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Original Article

Mental Health and Cognitive Function across Multiple Sclerosis Subtypes

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Abstract

Background and Objective: Mental health problems (e.g., depression, stress, and anxiety) are debilitating symptoms in individuals with multiple sclerosis (MS), and may be associated with cognitive dysfunction across different subtypes of the disease. This study aimed to compare cognitive performance across MS subtypes and examine the relationships between mental health symptoms and cognitive functions, in order to explore potential patterns of cognitive vulnerability in patients at various stages of MS, compared to healthy controls.

Materials and Methods: A total of 97 participants aged 18-49 years old were included in this study. They consisted of 25, 24, and 24 patients with Newly-Diagnosed MS (ND), Relapsing-Remitting MS (RRMS), and Secondary Progressive MS (SPMS), respectively, as well as 24 healthy controls (HC). All participants completed standardized assessments of cognitive function and mental health status.

Results: Comparisons among the patient groups revealed differences in cognitive functions and mental health problems, particularly depression and stress. The HC and ND groups had higher scores in most cognitive tests, especially when compared to the SPMS group. However, the ND group showed higher levels of depression and stress, compared to others. Significant negative correlations were observed between ND and RRMS groups in terms of mental health problems and certain cognitive functions.

Conclusion: These findings suggest that mental health difficulties may be linked to cognitive performance even in the early stages of MS. The results underscore the importance of early psychological screening and supportive interventions to help mitigate cognitive challenges throughout the course of the disease.

Keywords: Cognitive functions, Mental health, MS subtypes, Multiple sclerosis

Background

Multiple sclerosis (MS) is a progressive and chronic disease of the central nervous system, characterized by widespread demyelinating lesions in the brain and spinal cord. These lesions lead to a range of symptoms, including motor deficits, sensory disturbances, and cognitive impairments. Cognitive dysfunction significantly affects the quality of life of the patient, reducing their ability to perform daily activities, maintain employment, and participate in social interactions [1].

Clinical presentation of MS is diverse and depends on the location and extent of demyelination and gray matter atrophy. This disease typically begins with an initial episode referred to as Clinically Isolated Syndrome. Most patients subsequently develop Relapsing-Remitting Multiple Sclerosis (RRMS), marked by episodes of relapse followed by periods of remission. Over time, the majority of RRMS patients progress to Secondary Progressive Multiple Sclerosis (SPMS), characterized by a steady decline in neurological function. Additionally, approximately 10% of MS patients present with Primary Progressive Multiple Sclerosis (PPMS), where symptoms worsen continuously from the onset without distinct relapses [2-4].

Cognitive dysfunction affects 40-70% of MS patients, even in earlier disease stages, such as Newly Diagnosed (ND) MS and RRMS [5]. The most frequently affected domains include processing speed, working memory, and executive functions. As the disease progresses, especially in patients with SPMS, deficits become more pronounced, affecting multiple domains, including visuospatial skills and episodic memory [6, 7]. In a large-scale study performed on over 1,000 MS patients, cognitive dysfunction was reported in 34.5%, 44.5%, and 79.4% of those with Clinically Isolated Syndrome, RRMS, and SPMS, respectively [8].

While cognitive impairment in MS is well-documented, the role of mental health problems, such as depression, anxiety, and stress, on cognitive performance is less understood. Depression affects up to 60% of MS patients [9] and is associated with poor performance in domains, such as processing speed, attention, and executive function [10]. Anxiety is also prevalent in MS, with rates ranging from

23.5% to 41%, and has been linked to deficits in verbal learning and episodic memory [11, 12]. Stress is another important factor contributing to the exacerbation of MS symptoms. Unpredictable nature of the disease, coupled with the stress of receiving a chronic diagnosis, can activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels [13]. Chronic stress is believed to negatively impact cognitive functions, particularly processing speed and executive functioning. For example, Prokopova *et al.* [13] found that elevated levels of anxiety, depression, and stress were correlated with poor performance on cognitive tests, such as the Stroop test in MS patients, compared to healthy controls (HCs).

Despite the established association between MS and cognitive impairments, as well as the high prevalence of mental health issues within this population, there remains a lack of consensus. Specifically, this concerns the relationship between these psychological factors and cognitive functioning across the various stages of MS. Some studies have suggested that depression may have a more pronounced association with cognitive performance, compared to anxiety, particularly in early-stage MS, where it is associated with slower information processing and reduced working memory [14, 15]. Other findings have indicated that cognitive deficits are more severe in SPMS and may co-occur with higher levels of psychological symptoms [16, 17].

Objectives

Given the substantial impact of both cognitive dysfunction and mental health problems on the quality of life in MS patients, this study aimed to examine how depression, anxiety, and stress each relate to cognitive functions across different MS subtypes, including ND, RRMS, and SPMS. By examining these associations, the study sought to provide insight into how psychological symptoms may be related to cognitive performance at different disease stages. Comprehension of these dynamics could facilitate early interventions and inform rehabilitation strategies to enhance patient outcomes.

Materials and Methods

Participants

Participants were recruited using convenience sampling. The total sample consisted of 97 individuals (20 males and 77 females), including 73 patients diagnosed with MS and 24 HCs matched to the MS patients in terms of age, gender, and education level. All participants were aged between 18 and 49 years.

The 73 MS patients were categorized into three groups, namely ND patients (mean disease duration ~2 years), 24 RRMS patients (mean duration ~4 years), and 24 SPMS patients (mean duration ~10 years). The ND patients were defined as individuals with a confirmed MS diagnosis who had not yet initiated disease-modifying therapy. This group also included individuals with clinical symptoms consistent with MS who were not yet receiving treatment.

All MS patients were diagnosed according to the McDonald Criteria by a neurologist and were selected from Imam Reza Clinic, affiliated with Shiraz University of Medical Sciences in Shiraz, Iran. All patients had an Expanded Disability Status Scale (EDSS) score between 0 and 6 and were under neurologist care between September 2021 and May 2022. Inclusion criteria were a confirmed MS diagnosis, no intravenous corticosteroid use or MS relapse within six weeks prior to assessment, no developmental disorders, and no history of drug or alcohol abuse.

All participants completed questionnaires and standardized clinical and neuropsychological assessments. For ND patients, neuropsychological assessments were conducted prior to the initiation of immunomodulatory therapy. The study protocol was approved by the Ethics Committee of the University of Isfahan, Isfahan, Iran (IR.UI.REC.1399.097), and written informed consent was obtained from all participants.

Assessment of Cognitive Functions

Cognitive functioning was evaluated using some measures of the Minimal Assessment of Cognitive Function in MS, as outlined by Benedict *et al.* [18]. The Persian version, validated by Eshaghi *et al.* [19], includes several standardized tests.

The California Verbal Learning Test-Second Edition (CVLT-II) assessed verbal learning and memory. Participants recalled 16 words grouped into four semantic categories immediately (Trials 1-5). The list was read aloud five times, and after each reading, participants were asked to recall as many words as possible. Scores included immediate recall, short-delay recall (free and cued), and long-delay recall after 20 min.

The Symbol Digit Modalities Test (SDMT) evaluated attention, working memory, and information processing speed. Participants matched symbols to corresponding digits within 90 sec, with correct responses scored out of 110 points.

The Brief Visuospatial Memory Test-Revised (BVMT-R) assessed visuospatial learning and memory. Participants viewed six abstract shapes in a 2 × 3 grid for 10 sec and then drew them from memory. This task was repeated three times, with a delayed recall after 25 min. Scores were based on accuracy and correct positioning.

The Controlled Oral Word Association Test (COWAT) measured verbal fluency. This test measures the ability of an individual to make parallel links between concepts and correlates with creative problem-solving. Participants generated words starting with specific letters (M, B, and T) within 1 min, and the total number of correct words was recorded.

Assessment of Depression, Anxiety, and Stress

Depression, anxiety, and stress levels were assessed using the Depression, Anxiety, and Stress Scale-21 Items (DASS-21), developed by Lovibond and Lovibond [20] and validated in Persian by Moghaddam *et al.* [21]. This scale includes 21 items scored based on a four-point Likert scale, with higher scores indicating greater severity of depression, anxiety, or stress.

Assessment of Demographic and Clinical Characteristics

Demographic information (age, gender, marital status, education level, and employment status) was collected using a structured self-report questionnaire. Clinical characteristics, including disease duration (in months) and physical disability, were obtained from the medical records of participants and neurologist evaluations. These variables were used to describe the sample and explore their association with cognitive and psychological measures.

Statistical Analysis

Data analysis was conducted in SPSS software (version 26.0; IBM Corp., Armonk, NY). Discrete variables were presented as frequencies and percentages, while continuous variables were described using means and standard deviations. Group comparisons used univariate and multivariate analyses of variance (ANOVA and MANOVA), with post hoc tests when necessary. Pearson's correlation coefficient explored relationships between mental health problems and cognitive functions.

Shapiro-Wilk and Levene's tests were employed for the assessment of normality and equality of error variances, respectively. Moreover, Box's M test evaluated the homogeneity of covariance matrices for MANOVA, and linearity assumptions were verified for correlational analysis. Outliers were transformed into the median scores due to violations of normality, variance equality, and homogeneity. Robust tests and suitable post hoc adjustments (e.g., Games-Howell) were applied as needed.

Results

Demographics and Clinical Characteristics

Table 1 summarizes the demographic and clinical characteristics of the sample. The study included four groups, namely RRMS (N=24), SPMS (N=24), ND (N=25), and HCs (N=24). Majority of the participants were female (70.8-87.5%) and married (54.2-75%). Educational level of the participants was predominantly at the university or college level across all groups (66.7-76%), except for a higher proportion of postgraduate-level education among HC (29.2%). Employment rates varied, with HC participants having the highest employment rate (79.2%) compared to MS groups (37.5-52%). Mean age was highest in the SPMS group (38.21 ± 6.17 years) and ranged from 32.13 to 33.37 years in other groups. It is noteworthy that the mean disease duration was the longest in the SPMS group (119 months ± 55.72 months). The mean physical disability score (EDSS) was also the highest in the SPMS group (4.98 ± 0.86). Detailed group comparisons are presented in Table 1.

Table 1. Demographic and clinical characteristics of the participants

Variables	Groups			
	RRMS (n = 24)	SPMS(n = 24)	ND(n = 25)	HC (n = 24)
Gender		N (%)		
Male	7 (29.2)	3 (12.5)	4 (16)	6 (25)
Female	17 (70.8)	21 (87.5)	21 (84)	18 (75)
Marital status				
Married	16 (66.7)	18 (75)	18 (72)	13 (54.2)
Single	8 (33.3)	6 (25)	7 (28)	11 (45.8)
Education level				
Elementary	3 (12.5)	3 (12.5)	-	-
High school	2 (8.3)	3 (12.5)	4 (16)	-
University/college	17 (70.8)	16 (66.7)	19 (76)	17 (70.8)
Postgraduate	2 (8.3)	2 (8.3)	2 (8)	7 (29.2)
Employment status				
Employed	12 (50)	9 (37.5)	13 (52)	19 (79.2)
Not employed	12 (50)	15 (62.5)	12 (48)	5 (20.8)
		Mean ± SD		
Age (year)	33.37 ± 7.08	38.21 ± 6.17	32.28 ± 6.42	32.13 ± 9.13
Education (year)	12.46 ± 4.02	12.21 ± 4.11	13.52 ± 2.64	14.66 ± 3.37
Duration of disease (month)	47.25 ± 49.11	119 ± 55.72	26.36 ± 34.08	-
Physical disability (EDSS)	1.10 ± 0.66	4.98 ± 0.86	0.84 ± 0.86	-

RRMS: Relapsing-Remitting Multiple Sclerosis, SPMS: Secondary Progressive Multiple Sclerosis, ND: Newly-Diagnosed Multiple Sclerosis, HC: Healthy Control, EDSS: Expanded Disability Status Scale

Cognitive Function Analysis

Group differences in cognitive functions (measured by CVLT-II, SDMT, BVMT-R, and COWAT) were analyzed using univariate and multivariate ANOVA. Table 2 summarizes the mean scores, standard deviations, F values, and p values. Significant differences were observed between groups across all cognitive measures ($p < 0.05$). Multivariate analysis of the short- and long-delay conditions of CVLT-II yielded significant Pillai's trace values (0.97 and 0.26, respectively; $p < 0.01$).

Table 2. Analysis of variance to examine differences in cognitive functions among groups

Dependent Variables		Groups				*F*	*p*
		RRMS (n = 24)	SPMS (n = 24)	ND (n = 25)	HC (n = 24)		
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
CVLT- II	Free Recall	51.58 (11.19)	50.67 (10.01)	54.84 (5.49)	60.08 (4.54)	6.34	0.001
	Short Delay-Free Recall	10.88 (2.58)	9.92 (3.26)	12.16 (1.70)	12.92 (2.15)	6.97	0.0001
	Short Delay-Cued Recall	11.46 (2.55)	11.88 (2.51)	12.36 (1.80)	13.54 (1.56)	4.23	0.008
	Long Delay-Free Recall	11.50 (2.87)	10.96 (2.73)	12.56 (2.43)	13.75 (1.70)	5.97	0.001
	Long Delay-Cued Recall	11.75 (2.67)	11.54 (2.57)	12.88 (1.54)	13.88 (1.45)	5.48	0.002
	Long Delay-Recognition	13.88 (1.45)	13.42 (1.74)	14.72 (0.61)	14.67 (0.56)	6.71	0.0001
SDMT		39.04 (12.89)	30.33 (10.84)	44.32 (10.61)	50.04 (7.46)	14.93	0.0001
BVMT-R		24.04 (6.29)	18.79 (7.90)	25.92 (5.32)	30.42 (2.64)	16.23	0.0001
BVMT-R; Long Delay		21.83 (1.86)	18.75 (4.15)	22.56 (1.65)	22.67 (5.54)	6.63	0.0001
BVMT-Recognition		11.96 (0.91)	11.21 (1.18)	11.80 (0.65)	11.88 (0.45)	3.96	0.01
COWAT		31.33 (10.91)	26.25 (12.59)	32.00 (11.39)	38.04 (8.26)	4.70	0.004

CVLT-II: California Verbal Learning Test, SDMT: Symbol Digit Modalities Test , BVMT-R: Brief Visuospatial Memory Test-Revised, COWAT: Controlled Oral Word Association Test, RRMS: Relapsing-Remitting Multiple Sclerosis, SPMS: Secondary Progressive Multiple Sclerosis, ND: Newly-Diagnosed Multiple Sclerosis, HC: Healthy Control

Post hoc analysis using the Games-Howell test, which is robust to unequal variances and sample sizes, revealed specific group differences. Accordingly, HC participants had significantly higher mean scores than all MS groups on CVLT-II free recall. The ND patients performed better than SPMS patients in some CVLT-II and BVMT-R measures. The SPMS patients showed the lowest performance across most cognitive indicators, particularly in SDMT, BVMT-R, and COWAT tests.

Table 3. Games-Howell post hoc test to explore mean differences among groups

Groups (n)		Mean differences in cognitive function indicators										
		1	2	3	4	5	6	7	8	9	10	11
RRMS (24)	SP (24)	0.92	0.96	-0.42	0.54	0.21	0.46	8.71*	5.25	3.84*	0.75*	5.08
	ND (25)	-3.26	-1.28	-0.90	-1.06	-1.13	-0.85	-5.28	-1.88	-0.73	0.16	-0.66
	HC (24)	-8.50*	-2.04*	-2.08*	-2.25*	-2.12*	-0.79	-11.00*	-6.37*	-0.84	0.08	-6.71
SPMS (24)	ND (25)	-4.17	-2.24*	-0.48*	-1.60	-1.34	-1.30*	-13.99*	-7.13*	-3.81*	-0.59	-5.75
	HC(24)	-9.42*	-3.00*	-1.67*	-2.79*	-2.33*	-1.25*	-19.71*	-11.62*	-3.92*	-0.67*	-11.79*
ND (25)	HC (24)	-5.24*	-0.76	-1.18	-1.19	-0.99	0.53	5.72	-4.50*	-0.11	-0.08	-6.04

1. CVLT-II (California Verbal Learning Test): Free Recall, 2- Short Delay-Free Recall, 3- Short Delay-Cued Recall, 4- Long Delay-Free Recall, 5- Long Delay-Cued Recall, 6-Long Delay-Recognition, 7- SDMT (The Symbol Digit Modalities Test), 8- BVMT-R (The Brief Visuospatial Memory Test – Revised), 9- BVMT-R; Long Delay, 10- BVMT-Recognition, and 11- COWAT (Controlled Oral Word Association Test).

Mental Health Analysis

To examine mental health problems (depression, anxiety, and stress), a multivariate ANOVA was conducted (Table 4). The results showed significant differences between groups in terms of depression ($p = 0.02$) and stress ($p = 0.04$). The ND patients had

higher scores in both depression and stress, compared to other groups. Post hoc tests indicated that ND patients were significantly more depressed than RRMS patients and they experienced higher stress levels than HC participants. There were no significant intergroup differences in terms of anxiety ($p = 0.14$).

Table 4. Multivariate analysis of variance to examine differences in mental health problems among groups

Dependent Variables	Groups				*F*	*p*
	RRMS (n = 24)	SPMS (n = 24)	ND (n = 25)	HC (n = 24)		
Depression	10.54 (2.83)	12.96 (5.29)	14.36 (5.76)	10.92 (4.18)	3.61	0.02
Anxiety	10.29 (2.68)	12.25 (5.42)	11.84 (3.56)	10.21 (2.67)	1.89	0.14
Stress	15.21 (5.48)	15.58 (2.85)	17.68 (5.80)	13.67 (3.40)	2.98	0.04

RRMS: Relapsing-Remitting Multiple Sclerosis, SPMS: Secondary Progressive Multiple Sclerosis, ND: Newly-Diagnosed Multiple Sclerosis, HC: Healthy Control

Correlations between Mental Health and Cognitive Functions

Pearson's correlation coefficients were calculated to assess the relationship between mental health problems and cognitive functions (Table 5). The overall correlations were relatively weak, with only a few significant associations. Depression was inversely correlated with BVMT-R long delay scores ($r = -0.28$, $p \leq 0.05$). For ND patients, depression, stress, and anxiety were significantly correlated with CVLT-II free recall scores, while depression was also related to BVMT-R long delay and COWAT. In RRMS patients, depression was negatively correlated with CVLT-II measures, and anxiety was associated with SDMT and BVMT-R scores. No significant correlations were observed in the SPMS group.

Table 5. Pearson correlation between mental health and cognitive functions

Cognitive functions		Depression				Anxiety				Stress			
		RRMS (n =24)	SPMS (n =24)	ND (n=25)	Total	RRMS (n =24)	SPMS (n =24)	ND (n=25)	Total	RRMS (n =24)	SPMS (n =24)	ND (n=25)	Total
CVLT- II	Free Recall	-0.24	-0.33	-0.41*	-0.22	-0.38	-0.13	-0.53**	-0.20	0.02	-0.27	-0.49**	-0.10
	Short Delay-Free Recall	-0.41*	-0.36	-0.22	-0.11	-0.40*	-0.15	-0.21	-0.08	0.05	-0.29	-0.29	-0.03
	Short Delay-Cued Recall	-0.35	-0.14	-0.13	-0.17	-0.39	-0.06	0.04	-0.07	-0.01	-0.05	-0.14	-0.01
	Long Delay-Free Recall	-0.41*	-0.18	-0.21	-0.08	-0.29	-0.04	0.04	-0.06	0.12	-0.13	-0.14	0.02
	Long Delay-Cued Recall	-0.28	-0.14	-0.08	-0.07	-0.35	-0.02	0.09	-0.15	0.07	-0.08	-0.07	0.02
	Long Delay-Recognition	-0.38	-0.11	-0.11	-0.12	-0.30	-0.18	0.07	-0.18	0.14	-0.22	-0.01	-0.09
SDMT		0.10	-0.23	-0.23	-0.13	-0.52**	-0.01	-0.20	-0.17	-0.07	-0.11	-0.31	-0.10
BVMT-R		0.12	-0.21	-0.32	-0.14	-0.58**	0.00	-0.33	-0.08	-0.27	-0.09	-0.38	-0.01
BVMT-R; Long Delay		-0.17	-0.01	-0.44*	-0.28*	-0.22	0.07	-0.11	-0.22	-0.03	-0.01	-0.22	-0.17
BVMT-Recognition		0.14	-0.21	-0.02	-0.09	-0.29	-0.15	-0.08	-0.08	-0.32	-0.01	0.09	-0.14
COWAT		-0.01	-0.29	-0.46*	-0.22	-0.05	-0.17	-0.38	-0.20	0.11	-0.31	-0.34	-0.10

CVLT-II: California Verbal Learning Test, SDMT: Symbol Digit Modalities Test, BVMT-R: Brief Visuospatial Memory Test-Revised, COWAT: Controlled Oral Word Association Test
RRMS: Relapsing-Remitting Multiple Sclerosis, SPMS: Secondary Progressive Multiple Sclerosis, ND: Newly-Diagnosed Multiple Sclerosis, HC: Healthy Control
*Significant at the 0.05 level , **Significant at the 0.01 level

Discussion

The current study demonstrated significant cognitive impairments in MS patients, particularly in RRMS and SPMS subtypes, compared to the HC group. Across all cognitive domains, HC consistently outperformed MS patients. The SPMS individuals

exhibited widespread dysfunctions in all assessed domains, RRMS patients showed impairments in seven domains, and ND patients displayed difficulties in at least two domains. These findings align with those of prior studies indicating a progressive decline in cognitive functioning from ND to RRMS and further deterioration in SPMS [6, 22].

Across MS subtypes, SPMS patients showed the most severe deficits, particularly in verbal learning and memory (CVLT-II, free recall), information processing speed (SDMT), visuospatial memory (BVMT-R), and verbal fluency (COWAT). This cognitive profile is consistent with those of cohort studies of SPMS and likely reflects the cumulative impact of prolonged disease duration, greater neurological disability, and extensive neurodegeneration [6, 22]. The significantly lower scores in SPMS participants are consistent with the neurodegenerative hypothesis of cognitive decline in progressive MS, where axonal loss and brain atrophy become more prominent [22].

The RRMS patients, displayed an intermediate cognitive profile, with lower scores than HC but generally better performance, compared to SPMS patients. Cognitive impairments in RRMS were most evident in verbal learning and memory (CVLT-II, free recall). These deficits may be attributed to focal inflammatory activity and demyelination, which are characteristics of the relapsing-remitting phase of the disease [1]. It is noteworthy that recognition memory tasks (CVLT-II recognition and BVMT-R recognition) which require identification of previously presented information rather than actively retrieving it, remained relatively preserved in RRMS participants. Both verbal (CVLT-II recognition) and visuospatial memory recognition (BVMT-R) scores were comparable to those of healthy controls. This pattern suggests that while encoding and retrieval processes may be disrupted in RRMS, storage, and familiarity-based recognition processes remain more intact, supporting the findings of Drew *et al.* [23], who emphasized the relative resilience of recognition memory in MS populations.

Similarly, repetition-based recall tasks, such as short and long delay-free and cued recall trials, showed milder impairments, compared to initial free recall. These tasks assess not only retrieval but also the capacity for retention and consolidation over time, with repeated exposure to the same information. The relatively better performance of RRMS patients in these delayed trials further suggests preserved storage mechanisms and the benefits of structured cueing or repetition in facilitating recall [23]. However, findings of the present study on verbal fluency (COWAT) diverge from those reported by Amato *et al.* [24], who found a more marked decline in this domain among RRMS patients. This discrepancy may reflect methodological differences, such as variations in sample size, disease duration, or educational background, as well as potential differences in the distribution of disease subtypes included in the respective studies.

In contrast, the cognitive profile of ND patients revealed significant impairments in learning and verbal memory (CVLT-II free recall) and visuospatial memory (BVMT-R). This finding is partially consistent with those reported by Anhoque *et al.* [3]. However, ND patients performed comparably to healthy controls (HC) on other cognitive measures, suggesting that cognitive deficits in this group are still mild and selective. Notably, tasks involving repetition and structured retrieval, such as short and long delay-free and cued recall trials, showed relatively preserved performance in the ND group. These tasks rely on repeated exposure and the use of cues to facilitate memory consolidation and retrieval, pointing to the benefits of repetition and external support in bolstering cognitive function at early disease stages.

This pattern supports the notion that early-stage MS patients may benefit from neuroplastic compensatory mechanisms [25], particularly when tasks involve multiple learning trials or external cues. The relatively intact performance of ND patients on measures of information processing speed (SDMT) and verbal fluency (COWAT) further underscores their preserved cognitive reserve in these domains [26]. These findings highlight the potential value of early cognitive rehabilitation interventions focused on enhancing learning strategies, repetition, and cue-based recall to maintain cognitive function and delay the progression of impairments in individuals newly diagnosed with MS.

Overall, the progression of cognitive dysfunction from ND to RRMS and SPMS highlights the importance of early intervention. Timely administration of immunomodulatory therapies may delay the transition to progressive subtypes [26], and early cognitive assessments can inform treatment strategies. Differentiation of cognitive profiles by MS subtype is crucial, as they are influenced by disease duration, disability (EDSS), and possibly education level. Early detection and cognitive rehabilitation may help preserve function and quality of life in MS patients.

This study also investigated differences in mental health among groups. In examining differences in mental health (depression, anxiety, and stress) among groups, ND patients exhibited significantly higher levels of depression and stress, compared to other groups, as evidenced by multivariate ANOVA

results. Specifically, ND patients scored significantly higher on depression than RRMS patients and reported greater stress levels, compared to healthy controls. These findings likely reflect the acute psychological impact of receiving a new MS diagnosis, a period often marked by uncertainty, fear of disease progression, and adjustment-related distress [27].

Unlike those with a longer disease duration, newly diagnosed individuals may not yet have developed effective coping mechanisms or received adequate psychological support. This highlights the importance of early mental health screening and intervention following diagnosis. Notably, no significant group differences were observed in anxiety levels, suggesting that anxiety may manifest more uniformly across disease stages or that its fluctuations are less sensitive to the disease phase than depression and stress. Given that only depression and stress, but not anxiety, were significantly elevated in ND patients, future longitudinal research should investigate whether these emotional states change over time and how they may influence cognitive and neurological outcomes throughout the MS trajectory.

Although the overall correlations between mental health symptoms and cognitive function were modest, several significant associations emerged, particularly in the ND and RRMS groups. Depression was negatively correlated with visuospatial memory (BVMT-R long delay) in the total sample, supporting the notion that depressive symptoms may broadly impact memory consolidation across MS subtypes. More strikingly, in ND patients, depression, anxiety, and stress showed significant associations with verbal memory (CVLT-II free recall), suggesting that emotional distress may particularly disrupt initial learning and retrieval processes during the early disease phase. Additionally, depression in this group was also related to poorer performance on COWAT and BVMT-R, indicating that verbal fluency and visuospatial memory might also be sensitive to early psychological disturbances.

In the RRMS group, depression was primarily associated with reduced short- and long-term verbal memory. This aligns with studies reporting that depression correlates with impairments in verbal memory in MS patients [28, 29]. Similarly, anxiety showed significant negative correlations with short-term verbal memory, information processing speed (SDMT), and visuospatial memory (BVMT- R), underscoring the diverse cognitive effects of anxiety symptoms in more chronic MS stages. These results are consistent with those of previous research on the cognitive impact of anxiety in MS populations [30, 31]. Ribbons *et al.* [32] also reported that anxiety remained a significant predictor of cognitive performance, particularly in memory tasks, after controlling for other variables. Their use of the DASS-21 closely parallels the methodology applied in the present study and supports its findings in the RRMS group.

Although stress did not correlate with cognitive performance in RRMS and SPMS patients, it was significantly associated with verbal memory decline in ND patients. This may reflect the heightened HPA axis reactivity in response to recent stressors, including diagnosis-related uncertainty. Acute stress is known to impair hippocampal-dependent memory processes, particularly in populations with heightened emotional sensitivity [13, 27]. Therefore, early psychological distress may transiently impair cognitive performance even in patients with minimal neurological damage.

It is noteworthy that no significant correlations were observed in the SPMS group, which may reflect a decoupling of cognitive and emotional domains in more advanced disease stages, where neurodegeneration plays a dominant role over psychological factors. This may reflect the increasing influence of irreversible pathological changes, such as gray matter atrophy, demyelination, and axonal loss, that override the modulatory effects of mood symptoms [33]. In SPMS, the brain may reach a form of saturation, where the extent of cognitive dysfunction becomes so severe that additional psychological distress no longer has a measurable impact on performance.

This pattern aligns with neuroimaging findings showing that progressive MS is characterized by widespread cortical and subcortical damage [34], which correlates with cognitive impairment independently of mood. Furthermore, chronic neuroinflammation and prolonged HPA axis dysregulation in SPMS may blunt the stress response of the brain, further diminishing the observable relationship between mood and cognition. These findings emphasize the need for different clinical strategies in the early stages of MS, compared to its progressive stages. While psychological support may improve cognitive functioning in RRMS, neuroprotective interventions may be more relevant for addressing cognitive decline in SPMS.

The findings underscore the importance of routine cognitive assessments in MS patients, even at the early stages of the disease, to detect cognitive impairments that might worsen over time. Early detection could enable timely cognitive rehabilitation interventions to slow down cognitive decline. Additionally, addressing mental health comorbidities, such as depression, anxiety, and

stress, may also enhance cognitive outcomes in MS patients.

The study has several limitations, including its cross-sectional design, which limits causal interpretations between mental health problems and cognitive performance; observed associations should be interpreted as correlational rather than causal. Additionally, the use of convenience sampling may have introduced selection bias, as individuals who chose to participate may differ systematically from the broader MS population in terms of motivation, cognitive function, or psychological profile. This limits the external validity of the results and suggests caution when generalizing to all MS patients.

Participants of this study consisted of a predominantly female population, reflecting the known epidemiological distribution of multiple sclerosis, which is significantly more prevalent among women. Studies have consistently reported a female-to-male ratio of approximately 3:1 in MS populations [35]. Accordingly, the gender imbalance in the participants of this study aligns with the natural occurrence of the disease and may enhance the ecological validity of the findings.

Nonetheless, the authors acknowledge this as a limitation in terms of generalizability, particularly when interpreting results related to gender-specific cognitive or psychological profiles. Future research should aim for more gender-balanced samples to explore possible gender-related differences in cognitive impairment and mental health in MS patients. In addition, future studies should consider longitudinal designs with more homogeneous ND populations to better understand the impact of early interventions on cognitive trajectories in MS patients.

Conclusion

This study highlights distinct cognitive and mental health profiles across multiple sclerosis subtypes, underscoring the progressive nature of cognitive decline from ND to RRMS and SPMS. While SPMS patients demonstrated the most severe and widespread impairments across cognitive domains, RRMS patients showed intermediate deficits with relative preservation of recognition memory, and ND patients exhibited selective but milder dysfunctions, likely supported by compensatory mechanisms. Importantly, depression and stress were most elevated in newly diagnosed individuals, reflecting the psychological burden of receiving an MS diagnosis, whereas mood–cognition associations were strongest in ND and RRMS patients but largely absent in SPMS, where neurodegeneration predominates. These findings emphasize the need for early cognitive screening and mental health evaluation to inform timely interventions. Targeted strategies- such as cognitive rehabilitation, psychological support, and disease-modifying therapies- may help preserve function, mitigate emotional distress, and improve quality of life. Future longitudinal studies are warranted to clarify causal pathways, explore sex-related differences, and evaluate the long-term benefits of early intervention on cognitive and emotional outcomes in MS.

Ethical Considerations

This study was reviewed and approved by the Ethics Committee of the University of Isfahan, Isfahan, Iran (Approval ID: IR.UI.REC.1399.097).

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Authors' Contributions

Dr. Narges Arab-Moghaddam: Conception and design, Acquisition of data, Analysis and interpretation of data, Statistical analysis, Administrative support, technical support, material support, Drafting of the manuscript

Dr. Karim Asgari: Conception and design, Supervision, Critical revision of the manuscript for important intellectual content, Administrative support, technical support, material support, Editing of the manuscript.

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Conflicts of Interest

The authors declare that there are no conflicts of interest related to this submission.

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