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Evaluation of visual reaction time in patients with fibromyalgia syndrome

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Abstract

Fibromyalgia syndrome (FMS) has previously been linked to cognitive dysfunction. The aim of this study was to compare visual reaction time (RT) between FMS patients and healthy subjects. The relationship was examined between RT and clinical parameters in FMS patients, and it was aimed to evaluate the effect of drugs used in the treatment of FMS on RT. A total of 112 FMS patients and 110 healthy volunteers were included in this cross-sectional research. Cognitive performance was evaluated with visual RT measurements. FMS patients were assessed using the Fibromyalgia impact questionnaire (FIQ), Beck Depression Inventory (BDI), Fatigue Severity Scale (FSS) and Pittsburgh Sleep Quality Index (PSQI). The drugs used in the treatment of FMS were recorded. Significantly prolonged visual RT measurements were detected in FMS patients ($p < 0.001$). There was no significant difference in RT measurements between the patients who did not use drugs and those who were treated with serotonin noradrenaline reuptake inhibitor, gabapentinoid and combination therapy ($p > 0.05$). RT was significantly correlated with FIQ, BDI and PSQI scores in FMS patients (rho: 0.290, $p = 0.002$ for FIQ; rho: 0.253, $p = 0.007$ for BDI and rho: 0.312, $p = 0.001$ for PSQI). No significant correlation was detected between RT scores and FSS values ($p > 0.05$). Visual RT measurements were seen to be deteriorated in FMS patients. As the disease severity, depression level, and sleep disturbance increased, so the impairment in visual RT values became more prominent. The drugs used in the FMS treatment did not influence the RT scores. Cognitive performance tests should be incorporated in the physical examination and follow-up courses of FMS patients.

Keywords Fibromyalgia · Cognitive dysfunction · Visual reaction time · Cognitive performance

Introduction

Fibromyalgia (FMS) is a complex of symptoms included in the class of rheumatological disorders, in which chronic musculoskeletal pain is the leading complaint. This complex condition can be accompanied by fatigue, impaired sleep quality, stiffness, tenderness, perturbed psychiatric condition, and cognitive imbalance [1, 2]. The etiopathogenesis of FMS is complex [3]. Deteriorations in cognitive functions in this patient group are defined as "fibrofog" and may be more troublesome to the patient than the main symptom of chronic pain. Difficulties in focusing and shifting attention are common problems in FMS patients [4]. In addition, a considerable proportion of FMS patients experience memory problems and difficulties in completing multiple tasks [5].

Reaction time (RT) is defined as the interval between the appearance of a stimulus and the appropriate response. Prior to this measurement, the subject is instructed to respond as soon as possible [6]. Thus, the time it takes to react to external stimuli is revealed. RT is an indicator of data processing and is used to assess the capacity of the individual to concentrate and coordinate. It is considered an indirect measure of the information processing period of the central nervous

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system and is a simple and reproducible method for determining synchronization between the sensory system and the motor response [7, 8]. RT can be classified as simple and complex. In Simple RT, there is no choice between stimuli, and a response must be given to each stimulus. Complex RT is a more challenging process for the subjects as it includes recognizing the correct stimulus, avoiding the incorrect stimulus and not responding [9].

There are various studies revealing that reaction time is prolonged and cognitive performance is impaired in FMS patients [5, 10]. Reyes Del Paso et al. [10] reported that RT was prolonged in FMS patients. In this study, it was found that clinical factors and cerebral blood flow were effective on RT and cognitive function. However, data on the impact of drug use on RT in FMS patients are limited. The aim of this study was to compare the simple visual RT between female FMS patients and healthy control subjects. The second aim was to evaluate the correlations between RT measurements and disease activity, depression, sleep disturbance and fatigue in the FMS group. Comparisons were also made of the RT values of the patients who were not taking any drugs and those under different FMS medical treatments to be able to assess whether different pharmacological treatments affect the RT.

Materials and methods

This cross-sectional study was conducted between March 2019 and September 2019, and included a total of 112 female FMS patients who presented at the Physical Medicine and Rehabilitation outpatient clinic and 110 healthy control subjects selected from individuals who were referred for periodic check-ups and had no complaints. The patients in the FMS group met the 2010 American College of Rheumatology criteria [11]. All the study participants in both groups were aged 18–65 years.

The study exclusion criteria were defined as visual impairment, the presence of diseases that prevent adequate upper extremity function (radiculopathy, myelopathy, mononeuropathy, polyneuropathy, stroke, multiple sclerosis, motor neuron disease, brachial plexopathy, Parkinsonism, mechanical joint disease, inflammatory joint disease, entrapment neuropathy, joint ankylosis, complex regional pain syndrome, and amputated extremity), hypothyroidism, dementia, major depression or other psychiatric diseases, hypertension, diabetes mellitus, presence of disease that may impair cognitive functions or the use of any drugs other than FMS treatment that can affect RT. Visual impairment was questioned verbally to the participants. Additionally, the hospital registration system and the ministry of the health system were examined in this respect. All participants were evaluated in a separate outpatient clinic for visual impairment with a Snellen chart.

Routine blood tests (complete blood count, sedimentation, C-reactive protein, liver function tests, kidney function tests, thyroid function tests, vitamin D level, vitamin B12 level, calcium, phosphorus, and alkaline phosphatase) were performed for all participants. Any subjects who did not meet the study criteria were excluded from the study.

The FMS group comprised patients who did not use medication and those who were treated with serotonin-noradrenaline reuptake inhibitör (SNRI), gabantinoid or combination therapy for at least six months. One patient under tricyclic antidepressant therapy was excluded from the study. No patients were using opioids.

A record was made for each subject of age, body mass index (BMI), educational status, marital status, occupational status, exercise status, alcohol, cigarette, and coffee consumption, and dominant upper extremity. Medication use of all participants was questioned. Prescribed drugs were checked through the Ministry of Health system. In addition, the symptom duration of FMS patients was determined.

Prior to the research, approval was obtained from the Faculty of Medicine Clinical Research Ethics Committee of our university (dated 20.02.2019 and numbered 15.03.2019). Before the data collection process, all participants were informed and the research was conducted on a voluntary basis.

Fibromyalgia ımpact questionnaire

The Fibromyalgia Impact Questionnaire (FIQ) is a scale used to assess the clinical severity of FMS patients. There are 10 sub-headings on the scale, each of which is scored from 0 to 10 points, giving a maximum possible score of 100. Increasing scores indicate more pronounced clinical involvement [12, 13].

Fatigue severity scale

The severity of fatigue symptoms in the last week is evaluated through the 9 sub-headings covered by the Fatigue Severity Scale (FSS). Each sub-heading is scored between 1 and 7 points (1 point = strong disagreement and 7 points = strong agreement). Then, the arithmetic average of the scores originating from the nine sub-headings is calculated to give an overall score. A higher score is associated with more pronounced fatigue severity [14, 15].

Beck depression ınventory

The Beck Depression Inventory (BDI) was created as a self-reported form containing a total of 21 items. The last week is taken into account in the scoring of each item and a score between 0 and 3 is given. Therefore, the maximum score from this scale is 63 points. Higher scores are associated with more severe depression [16, 17].

Pittsburgh sleep quality ındex

The Pittsburgh Sleep Quality Index (PSQI) is used to evaluate sleep quality and sleep-related disorders in the last month. The total score ranges from 0 to 21 points, and increasing scores are associated with impaired sleep quality [18, 19].

Simple visual reaction time measurement

The subjects were instructed to concentrate on a computer screen and press the button on the remote control as quickly as possible when the visual stimulus changed on the screen. There were fixed time intervals between the visual stimuli. RT was determined by measuring the time between the change of the visual stimulus and pressing the button. During the visual stimulus, the color of the screen changed. All measurements were made on the same computer and the program to be used in RT calculation was installed into the computer before the measurements. Before taking the measurements, a trial was performed with 10 visual stimuli to familiarize the subjects with the task. During the test, all the subjects were seated comfortably in the same chair. All the measurements were taken in the same quiet room between 10 and 11 am. In the RT task, a total of 15 visual stimuli were given and the RT was measured for each stimulus. The RT score was calculated as the average of the 15 values [7, 10] (Fig. 1). Another physician who was unaware of the participants' characteristics performed the visual RT measurements. All measurements were made by the same physician.

Statistical analysis

Data analysis was performed using SPSS vn. 25.0 software (Statistical Package for the Social Sciences, SPSS Inc. Chicago, IL, USA). The results were presented in the text and tables as numbers, percentages, mean ± standard deviation, and median (minimum–maximum) values. Conformity of the data to normal distribution was assessed with the Shapiro–Wilk test. Comparisons of continuous variables between two groups were made with the Independent Samples *t* test, and the Chi-square test was applied to categorical variables. Comparisons of multiple groups were performed with the Kruskal–Wallis test. Correlations were assessed with the Spearman rho test. A value of $p < 0.05$ was accepted as statistically significant.

Results

Evaluation was made of 112 female FMS patients and 110 female healthy control subjects. The mean age was 46.93 ± 9.25 years in the patient group and 44.90 ± 10.57 years in the control group ($p > 0.05$). The mean BMI value was 31.59 ± 5.65 in the patient group and 30.39 ± 6.33 in the control group ($p > 0.05$). The demographic characteristics of the groups are presented in Table 1, and there was no statistically significant difference between the groups in the specified parameters. ($p > 0.05$). No statistically significant difference was determined between the groups in respect of dominant extremity, smoking status, alcohol and coffee consumption, and exercise status ($p > 0.05$) (Table 1).

The mean RT of the FMS and control groups was 320.08 ± 45.33 ms (msec) and 248.85 ± 28.64 ms,

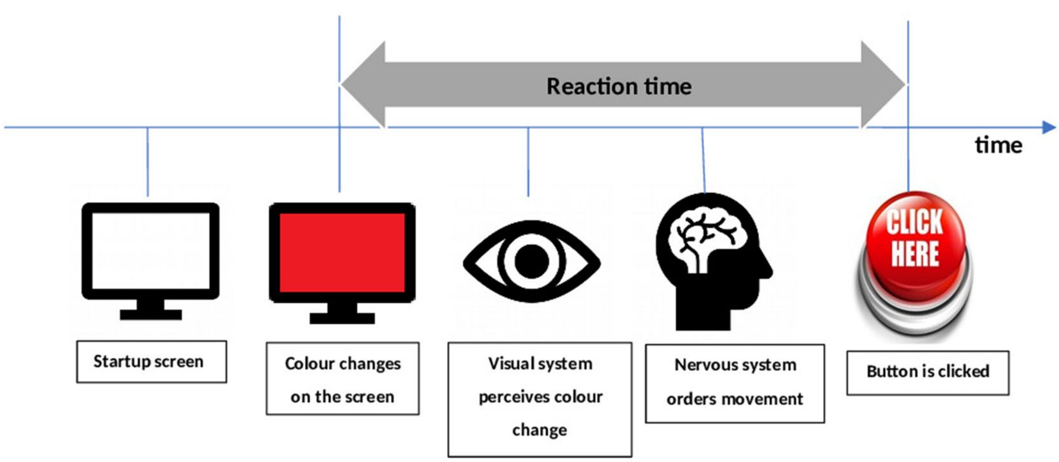

Fig. 1 Demonstration of the visual reaction time measurement

Table 1 The baseline features of the patient and control groups

	Patient (n = 112)	Control (n = 110)	p
Age* (years)	46.93 ± 9.25	44.90 ± 10.57	0.128
BMI* (kg/m²)	31.59 ± 5.65	30.39 ± 6.33	0.139
Income level (n) (%)			
Below minimum wage	3 (2.78)	1 (0.90)	0.471
Minimum wage	33 (29.46)	38 (34.55)	
Above minimum wage	76 (67.86)	71 (64.55)	
Marital status (n) (%)			
Married	101 (90.18)	98 (89.09)	0.472
Single	6 (5.36)	8 (7.27)	
Widowed/divorced	5 (4.46)	4 (3.64)	
Educational status (n) (%)			
Literate	21 (18.74)	18 (16.36)	0.074
Primary school	58 (51.79)	44 (40)	
Middle school	11 (9.82)	8 (7.27)	
High school	13 (11.61)	19 (17.27)	
University or above	9 (8,04)	21 (19.10)	
Occupational status (n) (%)			
Working	13 (11.61)	18 (16.36)	0.388
Not working/housewife	97 (86.61)	88 (80)	
Retired	2 (1.78)	4 (3.64)	
Dominant extremity (n) (%)			
Right	107 (95.54)	105 (95.45)	0.977
Left	5 (4.46)	5 (4.55)	
Smoking status (n) (%)			
Yes	9 (8.04)	12 (10.91)	0.465
No	103 (91.96)	98 (89.09)	
Alcohol consumption (n) (%)			
Yes	112 (100)	109 (99.09)	0.312
No	0 (100)	1 (0.91)	
Coffee consumption (n) (%)			
Never	64 (57.14)	68 (61.82)	0.514
1–2 cups a day	44 (39.28)	40 (36.36)	
3–4 cups a day	2 (1.79)	2 (1.82)	
More than 4 cups a day	2 (1.79)	0 (0)	
Exercise status (n) (%)			
Never	68 (60.71)	62 (56.36)	0.540
1–2 days a week	19 (16.97)	27 (24.55)	
3–4 days a week	14 (12.50)	13 (11.82)	
More than 4 days a week	11 (9.82)	8 (7.27)	

BMI body mass index, *kg* kilogram, m^2 square meter, *n* number % percentage

*Data are expressed as mean ± standard deviation.

respectively, and the difference was statistically significant ($p < 0.001$) (Table 2).

In the comparison of the Visual RT between FMS patients who did not receive pharmacological treatment and the healthy control group, the RT of FMS patients was found to be significantly higher than that of the healthy control group ($p < 0.001$) (Table 3). There was a statistically significant difference in RT between patients under pharmacological treatment (median = 319.50; minimum = 210 and maximum = 434), without pharmacological treatment (median = 322.50; minimum = 231 and maximum = 439), and healthy controls (median = 246.50; minimum = 185 and maximum = 329) ($p < 0.001$).

The FMS patients were separated into four groups: those not receiving pharmacological treatment, those who took gabapentinoid class drugs, those who took SNRI class drugs, and those who combined these two drug groups. There was no statistically significant difference between these four groups in terms of visual RT ($p > 0.05$) (Table 4).

RT was significantly and positively correlated with the FIQ, BDI and PSQI scores in FMS patients. (rho: 0.290, $p = 0.002$ for FIQ; rho: 0.253, $p = 0.007$ for BDI and rho: 0.312, $p = 0.001$ for PSQI). No significant correlation was found between RT and FSS scores ($p > 0.05$) (Table 5).

Discussion

The results of this study revealed that visual RT, which is an indicator of cognitive dysfunction, is prolonged in FMS patients compared to healthy control subjects. RT values did not differ significantly according to drug groups in FMS patients. Disease severity, depression, and sleep disturbance data were significantly correlated with RT scores in FMS patients.

Consistent with these results, there are several studies reporting impaired RT data and cognitive function tests in

Table 2 Comparison of the reaction time between the patient and control groups

	Patient (n = 112)	Control (n = 110)	p
Reaction time (msec)	320.08 ± 45.33	248.84 ± 28.64	< 0.001

n number, *msec* milliseconds

Table 3 Comparison of the reaction time between FMS patients not receiving pharmacological treatment and the healthy controls

	Patient (n = 46)	Control (n = 110)	p
Reaction time (msec)	319.91 ± 47.30	248.84 ± 28.64	< 0.001

FMS fibromyalgia syndrome, *n* number, *msec* milliseconds

Table 4 Comparison of reaction time scores according to the drug groups

	Not taking medication ($n=46$)	SNRI group ($n=34$)	Gabapentinoid group ($n=12$)	Combination group ($n=19$)	p
Reaction time* (msec)	322.5 (231–439)	309 (210–434)	335 (261–519)	337 (262–397)	0.064

FMS fibromyalgia syndrome, *n* number, *msec* milliseconds, *SNRI* serotonin and norepinephrine reuptake inhibitör

*Data are expressed as median (minimum–maximum)

Table 5 Correlations between reaction time and clinical scales in FMS patients

	Reaction time Rho	p
FIQ	0.290	0.002
BDI	0.253	0.007
FSS	0.158	0.095
PSQI	0.312	0.001

FMS fibromyalgia syndrome, *FIQ* fibromyalgia ımpact questionnaire, *BDI* beck depression ınventory, *FSS* fatigue severity scale, *PSQI* pittsburgh sleep quality ındex

FMS patients [5, 10, 20–22]. However, there are also studies that have reported no difference in cognitive function tasks and RT scores [23, 24]. This discrepancy in outcomes may be explained by differences in task methodology. The variety of tests used in the evaluation is one of the parameters to be considered, and the limited sample size in research showing contradictory outcomes should also be noted. It can also be considered that differences in education level and test motivation of the FMS patients may have affected the results.

The RT results of the current study suggest poor attentional arousal, and reduced capacity to enhance care taken during the response to an external signal in FMS patients. Longer RT scores are an indirect indicator of cognitive dysfunction in FMS patients. Various mechanisms may play a role in the emergence of impaired RT results in FMS patients, one of which is a change in cerebral blood flow occurring during the tasks [10]. Pain is a condition that activates brain regions involved in cognitive processes, such as the cingulate and prefrontal cortex [25]. Functional and structural changes in the central nervous system secondary to pain and other FMS symptoms may affect RT outcomes [26]. FMS patients may tend to have a slower RT to respond more accurately. Another possible mechanism for the longer RT values detected in FMS patients is that patients do not exert in the same amount of effort as healthy subjects to achieve excellent test results. Patients may purposefully or inadvertently present their cognitive impairment as worse than their actual condition [27, 28].

There was no statistically significant difference between the RT values of the patients who were not under drug therapy and those who received SNRI, gabantinoid and combination therapy. Consistent with these results, various studies have shown that these drug groups have no positive or negative effects on cognitive performance in FMS patients and other subjects [20, 21, 28, 29]. In contrast, Reyes Del Paso et al. [10] reported that anxiolytics had a slight unfavorable impact on RT in FMS patients. Altiparmak et al. [30] suggested that pregabalin and duloxetine, used in postoperative pain management, negatively affect cognitive performance. Salinsky et al. [31] also reported that pregabalin caused cognitive dysfunction in healthy individuals. Although there is no consistency in the literature data, the current study results suggest that cognitive dysfunction in FMS patients is independent of drug use. Cognitive function is thought to be affected by components of the FMS clinical status rather than the drugs indicated.

The RT measurements in the current study were significantly correlated with disease severity, depression level and sleep disturbance in FMS patients. This significance was not detected between fatigue level and RT values. Gelonch et al. [32] found a relationship between cognitive test results and anxiety and depression. Veldhuijzen et al. [25] reported a relationship between cognitive performance and pain level but did not suggest any significant correlation with fatigue scores and psychosocial measures. Montoro et al. [21] detected a link between pain and cognitive processing speed, but not with depression. Reyes Del Paso et al. [10] reported pain, depression and anxiety as markers of slowed RT. Tesio et al. [33] revealed a significant correlation between disease severity and cognitive performance in FMS, but the relationship between pain, depression and anxiety levels was not significant. It can be speculated that increased disease activity, depression level, and sleep impairment in FMS patients exacerbate disturbances in the central nervous system. Both functional and structural changes induced in the central nervous system may adversely affect cognitive performance and RT measurements in FMS patients with severe clinical findings. In addition, high disease activity, depression level, and sleep disturbance may trigger disinclination to the RT test.

This study has some limitations. As a result of the relatively small sample size, the number of patients in the drug groups is limited. Since there were no patients under tricyclic antidepressant and opioid treatment, the effect of these drug groups could not be evaluated. Cognitive function was assessed only with simple visual RT, and complex tests were not administered. Cerebral blood flow was not investigated during the visual RT measurement. Although the exercise status of the patient and control groups was questioned, this parameter was not examined quantitatively. The cross-sectional design of the research restricted the probability of drawing inferences regarding the causation of any of the discovered associations in FMS patients.

Conclusion

The results of the current study demonstrated that visual RT measurements were prolonged as an indicator of cognitive dysfunction in FMS patients. The drugs used in the treatment of FMS did not affect the RT values. Significant correlations emerged between RT measurements and disease severity, depression and sleep disturbance in FMS patients. These results suggest that the severity of disease parameters rather than drug use impacts cognitive performance in FMS patients. Cognitive function in FMS patients can be better evaluated objectively with relatively simple tests rather than with subjective questionnaires. The course of cognitive performance over time can be documented through changes observed in measurements during clinical follow-up. In future studies, the effect on RT of exercise, which is one of the cornerstone methods of FMS treatment, can be examined in combination with functional magnetic resonance imaging and cerebral blood flow measurements. These types of studies will help to elucidate cognitive dysfunction in FMS.

Author contributions MEK, BFK, AA and VN: designed the study. MEK, BFK, EB, TTK and VN: reviewed the articles and provided the data. BFK and AA: analyzed the data. MEK, EB and TTK: contributed the analysis tools. MEK, BFK, EB, TTK, AA and VN: authored and reviewed drafts of the paper. MEK, BFK and AA: prepared the tables and figure. MEK, BFK, EB, TTK, AA and VN: approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval Ethics committee approval was obtained from the Faculty of Medicine Clinical Research Ethics Committee of our university (dated 20.02.2019 and numbered 15.03.2019). Before the data collection process, all participants were informed and the research was conducted on a voluntary basis.

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