



## Brain correlates of cognitive inhibition in fibromyalgia: Emotional intrusion of symptom-related words

Francisco Mercado <sup>a,\*</sup>, José Luis González <sup>a</sup>, Paloma Barjola <sup>a</sup>, Marisa Fernández-Sánchez <sup>a</sup>, Almudena López-López <sup>a</sup>, Miriam Alonso <sup>a</sup>, Francisco Gómez-Esquer <sup>b</sup>

<sup>a</sup> Department of Psychology, Faculty of Health Sciences, Rey Juan Carlos University, 28922 Madrid, Spain

<sup>b</sup> Department of Anatomy and Human Embryology, Faculty of Health Sciences, Rey Juan Carlos University, 28922 Madrid, Spain

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### ABSTRACT

Evidence coming from neuropsychological studies has showed the presence of cognitive alterations in fibromyalgia. Such dysfunctions are especially remarkable when the set in motion of executive control processes, such as inhibition, is required to perform successfully; however, neural data related to these mechanisms are very scarce. Present study tried to characterize cognitive inhibition mechanisms, as part of the attentional control functions, in patients with fibromyalgia. Participants (two groups: fibromyalgia patients and healthy control participants) were asked to perform in an emotional Stroop task while event-related potentials (ERP) were recorded. Four different emotional interference conditions were created: fibromyalgia symptom-related words, arousing-negative, arousing-positive and neutral words. Brain activity and behavioral data were analyzed. Principal component analyses were employed to reliably define ERP components along with a source-estimation technique. Symptom-related words elicited greater frontal P450 amplitudes and enhanced activation within right inferior frontal gyrus as compared to the rest of stimuli. This effect was only true for the fibromyalgia group. Behavioral contrasts, however, did not produce significant differences. Scalp and source estimation findings suggest the presence of a specific difficulty in cognitive inhibition in fibromyalgia patients (under conditions intimately linked with the core concerns of their disease). Data point to the involvement of right inferior frontal cortices in this inefficient mechanism, which might cause an enhanced and dysfunctional effort of processing to achieve only a comparable performance to healthy people. Implications of these results are discussed. Nevertheless, further investigations are needed to better understand dysfunctional cognition in fibromyalgia.

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### 1. Introduction

Growing evidence coming from fibromyalgia (FM) investigations suggests that psychoneurobiologic dysfunctions might play a relevant role in the explanation of this multifactorial and still not fully understood syndrome (Dadabhoy et al., 2008; Geisser et al., 2008). Apart from the widespread musculoskeletal pain and tenderness to palpation at specific locations, the traditionally so-called 'tender points' (Wolfe et al., 1990), cognitive failures represent one of the most important complaints of these patients, denominated as *fibrofog* (Glass, 2008; Williams et al., 2011), leading to produce even greater functional impact than pain itself (Arnold et al., 2008). These cognitive difficulties manifest persistently in many daily activities involving the allocation of executive control resources (e.g., to inhibit thoughts that do not allow them developing other concurrent daily tasks).

Experimental data have recently suggested that attentional control impairments seem to be the key to explain this cognitive dysfunction in FM (Glass, 2009). Specifically, patients perform poorly in alternating between cognitive sets (Verdejo-García et al., 2009), setting in motion working memory resources (Luerding et al., 2008), or facing with a task-switching test (Glass, 2006), as those are similar to everyday attentional tasks (Dick et al., 2008). Such attentional control difficulties in FM could become more evident during stimulus competition as a source of distraction (Dick et al., 2008; Leavitt and Katz, 2006).

One of the most important features involved in many daily activities refers to the ability to detect conflicts and automatically inhibit unwanted irrelevant responses. This capability allows individuals to regulate information processing to deal with a concurrent task (Aron et al., 2004; Miller and Cohen, 2001), as it occurs during Stroop tasks. Although Stroop paradigms have been very used to study both automatic and controlled cognitive processes, findings in chronic pain patients have been mixed (Gonzalez et al., 2010; Roelofs et al., 2002; Crombez et al., 2000). Additionally, affective co-morbid symptoms, especially anxiety, have been highlighted as relevant factors

\* Corresponding author at: Department of Psychology, Faculty of Health Sciences, Rey Juan Carlos University, Av. Atenas s/n, 28922 Alcorcón, Madrid, Spain. Tel.: +34 91 488 9022; fax: +34 91 488 8957.

E-mail address: [francisco.mercado@urjc.es](mailto:francisco.mercado@urjc.es) (F. Mercado).

that may contribute to the performance in emotional Stroop tasks (Pincus et al., 1998; Pincus and Morley, 2001). However, recent studies demonstrate greater interfering effect derived from other factors such as pain or medication on cognitive functioning (Glass et al., 2011).

The introduction of brain techniques could help to solve these contradictory results. Recent ERP studies using Stroop tasks have interpreted the N/P450 component as an index of executive control and inhibitory mechanisms in both healthy (Markela-Lerenc et al., 2004; Lansbergen et al., 2007) and clinical populations (McNeely et al., 2008; Markela-Lerenc et al., 2009), showing highest amplitudes to emotionally negative words. In the same line, musculoskeletal chronic pain patients have been characterized by an enhancement of positive ERP amplitudes in response to affective pain words (Sitges et al., 2007). Alterations in cognitive processing of pain-related information have been also found in FM patients (Montoya et al., 2005). It has been argued that information processing in FM patients might be characterized by an exaggerated vigilance to pain (Crombez et al., 2005). Nevertheless, such deficit could be circumscribed not only to pain-related stimulation but also to information that represents the core concerns of the FM patients, such as a number of diverse symptoms (Crombez et al., 2000). Indeed, ERP and behavioral evidence have indicated that patients with FM showed a generalized hypervigilance (Carrillo de la Peña et al., 2006) even for non-painful task-irrelevant stimuli presented during situations with competing attentional demands (Gonzalez et al., 2010). Consequently, in the present study we employed words referring to different types of stimulation: FM symptom-related (SF) together with arousing-negative (A−), arousing-positive (A+), and neutral (N) words.

Finally, accumulated pieces of evidence support the idea that dyscognition in FM is linked to the existence of an underlying dysfunctional neural substrate, presumably within prefrontal regions (Glass et al., 2011), such as inferior prefrontal cortex (IPC) or anterior cingulate cortex (ACC) (Aron et al., 2004). However, direct evidence describing these neural mechanisms is surprisingly scarce (Glass et al., 2011; Seo et al., 2012).

Therefore, this study aimed to examine cognitive inhibition processes and their underlying neural indices in FM patients compared with matched healthy controls. Event-related potentials were recorded and a source-estimation technique was used, while participants performed in an emotionally modified from the classical Stroop task where words conveyed different affective meanings acting as emotional distracters. Additional analyses were carried out to explore potential influences of psychological factors, pain, co-morbid anxiety and drugs on cognitive inhibition functioning.

## 2. Methods

### 2.1. Participants

A total of fifty right-handed women (25 healthy control (HC) subjects and 25 FM patients) took part in the experiment. All participants were aged between 35 and 65 years old. Patients fulfilled the 1990 American College of Rheumatology (ACR) diagnostic criteria for FM (Wolfe et al., 1990). Different rheumatologists belonging to the public hospitals of the Community of Madrid carried out diagnostic of FM. Finally, only data from 36 (21 HC subjects and 15 FM patients) of 50 whom starting the experiment were analyzed, as it will be explained later. Patients were recruited from the Fibromyalgia and Chronic Fatigue Syndrome Association of Getafe (AFFAG) and from the Fibromyalgia Association of Madrid (AFIBROM). HC participants were recruited from the relatives of students belonging to the Rey Juan Carlos University (Madrid, Spain), by means of both emailed advertisements and public advertisements located along the campus. Sample of HC participants was made up in such a way as to allow matching for age and education level with patients. No differences were found when age ( $t = -0.74$ ,  $p = 0.94$ ) or educational level ( $\chi^2(2) = 3.16$ ,  $p = .20$ ) of both groups were compared. Most of FM patients were taking analgesics or NSAIDS. Patients who were taking

medications (42.22%; low-dose of benzodiazepines, SSRI or tricyclic antidepressants) kept doing it because of both medical prescription and ethical considerations. Neurological disease or disorders that impair cognitive functions, psychosis, substance abuse/dependence, and color blindness were set as exclusion criteria, so participants with these medical conditions were excluded from the study. All participants had normal or corrected-to-normal eyesight and ability to read and write in Spanish to the equivalent of English grade 8 level. Socio-demographic and psychological data of patients whose data were finally processed are shown in Table 1, along with information about medication.

Participants gave written informed consent for their involvement in the experiment and they were paid for it. Informed consent was approved by the Rey Juan Carlos University Research Ethics Board and it followed all requirements from this committee. Some self-report instruments were administered to the participants. They completed the State-Trait Anxiety Inventory, STAI (Spielberger et al., 1988). This is a well-known 40-item self-report questionnaire designed to measure state and trait anxiety. Both groups showed significantly different anxiety scores for trait [ $t(34) = -5.59$ ,  $p < 0.000$ ] and state [ $t(34) = -5.12$ ,  $p < 0.000$ ] variables. FM patients showed higher anxiety levels than HC participants in both trait and state measures. Additionally, the FM patients filled out the Fibromyalgia Impact Questionnaire, FIQ (Burckhardt et al., 1991), a specific questionnaire to evaluate their current health and functional status. More specifically, the FIQ assesses physical functioning, work, and well-being, and it contains numeric scales for pain, sleep, fatigue, stiffness, anxiety and depression. Once in the laboratory, and just before the beginning of the electrophysiological recording, participants completed the state form of the STAI. The trait scales of the STAI and the FIQ were completed at home.

**Table 1**

Mean and standard deviations of age, education, level of anxiety, functional impact of the disease and time elapsed since the diagnosis. Information about the percentage of participants (healthy controls and fibromyalgia patients) who were taking medications is also included.

Variables	Healthy control participants	Fibromyalgia patients
Age (years)	48 (7.48)	47.8 (8.34)
Education		
Elementary studies (%)	46.66	38.09
Middle level (%)	26.66	24.28
Superior university studies (%)	26.66	37.61
Fibromyalgia Impact Questionnaire (total score)	–	67.58 (10.32)
Item 1 (physical functioning)	–	4.86 (1.88)
Item 2 (well-being)	–	1.81 (1.74)
Item 3 (work)	–	2.00 (1.25)
Item 4 (work/pain)	–	7.86 (1.69)
Item 5 (pain)	–	7.70 (1.75)
Item 6 (fatigue)	–	8.70 (1.50)
Item 7 (fatigue)	–	9.20 (1.14)
Item 8 (stiffness)	–	7.73 (2.31)
Item 9 (anxiety)	–	8.43 (1.47)
Item 10 (depression)	–	7.06 (2.34)
Time elapsed since the diagnosis (months)	–	107.28 (52.49)
Spielberger State Anxiety Inventory (STAI-Trait)	29.69 (27.43)	77.33 (23.42)
Spielberger State Anxiety Inventory (STAI-State)	18.83 (17.37)	54.20 (22.31)
Medications		
Analgesics (%)	0.00	66.66
NSAIDS (%)	0.00	40.00
Tricyclics (%)	0.00	33.33
SSRI (%)	0.00	33.33
Benzodiazepines (%)	0.00	60.00
Others (%)	14.28	80.09

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