

# Correlation between Cognitive Functions, Fatigue, Depression and Disability Status in a Cohort of Multiple Sclerosis Patients

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## Abstract

**Objective:** To investigate the relationship between depression, fatigue, disability and cognitive skills of patients with multiple sclerosis in a cohort of patients with multiple sclerosis in a single center in Tehran, Iran. **Methods:** One hundred and forty-seven patients with multiple sclerosis with mean age of 33 years, mean disease duration of 20.20 months, mean EDSS of 2.13, and F to M ratio of 76.5% over 23% were recruited for the purpose of this study. Cognitive function was compared with healthy control subjects (n = 100). Depression was measured by Beck Depression Inventory (BDI), fatigue was assessed using Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS), disability was evaluated by Expanded Disability Status Scale (EDSS), and cognitive function was assessed by Brief Repeatable Battery of Neuropsychological tests (BRB-N). All data were analysed using Pearson correlation. **Results:** Age and disability level generally correlated negatively and significantly with task performance, whereas a higher level of education was associated with better task performance. While the correlation between BDI, FSS, and MFIS was significantly positive, BDI was negatively correlated with the two subscales of BRB, namely PASAT and WLG. Higher levels of depression in patients with MS are associated with lower cognitive performance in tasks requiring higher-order working memory (WM) processes. FSS showed the

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**strongest negative correlation score with BRB, however, the same parameter displayed significant positive correlation with MFIS. Moreover, the global EDSS scores were negatively correlated with BRB. Relative to controls, cognitive performance of MS patients was deficient in all BRB-N measures except Symbol Digit Modalities Test which is a measure of attention and processing speed. Conclusions: Depression, fatigue, and disability (the most common problems observed in MS patients) are clearly related with cognitive impairment in MS patients. Also, MS patients exhibit a pattern of cognitive impairment running across the studied cognitive domains in comparison to healthy subjects.**

## Keywords

**Fatigue, Depression, Cognitive Dysfunction, Disability, Multiple Sclerosis**

## 1. Introduction

Fatigue, depression, cognitive problem, and disability usually complicate the course of multiple sclerosis. Fatigue has been identified in a broad range of neuroimmunological disorders like multiple sclerosis (MS) [1]. Fatigue is considered an important symptom in MS patients because it affects patients' social lives, occupation, overall quality of life, and mood. Between 60% and 90% of all MS patients occasionally complain of overpowering fatigue [2]. Several areas of the CNS (e.g. the premotor cortex, the limbic system, the basal ganglia, and the brainstem) are believed to be involved in the pathophysiology of MS fatigue [1]. According to fMRI fatigue may be related to impaired interactions between functionally related cortical and subcortical areas [3].

Moreover, a considerable incidence and prevalence of psychological and psychiatric symptoms in patients with multiple sclerosis, compared to individuals with similar degrees of disability, has been reported in the literature [4]-[8]. Depression is by far the most common psychological disturbance in MS, though other mood disorders can occur. Several studies have reported high rates of depressive symptoms in MS patients compared to controls with other chronic neurological conditions, with an overall lifetime frequency of major depression reaching 50% [9]-[12] and an annual prevalence around 20% [13]. In spite of depression, neuropsychological deficits occur in about 40% - 65% of individuals with MS [14]. These symptoms often impair quality of life and social participation [15]. Neuropsychological impairment, known as "soft symptom", is usually manifested in the following areas of cognition: memory, attention, information processing, abstract reasoning, and visuospatial skills, while primary language skills, immediate and implicit memory, and verbal intelligence appear to be unaffected [16].

Considering all the above facts, some of these symptoms can influence and even exacerbate each other. For example, fatigue or depression can influence cognitive performance of a patient in neurocognitive tests due to their psychomotor retardation and other cognitive outcomes. In this study we aim to investigate the relationship between fatigue, depression, cognitive functions, and disability status according to EDSS in MS patients.

## 2. Methods

### 2.1. Participants

One hundred and forty-seven consecutive MS patients (female = 112 [76.19%], male = 35 [23.81%]; mean age = 33 years) followed up at Mostafa MS research center in Tehran, Iran, were enrolled in this study. After obtaining a written informed consent, patients were asked to take part in a number of assessments (see below) and then a neuropsychological test (BRB-N) was conducted by a psychologist.

### 2.2. Measurements

*Expanded Disability Status Scale (EDSS)*. Physical disability of the patients was scored using EDSS.

*Beck Depression Inventory-Second Edition (BDI-II)*. The BDI-II is a 21-item self-report measure designed to assess DSM-IV depressive symptomatology in adolescents and adults. It is a revised version of the amended DI [1]. Respondents are asked to rate each of the depression symptoms, ranging from 0 (not present) to 3 (severe),

in terms of how they have been feeling during the past two weeks, recording the date of completing the questionnaire. The BDI-II is designed to provide a single overall score that can range from 0 to 63. The following cut-score guidelines are suggested for patients diagnosed with major depression: minimal (0 - 13), mild (14 - 19), moderate (20 - 28), and severe (29 - 63). Authors have reported convergent validity (e.g.,  $r = 0.93$  with the BDI-IA,  $r = 0.71$  with the Hamilton Psychiatric Rating Scale for Depression), and excellent internal consistency ( $\alpha = 0.91$  among psychiatric outpatients,  $\alpha = 0.93$  among undergraduate students) [2].

*Fatigue Severity Scale (FSS).* The primary measurement of subjective fatigue in this study was done by FSS. This is one of the best known and most used fatigue scales. The FSS principally measures the impact of fatigue on specific types of functioning rather than the intensity of fatigue-related symptoms [3]. It has high internal consistency, has good test-retest reliability and is sensitive to change with time and after treatment. It also has good concurrent validity and is able to distinguish patients with different diagnoses (between systemic lupus erythematosus (SLE) and MS, and between CFS, MS, and primary depression) [3]. This scale shows high sensitivity, reliability and internal consistency in the assessment of fatigue. The internal consistency was found to be highly satisfactory (Cronbach's  $\alpha = 0.96$  in patients and  $0.88$  in controls) [4]. The FFS is a nine-item self-report scale developed for use among patients with chronic illnesses. In this questionnaire, people have to rate their agreement (range 1 - 7) with nine statements concerning the severity, frequency and impact of fatigue on their daily life style. Scores can range between 9 (no fatigue) and 63 (maximum fatigue). This scale was chosen for this study because it is a short questionnaire, and hence a convenient method for the patients, which provides a simple unitary measure of global fatigue severity.

*Modification of the Fatigue Impact Scale (MFIS).* The MFIS is a component of the Multiple Sclerosis Quality of Life Inventory and, evaluates the impact of fatigue on physical, cognitive and psychosocial functioning [5]. It was developed to assess the perceived impact of fatigue on a variety of daily activities. These scores are designed to measure the disability associated with fatigue (the extent to which fatigue limits activities), not the severity of symptoms [6]. Patients are asked to rate on a Likert scale (range 0 - 4) how often they have experienced 21 problems due to fatigue during the last month. MFIS total score ranges from 0 to 20, with the following ranges reflecting how often the person is limited in activities by fatigue: 0 - 5 (never), 6 - 9 (rarely), 10 - 14 (sometimes), 15 - 19 (often) and 20 (almost always).

*Brief Repeatable Battery of Neuropsychological Tests (BRB-N).* BRB uses as a research tool for evaluating short-term changes in cognitive function in patients with MS and was designed to be brief [7]. This test consists of 5 subtests as follows:

*Selective Reminding Test (SRT).* The SRT is a measure of verbal learning and delayed recall of a 12-word list and uses six consecutive learning trials and a delayed trial [7]. The Long-Term Storage (LTS) score represents the sum of words recalled on two consecutive trials without reminding. The total sum of the words in LTS of all six trials is recorded (SRT-LTS). The Consistent Long-Term Retrieval (CLTR) score is the sum of words recalled on all the subsequent trials without reminding. The total sum of the words in CLTR of all six trials is taken (SRTCLTR). The Total Delay score is the number of words recalled after a delay of 10 minutes [8].

*Spatial Recall Test.* The 10/36 SPART measures visuospatial learning and memory [8]. It requires subjects to recall the placement of 10 checkers that are randomly placed on checkerboard. One score is the sum of correct responses in the three immediate recall trials (10/36 SRT). The other score is delayed recall after 15 minutes (10/36 SRT Delay).

*Symbol Digit Modalities Test.* The SDMT investigates sustained and complex attention, information processing speed and working memory [9]. It presents a series of nine symbols, each paired with a single digit, labeled 1 - 9, in a key at the top of a sheet. During 90 seconds, the subject substitutes as many symbols as possible by the corresponding number and responds verbally. The score is the number of correct substitutions.

*Paced Auditory Serial Addition Test.* The PASAT requires cognitive abilities such as mental calculation, interference suppression, and information-processing speed. Subjects must be able to rapidly refresh WM content and resist interference from a previous response. The subject is instructed to add 60 pairs of digits such that each number is added to the one that immediately precedes it and report the outcome verbally. The digits are presented by tape, first at a rate of every 3 seconds per digit, the second trial with every 2 seconds per digit. The score is the number of correct responses per trial (PASAT\_3, PASAT\_2) [8].

*Word List Generation.* The WLG explores verbal fluency on semantic stimulus by asking the subject to produce as many words as possible belonging to a semantic category (vegetables and fruits in version A, animals in version B) within 90 seconds [10]. The score is the number of correct words.

## 2.3. Statistical Analysis

All results were analyzed using the software package SPSS for Windows Standard Version 18. The relationships between depression, fatigues, expanded disability, and neurological performance in patients with MS were analyzed by Pearson correlation.

## 3. Results

Descriptive statistics and correlations on each of the research variables are given in **Table 1**. As results show, BDI has statistically significant positive correlation with FSS and MFIS, but is negatively correlated with two subscales of BRB (PASAT & WLG). It means that higher levels of depression in patients with MS are associated with higher levels of fatigue and less functionality in consternation and semantic retrieval. FSS is negatively associated with all subscales of BRB (except CLTR), and conversely displayed significant positive correlation with MFIS. The relationship between FFS and subscales of BRB is more related with cognitive disturbance (like verbal learning, delayed recall, visuospatial learning and delayed recall) in comparison of BDI.

In addition to the other scale that measures fatigue among patients, MFIS indicate the correlation between EDSS, PASAT, 10/36 SRT, WLG and total delay in selective reminding test subscale.

Most relationships among EDSS and subscales of BRB (except PASAT-3 and WLG) were again significant and negative. These results approve that the higher expanded disability is associated with less cognitive function.

According to the results, the brief repeatable battery proved to be internally reliable in Iran ( $\alpha = 0.70$ ). As **Table 1** reviews the correlations, the subscales of BRB have a desirable pattern of correlations since they are associated with each other.

## 4. Discussion

In this study, there was a significant correlation between depression, fatigue and cognitive dysfunction in MS patients using different assessment tools. The association found between the studied variables can imply that there is a causal factor responsible for these events.

**Table 1.** Mean, standard deviation, and correlation of main study variables.

	M	SD	1	2	3	4	5	6	7	8	9	10	11	12	13
1) BDI	17.85	11.77	-	0.47**	0.64**	0.10	-0.10	-0.14	-0.13	-0.20*	-0.22**	-0.10	-0.16	-0.11	-0.19*
2) FSS	38.99	15.03		-	0.67**	0.11	-0.19*	-0.15	-0.26**	-0.36**	-0.33**	-0.10	-0.27**	-0.29**	-0.25**
3) MFIS	33.73	19.53			-	0.20*	-0.14	-0.13	-0.17*	-0.31**	-0.34**	-0.11	-0.29**	-0.30**	-0.18*
4) EDSS	49.07	12.12				-	-0.19*	-0.28**	-0.29**	-0.18*	-0.15	-0.30**	-0.26**	0.23**	-0.09
5) LTS	36.73	16.46					-	0.68**	0.77**	0.38**	0.38**	0.17*	0.47**	0.45**	0.35**
6) CLTR	31.96	15.02						-	0.68**	0.33**	0.31**	0.27**	0.46**	0.39**	0.30**
7) Total Delay	7.61	2.83							-	0.41**	0.36**	0.21*	0.51**	0.49**	0.37**
8) PASAT-2	36.96	13.00								-	0.76**	0.15	0.35**	0.35**	0.43**
9) PASAT-3	28.32	10.72									-	0.18*	0.37**	0.34**	0.40**
10) SDMT	38.21	30.91										-	0.27**	0.23**	0.23**
11) 10/36 SRT	18.42	5.66											-	0.84**	0.30**
12) 10/36 SRT Delay	6.27	2.50												-	0.28**
13) WLG	24.75	9.75													-

N = 147, \*\*p < 0.001, \*p < 0.05. BDI = Beck Depression Inventory; FSS = Fatigue Severity Scale; MFIS = Modified Fatigue Impact Scale; EDSS = Expanded Disability Status Scale; SRT = Selective Reminding Test; LTS = Long-Term Storage; CLTR = Consistent Long-Term Retrieval; PASAT = Pacad Auditory Serial Addition Task (PASAT-2 = 2 s/digit; PASAT-3 = 3 s/digit); SDMT = Symbol Digit Modalities Test; 10/36 SRT = Spatial Recall Test (10/36 SRT = Immediate Recall; 10/36 SRT Delay = Delayed Recall); WLG = Word List Generation.

In line with previous research, the present study showed that EDSS and BDI are significantly disturbed in patients with MS [11] [12]. However, the mean BDI score and therefore the rate of depression found in this study was higher than that observed in similar studies.

At baseline, the evolution of depression in MS patients has been shown to be independent from disability. Moreover, depression appeared to be endogenous and predictive of a poor EDSS score, suggesting that depression could be an early predictive factor for the progression of disability. These concepts are supported in the present study. A higher BDI score was observed with more fatigue symptoms and poorer EDSS scores, although we did not follow up the patients to see if increased BDI score is accompanied by worse EDSS score [13].

Little is known about pathophysiology of fatigue and psychological dysfunction in MS. Many factors are said to influence fatigue in MS, such as medications, sleep disorders, body temperature, and depression. However, even after correction for common causes, the association between fatigue and depression persists [14]. Also, this phenomenon has been related to MS lesions and neurological involvements, albeit not supported with enough evidence [15]. Meanwhile, the current findings support the theory that inflammation and immune deregulation can influence neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and growth factor production, thus altering neural circuitry and contributing to depressive symptomatology [16]. On this basis, the presence of such significant correlation between different factors including fatigue, depression, and psychological status may support the universal nature of neurocognitive involvement in MS.

Moreover, the quality of life in MS patients has been found to be associated with physical disability, disease-related fatigue, and depression. Furthermore, the impact of fatigue and depression on quality of life is independent of physical disability and the other factors associated with MS [17]. Therefore, early recognition of fatigue and depression, and rapid intervention in order to correct these problems can certainly increase the quality of life in MS patients.

This study has some limitations. First, it is a cross sectional study and does not evaluate each patient through time. Therefore, there is a probability that some patients might appear weaker or stronger in their measurements due to environmental situations. Secondly, it is a single center study and patients are not in the same stage of the disease as they were chosen consecutively. We are aware that recent exacerbation of the disease or occurrence of MS complications may influence our results reported here. The strength of this study is investigating different psychological variables in MS patients at the same time which can provide a good overview of this group of patients within a short time.

## 5. Conclusion

In conclusion, we believe that fatigue, depression and cognitive dysfunction may be various features of a broad neurological dysfunction related to MS which needs to be fully identified. Further studies are needed to establish the pathophysiology of fatigue and cognitive dysfunction in MS in order to provide enough information for developing treatment modalities.

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