, physical, activity, motivational and mental) did not reveal any clear subsets of patients with different subtypes of fatigue[165–167]. Additional research is needed to determine if these fatigue subtypes exist in inflammatory rheumatic diseases. Our view is that different subtypes of fatigue are different facets of the same symptom, with the relative manifestations of each facet of fatigue depending on the relative contribution of the various mechanisms discussed in this Review (FIG. 3). For instance, autonomic dysfunction might contribute more to the 'physical' than to the 'mental' facet of fatigue, whereas depression might contribute more to the 'mental' and 'motivational' than the 'physical' facet of fatigue. Individual differences in how patients interpret and respond to fatigue complicate the identification of the underlying mechanisms.

Overall, fatigue is a phenomenon that is experienced physically and mentally and is driven by physiological, psychological, behavioural, socio-cultural and temporal factors. The relative contribution of these factors is dynamic and varies between individuals.

Conceptual model of fatigue

What is the physiological or functional relevance of fatigue in chronic conditions? Fundamentally, fatigue describes an inability to achieve the expected or maximal

Box 3 | **Important consideration for developing mechanistic and conceptual models of fatigue**

Below are some of the most consistent clinical observations that should be considered in the development of mechanistic and conceptual models of fatigue.

- Defining features of fatigue include a multifaceted, overwhelming, highly variable and unpredictable nature, and lack of improvement with rest[1].
- Shared predictors of fatigue exist across different diseases, with pain and depression often being the strongest predictors[21–23].
- There is an inconsistent relationship between systemic inflammation and fatigue — perhaps stronger correlation exists in the early stages and during acute flares, but poor, or even inverse, correlation exists with systemic inflammation in the chronic stages[14,25–27,35,38,46,47].
- Fatigue often persists despite the underlying inflammatory rheumatic disease being in remission[37,48].
- Some people with inflammatory rheumatic disease do not experience fatigue despite clear evidence of systemic inflammation[38,39].

levels of performance. Fatigue can be considered as part of the sickness behaviour response to inflammation, and chronic fatigue a consequence of maladaptive sickness behaviour. However, fatigue is not a condition that a person either has or not, but a continuum. Therefore, we believe that fatigue is a bio-psycho-physiological state reflecting the body's overall resource (energy) management strategy. These resources include the energy needed for physical activities and other bodily functions, cognition and emotions, providing an explanation for the multifaceted nature of fatigue. Interestingly, in the aforementioned qualitative metasynthesis of the experience of fatigue, the most prominent themes noted by participants were 'running out of batteries' and having a 'bad life' (defined as restrictions in their ability to engage in physical and social activities)[20], which could be considered consistent with our model in that patients with fatigue perceive a (relative) lack of energy or resources in the context of perceived sustained threat and they adopt a rationing approach to restrict energy use for essential activities at the expense of other activities such as leisure. Furthermore, resource management is part of a coordinated bio-psycho-physiological response to perceived current and anticipated stress. Therefore, fatigue can be accompanied by responses of multiple systems, such as altered ANS activity, altered pain sensitivity, changes to the immune system and changes to diurnal rhythm. Several factors could determine resource management strategies, including perceived current dangers or stressors, the anticipated dangers or stressors, assessment of the body's physiological state (interoception), outcomes from previous exposure to danger or stressors, and various other factors (such as genetic and environmental factors). In addition, perceptions and related behavioural responses are shaped by individual beliefs, expectations and cultural norms.

There are several non-mutually exclusive explanations for the persistence of fatigue despite remission of the underlying disease. First, clinical remission does not always equate to molecular remission. Furthermore, in the context of inflammatory rheumatic diseases, if immune tolerance has not been restored, the 'threat' remains. After all, resource management has as much to do with planning for the future (perceived threats) as for the present. Additionally, irreversible or semi-permanent changes might occur in some of the mechanistic pathways that mediate fatigue (for example, through epigenetic changes, changes in neural connections or depletion of certain proteins or other bioactive substances). Furthermore, other comorbidities that perpetuate fatigue can develop. For instance, chronic fatigue can lead to reduced cardiovascular fitness or sleep disorders. Finally, factors such as genetics, medical or life history, or other psychosocial factors can influence the susceptibility of an individual to fatigue. If fatigue reflects the body's resource management, genetics and past medical and life events might shape interoception and anticipatory danger perception. Psychologically, a patient's coping resources might reduce over time, which can affect their experiences of fatigue[168]. As well as fatigue and flares, other health and life circumstances can affect the coping strategy of the patient. Patients whose inflammatory rheumatic disease is stable can still be inconsistent in their ability to cope with their circumstances and distress can steadily increase. Rather than a gradual deterioration, a patient's ability to cope with their disease might not fully recover from a setback even though their symptoms have returned to the previous state. They might withdraw from social activities, discontinue regular exercise or increase their reliance on medication, all of which can exacerbate or maintain fatigue.

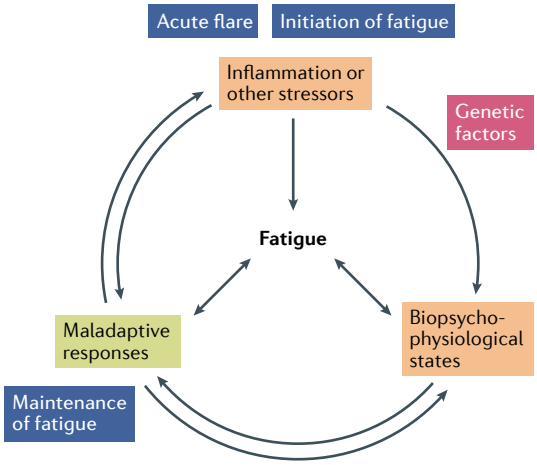


Fig. 3 | **Mechanistic model of fatigue.** Fatigue is driven by physiological, psychological, behavioural, socio-cultural and temporal factors. The relative contribution of these factors is dynamic and varies between individuals. Inflammation, the central pathological condition in inflammatory rheumatic diseases, is probably the main initiator of fatigue through several interconnecting biological, physiological and psychological mechanisms. As the underlying inflammatory condition becomes chronic, maladaptive responses might develop that perpetuate fatigue. During this chronic stage of disease, systemic inflammation might have a much smaller or even no role in the maintenance of fatigue. However, it is likely that an acute disease flare would disturb the established equilibrium, with systemic inflammation again contributing to fatigue. In addition, genetic factors might also influence the biological, physiological and psychological responses to stressors, which, in turn, can affect fatigue pathogenesis.

To summarize, fatigue might be a consequence of the body's resource management strategy favouring conservation over expenditure in response to a stressor; in the context of inflammatory rheumatic disease, the stressor could be inflammation or loss of immunological tolerance, but other factors might also contribute.

Conclusions

Fatigue is a symptom that is prevalent, disabling and difficult to manage for patients with inflammatory rheumatic diseases, as well as those with many other rheumatic and non-rheumatic conditions[5,169,170]. Consensus on how to define and measure fatigue is urgently needed, to provide a broad framework covering the various facets of fatigue. For example, fatigue could be described as a multifaceted phenomenon in which the biological, physiological, cognitive, motivational and emotional state of the body is affected, resulting in

impairment of an individual's ability to function in their normal capacity. Such a definition is still up for debate but could function as a starting point for future discussions. The mechanistic and conceptual models of fatigue presented in this Review could also provide a framework for future research into the mechanisms underlying this condition in the context of inflammatory rheumatic diseases and other diseases. Recommendations on the categories of data to be included and reported in fatigue research will facilitate harmonization of datasets for comparison and meta-analysis. Caution is needed in extrapolating findings based on experimental models of induced physiological fatigue unless they have been replicated in patients with pathological fatigue. This is because many induced fatigue models are transient and self-limiting, unlike fatigue in chronic conditions, which is often long-standing and not relieved by rest. Identification of objective biomarkers of fatigue should improve fatigue assessment and understanding of pathophysiology. Given the complexity of the underlying mechanisms of fatigue, future research should ideally involve multidisciplinary expertise to enable concurrent investigation of different mechanisms and confounding factors. Future studies investigating fatigue pathogenesis could help to identify targets for interventions across multiple chronic diseases. Optimal management of fatigue is likely to require a personalized and holistic approach.

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1. Dures, E. et al. Patients' perspectives on the psychological impact of inflammatory arthritis and meeting the associated support needs: open-ended responses in a multi-centre survey. *Musculoskeletal Care* **15**, 175–185 (2017).
2. Overman, C. L., Kool, M. B., Da Silva, J. A. P. & Geenen, R. The prevalence of severe fatigue in rheumatic diseases: an international study. *Clin. Rheumatol.* **35**, 409–415 (2016).
3. Dures, E. et al. "They didn't tell us, they made us work it out ourselves": patient perspectives of a cognitive-behavioral program for rheumatoid arthritis fatigue. *Arthritis Care Res.* **64**, 494–501 (2012).
4. Dures, E. et al. Patient preferences for psychological support in inflammatory arthritis: a multicentre survey. *Ann. Rheum. Dis.* **75**, 142–147 (2016).
5. Swain, M. G. Fatigue in chronic disease. *Clin. Sci.* **99**, 1–8 (2000).
6. Druce, K. L. & Basu, N. Predictors of fatigue in rheumatoid arthritis. *Rheumatology* **58** (Suppl. 5), v29–v34 (2019).
7. Meijer, J. M. et al. Health-related quality of life, employment and disability in patients with Sjögren's syndrome. *Rheumatology* **48**, 1077–1082 (2009).
8. Westhoff, G., Dörner, T. & Zink, A. Fatigue and depression predict physician visits and work disability in women with primary Sjögren's syndrome: results from a cohort study. *Rheumatology* **51**, 262–269 (2012).
9. McCormick, N., Marra, C. A., Sadatsafavi, M., Kopec, J. A. & Aviña-Zubieta, J. A. Excess productivity costs of systemic lupus erythematosus, systemic sclerosis, and Sjögren's Syndrome: a general population-based study. *Arthritis Care Res.* **71**, 142–154 (2019).
10. Basu, N. et al. Markers for work disability in anti-neutrophil cytoplasmic antibody-associated vasculitis. *Rheumatology* **53**, 953–956 (2014).
11. Borrell-Carrió, F., Suchman, A. L. & Epstein, R. M. The biopsychosocial model 25 years later: principles, practice, and scientific inquiry. *Ann. Fam. Med.* **2**, 576–582 (2004).
12. Ng, W.-F. & Bowman, S. J. Primary Sjögren's syndrome: too dry and too tired. *Rheumatology* **49**, 844–853 (2010).
13. Ahn, G. E. & Ramsey-Goldman, R. Fatigue in systemic lupus erythematosus. *Int. J. Clin. Rheumatol.* **7**, 217–227 (2012).
14. Pope, J. E. Management of fatigue in rheumatoid arthritis. *RMD Open* **6**, e001084 (2020).
15. Korte, S. M. & Straub, R. H. Fatigue in inflammatory rheumatic disorders: pathophysiological mechanisms. *Rheumatology* **58** (Suppl. 5), v35–v50 (2019).
16. Hackett, K. L. et al. Impaired functional status in primary Sjogren's syndrome. *Arthritis Care Res.* **64**, 1760–1764 (2012).
17. Hewlett, S. et al. Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. *Arthritis Rheum.* **53**, 697–702 (2005).
18. Primdahl, J. et al. The experience of people with rheumatoid arthritis living with fatigue: a qualitative metasynthesis. *BMJ Open* **9**, e024338 (2019).
19. Jones, D. E. J., Gray, J. C. & Newton, J. Perceived fatigue is comparable between different disease groups. *QJM* **102**, 617–624 (2009).
20. Jaime-Lara, R. B., Koons, B. C., Matura, L. A., Hodgson, N. A. & Riegel, B. A qualitative metasynthesis of the experience of fatigue across five chronic conditions. *J. Pain. Symptom. Manag.* **59**, 1320–1343 (2020).
21. Norheim, K. B., Jonsson, G. & Omdal, R. Biological mechanisms of chronic fatigue. *Rheumatology* **50**, 1009–1018 (2011).
22. Bower, J. E. Cancer-related fatigue — mechanisms, risk factors, and treatments. *Nat. Rev. Clin. Oncol.* **11**, 597–609 (2014).
23. Jhamb, M., Weisbord, S. D., Steel, J. L. & Unruh, M. Fatigue in patients receiving maintenance dialysis: a review of definitions, measures, and contributing factors. *Am. J. Kidney Dis.* **52**, 353–365 (2008).
24. James, K. et al. A transcriptional signature of fatigue derived from patients with primary Sjögren's syndrome. *PLoS ONE* **10**, e0143970 (2015).
25. Da Costa, D. et al. Dimensions of fatigue in systemic lupus erythematosus: relationship to disease status and behavioral and psychosocial factors. *J. Rheumatol.* **33**, 1282–1288 (2006).
26. Bruce, I. N., Mak, V. C., Hallett, D. C., Gladman, D. D. & Urowitz, M. B. Factors associated with fatigue in patients with systemic lupus erythematosus. *Ann. Rheum. Dis.* **58**, 379–381 (1999).
27. Tench, C., McCurdie, I., White, P. & d'Cruz, D. The prevalence and associations of fatigue in systemic lupus erythematosus. *Rheumatology* **39**, 1249–1254 (2000).
28. Azizoddin, D. R. et al. Fatigue in systemic lupus: the role of disease activity and its correlates. *Lupus* **28**, 163–173 (2019).
29. Hewlett, S., Dures, E. & Almeida, C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). *Arthritis Care Res.* **63** (Suppl. 11), S263–S286 (2011).
30. Santos, E. J. F., Duarte, C., da Silva, J. A. P. & Ferreira, R. J. O. The impact of fatigue in rheumatoid arthritis and the challenges of its assessment. *Rheumatology* **58** (Suppl. 5), v3–v9 (2019).
31. Geenen, R. & Dures, E. A biopsychosocial network model of fatigue in rheumatoid arthritis: a systematic review. *Rheumatology* **58** (Suppl. 5), v10–v21 (2019).
32. Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W. & Kelley, K. W. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* **9**, 46–56 (2008).
33. Lopes, P. C., Block, P. & König, B. Infection-induced behavioural changes reduce connectivity and the potential for disease spread in wild mice contact networks. *Sci. Rep.* **6**, 31790 (2016).
34. Muskardin, T. L. W. & Niewold, T. B. Type I interferon in rheumatic diseases. *Nat. Rev. Rheumatol.* **14**, 214–228 (2018).
35. Howard Tripp, N. et al. Fatigue in primary Sjögren's syndrome is associated with lower levels of proinflammatory cytokines. *RMD Open* **2**, e000282 (2016).
36. Umare, V. et al. Effect of proinflammatory cytokines (IL-6, TNF-α, and IL-1β) on clinical manifestations in Indian SLE patients. *Mediators Inflamm.* **2014**, 385297 (2014).
37. Druce, K. L., Bhattacharya, Y., Jones, G. T., Macfarlane, G. J. & Basu, N. Most patients who reach disease remission following anti-TNF therapy continue to report fatigue: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Rheumatology* **55**, 1786–1790 (2016).
38. Tarn, J. R. et al. Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials. *Lancet Rheumatol.* **1**, e85–e94 (2019).
39. Lendrem, D. et al. Do the EULAR Sjögren's syndrome outcome measures correlate with health status in primary Sjögren's syndrome? *Rheumatology* **54**, 655–659 (2015).
40. Devauchelle-Pensec, V. et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). *Arthritis Care Res.* **57**, 310–317 (2007).
41. Dass, S. et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. *Ann. Rheum. Dis.* **67**, 1541–1544 (2008).
42. Carubbi, F. et al. Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study. *Arthritis Res. Ther.* **15**, R172 (2013).
43. St Clair, E. W. et al. Rituximab therapy for primary Sjögren's Syndrome: an open-label clinical trial and mechanistic analysis. *Arthritis Rheum.* **65**, 1097–1106 (2013).
44. Devauchelle-Pensec, V. et al. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. *Ann. Intern. Med.* **160**, 233–242 (2014).
45. Bowman, S. J. et al. Randomized controlled trial of rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjögren's Syndrome. *Arthritis Rheumatol.* **69**, 1440–1450 (2017).
46. Posada, J. et al. Improvement of severe fatigue following nuclease therapy in patients with primary Sjögren's syndrome: a randomized clinical trial. *Arthritis Rheumatol.* **73**, 143–150 (2021).
47. Davies, K. et al. Fatigue in primary Sjögren's syndrome (pSS) is associated with lower levels of proinflammatory cytokines: a validation study. *Rheumatol. Int.* **39**, 1867–1873 (2019).
48. Almeida, C. et al. Biologic interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst. Rev.* **2016**, CD008334 (2016).
49. Pollard, L. C., Choy, E. H., Gonzalez, J., Khoshaba, B. & Scott, D. L. Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology* **45**, 885–889 (2006).
50. Navarra, S. V. et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* **377**, 721–731 (2011).

51. Furie, R. et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum.* **63**, 3918–3930 (2011).
52. Bangert, E., Wakani, L., Merchant, M., Strand, V. & Touma, Z. Impact of belimumab on patient-reported outcomes in systemic lupus erythematosus: review of clinical studies. *Patient Relat. Outcome Meas.* **10**, 1–7 (2019).
53. Strand, V. et al. Long-term impact of belimumab on health-related quality of life and fatigue in patients with systemic lupus erythematosus: six years of treatment. *Arthritis Care Res.* **71**, 829–838 (2019).
54. Russell, A. et al. Persistent fatigue induced by interferon-alpha: a novel, inflammation-based, proxy model of chronic fatigue syndrome. *Psychoneuroendocrinology* **100**, 276–285 (2019).
55. Sharpe, M. & Wilks, D. Fatigue. *BMJ* **325**, 480 (2002).
56. Taylor, J. L., Amann, M., Duchateau, J., Meeusen, R. & Rice, C. L. Neural contributions to muscle fatigue: from the brain to the muscle and back again. *Med. Sci. Sports Exerc.* **48**, 2294–2306 (2016).
57. Quan, N. & Banks, W. A. Brain-immune communication pathways. *Brain Behav. Immun.* **21**, 727–735 (2007).
58. Stetler, R. A. et al. Heat shock proteins: cellular and molecular mechanisms in the central nervous system. *Prog. Neurobiol.* **92**, 184–211 (2010).
59. Elenkov, I. J., Kovács, K., Duda, E., Stark, E. & Vizi, E. Z. Presynaptic inhibitory effect of TNF-alpha on the release of noradrenaline in isolated median eminence. *Neuroimmunology* **41**, 117–120 (1992).
60. Yamashita, M. & Yamamoto, T. Tryptophan circuit in fatigue: from blood to brain and cognition. *Brain Res.* **1675**, 116–126 (2017).
61. Åkesson, K. et al. Kynurenine pathway is altered in patients with SLE and associated with severe fatigue. *Lupus Sci. Med.* **5**, e000254 (2018).
62. Schröcksnadel, K., Wirleitner, B., Winkler, C. & Fuchs, D. Monitoring tryptophan metabolism in chronic immune activation. *Clin. Chim. Acta* **364**, 82–90 (2006).
63. Karageorgas, T. et al. Fatigue in primary Sjögren's syndrome: clinical, laboratory, psychometric, and biologic associations. *Arthritis Care Res.* **68**, 123–131 (2016).
64. Strasser, B. et al. Effects of exhaustive aerobic exercise on tryptophan-kynurenine metabolism in trained athletes. *PLoS ONE* **11**, e0153617 (2016).
65. Malhotra, R. et al. Tryptophan and kynurenine levels and its association with sleep, nonphysical fatigue, and depression in chronic hemodialysis patients. *J. Ren. Nutr.* **27**, 260–266 (2017).
66. Larssen, E. et al. Fatigue in primary Sjögren's syndrome: a proteomic pilot study of cerebrospinal fluid. *SAGE Open Med.* **7**, 2050312119850390 (2019).
67. Harboe, E. et al. Fatigue in primary Sjögren's syndrome — a link to sickness behaviour in animals? *Brain Behav. Immun.* **23**, 1104–1108 (2009).
68. Bårdsen, K. et al. Interleukin-1-related activity and hypocretin-1 in cerebrospinal fluid contribute to fatigue in primary Sjögren's syndrome. *J. Neuroinflammation* **16**, 102 (2019).
69. Schrepf, A. et al. A multi-modal MRI study of the central response to inflammation in rheumatoid arthritis. *Nat. Commun.* **9**, 2243 (2018).
70. Basu, N. et al. Neural correlates of fatigue in granulomatosis with polyangiitis: a functional magnetic resonance imaging study. *Rheumatology* **53**, 2080–2087 (2014).
71. Kraynak, T. E., Marsland, A. L., Wager, T. D. & Gianaros, P. J. Functional neuroanatomy of peripheral inflammatory physiology: a meta-analysis of human neuroimaging studies. *Neurosci. Biobehav. Rev.* **94**, 76–92 (2018).
72. Goñi, M., Basu, N., Murray, A. D. & Waiter, G. D. Neural indicators of fatigue in chronic diseases: a systematic review of MRI studies. *Diagnostics* **8**, 42 (2018).
73. Kutlubaev, M. A., Duncan, F. H. & Mead, G. E. Biological correlates of post-stroke fatigue: a systematic review. *Acta Neurol. Scand.* **125**, 219–227 (2012).
74. Mastorakos, G., Chrousos, G. P. & Weber, J. S. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *J. Clin. Endocrinol. Metab.* **77**, 1690–1694 (1993).
75. Tsigos, C. et al. Dose effects of recombinant human interleukin-6 on pituitary hormone secretion and energy expenditure. *Neuroendocrinology* **66**, 54–62 (1997).
76. Johnson, E. O., Vlachoyiannopoulos, P. G., Skopouli, F. N., Tzioufas, A. G. & Moutsopoulos, H. M. Hypofunction of the stress axis in Sjögren's syndrome. *J. Rheumatol.* **25**, 1508–1514 (1998).
77. Crofford, L. J. et al. Circadian relationships between interleukin (IL)-6 and hypothalamic-pituitary-adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. *J. Clin. Endocrinol. Metab.* **82**, 1279–1283 (1997).
78. Straub, R. H., Paimela, L., Peltomaa, R., Schölmerich, J. & Leirisalo-Repo, M. Inadequately low serum levels of steroid hormones in relation to interleukin-6 and tumor necrosis factor in untreated patients with early rheumatoid arthritis and reactive arthritis. *Arthritis Rheum.* **46**, 654–662 (2002).
79. Gutiérrez, M. A., Garcia, M. E., Rodriguez, J. A., Rivero, S. & Jacobelli, S. Hypothalamic-pituitary-adrenal axis function and prolactin secretion in systemic lupus erythematosus. *Lupus* **7**, 404–408 (1998).
80. Evers, A. W. et al. Does stress affect the joints? Daily stressors, stress vulnerability, immune and HPA axis activity, and short-term disease and symptom fluctuations in rheumatoid arthritis. *Ann. Rheum. Dis.* **73**, 1683–1688 (2014).
81. Jump, R. L. et al. Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support. *J. Rheumatol.* **32**, 1699–1705 (2005).
82. Cutolo, M., Sulli, A., Pizzorni, C., Craviotto, C. & Straub, R. H. Hypothalamic-pituitary-adrenocortical and gonadal functions in rheumatoid arthritis. *Ann. N. Y. Acad. Sci.* **992**, 107–117 (2003).
83. Moulton, V. R. Sex hormones in acquired immunity and autoimmune disease. *Front. Immunol.* **9**, 2279 (2018).
84. Johnson, E. O. & Moutsopoulos, H. M. Neuroendocrine manifestations in Sjögren's syndrome. Relation to the neurobiology of stress. *Ann. N. Y. Acad. Sci.* **917**, 797–808 (2000).
85. Sundman, E. & Olofsson, P. S. Neural control of the immune system. *Adv. Physiol. Educ.* **38**, 135–139 (2014).
86. Porges, S. W. The polyvagal theory: phylogenetic substrates of a social nervous system. *Int. J. Psychophysiol.* **42**, 123–146 (2001).
87. Brunetta, E. et al. Autonomic abnormalities in patients with primary Sjogren's syndrome — preliminary results. *Front. Physiol.* **10**, 1104 (2019).
88. Newton, J. L. et al. Autonomic symptoms are common and are associated with overall symptom burden and disease activity in primary Sjögren's syndrome. *Ann. Rheum. Dis.* **71**, 1973–1979 (2012).
89. Koh, J. H. et al. Pain, xerostomia, and younger age are major determinants of fatigue in Korean patients with primary Sjögren's syndrome: a cohort study. *Scand. J. Rheumatol.* **46**, 49–55 (2017).
90. Mandl, T., Wollmer, P., Manthorpe, R. & Jacobsson, L. T. Autonomic and orthostatic dysfunction in primary Sjögren's syndrome. *J. Rheumatol.* **34**, 1869–1874 (2007).
91. Fox, R. I., Kang, H. I., Ando, D., Abrams, J. & Pisa, E. Cytokine mRNA expression in salivary gland biopsies of Sjögren's syndrome. *J. Immunol.* **152**, 5532–5539 (1994).
92. Barendregt, P. J. et al. Parasympathetic failure does not contribute to ocular dryness in primary Sjögren's syndrome. *Ann. Rheum. Dis.* **58**, 746–750 (1999).
93. Kovács, L. et al. Cardiovascular autonomic dysfunction in primary Sjögren's syndrome. *Rheumatology* **43**, 95–99 (2004).
94. Barendregt, P. J., Tulen, J. H., van den Meiracker, A. H. & Markusse, H. M. Spectral analysis of heart rate and blood pressure variability in primary Sjögren's syndrome. *Ann. Rheum. Dis.* **61**, 232–236 (2002).
95. Niemelä, R. K., Hakala, M., Huikuri, H. V. & Airaksinen, K. E. Comprehensive study of autonomic function in a population with primary Sjögren's syndrome. No evidence of autonomic involvement. *J. Rheumatol.* **30**, 74–79 (2003).
96. Tumiati, B., Perazzoli, F., Negro, A., Pantaleoni, M. & Regolisti, G. Heart rate variability in patients with Sjögren's syndrome. *Clin. Rheumatol.* **19**, 477–480 (2000).
97. Tarn, J., Legg, S., Mitchell, S., Simon, B. & Ng, W. F. The effects of noninvasive vagus nerve stimulation on fatigue and immune responses in patients with primary Sjögren's syndrome. *Neuromodulation* **22**, 580–585 (2019).
98. Ingegnoli, F. et al. The link between autonomic nervous system and rheumatoid arthritis: from bench to bedside. *Front. Med.* **7**, 589079 (2020).
99. Bortoluzzi, A., Silvagni, E., Furini, F., Piga, M. & Govoni, M. Peripheral nervous system involvement in systemic lupus erythematosus: a review of the evidence. *Clin. Exp. Rheumatol.* **37**, 146–155 (2019).
100. Stojanovich, L. Autonomic dysfunction in autoimmune rheumatic disease. *Autoimmun. Rev.* **8**, 569–572 (2009).
101. Koopman, F. A. et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc. Natl Acad. Sci. USA* **113**, 8284–8289 (2016).
102. Genovese, M. C. et al. Safety and efficacy of neurostimulation with a miniaturised vagus nerve stimulation device in patients with multidrug-refractory rheumatoid arthritis: a two-stage multicentre, randomised pilot study. *Lancet Rheumatol.* **2**, e527–e538 (2020).
103. Thomas, K. S., Motivala, S., Olmstead, R. & Irwin, M. R. Sleep depth and fatigue: role of cellular inflammatory activation. *Brain Behav. Immun.* **25**, 53–58 (2011).
104. Meerlo, P., Sgoifo, A. & Suchecki, D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Med. Rev.* **12**, 197–210 (2008).
105. Lewis, I., Hackett, K. L., Ng, W.-F., Ellis, J. & Newton, J. L. A two-phase cohort study of the sleep phenotype within primary Sjögren's syndrome and its clinical correlates. *Clin. Exp. Rheumatol.* **37** (Suppl. 118), 78–82 (2019).
106. Irwin, M. R. Sleep and inflammation: partners in sickness and in health. *Nat. Rev. Immunol.* **19**, 702–715 (2019).
107. Guyon, A. et al. Adverse effects of two nights of sleep restriction on the hypothalamic-pituitary-adrenal axis in healthy men. *J. Clin. Endocrinol. Metab.* **99**, 2861–2868 (2014).
108. Grabovac, I. et al. Sleep quality in patients with rheumatoid arthritis and associations with pain, disability, disease duration, and activity. *J. Clin. Med.* **7**, 336 (2018).
109. Sariyildiz, M. A. et al. Sleep quality in rheumatoid arthritis: relationship between the disease severity, depression, functional status and the quality of life. *J. Clin. Med. Res.* **6**, 44–52 (2014).
110. Palagini, L. et al. Sleep disorders and systemic lupus erythematosus. *Lupus* **23**, 115–123 (2014).
111. Hackett, K. L. et al. An investigation into the prevalence of sleep disturbances in primary Sjögren's syndrome: a systematic review of the literature. *Rheumatology* **56**, 570–580 (2017).
112. Reinisch, T. & Hinz, H. In Encyclopedic Reference of Genomics and Proteomics in Molecular Medicine (eds Ganten, D. & Ruckpaul, K.) Vol. 9, 919 (Springer, 2006).
113. Hausladen, A., Privalle, C. T., Keng, T., DeAngelo, J. & Stamler, J. S. Nitrosative stress: activation of the transcription factor OxyR. *Cell* **86**, 719–729 (1996).
114. Avalos, I. et al. Oxidative stress in systemic lupus erythematosus: relationship to disease activity and symptoms. *Lupus* **16**, 195–200 (2007).
115. Shah, D., Kiran, R., Wanchu, A. & Bhatnagar, A. Oxidative stress in systemic lupus erythematosus: relationship to Th1 cytokine and disease activity. *Immunol. Lett.* **129**, 7–12 (2010).
116. Powers, S. K., Ji, L. L., Kavazis, A. N. & Jackson, M. J. Reactive oxygen species: impact on skeletal muscle. *Compr. Physiol.* **1**, 941–969 (2011).
117. Novelli, G. P., Bracciotti, G. & Falsini, S. Spin-trappers and vitamin E prolong endurance to muscle fatigue in mice. *Free Radic. Biol. Med.* **8**, 9–13 (1990).
118. Shindoh, C., DiMarco, A., Thomas, A., Manubay, P. & Supinski, G. Effect of N-acetylcysteine on diaphragm fatigue. *J. Appl. Physiol.* **68**, 2107–2113 (1990).
119. Dassouki, T. et al. Objectively measured physical activity and its influence on physical capacity and clinical parameters in patients with primary Sjögren's syndrome. *Lupus* **26**, 690–697 (2017).
120. Miyamoto, S. T. et al. Supervised walking improves cardiorespiratory fitness, exercise tolerance, and fatigue in women with primary Sjogren's syndrome: a randomized-controlled trial. *Rheumatol. Int.* **39**, 227–238 (2019).
121. Ng, W. F. et al. Physical activity but not sedentary activity is reduced in primary Sjogren's syndrome. *Rheumatol. Int.* **37**, 623–631 (2017).

122. Wouters, E. J. M. et al. Physical activity and physical activity cognitions are potential factors maintaining fatigue in patients with primary Sjögren's syndrome. *Ann. Rheum. Dis.* **71**, 668–673 (2012).
123. Keyser, R. E. et al. Evidence for aerobic insufficiency in women with systemic lupus erythematosus. *Arthritis Rheum.* **49**, 16–22 (2003).
124. Metsios, G. S. et al. Cardiorespiratory fitness levels and their association with cardiovascular profile in patients with rheumatoid arthritis: a cross-sectional study. *Rheumatology* **54**, 2215–2220 (2015).
125. Løppenthin, K. et al. Physical activity and the association with fatigue and sleep in Danish patients with rheumatoid arthritis. *Rheumatol. Int.* **35**, 1655–1664 (2015).
126. Rongen-van Dartel, S. A. et al. Effect of aerobic exercise training on fatigue in rheumatoid arthritis: a meta-analysis. *Arthritis Care Res.* **67**, 1054–1062 (2015).
127. Cramp, F. The role of non-pharmacological interventions in the management of rheumatoid-arthritis-related fatigue. *Rheumatology* **58** (Suppl. 5), v22–v28 (2019).
128. Cramp, F. et al. Non-pharmacological interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst. Rev.* **8**, CD008322 (2013).
129. Robb-Nicholson, L. C. et al. Effects of aerobic conditioning in lupus fatigue: a pilot study. *Rheumatology* **28**, 500–505 (1989).
130. Tench, C., McCarthy, J., McCurdie, I., White, P. & D'Cruz, D. Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise. *Rheumatology* **42**, 1050–1054 (2003).
131. Andonian, B. J. & Huffman, K. M. Skeletal muscle disease in rheumatoid arthritis: the center of cardiometabolic comorbidities? *Curr. Opin. Rheumatol.* **32**, 297–306 (2020).
132. An, H. J. et al. Sarcopenia in autoimmune and rheumatic diseases: a comprehensive review. *Int. J. Mol. Sci.* **21**, 5678 (2020).
133. Lindvall, B., Bengtsson, A., Ernerudh, J. & Eriksson, P. Subclinical myositis is common in primary Sjögren's syndrome and is not related to muscle pain. *J. Rheumatol.* **29**, 717–725 (2002).
134. Baker, J. F. et al. Deficits in muscle mass, muscle density, and modified associations with fat in rheumatoid arthritis. *Arthritis Care Res.* **66**, 1612–1618 (2014).
135. Caimmi, C. et al. Malnutrition and sarcopenia in a large cohort of patients with systemic sclerosis. *Clin. Rheumatol.* **37**, 987–997 (2018).
136. Tournadre, A., Pereira, B., Gossec, L., Soubrier, M. & Dougados, M. Impact of comorbidities on fatigue in rheumatoid arthritis patients: results from a nurse-led program for comorbidities management (COMEDRA). *Joint Bone Spine* **86**, 55–60 (2019).
137. Feldthusen, C., Grimby-Ekman, A., Forsblad-d'Elia, H., Jacobsson, L. & Mannerkorpi, K. Explanatory factors and predictors of fatigue in persons with rheumatoid arthritis: a longitudinal study. *J. Rehabil. Med.* **48**, 469–476 (2016).
138. Katz, P. et al. Role of sleep disturbance, depression, obesity, and physical inactivity in fatigue in rheumatoid arthritis. *Arthritis Care Res.* **68**, 81–90 (2016).
139. Chaiamnuay, S. et al. The impact of increased body mass index on systemic lupus erythematosus: data from LUMINA, a multiethnic cohort (LUMINA XLVI) [corrected]. *J. Clin. Rheumatol.* **13**, 128–133 (2007).
140. Oeser, A., Chung, C. P., Asanuma, Y., Avalos, I. & Stein, C. M. Obesity is an independent contributor to functional capacity and inflammation in systemic lupus erythematosus. *Arthritis Rheum.* **52**, 3651–3659 (2005).
141. Pajoutan, M., Ghesmaty Sangachin, M. & Cavuoto, L. A. Central and peripheral fatigue development in the shoulder muscle with obesity during an isometric endurance task. *BMC Musculoskelet. Disord.* **18**, 314 (2017).
142. Osborn, O. & Olefsky, J. M. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat. Med.* **18**, 363–374 (2012).
143. Matcham, F., Rayner, L., Steer, S. & Hotopf, M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology* **52**, 2136–2148 (2013).
144. Gold, S. M. et al. Comorbid depression in medical diseases. *Nat. Rev. Dis. Prim.* **6**, 69 (2020).
145. Hackett, K. L. et al. Pain and depression are associated with both physical and mental fatigue independently of comorbidities and medications in primary Sjögren's syndrome. *RMD Open* **5**, e000885 (2019).
146. Wilson, N., Lee, J. J. & Bei, B. Postpartum fatigue and depression: a systematic review and meta-analysis. *J. Affect. Disord.* **246**, 224–233 (2019).
147. World Health Organisation. ICD-10 classification of mental and behavioural disorders (WHO, 2016).
148. Nerurkar, L., Siebert, S., McInnes, I. B. & Cavanagh, J. Rheumatoid arthritis and depression: an inflammatory perspective. *Lancet Psychiatry* **6**, 164–173 (2019).
149. Bårdsen, K. et al. Heat shock proteins and chronic fatigue in primary Sjögren's syndrome. *Innate Immun.* **22**, 162–167 (2016).
150. Mondelli, V. & Vernon, A. C. From early adversities to immune activation in psychiatric disorders: the role of the sympathetic nervous system. *Clin. Exp. Immunol.* **197**, 319–328 (2019).
151. Rossi, S. et al. Neuroinflammation drives anxiety and depression in relapsing-remitting multiple sclerosis. *Neurology* **89**, 1338–1347 (2017).
152. Omdal, R., Mellgren, S. I. & Norheim, K. B. Pain and fatigue in primary Sjögren's syndrome. *Rheumatology* https://doi.org/10.1093/rheumatology/kez027 (2019).
153. Nichilatti, L. P., Fernandes, J. M. & Marques, C. P. Physiopathology of pain in systemic erythematosus lupus. *Lupus* **29**, 721–726 (2020).
154. Morgan, C., Bland, A. R., Maker, C., Dunnage, J. & Bruce, I. N. Individuals living with lupus: findings from the LUPUS UK Members Survey 2014. *Lupus* **27**, 681–687 (2018).
155. Sanderson, T., Morris, M., Calnan, M., Richards, P. & Hewlett, S. Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res.* **62**, 647–656 (2010).
156. Bower, J. E. Behavioral symptoms in patients with breast cancer and survivors. *J. Clin. Oncol.* **26**, 768–777 (2008).
157. Treharne, G. J. et al. Predictors of fatigue over 1 year among people with rheumatoid arthritis. *Psychol. Health Med.* **13**, 494–504 (2008).
158. Camacho, E. M., Verstappen, S. M., Chipping, J. & Symmons, D. P. Learned helplessness predicts functional disability, pain and fatigue in patients with recent-onset inflammatory polyarthritis. *Rheumatology* **52**, 1233–1238 (2013).
159. Jacobsen, P. B., Andrykowski, M. A. & Thors, C. L. Relationship of catastrophizing to fatigue among women receiving treatment for breast cancer. *J. Consult. Clin. Psychol.* **72**, 355–361 (2004).
160. Segal, B. M. et al. Pain in primary Sjögren syndrome: the role of catastrophizing and negative illness perceptions. *Scand. J. Rheumatol.* **43**, 234–241 (2014).
161. Hewlett, S. et al. Reducing arthritis fatigue impact: two-year randomised controlled trial of cognitive behavioural approaches by rheumatology teams (RAFT). *Ann. Rheum. Dis.* **78**, 465–472 (2019).
162. Sanada, K. et al. Effects of mindfulness-based interventions on biomarkers and low-grade inflammation in patients with psychiatric disorders: a meta-analytic review. *Int. J. Mol. Sci.* **21**, 2484 (2020).
163. Nadarajah, M. & Goh, H. T. Post-stroke fatigue: a review on prevalence, correlates, measurement, and management. *Top. Stroke Rehabil.* **22**, 208–220 (2015).
164. Sterling, P. Allostasis: a model of predictive regulation. *Physiol. Behav.* **106**, 5–15 (2012).
165. Smets, E. M., Garssen, B., Bonke, B. & De Haes, J. C. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J. Psychom. Res.* **39**, 315–325 (1995).
166. Chorus, A. M., Miedema, H. S., Boonen, A. & van der Linden, S. Quality of life and work in patients with rheumatoid arthritis and ankylosing spondylitis of working age. *Ann. Rheum. Dis.* **62**, 1178–1184 (2003).
167. Barendregt, P. J. et al. Fatigue in primary Sjögren's syndrome. *Ann. Rheum. Dis.* **57**, 291–295 (1998).
168. Evers, A. W., Kraaimaat, F. W., Geenen, R., Jacobs, J. W. & Bijlsma, J. W. Stress-vulnerability factors as long-term predictors of disease activity in early rheumatoid arthritis. *J. Psychosom. Res.* **55**, 293–302 (2003).
169. Zautra, A. J., Fasman, R., Parish, B. P. & Davis, M. C. Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *Pain* **128**, 128–135 (2007).
170. Drewes, A. M. Pain and sleep disturbances with special reference to fibromyalgia and rheumatoid arthritis. *Rheumatology* **38**, 1035–1038 (1999).

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