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Characterizing "fibrofog": Subjective appraisal, objective performance, and task-related brain activity during a working memory task

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ABSTRACT

The subjective experience of cognitive dysfunction ("fibrofog") is common in fibromyalgia. This study investigated the relation between subjective appraisal of cognitive function, objective cognitive task performance, and brain activity during a cognitive task using functional magnetic resonance imaging (fMRI). Sixteen fibromyalgia patients and 13 healthy pain-free controls completed a battery of questionnaires, including the Multiple Ability Self-Report Questionnaire (MASQ), a measure of self-perceived cognitive difficulties. Participants were evaluated for working memory performance using a modified N-back working memory task while undergoing Blood Oxygen Level Dependent (BOLD) fMRI measurements. Fibromyalgia patients and controls did not differ in working memory performance. Subjective appraisal of cognitive function was associated with better performance (accuracy) on the working memory task in healthy controls but not in fibromyalgia patients. In fibromyalgia patients, increased perceived cognitive difficulty was positively correlated with the severity of their symptoms. BOLD response during the working memory task did not differ between the groups. BOLD response correlated with task accuracy in control subjects but not in fibromyalgia patients. Increased subjective cognitive impairment correlated with decreased BOLD response in both groups but in different anatomic regions. In conclusion, "fibrofog" appears to be better characterized by subjective rather than objective impairment. Neurologic correlates of this subjective experience of impairment might be separate from those involved in the performance of cognitive tasks.

1. Introduction

Perceived cognitive dysfunction ("fibrofog") is an increasingly appreciated clinical complaint in fibromyalgia. Along with painful symptoms, over 50% of fibromyalgia patients experience distressing subjective cognitive impairment (Katz et al., 2004; Yunus et al., 1981). The most common complaints encompass the abilities to attend, concentrate, remember, use language, multi-task, and organize information. Dyscognition contributes significantly to both functional and work disability in fibromyalgia. Commensurate with its increasing recognition, its subjective evaluation has been incorporated into the 2010 preliminary American College of Rheumatology fibromyalgia diagnostic criteria (Wolfe et al., 2010).

Persons with fibromyalgia commonly perceive discordance between how they feel about their abilities and how they actually perform. In one seminal study, patients with rheumatoid arthritis, ankylosing spondylitis, and fibromyalgia were asked to rate their ability to perform several physical activities and were then videotaped actually performing these activities (Hidding et al., 1994). A striking discordance between self-reported ability and observed functional disability was observed in fibromyalgia that was not found in other patients with rheumatic disease. It is possible that the dyscognition of fibromyalgia may reflect a similar phenomenon, with discordance between the subjective experience of performing cognitive tasks and objective performance on those tasks.

To date, the entire body of science on dyscognition in fibromyalgia includes ~20 publications, mostly small population comparisons of fibromyalgia patients to controls performing cognitive tests (Ambrose et al., 2012). In summary, objective differences of small effect sizes have been demonstrated in performance on some neuropsychological tests of attention, executive function, and memory (Glass and Park, 2001). However, these findings often required experimental provocation (i.e. distraction, stress) to demonstrate effects (Dick et al., 2002; Glass, 2009; Glass et al., 2011; Leavitt and Katz, 2006; Leavitt and Katz, 2009; Reyes Del Paso et al., 2012; Seo et al., 2012) and effects are

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often not found with standard cognitive tests (Glass et al., 2011; Mohs et al.; Walitt et al., 2008).

Only a few studies have investigated the neurocognitive correlates of cognitive impairment in fibromyalgia. Using fMRI and a simple response inhibition task selected to ensure comparable performance (Go/No-Go task), Glass, et al. found that, compared to controls, fibromyalgia patients had less activation in several task-related brain areas and increased activation elsewhere in the brain (Glass et al., 2011). Using the 2back working memory task paradigm, Seo, et al. also found that fibromyalgia patients had less activation in brain areas related to working memory together with a small clinical difference in performance (88.26% vs. 95.56% accuracy) (Seo et al., 2012). More recently, Čeko, et al. reported finding no difference in performance or BOLD response between 28 fibromyalgia patients and 23 healthy controls on multiple levels of the N-back task (Čeko et al., 2015). All studies used methods that contrasted two different task difficulty levels (NoGo > Go; Nback > 0back). These papers present a variety of interpretations; 1) that decreases in task-related brain activity represent a deficit in task ability, perhaps due to overlapping networks leading to reduced resources to perform task) (Glass et al., 2011), 2) that impairment of the prefrontal cortex may lead to inappropriate organization of information (Seo et al., 2012), and 3) that there is no evidence of a measureable difference in Nback cognitive performance or compensatory neural recruitment in task-related brain networks (Čeko et al., 2015). All three studies adjusted for patient characteristics in their analyses but did not consider the discordance between the severity of subjective cognitive complaint and (objective) task performance.

Clinically, the objective consequences of dyscognition in fibromyalgia are not clear (Shmygalev et al., 2014). Cognitive deficits are not overtly obvious to medical observation, certainly far less than what is seen in pathologically-defined neuropsychiatric dementias such as Alzheimer's disease and vascular dementia. Objective differences noted on cognitive testing also correlate poorly with self-perception of cognitive deficits (Tesio et al., 2015). The dyscognition of fibromyalgia is perhaps better defined by the distressing intrusiveness of subjective cognitive symptoms rather than by a clinically-relevant cognitive deficit.

Here, we aimed to separate brain mechanisms related to subjective appraisal (subjective dyscognition) from those related to performance on a cognitive working memory task (objective dyscognition). We evaluated subjective cognitive function, as well as objective cognitive task performance, and brain activity during a cognitive task using BOLD functional magnetic resonance imaging (fMRI).

2. Materials and method

2.1. Subjects

Eighteen right-handed, female fibromyalgia patients and a group of 16 age-matched female right-handed healthy controls participated in this study. One fibromyalgia patient was excluded from the study because she was found to be pregnant during screening. One fibromyalgia patient and three healthy controls were unable to demonstrate understanding of the N-back task during the practice sessions and were excluded from analyses. All fibromyalgia patients ($n = 16$) met the 1990 American College of Rheumatology fibromyalgia criteria and did not have concomitant medical diagnoses. Healthy controls ($n = 13$) did not have any medical or psychiatric diagnoses, were not taking any medications, and did not meet fibromyalgia diagnostic criteria. Exclusion criteria for fMRI participation included left-handedness, pregnancy, cardiac pacemakers or other body metals, and claustrophobia. Behavioral data are missing on one patient for N-back task and one control for the N-back task and Multiple Ability Self-Report Questionnaire (MASQ).

This study was approved by the MedStar Health Institutional Review Board (protocol number 2010–050).

2.2. Measures of fibromyalgia impact and symptoms

Fibromyalgia Impact Questionnaire (FIQ) is a validated questionnaire designed to assess the spectrum of problems related to fibromyalgia and treatment responses (Burckhardt et al., 1991). It evaluates three domains: function, overall impact, and polysymptom burden related to pain, fatigue, sleep, and mood issues. The original FIQ is scored on a 0–100 scale with high scores indicating more severe symptoms. A 14% change in FIQ scores is considered the minimally clinical important difference (MCID) in fibromyalgia symptoms (Bennett, 2005). Patients enrolled in fibromyalgia clinical trials typically have FIQ scores of 50 or greater (Bennett, 2005; Hauser et al., 2013; Williams and Arnold, 2011). As FIQ scores represent the full spectrum of fibromyalgia complaints, FIQ score was used as a representative score of symptom burden in our imaging analyses.

Brief Pain Inventory (BPI) is a validated measurement of pain severity and pain interference (Tan et al., 2004). Both are scored on a 0–10 scales, with high scores indicating more severe pain. Patients enrolled in fibromyalgia clinical trials typically have BPI scores of about 6 (Hauser et al., 2013). A 2-3 point change is typically considered the MCID in pain (Keller et al., 2004; Williams and Arnold, 2011).

Multidimensional Fatigue Inventory (MFI) is a validated measure of fatigue severity that provides subscales of general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue (Smets et al., 1995). The MFI is scored on a 4–20 scale with high scores indicating more severe symptoms. There is no proposed MCID cut-off with the MFI. Patients enrolled in fibromyalgia clinical trials typically have MFI scores of approximately 14 (Hauser et al., 2013). In this study, scores are reported in terms of "general fatigue" and "mental fatigue" (Smets et al., 1995; Williams and Arnold, 2011). The MFI questions to determine mental fatigue are currently used in other tools to assess "fibrofog" (Boomershine, 2010).

2.3. Measures of subjective and objective dyscognition

Subjective dyscognition (subjective cognitive appraisal) was measured using the Multiple Ability Self-Report Questionnaire (MASQ), which assesses the subjective appraisal of cognitive difficulties in five cognitive domains: language, visual-perceptual ability, verbal memory, visual–spatial memory, and attention/concentration. The MASQ subscales are scored on an 8–40 scale with high scores indicating greater perceived difficulties. There is no proposed MCID cut-off with the MASQ. Patients enrolled in a fibromyalgia research clinic typically have MASQ subscales scores of approximately 20. In this study, subscale scores are reported in terms of "Verbal Memory", "Language", and "Attention/Concentration" (Seidenberg et al., 1994; Williams and Arnold, 2011) as these three domains are most highly related to the cognitive task during fMRI imaging (see below). The correlation coefficients for Verbal Memory, Language, and Attention/Concentration with 2back accuracy in healthy controls were -0.68, -0.59, and -0.2, respectively. For this reason, Verbal Memory is used as a representative score of subjective cognitive appraisal in our imaging analyses.

2.4. Cognitive task during fMRI

Objective dyscognition was measured using a modified version of the N-back working memory task while undergoing fMRI. The modified N-back task used in this study has an increased overall cognitive demand compared to the classic N-back task. This task was employed previously by our group in other patient populations (Rayhan et al., 2013). Briefly, blocks of 9 pseudo-randomized uppercase letters (A, B, C, and D) were displayed for 1000 ms followed by 1500 ms of blank screen. Subjects responded using a four button box. In the 0back condition, subjects were asked to press the button that corresponds to the letter currently displayed on the screen. In the 2back condition, subjects