Fibromyalgia dyscognition: concepts and issues

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SUMMARY

Fibromyalgia is characterized by widespread pain and tenderness; however, comorbid cognitive difficulties are a common complaint among patients. Known as *fibro fog* or dyscognition, this symptom comprises difficulties with complex cognitive processes including memory, executive function, concentration and attention. While the mechanisms that initiate and maintain these cognitive deficits are still largely unknown, recent research has increased the understanding of subjective symptoms and objectively-determined deficits in cognitive performance. Treatments have also improved to include complementary cognitive and physical strategies. This review focuses on issues of dyscognition in fibromyalgia. Details of objective testing methods are not within the scope of this paper.

Key words: *Fibromyalgia, cognitive dysfunction, cognition.*

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INTRODUCTION

Fibromyalgia (FM) is characterized primarily by widespread pain and tenderness; however, comorbidities such as fatigue, poor sleep and cognitive impairments contribute substantially to the overall affective well-being of patients (1, 2). Cognitive difficulties are a common complaint of patients but until recently have not received much attention from the medical community. In a 2001 review, Glass (3) noted that the body of research devoted to cognitive impairments was small but supported deficits in access to working, semantic, and episodic memory.

Since 2001, the literature has grown significantly with an increased understanding of the nature of the deficits in cognitive processing and, importantly, the impact of distraction (4-6). In contrast, studies of the subjective experience of patients have lagged behind studies of objective function. Patients struggle to think clearly or quickly in everyday life situations (7). These negative symptoms have been referred to colloquially as *fibro fog*; more recently, the term *dyscognition* has been used to describe both the subjective symptoms and objectively-determined deficits in cognitive performance. There is also increased appreciation of the complementary positive effects of cognitive and physical treatment strategies on these cognitive symptoms (5, 8).

The mechanisms that initiate and maintain these cognitive deficits, however, are still largely unknown. They may manifest from the FM symptom complex including fatigue, poor sleep, pain, medication side effects, or even personality characteristics (9, 10) or altered neural mechanisms that mediate fibromyalgia (11-13).

This review focuses on issues of dyscognition without detailed descriptions of the testing paradigms.

Dyscognition is an important and prominent symptom in fibromyalgia

Dyscognition has always been included in the list of known symptoms of fibromyalgia; however, patients and clinicians have disagreed on its importance or overall impact. Two fairly recent independent studies have assessed patients' perceptions of symptom impact and importance; and in both studies, *fibro-fog* ranked among

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the top 5 complaints, along with pain and stiffness, aching joints, fatigue, and non-restorative sleep (7, 14). In contrast, Delphi evaluation of symptom importance among physicians found that dyscognition ranked 10th behind pain, fatigue, mood, treatment side effects and other considerations (15). This relative dismissal of the importance of dyscognition by physicians has been reflected also in research of fibromyalgia. A large number of studies have investigated pain and tenderness while relatively few have assessed cognitive difficulties. While it is understandable that investigators and clinicians focus on the cardinal symptom of pain or treatment side effects, there is clearly a discrepancy in symptom relevance between patients with fibromyalgia and those treating or investigating this disorder.

Studies have focused on objective tests of cognitive function rather than on subjective symptom reports

The lack of research on dyscognition in fibromyalgia is further compounded by a preference for objective tests of cognitive function rather than for subjective symptoms. Most studies of fibromyalgia dyscognition evaluate objective cognitive performance on specific tasks. Very few assess patients' reports of their cognitive difficulties (16).

Patient reports of dyscognition are not minor complaints. Difficulty with memory or memory lapses, confusion, concentration, finding appropriate words or responding quickly, and problems in organization and planning ahead substantially impact daily life and function. What may seem like small deficits in working memory function, for example, will have a large impact on performance of more complex tasks (4).

Many objective tests of dyscognition are normal in fibromyalgia

A number of studies have assessed the cognitive performance of fibromyalgia patients and found no differences in comparison to healthy control subjects. Fibromyalgia patients perform as well as control subjects on many standard neuropsychological tests (17, 18) and on specific tests of speed of information processing (19), visual memory (20, 21), recognition of figures or short-term memory storage (22), verbal memory (23, 24), specific tests of cognitive flexibility and emotion-based decision making (9), attention (25-27), involuntary orienting (27), visual memory and recognition (21).

Interpretation of normal objective tests

A finding of a normal objective test is not necessarily evidence against the presence of cognitive dysfunction in FM. A *normal* finding may have a number of possible interpretations:

Insensitive evaluation

Studies that do not show differences between patient and control groups may simply be insufficiently powered to show such differences, or the experimental situation introduced unintended factors that masked any true differences. Since it is difficult to prove the null hypothesis, the lack of an effect should be interpreted with caution, especially if the study used few subjects and liberal inclusion criteria. For example, several studies have identified distinct subgroups of fibromyalgia patients (28, 29) and the relative frequencies of these groups in the sample may influence the results. In certain studies with suspect power, findings of normal function in certain domains may be balanced by findings of dysfunction in others, providing some measure of validity for the normal results. However, even in this case statistical power may vary over subscales.

Reference values for normal function

Some studies choose a measurement strategy of comparing FM patients to a selected group of healthy control participants, who are typically matched for age and gender, and should be matched for level of education. Thus, researchers may be able to find statistically significant differences between the two groups. Another strategy is to evaluate performance against normative values for standardized tests of neuropsychological function. These approaches may yield different results with the same tests. For

example, careful evaluation using control groups may reveal significant differences, even if the performance of the FM patients does not fall into the impaired range.

Wrong target
The functional domains assessed by the tests may not adequately evaluate the domains with deficits. This is mostly a matter of choosing the affected domains correctly although many testing situations are limited by time and may not assess the behavior of interest. For example, in the evaluation of working memory, specific tests of memory storage or short-term recall do not seem to be affected. However, tasks that place heavy demands on the entire working memory system, including the ability to delete and add stored information, are more sensitive and reveal deficits.

Rising to the occasion
In the case of fibromyalgia, there is considerable anecdotal evidence that patients can marshal their resources and perform well on relatively short cognitive tests. Patients may perform similarly to controls in a single testing session or in a single testing day. The difference is that perhaps this level of performance cannot be sustained; control subjects may do as well on the next day while patients may have to recover from their performance. This concept is supported by preliminary evidence from the neuroimaging literature that suggests that fibromyalgia patients can achieve levels of performance comparable to controls, but use more brain resources to accomplish the task (30, 31). They may s*print* while controls proceed at a normal pace. Similar findings have been observed in patients with chronic fatigue syndrome who are able to perform comparably to controls on complex cognitive tasks but recruit far more brain resources to do so and, notably, report more mental fatigue (32). In this case, adequate assessment is obvious: evaluate controls and patients for several successive days. This type of extended testing has actually been performed for tests of physical function and could be applied to tests of cognitive function. However, many testing protocols are restricted to one day for reasons such as limited resources and minimizing patient burden. But how do we assess a second-day deficit on the first day? Neuroimaging may provide a sensitive test of patients working harder to achieve levels of normal function. However, even if validated, methods such as fMRI are too costly and time consuming for routine use. Another approach is to use tests that may be sensitive to increased effort. Indeed, as described below, some of the differences in cognitive function that are found could relate to patients using available resources to increase performance to normal levels. Deficits may become obvious when tested in a multi-task environment. The healthy controls will be able to use other neurocognitive systems to perform the tasks, whereas the FM patients are already using the other neurocognitive systems and will not be able to recruit more resources to complete the tasks successfully.

Normal function
Finally, a lack of a difference between fibromyalgia patients and controls may correctly indicate normal function in the assessed domains. We do not expect fibromyalgia to adversely affect all possible domains of cognitive function. A valid finding of normal function provides useful information about the nature of the deficits that are found.

Objective deficits in cognitive processing in fibromyalgia

Attention and executive function
It is convenient to describe cognitive function from the viewpoint of a watchman. The most immediate functions are attention, including processes of alerting (there is something in the environment), orienting (it is over there) and executive functioning (do something about it) (27, 33). In a recent study of these processes, Miró et al. (27) found that fibromyalgia patients demonstrated a mix of increased alertness and decreased vigilance. These seemingly opposite effects were explained in terms of a ceiling effect of vigilance. Alerting is more effective with less vigilance and becomes

less useful as vigilance increases. This study also found impaired executive functioning described as increased negative influence of distracting information. Executive functioning is described as part of the attention network and also as a separate constellation of functions. It encompasses a number of processes including planning and long-term goals and more immediate decision-making, and suppression of inappropriate responses in addition to resisting distracting information (30). Fibromyalgia appears to have selective effects on this group of processes. Verdejo-Garcia et al. (9) found that patients showed poor performance on some but not all measures of cognitive flexibility and a deficit in emotion-based decision making, but normal performance in a task with delayed rewards, the combination suggesting a hypersensitivity to reward. Glass et al. (30) assessed performance in a simple task that minimized the influence of distraction (Go/No-Go task). As expected, patients performed as well as controls, although fMRI analysis revealed significant differences in brain activation between patients and controls suggesting recruitment of compensatory brain activity to supplement processing that is limited by overlapping processing of chronic pain. This finding provides neuroimaging evidence for the concept that fibromyalgia patients are capable of increasing performance to normal levels for these short tests. They *rise to the occasion* by tapping into additional cognitive resources.

Memory (working, episodic, semantic)

Once alerted, the watchman must produce a response that integrates job protocols such as communication, evaluation, maintaining personal safety, and drawing upon personal experience, all of which depend on memory function. Fibromyalgia patients complain of memory lapses and many of the original demonstrations of deficits are in tests of memory. Cognitive processing of memory is subdivided into working, episodic and semantic memory. Memory function is further divided between processing of adding items into memory (consolidation), the amount of memory capacity, and the ability to organize and retrieve items from memory. Working memory is a primary cognitive function that is necessary for functioning in complex situations in everyday life that includes managing interruptions and a degree of multitasking. Working memory is intertwined with attention and executive function.

Several studies of working memory in fibromyalgia, by different groups using different tests, have found salient decreases in performance (5, 19, 34-42). These converging lines of evidence strongly suggest that these deficits are a cardinal feature of dyscognition in fibromyalgia. Deficits have also been observed in episodic memory, the ability to recall past events or episodes. However, the results of these studies are mixed. Some studies have shown deficits in both recall (19, 43) and recognition (19) while others have found deficits or no effect with tests of the same domain (22) or even with the same test (20, 26, 37). The evidence for deficits in semantic memory is less mixed, with studies showing impaired verbal fluency (19, 22, 37), vocabulary (16, 19) and naming speed (44).

Thus, results are equivocal for studies of episodic memory and more consistent for studies of impaired working and semantic memory. One exception is an investigation by Suhr (26) that found no deficit in either working memory or a verbal fluency test of semantic memory suggesting that perception of cognitive impairments may exceed objective impairments.

Given that distraction has been shown to negatively affect working memory and attention in FM patients, we would expect that executive function is also compromised in FM patients. Indeed, Verdejo-Garcia et al. (9) found performance deficits among FM patients in tasks employing executive function in decision-making. These results are compelling and illustrate the need for further research on executive function.

Interpretation of objective deficits

Cognitive function is influenced by numerous factors unrelated to fibromyalgia that must be controlled in objective testing. Obvious examples are age, medication use, re-

cent sleep history, concomitant conditions and emotional arousal. Additional factors may be associated with fibromyalgia. Studies have examined the possible influence of pain, mood, sleep and similar moderating variables, and the potent influence of distraction.

Factors that mediate dyscognition in fibromyalgia

Pain, mood, sleep

Glass (4) reviewed factors that likely mediate fibromyalgia cognition. Fibromyalgia is characterized by high levels of widespread pain so it is not surprising that the presence of pain, which is physiologically designed to command attention and motivate behavior, interferes with cognitive functioning. This effect has been observed in fibromyalgia and in pain from other sources, including both regional and widespread pain conditions (4, 21). A further line of evidence is provided by the association between the amount of pain and amount of dysfunction. Within fibromyalgia the impairment in cognitive function is related to the level of pain (9, 16, 20, 40, 45).

It is also reasonable to suspect that negative mood would impair cognitive function. There are a number of reports that associate anxiety (20, 40) and depression (22, 26, 40, 46) with cognitive function in fibromyalgia. However, impairments remain after controlling for these effects (40) and other studies have not demonstrated an association between objective deficits and mood (9, 19). Thus, the effects of mood appear to be secondary to pain, they may obviously affect performance but do not account for the full range of observed deficits (4).

Unrefreshing sleep is a major clinical complaint in fibromyalgia and sleep problems are known to negatively impact cognition. There is evidence for an influence of sleep disorders on cognitive function in fibromyalgia (19, 26) but also evidence that cognitive deficits remain after controlling for sleep problems (40).

The bivalent influence of medication

One important factor that may mediate dyscognition in fibromyalgia is the influence of medication. It is extremely rare to find an individual with the diagnosis who is not taking continued doses of antidepressants (*e.g.* amitriptyline, duloxetine, milnacipran), antiepileptics (gabapentin, pregabalin) or strong analgesics (tramadol, opioids). It is entirely reasonable to expect that medications, some with warnings to not operate heavy machinery, may cause poor functioning on cognitive tests (27). Furthermore, studies have shown no differences between medicated and non-medicated patients (27) and the low doses taken by many patients may not be sufficient to cause untoward effects (20, 36). Interestingly, there is evidence for beneficial effects of medication. Use of strong analgesics may actually improve cognitive performance (40). This provides indirect evidence for the association between pain magnitude and the magnitude of cognitive deficit. Any detriment due to drug side effect is overcompensated by the increase in function associated with decreased pain.

Low effort and the possibility of Tptests that detect increased effort

There is concern that poor performance on a cognitive test reflects lack of motivation or effort spent. Evidence suggests low effort on tests in patients seeking disability, which may be a general effect found for many disorders (47). Apart from seeking disability, it would be reasonable to assume that FM patients do not put as much effort into these tests given concomitant pain, fatigue, medication side effects or expectations of poor performance. Few studies have explored effort formally; however, the evidence does not support poor effort as a cause of performance deficits among FM patients (9, 19, 48). For example, Glass *et al.* found that fibromyalgia patients scored significantly higher on achievement motivation and strategy use than age-matched controls (16). A more intriguing hypothesis is that patients perform adequately on some tests because they *rise to the occasion* and use more effort and brain resources to achieve normal function. This increased level of effort requires a *behavioral momentum* that can be detected by an appro-

priate testing situation; for example, the increased effort may result in an increased vulnerability to distraction as well.

The prominent role of distraction in fibromyalgia dyscognition

Why do fibromyalgia patients perform normally on some cognitive tests and not on others? Leavitt and Katz (23) propose that the key variable is the absence or presence of distraction within the test, *i.e.* whether the test includes tasks that compete for attention. They showed a clear effect of distraction in a study evaluating working memory function in a group of fibromyalgia patients and a group of subjects without fibromyalgia who complained of memory problems similar to those of fibromyalgia. Both groups were administered a battery of tests to assess verbal working memory. Tests with minimal distraction showed minimal deficits in fibromyalgia, while tests that included distraction showed the most impairments. These results highlighted the importance of distraction and suggest that the observed deficits reflect a problem in executive management of distraction rather than in the management of stored information. Thus tests such as simple short-term memory may reveal little impairment while tests with an executive component such as working memory, are likely to reveal impaired function in fibromyalgia.

The association of objective and subjective measures of dyscognition

The research on dyscognition in fibromyalgia has focused almost exclusively on objective cognitive tests, with little attention to patients' descriptions of cognitive difficulties. Glass et al. (16) addressed this disparity and evaluated the association between subjective and objective performance. This innovative study employed two control groups. Twenty-three patients with fibromyalgia were compared to 23 age - and education - matched controls and to 22 control subjects matched for education but matched for age + 20 years, meaning that this control group was 20 years older than the other two groups. This older control group was included because of evidence that the cognitive function in fibromyalgia is similar to older controls, suggesting an accelerated cognitive ageing process (19). The results showed that reports of several domains of memory function were significantly different in the patient group compared to both control groups. Of these, perceived lowered memory capacity, self-efficacy and increased achievement motivation were significantly associated with a recall test that assessed the main components of memory encoding, storage and retrieval. Similar associations were not observed in either of the control groups. For the fibromyalgia patient group, these results suggest the presence of specific deficits more severe than would be expected from premature aging.

In a subsequent study, 74 patients with fibromyalgia and 24 age-matched healthy control subjects completed a questionnaire battery designed to assess perceived cognitive function (49). Objective function was not assessed. The results confirmed the presence of perceived difficulties in a wide variety of domains: perceived difficulties in attention/concentration, language, visual perception, and both verbal and visuospatial memory. Regression analyses showed that pain ratings were associated with perceived language deficits and not associated with perceived attention/concentration, while all of the domains were associated with self-reports of fatigue and negative mood. Sleep was associated with perceived deficits in memory. The finding that perceived memory was influenced by sleep, mood and fatigue is consistent with the decrements found with objective testing. In contrast, the finding that pain was not associated with perceived difficulties in memory or attention/concentration is not consistent with previous results of objective testing. The authors note that the results of objective testing do not include the subjective certainty or perceived effort associated with the responses, factors that could influence subjective perception. They also note that their statistical results accounted for only a third of the variance and that they did not monitor medication consumption, suggesting future studies

that incorporate additional controls with increased number of subjects and that assess all relevant domains

A symptom of pain or of fibromyalgia?

The experimental evidence has examined the contribution of pain, mood, sleep and other variables and found pain to be the highest predictor of objective testing and uniquely of perceived language problems when assessed by subjective questionnaire. If pain is the primary determinant, is it the same for other painful conditions such as chronic low back pain, osteoarthritis and diabetic neuropathy? A recent review concludes that cognitive impairment is associated with a variety of pain conditions including the regional condition of low back pain, the widespread condition of fibromyalgia, and the neuropathic condition of diabetic neuropathy (50). These conditions interfere with both subjective and objective measurements of attention. Objective deficits are robust in tasks involving attention switching or attention interference. Since pain inherently commands attention, these effects are consistent with competition for a finite set of resources (30, 31). These complex attention tasks may also be classified as measures of executive function or provide an overlap between attention and executive function. The evidence suggests that impairments in executive functioning are related to complexity, with minimal deficits for automatic tasks and increasing dysfunction with increasing complexity. Finally, the neural networks that subserve pain and subserve executive attention are integrated, suggesting a physiological basis for executive function performance that is compromised by pain (51).

The most significant deficits in fibromyalgia have been found for memory tasks. Deficits in memory have been observed for other pain conditions (50) but they appear to be most pronounced in fibromyalgia, suggesting a unique effect in this syndrome. Indeed, the literature suggests different patterns of deficits among syndromes of fibromyalgia, diabetic neuropathy, chronic regional pain syndrome and headache.

These differences among different pain syndromes may represent the modulating effect of other symptoms. This concept suggests that the presence of a group of symptoms in any disorder may enhance the magnitude of specific symptoms such as pain (10, 49). Thus the concomitant presence of fatigue and mood disturbance may augment pain-induced cognitive dysfunction. These accompanying comorbidities and symptoms may determine both differences between pain conditions and differences within a pain condition such as fibromyalgia.

Finally, the association of pain and dyscognition may be indirect rather than causal, both resulting from the mechanisms mediating fibromyalgia. In this scenario, the link is not fibromyalgia to pain to dyscognition. Rather, pain and dyscognition arise from parallel processes. Both may be augmented by the underlying pathology, but they are not necessarily causally related. For example, fibromyalgia could represent the orchestrated activation of parallel pathways with a recuperative purpose of inducing inactivity and rest. It may represent an intrinsic *illness response* that can be activated by multiple triggers and that results in a stereotypic set of symptoms of widespread pain, tenderness, disordered sleep, stiffness, sensory sensitivity and dyscognition (52). Fibromyalgia or a common illness could share a symptom cluster that is designed to reinforce behaviors of quiescence. In this case, the source of the pain matters. Even though pain generally can degrade cognitive function, the mechanisms mediating fibromyalgia may have a unique effect on cognition that is indirectly related to the pain of the disorder. In other words, fibromyalgia represents an intrinsic mechanism that causes multiple symptoms in parallel: pain, dyscognition and other symptoms such as sensitivity to stimulation and stiffness.

Treating fibromyalgia dyscognition

At present, there is neither a cure nor a single best treatment to address the pain of fibromyalgia. Often, the goal is to reduce pain or manage it with a variety of treat-

ment methodologies. The same could be said for dyscognition. While there is no singularly ideal treatment for dyscognition, several management strategies have been known to lessen its severity.

Suhr (26) suggests that treating the pain, depression, fatigue and other fibromyalgia symptoms that have been linked to poor cognitive performance, in turn, may improve cognitive performance. However, as noted above, these symptoms do not account for the full range of cognitive deficits so treating them may yield only modest improvements in cognitive performance. Following memory tests with distraction in which FM patients performed poorly, Leavitt and Katz found that these same patients could employ rehearsal techniques to significantly counteract interference from distraction to maintain their focus on the task and perform near normal levels once again (5).

Another treatment strategy is based on the observations that physical activity benefits alertness, mental acuity, and sleep quality. Exercise, a known treatment for fibromyalgia (53, 54), may likewise treat dyscognition. Objectively evaluated physical performance in fibromyalgia has been shown to be positively associated with cognitive attention and executive function, problem solving and processing speed (8). Achieving improved physical performance through exercise programs has also increased cognitive function (36, 37). Furthermore, the concept that fibromyalgia dyscognition is qualitatively similar to cognitive deficits in aging populations also suggests a link between exercise and cognitive function. Exercise is a proven means of improving cognitive function in older individuals (55, 56).

Future directions

Future studies are needed to fill the gap between the relatively few studies of cognition in fibromyalgia, and within cognition, the paucity of studies of perceived cognitive deficits. For example, there is little evidence about the impact of dyscognition on the quality of everyday life. Are these perceived deficits minor annoyances or do they negatively impact important components of everyday life including work, activities of daily living, parenting, and social activities? New studies of physiological brain function are needed to further increase knowledge about the neural underpinnings of dyscognition in fibromyalgia and the features that are either common to other pain syndromes or unique to fibromyalgia. The studies showing the benefits of rehearsal or exercise are encouraging, and future studies will likely uncover improved treatment strategies that improve dyscognition and function while alleviating pain.

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