

The Relationship Between Fatigue Levels and Cognition in Patients with Epilepsy

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ABSTRACT

Introduction: Fatigue is a common symptom reported in epilepsy. The effect of fatigue on cognitive functions in patients with epilepsy (PWE) is unknown. The aim of this study is to examine the relationship between fatigue and cognitive functions in PWE.

Methods: Thirty-three PWE and twenty-two healthy controls participated in the study. Psychological examinations (Fatigue Impact Scale, Hospital Anxiety and Depression Scale, Epworth Sleepiness Scale, Quality of Life) and cognitive tests (Wisconsin Card Sorting Test, Serial Digit Learning Test, Stroop Test, Raven's Progressive Matrices Test) were administered to the participants.

Results: The results revealed that fatigue scores were significantly higher in PWE compared to the control group ($p < .001$). Fatigue was found to be associated with anxiety ($p < .001$), depression ($p < .001$) and quality of life

($p < .05$). The results demonstrated a significant difference between the groups in terms of Raven scores ($p < .001$), and a significant correlation between fatigue and Raven scores in the general epilepsy group ($p < .001$). Fatigue was found to be correlated with Stroop Test ($p < .05$) and Raven's Test in the focal epilepsy group ($p < .001$).

Conclusion: In conclusion, PWE experience higher levels of fatigue compared to healthy controls and this fatigue has a relationship with visuospatial perception. Fatigue is also associated with attention and visuospatial perception in patients with focal epilepsy. However, it remains unclear whether cognitive impairments are a direct consequence of fatigue or whether cognitive impairments contribute to fatigue.

Keywords: Cognitive dysfunction, epilepsy, fatigue

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INTRODUCTION

Fatigue is a subjective and complex concept to define. However, it can be defined as a state of exhaustion that does not correspond to levels of effort and does not improve with regular rest. Sometimes, fatigue can be intermittent, and sometimes it is continuous. It is pretty standard in the general population and some medical conditions, including epilepsy (1). Fatigue can be categorized as cognitive, physical, and affective/social fatigue (2). Cognitive fatigue (CF) is a psychobiological condition that usually occurs after a long period of self-regulated activity and causes a decline in performance in cognitive processing over some time independent of sleepiness (1). People with this type of fatigue may have difficulty sustaining long conversations, need more time to process information, and have difficulty recalling information. It can manifest itself with symptoms such as difficulty in suppressing irrelevant information during selective attention, increased obsessive thinking and increased need of time required for planning, decreased cognitive control, and decreased information processing skills (3,4). Physical fatigue (PF) may begin with inadequate rest, physical exertion, or mental strain unrelated to an underlying medical condition (5). Symptoms such as muscle fatigue, low energy, and the need for frequent interrupting of physical activities may be observed. In the affective dimension, people may experience low mood, irritability, lack of interest and motivation, and withdrawal. Social fatigue (SF) refers to burnout resulting from prolonged exposure to social situations or interactions or a feeling of exhaustion. Social fatigue can

Highlights

- Epilepsy patients experience fatigue more than healthy controls.
- Fatigue is related with anxiety, depression, and quality of life in epilepsy.
- Fatigue has a relationship with visuospatial perception in epilepsy.
- Fatigue is related with attention and visuospatial perception in focal epilepsy.

manifest in different ways, such as feeling mentally drained, emotionally exhausted, or physically tired after socializing.

Fatigue in patients with epilepsy (PWE) has been studied very little; therefore, our knowledge about it and the possible processes underlying fatigue in PWE is limited. The relationships between the characteristics of epilepsy disease, biopsychosocial factors, comorbidities, and fatigue

symptoms have not yet been elucidated (6). The relationship between fatigue and cognition in epilepsy is among the least studied subjects. Cognitive impairments commonly seen in PWE include intellectual decline, decreased information processing speed, decreased reaction time, attention deficits, and memory problems.

Recurrent seizures may cause short—or long-term impairments in patients' cognition (6). However, the relationship between seizures, cognition, and fatigue in epilepsy has not been fully highlighted. Therefore, in this study, we aimed to investigate the relationship between fatigue and cognitive functions in patients with epilepsy.

METHODS

Study Population

The data obtained in this study were approved by the Ankara Yildirim Beyazit University Institute of Health Sciences Ethics Committee with the decision date 09.12.2021, number 33, and conformed with the World Medical Association Declaration of Helsinki. A total of 34 PWE, comprising 22 women and 12 men, were included in the study. These participants met the following criteria: being at least 18 years of age, having received a diagnosis of epilepsy for a minimum of 1 year, and having been followed at the Ankara Bilkent City Hospital Epilepsy Outpatient Clinic between February 21, 2022, and October 8, 2022. Additionally, a control group of 22 healthy individuals, thirteen women and nine men, participated in the study. All participants were provided with detailed information about the study and required to provide informed consent. Exclusion criteria included the presence of any other neurologic, psychiatric, or chronic comorbidity, pregnancy, and individuals under the age of 18 or over 65. One participant was excluded from the study due to the presence of a brain tumor associated with epilepsy. Consequently, the final analysis included data from the remaining 33 patients. Prior to the assessments, participants completed a sociodemographic questionnaire.

Psychological Tests

We used The Fatigue Impact Scale (FIS) for fatigue assessment, The Hospital Anxiety Depression Scale (HADS) for anxiety (HADS-A) and depression (HADS-D) screening, Epworth Sleepiness Scale (ESS) for excessive daytime sleepiness, Quality of Life in Epilepsy Scale-10 (QOLIE-10) for quality of life assessment designed for patients with epilepsy, and Wisconsin Card Sorting Test (WCST), Stroop Test TBAG Form, Serial Digit Learning Test (SDLT) and Raven Standard Progressive Matrices Test (RSPM) for neuropsychological assessments.

Neurocognitive Assessment

WCST is used to assess executive functions. This test measures cognitive domains such as concept formation, abstract thinking, working memory, attention, and perseveration. We used the Serial Digit Learning Test to assess memory and learning. This test includes a repeated presentation of an eight- or nine-digit sequence. There are three alternative forms for both 8-digit and 9-digit sequences. We applied sequences to participants based on their education level. The Stroop Test (TBAG Form) assesses focused attention, selective attention, response inhibition, and information processing speed. It has been associated with a large frontoparietal network, including the anterior cingulate cortex, dorsolateral prefrontal cortex, inferior frontal gyrus, inferior and superior parietal cortex, and insula (7).

Raven Standard Progressive Matrices Test (RSPM) is a neuropsychological test that measures visual-spatial perception and IQ. In this test, five sets go from easy to difficult, each containing 12 questions. However, the first four questions from each set were not presented to the participants because it might cause fatigue during the application. Participants solved a total of 40 questions in this test.

Statistical Analyses

We used the IBM SPSS 26 program (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) for all analyses. Mean and standard deviation are given in statistics for continuous data, and number and percentage values are given in discrete data. We applied the Shapiro-Wilk test to determine whether the data fit the normal distribution. The chi-square test was included to compare the categorical variables between PWE and healthy controls (HC). We used parametric analysis methods and independent samples t-tests to distribute the data that is usually distributed in FIS. Mann-Whitney U test was used to compare PWE and control groups regarding psychological and neurocognitive tests. Spearman's rho correlation coefficient measured the relationship between fatigue and other psychological evaluations. Thus, we also used it to determine the relationship between fatigue and neuropsychological tests for all epilepsy groups and in focal epilepsy. $<.05$ was accepted as a significance value.

RESULTS

The results revealed no statistical difference in age, gender, marital status, or employment status between the patient and control groups ($p>.05$). However, we found a significant difference between the educational backgrounds. ($p<.05$). The results showed that the rate of university graduates in the control group was higher, and the rate of primary and high school graduates was lower compared to the patient group (Table 1).

The most common epilepsy type in the patient group was focal epilepsy, with 26 patients (78.8%). The Generalized epilepsy group followed the focal epilepsy group with 7 patients (21.2%). The most common epilepsy type within the focal epilepsy group was TLE, with 16 patients (48.5%). The most common seizure type was focal bilateral tonic-clonic seizures, seen in 9 patients (27.3%), followed by 5 patients with focal nonmotor onset with preserved awareness (15.2%), 5 patients with generalized tonic-clonic (15.2%), 3 patients with focal nonmotor onset with impaired awareness (9.1%), 3 patients had generalized motor onset seizures (9.1%), 2 patients had focal motor onset with impaired awareness (6.1%), 2 patients had focal motor onset with preserved awareness (6.1%), 2 patients had generalized nonmotor onset (6.1%), a patient had generalized nonmotor onset myoclonic seizures (3.0%), and a patient with generalized clonic seizures (3.0%).

As for anti-epileptic drugs (AED), 15 participants (57.7%) received monotherapy, 9 participants received polytherapy (34.6%), and 2 of the participants did not receive any AEDs within the focal epilepsy group. In the generalized epilepsy group, 5 patients received monotherapy (71.4%), and 2 received no medications. None of the patients received polytherapy in the generalized epilepsy group. The mean disease duration in the focal epilepsy group is 12.5 years (1–41 years). At the same time, the mean disease duration for generalized epilepsy is 3 years (1–19). Seizure frequency in the focal epilepsy group is 2 seizures/year (0–210). For the generalized epilepsy group, the seizure frequency changed from 0 seizures to 36 seizures/year.

Regarding the fatigue ratings of the patients, 12.1% ($n=4$) described their fatigue as low, 30.3% ($n=10$) as a bit, 33.3% as moderate ($n=11$), and 24.2% as significant ($n=8$). None of the patients described their fatigue as very significant. There was not any significant difference within PWE regarding fatigue levels and age ($p>.05$). In the PWE group, the Mann-Whitney U test did not reveal a statistically significant difference in fatigue levels for gender ($p>.05$). As we looked for any relation between epilepsy disease features and fatigue levels in PWE, we did not find any statistically significant correlation between disease duration, seizure frequency, and FIS sub-scales ($p>.05$).

Table 1. Sociodemographic variables

	PWE (n = 33)	HC (n = 22)	Test Statistics (χ^2)	p value
Sex (n, %)			0.116	0.734
Male	12 (36.4)	9 (41.9)		
Female	21 (63.4)	13 (59.1)		
Marital Status			2.447	0.294
Single	12 (60.6)	11 (40.9)		
Married	20 (36.3)	9 (50.0)		
Divorced	1 (3.0)	2 (0.1)		
Educational Status (n, %)			12.099	0.017*
Primary	4 (12.1)	0 (0)		
Middle School	2 (6.1)	0 (0)		
High School	19 (57.6)	8 (36.4)		
Bachelors	7 (21.2)	14 (63.6)		
Distance Education	1 (3.0)	0		
Employment Status (n, %)	18		0.109	0.741
Employed	18 (54.5)	11 (50.0)		
Unemployed	15 (45.5)	11 (50.0)		

HC= Healthy control; PWE=Patients with epilepsy; *= p<0.05

Table 2. Mann Whitney U test to compare subscales of the FIS between PWE and HC

	PWE				HC				Statistics	p value
	Med	Min	Max	IQR	Med	Min	Max	IQR		
CF	17	2	39	11.5	3	1	16	6.25	U = 65.0	<0.001**
PF	15	0	29	15.5	3.5	0	30	6	U=124.0	<0.001**
SF	31	0	62	21	8.5	0	37	11.75	U=110.0	<0.001**

CF= Cognitive fatigue; HC= Healthy control; IQR= Interquartile range; PWE=Patients with epilepsy; PF=Physical fatigue; SF=Social fatigue;**= p<0.001

Table 3. Fatigue scores in PWE

	Focal Epilepsy (n=26)	Generalized Epilepsy (n= 7)			
	Mean \pm SD	Mean \pm SD	t	df	p*
FIS	64.34 \pm 26.53	54.85 \pm 43.19	0.731	31	0.021*
CF	17.88 \pm 8.08	18.28 \pm 14.04	-0.099	31	0.046*
PF	15.73 \pm 8.49	14.0 \pm 10.11	0.460	31	0.818
SF	30.38 \pm 13.97	23.42 \pm 19.89	1.068	31	0.083

CF= Cognitive fatigue; FIS= Fatigue impact scale; HC= Healthy control; IQR= Interquartile range; PWE=Patients with epilepsy; PF=Physical fatigue; SF=Social fatigue;**= p<0.001 *p<0.05

Independent samples t-test demonstrated statistically significant differences between the general fatigue levels of PWE (M=62.33, SD=30.25) and the HC (M=20.72, SD= 13.80), PWE significantly suffering from fatigue more than the control group (t(53)= 6.031, p<.001). Mann Whitney U test revealed that CF, PF, and SF scores were significantly higher in PWE than HC (p<.001 for each) (Table 2). These results indicated that the fatigue levels, including cognitive, physical, and social fatigue, were higher in PWE than in the control group.

When we compared the focal epilepsy and generalized epilepsy groups in terms of fatigue, Table 3 illustrates statistically significant differences between FIS (p<.05) and CF (p<.05), while no significant results were found between PF and SF (p>.05). Accordingly, general fatigue was significantly higher in the focal epilepsy group and cognitive fatigue was higher in the generalized epilepsy group (p<.05).

A positive correlation was found between fatigue, its sub-scales, and HADS-A, HADS-D, and total HADS scores in PWE (p<.05). The results

did not reveal any correlation between fatigue and ESS. Regarding QoL, significant correlations were observed with all sub-scales except PF (p<.05). Table 4 illustrates the correlation coefficients.

There was a statistically significant difference between PWE and HC regarding neuropsychological performances (Table 5). We also searched for a relationship between fatigue levels and cognition of PWE. We did not find any correlation between FIS sub-scales, WCST, SDLT, and Stroop test duration in the PWE group (p>.05). However, Spearman's rho test revealed statistically negative correlations between FIS, sub-scales, and RSPM scores (p<.05). The results did not demonstrate a significant correlation between FIS sub-scales and RSPM test duration (p>.05) (Table 6).

Spearman's rho correlation did not reveal any significant relationship between SDLT score and fatigue sub-scales (p>.05). However, we found a positive correlation between CF and Stroop-4 test duration (r=.431, p<.05). In addition, we also found a significant correlation between FIS,

Table 4. Spearman correlation coefficients between FIS subscales and psychological variables

	Mean ± SD	FIS	CF	PF	SF
HADS-A	8.96 ± 5.01	0.506**	0.414*	0.358*	0.464**
HADS-D	6.63 ± 4.18	0.690**	0.675**	0.520**	0.636**
HADS	15.36 ± 8.44	0.610**	0.544**	0.448**	0.750**
ESS	6.57 ± 4.47	0.281	0.262	0.192	0.249
QOLIE-10	26.42 ± 7.89	0.416*	0.398*	0.207	0.465**

ESS= Epworth Sleepiness Scale; HADS= Hospital Anxiety and Depression Scale; HADS-A= Hospital Anxiety and Depression Scale-Anxiety; HADS-D= Hospital Anxiety and Depression Scale-Depression; QOLIE-10= Quality of life in epilepsy-10; **p<0.001; *p < 0.05

Table 5. Mann Whitney U tests to compare participants' neuropsychological tests

	PWE			HC			Test value	P value
	Min	Max	Med (IQR)*	Min	Max	Med (IQR)		
WCST-2	8	97	55.0 (47.5)	7	44	14.5 (12)	82.5	<0.001**
WCST-5	10	73	30.0 (26.5)	9	43	12.0 (6.25)	90.0	<0.001**
WCST-6	6	72	26.0 (27.5)	4	35	7.0 (6.5)	84.0	<0.001**
SDLT-Score	0	22	14.0 (12.5)	12	24	20.0 (4.0)	611.5	<0.001**
Stroop-1	7.33	18.01	11.1 (4.33)	5.99	11.64	8.61 (2.74)	171.0	0.001**
Stroop-2	7.47	21.82	12.37 (5.77)	6.96	12.44	9.45 (1.90)	149.0	<0.001**
Stroop-3	9.67	23.53	13.17 (6.67)	8.68	17.94	12.11(1.93)	195.5	0.004*
Stroop-4	12.08	41.26	18.29 (10.59)	9.38	18.76	15.61 (4.40)	206.0	0.007*
Stroop-5	13.40	100.61	28.20 (11.68)	12.62	32.37	22.28 (9.26)	204.0	0.006*
RSPM Duration	5.41	50.04	18.04 (11.80)	10.09	40.21	28.76 (14.25)	534.0	0.003*
RSPM-Score	1	32	18 (10.5)	3	39	32.0 (6.25)	650.0	<0.001**

IQR = Interquartile range; Max= Maximum; Med=Median; Min= Minimum, RSPM= Raven Standart Progressive Matrices; SDLT= Serial Digit Learning Test; WCST= Winconsin Card Sorting Test; **= p < 0.001 *= p < 0.05

Table 6. Spearman's rho correlation results between FIS subscales and RSPM in PWE and patients with focal epilepsy

	Mean ± SD	FIS	CF	PF	SF
Patients with epilepsy					
RSPM-Duration	19.21 ± 10.17	-0.344	0.319	-0.240	-0.343
RSPM-Score	18.61 ± 8.19	-0.521**	-0.509**	-0.455**	-0.439*
Patients with focal epilepsy					
RSPM-Duration	19.59 ± 11.09	-0.522**	-0.509**	-0.380	-0.528**
RSPM-Score	18.01 ± 8.45	-0.629**	-0.638**	-0.545**	-0.536**

CF= Cognitive fatigue; FIS= Fatigue impact scale; PF= Physical fatigue; RSPM= Raven Standart Progressive Matrices; SF=Social fatigue**= p < 0.001 *= p < 0.05

CF, SF, and RSPM test durations in people with focal epilepsy (p<.05). Thus, we also found statistically significant negative correlations between, FIS, CF, PF, SF, and RSPM scores (p<.05) (Table 6). Due to the small number of participants, no statistical analysis was performed in the generalized epilepsy group.

DISCUSSION

Previous models of fatigue in neurological diseases have suggested that dysfunction in the basal ganglia and medial frontal cortex produces fatigue through disrupted networks that serve voluntary effort (1). Executive functions, one of the cognitive roles of the frontal cortex, are complex functions that involve many separate areas and several different networks. It may be expected that tasks related to executive

functions are more closely related to fatigue in epilepsy due to the impairment. Our study found no significant correlation between fatigue, its sub-scales, and WCST sub-dimensions, SDLT, and Stroop tests specific to executive functions, memory, and attention deficits, respectively. Bol et al. (2010) examined the relationship between fatigue and neuropsychological functions in patients with Multiple Sclerosis (MS). They used the Multidimensional Fatigue Index to measure fatigue, WCST, Stroop, Digit Span Test, and RSPM tests to assess cognitive skills such as attention, executive functions, memory, and abstract reasoning. Accordingly, no relationship was observed between mental and physical fatigue and executive functions, attention, memory, and abstract reasoning in MS patients (8). Parmenter et al. (2003) investigated the difference between high and low fatigue levels in cognitive skills such as attention, planning, and learning in MS patients. They found

no statistically significant difference between the participants in both conditions, even if subjective performance appeared low (9). Lorist et al. (2000) used EEG data and behavioral measures to examine the effects of mental fatigue on planning and task switching in healthy volunteers during the task. The EEG data showed that the involvement of brain regions related to executive functions, especially the frontal lobe, decreased performance with increasing time on task (10). Our study evaluated fatigue using the FIS and executive functions with the WCST; no significant relationship was found. Other two studies investigating the relationship between fatigue and executive functions mentioned above were conducted with MS, and the other was conducted with healthy participants. In the study with healthy participants, the participants were given a task that they could feel mentally fatigued, and then their executive functions were evaluated. Fatigue affects cognitive skills in some studies but not in others. This may be due to the different definitions of fatigue in the studies and the difference in the clinical dimension of the scales used to evaluate fatigue. Another explanation may be that the mechanisms underlying fatigue and neuropsychological assessments differ. Our study observed no correlation between the SDLT, learning and memory test, and fatigue and its sub-scales in patients with focal epilepsy. Jougoux-Vie et al. (2014) evaluated fatigue and memory in MS patients in their study. The results showed that although fatigue was associated with memory complaints in MS, subjective fatigue was not statistically associated with memory decline. The researchers attributed this to the fact that MS patients may have poor self-assessment skills for memory difficulties and stated that complaints related to memory decline reflected subjective fatigue complaints; therefore, they considered it necessary to evaluate fatigue when memory-related complaints occurred (11). Based on this information, it can be interpreted that findings related to memory impairment in patients with focal epilepsy are not directly related to fatigue dimensions, similar to the results of studies conducted in MS patients.

Our results revealed a significant relationship between cognitive fatigue and the time spent on the Stroop-4 task in individuals with focal epilepsy. In their review study, Hanken et al. (2014) concluded that fatigue associated with MS does not impair cognitive speed/selective attention performance, language, visuospatial processing, and working memory performance, while the state of alertness has an essential effect on maintaining attention (12). Accordingly, general and cognitive fatigue in patients with focal epilepsy may affect complex attentional areas related to awareness and alertness, leading to decreased performance in attentional tasks. Our findings revealed a negative correlation between general fatigue, PF, SF, and RSPM tests in patients with focal epilepsy. As fatigue and its sub-scales scores were increased, the time spent on the test decreased. The reason may be that the RSPM test is more expanded, and requires more abstract thinking than the other tests, so the patients may have solved the test in a shorter time with the desire to finish the test quickly. In addition, it was found that RSPM scores decreased as general fatigue, PF, and SF scores increased. Bilo et al. (2013) found that the score in visual-spatial perception tests was low as a result of various neuropsychological tests applied to patients with focal occipital lobe epilepsy (OLE). They emphasized that since the occipital lobe is involved in both low-level and high-level visual processing, seizures in OLE patients may alter the normal functioning of occipital circuits and lead to cognitive visual-perceptual and visual-structural deficits (13). In a study that assessed the relationship between fatigue and visual-spatial perception in Parkinson's disease, the findings revealed that fatigue affected visual-spatial perception. Fatigue and visual-spatial perception differentiation could result from the commonality of one or more pathophysiological mechanisms in this population (14). In the patient sample of our study, temporal lobe seizures were more frequent in the focal group. It can be interpreted that fatigue affects

visual-spatial perception in focal epilepsy due to the networks of the temporal and occipital lobes while performing visuospatial tasks. In addition, impairments in visuospatial functions are likely to trigger fatigue in focal epilepsy by increasing the effort required to perform tasks requiring visuospatial attention or calculations.

Our study contributes to the literature as it is the first study examining fatigue and neurocognitive evaluation in epilepsy patients; however, it has several limitations. The difference between the patient and control groups regarding education level is a limitation, even though the neuropsychological tests (SDLT) were applied according to the participant's education level. In addition, the long duration of the tests and scales applied may trigger fatigue in patients. The lack of a general definition of fatigue, the scales used to evaluate fatigue addressing different dimensions of fatigue, and the different neuropsychological tests used are other factors that make it difficult to generalize our findings with the studies in the literature.

As a result, fatigue levels (physical fatigue, cognitive fatigue, social fatigue) were higher in PWE than in healthy participants, and cognitive functions such as executive functions, attention, visual-spatial perception, and memory were more impaired. In contrast, fatigue in PWE was only associated with visual-spatial perception. Our study is the first to evaluate the relationship between fatigue and cognitive functions in adult PWE, and the significant relationship between fatigue and visual-spatial cognitive impairment is valuable. It is expected that visual-spatial functions are impaired in patients with temporal lobe epilepsy, which constitutes the majority of our study, and it is not clear whether this impairment causes fatigue or whether fatigue increases visual-spatial dysfunction. Using functional imaging techniques in future studies or studies performed in larger cohorts may provide more precise information on this issue.

Ethics Committee Approval: This study protocol received approval from the Institutional Review Board Ankara Yildirim Beyazit University Institute of Health Sciences Ethics Committee under approval code 33 on 09.12.2021, conforming to the Declaration of Helsinki.

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