Comparison of The Cognitive Performance Between Healthy Controls, Rheumatoid Arthritis and Fibromyalgia Patients Without Depression

Depresyonu Olmayan Sağlıklı Kontrol, Romatoid Artrit ve Fibromyalji Hastalarında Kognitif Fonksiyonların Karşılaştırılması

Fibromyalji Hastalarında Kognitif Performans / The Cognitive Performance in Fibromyalgia Patients

Ayhan Bilgici[1], Murat Terzi[2], Hatice Güz[3], Ömer Kuru[1]
[1]Department of Physical Medicine and Rehabilitation, [2]Department of Neurology, [3]Department of Psychiatry,
Ondokuz Mayis University, Medical Faculty, Samsun, Turkey

Özet

Amaç: Bu çalışmanın amacı depresyonu olmayan fibromyalji(FM) hastalarında kognitif performansı değerlendirmek, romatid artritli(RA) hastalar ve 15 sağlıklı kontrolle karşılaştırmaktır. Gereç ve Yöntem: Bu çalışmaya 16 FM ve 15 RA hastası katıldı. Tüm katılımcılar çeşitli psikolojik ölçümleri tamamladı. Kognitif ölçümler global dikkat, dil, görsel ve sözel hafıza, görsel-uzaysal işlevler ve yürütücü fonksiyonlardan oluştu. FM'li hastalarda ağrı şiddeti, yorgunluk ve uyku kalitesi visual analog skala(VAS)(0-10) tarafından değerlendirildi. FM'nin diğer semptomlarının değerlendirilmesinde Fibromyalji Etki Sorgulaması(FES) kullanıldı. Bulgular:FM ve RA hastaları sağlıklı kontrollerle karşılaştırıldıklarında bir çok kognitif ölçümde kötü performans sergilediler. FM hastalarının performansı bir çok kognitif ölçümde RA hastalarına benzerdi. Bununla beraber FM hastaları yürütücü fonksiyonlarda RA hastalarından çok daha kötü performans gösterdiler($p<0,05$). Ağrı iki cognitive ölçümle koreleydi: global dikkat ve yürütücü fonksiyonlar (sırasıyla $r=0.51$, $p<0.05$ and $r=0,68$, $p<0,05$). Yorgunluk yalnızca yürütücü fonksiyonlarla korele bulundu ($r=0,51$, $p<0,05$). Tartışma: Bizim sonuçlarımız depresyonsuz FM hastalarının tüm kognitif tasklarda kötü performansa sahip olduğunu gösterdi. Ek olarak ağrı, yorgunluk gibi değişkenler kognitif performansla anlamlı ilişkiliydi.

Anahtar Kelimeler

Fibromyalji; Romatoid Artrit; Depresyon; Bellek; Kognitif Disfonksiyon

Abstract

Aim:The purpose of this study was to assess the cognitive performance in fibromyalgia(FM) patients without depression and to compare it with rheumatoid arthritis(RA) patients and 15 healthy controls. Material and Method:16 FM and 15 RA patients participated in the present study. All participants completed several psychological measures. The cognitive functions measured were global attention/working memory, language, visual and verbal memory, visuo-spatial processes and executive functions. Pain severity, fatigue and sleep quality in FM patients were evaluated by the visual analog scale(VAS)(0-10). Other symptoms of FM were evaluated using the Fibromyalgia Impact Questionnaire(FIQ). Results: FM and RA patients performed poorly on most cognitive measurements compared with healthy controls. The performance of the FM patients was similar to that of the RA patients on most cognitive measures. However, FM patients performed more poorly than RA patients on measures of executive functions($p<0,05$). Self reported pain correlated with two cognitive measures: global attention/working memory and executive functions($r=0.51$, $p<0.05$ and $r=0,68$, $p<0,05$ respectively). The fatigue correlated only with executive functions($r=0,51$, $p<0,05$). Discussion: Our results indicated that FM patients without depression had poor cognitive performance on complex cognitive tasks. In addition, the present results show that some variables such as pain and fatigue were significantly related to cognitive performance.

Keywords

Fibromyalgia; Rheumatoid Arthritis; Depression; Memory; Cognitive Dysfunction

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Corresponding Author: Ayhan Bilgici, Ondokuz Mayıs Üniversitesi, Tıp Fakültesi, Fizik Tedavi ve Rehabilitasyon Anabilim Dalı, Samsun, Türkiye.
T.: +90 3624576041 E-Mail: abilgici@yahoo.com

Introduction

FM is a chronic syndrome that occurs predominantly in women and is marked by generalized pain, multiple defined tender points, fatigue, disturbed and nonrestorative sleep, and numerous other somatic complaints [1-3]. Additionally, patients who have FM report more cognitive problems and dissociative states than other rheumatology patients. The memory impairment, poor concentration and difficulty in performing mental tasks are frequent complaints in patients with FM. This condition is so-called 'fibro fog' [4-6].

The memory and concentration problems are very common symptoms in FM patients [4-10]. FM patients are more sensitive to their memory loss because their memory function may have declined over a shorter time period than is typical with normal aging. Landro et al evaluated long-term memory performance and found that FM patients performed more poorly than the healthy controls on many memory measures and the word fluency tasks [9]. Clauw et al reported that FM patients scored below the expected level on some attention and memory tests [10].

The pathogenetic mechanisms leading to diminished cognitive performance in FM patients are unknown and few objective data are available on this topic [4-10]. Cognitive symptoms in these patients may be exacerbated by the presence of depression, anxiety, sleep problems, endocrine disturbances, and pain, but the relationship of these factors to cognitive problems in FM patients is unclear [9, 11]. Additionally, inclusion of comparison groups who have other painful conditions such as rheumatoid arthritis are needed in order to clarify whether cognitive problems are specific to FM or a function of chronic pain more generally.

In this study, we assessed the cognitive performance in FM patients without depression and compared with RA patients and 15 healthy controls. In addition, we investigated the relationship between cognitive functioning and other physical symptoms.

Material and Method

Eligible subjects included women 18-65 years of age, who fulfilled American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia [1]. Rheumatoid arthritis diagnosis was based on the ACR criteria [12]. We excluded patients with RA who had concurrent fibromyalgia. Fifteen healthy women were selected from the hospital staff to match the patient groups for age by years. Subjects were excluded for any of the following reasons; concomitant depression, diagnosis of a primary psychiatric disorder, current use of medications known to affect cognitive function, less than 5 years of formal education. Depression was diagnosed according to DSM IV criteria [13,14]. Patients discontinued all psychoactive medications for at least 15 days. Eligible subject were required to discontinue all prescription medications for fibromyalgia. Pain was measured by a standard 10-cm visual analog scale (VAS) (0 = no pain, 10 = pain as bad as it could possibly be). We also used a VAS to measure the intensity of fatigue (0 = none, 10 = worst ever), sleep quality (0 = worst ever, 10 = best), and overall well-being (0 = worst ever, 10 = best ever). Other symptoms of the FM were evaluated using the Fibromyalgia Impact Questionnaire. The FIQ is a 10-item, self-report instrument that measures multiple symptoms, functioning, and overall well-being. The scores range from 0 to 80 [15]. The FIQ has been found to have good reliability and validity in clinical trials [16]. Pain intensity in RA patients was measured using a 10cm VAS. All participants completed several psychological measures.

Neuropsychological Evaluation

The evaluation of the cognitive functions in all individuals was done by the same neurologist (MT), who had no knowledge of the clinical data and diagnosing the disease. The neuropsychological test battery was designed to assess different domains of cognitive functions; global attention, language, memory, visuo-spatial functions and executive functions [17-20]. All tests are presented in Table 1. All subjects gave written consent to participate in the study.

Table 1. Neuropsychological Test Battery

Attention
WAIS-R, Digit Span (DS)
Forward
Backward
Verbal Fluency (K-A-S Test)
Language
Boston Naming Test (30-Items)
Visio-spatial functions
Benton's Facial Recognition (BFR)
WAIS-R Block Design (BD)
Hooper Visual Organization Test (HVOT)
Clock Drawing
Verbal Memory
California Verbal Learning Test
Visual Memory
Rey-Osterreith Complex Figure (ROCF)
Executive Functions
Wisconsin card sorting test (WCST)
Stroop Test
Trail Making Test A and B (TMT A-B)
WAIS = Wechsler Adult Intelligence Scale

Statistical analysis

One-way analysis of variance (ANOVA) with Tukey's test was used to compare the differences in cognitive measures among the three groups. Categorical demographic variables were analyzed across the three groups using chi-square analyses. FM and RA patients were compared for continuous variables such as pain, fatigue using the Mann-Witney U test. Kolmogorov Smirnov test was applied to determine normally distributed continuous variables. Correlations between pain, fatigue, sleep quality and cognitive measures were analysed by Pearson or Spearman test as appropriate. $P<0.05$ was accepted as statistically significant.

Results

16 FM and 15 RA patients and 15 healthy controls participated in the present study. The study participants (FM patients) were all the women, with a mean age of 37 years. A self-reported duration of fibromyalgia symptoms were 8. 6 ± 3. 2 years. The mean duration of RA was 10.2 ± 5.7years. Healthy subjects had more years of education than FM and RA patients; however, there was not a significant difference. The groups were not different in age and duration of disease. Demographic and clinical data of FM and RA patients and healthy controls are given in

Table 2.

The average score on the VAS in FM patients was 7. 3 ± 3. 6 cm for pain intensity, 7. 7 ± 4. 5 cm for fatigue intensity, 6. 5 ± 4. 3 cm for sleep quality, and 4. 2 ± 3. 4 cm for overall well-being. The mean score for pain was 6. 8 ± 4. 1 in patients with RA. There was not a significant difference in pain scores in between two patients groups.

Table 2. Demographic and clinical data for all patients and 15 health controls who enrolled in this study.

	Fibromyalgia n= 16	Rheumatoid arthritis n=15	Controls n=15
Mean age (years)	36.8±9.3	38.1±11.9	35.3±7.1
Mean education level (years)	8.4±3.2	7.3±2.1	9.2±5.6
Mean disease duration (years)	8.6±3.2	10.2±5.7	-
Pain (VAS)	7.3±3.6	6.8±4.1	-
Fatigue (VAS)	7.7±4.5	6.1±5.2	-
Sleep quality (VAS)	6.5±4.3	5.9±2.1	-
Overall well-being	4.2±3.4	5.3±4.1	-
FIQ	59.7±20.6	-	-

FIQ: Fibromyalgia Impact Questionnaire

FM and RA patients performed poorly on most cognitive measurements compared with healthy controls. FM patients showed global cognitive impairment as compared to healthy controls. The performance of the FM patients was similar to that of the RA patients on most cognitive measures. However, FM patients performed more poorly than RA patients on many measure of executive functions (Wisconsin Card Scoring Test) (p<0,05). The performance of the RA patients on cognitive tests of information processing (executive performance) was impaired when compared to healthy control participants (p = 0, 05).

Comparison of patients with FM and RA revealed no significant differences except for the executive functions. No significant differences were found between FM and RA patients on the attention, memory, word fluency, and visuo-spatial tasks. Neuropsychological test results are summarized in Table 3. RA and FM patients performed poorly on more of the verbal memory tests when compared with control groups. Moreover, RA patients had similar visual memory tests with healthy controls (Rey –Osterreith Test). Results indicated that patients with FM displayed slower performance on executive functions, difficulty maintaining attention, poor verbal and visual memory, and impairment in visual-spatial tasks. In addition, the FM patients had significantly worse word fluency than healthy controls.

Self reported pain correlated with 2 cognitive measures: attention and executive functions(r=0.51, p<0.05 and r=0,68, p<0,05 respectively). Fatigue was not related to attention/working memory. The fatigue correlated only with executive functions in FM patients(r=0.51, p<0.05). No significant correlations were noted between the cognitive variables and sleep quality. Also, there was no significant correlation between total FIQ score with any cognitive task in patients with FM. The comparison of neuropsychological test results in FM patients with healthy controls are shown in Table 4. Pain in patients with RA was only related to attention skills. No significant association was detected between pain severity and others cognitive functions in patients with RA.

Table 3. The comparison of neuropsychological test results in patients with Fibromyalgia and Rheumatoid Arthritis.

	Patients (FM) (n= 16)	Patients (RA) (n= 15)	p[a]
Attention			
WAIS-R-DS-fwd	5	5.08	
WAIS-R-DS-bwd	3.44	3.42	
K-A-S perseveration	0.38	0.67	
Language			
BNT	26.81	27.25	
Visuo-spatial functios			
BFR	19.4	18.6	
BD	24.06	23.83	
HVOT	16.44	18.08	
Clock drawing	10	10	
Memory			
CVLT			
Total of 5 trials	47	48.33	
1th trial	6.08	6.19	
5th trial	11.58	11.75	
Short-delay free recall	5.81	6	
Short-delay cued recall	9.75	9.75	
Long-delay free recall	11.56	10.92	
Long-delay cued recall	10.5	10.38	
Perseverations	7.88	6.83	
Free recal intrusions	3.31	4	
Recognition	13.81	14.17	
Discriminability (%)	91.89	93.36	
ROCF			
1	19.75	21.33	
2	14.5	17.92	
3	14	18.25	
Executive functions			
WCST			
Total number of responses	123	116.5	
Total categories completed	2.8	4.58	0.03
Number of perseverative responses	38.3	28.5	0.02
Total number of Errors	29.33	18.25	0.02
Total number of correct responses	32.99	50.83	0.01
Stroop Test 1	12.58	13.9	
Stroop Test 2	12.27	15.24	
Stroop Test 3	14.97	14.59	
Stroop Test 4	21.36	18.41	
Stroop Test 5	31.06	30.94	
TMT A	48.16	50.05	
TMT B	93.63	89.38	

CVLT= California Verbal Learning Test; ROF= Rey-Osterreith Complex Figure; BFR= Benton Facial Recognition; BD= Blok design; HVOT= Hooper Visual Organization Test; WAIS-R =Wechsler Adult Intelligenve Scale-Revised; WCST =Wisconsin Card Sorting Test; TMT= Trail Making Test aOnly significant p values are shown.

Discussion

The cognitive impairment may be a common problem in patients with chronic pain. However, little is known about the possible impacts of the chronic pain on cognitive functions [21-22]. The prevalence of cognitive dysfunction is high among FM patients than other patients with rheumatic disease. We compared the cognitive performance of FM patients with RA patients and

Table 4. The Comparison of Cognitive Test Results in FM Patients with Healthy Controls and the Correlations between Variables such as Pain, Fatique and the Scores of the Neuropsychological Tests in the Fibromyalgia Group.

	Patients (FM) (n= 16)	Controls (n= 15)	p[a]	Pearson Correlation Coefficient[b]
Attention				
WAIS-R-DS-fwd	5	6.4	0.04	[c]r= 0.51
WAIS-R-DS-bwd	3.44	4.93	0.03	[c]r= 0.53
K-A-S perseveration	0.38	0.27		
Language				
BNT	26.81	29.27	0.04	
Visuo-spatial functios				
BFR	19.4	19.2		
BD	24.06	37	0.03	
HVOT	16.44	20.47	0.03	
Clock drawing	10	10		
Memory				
CVLT				
Total of 5 trials	47	58.73	0.02	
1th trial	6.08	7.73	0.03	
5th trial	11.58	14.33	0.02	
Short-delay free recall	5.81	7.87	0.02	
Short-delay cued recall	9.75	12.73	0.01	
Long-delay free recall	11.56	13.33	0.03	
Long-delay cued recall	10.5	13.27	0.02	
Perseverations	7.88	4.27	0.02	
Free recal intrusions	3.31	0.93	0.01	
Recognition	13.81	18.67	0.01	
Discriminability (%)	91.89	98.26	0.02	
ROF				
1	19.75	22.73	0.04	
2	14.5	21.2	0.03	
3	14	21.13	0.03	
Executive functions				
WCST				
Total number of responses	123	96.14	0.03	[c]r=0.68, [d]r= 0.51
Total categories completed	2.8	5.57	0.03	[c]r=0.65
Number of perseverative responses	38.3	12.21	0.02	[c]r=0.7, [d]r= 0.56
Total number of Errors	29.33	13.79	0.02	[c]r=0.71, [d]r= 0.6
Total number of correct responses	32.99	69.79	0.01	[c]r=0.73
Stroop Test 1	12.58	7.9	0.03	[c]r=0.68, [d]r= 0.52
Stroop Test 2	12.27	8.4	0.03	[c]r=0.61
Stroop Test 3	14.97	11.15	0.03	[d]r= 0.56
Stroop Test 4	21.36	14.83	0.02	[c]r=0.72, [d]r= 0.54
Stroop Test 5	31.06	22.53	0.03	[d]r= 0.56
TMT A	48.16	31.46	0.01	[c]r=0.66, [d]r= 0.62
TMT B	93.63	61.69	0.01	[c]r=0.64, [d]r= 0.58

CVLT= California Verbal Learning Test; ROF= Rey-Osterreith Complex Figure; BFR= Benton Facial Recognition; BD= Blok design; HVOT= Hooper Visual Organization Test; WAIS-R =Wechsler Adult Intelligenve Scale-Revised; WCST =Wisconsin Card Sorting Test; TMT= Trail Making Test
aOnly significant p values are shown.
bOnly significant correlations are shown.
cThe correlation between self reported pain and the scores of the neuropsychological tests.
dThe correlation between fatigue and the scores of the neuropsychological tests.

age-matched controls. Depressed patients were not included to this study because of the possibility of influencing with cognitive functions [23, 24].

Neuropsychological studies in FM patients have focused most frequently on attention and memory function. Our results demonstrated impairment visual memory, verbal memory, and sustained attention in FM patients. Memory impairments may result from slowed rate of information processing or slowed psychomotor speed [25]. These patients have particular difficulty with memory when tasks are complex and their attention is divided [11]. In addition, poor attention can also contribute to reduce in other cognitive measures such as problem solving and reasoning, reading, calculation skills. Dick et al [26] suggested that performance of standardized everyday attentional tasks was impaired in the FM group compared to controls.

The frontal cortex is critically important in tasks that require the temporal integration of information [27]. Working memory and encoding and retrieval operations are functions that reside primarily in the dorsolateral prefrontal cortex. In our study, verbal fluency measured by the KAS-test was found to be impaired in the FM. This condition resembles that delayed verbal recall was seen in patients with frontal lobe dysfunction. Johansson et al. found that regional cerebral blood flow (rCBF) measurements showed significant decrease in dorsolateral frontal cortical areas of both hemispheres in FM patients [28]

The speed of processing is the most sensitive measure of cognitive function. Past research has demonstrated a convincing relationship between slow speed processing and FM. We assessed executive functions for the speed of information processing, which measures how rapidly an individual can make simple perceptual decisions. In contrast to our study, Park et al found that speed processing was intact in FM patients [8]. In a later study, Grace et al [7] reported that although FM patients processed information as rapidly as age-matched controls, they had poorer working memory and long-term memory function. They did not collect measures of verbal knowledge. But, similarly to our study, Sletvold et al examined a number of cognitive tasks in FM patients and found evidence of declines in the speed of processing and attention [23]. Insufficiency on measures of psychomotor speed, verbal fluency and verbal memory in our study is consistent with cerebral cortical dysfunction. In a recent study, Verdejo-Garcia et al [29] examined executive function and decision making in FM using the Wisconsin Card Sorting Task (WCST). They found that FM patients achieved a lower number of categories and made more nonperseverative errors on the WCST.

Cognitive symptoms may be exacerbated by the presence of fatigue, sleep problems, and pain, but the relationship of these factors to cognitive problems in FM patients is unclear. Results of our study suggested that self-reported fatigue was related to executive functions/psychomotor speeding FM patients. Our findings are consistent with Cote and Moldofsky [30] in suggesting fatigue is related to psychomotor slowing in patients with FM. They suggested that fatigue associated with disturbed sleep may be the primary reason for the cognitive dysfunction observed in FM patients(The Stanford Sleepiness Scale was used to evaluate the sleep disturbance). On the contrary, no relationship was found between cognitive dysfunction and sleep

disturbance in our study. This condition may be explained by the use of different sleep scales. Sleep deprivation will result in fatigue, negative mood, and impaired cognitive functioning [11,31]. However, Dick et al [26] reported that significant differences remained between FM and healthy control groups even when controlling for self-reported sleep disruption (number of awakenings per night).

Cognitive complaints would be most closely related to pain severity, and excessive preoccupations with the pain stimulus. There is evidence that intense bodily preoccupation is associated with disturbances in attention, and verbal memory [22,31-34]. In our study, the severity of pain was significantly associated with declines in the attention and impairment in the executive functions. Whereas, the pain in patients with RA was not related to cognitive functioning except for global attention. This condition may suggest that the underlying mechanisms of pain may have a role more than the severity of pain in cognitive functioning. The characteristics of central pain are quite different from peripheral pain. The general and widespread nature of pain in FM strongly suggests the involvement of central mechanisms, which leads to an altered processing of nonpainful body information [35-38]. FM is currently to be a disorder of pain regulation, classified often under the term central sensitization. Central sensitization may occur in the form of increased excitability of spinal cord neurons, enlargement of the receptive fields of these neurons, reduction in pain threshold, or recruitment of novel afferent inputs [38-41].

Overall, multiple techniques and approaches support the idea that FM is a CNS disorder involving central sensitization, with CNS dysregulation at the root of FM symptomatology, such as pain, fatigue, sleep disturbance and cognitive difficulties [27, 28, 34-36]. Montoyo et al suggested that in FM patients, there was abnormal information processing, which might be characterized by a lack of inhibitory control to repetitive nonpainful somatosensory information during stimulus coding and cognitive evaluation [35].

Recently, there has been accumulating evidence that chronic pain is associated with changes in brain anatomy. The brain imaging studies of FM that measured regional cerebral blood flow (rCBF) at rest using positron emission tomography (PET) or single photon emission computed tomography (SPECT) have shown hypoperfusion in various brain regions of FM patients compared to controls [40, 42]. Consistent with the findings of hypoperfusion in the thalamus is a recent structural study reporting decreased gray matter density in the thalamus of FM patients [43]. In a study that evaluated 14 FM patients and 14 healthy controls, Burgmer et al [44] found decreased gray matter volume in several brain region, including the prefrontal cortex, the amygdale, and anterior cingulated cortex (ACC). The functional significance of gray matter atrophy in FM might include a decreased capacity for endogenous pain inhibition and impaired cognitive functioning in FM [45]. ACC play an essential role in selective attention [46]. The prefrontal cortex is critically involved not only in pain modulation, but also in executive functioning, attention, and recognition and especially in the free recall [11, 46, 48].

The other determining area in cognitive function is hippocampus. The hippocampus is an integral component of limbic system, and it plays crucial roles in maintenance of cognitive function, and sleep regulation. More recently, in a case study by Emad et al it was suggested that the hippocampus was dysfunctional in patients with FM [47]. The hippocampus is critically involved not only in memory and spatial orientation but also in pain perception and modulation of the central stress responses, all of which are altered in FM [45].

Several different hypotheses can be formulated about the mechanism determining these cognitive defects in RA. Firstly, a disconnection between cortical and subcortical areas due to vasculitis located at the small penetrating arterioles can be postulated [48]. A further hypothesis that may explain the cognitive impairment in RA is related to deafferentation: a defective proprioceptive input to the brain from joints altered by inflammation and chronic damage could cause an impairment in the cognitive mechanisms of elaboration and planning motor activity [49].

The results of the present and previous studies are important for our understanding of the pathophysiology of FM. However, the relationship between CNS alterations and FM is still unclear. That FM is a primary disorder of the brain or all the changes in the brain could be driven by physiological alterations outside the brain is yet to be answered. The other idea is that FM might not be primary disorder of the brain in the sense that CNS alterations might not be at the beginning in the chain of events leading to FM. It is not clear whether CNS changes are the primer reason of FM or the result of chronic pain.

The results of this study suggests that many of the comorbid symptoms such as pain, fatigue often present in FM can have a negative impact on cognitive functions. FM patients might devote less effort to cognitive testing due to ongoing pain and fatigue or the belief that they will not perform well. But these do not seem to completely explain the cognitive dysfunction. The current research and our study show common involvement rather than specific areas of the brain in FM. However, due to use of different cognitive tests in previous studies, it is difficult to fully evaluate the results. In this study we had some limitations. More important limitations of the present study are the lack of new techniques of brain imaging such as SPECT imaging, PET and MRI of patients. Another limitation was the relatively low number of patients. The larger patient numbers were required for a more accurate profile of impairment to emerge. Further studies of cognition in FM could lead to a better understanding of CNS mechanisms responsible for fibromyalgia. Future research should focus on the specific neurocognitive systems involved in cognitive dysfunction in FM.

Competing interests

The authors declare that they have no competing interests.

References

1. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL,et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committe. Arthritis Rheum 1990;33(2):160-72.

2. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristic of fibromyalgia in the general population. Arthritis Rheum 1995;38(1):19-28.

3. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2.596 people with fibromyalgia. BMC Musculoskel Disord 2007;8:27.

4. Katz RS, Heard AR, Mills M, Leavitt F. The prevalence and clinical impact of reported cognitive difficulties (fibrofog) in patients with rheumatic disease with

and without fibromyalgia. J Clin Rheumatol 2004;10(2):53-8.
5. Leavitt F, Katz RS. Distraction as a key determinant of impairment memory in patients with fibromyalgia. J Rheumatol 2006; 33(1):127-32.
6. Glass JM, Park DC, Minear M, Crofford LJ. Memory beliefs and function in fibromyalgia patients. J of Psychosomatic Research 2005;58(3):263-9.
7. Grace GM, Nielson WR, Hopkins M, Berg MA. Concentration and memory deficitis in patients with fibromyalgia syndrome. J Clin Exp Neuropsychol. 1999;21(4):477-87.
8. Park DC, Glass JM, Minear M, Crofford LJ. Cognitive Function in Fibromyalgia Patients. Arthritis Rheum 2001; 44(9):2125-33.
9. Landro NI, Stiles TC, Sletvold H. Memory functioning in patients with primary fibromyalgia and major depression and healthy controls. J Psychosom Res 1997;42(3):297-306.
10. Clauw DJ, Morris S, Starbuck V. Impairment in cognitive function in individuals with fibromyalgia. Arthritis Rheum 1999;37 (suppl 9):347.
11. Glass JM. Cognitive dysfunction in fibromyalgia syndrome. J Musculokeletal Pain 2010;18(4):367-71.
12. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS. The American Rheumatism Association 1987: revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-24.
13. American Psychiatric Association Diagnostic and Statistical Manual of mental Disorders, Fourth Edition.Washington, DC:American Psychiatric Press, 1994.
14. Özkürkçügil A, Aydemir Ö, Yıldız M. Adaptation and reliability study of structured clinical interview for DSM-IV axis I disorders. Turkish J Drug Ther 1999;12(3):233-6.
15. Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol 2005;23(Suppl. 39):154-62.
16. Burckhardt CS, Clark SR, Bennett RM. The Fibromyalgia Impact Questionnaire (FIQ): development and validation. J Rheumatol 1991;18(5):728-33.
17. Weintraub S. Neuropsychological assessment of mental state, in principles of behavioral and cognitive neurology, Edited by Mesulam M. New York, Oxford University Press, 2000, p. 121-73.
18. Lezak MD. Neuropsychological assessment. New York, Oxford University Press, 1983.
19. Delis DC, Kramer JH, Kaplan E. California Verbal Learning Test: Adult version. San Antanio, The Psychological Corporation, 1987.
20. Heaton RK, Chelune GJ, Talley JL. Wisconsin Card Sorting Test Manual, revised and expanded. Odessa, Fla, Psychological Assessment Resources, Inc 1993.
21. Kewman DG, Vaishampayan N, Zald D, Han B. Cognitive impairment in musculoskeletal pain patients. Int J Psychiatry Med 1991;21(3):253-62.
22. Lee DM, Pendleton N, Tajar A, O'Neill TW, O'Connor DB, Bartfai G et al. Chronic widespread pain is associated with slower cognitive processing speed in middle-aged and European men. Pain 2010;151(1): 30-6.
23. Sletvold H, Stiles TC, Landro NI. Information processing in primary fibromyalgia, major depression, and healthy controls. J Rheumatol 1995; 22(1):137-42.
24. Suhr JA. Neuropsychological impairment in fibromyalgia relation to depression, fatiue, and pain. J Psychosom Res 2003;55(4):321-9.
25. Salthouse TA. The processing-speed theory of adult age differences in cognition. Psychological Reiew 1996;103(3):403-28.
26. Dick BD, Verrier MJ, Harker KT, Rashiq S. Distruption of cognitive function in fibromyalgia syndrome. Pain 2008;139(3):610-6.
27. Kimberg DY, D'Esposito M, Farah MJ. Cognitive functions in the prefrontal cortex-working memory and executive control. Current Directions in Psychological Science: Cambridge University Press 1998;185-92.
28. Johansson G, Risberg J, Rosenhall U, Orndahl G, Svennerholm L, Nyström S. Cerebral dysfunction in fibromyalgia:evidence from regional cerebral blood flow mesurements, otoneurological tests and cerebrospinal fluid analysis. Acta Psychiat Scand 1995;91(2):86-94.
29. Verdejo-Garcia A, Lopez-Torrecillas F, Calandre EP, Delgado-Rodríguez A, Bechara A. Executive function and decision-making in women with FM. Arch Clin Neuropsychol 2009;24(1):113-22.
30. Cote KA, Moldofsky H. Sleep, daytime symptoms, and cognitive performance in patients with fibromyalgia. J Rheumatol 1997;24(10):2014-23.
31. Dinges DF, Barone-Kribbs N. Performing while sleepy: effects of experimentally- induced sleepiness. In:TH Monk, ed. Sleep, sleepiness and performance. New York:john Wiley, 1991; 97-128.
32. Roth SR, Geisser ME, Theisen-Goodvich M, Dixon PJ. Cognitive complaints are associated with depression, fatigue, female sex, and pain catastrophizing in patients with chronic pain. Arch Phys Med Rehabil 2005;86(6):1147-54.
33. Niemi PM, Portin R, Alto S, Hakala M, Karlsson H. Cognitive functioning in severe somatization: a pilot study. Acta Psychiatr Scand 2002;106(6):461-3.
34. Williams DA, Gracely RH. Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. Arthritis Res Ther 2006;8(6):224.
35. Monyoto P, Sitges C, Garcia-Herrera M, Rodríguez-Cotes A, Izquierdo R, Truyols M et al. Reduced brain habituation to somatosensory stimulation in patients with fibromyalgia. Arthritis Rheum 2006;54(6);1995-2003.
36. Giesecke T, Gracely RH, Grant MA. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum 2004;50(2):613-23.
37. Staud R, Domingo M. Evidence for abnormal pain processing in fibromyalgia syndrome. Pain Med 2001;2(3):208-15.
38. Bennett R. Fibromyalgia: present to future. Curr Rheum Rep 2005;7(5):371-6.
39. Desmeules JA, Cedraschi C, Rapiti, Baumgartner E, Finckh A, Cohen P et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum 2003;48(5):1420-9.
40. Schweinhardt P, Sauro KM, Bushnell MC. Fibromyalgia: A disorder of the brain. Neuroscientist 2008;14(5): 415-2.
41. Arendt-Nielsen L, Henriksson KG. Pathophysiological mechanisms in chronic musculoskeletal pain(fibromyalgia):the role of central and peripheral sensitization and pain disinhibision. Best Pract Res Clin Rheum 2007; 21(3):465-80.
42. El-Gabalaway H, Ryner L. Central nervous system abnormalities in fibromyalgia: Assessment using proton magnetic resonance spectroscopy. J Rheumatol 2008;35(7):1242-4.
43. Scmidt-Wilcket T, Luerding R, Weiand T, Jürgens T, Schuierer G, Leinisch E et all Striatal grey matter increase in patients suffering from fibromyalgia-a voxel-based morphometry study. Pain 2007;132(Suppl 1):109-16.
44. Burgmer M, Gaubitz M, Konrad C, Wrenger M, Hilgart S, Heuft G, et al. Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with FM. Psychosomatic Med 2009;71(5):566-73.
45. Canovas R, Leon I, Roldan MD, Astur R, Cimadevilla JM. Virtually reality tasks disclose spatial memory alterations in fibromyalgia. Rheumatology 2009;48(10):1273-8.
46. Luerding R, Weigand T, U Bogdahn, Schmidt-Wilcke T. Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in FM patients: structural correlates of pain-cognition interaction. Brain 2008;31:3222-31.
47. Emad Y, Ragad Y, Zeinbom Z, El-Khouly G, Abou-Zeid A, Rasker JJ. Hippocampus dysfunction may explain symptoms of fibromyalgia syndrome. A study with single-voxel magnetic resonance spectroscopy. J Rheumatol 2008;35(7):1371-7.
48. Puechal X, Said G, Hilliquin P, Coste J, Job-Deslandre C, Lacroix C, Menkès CJ. Peripheral neuropathy with necrotizing vasculitis in rheumatoid arthritis. Arthritis Rheum 1995;38(11):1618-29.
49. Bartolini M, Candela M, Brugni M, Catena L, Mari F, Pomponio G et al. Are behaviour and motor performances of rheumatoid arthritis patients influenced by subclinical cognitive impairments? A clinical and neuroimaging study. Clin Exp Rheumatol 2002;20(4):491-7.