

Cognitive impairment in fibromyalgia: cognitive profile, neuroimaging assessment, and therapeutic avenues

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Abstract: Fibromyalgia (FM) is a chronic pain syndrome accompanied by a range of other symptoms. Cognitive impairment is a core sign and symptom in FM, yet sometimes neglected, with a profound effect on instrumental things to do of each day living. The occurrence may affect people of all ages, although it is most frequent in the woman middle-aged. Working memory, attention, and executive function are the most frequently affected cognitive domains. Neuroimaging studies show that atrophy and changeable functional connectivity of grey matter are related to cognitive dysfunction. Currently, the absence of clinically effective biomarkers for detection and quantification of cognitive symptoms makes traditional neuro-psychiatric scales and tests remain the most important tools in the assessment of cognitive impairment in FM. This review addresses the prevalence, abnormalities, neuroimaging of cognitive impairments in patients with FM while explaining currently available assessments and therapeutic options.

1. Introduction

Fibromyalgia is a common rheumatic disease with the main symptoms of chronic, widespread pain, accompanied by fatigue, cognitive impairment and so on¹. FM influences approximately 2% to 4% of the general population². The prevalence increases with age, and it is more frequent in women than in men about an approximately 6:1 to 9:1 female-to-male ratio¹.

Patients with FM regularly whining about an extensive vary of cognitive difficulties such as forgetfulness as well as declines in mental clarity, memory, and attention impairment³. These subjectively experienced cognitive dysfunctions associated with FM are commonly called “fibro-fog”¹. The term dys-cognition referred to both the subjectively and objectively determined cognitive deficits⁴, which is so common that it has been reported in 50% to 80% of FM patients⁵ but commonly ignored or untreated, always has adverse harm on activities of daily living and quality of life.

Indeed, FM is the only pain syndrome that incorporates cognitive impairment into its diagnostic criteria. Although the American College of Rheumatology (ACR)⁶ has already recognized and added the presence of cognitive impairment into the preliminary diagnostic criteria of fibromyalgia, cognitive impairment remains one of the minimal assessed and treated FM domains in general clinical practice⁷.

In this review, we attempt to furnish a concise and up-to-date viewpoint of fibromyalgia-associated cognitive impairment. We would like to point out the prevalence and cognitive abnormalities in FM patients with cognitive impairment and aim to increase attention and comprehension of the clinician and public. The results of cognitive impairment are related to multiple neuroimaging changes in brain function and structure. Cognitive screening tests can be utilized routinely to screen for cognitive dysfunction and verified the effects of treatment. Currently, for the treatment of cognitive impairment in FM, combined application of symptom-based pharmacologic and non-pharmacologic therapies is recommendable and most commonly used. It seems to be beneficial to apply some compensatory interventions for enhancing cognitive impairment. More extra randomized controlled trials with

cognition for FM as the primary end-point are needed to inspect the results of those treatment plans on cognition.

2. Prevalence

Cognitive dysfunction is a universal and frequent symptom of FM with rates ranging from around 50% to 90%⁸. It has been reported in 76.4–82.5 % of FM patients in rheumatology practice, these symptoms are 2.5 times more prevalent in FM patients than in other patients with other rheumatologic disorders⁹. Regarding gender differences, a higher prevalence is found in women, with a female-to-male ratio of 2:1¹⁰.

The incidence of cognitive symptoms may differ, previous studies showed that the high incidences of concentration difficulties was 95% and failing memory was 93%¹¹, and forgetfulness and concentration were ranked as the fifth and sixth most severe symptoms¹². On the contrary, specialist clinicians ranked the relevance of cognitive symptoms solely tenth in importance.

The so-called juvenile primary fibromyalgia syndrome (JPFS) merits discussion, which is defined as a chronic pain syndrome of musculoskeletal mainly affecting children and adolescents^{13,14}. JPFS has prevalence within the range of 1.2% to 6.2%¹⁴. At present, related research on JFMS with cognitive impairment is relatively scarce. Elevated emotional distress (anxiety and depressive symptoms) in the JFM group in comparison with healthy control subjects have been noted in several studies. Taken as a whole, more attention should be given to cognitive impairment in JPFS, and long-lasting cognitive symptoms may contribute to deleterious long-term consequences and influence patients of normal life and vocational opportunities.

3. Cognitive abnormalities

Like all signs and symptoms of FM, cognitive impairment is characterized via high variability among patients. Individuals reported cognitive symptoms including forgetfulness, distractibility, disorganized thinking, etc, and forgetfulness and concentration were ranked as the fifth and sixth most severe symptoms^{8,12}. According to recent reviews, attention and executive function are most frequently involved^{3,4,9}. In particular, the frequencies of impairments in a representative fibromyalgia group were as follows⁸: 70.2% in memory decline, 56.1% in mental confusion, and 40.4% in difficulties with speech.

The performance and extent of objective neuropsychological abnormalities are more complex and mutative in FM patients. When studying cognitive impairment in FMS, memory problems have received great attention, involving deficit mostly in working memory (WM), then semantic memory and episodic memory^{8,9}. Studies showed that compared to controls, persons with FM perceived more memory impairment evidenced by lower capacity, more negative change, and increased anxiety associated with memory performance³.

Attention, executive function (EF), and WM are not only closely interconnected but also interact with each other. Attention permits the brain to pick out the applicable inputs for storage and processing into WM, it has been related to an extended vulnerability of memory when faced with distractions from a competing source of information^{9,15}. The capacity to dealing with distraction is part of EF, however, plenty of results strongly recommend that individuals with FM appear to have selective deficits on the latter EF process^{4,5,9}.

During language and other cognitive domains, patients with FM performed abnormalities in verbal fluency, naming speed, and vocabulary access speed¹⁶. Research has also shown pervasive impairment in social cognition in individuals with FM, such as recognition of other's emotions, as well as representing other's affective mental states¹⁷.

4. Neuroimaging assessment

The value of neuroimaging for decision-making is still fairly limited in regard to cognitive impairment in FM patients, who showcase substantial changes in brain function and structure, but the most transformation of brain imaging studies related to pain.

Grey matter atrophy is an early signal of latent future cognitive decline. Studies exhibit that suffers with FM exist structural and quantitative abnormalities in cortical thickness, and volumes^{18,19}. Kuchinad et al.¹⁸ analyzed that the magnitude of annual gray matter decrement in middle-aged women with FM was equivalent to 9.5 times the loss in normal aging. DPCC is the initial region demonstrating damage in mild cognitive impairment, and Lin et al.¹⁹ identified the FM patients to have GM reduction in left mPFC and right dPCC (comprises of dPCC and pMCC).

In addition to structural damage, researches stated altered connectivity patterns in FM patients and centered on the functional connectivity of grey matter structures by use of resting-state functional MRI²⁰. The dorsolateral prefrontal cortex (DLPFC) is a key region in the processes of cognitive control. Kong et al.²⁰ indicated that FM patients exhibited significantly greater rsFC amongst the DLPFC compared with healthy subjects. FM patients showed greater connectivity within the default mode networks and both the insula and the right executive attention network²¹.

To sum up, these neuroimaging studies indicate an accruing instability within the brain network physiology might have clinical relevance in cognitive decline. In the future, it is expected that neuroimaging methods would serve many critical roles in the management of FM patients with cognitive impairment by providing diagnostic guidance, planning therapy, and assessing treatment outcomes.

5. Cognitive assessment

The studies performed to date have shown that such biomarkers for detecting and quantifying cognitive impairment in fibromyalgia are still lacking. Although some neuroimaging research has yielded some important experimental results, it remains reliance on traditionally validated scales for assessment⁵. Clinicians easily missed cognitive decline in FM patients, concurrent FM patients may not mention cognitive difficulties if clinical symptoms are not significant yet have potential impact. Thus, identifying a valid and feasible measurement is vital for assessing cognitive impairments commonly occurring in FM patients.

Diagnosis of FM-associated cognitive impairment should include attention self-reported measures and appropriate neuropsychological tests. The ACR preliminary diagnostic criteria⁶ for fibromyalgia included two scales: the Widespread Pain Index (WPI) for measuring painful body regions, and the Symptom Severity Scale (SSS) scale. However, the weight of cognitive diagnostic criteria may be considered low, and these scales are not specific for diagnosis or evaluation of cognition⁵. However, there was a dis-correlation between SSS-Cog, a subscale of the SSS, and objective cognitive performance in FM patients²².

Comprehensive neuropsychological batteries are very useful and comprehensive for ascertaining cognitive impairment, but these are difficult and length to use. The Mini-Mental State Examination (MMSE) is one of the most widely used scales for cognitive screening, however, FM patients have lower scores on it than patients with other pain syndromes²³. The Clock Drawing Test (CDT) has been employed as a reliable screening tool for cognitive decline in FM patients, which is useful for assessing especially executive function²⁴.

With regard to assessing the memory beliefs and function in FM patients, clinicians can apply the Meta-memory in Adulthood (MIA) questionnaire and Test of Memory Malingering (TOMM) to evaluate memory capacity and memory deterioration in FM patients. Kalfon et al.²⁵ combined TOMM and the NeuroTrax™ computerized cognitive assessment battery and found that FM patients expressed lower scores on all cognitive indices.

Self-reported measures could provide a simple and first cognitive impairment screening technique for FM patients in clinical practice. The Derogatis Symptom Checklist-90-Revised (SCL-90-R) is one of the most common self-report checklists that reports important information of psychopathology, and

it has been demonstrated to be moreover sensitive enough to differentiate between FM patients and healthy subjects^{5,26}.

In sum, more and more new assessment and evaluation of cognitive dysfunction tools are increasingly being used, whereas clinicians still should pay more attention to subjective complaints of patients that might reflect veritable cognitive deficits to a larger extent.

6. Treatment of cognitive impairment

Currently, there is no cure or a defined and best treatment for cognitive impairment in FM patients, but several symptom-based treatment strategies may boost in quality of life for FM patients. A multidimensional approach is therefore required for cognitive management.

Pharmacological Treatment

First of all, improving cognitive performance is related to greater control of pain, depression, fatigue, and other symptoms³, therefore, pharmacological strategies have to be considered when these FM symptoms are needed to manage. There are no specific pharmaceutical treatments approved for cognitive impairment in patients with FM. Moreover, due to limited effectiveness of most pharmacotherapies, many pharmacological treatments were tried over the years, with varying efficacy.

Pregabalin could improve in pain, fatigue, and sleep abnormalities in FM patients, but it had significant adverse cognitive effects for healthy volunteers and paralleled with complaints of neurotoxicity²⁷. Duloxetine and milnacipram had been proved that can provide pain relief and reduced fatigue in patients with FM²⁸. Milnacipram could decrease in cognitive dysfunction, an increase vitality and physical functioning in FM patients, and combine between milnacipram and pregabalin could improve in measures of cognition²⁹.

Amitriptyline was found that improvements in pain, fatigue, sleep, and quality of life, but it may lead to more anti-cholinergic side effects including possible cognitive disturbances⁵. Medical cannabis use is now increasingly common in FM patients, but long-term recreational cannabis use may drive a decline in various cognitive domains, as well as structural and functional brain differences³⁰. Some opioids could improve FM syndromes, whereas cognitive dysfunction is one of the most common opioid-related adverse effects³¹.

Non-pharmacological Treatment

Although the majority of patients with FM are treated with medication, most of the pharmacological therapies have been suggested to provide only a weak benefit except pain, and are not adequately effective for the relief of other symptoms such as cognitive impairment. Hence, it is highly significant to develop multidimensional therapeutics.

Recent studies recommend that microbes in the gut may modulate the physical, psychological, and cognitive state thru the gut microbiota–brain axis, it could enhance cognition, emotional symptoms, and functional state in a population diagnosed with FM³². Considering that hypovitaminosis D to be highly prevalent in FM patients, simultaneously experimental data indicated improvement in certain FM symptoms through vitamin D supplementation³³.

Exercise training would seem a viable approach in patients with FM, considering the beneficial effects of aerobic exercise and physical activity on cognitive performance. Based on the 2017 EULAR guidelines, exercise was the only 'strong for' therapy-based recommendation for FM³⁴. Zumba dancing, Tai Chi training, and yoga can improve working memory, motor function, and depressive symptoms in patients with FM^{35,36}.

Cognitive-behavioral therapy (CBT) changes individuals in effect and behavior through modifying negative thoughts and feelings, it is strongly recommended in practice guidelines. Lumley and colleagues created a brief approach- Emotional Awareness and Expression Therapy (EAET), which led to greater reductions in cognitive difficulties³⁷. CBT for insomnia may likewise improve alertness and executive functioning in FM patients, while mindfulness meditation could enhance cognitive flexibility and the ability to regulate emotional reactions³⁸.

Acupuncture therapy is widely used in depression, vascular cognitive impairment, and other cognitive difficulties, with a positive outcome to change cognitive symptoms. In FM patients, anodal

transcranial direct current stimulation could enhance short-term memory, and increase orthographic and semantic verbal fluency scores³⁹. A new trial supported transcranial alternating current stimulation (tACS) coupled with physiotherapy in treating FMS cognitive symptoms with better clinical outcomes⁴⁰. Hyperbaric oxygen therapy (HBOT) has shown beneficial effects on inducing neuroplasticity and significantly rectifying abnormal brain activity, which can lead to enhance the brain activity in special regions were linked with cognition and memory⁴¹.

What's more, providing and maintaining FM patients with the correct information about their disorders may help them receive and carry out pharmacological and alternative therapies, so education should be a part of the treatment plan. In summary, a multidisciplinary therapeutic approach, based on pharmacologic and non-pharmacological treatment could partially improve cognitive impairment related to FM. However, sometimes cognitive dysfunction as such would have a negative effect on the ability of FM patients to take part in alternative therapies.

7. Conclusions

Cognitive impairment is an important signs and symptoms of fibromyalgia patients yet comparatively less well-studied and includes mental foggy as well as memory and attention impairment. Both woman and man, every age may be affected. Cognitive abnormalities as being more than a memory problem and having a relatively broad range of this construct, indicates that clinicians will need to specify the type of cognitive dysfunction for better interventions and treatment.

However, the process of cognitive decline in FM is still poorly understood, and further study is required. As shown by neuroimaging, regional grey matter atrophy and neural network functional connectivity alteration are the ones that are most closely related to cognitive dysfunction. Diagnosis of cognitive impairment should include neuropsychological scales and tests, as well as attention to self-report. Although simple neuropsychological tests are to be useful for a routine clinical assessment for patients with fibromyalgia, a more comprehensive assessment of this cognitive impairment is required, so as to future studies could properly address the effect of illness and treatment on the brain.

Treatment options remain inadequate, although some studies are encouraging. Pharmacological strategies have to be considered to manage some FM symptoms, even though the role of it for cognition remains uncertain. A growing literature and guideline is supporting the effects of exercise training and cognitive training as well as other treatments should be made available to patients with cognitive impairment in fibromyalgia. Concomitantly, these interventions should also be applied at the early stage of cognitive impairment in FM.

In summary, cognitive dysfunction appears to be a manifold clinical complaint common to FM. To address this issue which was reported to be a very important issue for FM patients, much more studies are needed on this topic.

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