Neurodegenerative Diseases

Review Article

Neurodegener Dis 2025;25:21–35
DOI: 10.1159/000544813

Received: September 29, 2024
Accepted: February 12, 2025
Published online: February 19, 2025

A Review of Sex Differences in Neurodegeneration and Psychological Comorbidities in Multiple Sclerosis and Related Disorders

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Keywords
Neurodegeneration · Magnetic resonance imaging · Multiple sclerosis · Sex differences in lifespan · Cognition and psychiatric disorders

Abstract
Background: Multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are chronic neuroinflammatory conditions that disproportionately affect women, with a 2:1 ratio in MS and up to 8.9:1 in NMOSD. Cognitive impairment is one of the earliest and most debilitating symptoms of MS, while mood disorders are common and significantly impact the quality of life and disease prognosis. Understanding sex differences in disease progression, particularly the potential differences in the mechanisms behind disability, is critical for advancing patient care. ***Summary:*** This review synthesizes current knowledge of sex-specific differences in MS and NMOSD, with a focus on neuroinflammation and neurodegeneration, as well as cognitive symptoms, and psychiatric comorbidities. The current state of research highlights the role of hormonal changes over the patient's lifespan, such as estrogen and testosterone, as well as their role in modulating neuroinflammatory responses and subsequent neurodegeneration. ***Key Messages:*** Sex differences research in MS and NMOSD is scarce. Here, we discuss implications of disease monitoring and furthering knowledge in the field with a sex-specific lens, including recommendations for evaluating sex differences and personalized care in MS and NMOSD.

Introduction

Multiple sclerosis (MS) and related disorders, such as neuromyelitis optica spectrum disorder (NMOSD), are characterized by two components: neuroinflammation and neurodegeneration. These lead to different degrees of disease severity and have unique pathogenic mechanisms. Disease-specific inflammation in the central nervous system (CNS) can lead to cascades of events that eventually cause neurodegeneration [1]. Physical disability in MS, however, is not always associated with clinical symptoms or relapses, as demonstrated by the recently termed "progression independent of relapse activity",

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which may indicate neurodegeneration occurs without concurrent overt inflammatory activity [2]. Furthermore, there are different types of MS characterized by the initial disease course [3]. Relapsing-remitting MS (RRMS) is the more common type (affecting 85–90% of patients), diagnosed at a younger age (mean age at onset = 30 years old), and characterized by disease activity (i.e., neurologic dysfunction lasting at least 24 h) with periods of remission [4]. Meanwhile, primary progressive MS (PPMS) is less common with an older age at onset (mean of 40 years old) and affects 10–15% of patients with characteristic slow progression of neurological disability over time, mostly without relapses [5]. Since the preponderance of MS and NMOSD is higher in women versus men (2:1 in MS [6, 7] and up to 8.9:1 in NMOSD patients with seropositivity for aquaporin-4 IgG (AQP4−IgG+) [8]), researching more into the sex differences in these diseases would most certainly impact patient care positively.

Recently, it has been found that more patients with MS have a later age at onset (>40 years of age) compared to the 1990s, where greater than 60% of people with MS had an age at onset that ranged between 18 and 29 years [9]. Currently, 40% of people with MS have an age at onset in that 18–29 range, while a doubling in people with an age of onset from 40 to 49 years has occurred in the last 3 decades and is now comparable to that of most patients with NMOSD [8].

With normal aging, the CNS also ages, undergoing cerebral, gray and white matter volume loss, ventricular enlargement and general atrophy [10]. Magnetic resonance imaging (MRI)-based quantitative measurements of brain subregional volumes and atrophy are established methods in the investigation of normal CNS aging [11] and are often used in these chronic, neuroinflammatory diseases since they are a reliable and well-characterized method for in vivo evaluation of damage in the CNS. Indeed, the diagnostic criteria for MS [3] and NMOSD [12] rely heavily on MRI for correct diagnoses, as well.

It has long been proposed that degeneration or atrophy of gray matter in the brain of MS [13] and NMOSD [14] may lead to cognitive impairment, however more so in MS than in NMOSD [14]. This is in line with the finding that cognitive impairment appears to be more consistently reported in MS than in NMOSD. Some studies report higher frequency in neuropsychological assessments in patients with MS (50% vs. 29%), particularly when it comes to impairments in learning and memory performance [14], although findings are still inconclusive. Although higher rates of comorbid depression and suicidality were observed in patients with NMOSD compared to MS, that may mask cognitive decline in this rare disease [15]. Neuropsychiatric comorbidities, including depression and anxiety, are common in both MS and NMOSD, significantly affecting quality of life and daily functioning, underscoring the importance of their thorough evaluation and management across both conditions [16, 17].

Even though there is a high discrepancy in prevalence of these neuroinflammatory and neurodegenerative diseases between the sexes, sex as a biological factor has often been ignored [18].

This review focuses on current knowledge of sex differences and provides future considerations to evaluate in adult MS and AQP4−IgG+ NMOSD with an overview of neurodegeneration, cognitive, and psychiatric affections in these diseases. References to sex and gender in this article follow the guidelines of the American Psychological Association (APA, https://apastyle.apa.org/style-grammar-guidelines/bias-free-language/gender).

Common Symptoms and Regions of Interest

The Netherlands Neurogenomics Database (NND, https://nnd.app.rug.nl/app/NND) contains the frequency of cognitive and psychiatric symptoms observed in MS and NMOSD patients. The Netherlands Brain Bank (NBB) donor clinical and neuropathological traits can be searched for in the NND and compiled based on disease diagnosis. Although there is an option to include NMOSD in the search field, when filtering for over 16 years of age, no patients with NMOSD remained in the database and 256 patients with MS were found. Out of these patients, 168 (65.6%) were female and 88 (34.4%) were male.

Here, retrospective chart review revealed that the most prevalent cognitive symptoms were related to verbal impairment (72%), impaired memory (64%), and general cognitive decline (50%). This description of clinical presentations is in line with common findings in systematic neuropsychological assessments in patients with MS [19, 20]. When it comes to psychiatric symptoms, the results from this database indicate by far the most prevalent presence of depressed mood (84%), followed by changed mood and emotions (41%) and anxiety (29%). These results illustrate how common and influential psychiatric symptoms are in affecting patient quality of life and disease prognosis (Fig. 1).

A method that automatically maps brain regions to disease states by text-mining, meta-analysis, and machine-learning [21] was used to create Figure 2. This figure illustrates brain regions most often affected in MS using a meta-analysis of 81 functional MRI studies from a separate literature search (not from the NDD) conducted on June 10, 2024 (online suppl. Material; for all online suppl. material, see https://doi.org/10.1159/000544813).

Fig. 1. Common cognitive and psychiatric symptoms found in MS. Analysis of the clinical charts of 256 patients with MS from the Netherlands Brain Bank showed frequent reporting of verbal and memory impairment and cognitive decline (**a**), as well as depressed mood and changes in effect (**b**) in over 40% of patients.

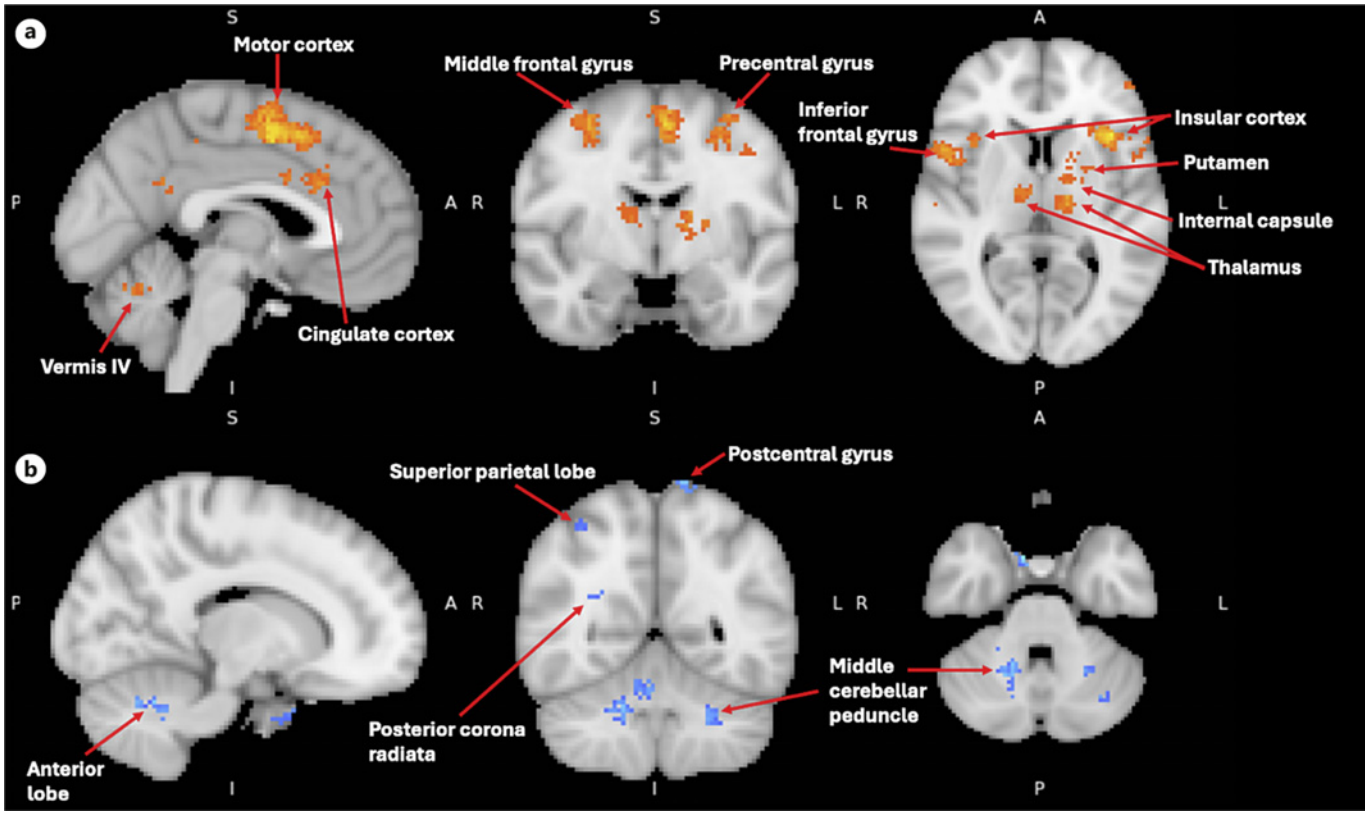


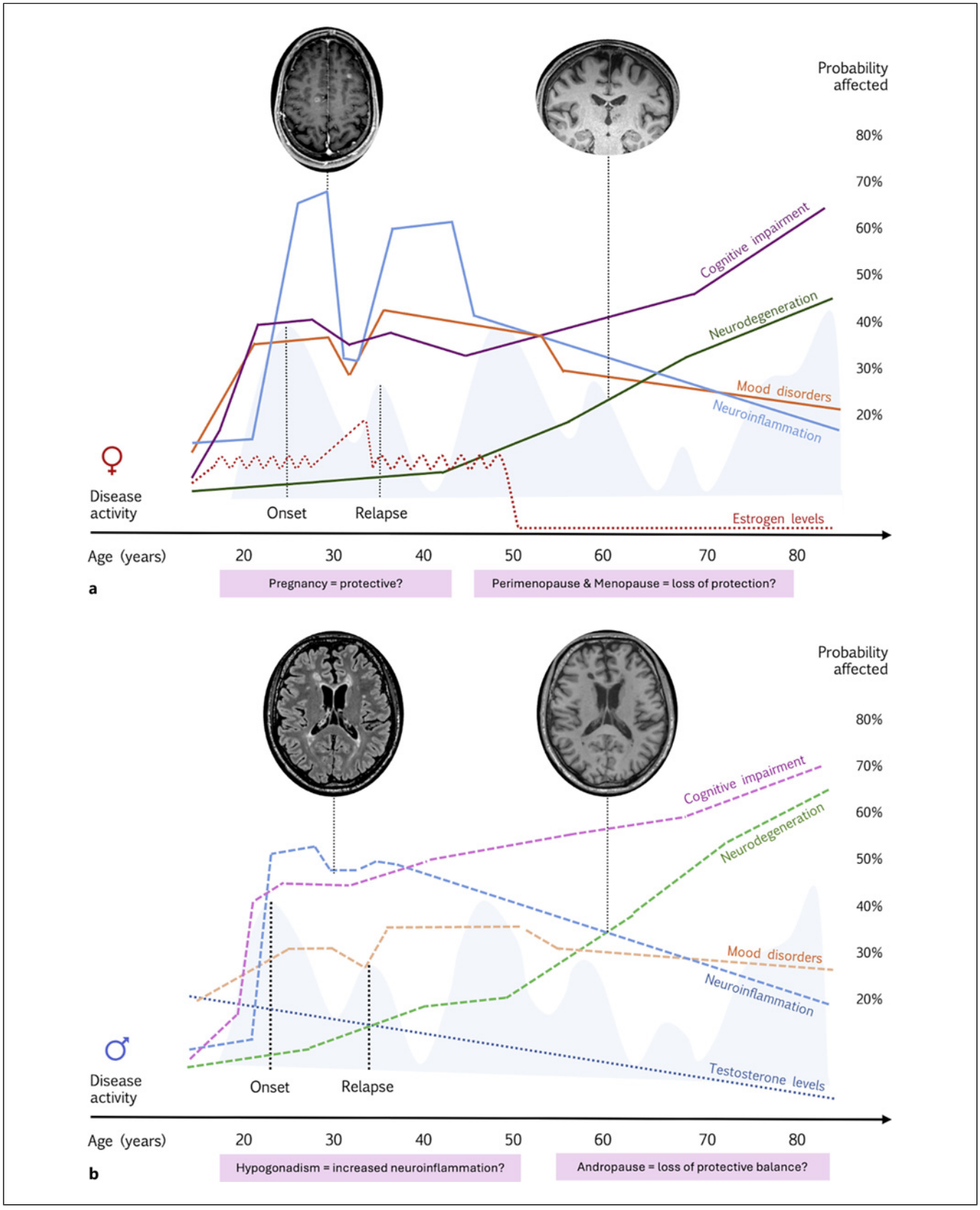
Fig. 2. Regions of interest found in an automated meta-analysis of 81 MS MRI studies. **a** Uniformity test map of brain regions that are consistently active in functional MRI studies when the term "multiple sclerosis" is searched for. The more yellow the color, the larger the z-scores are related with that brain region in relation to the term "multiple sclerosis." **b** Association test map of regions reported in studies with the term "multiple sclerosis" than in studies without that term in their abstracts.

It is evident that many regions related to motor function (e.g., motor cortex, anterior lobe of the cerebellum, middle cerebellar peduncle), as well as brain regions that are known to affect cognition and mood (e.g., putamen, thalamus, insular cortex) are implicated in MS.

Neuroinflammation and Neurodegeneration

Immune responses that are chronic in nature and occur in the CNS are termed neuroinflammatory. Microglia are recognized as part of the innate immune system that are responders to CNS damage by way of inflammatory cytokine production and cascades of processes. Meanwhile, adaptive immune responses, such as T cells and antibodies, are produced as a response to peripheral inflammation [22]. There is evidence that MS differs in early versus progressive phases, with initial relapsing MS likely initiating with a peripheral immune response that targets the CNS; and later stages in MS are dominated by immune reactions within the CNS [1]. Research regarding neuroinflammation in NMOSD shows both peripheral and CNS inflammation [23]; however, evidence of neurodegeneration due to inflammation varies [24, 25].

Estrogen receptor alpha (ER) has been found to mediate inflammatory activity via 17-estradiol (E2) [26]. E2 is the biologically active hormone released by the ovaries [27], but it is also produced by brain cells, including microglia [27]. Systemic E2 administration has also been shown to inhibit microglial reactivity to inflammation when it was experimentally induced using lipopolysaccharide [28]. Thus, it would stand to reason that biological females that produce higher levels of E2 would gain some neuroprotective properties from this hormone. However, it seems that in MS, women had significantly higher annualized relapse rates than men (0.32 versus 0.28) although this sex difference disappeared after the age of 50 [29]. Another study found that women with MS had higher occurrence of gadolinium-enhancing brain lesions (an



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MRI-marker of ongoing inflammation [30]) than men, although male patients with MS showed higher evolution of lesions into destructive black holes [31]. One other study found that women with MS have greater numbers of gadolinium-enhancing brain lesions, those of which with the highest counts had the lowest levels of testosterone. Men with higher E2 also showed higher brain lesion loads [32]. These findings suggest that neuroinflammation may be inherently higher in women; however, neuronal damage may be mitigated better in women, possibly with the help of E2. Unfortunately, very few studies have been able to evaluate sex differences in NMOSD. One study found that the annualized relapse rate in women is higher than in men (0.72 versus 0.5) [33] and since progesterone increases the risk of AQP4–IgG+ NMOSD development [34], this suggests that higher neuroinflammation in female patients with NMOSD also exists.

Although both E2 and progesterone levels fluctuation throughout menses and especially during pregnancy, there have been conflicting results of protective effects of these hormones in MS. However, most studies have reported a neutral or positive effect of pregnancy on reduced disability accrual [35]. Meanwhile, in NMOSD, disease activity (neuroinflammation) has been found to vary during pregnancy with an increase in relapse rate post-partum and likely causing irreversible neuronal damage [36].

With pro-inflammatory immunological profiles, it has been suggested that patients with MS and NMOSD may experience more fatigue and depression [37, 38], as well as chronic pain [39, 40]. Naturally, these studies have endeavored to link neuroinflammation to neurodegeneration using MRI as atrophy in brain and spinal cord volumes and thicknesses are commonly measured.

Neurodegeneration or atrophy, particularly in the deep gray matter (DGM), has long been implicated as a mode of cognitive impairment in patients with MS [13]. Since female patients with MS often exhibit more neuroinflammation, it would be expected that perhaps there would be more neurodegeneration in the brain leading to higher physical and cognitive disability than in male patients. Several studies have shown that this is not the case. In one relatively large study, 52 women and 37 men with MS showed more regional gray matter atrophy, particularly in the putamen and cortical thinning in the parietal lobe and occipital sulci. These male patients with MS also had worse upper extremity functions compared to the women [41]. Interestingly, it was previously also observed that male patients with MS with lower testosterone levels (or hypogonadism) without compensatory elevation of E2 had higher clinical disability at one cross-sectional timepoint. Moreover, the male patients with lower first visit testosterone levels also showed more cognitive decline at a later timepoint, approximately 3 years after the first clinical visit [42]. There has been less evidence in NMOSD that a sex difference in CNS atrophy exists, most likely due to the rarity of the disease [43] and the high preponderance of women versus men of developing the disease [44]. However, it would stand to reason that higher relapse rates in female patients with AQP4-IgG+ NMOSD [33] would relate to higher atrophy and disability (including cognitive impairments) than male patients, due to the destructive nature of attacks in the disease [45, 46].

Cognition

Cognitive impairment is one of the earliest and most debilitating symptoms of MS, affecting about 40–65% of the patients [20]. With its onset in early to middle adulthood, MS often develops at a time in which cognitive deficits are highly interfering. Specifically, common symptoms such as slowed processing speed, memory difficulties, and impaired focus and planning abilities can leave patients with MS less likely to be employed, impede driving and social activities, and make it difficult to live independently [47].

Recent findings indicate that the early presence of cognitive impairment predicts how fast disability develops over the course of the disease. In a 10-year longitudinal study, patients with cognitive impairment at diagnosis were three times more likely to progress to higher disability on the Expanded Disability Status Scale (EDSS ≥4) and convert from relapsing-remitting MS to secondary progressive MS (SPMS) [48]. Interestingly, risk factors for reaching an EDSS ≥4 at a 5-year follow-up were not only the number of white matter lesions and how many neuropsychological tests were affected – but also male sex [49]. Although the picture of how biological sex effects the disease course, symptom severity, and

Fig. 3. Depiction of lifespan changes in patients with typical RRMS. Sex-specific representative disease courses are shown with respect to overlapping disease activity, hormonal changes, neurodegenerative and neuroinflammatory trajectories, as well as cognitive and affective symptoms. **a** In women, where between onset and relapse often, early disease neuroinflammation is detected using gadolinium-enhancing contrast agents to visualize active BBB leakage at lesion sites. Also, at later ages, neurodegeneration can be often seen by visual inspection of the cortex. **b** In men, between onset and relapse, neuroinflammation often leads to chronic T2-hyperintense lesions that do not resolve over time. At later stages, chronic T2-hyperintense lesions often lead to necrotic regions seen as T1-black holes.

Table 1. Recommendations for future directions for sex differences research in MS, NMOSD, and related diseases

Current sex differences in MS and related diseases research	Recommendations
Lack of studies with focused matching and comparison between the sexes	Institutes and funding bodies should provide more incentives (e.g., funding/special calls) to conduct sex differences research and/or publishers include sex and gender specific reporting of clinical, imaging, cognitive, and psychiatric data
Very little communication of or education on sex differences in research and in clinical settings	Inclusion of sex differences research in journal articles in journal clubs and at least one speaker at department seminars could present on their research on sex differences in healthy aging and in disease
Minimal involvement of patients in conducting research that reflects their quality of life	Patient representatives could be recruited during clinical trial/study enrollment and representatives could aid in standardization of questionnaires related to patient quality of life
Low number of studies reporting standard norms calculated specifically for the different sexes in cognitive and neuropsychological measures	Publishers could include special calls for studies evaluating large datasets to calculate and validate standardized sex, age, and education corrected norms for cognitive and neuropsychological measures
Lack of reporting whether sex differences were observed in studies including patients with MS and/or related disorders	Publishers could include reviewer notes/tips that detail publication standards that include information reporting separated based on patient sex, such as demographics tables with each metric of interest (i.e., age, age at disease onset, etc.) that are specific to each sex in the patient cohort

treatment response in patients with MS is not fully clear, it is crucial to take potential sex differences into account. Below, we provide an overview of current studies relevant for diagnosis and treatment planning in MS.

Cognitive Assessment in MS: Neuropsychological Batteries, Norms, and Sex Effects

Neuropsychological test batteries are the most common approach to evaluate cognitive deficits in MS. They typically consist of a collection of cognitive tests, take between 15 and 90 min to administer, and cover multiple cognitive domains. There are several batteries specifically designed to assess patients with MS, such as the Brief Repeatable Battery of Neuropsychological Tests (BRB-N [50]), the Minimal Neuropsychological Assessment of MS Patients (MACFIMS [51]), and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS [52]).

Normative evaluations have shown that sex, besides age and level of education, can impact the performance on some of these tests. For instance, sex effects have been reported for the California Verbal Learning Test (CVLT-II) of the BICAMS, with better verbal memory performance in healthy women [53]. In a similar word list learning paradigm, healthy women performed better than men on the BRB-N's Selective Reminding Test (SRT) in the Dutch and Italian normative studies [50, 54]. Further sex effects describing a female advantage have been reported for the BRB-N's Word List Generation Test (WLG [50, 54]), a measure of executive function and verbal fluency, as well as the Symbol Digit Modalities Test (SDMT), a test of sustained attention and visual scanning [50].

Given the potential influence of demographic variables, it is recommended to use sex-, age-, and education-adjusted norms when evaluating the cognitive status of patients with MS. As pointed out previously [55], a difference in performance between female and male patients with MS may otherwise simply reflect baseline differences as seen in the healthy comparison group instead of reflecting a true, disease-related sex effect that is specific to MS. Moreover, using sex-specific norms has been shown to improve the diagnostic accuracy in amnestic mild cognitive impairment [56]. Whether similar diagnostic advantages can be seen in patients with MS, for instance in classifying MS subtypes, remains to be seen.

Sex Differences in Cognitive Performance in Patients with MS

Studies investigating MS-related sex effects on neuropsychological outcomes have shown mixed evidence. Several studies report no difference on cognitive tests between male and female patients with MS [20, 41, 57–63]. A meta-analysis of 4,460 patients found no

moderating effect of sex on cognition [64]. In a study of 114 patients with RRMS and SPMS, female and male patients with MS showed a comparable performance on the SDMT [41]. While sex was not related to cognitive performance in a large cross-sectional study of 150 patients with RRMS, PPMS, and SPMS, a protective effect of hormonal therapy was found in female patients [57]. In a 3-year follow-up study of 49 patients with RRMS, patients with and without cognitive deficits on the BRB-N did not differ in terms of sex but only with regard to baseline cognitive performance [20]. Furthermore, no sex differences were found in social cognition [58], a prevalent cognitive symptom of MS involving theory of mind and emotion recognition [65].

In contrast, other studies observed MS-related sex differences in cognition [55, 66–73]. A large cross-sectional study of 1,040 patients with MS revealed better performance of female patients in the domain of verbal memory, while overall cognitive performance (defined as ≥2 domains affected on the BRB-N and Stroop test) did not differ between sexes [68]. Better verbal memory performance in women [55, 69, 71] and worse visuospatial memory performance in men with MS [70] have been observed in several studies. Other studies described better performances for women with MS in tests of executive function and attention, including the Trail Making Test (TMT [72]), the Symbol Digit Modalities Test [71], the Wisconsin Card Sorting Test (WCST [72]), and tests of processing speed [70]. Only one study reported a male advantage on the Paced Auditory Serial Addition Test (PASAT [69]). Another study described lower verbal fluency performance in women with MS [73].

Mechanisms of Sex Effects in Cognition

Several mechanisms have been proposed to explain sex effects in the extent and frequency of cognitive impairment in MS. First, differences in disease courses may cause men with MS to progress faster and develop worse clinical outcomes [19, 74]. These include differences in brain lesion profiles in men with MS compared to women, such as more extensive white matter damage [75], cortical atrophy [73], and decreased network efficiency on resting-state MRI [70]. Differential patterns in regional brain atrophy appear to play the most important role here, with decreased thalamic and hippocampal volumes affecting cognition [70, 76]. Moreover, a meta-analysis in 1,903 patients suggested a greater role for cognitive reserve in older patients and women with MS [77].

Lately, hormonal effects on cognition in MS have gained more attention. Specifically, estriol has been discussed in the context of potential neuroprotective and anti-inflammatory effects [32, 78]. Lower estrogen levels after menopause may thus particularly affect cognition in MS [35]. Moreover, studies have shown a decrease in relapse risk during pregnancy with a subsequent postpartum increase in risk [35, 79]. Detailed research on whether this also affects cognition is needed. In men with MS, a pilot study reported improved spatial memory performance when treated with testosterone supplementation [80].

Neuropsychiatric Comorbidities

Psychiatric comorbidities in MS are common and profound contributors to patient quality of life and daily activities [81]. Among them, depression and anxiety are the most frequent psychiatric disorders [82]. Unfortunately, they are often underdiagnosed and overlooked in everyday clinical practice leaving patients without much-needed support and treatment [17]. Taking that into account, it is no surprise data on sex differences in psychiatric comorbidities are sparse and more research is needed to acquire a comprehensive picture.

Depression: Etiology, the Role of Inflammation, and Sex Effects

With a prevalence 3–5 times higher than in the general population [83], depression is the most common comorbidity in MS with a prevalence of 23.7% according to a comprehensive systematic review [84]. Exact numbers differ among studies, a meta-analysis of 58 studies reported a prevalence of clinical depression in MS of 30.5% [85], while the prevalence of clinically significant depressive symptoms has been 40–50% [86]. These findings are highly relevant as depression is linked to the worsening of disability in MS, poor cognitive performance and progressive MS disease course [87]. The prevalence of depression in MS, however, does not seem to increase with age [88].

Similarly, depression is frequently observed as a comorbidity associated with chronic medical conditions, frequently occurring alongside illnesses such as cancer, cardiovascular diseases, metabolic syndromes, inflammatory disorders, and neurological conditions [89]. Its etiology is multifactorial, with heritability estimates of approximately 35% [90]. Stressful experiences, especially adverse events like childhood sexual, physical, or emotional abuse, are significant risk factors for major depressive disorder (MDD). Additionally, social and psychological determinants of health, including unhealthy lifestyle behaviors such as excessive alcohol consumption, smoking, diets high in fat or sugar, and physical inactivity,

contribute to the development of MDD [90]. Depression is notably at least twice as prevalent in women compared to men, a disparity that emerges during puberty and persists into adulthood [91, 92].

As a heterogeneous disorder, depression manifests with varied clinical presentations and symptoms among individuals [93]. Approximately 39% of individuals with MDD exhibit an "inflammatory subtype," characterized by elevated levels of monocytes, CD4+ T cells, neutrophils, C-reactive protein (CRP), and interleukin-6 (IL-6), alongside more severe symptoms compared to non-inflammatory cases [94]. This inflammatory subtype is often enriched in conditions like MS and other inflammatory diseases comorbid with depression. Psychiatric comorbidities, including depression and anxiety, have been reported to precede MS diagnoses by as much as 10 years [95] and even longer, over 15 years, in some cases [96]. The extended duration of mental health issues prior to MS onset suggests a potential etiological role in the development of MS, rather than solely reflecting a prodromal stage of the disease [96].

Sex differences are evident in the relationship between inflammation and depression. A systematic review and meta-analysis by Jarkas et al. [97] found that women with depression have significantly elevated levels of inflammatory biomarkers, such as CRP (Cohen's d = 0.19, $p = 0.02$) and IL-6 (Cohen's d = 0.51, $p = 0.04$), compared to healthy controls, whereas similar effects were not observed in men. These findings underscore the role of inflammatory pathways in the pathology of depression among women. Additionally, women with depression tend to experience greater symptom severity than men [98] and exhibit distinct biomarker profiles [99]. Women are more likely to report somatic and cognitive-affective symptoms [98, 100] and frequently present with atypical depression linked to immunometabolic dysregulations [101], which includes hypersomnia, weight gain, and fatigue [102]. Sex differences also extend to comorbidities: women with depression are more prone to anxiety disorders, whereas men are more likely to have substance use disorders [98, 102]. For an in-depth overview of sex differences in depression, including both clinical and preclinical studies, see Eid et al. [103].

Sex Differences in Depression in Patients with MS

The majority of the studies investigating depression in MS focused on the most common type of MS, RRMS, with fewer investigations involving primary and/or SPMS. In the largest study evaluating sex differences in depression in patients with RRMS, Mayo and colleagues [104] investigated not only overall scores for depressive symptoms but also separate somatic and cognitive domains of depression. They analyzed data from 494 participants, out of which 354 were women and 140 men who did not differ in age and disability status. Their results showed significantly higher Beck Depression Inventory II (BDI-II) scores of overall depressive symptoms (median BDI-II in women: 9, in men: 7) as well as somatic symptoms among women (7 vs. 5), while there was no difference reported for cognitive symptoms (2 vs. 1) of depression, suggesting a sex-specific experience of depression and urging further approach to treatment. The study by Patten et al. [105] involved MS patients with all types of disease from a large-scale national survey conducted in Canada. Their results showed a slightly higher prevalence of major depression in women with MS 16.7% compared to 13.1% in men after adjustment for age.

Furthermore, a population-based Canadian study [106] aimed at determining the prevalence of comorbidities at the time of diagnosis of MS, revealed depression was the most prevalent one with 19.1%. Both in MS and the general population, depression, anxiety and bipolar disorder were more common in women, while schizophrenia was more prevalent in men. Surprisingly, when compared to the matched general healthy population, men with MS displayed a higher prevalence of all of the psychiatric comorbidities studied than women with MS.

Taken together, the results demonstrate a high burden of psychiatric comorbidity for both sexes even at MS diagnosis. Contrary to the previous findings, a retrospective study by Theaudin et al. [107] using data from 711 patients with confirmed MS diagnosis but with different disease courses (RRMS, PPMS, and SPMS), did not report significant sex differences in depression scores using Hospital Anxiety and Depression Scale (HADS) ($t = -0.281$, $p = 0.78$) or the percentage prevalence for depression (37.6% in women and 38.3% in men). What the authors found instead were higher HADS anxiety scores in women ($t = -4.555$, $p < 0.001$), and the overall higher percentage prevalence for anxiety in women 52.1%, while 37.8% was reported for men. Comparison of depression cases with comorbid anxiety showed higher frequencies in women than in men (32.3% of women depressed and anxious vs. 23.4% of men) [107].

Sex Differences in Anxiety in Patients with MS

Anxiety is usually the second most common comorbidity in MS, following depression with a point prevalence of 21.9% according to a systematic review [84]. More recent studies report an even higher prevalence of

anxiety in MS, going up to 41.4% [108]. Among persons with MS, anxiety was more prevalent in women with 43% in comparison to men with 34.1%. Younger MS patients experience higher rates of anxiety, especially when recently diagnosed and with disease progression [82]. Impairments in executive functioning, visual memory, and information processing speed are all related to anxiety in MS [82]. Additionally, anxiety usually coincides with fatigue, pain, and sleep disturbances, exacerbating the overall burden of disease [109, 110]. Timely screening and diagnosis are of crucial importance for managing MS and prevention of further comorbidities.

Neuropsychiatric Comorbidities and Disease Progression

One retrospective cohort study [111] followed 2,312 adults with newly diagnosed MS over a period of about 10 years and found that 38.5% of participants developed mood and anxiety disorders, which were then associated with subsequent neurological disability progression. This effect was statistically significant in women but not in men. Similarly, a Swedish cohort study [112] found that MS patients with depression, whether diagnosed or treated with antidepressants, experienced faster disease progression compared to non-depressed MS patients. Notably, this study reported significant results for both men and women, suggesting that the lack of significant results for men in the previous study may have been due to the smaller number of male participants.

Few studies have examined depression in MS over an extended period. Beal and colleagues [113] conducted a study over 7 years, analyzing changes in depressive symptoms. Their findings indicated that gender was not a significant predictor of depression, nor did it influence individual changes in depression among MS patients [113]. The authors suggested that the experience of living with a chronic illness might diminish the typical gender differences in depression. Alternatively, it could be that the higher rates of depression observed were linked to progressive forms of the disease, which were more common among men in their sample. Their results are in the line with an Italian multi-center study comparing depression across MS subtypes which reported that overall depression scores were similar in RRMS and SPMS but higher than in PPMS, with no significant gender differences [114]. These distinct depression profiles across MS types support the hypothesis that depressive symptoms in MS are associated with disease progression.

In summary, both MS and depression are more prevalent in women than men [92], and according to several studies that looked particularly into sex differences in MS-associated depression, a similar trend could be observed in RRMS. However, there are some mixed results due to different measurement instruments used or different MS disease-type populations studied (RRMS vs. combined) and the difference seems to disappear with disease progression. All these findings underscore the importance of investigating sex differences in psychiatric symptoms in MS with greater detail, across all disease subtypes, and through longitudinal studies to better understand if and how these differences evolve over time and with disease progression. With regards to NMOSD, a systematic review of 31 studies involving 4,213 participants revealed a pooled prevalence of 40% for depression and 45% for anxiety [16]. Despite the high prevalence of these psychiatric symptoms in NMOSD investigations of sex differences are currently lacking.

Lifespan Perspective

It is well known that the trajectory of normal age-related neurodegeneration is different in women and men. While atrophy rates in the brain are similar [115], men tend to start with larger volumes, mainly due to larger head-sizes [116]. Over the lifespan, people with chronic, neuroinflammatory diseases such as MS and NMOSD experience sex-dependent changes in disease progression. As illustrated in Figure 3, these changes can diverge depending on hormone levels and inflammatory disease activity.

Cognitive decline in patients with MS and NMOSD may begin very early on in the disease course, with more rapid impairment accrual, especially past the age of 50. Mood disorders, such as depression and anxiety, tend to be more prevalent in younger individuals. Anxiety is particularly common around the time of diagnosis, while depression often coincides with increased inflammatory activity, especially during relapses, which are more typical in the early years of the disease. In contrast, neurodegeneration, which is more characteristic for older age, tends to be associated with lower levels of depressive symptoms. In general, mood disorders are more common in women than men during youth, but as people age, the prevalence between genders becomes more balanced. A recent study showed that while self-reported neuropsychiatric symptoms (e.g., depression and fatigue), subjective and objective neuropsychological outcomes clustered separately in a network analysis, they are still represented as one network [117]. The interconnectedness of these clinical symptoms may prompt the need for further assessments in patients with MS and beyond.

Limitations

One significant limitation in furthering sex differences research in MS and related disorders is the frequent conflation of the terms "sex" and "gender," despite their distinct meanings. Sex refers to biological differences, while gender encompasses societal and cultural constructs ("Sex and Gender – Gender Matters – www.Coe.Int," n.d.). This distinction is critical and should be consistently applied, as outlined in the SAGER guidelines [118].

Additionally, there is a noticeable lack of studies addressing sex differences in NMOSD and, to some extent, MS, in all areas we have covered in this review. This could be due to the large female preponderance in the diseases [8, 119]. More collaborative studies are required to gather, match, and collate data from different centers around the world so that studies can be better powered and potentially sex-matched in a 1-to-1 ratio. One such framework has been set up with the ENIGMA Neuroendocrinology group, which aims to bring together expert researchers in the field of neuroendocrinology for meta- and mega-analyses of existing datasets available to answer questions regarding hormonal changes and brain health throughout the lifespan [120].

Along the same lines, large-scale longitudinal studies tracking sex differences in cognitive decline and neuropsychiatric comorbidities across the lifespan are still missing in these diseases. Due to this knowledge gap, subtle signs of cognitive impairment or affective symptoms may be missed during clinical routine evaluations or get lost in test score averages. The underlying mechanisms of psychiatric comorbidities, particularly the role of hormone levels, are also still poorly understood. Together with larger, multi-centered, collaborative studies, we believe there are further actions that could be implemented by publishers, researchers, and clinicians in the MS and related disorders field, which we detail in the next section.

Recommendations and Future Directions

Table 1 details the current state of sex differences research in MS and related disorders and includes recommendations and strategies on how to overcome some of these limitations. Several key recommendations should be implemented to advance research and treatment in MS. First, increased incentives, such as funding and targeted calls for proposals, should be provided to encourage more studies examining sex differences in MS. Additionally, healthcare providers need to be educated on the importance of considering sex-specific factors when treating MS and other related conditions. Collaboration between researchers and patients is crucial for developing standardized questionnaires that accurately reflect patients' true quality of life. Moreover, when assessing cognitive performance using neuropsychological tests, it is essential to employ sex-, age-, and education-adjusted norms to ensure accurate and fair assessments. Lastly, more research is needed to investigate neuropsychiatric symptoms such as depression and anxiety across different MS subtypes, as well as to decipher the underlying biological mechanisms of potential sex differences in MS. This includes exploring the possible influence of sex hormones and life stage on disease presentation and progression. Such studies will deepen the understanding of MS and promote more personalized, effective treatments.

Conclusion

It is clear, that differences in neuroinflammation, neurodegeneration, cognitive symptoms and psychiatric comorbidities based on sex hormone levels are pertinent in MS and related disorders. The very fact that the sex ratios in these patient populations are highly skewed toward women is an indication that more can be done to research sex differences in these neurological diseases. Changes based on this research in clinical practice are required to treat patients effectively as a whole. Our recommendations to include sex-specific metrics and standardized norms into studies and publications will initiate interest, advance education, and further personalized medicine in MS, NMOSD, and beyond.

Conflict of Interest Statement

J.B. has nothing to disclose. J.H. has received research support from Alexion AstraZeneca Rare Diseases, unrelated to this study. C.C. has received research funding from Novartis and Alexion AstraZeneca Rare Diseases and is a Standing Committee on Science Member for the Canadian Institutes of Health Research and is a part of a consortium funded by the US Department of Defense, unrelated to this study.

Funding Sources

No funding was received for the study.

Author Contributions

J.B., J.H., and C.C.: conceptualization, investigation, writing – original draft, and writing – review and editing.

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