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RESEARCH ARTICLE

The Relationship between Depression, Anxiety, Fatigue, and the Symbol Digit Modalities Test in Persons with Multiple Sclerosis

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Abstract

Objective: Cognitive impairment, fatigue, and neuropsychiatric symptoms are commonly intertwined in multiple sclerosis. The multifactorial etiology of these disease-related symptoms has not been delineated clearly. This study aimed to investigate the relationship between fatigue, anxiety, depression, and cognitive function, as assessed by Symbol Digit Modalities Test (SDMT), in people with multiple sclerosis (pwMS).

Materials and Methods: The oral version of the SDMT was used to measure cognitive function, the Hospital Anxiety and Depression Scale (HADS) for depression and anxiety, and the shortened version of the Modified Fatigue Impact Scale in MS (MFIS-5) for fatigue.

Results: This single-center study included 269 pwMS (206 female, mean age: 33.66±9.57, mean education years: 11.97±3.5). The demographic and clinical outcomes were collected retrospectively. The hierarchical regression analyses demonstrated that the model was significant and explained the 44% of the variance (R^2=0.44). The SDMT scores were not associated with fatigue, depression, and anxiety symptoms. Longer disease duration, fewer education years, and younger age were also independently associated with lower SDMT scores. PwMS with cognitive impairment (CI) (15.6%) and without CI differ significantly in disability level, age, HADS-depression score, and subscores and overall score of MFIS-5 ($p<0.05$).

Conclusion: In conclusion, lower education level, longer disease duration, and older age were associated with lower information processing speed in pwMS. No associations were found between SDMT and fatigue, anxiety, or depression levels.

Keywords: Multiple sclerosis, information processing, fatigue, anxiety, depression

Introduction

Cognitive impairment (CI) is a common symptom at all stages of multiple sclerosis (MS), present in 43-70% of patients (1). Previous research has shown the relationship between the disability level and CI (2). CI is often correlated to disability progression, decreased brain volume, and cortical thinning in persons with MS (pwMS) (3,4). A preliminary study showed that total lesion area is a strong predictor of impairment in memory, executive functions, language, and visuospatial functions (5). Meanwhile, risk of CI was associated with normal-appearing white matter and gray matter (6). One study evaluated 240 pwMS and 60 healthy controls in terms of cognitive functions for five years and found that occurrence of CI can be predicted by evaluating the volume of the anterior thalamus, superior longitudinal fasciculus, and temporal cortex (7).

Although studies continue to elucidate the complex relationship between brain structure and CI, this is not replicable in daily practice. Nevertheless, CI negatively affects the quality of life of pwMS, independent of physical deficiency (8). Information processing speed is the most most common cognitive deficit in pwMS, which is frequently measured in clinical practice with the Symbol Digit Modalities Test (SDMT) (9).

PwMS face difficulties caused by cognitive deficiency (10). Intervention studies developed to reduce CI in pwMS have

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increased. However, underlying factors need to be well-defined to design future intervention studies. Several studies have reported a high prevalence of psychiatric symptoms in pwMS, especially depression and anxiety (11), which are closely associated with other MS symptoms, such as fatigue, sleepiness, and pain. Meanwhile, other studies suggest that depression and fatigue are the most critical factors in the quality of life of pwMS (12). Moreover, these symptoms correlated with the cognitive but not the physical components of fatigue (13). Previous studies examined the relationship between information processing speed and fatigue, depression, and anxiety. However, these did not evaluate all these variables together and did not reach a large sample size that included all disability levels. Therefore, this study aimed to investigate the relationship between fatigue, anxiety, depression, and CI assessed by SDMT in pwMS.

Materials and Methods

Participants

The Non-Invasive Research Ethics Committee of Dokuz Eylul University approved the study on December 2022 (protocol number: 7368-GOA). The criteria for pwMS inclusion were: aged 18-55 years, a defined diagnosis of MS according to the McDonald criteria (14), a relapse-free period of 6 months before the study, and a signed written informed consent. The exclusion criteria were a history of severe head trauma, comorbid neurological and/or psychological disorders, substance abuse, mental retardation, or learning disability.

Outcome Measures

We recorded participant demographics and disease-related outcomes. We measured cognitive processing speed using the oral version of the SDMT (15), fatigue and its four components (physical, social, cognitive, and psychological) with a shortened version of the Modified Fatigue Impact Scale in MS (MFIS-5) (16), and depression and anxiety with the Hospital Anxiety and Depression Scale (HADS) (17). The SDMT was applied by psychologist and physiotherapist. Level of disability was assessed with Expanded Disability Status Scale (EDSS) by the neurologist at the MS Clinic of the Faculty of Medicine of Dokuz Eylul University.

Statistical Analysis

The normality of data was assessed with Shapiro-Wilk and Levene's tests. Numeric variables were shown as means, standard deviations (SD), percentages for discrete variables, and medians (interquartile range) according to data distribution. Group comparisons were conducted by the independent samples t-test and the Mann-Whitney U test according to data distribution for continuous variables, and the chi-squared test for categorical variables. Spearman's correlation coefficient was used to determine relationships between numerical variables. Participants with or without CI were compared based on a SDMT z-score cut-off of less than -1 SD. Hierarchical linear regression analyses were used to test the relationship between CI, fatigue, depression, and anxiety symptoms. In the regression analyses, EDSS, disease duration, age, gender, and education years were entered in the first step as initial control variables. In the second step, total MFIS-5, HADS-anxiety, and depression scores were entered. The statistical significance level was accepted to be $p<0.05$. Statistical analysis was carried out using SPSS statistical software 25.0 (IBM Corp., Armonk, NY, USA).

Results

Demographics, medications used, and clinical characteristics are summarized in Tables 1-3. This study included a sample of 269 participants of which 206 (76.6%) were female, 155 (57.6%) were married, 132 (49.1%) were employed, and 134 (49.8%)

Table 1. Demographic characteristics of the participants

	Mean (SD)
Age (years)	33.66±9.57
Gender, n (%)	
Female	206 (76.6%)
Male	63 (23.4%)
Marital status, n (%)	
Married	155 (57.6)
Single	114 (42.4)
Educational years	11.97±3.5
Educational status, n (%)	
Primary school	38 (14.1)
Secondary school	14 (5.2)
High school	83 (30.9)
University	134 (49.8)
Employment status, n (%)	
Employee	132 (49.1)
Unemployed/retired	102 (37.9)
Student	35 (13.0)

SD: Standard deviation

Table 2. Medications used for MS

	n (%)
Fingolimod	110 (41.3)
Interferon-beta	73 (26.6)
Glatiramer acetate	43 (16.0)
Natalizumab	13 (4.7)
Dimethyl fumarate	14 (5.1)
Ocrelizumab	2 (0.7)
Cladribine	1 (0.4)
Rituximab	1 (0.4)

MS: Multiple sclerosis

educated more than 11 years. The median value of EDSS was 1.0 (1.5), and the disease duration was 4.0 (8.0) years. The SDMT mean raw score was 50.49 (±12.74).

The clinical and cognitive features of the pwMS with CI or without CI are shown in Table 4. Fourty-two pwMS with CI have older age, lower education level, higher EDSS, HAD depression, MFIS-5 total score, cognitive, physical and psychosocial (p<0.05), but not in higher disease duration and HAD anxiety scores. Eighty-three pwMS with depression (30.8%) had lower SDMT scores, higher EDSS, HADS anxiety, and MFIS-5 total and subscores (p<0.001). Meanwhile, 109 pwMS with anxiety (40.5%) had higher HADS depression and MFIS-5 total and subscores (p<0.001) but not SDMT, age, disease duration, and EDSS. HADS scores did not correlate with age and disease duration.

A weak negative correlation was found between the SDMT and HAD-depression scores (r=-0.181, p=0.03), but not for the HAD-anxiety scores; and in SDMT and MFIS-5 total score, and physical and psychosocial subscores (respectively, r=-0.125, r=-0.126, r=-0.162, p<0.05), but not for cognitive subscores. HADS-depression and -anxiety scores were moderately correlated with MFIS-5 total score and subscores (correlation coefficients ranged from 0.411 to 0.567). EDSS was correlated with MFIS-5 total score and subscores (p<0.001), but not HAD scores.

Table 3. Clinical characteristics of the participants

	Median (IQR)
EDSS*	1.0 (1.5)
Disease duration (years)	4.0 (8.0)
HADS depression	4.0 (6.0)
HADS anxiety	6.0 (7.0)
PwMS with anxiety, n (%)**	109 (40.5)
PwMS with depression, n (%)**	83 (30.9)
MFIS-5 total	6.0 (9.0)
MFIS-5-physical	2.0 (5.0)
MFIS-5-cognitive	3.0 (4.0)
MFIS-5-psychosocial	1.0 (2.0)

*EDSS: Expanded Disability Status Scale, HADS: Hospital Anxiety and Depression scale, MFIS-5: The five item Modified Fatigue Impact Scale in MS, **HAD ≥8, IQR: Interquartile range, PwMS: People with multiple sclerosis

Association of SDMT with the MFIS-5 and the HAD Scores

Hierarchical regression analyses were performed to assess the relationship between SDMT and MFIS-5 total scores, HADS-depression and -anxiety scores after controlling for EDSS, disease duration, age, gender, and education years (Table 5). The model was significant [F (8,265) = 25.274, p<0.001) and explained 44% of the variance (R^2=0.44). Age [β=-0.437, (-0.581; -0.293), p<0.001] was associated with lower scores of SDMT, and education [β=1.639, (1.287; 1.991), p<0.001] was associated with higher scores of SDMT. HADS-depression and -anxiety scores, MFIS-5 total scores, male gender, duration of disease, and EDSS were not associated with SDMT scores.

Discussion

This study examined the relative effect between CI as measured by SDMT and the level of depression, anxiety, and fatigue in pwMS, controlling for confounding demographic and clinical variables. Our findings showed no association between information processing speed, fatigue, anxiety, or depression symptoms. Lower education level, longer duration of illness, and older age were associated with lower information processing speed in pwMS.

The relationship between CI and depression in pwMS is not yet clearly defined. This may be due to the inability to evaluate depressive symptoms in detail and the notion that depressive mood has little effect on memory. The absence of severe

Table 4. Results of cognitive and clinical features in the pwMS with and without CI

	MS patients with CI*	MS patients without CI	p
SDMT (mean, SD)	28.88±6.40	54.49±9.06	**<0.001**
HAD-anxiety	8.0 (7.0)	6.0 (8.0)	**0.354**
HAD-depression	7.0 (7.25)	4.0 (6.0)	**0.020**
MFIS-5			
Total	10.0 (10.25)	6.0 (8.0)	**0.354**
Cognitive	4.0 (4.0)	3.0 (3.0)	**0.024**
Physical	4.0 (6.0)	2.0 (4.0)	**0.008**
Psychosocial	2.0 (3.0)	1.0 (2.0)	**<0.001**
EDSS	1.75 (1.5)	1.0 (1.5)	**<0.001**
Disease Duration	5.0 (13.0)	3.0 (7.0)	**0.059**

Data are presented as median (IQR, Interquartile range)

SDMT: Symbol Digit Modalities Test, HAD: Hospital Anxiety and Depression scale, MFIS-5: The five item Modified Fatigue Impact Scale in MS, EDSS: Expanded Disability Status Scale, PwMS: People with multiple sclerosis

*Scored below 5th percentile in terms of cognitive performance

Table 5. Association of SDMT with the MFIS-5 and HAD scores

Variable	B	SE B	β	R^2	ΔR^2	p-value
Step 1						
Age	-0.434	0.73	-0.326*	0.43	0.42	<0.001
Gender	-2.860	1.410	-0.095*			
Education (years)	1.687	0.177	0.470*			
EDSS	0.210	0.513	0.021			
Disease duration (years)	-0.144	0.107	-0.071			
Step 2						
Age	-0.437	0.073*	-0.328	0.44	0.42	<0.001
Gender	-2.694	1.442	-0.90			
Education (years)	1.639	0.179*	0.457			
EDSS	0.274	0.542	0.027			
Disease duration (years)	-0.155	0.107	-0.077			
HAD depression	-0.309	0.217	-0.101			
HAD anxiety	-0.023	0.182	-0.009			
MFIS-5 total	0.038	0.152	0.016			

*p<0.05

[a]Regression model with HAD anxiety and depression and MFIS total as independent variable and EDSS, disease duration, age, gender, education years. EDSS: Expanded Disability Status Scale, HAD: Hospital Anxiety and Depression scale, MFIS-5: The five item Modified Fatigue Impact Scale in MS

depressive mood and a higher positive mood were associated with better cognitive performance. However, a decreased positive mood and high depressive mood did not show a close association, contrary to expectations. Although these indicate that anhedonia is associated with poorer memory function among pwMS, clinicians should evaluate other mood dimensions in MS (18).

Previous studies confirmed that depression and fatigue are independent predictors of quality of life in pwMS. Studies have also shown that fatigue, depression, and anxiety negatively affect cognitive function in pwMS (19-21). But as seen in this study, the relationships of these neuropsychological symptoms and other clinical factors are frequently intertwined and difficult to disentangle. For example, we found that pwMS with depression performed worse in information processing speed and had higher levels of disability, anxiety, and fatigue. However, anxiety and depression were not associated with age and disease duration. PwMS with anxiety had higher depression and fatigue but did not differ in CI, age, duration of illness, or disability. There was a weak negative correlation between information processing and depression but not with anxiety. Finally, cognitive performance was associated with the total score, and physical and psychosocial subscores of MFIS-5, but not with the cognitive dimension of fatigue. Consistent with our results, a study by Gill et al. (22) showed that HAD depression was positively associated with fatigue and HAD-anxiety scores were negatively associated with SDMT and EDSS. Additionally, disability level was only negatively and weakly associated with fatigue subscores and overall scores but not with anxiety and depression.

Studies have reported that demographic characteristics such as education and age were important predictors of cognitive function in pwMS (23-25). We investigated the relationship between information processing speed and fatigue, depression and anxiety while controlling for disability level, disease duration, age, gender, and years of education. Longer disease duration, fewer years of education, and younger subjects were also independently associated with lower SDMT scores. This could be because the disease progresses with age and, therefore, longer disease duration is characterized by more neuropathological changes. Furthermore, education has been used to represent cognitive reserve, making it significantly associated with cognition (26).

In the literature, the relationship between disability and CI in pwMS is contradictory and unclear (24,27). In this study, disability levels were not significant predictors of information processing speed. In addition, we showed that cognitive performance was not associated with fatigue, depression, and anxiety symptoms, even if the model explained 44% of the variance significantly after controlling for the confounding factors. Consistent with our findings, in a study conducted in Belgium that evaluated 66 pwMS, lower SDMT scores were associated with higher EDSS scores and psychological fatigue, but not with anxiety or depression. Thus, while disability and fatigue levels negatively affected cognitive function in pwMS, depression and anxiety do not seem to have a significant effect (28). A longitudinal

study by Beal et al. (29) reported that younger age, longer disease duration, more extent of functional limitation, and progressive forms of MS were predictive of more significant depressive symptoms. However, these variables did not predict the changes in depressive symptoms over time, albeit present at all periods (29).

The relationship between physical and cognitive disability in pwMS and the presence of depression and anxiety is unclear. Nevertheless, our findings show that SDMT is not closely related to depression and anxiety and that depression has no significant effect on SDMT performance. This implies the substantial value of the SDMT in the evaluation of CI in pwMS.

Study Limitations

Some limitations should be paid attention to when interpreting our data. First, given the retrospective cross-sectional design, the self-report scores of neuropsychological symptoms and fatigue might be prone to recall bias. Next, higher patient samples using extensive neuropsychological test batteries, fatigue scales, and a psychiatric interview could be done in future studies. Finally, our sample only included relapsing-remitting MS and thus, lacks representation of people with primary and secondary progressive MS types.

Conclusion

Age, education, and disease duration were substantial predictors of SDMT. Future research should investigate whether depression, anxiety, and fatigue symptoms occur with adverse effects of CI in pwMS. The results support the routine use of the SDMT in clinical practice for assessing CI in pwMS.

Ethics

Ethics Committee Approval: The Non-Invasive Research Ethics Committee of Dokuz Eylul University approved the study on December 2022 (protocol number: 7368-GOA).

Informed Consent: Informed consent was obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., Concept: P.Y., Z.A., Design: P.Y., Z.A., Data Collection or Processing: P.Y., Z.A., E.K., Analysis or Interpretation: P.Y., Z.A., E.K., Literature Search: P.Y., Z.A., Writing: P.Y., Z.A., E.K.

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