



Symptom Interconnectivity in Multiple Sclerosis: A Narrative Review of Potential Underlying Biological Disease Processes

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ABSTRACT

Introduction: Fatigue, cognitive impairment, depression, and pain are highly prevalent symptoms in multiple sclerosis (MS). These often co-occur and may be explained by a common etiology. By reviewing existing literature, we aimed to identify potential underlying biological processes implicated in the interconnectivity between these symptoms.

Methods: A literature search was conducted to identify articles reporting research into the biological mechanisms responsible for the manifestation of fatigue, cognitive impairment, depression, and pain in MS. PubMed was used to search for articles published from July 2011 to July 2021. We reviewed and assessed findings

from the literature to identify biological processes common to the symptoms of interest.

Results: Of 693 articles identified from the search, 252 were selected following screening of titles and abstracts and assessing reference lists of review articles. Four biological processes linked with two or more of the symptoms of interest were frequently identified from the literature: (1) direct neuroanatomical changes to brain regions linked with symptoms of interest (e.g., thalamic injury associated with cognitive impairment, fatigue, and depression), (2) pro-inflammatory cytokines associated with so-called ‘sickness behavior,’ including manifestation of fatigue, transient cognitive impairment, depression, and pain, (3) dysregulation of monoaminergic pathways leading to depressive symptoms and fatigue, and (4) hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis as a result of pro-inflammatory cytokines promoting the release of brain noradrenaline, serotonin, and tryptophan, which is associated with symptoms of depression and cognitive impairment.

Conclusion: The co-occurrence of fatigue, cognitive impairment, depression, and pain in MS appears to be associated with a common set of etiological factors, namely neuroanatomical changes, pro-inflammatory cytokines, dysregulation of monoaminergic pathways, and a hyperactive HPA axis. This association of symptoms and biological processes has important implications for disease management

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strategies and, eventually, could help find a common therapeutic pathway that will impact both inflammation and neuroprotection.

Keywords: Biological processes; Cognitive impairment; Co-occurrence; Depression; Fatigue; Multiple sclerosis; Symptoms; Pain

Key Summary Points

Fatigue, cognitive impairment, depression, and pain are highly prevalent symptoms that often co-occur in multiple sclerosis (MS); therefore, these symptoms may be explained by a common etiology.

By reviewing existing literature, we aimed to identify potential underlying biological processes implicated in the interconnectivity among fatigue, cognitive impairment, depression, and pain symptoms in MS.

We found that the co-occurrence of fatigue, cognitive impairment, depression, and pain in MS appears to be associated with a common set of underlying etiological factors, namely neuroanatomical changes, pro-inflammatory cytokines, dysregulation of monoaminergic pathways, and a hyperactive hypothalamic-pituitary-adrenal axis.

These findings have important implications for pharmacological and non-pharmacological disease management strategies as well as for future research activities in MS.

INTRODUCTION

Multiple sclerosis (MS) is a neurological disease characterized by inflammation and degeneration of the central nervous system (CNS) [1]. In 2020, it was estimated to affect 2.8 million people globally [2], with the number expected

to increase over time [3, 4]. There are a broad range of symptoms associated with MS, and they manifest differently between patients. However, common symptoms impacting the social and physical functioning of people living with MS (PlwMS) include fatigue [5], cognitive impairment [6], pain [7], and depression [8] and are estimated to affect approximately 37–78% [9], 34–65% [10], 29–86% [11], and 5–59% [12] of patients, respectively. The range of prevalence observed for each symptom likely reflects differences in study populations and methodologies used.

Notably, these symptoms often co-occur, having a significant impact on patients' lives. Co-occurrence of fatigue, pain, depression, and cognitive complaints has been shown to have a negative association with quality of life (QoL), with worsening symptoms being linked to poorer psychological and physical QoL. A single-factor model was found to explain the associations among these symptoms [13]. Other research suggests that these symptoms cluster in two distinct patterns: an 'emotional/cognitive' cluster comprising depression and cognitive impairment and a 'physical' cluster that includes pain and fatigue, each of which has been shown to contribute to the prediction of QoL and perceived health status [14, 15]. The cluster of fatigue, depression, and pain has shown a strong negative predictive relationship with physical activity behavior (i.e., the group of PlwMS who reported the worst clustered fatigue, depression, and pain was the least physically active). This relationship was driven predominantly by functional limitations [16].

Regarding the prevalence and relative impact of these clustered symptoms across the disease course, evidence suggests that symptom co-occurrence is evident immediately following diagnosis in the majority of patients, with pain and fatigue reported as the symptoms that most commonly co-occur [17]. The rate of symptom co-occurrence remains relatively stable during the first year post-diagnosis [17]. In older adults, symptom clusters are characterized by a predominance of fatigue, depression, and anxiety symptoms—and associated severe sleep problems [18].

Given that symptom co-occurrence is relatively widespread among PlwMS, it may be that there is a common etiology explaining this phenomenon. Identifying such a unifying pathway (or pathways) driving symptom interconnectivity might help to inform the development of behavioral and pharmacological interventions targeted at alleviating multiple symptoms simultaneously. Furthermore, a better understanding of the interconnected nature (or ‘clustering’) of these symptomatic domains may help to inform symptom assessment practices, including the development of more accurate patient-reported outcome (PRO) measures.

To this end, the objective of the present article was to provide a narrative review of existing literature to identify potential underlying biological processes that may explain the interconnected nature of fatigue, cognitive impairment, depression, and pain in PlwMS.

METHODS

The purpose of the literature search was to identify published articles containing the findings of primary research focused on investigating the biological processes implicated in the interconnectivity among fatigue, cognitive impairment, depression, and pain in PlwMS.

PubMed was used to search for all articles published during the 10 years prior to July 16, 2021, using the search terms ‘Multiple Sclerosis AND ((cognition AND fatigue AND depression) OR (cognition AND fatigue AND pain) OR (cognition AND pain AND depression) OR (fatigue AND pain AND depression)).’ Note that as the focus of the search was to identify interconnectivity between multiple symptoms, the search strategy would not necessarily identify articles that described fewer than three of the symptoms listed. Since this is a narrative review, no typical criteria for inclusion and exclusion were predefined. We simply retained papers that reported research related to the topic in question. Importantly, the intention was not to conduct a systematic review of the literature, but to pragmatically search for relatively recent literature on the topic, including previous

reviews that capture earlier research not detected during our search.

Titles and abstracts of returned articles were screened to identify papers reporting the findings of research into the biological processes linked with the symptoms of interest. Additional relevant articles were identified from the reference lists of a number of review articles returned during the search. The full texts of all relevant articles were then reviewed. For each paper, we used an Excel tracking document to record the respective symptoms and biological processes and the associated key findings. Based on this information, we identified a set of mechanistic groupings under which to categorize findings. These groupings serve to structure the results section in the present article.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. As such, ethics committee approval was not sought.

RESULTS

The literature search identified a total of 693 articles. Screening of titles resulted in the exclusion of 406 articles, with a further 212 articles excluded during screening of the abstracts. This resulted in 75 articles, consisting of 46 original articles and 29 review articles. An additional 206 articles were identified from the reference lists of the 29 reviews. This resulted in 252 original articles that were reviewed to extract relevant results that reported biological processes associated with fatigue, cognitive impairment, depression, or pain in MS (Fig. 1).

Following review of the relevant literature, articles were categorized based on one or more symptoms measured (fatigue, cognitive impairment, depression, and pain). In total, 222 articles contained results relevant to one of the symptoms of interest (i.e., associated the measurement of a biological process with the measurement of the symptom of interest), 25 articles studied 2 symptoms, and 5 articles measured ≥ 3 symptoms. Additionally, following categorization of the biological processes associated with the symptoms of interest across

all relevant articles, four primary biological processes were identified and named as follows: neuroanatomy, inflammation, monoamines, and the hypothalamic–pituitary–adrenal (HPA) axis. In total, 228 articles contained results relating to neuroanatomy (changes in the structure and function of the CNS assessed using traditional and novel imaging techniques); 9 articles contained results related to inflammation (changes in inflammatory cells, cytokines or other inflammatory mediators in MS); 3 articles contained results related to monoamines (serotonin, dopamine, norepinephrine, and/or associated pathways), and 4

articles contained results related to HPA axis function (changes in HPA axis hormones). Additionally, five studies included results that referred to more than one of the aforementioned biological processes, while three articles referred to processes not specifically captured by the previous categories (myelin oligodendrocyte glycoprotein antibody positivity, vitamin D levels, and resting muscle oxygen consumption in the upper limb; Table 1 and Table S1 in the electronic supplementary material).

Figure 2 provides a graphical representation of the literature search results and potential key biological processes underpinning the

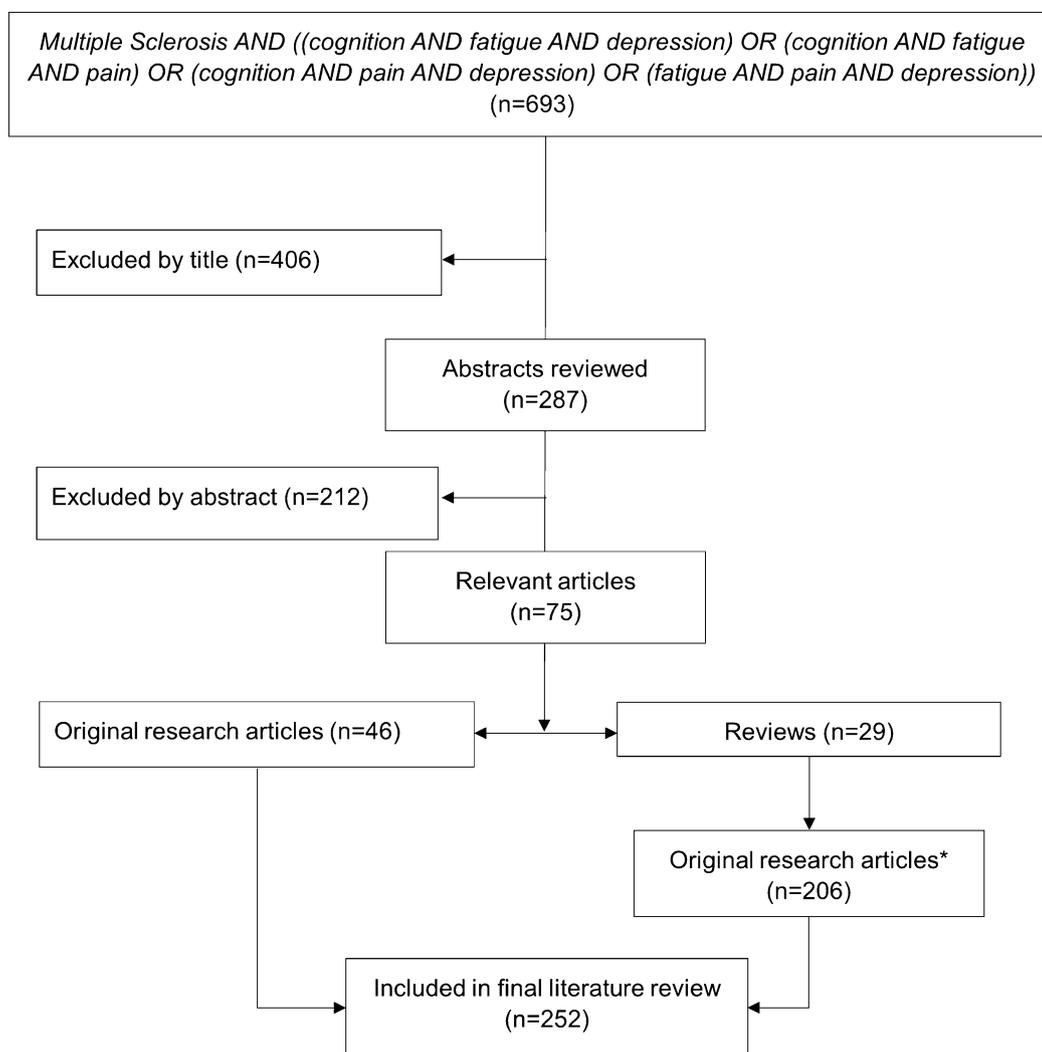


Fig. 1 Flow diagram of literature search and article screening. *Original research articles sourced from reviews were screened for duplicates with the $n = 46$ original research articles first identified in the search

Table 1 Articles stratified by symptoms and biological processes

Symptoms	Articles, <i>n</i>	Biological processes	Articles, <i>n</i>
Cognitive impairment	144	Neuroanatomy	228
Fatigue	48	Inflammation	9
Depression	25	Monoamines	3
Pain	5	HPA axis	4
Fatigue/depression	11	Neuroanatomy/HPA axis	1
Cognitive impairment/fatigue	9	Inflammation/HPA axis	2
Cognitive impairment/depression	5	Neuroanatomy/inflammation	1
Cognitive impairment/fatigue/depression	2	Neuroanatomy/inflammation/HPA axis	1
Fatigue/depression/pain	2	Other	3
Cognitive impairment/fatigue/depression/pain	1	Total	252
Total	252		

HPA hypothalamic–pituitary-adrenal

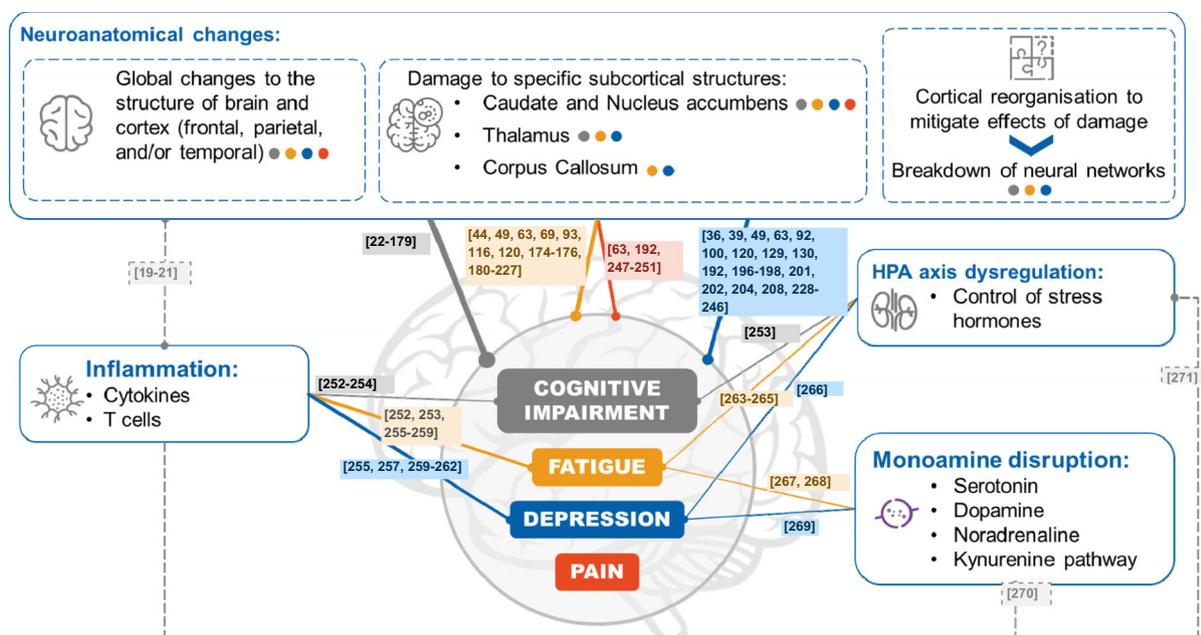


Fig. 2 Graphical representation of the literature search results and potential key biological processes underpinning the interconnectivity among fatigue, cognitive impairment, depression, and pain. The potential links between the biological processes and symptoms are color-coded, e.g., a blue circle or line indicates a link with depression. References shown in the colored boxes support the

relationships represented in the figure. The dashed gray lines and associated references represent the way in which each of the biological mechanisms may directly impact the others. HPA, hypothalamic-pituitary-adrenal

interconnectivity among fatigue, cognitive impairment, depression, and pain.

Neuroanatomy

Structural Brain Changes

Neuroanatomical changes were identified as the primary biological process associated with fatigue, cognitive impairment, depression, and pain, representing > 90% of all articles identified from our search.

Global brain atrophy begins at an early stage of MS and accelerates with disease progression (see [82, 272]). A longitudinal study found an association between progressive brain atrophy during a 2-year period and worsening fatigue over the subsequent 6 years in patients with MS [205], while associations were also seen between whole-brain lesion volume and fatigue [222], and impairments in processing speed [107, 224], and between a decrease in brain volume and depression [236] and impairments in processing speed [107, 224].

A degree of overlap is apparent between the locations of subcortical atrophy in PlwMS and the presence of cognitive impairments, fatigue, and pain. For example, PlwMS who reported fatigue showed greater atrophy in regions involved in the processing of effort and reward, such as the striatum, than those without fatigue. This is consistent with the idea that impairment of cortico-striatal networks contributes to fatigue in MS [181, 183, 185, 187]. However, atrophy of subcortical areas, including the striatum (caudate and putamen), globus pallidus, thalamus, and nucleus accumbens, was also associated with impairments in cognition, particularly processing speed [31, 107, 137]. In addition, changes in gray matter thickness of the caudate, putamen, and thalamus were associated with pain [251].

Furthermore, overlap was evident in the areas of cortex associated with fatigue, cognitive impairment, depression, and pain in PlwMS. Atrophy of frontal and/or parietal cortex was more extensive in individuals reporting fatigue [183, 185, 210] and in those with impairments in verbal learning, spatial learning, attention, conceptual reasoning, and processing speed

[32, 115, 159]. Atrophy of frontal cortex, along with atrophy of temporal [246], cingulate, and parietal cortex [228], was associated with depression in PlwMS [228, 232, 246]. Atrophy of frontal and parietal cortex was also associated with pain [251].

Functional Connectivity

Global CNS neurodegeneration, as well as damage to specific structures in the brain and spinal cord, can lead to disruption of neural networks and functional connectivity. The demyelination typical of MS may disrupt communication between the nodes of neural networks. Several articles identified from our literature search support the hypothesis that disruption to this functional connectivity is associated with the four symptoms of interest.

Disruption to the functional connectivity of the default mode network (DMN), which is involved in internally oriented cognitive processes such as ‘mind wandering,’ recall of past events, and simulation of future events [273], is associated with cognitive impairment and depression [65, 85, 139, 164, 241]. Decreased cognitive performance was associated with reduced resting-state network connectivity, including in the DMN, in people with relapsing–remitting MS (RRMS) [65, 105, 274] and progressive forms of MS [139]. By contrast, a group of individuals with early-stage MS showed increased functional connectivity in the DMN despite marked reductions in white matter integrity [85]. As the participants in the latter group were also cognitively impaired relative to controls, Hawellek et al. argued that their findings suggest reduced cognitive efficiency in early-stage MS.

However, it is important to consider that while neurodegenerative damage can directly influence symptoms associated with the affected brain structures, compensatory mechanisms may mitigate the impact of this damage via the increased or decreased recruitment of other brain structures. This is known as cortical reorganization (reviewed in [275–277]). It is thus possible that the increased functional connectivity observed by Hawellek et al. within the DMN reflects a compensatory process aimed at reducing cognitive impairment. Likewise,

increased DMN resting-state connectivity within the periphery of the posterior cingulate cortex was suggested to have a compensatory role in cognitively impaired individuals with RRMS [278].

Task-based functional magnetic resonance imaging (MRI) studies in MS have provided further evidence of cortical reorganization by showing that on certain cognitive function measures, PlwMS can perform comparably to healthy controls while recruiting different cortical and subcortical structures and demonstrating different brain activation patterns [27, 124, 125, 131, 220]. Patients with clinically isolated syndrome (CIS) who improved their performance on a test of working memory and processing speed over a 12-month interval showed increased activation of the right lateral prefrontal cortex (PFC) over the same period, suggesting that this may be a compensatory response [28]. Parry and colleagues proposed that medial PFC recruitment may be a form of adaptive plasticity that compensates for deficits related to reduced right PFC activity in MS [124]. At baseline, PlwMS performing a counting Stroop task showed stronger activation of left medial PFC, but weaker activation of right PFC, than healthy controls. However, after taking a central cholinesterase inhibitor, rivastigmine, this difference disappeared [124]. Furthermore, while patients with clinically definite MS and CIS did not differ significantly from healthy controls in performance on the Paced Visual Serial Addition Task, individuals with clinically definite MS showed increased activation of the hippocampus and parahippocampal area compared with patients with CIS, which may have indicated a need in the patients with clinically definite MS to bolster their working memory capacity via recruitment of these additional brain regions [131].

The capacity for compensation is, however, finite. PlwMS who showed minor impairment on attentional tasks relative to healthy controls displayed increased and additional activation of various brain areas, mainly in frontal cortex and posterior parietal cortex, that were not activated in healthy controls [125]. However, this additional activation was not observed in PlwMS whose performance was severely impaired,

suggesting that in individuals with severe cognitive impairment the capacity to compensate by recruiting additional brain areas may have been exhausted [125].

In addition to compensatory mechanisms, PlwMS may have a level of reserve capacity that offers some protection from the symptomatic changes associated with the disease. Greater intellectual enrichment (based on vocabulary knowledge) in PlwMS was associated with less deactivation of the DMN and with less recruitment of the PFC during both low (0-Back and 1-Back tasks) and high (2-Back task) cognitive demands, with a better cognitive performance during the high-demand tasks also associated with greater intellectual enrichment [164]. The authors proposed that the DMN and PFC provide a link between intellectual enrichment and cognitive status in PlwMS, with greater maintenance of the DMN and lower need for prefrontal recruitment representing a basis of cognitive reserve [164]. Taken together, these results suggest that damage to the DMN may contribute to cognitive decline, while intellectual enrichment may provide protection against the cognitive impacts of the disease. Given that disruption to the DMN is linked with both cognitive decline and depression, it is interesting to postulate that intellectual enrichment might also protect against depression in PlwMS.

Disrupted functional connectivity is also associated with fatigue and depression [85, 141, 194, 200, 219, 235, 240]. Fatigue severity in PlwMS has been negatively correlated with functional connectivity of certain brain regions, while positively correlated with connectivity between other regions [194, 200]. In people with RRMS, fatigue severity was negatively correlated with functional connectivity between the basal ganglia and frontal and parietal cortex (independent of age, sex, and disease severity), but positively correlated with functional connectivity between caudate nucleus and motor cortex [194]. No association between fatigue severity and basal ganglia functional connectivity was observed in healthy controls, suggesting that this phenomenon was specific to PlwMS [194]. Investigating the striatal subdivisions, Jaeger and colleagues found that fatigue severity negatively correlated with

functional connectivity of the caudate nucleus and ventral striatum with the sensorimotor cortex (SMC), while positively correlating with functional connectivity of the dorsolateral PFC with the rostral inferior parietal gyrus and the SMC [200]. In individuals with early-onset MS (onset < 30 years of age), fatigue severity negatively correlated with functional connectivity between the left insula and posterior cingulate gyrus and between the right thalamus and left parietal operculum [219]. The authors of the latter study reported increased connectivity between the right thalamus and right precentral gyrus and between the left hippocampus and left precentral gyrus in PlwMS reporting fatigue versus those without fatigue, although functional connectivity in these regions did not correlate with fatigue severity [219].

There is evidence that increased functional connectivity may be a compensatory mechanism for countering fatigue in PlwMS. For example, after performing a mentally challenging task, PlwMS with cognitive fatigue showed increasingly stronger resting-state functional connectivity between the left superior frontal gyrus and occipital, frontal, and temporal areas than healthy controls and PlwMS without cognitive fatigue [211]. Similarly, when performing a motor activity after completing a cognitive task, PlwMS with fatigue recruited significantly more of their brain than they had when doing the same motor activity prior to the cognitive task; this was not observed in healthy controls [220]. Notably, the increased brain activity required to perform mental or physical activities has also been proposed to potentially contribute to the fatigue observed in MS [279].

Disrupted activity in the limbic system is associated with levels of depression in PlwMS [235, 240]. People with MS and comorbid major depressive disorder (MDD) exhibited increased local path length in the right hippocampus and right amygdala compared with PlwMS without MDD and with healthy controls [235]. No significant difference was observed in the local path length between healthy controls and PlwMS without MDD [235]. Further analyses showed that, compared with the healthy controls and those with MS but no MDD, PlwMS with MDD had an increased shortest distance

between the right hippocampus/right amygdala and a series of frontal and prefrontal cortical regions, including the dorsolateral PFC [235], which is thought to play a key role in the pathophysiology of depression [280]. A large study in PlwMS ($n = 77$) demonstrated that depression scores negatively correlated with functional connectivity of both the hippocampus and amygdala with the dorsolateral PFC, providing further support for a role of these regions in mediating depression in PlwMS [240].

Inflammation

Pro-inflammatory cytokines released from lymphocytes that have infiltrated the CNS of PlwMS contribute to the inflammatory signaling pathways at the heart of MS pathogenesis [20, 21]. However, they also act directly on the brain to produce so-called “sickness behaviors,” including symptoms such as fatigue, depression, pain, and transient cognitive decline [281]. It is unsurprising, therefore, that these symptoms are commonly experienced by PlwMS, given the inflammatory component of the disease, particularly in its early stages. We identified several articles that demonstrate a relationship among inflammation, depression, and fatigue.

In a prospective study of peripheral immune cells in individuals with progressive MS ($n = 13$), the times of greatest depression (based on Center for Epidemiological Studies Depression [CES-D] score) were associated with fewer CD8+ T cells and a higher CD4+/CD8+ T cell ratio than the times of least depression [260]. The participants were enrolled in a placebo-controlled trial of cyclosporine, where 6 of the 13 individuals received cyclosporine and the others received placebo. In the placebo group, the number and percentage of CD4+ T cells were higher at the times of greatest psychological distress versus the times of least depression [260].

There were no differences in absolute numbers of CD4+ and CD8+ T cells between individuals with RRMS and comorbid MDD ($n = 10$) and those with RRMS without MDD ($n = 34$) [257]. However, differences in T cell function were observed, with more tumor necrosis factor

(TNF)- α - and interferon (IFN)- γ -producing CD8+ T cells detected in the comorbid MDD group—a trend that was retained when the authors controlled for Expanded Disability Status Scale score or disease-modifying therapy (DMT) [257]. The frequency of CD8+ T cells did not predict depression severity but was a significant predictor of fatigue scores [257]. This latter finding was consistent with that of a prior study, where levels of the pro-inflammatory cytokines TNF- α - and IFN- γ were significantly greater (both $p = 0.01$) in whole blood samples from PlwMS with fatigue ($n = 15$; Fatigue Severity Scale [FSS] mean scores ≥ 5) than PlwMS without fatigue ($n = 15$; FSS mean scores < 4) [253].

In samples of cerebrospinal fluid (CSF) from people with RRMS ($n = 47$), levels of interleukin (IL)-6 (but not IL-8) positively correlated with self-rated depression and fatigue symptoms ($p < 0.05$) [255]. It could not be determined whether these associations were specific to MS as the study did not include healthy controls. Using a multinomial logistic regression analysis, Kallaur and colleagues examined immune inflammatory markers in healthy controls ($n = 249$), PlwMS without MDD ($n = 108$; Hospital Anxiety and Depression Scale [HADS] depression subscale score ≤ 8), and PlwMS with MDD ($n = 42$; HADS depression subscale score > 8) [262]. Serum IL-6 levels were the highest in individuals with MS and comorbid MDD [262]. These data in PlwMS are consistent with previous reports that IL-6 is an inflammatory marker associated with depression in the general population [282, 283]. Of note, serum levels of the T helper 2 (Th2) cytokine IL-4 were higher in PlwMS without MDD than in healthy controls, but significantly lower in PlwMS with MDD than in those without MDD. According to the authors, the latter finding may indicate that depression in PlwMS is related to increased peripheral immune-inflammatory potential [262].

In the articles we identified, there was limited information on the relationship between inflammation and cognitive impairment. In a cohort of individuals diagnosed with either RRMS or secondary progressive MS, greater levels of depression and fatigue were detected in

participants classified as cognitively impaired ($n = 25$) than in those classified as cognitively preserved ($n = 25$) [254]; notably, the percentage of IFN- γ -producing CD4+ and CD8+ T cells was higher in the cognitively preserved group. The latter finding led the authors to conclude that inflammation might not contribute to cognitive dysfunction during remission in MS; however, they also acknowledged that measuring intracellular IFN- γ may not reflect the circulating levels of IFN- γ [254]. The participants were not on steroid therapy or taking psychoactive drugs or antidepressants, but it was not clear if they were receiving any other treatments that could have influenced the results of the study. For example, IFN- β therapy has been associated with lower levels of IFN- γ -producing CD8+ T cells [257].

The mechanistic role of inflammation in the symptoms of interest is further supported by evidence of worsening symptoms during MS relapses (i.e., periods of acute inflammatory activity) [284, 285], although we acknowledge that structural changes occurring during MS relapses may also contribute to symptom worsening at this time. While the exact mechanisms of inflammatory-mediated symptom manifestation are not fully understood, it is likely a combined result of acute inflammation, chronic inflammation, and immune-mediated neurodegeneration affecting specific regions of the CNS, as well as immune-mediated alterations to monoaminergic pathways and activation of the HPA axis, both of which are discussed in more detail below.

Monoamines

Monoamine neurotransmission plays an important role in mood regulation [286], and disruption of the associated monoaminergic pathways has been implicated in the manifestation of classic MDD symptoms, namely low mood and changes in appetite, pain responses, and sleep [287]. It has been proposed that in PlwMS, fatigue may result from an imbalance in dopamine secondary to abnormalities in, and disruption of communication between, the frontal and striatal regions of the brain, which

are heavily innervated by dopaminergic neurons. This hypothesis is supported by evidence of the successful treatment of fatigue in MS and other disorders (e.g., Parkinson's disease, chronic fatigue syndrome, cancer) using dopaminergic psychostimulants and other modulators of dopamine [288].

We identified three articles that explored the relationship between monoamines and the symptoms of fatigue and depression in PlwMS. In a study assessing the effect of the wakefulness-promoting drug modafinil on fatigue in MS, Niepel and colleagues found that PlwMS with fatigue ($n = 17$) had reduced autonomic function (assessed by diastolic blood pressure) and reduced levels of alertness (assessed by several subjective and objective measures) at baseline compared with PlwMS who did not have fatigue ($n = 9$) and with age- and sex-matched healthy volunteers ($n = 9$). However, there was no difference between PlwMS with fatigue and either PlwMS without fatigue or healthy volunteers in other measures of autonomic function (systolic blood pressure, heart rate, pupil diameter). The authors hypothesized that PlwMS with fatigue might be more sensitive to the alerting and sympathetic-activating effects of modafinil than PlwMS without fatigue or healthy controls, but found no difference among the three groups in the magnitude of increases in alertness and sympathetic measures following a single 200-mg dose of modafinil. Regardless, the authors postulated that the role of monoamines in fatigue in MS is supported by the anti-fatigue effect of modafinil and that this is likely achieved by stimulation (via the dopaminergic system) of the wakefulness-promoting noradrenergic locus coeruleus nucleus, which is damaged in MS [267].

The role of impaired serotonergic neurotransmission in depression is well established [269]. The kynurenine pathway is the primary non-protein route of metabolism for tryptophan (the precursor of serotonin) and is known to be disrupted in the inflammatory milieu characteristic of MS [269, 289]. Aeinehband et al. used liquid chromatography-mass spectrometry to determine levels of tryptophan, kynurenine, kynurenic acid, and quinolinic acid in CSF samples from 48 individuals with

RRMS. Of the 48 participants, 12 fulfilled criteria for depression based on clinical rating scales. A modest correlation was found between low levels of tryptophan and psychiatrist ratings of depression. However, the predictive value of this measure was limited, since low levels of tryptophan were also detected in some non-depressed PlwMS [289].

Fatigue, depression, and pain are all associated with signs of anhedonia, such as reduced motivation and a lack of positive affect, and with overlapping structural and functional alterations in areas of the brain involved in reward processing [270]. Dysfunctional reward processing may be a functional mechanism common to fatigue, depression, and pain in PlwMS since monoaminergic neurotransmission plays a key role in reward processing and is disrupted by neuroinflammation [270, 290]. Pardini and colleagues examined the relationship between reward-related cognition and fatigue in MS by assessing fatigue values among PlwMS at baseline and after 3 months of therapy with escitalopram or bupropion and determining correlation with these and patients' reward perception [268, 291]. Reward responsiveness was reduced in PlwMS who had fatigue compared with PlwMS who did not have fatigue. It should be noted that the investigators excluded individuals with depression from the study to control for possible confounding factors; these findings are therefore applicable only to this selected population [268, 291]. The authors concluded that the more marked response to bupropion (a dopamine/noradrenaline-enhancing drug) in individuals presenting with lower activation scale reward-responsiveness behavioral (BAS-RR) scores (i.e., with reduced dopaminergic tone) supported the theory that reward perception could underpin fatigue in PlwMS. However, in subjects with higher BAS-RR scores (i.e., with higher prefrontal dopaminergic tone), both escitalopram and bupropion alleviated fatigue, indicating that other mechanisms may also be at play in MS-related fatigue.

Recent studies that examined the structural and functional alterations in regions of the brain associated with monoaminergic neurotransmission further implicate the

monoaminergic pathways in MS-related fatigue [292, 293]. Carandini and colleagues identified damage to several of the monoaminergic fiber tracts projecting from the brainstem nuclei in individuals with RRMS ($n = 68$), but not in healthy controls ($n = 34$) [292]. Moreover, the damage to the brainstem monoaminergic nuclei tracts was moderately associated with worsening cognitive fatigue (assessed by the Modified Fatigue Impact Scale cognitive subscale [MFIS-Cog]). In PlwMS classed as highly fatigued (MFIS-Cog > 15 ; $n = 26$), noradrenaline transporter (NAT)-enriched functional connectivity was significantly lower in several frontal and prefrontal areas than in PlwMS in the mildly fatigued group (MFIS-Cog ≤ 15 ; $n = 29$) [293]. Furthermore, the NAT-enriched functional connectivity values negatively correlated with the MFIS-Cog scores [293]. No between-group differences in dopamine transporter- or serotonin transporter-enriched functional connectivity were observed [293]. The authors acknowledged that their results may appear to disagree with a role for dopamine in fatigue in MS, but noted that these data do not exclude a contribution of dopamine to the changes in NAT-related functional connectivity.

Hypothalamic–pituitary-adrenal axis

The HPA axis is the primary system responsible for the synthesis, release, and diurnal control of stress hormones [294]. Evidence suggests that communication between the immune system and the HPA axis is disrupted in MS and that HPA axis hyperactivity is implicated in neurodegeneration [295]. Notably, HPA axis dysregulation is also associated with depression [296] and, possibly, chronic fatigue [297]. Our literature search identified several studies linking stress hormones (particularly cortisol) with depression and fatigue in MS [230, 233, 253, 257, 263, 264, 266]. In their cross-sectional study of 23 PlwMS (RRMS subtype) and 50 age- and sex-matched controls, Fassbender et al. found that the former group had higher depression and anxiety scale scores and a failure of suppression of cortisol release after dexamethasone pretreatment. The authors

concluded that affective symptoms and dysfunction of the HPA system were associated with laboratory (cell counts) and neuroradiological (gadolinium enhancement of MS plaques) indicators of cerebral inflammation, which suggested that affective and neuroendocrinological disorders in MS are causally linked with inflammatory brain injury [230]. In their cross-sectional study, Gold et al. found that PlwMS with comorbid MDD ($n = 8$) had normal morning salivary cortisol levels but elevated evening salivary cortisol levels, resulting in a flattened slope, providing further evidence for a role of HPA axis hyperactivity in major depression in MS [233]. Gold et al. assessed the volume of hippocampal subregions, diurnal salivary cortisol, and depression in 29 PlwMS (RRMS subtype) and 20 matched healthy controls. PlwMS had smaller hippocampal volumes than the controls, particularly in the cornu ammonis (CA) 1 and subiculum subregions. In addition, PlwMS who had depressive symptoms had smaller CA2-CA3 and dentate gyrus (CA23DG) volumes and higher cortisol levels than the controls. In the MS group, CA23DG volume was correlated with depressive symptoms and cortisol levels. The authors concluded that this provided in vivo evidence for the selective association of smaller hippocampal CA23DG subregion volumes with cortisol hypersecretion and depressive symptoms in MS. A distinction between severity of depression and cortisol response was identified by Kern et al. These authors postulated that a hyperactive HPA axis is primarily present in PlwMS expressing moderately elevated depressive symptoms and that the cortisol-awakening response does not differ significantly between PlwMS with less severe depression and healthy controls [266].

Regarding fatigue in MS, Gottschalk et al. found that PlwMS (RRMS subtype) with fatigue had significantly higher adrenocorticotropin levels in the combined dexamethasone/corticotropin-releasing hormone (Dex-CRH) test than PlwMS without fatigue, indicating that the former exhibit higher HPA axis activity [263]. Powell et al. noted a similar association between HPA axis activity and recalled fatigue (but not same-day fatigue) in individuals with RRMS

[264]. In contrast, Heesen et al. found that fatigue was not significantly correlated with any parameter of the Dex-CRH test [254]. This inconsistency may potentially be explained by differences in disease subtype between the studies by Gottschalk/Powell and Heesen and the fact that MS treatment known to affect cytokines (which influence HPA activity) was not an exclusion criterion in the Heesen et al. study, nor was there categorization of participants into those with and without fatigue.

One explanation for the perturbations of the HPA axis identified by several research groups is modulation of HPA axis activity in an inflammatory environment. Specifically, it has been shown that pro-inflammatory cytokines, such as IL-1 and IL-6, can activate the HPA axis by promoting the release of brain noradrenaline, serotonin, and tryptophan [271], which, in turn, may contribute to the development of certain symptoms in MS (e.g., depression and fatigue).

DISCUSSION

We identified neuroanatomical changes, inflammation, monoaminergic pathway disruption, and dysregulation of the HPA axis as the common processes associated with the manifestation of fatigue, cognitive impairment, depression, and pain in MS. In addition, we have described the overlap between the areas of the brain which are subject to structural and functional changes associated with these frequently occurring MS symptoms. Some of this overlap may arise because lesions in MS often occur in highly connected deep gray matter 'hubs,' such as the thalamus, whereby the ripple effects of such lesions can affect many other brain circuits. Notably, in PlwMS, areas of the brain can exhibit increased connectivity with other regions. For example, functional connectivity between the thalamus and other areas typically increases rather than decreases, suggesting that the thalamus may play a more central role within brain networks in PlwMS than in healthy controls [298, 299].

The interpretation of functional brain changes in MS is complicated by the difficulty in

distinguishing between changes that are a direct effect of the disease process vis-à-vis compensatory changes as the brain attempts to avoid and overcome loss of function. The occurrence of compensatory changes may vary between individuals and over time, with the capacity for compensatory change diminishing as the disease progresses [125]. A further complication in interpreting measures of functional connectivity is that this is not a static property of brain networks, but rather one that changes dynamically, even during a resting-state functional MRI scan [300]. It is thus possible that methodological differences between studies may influence the changes in functional connectivity observed.

Studying common pathways underlying core symptoms in MS can provide additional insights into the mechanisms of disease pathogenesis and help to gain a better understanding of the symptoms experienced by people living with MS. Fatigue, depression, pain, and cognitive impairment are relatively common symptoms with which many patients present, and as such physicians may not always immediately associate them with MS. By highlighting their frequent co-occurrence and shared pathogenesis, our study suggests that it is worth investigating the possibility of MS in patients who present with these symptoms, particularly in combination, and especially when other risk factors are present.

Our findings also raise important considerations related to the measurement and monitoring of symptoms in PlwMS, as well as disease phenotyping. The ability to precisely measure the biological pathways we have identified, and predict the types and severity of consequent symptoms, would have important implications for intervention strategies. Such capabilities would also be invaluable in helping newly diagnosed patients to gain an insight into what they might expect from their particular disease phenotype. Current imaging methods typically available to most neurologists may not be suitable for detecting the nuanced and subtle features required to gain such clinical insights. For example, traditional MRI modalities may not be sensitive enough to detect thalamic changes or changes to structures implicated in

monoaminergic pathway disruption; however, more advanced MRI techniques such as susceptibility-weighted imaging, functional MRI, diffusion tensor imaging, and magnetic resonance spectroscopy could be used to assess these types of pathology [301, 302]. Alternative measurement approaches that promise utility in this regard include assessing the local connectivity of different structures by assessing the whole brain as one network using path lengths and clustering coefficients or by using magneto-/electroencephalography to assess the brain in a non-static way (i.e., microstates) [303].

Identifying common pathways underlying multiple symptoms could have important implications for pharmacological and non-pharmacological disease management. Most DMTs approved for use in MS exert their therapeutic effects via anti-inflammatory mechanisms [304]. Beyond the approved MS DMTs, additional symptomatic treatments include drugs that enhance monoamine neurotransmission and can treat symptoms with an anhedonic component, i.e., pain, fatigue, and depression [270], and drugs that can reduce cognitive dysfunction [305–307] and fatigue [305, 308]. There are also several non-pharmacological interventions with the potential to alleviate fatigue, cognitive impairment, depression, and pain by impacting the common pathways identified, e.g., sun exposure [309], diet [310], cognitive behavioral therapy [270, 311, 312], and exercise [313, 314]. Cognitive behavioral therapy may positively influence levels of inflammatory markers in addition to alleviating the anhedonic symptoms themselves [270, 311, 312]. Exercise, now viewed as a cornerstone in MS management, is an effective symptomatic treatment [313], exerting positive effects on the mechanistic pathways identified in our review [314].

Having demonstrated that several different symptomatic treatment strategies are available, it is interesting to note that in a sample of 35,755 PlwMS, 25.5%, 26.1%, 65.2%, and 73.0% had received neither pharmacological nor non-pharmacological therapy for depression, pain, fatigue, and cognitive dysfunction, respectively [316], suggesting that symptomatic

therapy may be an unmet need in MS. Given that these symptoms often remain untreated or incompletely treated, successfully targeting any or all of them could greatly enhance patients' QoL. As our understanding of the biological pathways leading to, and connecting, symptoms of interest increases, it may become possible to identify potential novel therapeutic and non-pharmacological strategies that target several of these symptoms at once. Future therapeutics that could plausibly alleviate multiple symptoms simultaneously include neurorestorative agents [301], kynurenine metabolites and analogues [317], and agents that regulate the HPA axis.

Our investigation into the biological processes involved in symptom interconnectivity provides a foundation for future research, which could investigate (1) sub-groups of PlwMS who experience some, none, or all of the symptoms in question to identify biological differences between these groups, (2) the causal relationship between the biological processes and symptoms discussed here, (3) the effectiveness of pharmacological and non-pharmacological interventions to assess their impact on multiple symptoms simultaneously, and (4) longitudinal relationships between structural brain changes and symptoms. Importantly, the measurement of symptoms (i.e., PROs) should be carried out using instruments that have been developed in line with best practice guidelines so that relationships between objectively assessed biological variables are being tested against the most accurate available measures of patient outcomes.

Limitations of our review include that the literature search was restricted to the previous 10 years, that a single database was used for the search, and that we did not conduct a strict systematic search with clearly predefined inclusion and exclusion criteria. However, because we included studies from the reference lists of previous systematic review articles identified during our search, we captured relevant studies published before our cutoff date. Some of the studies had a small sample size, and there was also a paucity of articles focused on the symptom of pain, suggesting that this may be another important area for future research

efforts. We acknowledge that due to the search strategy we employed, which used the symptoms of interest in groups of three, potentially informative papers that reported the etiology of individual symptoms may not have been captured. We also used broad terms for each symptom, e.g., we did not discriminate between different types of pain, which we appreciate could have different causes. It is important to note that correlation is not equivalent to causality, with further research necessary to determine the relationship between the biological processes and symptoms covered in this review. Finally, a limitation that has implications not only for the present article, but also for the field of MS symptomology more broadly, is the difficulty to accurately measure and discriminate between these often similar and overlapping symptoms. For example, depression typically presents with fatigue and fatigue can easily be misdiagnosed as depression. As such, to capture these symptomatic domains accurately, the target symptoms must be measured independently using instruments based on robust symptom definitions, with items derived from a sound conceptualization of the underlying construct.

CONCLUSIONS

The co-occurrence of fatigue, cognitive impairment, depression, and pain experienced by PlwMS appears to be associated with a common set of underlying etiological factors, namely neuroanatomical changes, pro-inflammatory cytokines, dysregulation of monoaminergic pathways, and a hyperactive HPA axis. These findings help to advance our understanding of the interconnected nature of MS symptoms, have implications for pharmacological and non-pharmacological disease management strategies, and highlight important topics for future research that might facilitate the development of approaches that target both the inflammatory and neurodegenerative components of MS.

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Data Availability. There are no data, per se, associated with this manuscript. Information extracted from the articles identified from the search can be requested from the authors.

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