Original

Fatigue Prevalence and its Association with MRI Findings in Multiple Sclerosis: A Cross-Sectional Study

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ABSTRACT

Background: Fatigue is a common and disabling symptom in Multiple Sclerosis (MS), yet its underlying mechanisms and neuroimaging findings remain unclear, particularly in understudied populations such as Iran.

Objective: This study aimed to determine the prevalence of fatigue in MS compared with healthy controls and to explore its associations with brain and spinal cord Magnetic Resonance Imaging (MRI) findings.

Material and Methods: In this cross-sectional study, 100 MS patients and 100 age- and sex-matched controls were enrolled. Fatigue was assessed using the Fatigue Assessment Scale (FAS). MRI data for MS patients, including lesion counts and volumetric measures, were analyzed using the volBrain platform. Statistical analyses (Mann-Whitney U, Kruskal-Wallis, and Spearman's correlation) were performed using SPSS.

Results: Significant fatigue (FAS ≥22) was reported by 92% of MS patients (mean =29.55±4.41) versus 62% of controls. In MS patients, fatigue correlated positively with total lesion count (rho=0.203, P=0.043) and juxtacortical lesion count. No significant associations were found with brain volume, spinal lesions, or demographic variables. Cervical plaques were present in 85% of patients, but were not significantly linked to fatigue.

Conclusion: Fatigue is highly prevalent and more severe in MS patients than in healthy individuals, correlating with total and juxtacortical lesion burden. These findings suggest a role for lesion load in MS-related fatigue and underscore the need for longitudinal and functional imaging studies to clarify its mechanisms and guide targeted interventions.

Keywords

Multiple Sclerosis; Fatigue; Magnetic Resonance Imaging; Lesion Burden, Brain

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Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease characterized by demyelination, axonal loss, and inflammation in the central nervous system, leading to a wide range of neurological impairments, including motor, sensory, and cognitive deficits [1]. Fatigue, reported by 50–80% of MS patients, is one of the most debilitating symptoms, profoundly affecting quality of life, employment, and mental health [2, 3]. Unlike typical tiredness, MS-related fatigue is often disproportionate to physical exertion and resistant to rest, making it a complex clinical challenge [4, 5].

The pathophysiology of MS-related fatigue is multifactorial, potentially involving lesion load, brain atrophy, and disruptions in cortical and subcortical networks [6, 7]. Magnetic Resonance Imaging (MRI) is the gold standard for assessing MS pathology, providing detailed insights into white matter lesions, gray matter atrophy, and spinal cord involvement [8, 9]. However, A study exploring the relationship between fatigue and MRI findings has yielded inconsistent results, with some reporting associations with white matter lesion load [10] and others with cortical atrophy or network dysfunction [11, 12]. Notably, some studies have compared fatigue prevalence between MS patients and healthy controls, and no such studies have been conducted in Iran, where MS prevalence is rising [13, 14].

This study addresses these gaps by investigating fatigue prevalence in MS patients compared to healthy controls. Additionally, it examines the association between fatigue and MRI findings in MS patients, focusing on lesion counts (total, periventricular, juxtacortical, deep white matter, infratentorial, spinal) and volumetric measures of brain structures (white matter, gray matter, subcortical, and cortical regions). The findings aim to contribute to a better understanding of fatigue mechanisms and guide clinical management in MS.

Material and Methods

Study Design and Population

This cross-sectional, descriptive-analytical study was conducted at Imam Reza Clinic, Shiraz University of Medical Sciences, Shiraz, Iran, from January 2023 to December 2024. The study population comprised 100 MS patients, diagnosed according to the revised McDonald criteria [15, 16], and 100 age and sex-matched healthy control group, recruited via convenience sampling. MS patients were selected from those with available MRI data in the university's Infinity system, ensuring comprehensive neuroimaging records. Controls were recruited from the local community, with no history of neurological or psychiatric conditions.

In this study, MS patients aged >18 years with a confirmed diagnosis based on clinical and MRI evidence; controls aged >18 years with no neurological, psychiatric, or chronic medical conditions were included. Additionally, the patients with incomplete medical records, concurrent neurological or psychiatric disorders, use of psychotropic medications, sleep disorders, pregnancy, substance abuse, or unreliable data (inconsistent Fatigue Assessment Scale (FAS) responses) were excluded from the study.

Data Collection

Fatigue Assessment: Fatigue was measured using the FAS, a validated, self-administered 10-item questionnaire with scores ranging from 10 to 50, where scores ≥22 indicate significant fatigue [17, 18]. The FAS assesses both physical and mental fatigue, with items addressing energy levels, task endurance, and cognitive impact. The questionnaire was completed in approximately 2 minutes during clinic visits or follow-up assessments.

MRI Analysis: For MS patients, MRI scans were performed using a standardized MS protocol on a 1.5 T scanner, including T1-weighted, T2-weighted, Fluid Attenuation Inversion Recovery (FLAIR), and gadolinium-enhanced sequences [19]. Data were analyzed using the volBrain platform, an automated tool for quantifying brain volumes and lesion characteristics [20]. Lesions were identified in periventricular, juxtacortical, deep white matter, infratentorial, and spinal regions, with counts recorded for each. Volumetric measures included white matter, gray matter, subcortical gray matter, cortical gray matter, cerebellar gray matter, and Cerebrospinal Fluid (CSF). A board-certified radiologist reviewed all MRI findings to ensure accuracy and consistency. Controls did not undergo MRI, as the study prioritized fatigue prevalence comparisons.

Demographic and Clinical Data: Demographic variables included sex and education level, categorized as below high school, high school, post-high school certificate, bachelor's degree, master's degree, and doctorate. For MS patients, clinical data included the presence of cervical plaques and cervical/spinal atrophy, extracted from medical records and MRI reports.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics (Version 26). Descriptive statistics, including means, standard deviations, and frequencies, were used to summarize fatigue prevalence, demographic characteristics, and MRI findings. Normality was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests, revealing non-normal distributions for FAS scores (P-value<0.001), justifying non-parametric tests. Mann-Whitney U tests compared FAS scores between MS patients and controls, and within MS patients by sex, cervical plaques, cervical atrophy, and spinal atrophy. Kruskal-Wallis tests evaluated FAS score differences across education levels. Spearman's rank correlation coefficients assessed associations between FAS scores and MRI measures (lesion counts and volumetric data) in MS patients. Statistical significance was set at P-value<0.05.

Results

The study enrolled 100 MS patients and 100 controls, all with valid FAS data. Table 1 presents demographic characteristics and fatigue prevalence. The MS cohort was 82% female, with education levels distributed as follows: 20% below high school, 30% high school, 11% post-high school certificate, 31% bachelor's degree, 6% master's degree, and 2% doctorate. The control cohort was 86% female, with education levels: 23% below high school, 30% high school, 13% post-high school certificate, 24% bachelor's degree, 9% master's degree, and 1% doctorate.

Fatigue Prevalence

In MS patients, the mean FAS score was 29.55±4.41 (range: 16–44, median: 30.00, Inter Quartile Range (IQR): 27–31), with 92% (92/100) reporting significant fatigue

Table 1: Demographic Characteristics and Fatigue Prevalence

Characteristic		MS Patients (n=100)	Controls (n=100)
Female, n (%)		82 (82)	86 (86)
Education, n (%)	Below high school	20 (20)	23 (23)
	High school	30 (30)	30 (30)
	Post-high school certificate	11 (11)	13 (13)
	Bachelor's degree	31 (31)	24 (24)
	Master's degree	6 (6)	9 (9)
	Doctorate	2 (2)	1 (1)
FAS Score, mean ±SD		29.55±4.41	25.86±6.06
Median FAS Score (IQR)		30.00 (27–31)	25.00 (20–30)
Significant Fatigue (FAS ≥22)		92 (92%)	62 (62%)

MS: Multiple Sclerosis, FAS: Fatigue Assessment Scale

(FAS ≥22). The distribution was slightly left-skewed (skewness: -0.172) with a kurtosis of 2.017, indicating near-normal distribution with minor outliers. In controls, the mean FAS score was 25.86±6.06 (range: 17–39, median: 25.00, IQR: 20–30), with 62% (62/100) reporting significant fatigue. The control distribution was positively skewed (skewness: 0.609) with a kurtosis of -0.731, suggesting moderate variability. The Mann-Whitney U test revealed significantly higher FAS scores in MS patients compared to controls (U=3107.500, Z=-4.639, *P*-value<0.001), indicating greater fatigue severity in MS patients.

MRI Findings (MS Patients)

MRI data for MS patients showed mean brain volumes (cm^3) as follows: white matter (503.29±73.55), gray matter (634.00±73.52), subcortical gray matter (37.62±5.46), cortical gray matter (499.02±76.86), and cerebellar gray matter (100.22±11.14). Cerebrospinal fluid volume was 188.05±50.52 cm^3. Lesions were identified in periventricular, juxtacortical, deep white matter, infratentorial, and spinal regions (Figure 1), with cervical plaques present in 85% of patients and cervical atrophy in 4%. Spinal atrophy was rare (1%).

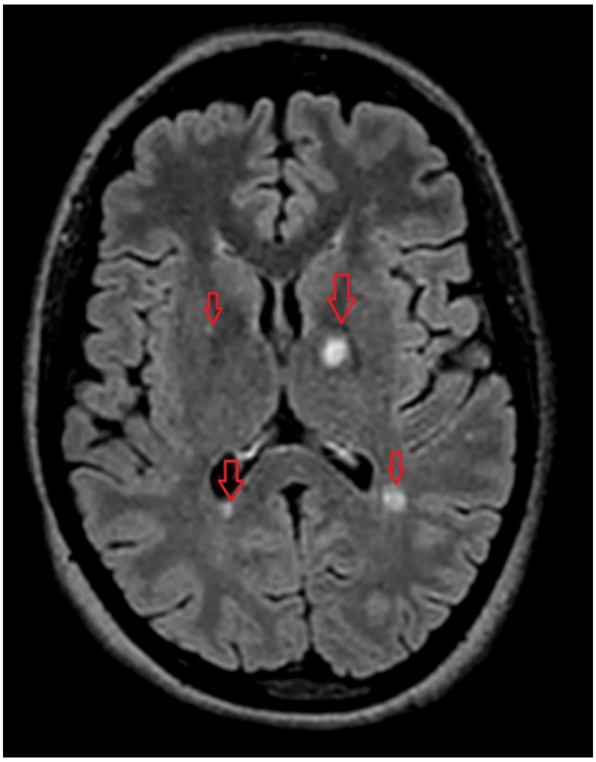

Figure 1: Shows the lesions in patients (Red Arrows)

Correlations with Fatigue (MS Patients)

Spearman's correlations identified significant positive associations between FAS scores and total lesion count (r=0.203, *P*-value=0.043) and juxtacortical lesion count (r=0.208, *P*-value=0.038). No significant correlations were found with other MRI measures, including white matter (r=-0.022, *P*-value=0.825), gray matter (r=0.047, *P*-value=0.639), subcortical gray matter (r=-0.144, *P*-value=0.153), cortical gray matter (r=0.056, *P*-value=0.577), cerebellar gray matter (r=-0.035, *P*-value=0.732), spinal lesions (r=0.018, *P*-value=0.858), or cortical regions such as the anterior cingulate gyrus (right: r=0.064, *P*-value=0.531; left: r=0.115, *P*-value=0.258) or insular cortex (right: r=0.044, *P*-value=0.662; left: r=0.025, *P*-value=0.808). Table 2 summarizes significant correlations.

Group Comparisons

In MS patients, Mann-Whitney U tests showed no significant differences in FAS scores by sex (*P*-value=0.383), presence of cervical plaques (*P*-value=0.065), cervical atrophy (P-value=0.777), or spinal atrophy (*P*-value=0.903). The Kruskal-Wallis test indicated no significant differences across education levels (χ^2=5.191, *P*-value=0.393), suggesting that demographic factors did not influence fatigue severity in this cohort. In controls, Mann-Whitney U tests revealed no significant difference in FAS scores by sex (*P*-value=0.231). The Kruskal-Wallis test showed no differences across education levels (χ^2=3.650, *P*-value=0.601).

The significant difference in FAS scores between MS patients and controls (*P*-value <0.001) highlights greater fatigue severity in MS patients (Figure 2).

Discussion

This study confirms a high prevalence of fatigue in MS patients (92%) compared to controls (62%), with significantly higher fatigue severity in MS patients (mean FAS: 29.55 vs. 25.86, *P*-value<0.001), reflecting the neurological burden of MS [21]. The higher prevalence and severity of fatigue in MS patients align with expectations, as fatigue is a hallmark symptom driven by central nervous system pathology [22]. The lower prevalence (62%) and fatigue severity in controls suggest that fatigue in healthy individuals may be influenced by factors such as lifestyle, occupational demands, or psychosocial stressors, though these were not assessed in this study [23].

In MS patients, fatigue was significantly associated with total lesion count (r=0.203, *P*-value=0.043) and juxtacortical lesion count (r=0.208, *P*-value=0.038), supporting evidence that lesion burden contributes to fatigue [12, 24, 25]. Juxtacortical lesions, located near the cortex, may disrupt cortical-subcortical networks involved in attention, motivation, and energy regulation, contributing to fatigue perception [26, 27]. The absence of significant correlations with volumetric measures (white matter, gray matter) or specific cortical regions (anterior cingulate gyrus, insular cortex) contrasts with studies suggesting a role for cortical atrophy in fatigue [28, 29]. This discrepancy may reflect cohort-specific factors, such as disease duration or lesion distribution, or the use of Spearman's correlations, which are sensitive to non-linear relationships. The non-significant association with spinal lesions (r=0.018, *P*-value=0.858) or cervical plaques (*P*-value =0.065) suggests that spinal pathology plays a limited role in fatigue compared to

Table 2: Significant Spearman's Correlations with Fatigue Assessment Scale (FAS) Scores in Multiple Sclerosis (MS) Patients

MRI Measure	Correlation Coefficient (r)	*P*-value
Total Lesion Count	0.203	0.043
Juxtacortical Lesions	0.208	0.038

MRI: Magnetic Resonance Imaging

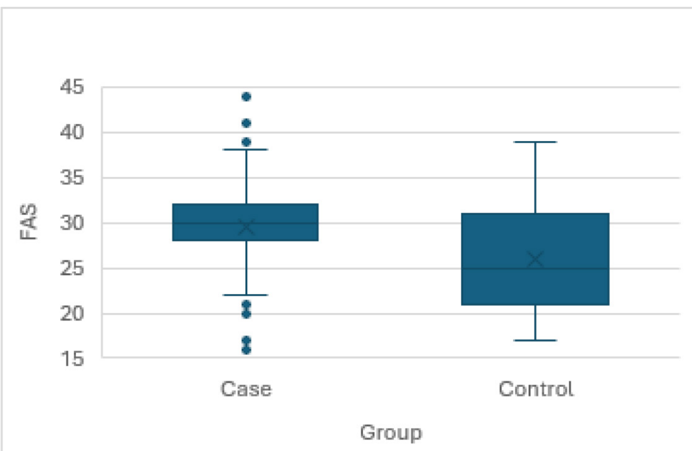

Figure 2: Shows the higher Fatigue Assessment Scale (FAS) score in Multiple Sclerosis (MS) patients compared to control group

supratentorial lesions [30].

The lack of MRI data for controls precludes direct comparisons of brain pathology, limiting mechanistic insights into their fatigue levels. Additionally, the absence of detailed lesion volume data restricts the ability to quantify the extent of lesion burden beyond counts.

The current study has some limitation, as follows: the cross-sectional design of the study precludes causal inferences regarding the relationship between fatigue and MRI findings. Additionally, the use of convenience sampling may introduce selection bias, particularly among the control group, which may not be fully representative of the general population. Although the FAS is a validated instrument, it relies on subjective self-reporting, which can be influenced by mood or cognitive factors [31]. Furthermore, the stressful conditions experienced by the Iranian population may contribute to higher levels of fatigue even among healthy individuals compared to other countries; this may partly explain the relatively high prevalence of fatigue (62%) observed in the healthy control group in the present study. Finally, the small subgroup sizes (e.g., spinal atrophy, n=1; control doctorate, n=1) limit the statistical power for some analyses.

The association between fatigue and lesion load in MS patients supports the use of disease-modifying therapies to reduce lesion accumulation, potentially alleviating fatigue [32]. The higher fatigue prevalence and severity in MS patients emphasize the need for targeted interventions addressing neurological contributors to fatigue. These findings highlight the importance of regional studies in understanding population-specific disease characteristics, particularly in Iran where MS prevalence is rising. Future studies should incorporate longitudinal designs, functional MRI to assess network connectivity, and tightly matched controls to validate these findings.

Conclusion

Fatigue is highly prevalent (92%) and more severe in MS patients compared to healthy controls (62% prevalence), reflecting the neurological burden of the disease. In MS patients, fatigue is associated with increased total and juxtacortical lesion counts, underscoring the role of lesion burden in its pathophysiology. These findings highlight the need for further research with longitudinal designs and advanced neuroimaging techniques, such as functional MRI, to elucidate the mechanisms of fatigue and develop effective therapeutic strategies. This study contributes valuable insights into fatigue in MS within an Iranian context, advancing progress toward improved clinical management.

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Authors' Contribution

A. Torabi-Jahromi: Conceptualization, Methodology, Data Curation, Formal Analysis, Writing – Original Draft. Z. Rastgoftar: Methodology, Investigation, Data Curation, Writing – Review & Editing. B. Zeinali-Rafsanjani: Methodology, Formal Analysis, Visualization, Writing – Review & Editing. B. Dousty: Investigation, Data Curation, Software, Writing – Review & Editing. F. Alizadeh: Investigation, Data Curation, Writing – Review & Editing. P. Pishdad: Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing, Project Administration. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

Ethical Approval

This study was approved by the Ethics Committee of Shiraz University of Medical

Sciences (Approval Number: IR.SUMS.MED.REC.1403.776). All procedures were conducted in accordance with the Declaration of Helsinki.

Informed Consent

All participants, including MS patients and healthy controls, provided written informed consent prior to enrollment in the study.

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Conflict of Interest

None

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to ethical and regulatory restrictions to protect participant privacy.

References

1. Heesen C, Schulz KH, Fiehler J, Von der Mark U, Otte C, Jung R, et al. Correlates of cognitive dysfunction in multiple sclerosis. *Brain Behav Immun*. 2010;**24**(7):1148-55. doi: 10.1016/j.bbi.2010.05.006. PubMed PMID: 20621641.
2. Penner IK, Paul F. Fatigue as a symptom or comorbidity of neurological diseases. *Nat Rev Neurol.* 2017;**13**(11):662-675. doi: 10.1038/nrneurol.2017.117. PubMed PMID: 29027539.
3. Yeni K, Terzi M. Multiple Sclerosis-related Fatigue: An Updated Review of Pathophysiology and Associated Variables Contributing Factors. *J Mult Scler Res.* 2025;**5**(2):33-42. doi: 10.4274/jmsr.galenos.2025.2025-4-4.
4. Kos D, Kerckhofs E, Nagels G, D'hooghe MB, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair.* 2008;**22**(1):91-100. doi: 10.1177/1545968306298934. PubMed PMID: 17409388.
5. Krupp LB, Serafin DJ, Christodoulou C. Multiple sclerosis-associated fatigue. *Expert Rev Neurother*. 2010;**10**(9):1437-47. doi: 10.1586/ern.10.99. PubMed PMID: 20819014.
6. Moore H, Nair KPS, Baster K, Middleton R, Paling D, Sharrack B. Fatigue in multiple sclerosis: A UK MS-register based study. *Mult Scler Relat Disord.* 2022;**64**:103954. doi: 10.1016/j.msard.2022.103954. PubMed PMID: 35716477.
7. Rocca MA, Parisi L, Pagani E, Copetti M, Rodegher M, Colombo B, et al. Regional but not global brain damage contributes to fatigue in multiple sclerosis. *Radiology.* 2014;**273**(2):511-20. doi: 10.1148/radiol.14140417. PubMed PMID: 24927473.
8. Bussas M, El Husseini M, Harabacz L, Pineker V, Grahl S, Pongratz V, et al. Multiple sclerosis lesions and atrophy in the spinal cord: Distribution across vertebral levels and correlation with disability. *Neuroimage Clin.* 2022;**34**:103006. doi: 10.1016/j.nicl.2022.103006. PubMed PMID: 35468568. PubMed PMCID: PMC9059154.
9. Filippi M, Rocca MA. MR imaging of multiple sclerosis. *Radiology.* 2011;**259**(3):659-81. doi: 10.1148/radiol.11101362. PubMed PMID: 21602503.
10. Palotai M, Mike A, Cavallari M, Strammer E, Orsi G, Healy BC, et al. Changes to the septo-fornical area might play a role in the pathogenesis of anxiety in multiple sclerosis. *Mult Scler.* 2018;**24**(8):1105-14. doi: 10.1177/1352458517711273. PubMed PMID: 28548605.
11. Riccitelli G, Rocca MA, Forn C, Colombo B, Comi G, Filippi M. Voxelwise assessment of the regional distribution of damage in the brains of patients with multiple sclerosis and fatigue. *AJNR Am J Neuroradiol.* 2011;**32**(5):874-9. doi: 10.3174/ajnr.A2412. PubMed PMID: 21393405. PubMed PMCID: PMC7965563.
12. Sepulcre J, Masdeu JC, Goñi J, Arrondo G, Vélez De Mendizábal N, Bejarano B, Villoslada P. Fatigue in multiple sclerosis is associated with the disruption of frontal and parietal pathways. *Mult Scler.* 2009;**15**(3):337-44. doi: 10.1177/1352458508098373. PubMed PMID: 18987107.
13. Zivadinov R, Le HH, Keenan A, Stocks SJ. A systematic literature review of the association between global brain atrophy and the Expanded Disability Status Scale score in people with multiple sclerosis. *Ther Adv Neurol Disord.* 2025;**18**:17562864241303681. doi: 10.1177/17562864241303681. PubMed PMID: 40689156. PubMed PMCID: PMC12276499.
14. Etemadifar M, Maghzi AH. Sharp increase in the incidence and prevalence of multiple sclerosis in Isfahan, Iran. *Mult Scler.* 2011;**17**(8):1022-7. doi: 10.1177/1352458511401460. PubMed PMID: 21459809.
15. Montalban X, Lebrun-Frénay C, Oh J, Arrambide G,

Moccia M, Pia Amato M, et al. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria. *Lancet Neurol.* 2025;**24**(10):850-65. doi: 10.1016/S1474-4422(25)00270-4. PubMed PMID: 40975101.

16. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;**17**(2):162-73. doi: 10.1016/S1474-4422(17)30470-2. PubMed PMID: 29275977.
17. De Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). *Br J Health Psychol.* 2004;**9**(Pt 3):279-91. doi: 10.1348/1359107041557048. PubMed PMID: 15296678.
18. Hendriks C, Drent M, Elfferich M, De Vries J. The Fatigue Assessment Scale: quality and availability in sarcoidosis and other diseases. *Curr Opin Pulm Med.* 2018;**24**(5):495-503. doi: 10.1097/MCP.0000000000000496. PubMed PMID: 29889115.
19. Hasanpour Khalesi E, Nikparast F, Ganji Z, Nahofteh N, Zare H. A Review of Normal Brain Aging: Detailed Study of Physiological Changes, Risk Factors, and Neuroimaging Techniques. *Iranian Journal of Medical Physics*. 2025;**22**(3):130-48. doi: 10.22038/ijmp.2025.83152.2465.
20. Manjón JV, Coupé P. volBrain: An Online MRI Brain Volumetry System. *Front Neuroinform*. 2016;**10**:30. doi: 10.3389/fninf.2016.00030. PubMed PMID: 27512372. PubMed PMCID: PMC4961698.
21. Nagaraj K, Taly AB, Gupta A, Prasad C, Christopher R. Prevalence of fatigue in patients with multiple sclerosis and its effect on the quality of life. *J Neurosci Rural Pract.* 2013;**4**(3):278-82. doi: 10.4103/0976-3147.118774. PubMed PMID: 24250159. PubMed PMCID: PMC3821412.
22. Yi X, Zhang Y, Du Q, Kang J, Song S, Li T, Jiang Y. Global prevalence of fatigue in patients with multiple sclerosis: a systematic review and meta-analysis. *Front Neurol.* 2024;**15**:1457788. doi: 10.3389/fneur.2024.1457788. PubMed PMID: 39416662. PubMed PMCID: PMC11479926.
23. Mohammadi I, Vaheb S, Rajai Firouzabadi S, Yazdan Panah M, Shaygannejad V, Mirmosayyeb O. Fatigue and its contributing factors in people with multiple sclerosis: a cross-sectional study. *Neurol Res.* 2026;**48**(5):555-67. doi: 10.1080/01616412.2025.2537328. PubMed PMID: 40711840.
24. Fuchs TA, Vaughn CB, Benedict RHB, Weinstock-Guttman B, Choudhery S, Carolus K, et al. Lower self-report fatigue in multiple sclerosis is associated with localized white matter tract disruption between amygdala, temporal pole, insula, and other connected structures. *Mult Scler Relat Disord.* 2019;**27**:298-304. doi: 10.1016/j.msard.2018.11.005. PubMed PMID: 30453198.
25. Pishdad P, Zeinali-Rafsanjani B, Poursadeghfard M, Kalaee M, Ostovarfar J, Salehi A. Investigating Depression and MRI Associations in Middle Eastern Relapsing-Remitting Multiple Sclerosis. *J Biomed Phys Eng*. 2026;**16**(2):153-64. doi: 10.31661/jbpe.v0i0.2505-1929. PubMed PMID: 42057981. PubMed PMCID: PMC13122374.
26. Krijnen EA, Kouwenhoven RM, Noteboom S, Barkhof F, Uitdehaag BM, Klawiter EC, et al. Subtypes and location of (juxta)cortical lesions relate to cognitive dysfunction in people with multiple sclerosis. *Mult Scler.* 2024;**30**(11-12):1556-60. doi: 10.1177/13524585241260968. PubMed PMID: 38872276.
27. Pareto D, Sastre-Garriga J, Auger C, Vives-Gilabert Y, Delgado J, Tintoré M, et al. Juxtacortical Lesions and Cortical Thinning in Multiple Sclerosis. *AJNR Am J Neuroradiol.* 2015;**36**(12):2270-6. doi: 10.3174/ajnr.A4485. PubMed PMID: 26450537. PubMed PMCID: PMC7964289.
28. Figueroa-Vargas A, Navarrete-Caro S, Cárcamo C, Ciampi E, Vásquez-Torres M, Soler B, et al. White matter volume and microstructural integrity are associated with fatigue in relapsing multiple sclerosis. *Sci Rep.* 2025;**15**(1):16417. doi: 10.1038/s41598-025-01465-6. PubMed PMID: 40355645. PubMed PMCID: PMC12069712.
29. Han XM, Tian HJ, Han Z, Zhang C, Liu Y, Gu JB, et al. Correlation between white matter damage and gray matter lesions in multiple sclerosis patients. *Neural Regen Res.* 2017;**12**(5):787-94. doi: 10.4103/1673-5374.206650. PubMed PMID: 28616036. PubMed PMCID: PMC5461617.
30. Granella F, Tsantes E, Graziuso S, Bazzurri V, Crisi G, Curti E. Spinal cord lesions are frequently asymptomatic in relapsing-remitting multiple sclerosis: a retrospective MRI survey. *J Neurol.* 2019;**266**(12):3031-7. doi: 10.1007/s00415-019-09526-3. PubMed PMID: 31494713.
31. Stanyte A, Podlipskyte A, Alonderis A, Macijauskiene J, Burkauskas J, Steibliene V. Relationship between subjective and objective fatigue and sleep characteristics in individuals with anxiety and mood disorders: An exploratory study. *Physiol Behav.* 2024;**274**:114429. doi: 10.1016/j.physbeh.2023.114429. PubMed PMID: 38065423.
32. Elkhooly M, Bao F, Bernitsas E. Impact of Disease Modifying Therapy on MS-Related Fatigue: A Narrative Review. *Brain Sci.* 2023;**14**(1):4. doi: 10.3390/brainsci14010004. PubMed PMID: 38275509. PubMed PMCID: PMC10813476.