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Cognitive Function in Fibromyalgia Patients

Denise C. Park, Jennifer M. Glass, Meredith Minear, and Leslie J. Crofford

Objective. **To evaluate fibromyalgia (FM) patients for the presence of cognitive deficits and to test the hypothesis that abnormalities would fit a model of cognitive aging.**

Methods. **We studied 3 groups of patients: FM patients without concomitant depression and in the absence of medications known to affect cognitive function (n = 23), age- and education-matched controls (n = 23), and education-matched older controls who were individually matched to be 20 years older (±3 years) than the FM patients (n = 22). We measured speed of information processing, working memory function, free recall, recognition memory, verbal fluency, and vocabulary. We correlated performance on cognitive tasks with FM symptoms, including depression, anxiety, pain, and fatigue. We also determined if memory complaints were correlated with cognitive performance.**

Results. **As expected, older controls performed more poorly than younger controls on speed of processing, working memory, free recall, and verbal fluency. FM patients performed more poorly than age-matched controls on all measures, with the exception of processing speed. FM patients performed much like older controls, except that they showed better speed of processing and poorer vocabulary. Impaired cognitive performance in FM patients correlated with pain complaints, but not with depressive or anxiety symptoms. FM patients reported more memory problems than did the older and younger controls, and these complaints correlated with poor cognitive performance.**

Conclusion. **Cognitive impairment in FM patients, particularly memory and vocabulary deficits, are documented in this study. Nevertheless, the intact performance on measures of information processing speed suggests that the cognitive deficits are not global. FM patients' complaints about their memory are likely to be legitimate, since their memory function is not age appropriate.**

Fibromyalgia (FM) is a disorder of uncertain etiology characterized by widespread musculoskeletal pain and the presence of at least 11 of 18 designated tender points distributed across soft tissues (1). Patients frequently report diminished cognitive performance, but few objective data are available on this topic, which is surprising, given the frequency of, and considerable disability associated with, cognitive complaints in FM.

Sletvold et al (2) examined a number of cognitive tasks in FM patients and found evidence of declines in the speed of processing and working memory. Speed and working memory are the building blocks of cognitive function and predict long-term memory (3) and reasoning (4). Speed of information processing is measured by how rapidly an individual can make simple perceptual decisions, and working memory is measured by how much information a person can simultaneously store and process—it is an index of the "mental horsepower" that an individual brings to any given situation. In a later study, Landro et al (5) evaluated long-term memory performance and found that FM patients performed more poorly on many measures of recall. When only nondepressed FM patients were examined, the investigators did not find such differences. However, in every non–statistically significant comparison between the nondepressed FM patients and the healthy controls, the FM patients performed worse. Although the study had limited power, the findings were suggestive of memory differences in FM patients.

In a recent study, Grace et al (6) found that FM patients evidenced intact speed of processing, but decreased working memory and long-term memory. They found that self-reported anxiety and pain correlated with working memory and long-term memory function. Cote

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Denise C. Park, PhD, Jennifer M. Glass, PhD, Meredith Minear, MS, Leslie J. Crofford, MD: University of Michigan, Ann Arbor.

Address correspondence and reprint requests to Denise C. Park, PhD, Department of Psychology, 3042 East Hall, The University of Michigan, Ann Arbor, MI 48109.

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and Moldofsky (7) also reported that FM patients had poor cognitive performance on complex cognitive tasks, and they related the abnormalities to poor stage 1 sleep quality. However, many of the effects those investigators found became nonsignificant when education was controlled, so that the deficits they observed are of doubtful significance. Overall, the limited extant data suggest that FM patients perform more poorly on a range of cognitive tasks. The studies are limited by small sample size, poorly matched patients and controls, and, in some cases (6), failure to eliminate pharmacologic agents that could have affected cognitive performance.

In the present study, we examined evidence of cognitive dysfunction in FM patients and addressed the appropriateness of FM patients' cognitive complaints. Grace et al (6) and Pincus et al (8) found that FM patients reported significantly greater memory problems than did controls. Finally, because the hypothalamic–pituitary–adrenal axis function in FM patients is similar to that in older adults (9), we considered whether FM patients might also have cognitive function similar to that of older adults, which might account for their high rate of memory complaints. It is well documented that speed of processing, working memory, and long-term memory decline continuously across the adult lifespan beginning in the second decade of life (10,11). Thus, to better understand cognitive function in FM patients, we included an older control group that consisted of individuals who were 20 years older than the FM patients and were matched for education level, as well as a traditional control group of age- and education-matched subjects.

PATIENTS AND METHODS

Subjects. We studied 3 different groups of female subjects: 23 FM patients, 23 healthy age-matched controls, and 22 older adults. The FM patients were recruited from the Rheumatology Clinic at the University of Michigan and met the American College of Rheumatology (ACR) classification criteria for FM. The patients did not have any other rheumatic diseases or significant health conditions. All patients underwent structured clinical interviews for diagnosis of disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; patients with a major depressive disorder or other major axis I diagnoses were excluded. Prior to testing, patients discontinued all psychoactive medications for 2 weeks, with the exception of selective serotonin-reuptake inhibitors, since these agents do not inhibit cognitive functioning (12).

The second group of subjects consisted of 23 female volunteers recruited from the community and matched individually to each FM patient for age and education. The third group of subjects consisted of 22 women individually matched to the FM patients for age plus 20 years (±3 years) and for education. None of the control subjects in either age group were taking psychoactive medication, nor did they have a current psychiatric diagnosis.

Table 1. Demographic characteristics of the study subjects*

	Fibromyalgia patients (n = 23)	Age-matched controls (n = 23)	Older controls (n = 22)
Age	47.83	47.83	66.91
Education	14.34	14.39	14.50

* All participants were women. Each older control subject was 20 years older (±3 years) than her matched fibromyalgia patient. The fibromyalgia patients discontinued medications (except for selective serotonin-reuptake inhibitors) 2 weeks prior to the beginning of the study.

None of the subjects in any group were smokers. All subjects signed informed consent forms that had been approved by the University of Michigan Institutional Review Board. The age and education of the 3 groups of subjects are displayed in Table 1.

Cognitive testing. Each testing session began at 1:00 PM. Cote and Moldofsky (7) reported that FM patients rated themselves as having the least fatigue and the least negative affect during the early afternoon. Thus, we were testing FM patients at a perceived optimum time of day. The cognitive testing occurred in 3 blocks, with all 3 blocks administered successively and completed in a single 2-hour session. Each block of cognitive tests included measures of 6 domains of cognitive function: speed of information processing, working memory capacity, long-term recall, recognition memory, verbal fluency, and vocabulary. Each task had 3 versions, 1 version in each block. The versions were all highly comparable to one another.

The 6 cognitive domains and the 3 tasks associated with each are described below. The presentation order was the same for all subjects.

Information-processing speed. Speed of information processing is fundamental to predicting performance on many higher-order cognitive tasks (10,13). This task is highly age sensitive and is a measure of how rapidly an individual can perform mental operations. The 3 tasks used were number comparison, pattern comparison, and letter comparison. Administration was identical for all 3 tasks. Subjects received sheets of paper with many pairs of digit strings, letter strings, or angular figures printed on them, depending on the tasks. They were required to make "same/different" judgments about the pairs as rapidly as possible. Each test had 3 parts that lasted 30 seconds each. In the first part, subjects made judgments of strings of 3 numbers or letters, or abstract figures with 3 line segments. In the second part, there were 6 segments to the items compared, and 9 segments in the last section. The score for each speed task is the sum of all correct comparisons completed on each of the 3 parts.

Working memory capacity. Working memory is a measure of how much information an individual can simultaneously process and store in consciousness. We used 3 computer-based versions of this task—2 versions of reading span and 1 version of computational span (14). The reading

span tasks involved presenting subjects with factual sentences and asking them multiple choice questions about the sentence immediately afterward. At the same time they were to answer the question about the sentence, they were to also remember the last word in the sentence. After seeing a certain number of sentences (between 1 and 6), subjects would be asked to recall the words from each presented sentence in order. Working memory span was measured by how many successive items for which subjects could both answer the question and remember the final word in the sentence without an error in either. Computational span is similar, except that subjects solve simple equations (e.g., 8 + 2) and choose the correct answer from a multiple choice computer display (e.g., "10") , but must also remember the last number in the equation (e.g., "2"). Subjects received 3 trials at each level of difficulty (e.g., 2 sentences in a row per trial, then 3 sentences in a row per trial). The total number of correct responses (i.e., correct on both the questions and recall of the final words) was summed across trials.

Free recall. Free recall is a measure of long-term memory and the ability to actively retrieve past episodic events. A list of items is presented for memorization, and then recall is tested. In free recall, subjects may recall the items in any order. Older adults recall fewer items than young adults in this memory paradigm (3). We tested free recall using 3 different 16-word lists of common nouns. Word lists were matched for frequency of occurrence in the English language. For each list, subjects studied 16 words presented one-at-a-time on the computer screen. Each word appeared for 5 seconds. Subjects were instructed to study the words and try to remember them. At the end of the list, the word "recall" appeared on the screen. This prompted subjects to write down as many words as they could remember, in any order, on their answer sheets. The score was the number of words correctly recalled.

Recognition memory. Recognition memory is a measure of a subject's ability to recognize a previously studied item. Because no active retrieval from memory is required, age differences tend to be small here, and we expected that the FM patients might perform as well as the age-matched controls on this task. For this task, subjects studied 32 words. Then they were presented with 32 more items—half from the studied list and half that were new. The subject's task was to identify each item as "old" (studied earlier) or "new" (never studied). There were 3 tests, 1 in each block; word frequency in the language was equated across the 3 lists. The dependent measure was d', an estimate of how effectively subjects can discriminate old from new items. A d' of zero indicates that a subject was unable to discriminate the old from the new items and essentially had no memory for them.

Verbal fluency. This task relies on the ability of the subject to quickly and efficiently retrieve information from their existing knowledge stores. It is age sensitive, in that it requires active retrieval or mental effort, and we expected that FM patients might have difficulty with this task. We used the F-A-S verbal fluency test (15). On each block of testing, subjects were given a sheet of paper with the letter F, A, or S on top. They were given 90 seconds to write down as many words as they could that began with the letter that was written on the page. The dependent measure was the number of words produced, excluding repeated words.

Verbal knowledge. We used 3 vocabulary tests to assess verbal knowledge. This task, like verbal fluency, relies on knowledge. It is different from verbal fluency in that it does not require active retrieval. Subjects were given a series of words in a multiple choice format. In the Antonym Task (14), they were to select the antonym of each word, in another test, the synonym of the word, and in the Shipley Institute of Living Vocabulary Test (16), they were to select a synonym of the word.

Assessment of depression, anxiety, pain, fatigue, and memory complaints. Ratings instruments, along with a demographic/health questionnaire, were completed before the cognitive testing. Depressive symptoms were measured with 2 questionnaires, the Beck Depression Inventory (BDI) (17) and the Geriatric Depression Scale (GDS) (18). The BDI has typically been used in FM research; the GDS was also used because it has less focus on somatic symptoms and might therefore be a more accurate assessment of depressive symptoms in FM patients independently of their health complaints.

Anxiety was measured with the Anxiety subscale of the Mental Health Inventory (19). Pain was measured with the McGill Pain Questionnaire (MPQ) (20) and with the Pain subscale of the Arthritis Impact Measurement Scales (AIMS) (21). Fatigue was measured with a questionnaire that we patterned after the AIMS Pain subscale; it measured the impact of fatigue on daily activities. Beliefs about memory function were measured with the Pincus Cognitive Symptoms Inventory (8). This inventory focuses on everyday cognitive tasks, such as remembering shopping items without a list, dialing a telephone number, or remembering the location of common items such as keys.

Study design and analysis. To test our hypotheses about differences in cognitive performance between the 3 groups, we first used a between-groups experimental design. Multivariate analysis of variance (MANOVA) was used to assess the overall between-group effects across the 6 cognitive domains. With a significant overall multivariate effect, planned univariate comparisons were completed to assess group differences for individual cognitive domains.

RESULTS

Cognitive measures. Although we expected interesting interactions of patient groups over time (e.g., effects of fatigue), preliminary analyses indicated that no main effects or interactions emerged as a function of the testing block on any tasks. That is to say, the performance of subjects in all groups was unchanged on each test across the 3 testing blocks. Thus, we report aggregate performance on the 3 tests and will not report analyses across the blocking measure.

A MANOVA was conducted on the 6 cognitive measures, with group as the independent variable. The MANOVA yielded a significant group effect (Pillai's trace[12,124] = 2.465, $P = 0.006$). To further assess these group effects, planned univariate analyses (1-tailed paired t-tests except where noted otherwise) for individ-

Table 2. Performance on the cognitive tasks, by study group*

	Fibromyalgia patients (n = 23)	Age-matched controls (n = 23)	Older controls (n = 22)
Information-processing speed	139.45 ± 29.55	139.23 ± 29.55	118.50 ± 19.15
Working memory	22.22 ± 7.85	26.30 ± 1.67	22.09 ± 6.27
Free recall	23.56 ± 7.80	27.83 ± 6.43	23.91 ± 6.77
Recognition memory	2.53 ± 1.19	2.95 ± 1.07	2.80 ± 1.19
Verbal fluency	49.78 ± 11.63	56.08 ± 15.65	49.43 ± 13.74
Verbal knowledge	43.17 ± 7.62	51.26 ± 6.01	50.56 ± 7.93

* Values are the mean ± SD.

ual cognitive tests are described below. The means and standard deviations for each cognitive domain are shown in Table 2.

Age-matched controls compared with older controls. We first established that we observed typical patterns of cognitive aging in the older versus the younger control groups. Older adults typically have poorer performance on measures that require intensive processing or active retrieval, and show small effects or no effects on recognition memory. In contrast, age differences in world knowledge are either absent or in favor of older adults (10). We observed this pattern of effects in the present sample, despite only a 20-year difference between older and younger subjects. The older subjects performed more poorly than the younger, age-matched control group on measures of information-processing speed ($t[21] = 2.5$, $P = 0.011$), working memory capacity ($t[21] = 1.929$, $P = 0.034$), free recall ($t[21] = 2.687$, $P = 0.007$), and verbal fluency ($t[21] = 1.937$, $P = 0.033$). There were no differences between these groups on measures of recognition memory ($t[21] = 0.615$, $P = 0.545$) and verbal knowledge ($t[21] = 0.674$, $P = 0.508$).

FM patients compared with age-matched controls. Next, we examined the performance of FM patients compared with age-matched controls. We noted cognitive differences in a number of domains. The FM patients performed more poorly than the age-matched control group on measures of working memory capacity ($t[22] = 1.811$, $P = 0.042$), free recall ($t[22] = 2.881$, $P = 0.005$), recognition memory ($t[22] = 1.915$, $P = 0.035$), and verbal knowledge ($t[22] = 4.06$, $P < 0.001$). Performance on verbal fluency was marginally worse in the FM patients compared with the age-matched controls ($t[22] = 1.667$, $P = 0.055$). There was no difference in performance for the information-processing speed ($t[22] = 0.031$, $P = 0.975$).

FM patients compared with older controls. The performance of the FM patients was similar to that of the older controls on measures of working memory ($t[21] = 0.103$, $P = 0.909$), free recall ($t[21] = 0.549$, $P = 0.588$), recognition memory ($t[21] = 1.394$, $P = 0.177$), and verbal fluency ($t[21] = 0.14$, $P = 0.89$). However, there were 2 important areas where FM patients performed differently from older controls. First, the FM patients were significantly faster on measures of information-processing speed ($t[21] = 2.721$, $P = 0.013$, 2-tailed) compared with older controls, suggesting that basic information-processing speed was intact. In contrast to this, FM patients performed more poorly than older controls on measures of verbal knowledge ($t[21] = 2.886$, $P = 0.009$, 2-tailed).

Psychological measures. A MANOVA was conducted on the psychological measures, with group as an independent variable. The psychological measures included 6 measures: 2 of depression, 2 of pain, 1 of anxiety, and 1 of fatigue. The means for these variables as a function of group are shown in Table 3. The MANOVA yielded a significant group effect (Pillai's trace[12,120] = 6.323, $P < 0.001$). To further assess these group effects, planned univariate analyses (one-way ANOVA) for individual psychological measures are described below. It should be noted that the cutoff scores for mild depression for the BDI and GDS are 19 and 15, respectively. Thus, due to initial screening, no group in the study had a mean score that was indicative of even mild depression.

Age-matched controls compared with older controls. In general, older controls reported somewhat more depression, fatigue, and pain than the younger controls. The older control subjects reported more depressive symptoms than the age-matched control group on the BDI ($F[1,42] = 7.845$, $P = 0.008$). The difference between these groups on the GDS did not reach significance ($F[1,42] = 2.906$, $P = 0.096$). There was no significant difference in anxiety for older controls and age-matched controls ($F[1,44] = 0.002$). Older controls reported more fatigue ($F[1,44] = 4.416$, $P = 0.041$).

Table 3. Psychological measures, by study group*

	Fibromyalgia patients (n = 23)	Age-matched controls (n = 23)	Older controls (n = 22)
Beck Depression Inventory	15.21 ± 10.92	4.05 ± 3.30	7.82 ± 5.39
Geriatric Depression Scale	11.96 ± 6.40	3.77 ± 3.34	5.91 ± 4.84
Anxiety†	36.17 ± 9.48	44.26 ± 5.62	44.17 ± 7.79
Fatigue	29.29 ± 5.55	13.70 ± 4.97	17.02 ± 5.74
McGill Pain Questionnaire	33.75 ± 9.15	9.57 ± 7.05	15.30 ± 13.35
AIMS Pain subscale	30.17 ± 6.64	9.98 ± 3.88	15.04 ± 6.85

* Values are the mean ± SD. AIMS = Arthritis Impact Measurement Scales.
† Higher scores indicate less anxiety.

Older controls also reported more pain on the AIMS Pain subscale ($F[1,44] = 9.516$, $P = 0.004$), but the difference on the MPQ did not reach significance ($F[1,44] = 3.322$, $P = 0.075$).

FM patients compared with age-matched controls. The FM patients reported more depressive symptoms on the BDI ($F[1,44] = 21.183$, $P < 0.0001$) and on the GDS ($F[1,44] = 28.75$, $P < 0.0001$). The FM patients reported more anxiety ($F[1,45] = 12.538$, $P = 0.001$) and more fatigue ($F[1,45] = 102.815$, $P < 0.0001$). The FM patients also reported more pain on the MPQ ($F[1,45] = 102.423$, $P < 0.0001$) and on the AIMS Pain subscale ($F[1,45] = 160.145$, $P < 0.0001$).

FM patients compared with older controls. The FM patients reported more depressive symptoms than the older controls on the BDI ($F[1,44] = 8.231$, $P = 0.006$) and on the GDS ($F[1,44] = 12.881$, $P = 0.001$). The FM patients reported more anxiety ($F[1,45] = 9.959$, $P = 0.003$) and more fatigue ($F[1,45] = 55.556$, $P < 0.0001$). The FM patients also reported more pain on the MPQ ($F[1,45] = 30.753$, $P < 0.0001$) and on the AIMS Pain subscale ($F[1,45] = 59.085$, $P < 0.0001$).

Memory complaints. A one-way ANOVA was conducted on the scores on the Pincus Cognitive Symptoms Inventory, with group as the independent variable. Older controls reported more cognitive problems than the age-matched controls ($F[1,44] = 3.989$, $P = 0.052$). FM patients also reported more cognitive problems than either the age-matched controls ($F[1,45] = 38.99$, $P < 0.0001$) or the older controls ($F[1,45] = 25.447$, $P < 0.0001$).

Relationship of psychological variables to cognitive performance in FM patients. To assess the relationship of the psychological measures to cognitive performance and to cognitive complaints, we correlated the 6 psychological measures with the 6 cognitive variables and with the memory complaint measure for FM patients. These correlations allowed us to determine if patients who scored high on depression, anxiety, pain, or fatigue performed more poorly on cognitive measures or had higher numbers of memory complaints. Of particular interest was whether depression or anxiety had a significant relationship to cognitive function, since this has been suggested in previous research.

We did not find any significant correlations between the anxiety, the BDI, or the GDS and the cognitive measures. In contrast, the AIMS Pain subscale correlated highly with 4 cognitive measures: information-processing speed ($r = -0.662$, $P = 0.001$), working memory capacity ($r = -0.466$, $P = 0.022$), free recall ($r = -0.607$, $P = 0.002$), and recognition memory ($r = -0.555$, $P = 0.005$). The MPQ correlated only with free recall ($r = -0.441$, $P = 0.031$). The difference in correlations between the 2 pain measures may be due to the focus of the AIMS on the functional impact of pain, rather than on the level of pain itself. There were no other significant correlations among the psychological and cognitive measures.

We also found that cognitive complaints were correlated with poor cognitive function in FM patients. When a measure of the total number of cognitive problems experienced most or all of the time was correlated with the 6 cognitive performance measures, there were significant correlations for information-processing speed ($r = -0.507$, $P = 0.005$), working memory capacity ($r = -0.406$, $P = 0.049$), and free recall ($r = -0.448$, $P = 0.028$).

DISCUSSION

The major findings from this study are as follows. First, FM patients performed more poorly on most cognitive measures compared with age- and education-matched controls, although they did evidence intact speed of information processing. Second, FM patients performed no differently from healthy adults 20 years

Table 4. Subject-by-subject matching for education and age (or age plus 20 years)

Age (years)			Education (years)		
Fibromyalgia patients (n = 23)	Age-matched controls (n = 23)	Older controls (n = 22)	Fibromyalgia patients (n = 23)	Age-matched controls (n = 23)	Older controls (n = 22)
55	53	75	13	13	13
53	53	75	17	17	17
56	54	78	13	13	13
48	49	69	16	16	16
42	44	62	12	13	12
29	27	50	16	16	16
57	56	76	12	13	13
47	49	66	17	17	17
59	61	79	13	12	13
46	44	64	18	17	17
52	50	70	13	13	13
51	53	69	16	16	16
46	45	64	16	16	16
49	47	69	17	17	17
37	36	54	13	13	13
58	62	–	11	12	–
45	45	64	12	12	12
46	45	64	17	17	17
31	30	55	16	16	16
39	41	59	13	13	13
54	52	74	13	13	13
46	46	66	13	13	13
54	58	73	13	13	13

older than their chronological age on most cognitive tasks, except that FM patients had a faster rate of information processing and poorer verbal knowledge than older adults. Third, within the FM group, only self-reported pain on the AIMS predicted poor cognitive performance. Measures of depression, anxiety, and the MPQ scores were all unrelated to poor cognitive performance in FM patients. Finally, cognitive complaints in FM patients were significantly correlated with poorer memory performance.

Cognitive performance of FM patients relative to age-matched controls. The finding that FM patients performed more poorly on measures of working memory function, free recall, verbal fluency, and verbal knowledge, but showed intact speed of processing relative to age-matched controls confirms the report by Grace et al (6), who found an almost identical pattern. Those investigators reported that although FM patients processed information as rapidly as age-matched controls, they had poorer working memory and long-term memory function. They matched their FM patients for reading ability, rather than for age and education as we did in the present study, and they did not collect measures of verbal knowledge.

We were surprised by the FM patients' poor performance on verbal knowledge tasks and considered the possibility that the poorer performance relative to age-matched controls could be due to imprecise subject matching for years of education or age, with FM having lower education or being older than their controls. However, as shown in Table 4, control subject matching was impeccable with respect to both age and education and cannot account for the differences observed. We believe that decreased access to word knowledge is a feature of cognitive dysfunction in FM, particularly since these findings confirm the frequently reported symptom by FM patients of decreased availability of word meaning. Thus, although further study is merited, the finding of decreased access to verbal knowledge appears reliable in the present study.

The fact that speed of processing was intact in FM patients suggests that the most basic and global information-processing ability—how fast we process new information—is not a problem for FM patients. Our findings do indicate that FM patients have more limited working memory and long-term memory than do age-matched controls. The cognitive symptoms described by these patients are likely to be related to difficulties in these domains.

One other important point with respect to the

FM patients is that they did not show any evidence of fatigue across testing blocks. We had hypothesized that the performance of the FM patients would deteriorate steadily over time, and we had 3 versions of each cognitive test performed at 3 different times within the 2-hour session. No subject group showed fatigue effects or evidence that their performance improved or decreased across these 3 test intervals. Thus, in addition to confirming evidence of cognitive dysfunction in FM patients, this study also found that the dysfunction is not exacerbated over a 2-hour period of intensive cognitive performance.

Similarities of FM to cognitive aging. If one excludes performance on information-processing speed and a recognition memory task that is relatively low in cognitive demands, FM patients performed much like adults 20 years older on measures of working memory and long-term memory. From a practical standpoint, this suggests that FM patients have as much trouble as older adults in harnessing working memory to perform cognitive tasks and, moreover, that they have more trouble remembering information once it is processed in their working memory. As noted above, however, cognitive aging is an imperfect model for FM, since FM patients differed from older adults in that they had intact information-processing speed.

Speed of processing is fundamental to nearly all cognitive abilities and is viewed as a global indicator of neurobiologic deterioration in elderly adults (22). Speed decreases that occur with age have been hypothesized to be related to age-related declines in dopamine receptors, decreased brain weight, increased dendritic branching that leads to circuitous cognitive processing, or decreases in myelin sheath (23,24). The failure to find a speed deficit in both this study and the study by Grace et al (6) is certainly good news for FM patients and suggests that the cognitive dysfunction associated with FM cannot be viewed simply as accelerated cognitive aging.

The processes that did decline in FM patients similarly to elderly adults, working memory function and encoding and retrieving words (the long-term memory task), have known neurobiologic substrates. Working memory and encoding and retrieval operations are functions that reside primarily in the dorsolateral prefrontal cortex (25,26). Moreover, there is evidence from the neuroimaging literature that older adults show compensatory hemispheric recruitment on working memory tasks. For example, younger adults use primarily the left frontal cortex when performing a verbal working memory task, whereas older adults show evidence of activation in both the left and right hemispheres when performing the same task (27). Similar compensatory patterns have been observed for the encoding and retrieval of words in long-term memory in older adults (28).

Some of the debate regarding the neurobiologic basis for observed FM memory dysfunction could be resolved by determining whether FM patients show recruitment patterns in the frontal cortex typical of young or older adults. Evidence that FM patients recruited cortical tissue in the same way as older adults or showed compensation in other cortical areas (such as the parietal or visual cortex) compared with controls would be strong evidence for an underlying neurobiologic alteration in information processing in FM patients. In short, there is both compelling behavioral evidence as well as available noninvasive technology that should allow us to resolve the neurobiologic underpinnings of poor cognitive performance in FM patients (29,30).

Psychological correlates of poor cognitive performance. We found no evidence that anxiety or depression was correlated with poor cognitive performance in FM patients. On the one hand, this is not surprising, because patients were carefully screened for depression, and mean symptom scores were below those for mild depression. On the other hand, depression is frequently cited as a cause of poor cognitive performance in FM patients, and the FM patients in this study scored higher than controls for symptoms of depression. One of the hallmarks of depressed individuals, however, is slowed psychomotor performance (31), and the FM patients had intact speed of processing. The pattern of intact speed of processing but decreased function in working memory and long-term memory observed in FM patients is not a pattern that would be typical of depressed or poorly motivated adults.

The symptom that did correlate with poor cognitive performance in FM patients was self reports of pain on the AIMS Pain subscale (21) but not the MPQ (20). The AIMS primarily measures everyday dysfunction due to pain and the MPQ measures pain intensity in a more focused manner. Given that the cognitive measures showed the stronger relationship to pain-related dysfunction in everyday life, it suggests that memory dysfunction and activity-limiting pain are concomitants in FM. That is, it may be that chronic pain and cognitive dysfunction co-occur with FM. An alternative explanation is that the cognitive deficits observed in FM patients are due to their attention being diverted to coping with pain while performing the cognitive tasks, so that they have decreased cognitive resource available for performing the working memory and long-term memory tasks. However, this argument would suggest that the MPQ

would show the higher correlations with cognitive function, since it is a better measure of pain at the time of test-taking. In any case, this issue is an interesting and important one and can be addressed in future studies in which FM patients are tested with matched pain controls. Grace et al (6) also concluded that the possibility of pain interfering with cognition was interesting and worthy of further research.

Cognitive complaints and cognitive performance. There are 4 lines of evidence that suggest that the complaints of FM patients about their memory are legitimate. First, FM patients performed more poorly than aged-matched controls on a range of cognitive tasks, which suggests a legitimate basis for complaints about their memory. Second, FM patients performed much like older adults on many cognitive tasks, although the patients complained more about their memory than the older adults who performed similarly. However, the older adults' performance was normative for their age group, whereas the FM patients' performance was not normative for their age. Thus, the greater complaints about memory in younger FM patients compared with older adults who are performing similarly appear warranted. Third, in older adults, there is little relationship between memory complaints and memory performance (for review, see ref. 32). We were very surprised to see that in FM patients, there was a significant correlation between their memory complaints and their actual memory performance. This is very convincing evidence that FM patients' complaints about their memory are legitimate. Finally, given that there was no relationship between cognitive function and either depression, anxiety, or fatigue, but there was a relationship between cognitive function and memory complaints, there is little validity to the notion that psychological distress is the basis for memory dysfunction or complaints about memory in FM patients.

Conclusions and future directions. The present pattern of findings demonstrates that FM patients have cognitive function that is poorer than that in age-matched controls and similar to that in adults 20 years older with respect to working memory and long-term memory. An important difference between FM patients and older control subjects, however, is an intact speed of processing. This suggests that the etiology of their memory dysfunction is different from that in older adults, since the cognitive decline in older adults is mediated by deficits in the speed of processing. We view the intact speed of processing as a hopeful sign that FM memory deficits can be remedied. The correlation analyses suggest that the poor memory function is related to pain, although we cannot assign a causal role based on these studies. The FM patients have more memory complaints than do young or old controls, but these complaints correlate with cognitive performance.

The present study documents that complaints of memory dysfunction in FM patients are accompanied by true cognitive dysfunction. In this study, depression did not explain cognitive impairment. Rather, pain or other neurobiologic perturbations may account for the findings.

The present study was not designed to address the etiology of FM. However, we are working from a model that suggests that FM is a neurobiologic disorder that occurs in response to a physical or environmental stressor (e.g., a viral illness, a car accident, emotional trauma) that disrupts hypothalamic–pituitary–adrenal axis function (9), resulting in a cascade of disabling symptoms, including pain and measurable cognitive dysfunction. Much more research needs to be done on this puzzling disorder to understand the neurobiologic substrates of associated dysfunction and to determine the reversibility of the dysfunction as well as treatment mechanisms for the symptoms. Understanding such connections should lead to more effective treatment.

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