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Brain mapping inflammatory arthritis related fatigue in the pursuit of novel therapeutics

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Summary

Despite advances in pharmacological treatments, chronic fatigue remains an unresolved issue for most people with inflammatory arthritis, severely disrupting their personal and working lives. Their fatigue does not strongly link with peripheral disease activity, but instead, associates with central nervous system-derived symptoms like chronic pain, sleep disturbance and depression. Thus, a neurobiological basis should be considered when pursuing novel fatigue-specific therapeutics. In this review, we will first focus on clinical imaging biomarkers that map candidate brain regions, critical in fatigue pathophysiology. Then we will evaluate neuromodulation techniques that could affect these culprit brain regions, serving as potential treatment strategies for fatigue in inflammatory arthritis. We will conclude with what work still needs to be done for neuroimaging and neuromodulation to become a part of a future clinical pathway to treat and manage fatigue.

Introduction

In health, acute fatigue is a natural physiological phenomenon that arises following physical and mental exertion. The chronic fatigue associated with inflammatory arthritis does not necessarily precede such activities and patients contrast this "tiredness" with an experience that is physically and mentally overwhelming, ongoing rather than short-lived, and lasting even after periods of rest or sleep (1). Fatigue in inflammatory arthritis varies in frequency, duration and intensity, both between and within patients. Ultimately, this vexing symptom leads to many patients struggling in their work and social lives, leaving them unmotivated, lonely, and misunderstood (2).

Chronic fatigue in inflammatory arthritis is notoriously difficult to manage due to limited treatments, poorly understood origins, and disease heterogeneity. Fatigue levels do not strongly correlate with the inflammatory activity of the underlying disease, and targeted immune therapeutics, which have positively transformed the visible disabilities of arthritis, have only modestly attenuated the invisible disability of fatigue (3). Fatigue frequently co-exists with central nervous system (CNS)-based symptoms such as chronic pain, poor sleep, cognitive dysfunction, and mental ill-health (4) that strongly highlights the importance of better understanding the neurobiology of fatigue. This is not to say peripheral mediators have no role, but any common final mechanistic paths are likely to reside in the CNS. Self-evident safety concerns preclude in vivo scrutiny of human brain tissue for mechanistic discovery; however, modern neuroimaging methods are now established in the research of depression and pain and are now providing similarly informative biological insights in the study of fatigue (5).

Here we review existing neurobiological markers of chronic fatigue and how they may inform mechanisms, patient stratification, and potential interventions.

Epidemiology and current management of fatigue

Fatigue is a prevalent and burdensome symptom in inflammatory arthritis. It is typically considered chronic when it lasts for six or more months (6). Severe fatigue affected half of the patients with a single inflammatory rheumatic diagnosis in n=6120 international participants across 30 rheumatic conditions. It was more prevalent in people with multiple rheumatic diseases and went up to 78% in people with comorbid fibromyalgia (7). Most patients rank fatigue as one of their most disabling factors, even more so than pain (8, 9). Population studies have identified fatigue as a primary determinant of stress, depression, activity impairment and productivity loss in rheumatoid arthritis but also in vasculitis, systemic lupus erythematosus (SLE), and primary Sjögren's syndrome (10-13).

Fatigue in inflammatory arthritis has been difficult to treat using currently available interventions. In standard practice, the initial approach to alleviating fatigue is to ensure remission of the underlying disease processes through immune therapeutics (3). For example, chronic fatigue is mitigated among patients with early rheumatoid arthritis if they achieve remission within three months but most patients who improve

their disease state will remain chronically fatigued at follow-up (14, 15). In established rheumatoid arthritis, up to 70% of patients with high disease activity and severe fatigue report a clinically significant reduction in fatigue following targeted immune therapy (16) and yet 62% of those patients who attain full disease remission following these advanced therapies still report significant fatigue (17). Similar inconsistent fatigue effects are observed after synthetic or biologic disease-modifying antirheumatic drugs (DMARDS) in primary Sjögren's syndrome and psoriatic arthritis, while some therapies, for example, methotrexate, may incur fatigue as a side effect (18-21). Epidemiological studies have reported significant fatigue associations with cardiorespiratory fitness and psychosocial factors such as coping strategies and illness perception in primary Sjögren's syndrome and rheumatoid arthritis (22, 23) that have justified the trialling of physical activity and psychosocial interventions. Indeed, a meta-analysis of such trials demonstrated reductions of fatigue in six physical activity and 13 psychosocial intervention studies in rheumatoid arthritis (24). The results were significant, but the effect sizes were modest. Most recently, a pragmatic trial of telephone-delivered physical activity support or cognitive behavioural approaches reported clinically and statistically important improvements compared to an educational booklet across the spectrum of inflammatory arthritis (25). However, overall effect sizes were again only moderate in size. In summary, drug treatments alleviate fatigue when dependent on disease activity but fail for the majority where fatigue appears to disassociate from the underlying condition. Non-pharmacological interventions can provide benefits but again do not help all, leaving most patients with inflammatory arthritis feeling ignored and disabled by their fatigue.

The central nervous system and fatigue mechanisms

Since inflammatory arthritis is primarily a disease of the periphery, it is intuitive to predict the basis of the fatigue related to these disorders will also be dominated by this compartment. However, the inconsistent fatigue response to immune therapies among patients with inflammatory arthritis demonstrates a far more complex relationship between fatigue and the periphery, which is restated in cohort studies. Fatigue can increase with inflammatory disease flares (26), but peripheral concentrations of pro-inflammatory cytokine fail to both predict the intensity of fatigue and explain its similar expression in people with non-inflammatory diseases (27). Conversely, it consistently correlates with factors such as low mood and appetite, anxiety, increased sleep, and hyperalgesia (4). These constructs along with fatigue are called sickness behaviours as they also emerge after immune challenges like interferon-α treatment, but patients continue to report them months after their peripheral inflammation had subsided (28). Central inflammation appears in individuals with sickness behaviours that may arise from peripheral cytokines passing the blood-brain barrier or signalling via the vagus nerve and affecting the brain (Figure 1), based on animals presented with peripheral immune challenges like lipopolysaccharide injections (29). The subsequent changes can potentially disrupt brain networks and then induce different sickness behaviours (30). Given fatigue's intrinsic relationship with these behaviours, biological insights from these more maturely studied symptoms could be transferred to accelerate our understanding of fatigue.

Apart from inflammation, other factors consistently contribute to sickness behaviours. Endocrine function appears critical; for instance, cortisol levels surged within six hours of a lipopolysaccharide injection compared to placebo in 128 healthy volunteers who then also experienced increased anxiety, pain, fatigue and decreased positive mood (31). Psychosocial factors also influence sickness behaviours; people with lower expectations of becoming sick before a lipopolysaccharide injection react more negatively than individuals with high expectations (32). A genome-wide association study in primary Sjögren's syndrome found fatigue was associated with variations in the gene for the receptor transporter protein 4 (RTP4), a Golgi chaperone protein that promotes expression of opioid receptors in pain-modulating descendent pathways but also in the limbic system and cortex of the brain (33). Changes in the CNS are commonly found in those with sickness behaviour. Fatigue is associated with changes in glutamatergic and decreased monoaminergic neurotransmission (34), such as diminished dopamine in the cerebrospinal fluid of patients treated with interferon-α (35). Glutamate changes have also been exploited. Ketamine, an antagonist to the glutamatergic N-methyl-D-aspartate (NMDA) receptor, has been to reduce fatigue in bipolar depressive disorder (36) and in multiple sclerosis (37). In the context of inflammatory arthritis, antibodies against the subunit of the NMDA receptor in serum have been shown to correlate with fatigue in patients with SLE (38). Overall, fatigue shares a potential neurobiological aetiology with other sickness behaviours like pain and depression. These have recently been explored with modern neuroimaging methods, which have the power to safely assay neurobiology.

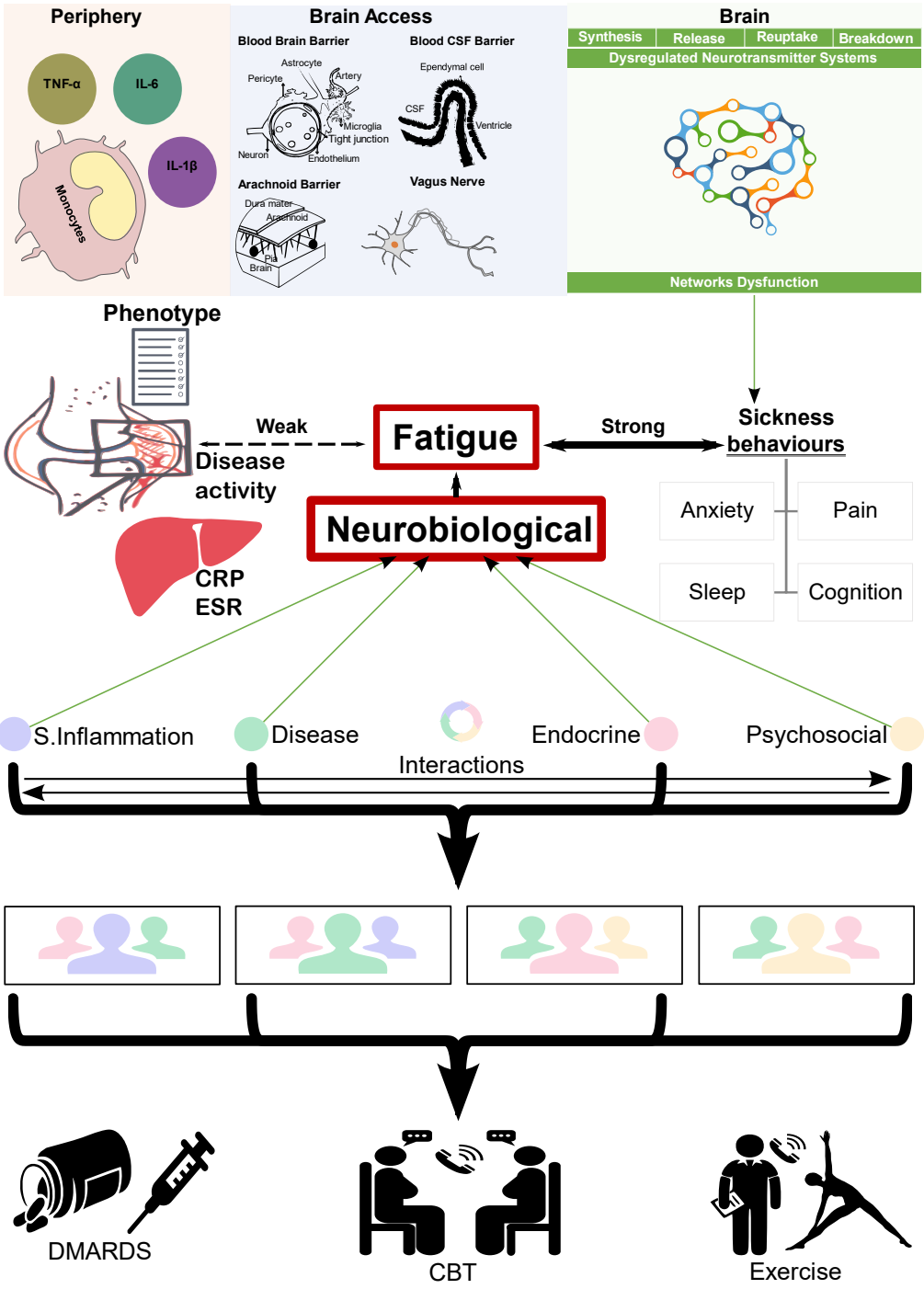

Figure 1: Theoretical model of fatigue as a multifaceted phenomenon and its management. *Pre-clinical experiments suggest cytokines such as TNF-α and IL-6 pass the neurovascular barriers through receptor-mediated transport, leaky tight junctions, or fenestrated vessels at certain locations (e.g., circumventricular organs) while the vagus nerve samples inflammatory mediators and indirectly passes these signals to the brain. Monocytes may also gain access to the brain by expressing signals like interleukin-1β and interacting with endothelial cells. The trafficking of these cells and signals likely interferes with synthesis, release, reuptake, and breakdown of multiple neurotransmitters either directly or through mechanisms such as oxidative stress. Fatigue cannot be explained by disease severity, peripheral inflammation (e.g., C-reactive protein, erythrocyte sedimentation rate), or phenotypic traits on their own. Immune cells and signals affecting the brain and its neurochemistry directly could fill that gap. Multiple interacting factors can generate and maintain the neurobiological drive of fatigue in each patient with some effects being more dominant in certain groups. Consistently stratifying such groups could inform selection in clinical trials and the appropriate treatment, which can be delivered remotely. CBT=cognitive-behavioural therapy. CRP=C-reactive protein. DMARDS=disease-modifying antirheumatic drugs. ESR=erythrocyte sedimentation rate. IL=interleukin. S. Inflammation=Systemic Inflammation. TNF-α=tumour-necrosis factor α.*

Neurobiological markers of fatigue

Neuroimaging methods can now measure different properties of brain function, structure and neurochemistry (Table 1). Magnetic resonance imaging (MRI) modalities can inform of all three properties and have the advantage of being completely non-invasive as they do not expose individuals to radiation. These studies identify brain differences by either contrasting clinical to healthy groups and co-varying with clinical outcomes or correlating clinical outcomes with measures extracted from the MRI scans.

Functional MRI typically defines activity as blood-oxygen-level-dependent (BOLD) signals, a surrogate marker of oxygen consumption. Data-driven analyses arrange brain regions into functional networks, reflecting the reality that complex clinical outcomes, such as fatigue, are unlikely to confine to single regions of the brain. These include the default mode, dorsal attention, and salience networks that are the basis for generating internal thoughts, executing external tasks, and filtering sensory cues, respectively. Neuroimagers can correlate the activity of networks with other parts of the brain (functional connectivity) to determine associations with clinical outcomes. Positive connectivity would delineate pairs of regions with synched activity, while negative connectivity delineates those with antagonising activity and purpose. Structural connectivity is alternatively described by diffusion tensor imaging (DTI). It estimates the fractional anisotropy (FA) and mean diffusivity (MD) of water that preferentially moves along neuronal tracts as reduced FA or increased MD indicate disrupted white matter integrity. Structural MRI estimates grey matter properties like volume and thickness. Since neurogenesis occurs prenatally, volume increases indicate expanded dendrites and thus stronger internal connectivity within the same region while volume reductions depict atrophy in the selected regions. Increased thickness implies reduced neuronal densities, but the functional significance is region-specific, as a thicker motor cortex associates with improved ability, while the inverse relationship is seen for the visual cortex, depicting differences in the neuronal organization required to perform these functions (39).

Magnetic resonance spectroscopy (MRS) can reveal biochemical metabolites. These include N-acetyl-aspartate (NAA), choline, myo-inositol, lactate, and the neurotransmitters gamma-aminobutyric acid (GABA) and glutamate. These metabolites quantify different processes, including neuronal integrity (NAA), anaerobic metabolism (lactate), cell membrane turnover (choline), and glial activity (myo-inositol). Consequently, decreased NAA can signify neuronal loss, while increases in lactate, choline, and myo-inositol can alert to oxidative stress, white matter degradation, and glial-related inflammation, respectively. In comparison, the levels of glutamate and GABA reveal consistent tones rather than temporary phases of excitation and inhibition in selected regions, composed of both the extracellular release of neurotransmitters and their metabolic turnover. Therefore, a stronger excitatory tone may identify persistent overactivation and potential damage caused by an overabundance and/or dysregulated turnover of glutamate. Overall, with the opportunities MRI modalities and other neuroimaging techniques can offer, it is now possible to probe for neurobiological changes in the context of fatigue and other sickness behaviours in inflammatory arthritis.

Modality (Mechanism)	Applications (brain)	Advantages (+)/ Disadvantages (-)
	Structural	
Computer tomography (CT)		
Uses differences in digital X-ray projections to reconstruct body regions of interest; the brain consists of soft tissue that is less attenuated by the passage of X-ray photons in comparison to bone	Identify large infarcts/ haemorrhage, and other gross brain abnormalities	(+) high detail on bony structures (+) faster, cheaper, and more widely available (cf. MRI, PET) (+) safe for all medical devices (-) involves ionizing radiation (-) less details of soft tissue
Structural MRI		
Uses magnetic properties of protons in tissues that differentially release radio wave energy in response to the application of magnetic fields and radiofrequency pulses	Differentiate grey/white matter and cerebrospinal fluid; detect old and new infarcts, as well as subtle brain abnormalities	(+) high detail for brain parenchyma (soft tissues) (+) lack of any ionizing radiation (-) limitations with medical devices like pacemakers (-) higher cost and longer scanning time (cf. CT)
Diffusion weighted imaging (DWI)		
MRI measure of water molecule random motion and thus microenvironment; **Diffusion tensor imaging (DTI)** measures the direction and strength of this diffusion (tractography evaluates its 3D shape)	Assess disturbance to cell integrity- specifically lesions and tumours; tractography estimates probability of connections between brain regions (structural connectivity)	(+) high sensitivity to early damage (+) can be acquired quickly (cf. structural MRI) (+) measures white matter integrity (-) confounded by regions where fibers cross each other
	Functional	
Electroencephalography (EEG)		
A cap with electrodes that measure summated electrical potentials from the scalp, originating from the activity of neuronal populations; analysed as synchronous activity (waves) or event-related potentials (ERP) as a response to a specific sensory, motor, or cognitive event	Diagnose epilepsy, monitor brain-state via specific frequency rhythms; reveal subclinical sensory system involvement	(+) direct neuronal activity signals (cf. functional MRI) (+) high temporal resolution (detect within milliseconds) (+) cheap and portable (-) covers only brain surface (-) low spatial resolution (-) distortion by the skull

Magnetoencephalography (MEG)		
A device that measures magnetic field changes, generated by the electrical activity of neural populations	Functionally localise the focus of epileptic activity and functions that resolve quickly in time	(+) undistorted direct signal from neuronal activity (+) high temporal and moderate spatial resolution (-) expensive due to shielding and sensor cooling (at -270°C) (-) only sensitive to sources parallel to scalp (brain sulci)
Functional near-infrared spectroscopy (fNIRS)		
Measures near-infrared light to estimate blood oxygenation changes as a proxy of neuronal activity based on differences in absorption of oxyhaemoglobin and deoxyhaemoglobin	Monitor anaesthetic depth; evaluate cognitive functions in neurodegenerative diseases	(+) moderate temporal resolution (detect within seconds) (+) low sensitivity to motion (+) portable and inexpensive (-) moderate spatial resolution (-) only brain cortical coverage (-) influenced by non-brain related dynamics of blood flow
Functional MRI		
Indirect MRI measure of brain activity via the blood oxygen level dependence (BOLD) signal that reflects changing haemoglobin oxygenation in active brain regions	Identify which regions should be spared during surgery; map brain activation to specific tasks or describe how networks of regions interact during rest (functional connectivity)	(+) whole brain coverage including deep (subcortical) structures, brain stem and cerebellum (+) high spatial resolution (cf. EEG, MEG, fNIRS) (+) lack of ionizing radiation (-) sensitive to motion artifacts (-) low temporal resolution (seconds) but superior to PET
Single photon emission computed tomography (SPECT)		
Administers radio-labelled agents that emit gamma-photons from the decay of the radioactive isotopes attached to the tracers to create a 3D image of where the agent accumulates	Informs of physiological processes at a molecular level, including inflammation and neurotransmission	(+) provides metabolic and functional information (+) cheaper device and tracers (cf. PET) (+) tracers with longer half-lives allowing more imaging time (cf. PET) (-) low spatial resolution (cf. PET) (-) radiation exposure

Positron emission tomography (PET) Employs radio-labelled tracers that emit positively charged particles as they decay. Most common tracers include fluorodeoxyglucose (FDG) and TSPO receptor (glial activation and neuroinflammation)	Visualise glucose consumption in tumours, cognitive and movement disorders, and activity of neurobiological drugs and glial cells	(+) availability of a variety of tracers (+) innovative tracers are more easily synthesised (cf. SPECT) (-) radiation exposure (-) very low temporal resolution (detect within minutes)
Neurochemical		
Magnetic resonance spectroscopy (MRS) Applied in the MRI scanner, quantifies biochemical substances non-invasively from hydrogen protons while suppressing signal received from water	Measures metabolites relevant to cancer, inflammation, neuronal damage, and neurotransmitters like glutamate and GABA	(+) metabolites relevant to both neuronal and glial cells (+) lack of ionizing radiation (-) limited to metabolites with high concentrations in the brain (-) overlap between certain metabolites
Magnetization transfer imaging (MTI) Uses the exchange of protons bound to lipids (large proteins, cell membranes, myelin) with nearby free water to inform of changes in the microstructural environment	Acts as a surrogate measure of myelin quantity, sensitive to central effects of inflammation and used to improve contrast of enhanced lesions in multiple sclerosis	(+) clarify microstructural damage within specific brain regions (+) inform of more widespread diffuse damage over whole brain (+) lack of ionizing radiation (-) distortions from cerebrospinal fluid (-) interpreting grey matter changes is more challenging
MRI=magnetic resonance imaging. GABA=gamma aminobutyric acid; TSPO=translocator protein		

Table 1: ***Neuroimaging modalities to measure brain properties***

To study fatigue using neuroimaging offers several challenges compared with cognitive neuroscience in healthy populations or other clinical behaviours like pain. Such challenges include: (1) heterogeneity of groups with chronic fatigue in the context of both fatigue expression and primary disease; (2) differences between physical and mental fatigue; (3) limited number of interventions frequently not specific to fatigue; (4) lack of fatigue reporting in studies of relevant cohorts that have other primary research objectives; (5) tasks that induce fatigue in functional MRI are less established and more difficult to interpret compared with ones for pain and cognition. However, clinical studies may have higher statistical power to identify neurobiological effects because disease likely affects the brain more than experimental ones in healthy participants (40). Studies can exploit the heterogeneity in inflammatory arthritis and compare groups with the same disease but with contrasting levels of fatigue. Finally, research on inflammatory-arthritis fatigue can also benefit from findings and tools of studies in conditions with more established neuroimaging literature, like multiple sclerosis, another inflammatory disorder where chronic fatigue is a patient priority.

In a different task that involved working and emotional processing, a study of patients with SLE (N=23) recorded BOLD and found that left caudate function positively correlated with cognitive fatigue (41). Functional MRI frequently implicates inflammatory arthritis-related fatigue with subcortical regions like the caudate. It along with the putamen are deep-lying grey matter nuclei that receive dopaminergic inputs and are jointly called the dorsal striatum. The striatum is part of the greater basal ganglia, a collection of subcortical brain regions that interact with other cortical and subcortical regions such as the thalamus to execute precise movements, but also affect working memory, decision-making, and emotional behaviour. Functional connectivity can integrate such individual regions and provide more holistic insights, important for complex behaviours like fatigue. In 54 patients with rheumatoid arthritis, current fatigue was positively correlated with functional connectivity between the dorsal attention network and the medial prefrontal cortex, extracted while performing the a fatigue-inducing task (42). This result was reproduced in the same cohort six months later. The medial prefrontal cortex is part of the default mode network, so these results demonstrate patients with higher current fatigue show stronger synchrony between two networks that would typically work in opposition to one another. Such excess activation and communication of the basal ganglia and regions of the default mode and dorsal attention networks when chronic may hypothetically start to deplete the functional reverse of the brain and surface as fatigue in patients, as suggested in multiple sclerosis (43).

Consistent with functional findings, structural changes in sub-cortical and frontal brain regions have been reported in inflammatory arthritis cohorts. In the same 54 study participants with rheumatoid arthritis, greater grey matter volume of the putamen correlated with higher fatigue (42), with similar results in 20 patients with ankylosing spondylitis (44). Generally, fatigue is associated with larger volumes of grey matter in specific subcortical regions that underlie stronger internal communication within the same region. The opposite trend of negative associations with fatigue is observed for cortical regions, such as those of the dorsal and default mode networks, with both

patterns observed in ankylosing spondylitis. How these alterations arise and genarate fatigue is difficult to disentangle as the discussed structural and functional imaging markers are not specific to a single disruptive process. The ankylosing spondylitis study further documented differences in white matter integrity between patients and 20 matched controls in the form of decreased FA in tracts that connect these regions, such as the superior longitudinal fasciculus that links posterior parietal regions (dorsal attention network) with frontal areas. The use of DTI can thus add further detail by focusing on processes that affect the microarchitecture of white matter. Overall, both structural and functional changes of the brain are linked to fatigue in inflammatory arthritis, while changes in white matter microstructure point towards potential disruptive processes like neuroinflammation and a necessity to assess the microenvironment of the brain.

Another method of sampling the brain microenvironment is MRS. Changes in the neuronal integrity marker NAA throughout the brain were a common finding in a recent systematic review of MRS studies, specifically in SLE, primary Sjögren's syndrome, rheumatoid arthritis, and systemic sclerosis compared to healthy controls (45). Longitudinal studies in SLE also depicted NAA reductions over time. In 24 patients with multiple sclerosis, fatigue correlated with higher glutamate and lower inhibitory GABA neurotransmitter levels in the prefrontal cortex using magnetic resonance spectroscopy (46). The subcomponent of physical fatigue was further negatively correlated with GABA in the sensorimotor cortex. MRS studies in multiple sclerosis observe that fatigue associates with increased glutamate, but also with decreased NAA (47). A recent study made such associations in rheumatoid arthritis, using multi-voxel MRS that selected 47 different brain regions (48). Specifically, fatigue in 13 patients with rheumatoid arthritis was negatively correlated with NAA in the lingual gyrus. Fatigue also positively correlated with lactate, and myo-inositol in different cortical and basal ganglia regions. As previously discussed, these metabolites are markers of different processes that can be generated by neuroinflammatory activity. In summary, both DTI and MRS methods distinguish differences between inflammatory arthritis and healthy populations in the brain microenvironment. Such alterations are also associated with fatigue in multiple sclerosis, suggesting fatigue in inflammatory arthritis may be related to subclinical signs of neuroinflammation.

Despite the prominent findings using MRI modalities, we previously observed inconsistencies in brain imaging of chronic fatigue disorders, both when studies examined different conditions or the same disease (49). Studies used diverse methods and lacked both statistical power and stratification. Furthermore, only 7/26 implemented a longitudinal design, which offers opportunities to replicate findings. Brain-behaviour associations are difficult to reproduce due to an imbalance of both small effect and sample sizes (50) compared with replicable mappings of brain functions like face perception, which have been shown to require only 15 participants (51). Studies in psychiatric and neurological conditions suffer less from low power as they have double or larger mean effect sizes (Cohen's d = 0·32) than ones in the general population (52). Although measures like structural MRI strongly correlate within repeated sessions of the same individuals ($r > 0{\cdot}8$), reliable neuroimaging requires a greater number of participants in studies and improvements in the quality of the data

acquired (53). To identify generalizable brain-behaviour associations, steps can be taken to: (1) internally and/or externally validate findings, (2) use within-subject longitudinal designs,(3) use both rest and task states tailored to the behaviour of interest in functional imaging, (4) use multiple modalities in the same cohort, (5) use multivariate rather than univariate analyses as brain functions are inherently complex and interdependent, (6) experimentally manipulate behaviour through pharmacological and/or psychological interventions, (7) experimentally manipulate brain signatures via neuromodulatory techniques relevant to the behaviour.

Some of the already mentioned studies in inflammatory arthritis have implemented these strategies such as using fatigue-inducing tasks, combining functional with DTI data, and analysing longitudinal data to replicate baseline findings. Longitudinal data also enables mapping correlates of fatigue through prediction methods that infer future changes in clinical variables by using baseline brain metrics. As fatigue correlates are spread throughout the brain in inflammatory arthritis, rather than focus on a small number of regions, we recently sought to predict fatigue using an agnostic multivariate approach in 54 patients with rheumatoid arthritis who had both structural MRI and DTI (52). Specifically, the approach considered 900 neuroimaging variables at baseline to classify patients who improved their fatigue levels from those who did not after six months. Both structural MRI (67·9%) and DTI (63·8%) performed better than chance unlike when clinical variables were used to make the same predictions. Although applying prediction methods does not offer mechanistic insight into fatigue, they do provide clinicians with useful biomarker tools to stratify patients and help in their decision-making. Methods that do provide mechanistic information like experimentally affecting behaviour, are yet unexplored as neuroimaging studies in inflammatory arthritis of fatigue interventions are still lacking. Neuromodulatory techniques, however, offer the opportunity to experimentally manipulate brain signatures and test causal hypotheses as experimenters need to decide which brain feature(s) they will target.

Brain-related treatments and its prospects in clinical care

The primary goal of mapping out the brain properties of fatigue is to deliver new solutions for patients. By more intelligently directing animal experiments, more clinically relevant molecular mediators and their temporal inter-relationships can be tested, ultimately directing more rational drug development. More immediate gains may be realised by testing approaches that directly modulate the human brain. These include neurofeedback and electrical/magnetic stimulation devices (Figure 2).

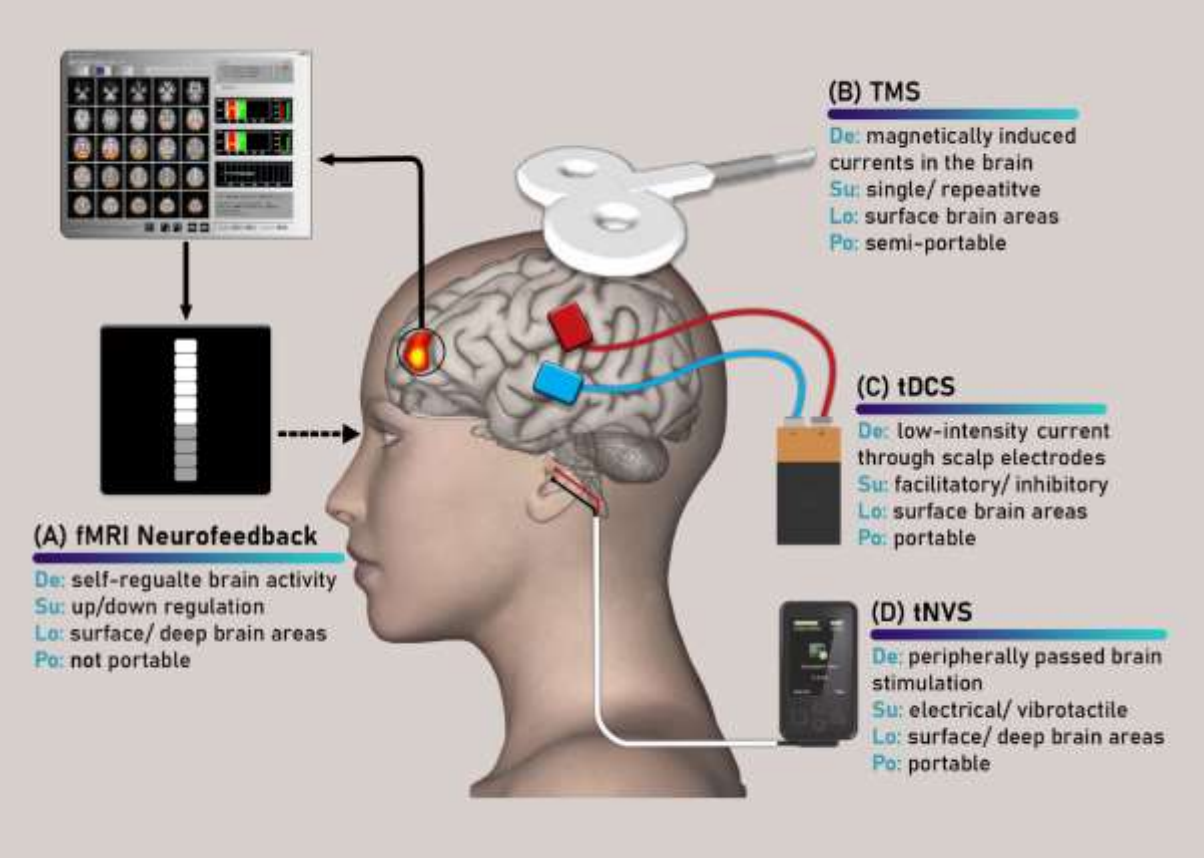

Figure 2: Subtypes and comparisons between brain-related treatments. *The figure illustrates the four neuromodulation techniques in relation to mode of delivery (De), subtypes (Su), localisation (Lo), and portability (Po). The benefits of accessible size and straightforward use apply to tVNS devices that in the context of inflammatory arthritis could exert both direct central effects on the cortical and subcortical areas of the brain and peripheral effects on inflammation through its parasympathetic activity. tVNS lacks the capacity to target specific regions of the brain like TMS and tDCS. Different setups of TMS and tDCS devices can act to facilitate, inhibit, or reset activity and have short-term (single TMS) and longer-lasting (repetitive TMS) effects. TMS and tDCS have limited spatial resolution, and so typically affect a small number of regions at any one time. fMRI feedback enables signals from the brain activity of deeper brain structures and with higher spatial resolution. TMS and tDCS more directly affect brain activity, and consequently, their effects are more easily distinguishable by patients. Compared to tDCS, TMS more focally implements stimulation to a specific area, while tDCS devices are both more cost-effective and portable and do not require significant prior expertise. Images to illustrate fMRI neurofeedback were produced using Turbo-BrainVoyager v3.2 (Brain Innovation, Maastricht, The Netherlands). fMRI=functional magnetic resonance imaging. tDCS=transcranial direct current stimulation. TMS=transcranial magnetic stimulation. tVNS=transcutaneous vagal nerve stimulation.*

Neurofeedback from functional MRI relays real-time data like BOLD signals to help individuals self-regulate brain activity, associated with specific behaviours. Although yet unclear, mechanisms of neurofeedback likely amend how the brain initially processes (bottom-up) and/or responds (top-down) to external and internal information (54, 55). To induce behavioural changes, participants aim to facilitate or inhibit activity or connectivity within relevant brain regions. During training, participants receive continuous visual or auditory cues of their neuroimaging measurements and attempt to alter them, while controls either receive feedback from an unrelated target or pre-recorded feedback that does not reflect current measurements. Researchers can explicitly instruct study participants on how to control their brain activity or encourage them to infer strategies of their own when no candidate strategies are available. For example, patients with chronic pain have been instructed to mentally recreate positive events and thus shift their attention, an approach they would already employ in their daily lives (62). Neurofeedback has yet to be tested in inflammatory arthritis but has been used in other relevant clinical conditions. A systematic review of fMRI feedback in conditions such as chronic pain and depression found that from 48 studies, 73% had a clinically significant or at least statistical improvement (56). Moreover, 11/17 linked clinical improvement to successful regulation—a change in the desired direction compared with rest and/or whether individuals still altered their signal in trials with no provided feedback. The positive findings depended on the average power of the studies, which could detect large and medium but not small effects. Neurofeedback may be applicable in some populations, but future work needs to optimise factors like the target area of the brain, the direction of modulation (up-or-downregulation), the type of signal (strength or pattern of activation; connectivity), the type of instruction (implicit or explicit), and the time spent applying the learned modulation after neurofeedback.

Instead of self-regulation, brain stimulation directly modulates activity either by scalp electrodes in transcranial direct current stimulation (tDCS) or through electromagnetic coils in transcranial magnetic stimulation (TMS). The brain region targeted for stimulation is based on the brain function or clinical condition of interest. For example, stimulating the motor cortex or visual cortex with TMS can evoke transient responses such as involuntary hand movements or illusory flashes of light (phosphenes) respectively. To explore such brain functions, TMS employs single magnetic pulses that modulate brain function. In clinical contexts, a repetitive TMS protocol is commonly utilised, where repetitive pulses are used over a variable timeframe to excite (high-frequency) or inhibit (low-frequency) brain activity. Repetitive TMS does not typically create transient effects such as motor or visual responses but targets more durable biological substrates such as neural oscillations or neurochemistry. Instead of frequency, tDCS uses the direction of the current it induces to alternate between exciting or inhibiting neuronal activity. Protocols can vary across many factors that can affect efficacy: amount of stimulation, strength of stimulation, brain region to target, number of treatment sessions, treatment length, and spacing between sessions. Research in inflammatory arthritis is yet to test stimulation techniques, but two studies in multiple sclerosis found 30% reductions in fatigue scores compared with baseline after 10-18 sessions of repetitive TMS in the left and right primary motor cortex. One of the studies failed to maintain these reductions after a longer 12-week follow-up (57),

while the other report showed superior results from targeting the motor cortex compared with the prefrontal cortex but had several patients (15%) who withdrew due to side effects of scalp irritation and headache (58). Applications of tDCS over sensorimotor regions similarly reduced 30% of multiple sclerosis fatigue but studies demonstrated longer-lasting effects when they targeted the prefrontal cortex, had more sessions (14-19), and spread them over a longer period (59). TMS and tDCS differed over results using sensorimotor and prefrontal regions as both techniques rely on but may differently affect the interconnectedness of the brain: stimulate one of the regions to modulate the larger network of fatigue.

Transcranial vagal nerve stimulation (tVNS) marks another non-invasive route to the brain as the vagus nerve innervates accessible locations in the cymba conchae of the ear or cervical portion of the neck. In inflammatory arthritis, studies primarily conduct tVNS to attenuate peripheral inflammation rather than central symptoms. In rheumatoid arthritis, tVNS decreased disease activity within three months compared with baseline (60-62). However, it also lowered mediators of sickness behaviours such as TNFα, interleukin-6 and interleukin-1β, improving secondary outcomes of pain, fatigue, and depression. In SLE, patients with active tVNS were 25-50 more likely to improve their pain and fatigue compared with sham stimulation (63), with similar fatigue reductions in primary Sjögren's syndrome (64). CNS effects likely play a role as vagal nerve afferents reach the nucleus tractus solitarius of the brain stem that engages noradrenergic and serotonergic neurons in the locus coeruleus and dorsal raphe, respectively (65, 66). Both acute and chronic vagus nerve stimulation increase noradrenaline and serotonin release throughout the brain, which is ablated if projections are lesioned (67). Modulating subcortical and cortical regions, long-term tVNS may then improve symptoms through brain plasticity: the ability of focal and widespread neuronal systems to reorganise their structure or function to better adapt to the internal/external environment (68). Studies that perform functional MRI during vagal nerve stimulation display alterations of the nucleus tractus solitarius and its connected regions (65). In depression, long-term tVNS increased insula activation (69) as well as both increased and decreased functional connectivity of the default mode network and hypothalamus with cortical regions such as the anterior cingulate cortex and prefrontal cortex but also subcortical areas like the nucleus accumbens (70, 71). These functional changes correlate with improvements in depression scores but are also related to regions of the brain mapped using measures of fatigue. Findings like insula activation also link with pain and affirm a neurobiological underpinning of all sickness behaviours that vagal nerve stimulation may be able to alleviate.

Neuromodulation may expand the arsenal against chronic fatigue if future work optimizes and incorporates these treatments into an easy-to-follow clinical pathway (Figure 3). Beginning with how to select treatment parameters, recent trials in depression have used functional connectivity from each individual to personalise the TMS position over an otherwise broad, heterogeneous brain area (72). The approach targets the region that most strongly connects with the brain network underlying treatment response and studies would need to develop similar neuromodulation protocols for fatigue. Beyond standardizing procedures, we would also suggest

experimental designs to increase their sensitivity by both selecting subpopulations that highly express central symptoms and performing a priori power calculations; investigators to document secondary and longer-term outcomes; analyses to link brain effects with clinical benefits. All are steps to better equip studies in unearthing mechanistic insights of fatigue but also infuse confidence in bigger trials to establish efficacy. Trials should compare treatments to recognize their different mechanisms and relate their cost-effectiveness to other options in terms of expenses, time, and applicability. Clinical care could thus progress by integrating both neuromodulation and neuroimaging. The final version of such a chronic fatigue pathway would better understand how other factors interact with neurobiological measurements, have prediction models that integrate all these modalities, and has clear guidelines on how such information should be used in making clinical decisions.

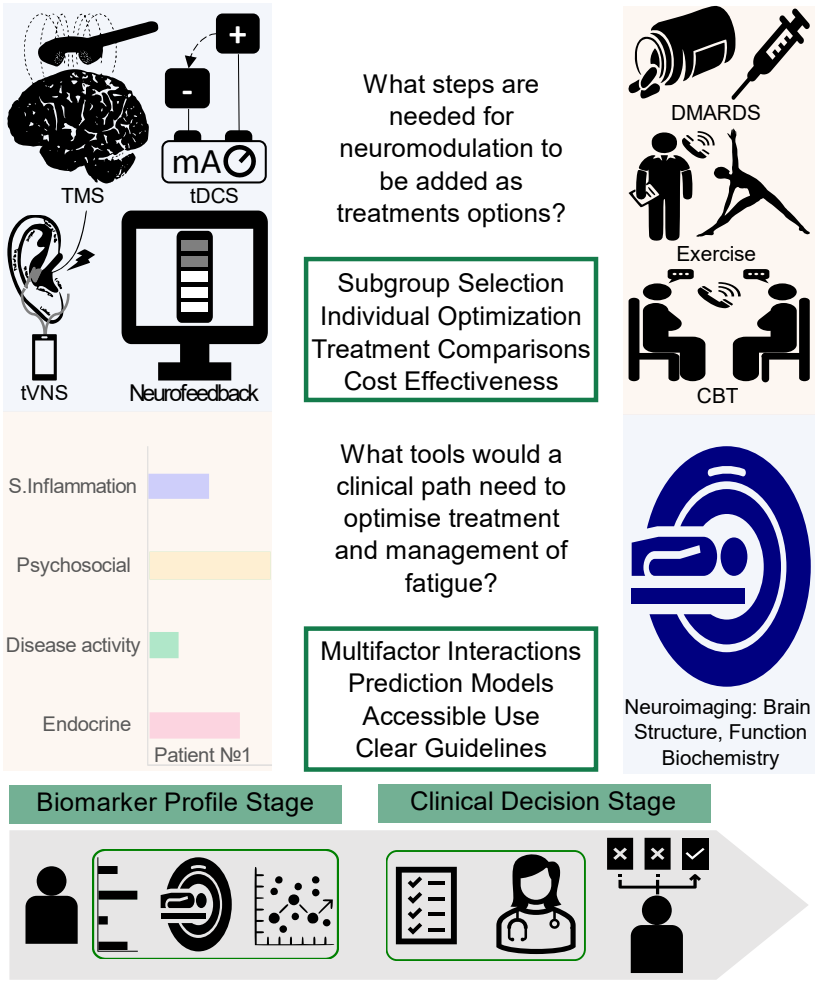

Figure 3: Steps towards implementing brain-related treatments and imaging into clinical care of chronic fatigue. *Neuromodulation techniques (TMS, tDCS, tVNS, neurofeedback) could supplement pharmacological, physical, and psychological treatments for fatigue. First, the treatments need to be tested in subgroups of patients with especially high fatigue levels and optimize device and target setup for each individual. Clinical trials would then need to compare these treatments, better understand the mechanisms behind their effects, and evaluate their cost-effectiveness. A clinical path would require models on how neurobiological and other factors interact in causing fatigue and apply clear guidelines on how to implement them for optimal care and management in patients. CBT=cognitive-behavioural therapy. DMARDS=disease-modifying antirheumatic drugs. tDCS=transcranial direct current stimulation. TMS=transcranial magnetic stimulation. tVNS=transcutaneous vagal nerve stimulation.*

Conclusions

Neurobiological and population studies have started to shift views of chronic fatigue in inflammatory arthritis away from a purely disease activity perspective. Instead, fatigue clusters with sickness behaviours like chronic pain, associates with neurobiological differences in basal ganglia and prefrontal brain regions, and thus agglomerates to common neurobiological mechanisms. Such mechanistic insight would require not only mapping fatigue onto regions of the brain but also reverse-translating them in pre-clinical models to unravel the molecular underpinnings of this symptom. For more immediate gains, studies could predict fatigue using neuroimaging and inform of how current drug, physical, and psychological treatments should be applied but also develop non-invasive brain-related therapeutics. Early work showed stimulation of the vagus nerve reduced the impact of the disease and fatigue in inflammatory arthritis as well as functionally affected the brain in depression while brain stimulation and regulation techniques have improved chronic pain, depression, and fatigue in different clinical cohorts. Heterogenous results plague studies on brain-related therapies that can be counteracted through a long-term strategy in design and applications. If clinical care develops a selective approach to who might benefit the most from neuromodulation and neuroimaging screening, we can both gain more insight into the pathophysiology of fatigue and optimise treatment gains.

Search strategy and selection criteria

We searched Embase and Web of Science from December 1, 2021, to July 30, 2022, using the alternatives of fatigue (“fatigue”, “lethargy”, “weakness”, ”weariness”, “debility”, “enervation”, “exhaustion”, “faintness”, “feebleness”, “heaviness”, “languor”, “lassitude”, “listlessness, “burnout”, “fatigation”, “tiredness”, “overtired*”, “asthenia”). These terms were filtered to specific diseases (“rheumatic”, “rheumatological”, “inflammatory arthritis”, “rheumatoid arthritis”, “psoriatic arthritis”, “lupus”, “SLE”, “osteoarthritis”, “ankylosing spondylitis”, “Sjogren*”, “fibromyalgia”). Sections were formed using terms for methods (“fMRI”, “neuroimaging”, “functional connectivity”, “diffusion tensor imaging”, “structural connectivity”, “voxel based morphometry”, “brain volume”, “magnetisation transfer ratio”, “magnetic resonance spectroscopy”) and treatments(“diagnosis”, “treatment”, “prognostic”, “prediction”, “brain stimulation”, “vagus nerve stimulation”, “vagal nerve stimulation”, “transcranial magnetic stimulation”, “TMS”, “transcranial direct current stimulation”, “tDCS”, “transcranial alternative current stimulation”, “tACS”, “cognitive behavio?ral therapy”, ”exercise”, “tumor necrosis factor”). We restricted search to articles in English language, excluding unpublished material and conference abstracts, and focused on systematic reviews, meta-analyses, and cohort studies.

Contributors

KS and NB planned the major points for the Review and conducted the literature search. All authors contributed to organising, editing and interpreting the content of the Review. KS drew figures 1 and 3 using Inkscape Project (2020), with recommendations from SA, NB, and JC. SA designed and drew figure 2 using Adobe Photoshop, while KS provided its content. KS, SA, and GW gathered content for table 1 while all authors contributed to its editing.

Declaration of interests

The authors report no biomedical financial interests or potential conflicts of interest.

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