



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

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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

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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

## 2.2. Stimuli and procedure

As mentioned in the [Introduction](#) section, the experimental paradigm used in this experiment (an emotional variant of the classical Stroop task) comprised the presentation of linguistic stimuli (words) referred to four different emotional categories: FM symptom-related (SF), arousing-negative or threatening (A−), arousing-positive (A+) and neutral (N). The whole sample of word stimuli used in this study is showed in Table S1 (online only material). The words belonging to the A−, A+ and N categories were selected on the basis of the results from an independent pilot study that was carried out previously to the experiment. A sample of 80 participants (25 women with FM, 25 middle-age healthy women and 30 young healthy women) were asked to rate the content of valence and arousal (the two main dimensions explaining the principal variance of emotional information) conveyed by a wide pool of 120 words (40 per category) by means of a bidimensional scaling test of five positions: valence (from 2, very pleasant, to −2, very unpleasant) and arousal (from 1, very relaxing, to 5, very arousing). Additionally, only the sub-sample of FM patients filled out the part of the scale referring to symptom-relatedness (from 1, not at all related, to 4, very related).

In order to test the validity of the selected words and to confirm that both the word affective valence and the level of arousal for A+, A− and N were that assumed a priori, a series of related-samples *t* tests were performed. These statistical analyses showed significant differences in both affective dimensions. Specifically, they showed significant differences between the mean pleasantness of the A+, A− and N categories of words ( $p < .001$ ), while significant differences in arousal levels were found only between the A+ and N words and the A− and N words, respectively (all  $p < .001$ ). In addition, no A−, A+ or N word was selected if it was observed as significantly rated by the FM subsample as an FM symptom (one sample *t*-tests on symptom-relatedness). Also, the level of familiarity of words rated by this independent sample, along with length of syllable and frequency of usage was equalled according to the Dictionary of Spanish Words ([Alameda and Cuetos, 1995](#)) across the three emotional categories. There were no significant differences between words from each experimental word category in reported 'word familiarity' (all  $p < .001$ ).

Thus, eight words belonging to the categories A+, A− and N were chosen among which complied with the following inclusion criteria: words with high levels of both arousal and pleasantness made up of A+ category, A− category comprised of words with both high arousing and unpleasantness values, and N words had both low levels on valence and arousal. Finally, eight words belonging to the SF category were selected following the list of the 16 clinical signs developed by [Baumstark and Buckelew \(1992\)](#) and from the symptoms and descriptors included in the Fibromyalgia Impact Questionnaire that represents the core concerns of FM patients. For each symptom, a one-sample *t* test for symptom-relatedness was performed, and those rated by the FM subsample as the most characteristic of the FM syndrome were finally chosen. Symptom-related words were significantly more identified with their own symptomatology by the FM group than A+, A− and N words, respectively (all  $p < .001$ ). In the same way, according to the Dictionary of Frequency of Usage of Spanish Words, it was guaranteed that there were no significant differences for length with respect to the A−, A+ and N categories (related samples *t* test;  $p < .001$ ). All of these results support the validity of the selected words and their use in the subsequent analyses.

Thirty-two words were finally selected for the experimental session (8 per category), which were presented in four different colors: red, blue, green and yellow. Thus, each word was presented four times, one by each color. A total of 128 pseudorandomized trials (the same color or stimulus category was not displayed in more than three consecutive trials) were presented (thirty-two for each emotional category: SF, A+, A− and N). All stimuli were substantives written in lower case letter and presented 'one by one'.

Each stimulus subtended about 1.05 vertical and 8.6 horizontal degrees of visual angle at a distance of 60 cm. As illustrated in the [Fig. 1](#), stimulus presentation lasted 300 ms with a fixed intertrial interval of 3000 ms.

Participants sat in an electrically and acoustically isolated room in a comfortable chair. They were told to press the key of a response device with four buttons corresponding to the color of each word as quickly as possible without sacrificing accuracy, while ignoring the meaning of the word. Each key of the response device was marked with a four red, blue, green or yellow color patch. Correspondence of the buttons to the four colors was changed four times along the course of the study. Measures of participant's reaction times, accuracy and ERP data were recorded and subsequently analyzed, as it will be seen in the [Results](#) section. Also, participants were requested to avoid blinking as much as possible and to look continuously at a small cross situated at the center of the screen where words would appear. Before the recording session, participants completed a practice block of eight trials to familiarize them with the task.

In the same way that occurred with the procedure for selecting words, thirty-six participants whose data were finally analyzed, completed a similar bidimensional scaling test for each word after the recording session. This test assessed the familiarity (from 1, very strange, to 5, very familiar), the symptom-relatedness (from 1, not at all related, to 4, very related), the valence (from 2, pleasant, to −2, unpleasant) and the arousal content (from 1, very relaxing, to 5, very arousing) of the words. The results of this test are described in the [Results](#) section.

## 2.3. Electrophysiological recording

Brain electrical activity was recorded using an electrode cap (ElectroCap International) with 60 homogeneously distributed scalp electrodes. All these electrodes were referenced to mastoids. Vertical and horizontal eye movements were controlled through an electrooculographic (EOG) recording. Electrodes were located infra- and supraorbitally (vertical EOG) as well as at the left and the right orbital rim (horizontal EOG). All electrode impedances were kept below 5 k $\Omega$ . A bandpass filter of 0.1–40 Hz (3 dB points for −6 dB/octave roll-off) was applied for the recording amplifiers. Further, data were digitally filtered with a 30 Hz 24 dB/octave low-pass filter. Channels were continuously digitizing data at a sampling rate of 250 Hz throughout the entire recording session. The continuous recording was divided into 1200 ms epochs for each trial, beginning 200 ms before stimulus onset. Baseline correction and EEG visual inspection was also carried out eliminating epochs with artifacts for further analyses. Additionally, data from fourteen out of the fifty participants were removed because: a) they deviated by more than 40% from the correct responses or b) due to the high rate of deleted trials (over 25%). ERP averages were categorized according to each type of stimulus: A+, A−, N and SF words.

## 2.4. Statistical analysis

### 2.4.1. Detection and quantification of ERPs: temporal principal component analysis

A temporal principal component analysis (tPCA) performed through covariance matrix was applied in order to detect and quantify the ERP components explaining most of the brain electrical activity variance. This technique has been strongly recommended for these tasks since its application avoids the subjectivity of selecting time windows for component analyses based on a visual inspection of grand-averaged ERPs. It can lead to several types of misinterpretation, especially when high-density montages are employed (see [Dien et al. \(2005\)](#) for a more detailed description of tPCA procedure and advantages). The main advantage of tPCA is that it represents each ERP component with its 'clean' shape, extracting and quantifying it free of the influences of adjacent or subjacent components. Indeed, the waveform recorded at a site on the head over a period of several hundreds of milliseconds

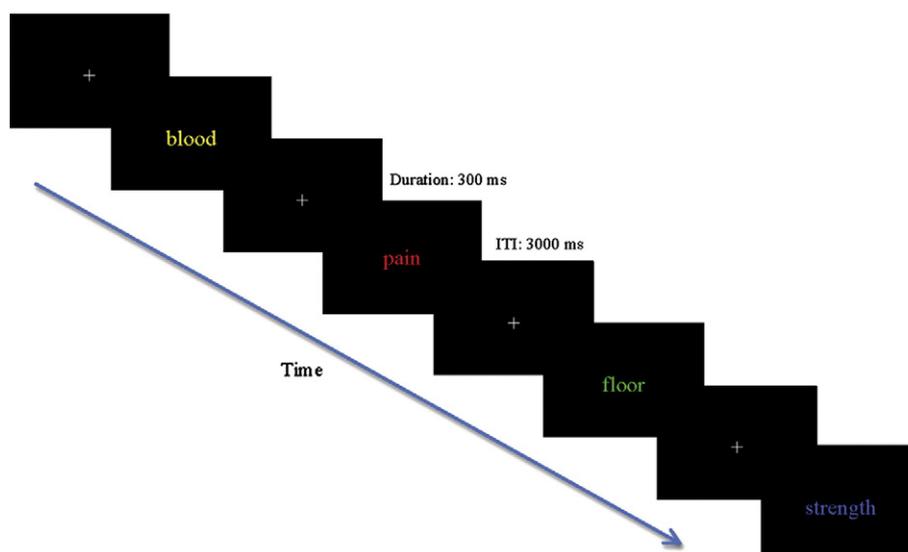


Fig. 1. Schematic representation of the emotional Stroop task described in the main text. ITI = inter-trial interval.

represents a complex superposition of different overlapping electrical potentials. Such recordings can stymie visual inspection. Additionally, this analysis can also facilitate efforts for source estimation analyses. In brief, the tPCA computes the covariance between all ERP time points, which tends to be high between those time points involved in the same component, and low between those belonging to different components. The solution is therefore a set of different factors made up of highly covarying time points, which ideally correspond to ERP components. Temporal factor score, the tPCA-derived parameter in which extracted temporal factors may be quantified, is linearly related to the amplitude of components. The decision on the number of factors to extract was carried out through the application of the scree test (Cliff, 1987). Selected factors were Promax rotated as recently recommended (Dien et al., 2005).

#### 2.4.2. ERP-waves and behavioral analyses

Analyses required the ERPs, recorded at 60 globally distributed scalp points, to be grouped into different scalp regions, since signal overlapping may occur also at the space domain and ERP components frequently behave differently in some scalp areas to others (e.g., present opposite polarity). At any time point, several electrical signals (underlying several neural processes) may coexist, and we have to be able to separate these different neural processes from the global electrical balance, which is recorded at any scalp site at a specific moment. While tPCA allows solving temporal overlapping of ERP components, spatial PCA (sPCA) separates ERP components along the space. In this sense, each spatial factor would ideally reflect one of the concurrent neural processes underlying each temporal factor. Therefore, this configuring and quantifying scalp region system is preferable to an a priori subdivision into fixed scalp regions for all components, since sPCA demarcates scalp regions according to the real behavior of each scalp-point recording (basically, each region or spatial factor is formed with scalp points where recordings tend to covary). Consequently, the shape of the sPCA-configured regions is functionally based, and scarcely resembles the shape of the traditional, geometrically configured regions. sPCAs were carried out, for each of the temporal factors, on their spatial factor scores representing, in this case, the single parameter that reflects the amplitude of the whole spatial factor. This regional grouping was determined through a covariance matrix-based spatial PCA and, also in this case, the decision on the number of factors to extract was based on the scree test. Extracted spatial factors were submitted to promax rotation. This analysis procedure comprised of both tPCA and sPCA has been

recommended to explore emotional processing through ERP (Pourtois et al., 2008).

In relation to ERP data, experimental effects were tested computing repeated-measures ANOVAs on the spatial factors of each temporal factor using word category (four levels: SF, A+, A– and N) and group of participants (two levels: FM and HC) as variables. Reaction time (RT) information and number of errors were included in the analyses to test behavioral data. Repeated-measures ANOVAs on RTs and number of errors were computed using the same factors included for analyses on the brain activity. The Greenhouse–Geisser (GG) epsilon correction was applied to adjust the degrees of freedom of the  $F$  ratios where necessary, and post hoc comparisons to determine the significance of pairwise contrasts were performed using the Bonferroni procedure ( $\alpha < 0.05$ ). Relationships between ERP amplitudes and both behavioral data and information from clinical questionnaires were assessed by mean regression analyses. Finally, possible effects of medication were also tested in the FM group for patients using and not using medications through a one-way analysis of variance model.

#### 2.4.3. Source-estimation

In order to explore cortical regions that could account for the experimental effects, standardized low-resolution brain electro-magnetic tomography (sLORETA) was applied to relevant temporal factor scores in accordance with the ANOVA results, as it will be explained later. sLORETA is a 3D, discrete linear solution for the EEG inverse problem (Pascual-Marqui, 2002) which refers to a three-shell spherical model registered to the MNI305 digitized structural human brain atlas template. Solutions are given, therefore, in three coordinates: 'x' is the distance in millimeters to the right (+) or left (–) of midline, 'y' is the distance anterior (+) or posterior (–) to the anterior commissure, and 'z' is the distance above (+) or below (–) a horizontal plane through the anterior and posterior commissures. Although, in general, it is recommended to interpret with caution EEG-based source-estimation solutions due to their potential error margins, LORETA solutions have shown significant correspondence with those provided by hemodynamic procedures in the same tasks (Mulert et al., 2004; Vitacco et al., 2002). Moreover, under ideal conditions solutions provided by sLORETA, being based on distributed brain activity, have no localization bias. In the present experiment we tried to minimize this error margin using the tPCA derived factor scores instead of voltages. This strategy has provided more accurate source-estimation analyses (Carretie et al., 2004). In its current version, sLORETA computes the standardized

current density at each of 6239 voxels in the cortical gray matter and the hippocampus.

Therefore, in order to identify the brain regions underlying cognitive inhibition processes, a two-step analysis was carried out for the temporal factor that was sensible to experimental manipulations (TF2: P450). In the first step, the voxel-based whole-brain sLORETA-images were compared among four experimental conditions (words belonging to SF, A–, A+ and N emotional categories) not taking into account the group (FM or HC). To that aim, sLORETA built-in voxelwise randomization tests (5000 permutations) based on statistical non-parametric mapping (SnPM) methodology were used. In the next step, we based on a region-of-interest (ROI) approach in order to explore the modulatory influences of the four emotional word categories over regions defined in the previous step for both groups – FM patients and HC participants. Thus, current densities of different ROIs (radius = 5 mm) were submitted to ANOVAs using emotional word category (four levels: SF, A–, A+ and N) and group (FM and HC) as factors. In addition, regression analyses with symptoms-relatedness stimuli, RTs, number of errors and comorbid factors (psychological, pain, and medication) taken as independent variables were carried out.

### 3. Results

#### 3.1. Control analyses

Assessments given by the participants on the valence, the arousal and the familiarity perceived for A+, A– and N words were analyzed in order to confirm what it was assumed a priori. Therefore, one-way repeated-measures ANOVAs were computed for the three mentioned variables, using stimuli (three levels: A+, A–, and N) as a factor. Post hoc comparisons were made to determine the significance of pairwise contrasts, using the Bonferroni test ( $\alpha = .05$ ). ANOVAs yielded significant differences in valence [ $F(2,68) = 189.754, p < .000$ ] and arousal [ $F(2,68) = 22.939, p < .000$ ], but did not reach significance in word familiarity [ $F(2,68) = 1.092, p = .303$ ]. Post-hoc contrasts indicated that A+ and A– showed different valence but not different arousal. Furthermore, A+ and A– differed from N in both arousal and valence. Additionally, one-way repeated-measures ANOVA tested the relationship between the set of words selected and FM symptoms using stimuli (four level: SF, A+, A– and N) as a factor. Significant differences were found [ $F(3,42) = 163.611, p < .000$ ] showing (through post hoc comparisons) that symptom-related words were perceived by FM patient as a part of their own symptoms compared to A+, A– and N words. Data about mean values for valence, arousal, familiarity and symptom-relatedness of the four word categories are displayed in Table 2. All of these results support the validity of the selected words and their use in the subsequent analyses.

#### 3.2. Behavioral data

Average values for RTs and number of errors for the four word categories (separated by group of participants) can be seen in the Table 3. We carried out two-way repeated-measures ANOVAs  $4 \times 2$  on the two mentioned variables regarding the interaction where we focused our main interest: word category by group of participants. Although RTs and number of errors made by FM patients to SF words

were faster and smaller, respectively, than the rest of stimuli, analyses did not reach significance for none of the two behavioral indices: RT [ $F(3,102) = 1.245, p = .297$ ] and number of errors [ $F(3,102) = 0.442, p = .704$ ] between FM patients and HC participants. Only a main effect was found to word category associated with both RTs [ $F(3,102) = 4.107, p = .011$ ] and number of errors [ $F(3,102) = 3.412, p = .025$ ]. With respect to RTs, trials linked to SF words showed faster RTs than A+ and N words. In the case of the number of errors, it was smaller for SF words compared to N words. With respect to the medication variable, patients using medication did not show different performance in both behavioral measure accuracy [ $F(3,39) = 2.215, p = .106$ ] and RTs [ $F(3,39) = 1.697, p = .187$ ] than patients not using such medication.

Stepwise regression analyses were carried out in the FM group, however, no significant predictors for behavioral indices (RTs and number of errors) were found among trait anxiety ( $\beta = 0.004, p > 0.05$ ;  $\beta = 0.006, p > 0.05$ ), state anxiety ( $\beta = -0.102, p > 0.05$ ;  $\beta = -0.342, p > 0.05$ ), the score in the FIQ Questionnaire ( $\beta = 0.069, p > 0.05$ ;  $\beta = 0.038, p > 0.05$ ) and in the item number five (pain) of this instrument ( $\beta = -0.083, p > 0.05$ ;  $\beta = -0.175, p > 0.05$ ).

#### 3.3. ERP data

Grand averages for the experimental conditions, once the baseline value has been subtracted from each ERP, are displayed in Fig. 2. This selection shows the most relevant experimental results (i.e., interaction between category of words and group of participants) related to the component P450 reflecting the interference conflict and cognitive inhibition processes (these effects will be detailed subsequently). Scalp locations where effects are more clearly appreciable are shown. As a consequence of the tPCA application, four temporal factors (TFs) were extracted from the ERPs (see Fig. 3 to observe the correspondence between ERP components and TFs derived from the application of the tPCA). These extracted factors explained 79.91% of the total variance (47.34%, 19.62%, 6.74% and 6.19%, respectively). Factor peak latency and topography distribution, maximal at frontal scalp sites, associate TF2 (peaking at 488 ms) with the wave signaled in the grand averages as P450 (Figs. 2 and 3). Through the subsequent application of the sPCAs to temporal factor scores four spatial factors were established for each temporal factor. As it was described earlier, ANOVAs on the spatial factor scores (directly related to amplitudes, as previously indicated) for each temporal factor were carried out. They included two factors: word category (four levels: SF, A+, A– and N) and group of participants (two levels: FM patients and HC). Spatial frontal factor of P450 reached statistical significance for the interaction word category by group of participants [ $F(3,102) = 4.006, p = .013$ ]. Post-hoc comparisons (Bonferroni; adjusted  $\alpha = .05$ ) showed that SF words elicited greater amplitudes than the rest word categories. This effect was significant only for patients with FM. The rest of pairwise comparisons were not significant according to these post hoc contrasts. Although a strong tendency to be significant was observed for word category, analyses did not reach significance [ $F(3,102) = 2.797, p = .06$ ]. When we tested main effects for group of participants no statistical significance was found either [ $F(1,34) = 2.064, p = .160$ ]. Finally, FM patients whose were taking medications did not significantly showed different P450 amplitude than patients not using this clinical treatment [ $F(3,39) = 0.707,$

**Table 2**

Means and standard deviations (in parenthesis) for the valence, arousal, and familiarity of the emotional word categories (A+, A–, N) evaluated by the whole sample of participants. Data for symptom-relatedness were evaluated from the sample of FM patients. Information about p-values for each statistical contrast is included.

	A+	A–	N	SF	p-Value
Valence	1.05 (.062)	– 1.13 (.091)	0.46 (.071)	–	0.000
Arousal	3.66 (0.82)	4.93 (1.05)	4.46 (0.95)	–	0.000
Familiarity	3.65 (.105)	6.59 (2.730)	3.89 (.117)	–	0.303
Symptom-relatedness	1.55 (.108)	1.66 (.108)	1.23 (.063)	3.70 (.108)	0.000

**Table 3**

Means and standard deviations (in parenthesis) of reaction times (RTs) and number of errors to each word category (FM symptom, negative-arousing, positive-arousing and neutral). Data are separated by group of participants: fibromyalgia (FM) and healthy control (HC).

		FM symptom-related words	Negative-arousing words	Positive-arousing words	Neutral words
FM group	RTs (ms)	1107.23 (75.55)	1184.68 (88.09)	1145.74 (85.10)	1173.51 (74.07)
	Number of errors	3.66 (0.82)	4.93 (1.05)	4.46 (0.95)	5.13 (0.92)
HC group	RTs (ms)	976.60 (63.85)	1011.16 (74.45)	1043.80 (71.92)	1022.99 (62.60)
	Number of errors	3.19 (0.69)	3.71 (0.88)	4.04 (0.80)	4.21 (0.78)

p-Values for behavioral indices.

RTs ( $p = 0.297$ ).

Errors: ( $p = 0.702$ ).

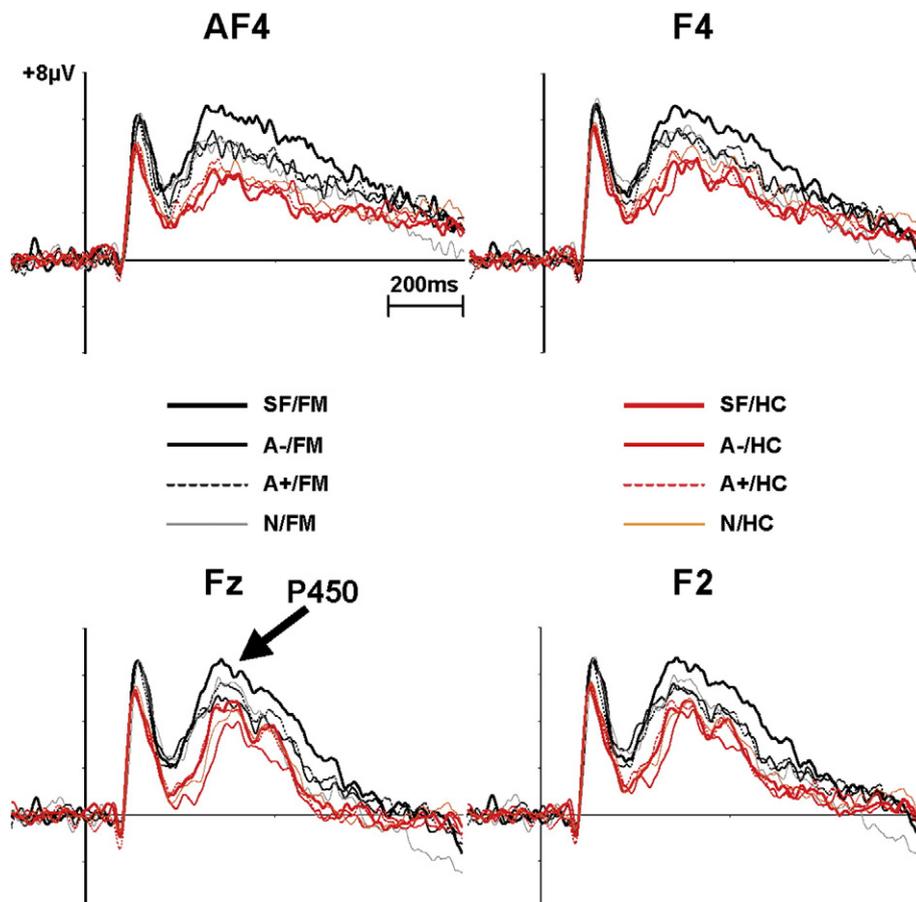
$p = .554$ ]. When analyses were conducted taking into account medications (benzodiazepines:  $F(3,39) = 0.947$ ,  $p = .415$ ; SSRI:  $F(3,39) = 1.709$ ,  $p = .189$ ; tricyclics:  $F(3,39) = 0.946$ ,  $p = .416$ ), was not neither found any effect on P450 amplitudes.

In the same way that occurred with respect to behavioral data, stepwise regression analyses were carried out in the FM group. Again, no significant predictors for P450 amplitude were found when we studied their association with trait anxiety ( $\beta = -0.254$ ,  $p > 0.05$ ), state anxiety ( $\beta = -0.118$ ,  $p > 0.05$ ), the score in the FIQ Questionnaire ( $\beta = 0.168$ ,  $p > 0.05$ ) and in the item number five (pain) of this instrument ( $\beta = 0.397$ ,  $p > 0.05$ ).

**3.4. Source estimation data and their relationship with affective assessment and behavior**

In order to explore the cortical regions that could account for the experimental effects, sLORETA was applied to the temporal factor scores

of P450, in accordance with the ANOVA results, for each participant, electrode and experimental condition. Firstly, in order to characterize brain areas involved in cognitive inhibition processes the voxel-based whole-brain sLORETA-images were compared among the four experimental conditions (words belonging to SF, A-, A+ and N emotional categories) for the whole sample of participants. To this aim statistical non-parametric randomization tests were performed. According to the computed comparisons three brain regions showed significant differences ( $t = 3.665$ ,  $p < .05$ ;  $x = 35$ ,  $y = 55$ ,  $z = 0$ ; BA10), ( $t = 3.709$ ,  $p < .05$ ;  $x = -65$ ,  $y = 25$ ,  $z = 10$ ; BA31), ( $t = 3.699$ ,  $p < .05$ ;  $x = 60$ ,  $y = 10$ ,  $z = 10$ ; BA44). Secondly, and as it was previously mentioned, possible cognitive inhibition dysfunctions in FM were analyzed in more detail using a region of interest (ROI) analysis. ROIs were defined with a radius of 5 mm according the MNI coordinates extracted from the non-parametric tests. ANOVAs were performed (group of participants: two levels and word categories: four levels) with repeated measures on each ROI. As it is showed in Fig. 4, the



**Fig. 2.** Grand averages corresponding to fibromyalgia (FM) and healthy control (HC) participants in response to FM symptoms (SF), negative-arousing (A-), positive-arousing (A+) and neutral (N) stimuli. Scales and polarity are shown at AF4.

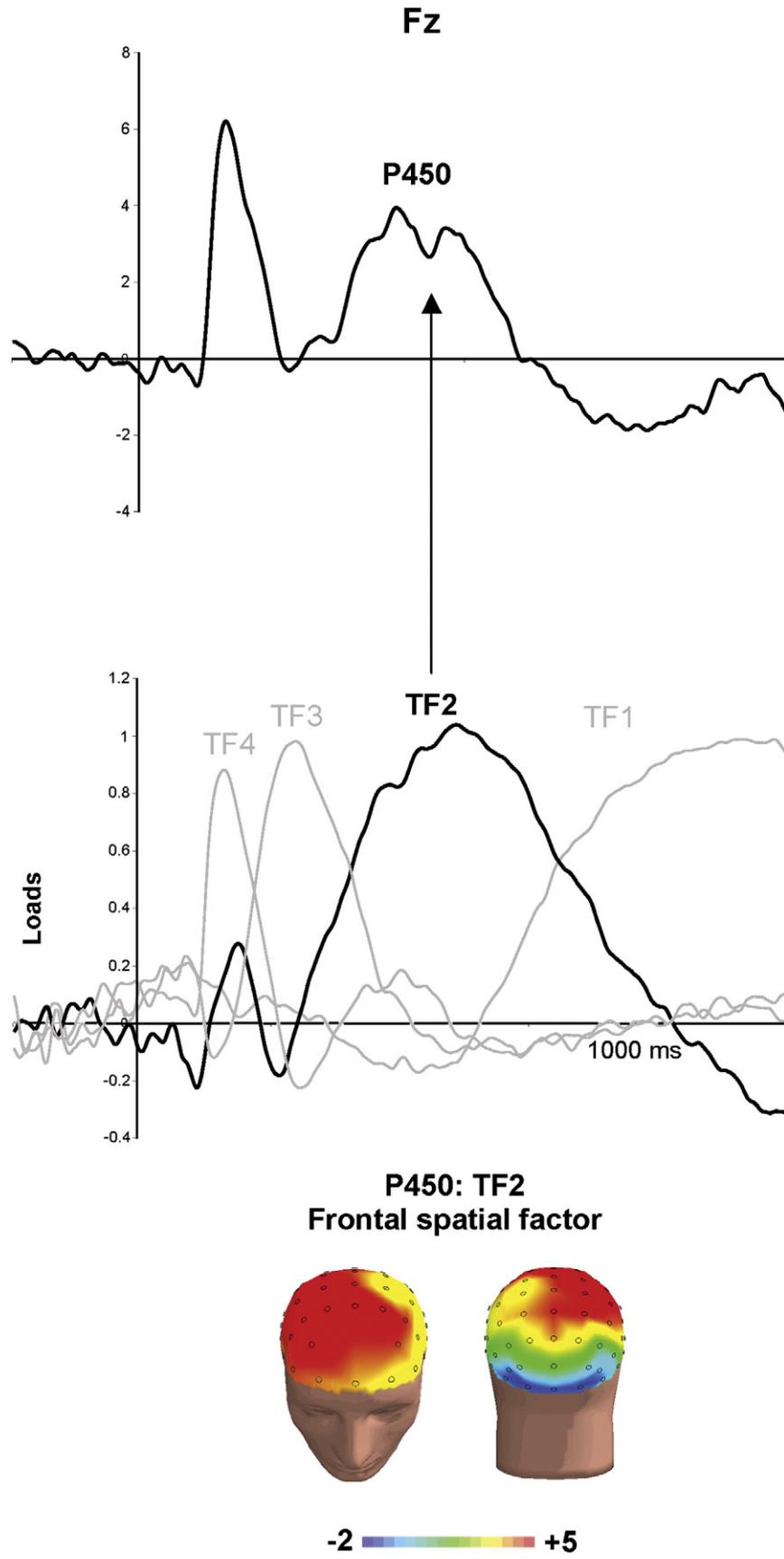


Fig. 3. tPCA: Factor loadings after Promax rotation. Temporal factor 2 (P450) is highlighted in bold. 3D maps show topographical distribution of the P450 component. Red areas reflect high activity.

ROI located within BA44 (right inferior frontal gyrus: IFG) revealed significant differences for the interaction group by word category [ $F(3,102) = 5.566, p < 0.01$ ]. Post hoc comparisons showed greater cortical activity within the right IFG for FM patients in response to SF word category compared to the rest of stimuli. Potential effects of medication were also tested in the FM group, but differences in activity within rIFG between patients with and without medication did not reach statistical significance [ $F(3,39) = 3.050, p = .088$ ].

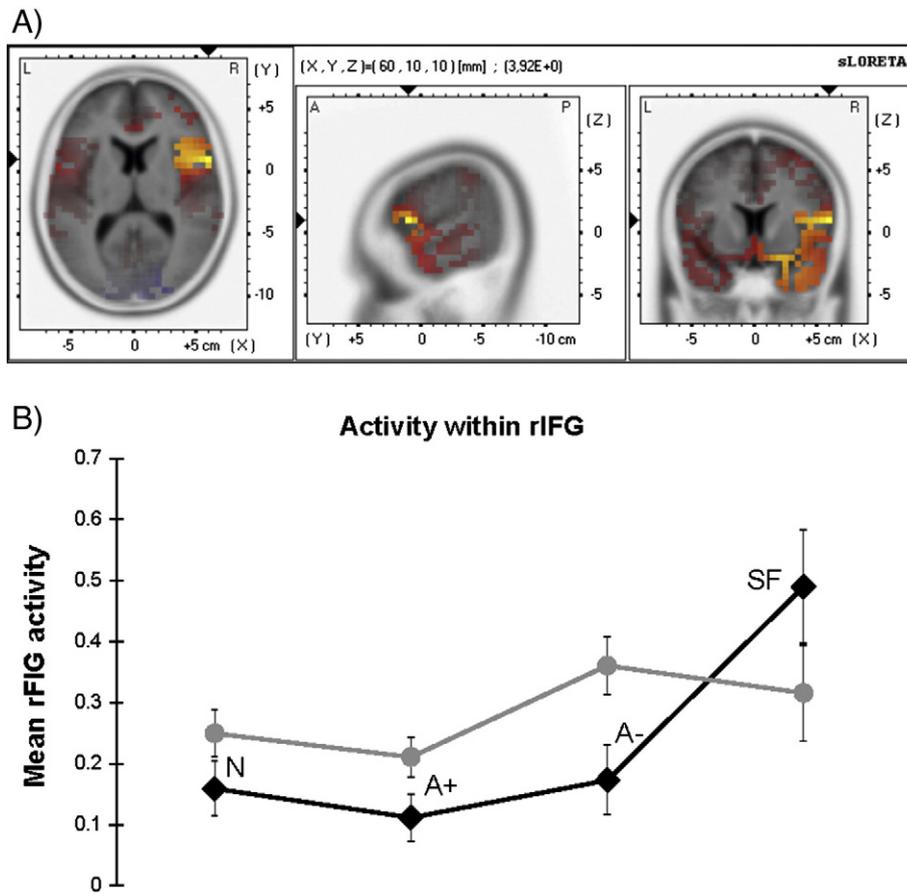
Another important issue to explore was how stimuli symptom-relatedness and behavioral indices (RTs and number of errors) were associated to cognitive inhibition processes on right IFG activity showed in FM patients. All of these data were analyzed using multiple regression through the stepwise method. Whereas right IFG cortical activity was the dependent variable, stimuli symptom-relatedness and behavioral indices were taken as predictor variables. Although a strong association with stimuli symptom-relatedness can be expected looking at previous results (SF produced greater activity in right IFG than other words), this trend should be statistically confirmed. Thus, this variable was significantly associated with right IFG activity in FM ( $\beta = 0.496, p < 0.001$ ), presenting its linear association a positive slope: the higher the former, the greater the latter. Additionally, the possible interrelations between behavior performance, anxiety (trait and state), pain and cortical activity on right IFG were also tested. Anxiety (only trait variable) was inversely associated with right IFG ( $\beta = -0.331, p < 0.01$ ). Despite that behavioral indices (mainly number of errors) showed a strong statistical trend, their association with right IFG

cortical activity did not reach statistical significance (number of errors:  $\beta = -0.225, p = 0.08$ ; RTs:  $\beta = 0.074, p > 0.05$ ). Finally, neither score in the FIQ questionnaire ( $\beta = -0.020, p > 0.05$ ) nor in the item number five of that scale (directly related with level of pain) showed any statistical association with IFG activity ( $\beta = 0.136, p > 0.05$ ).

**4. Discussion**

The present study aimed to characterize cognitive inhibition responses in FM through an emotional Stroop paradigm. Brain activity analyses revealed a prominent emotional Stroop interference effect in FM patients. Main results have shown that the cognitive inhibition of a very automatic response (i.e., such as reading a word) elicited greater frontal P450 amplitudes in FM individuals when symptom-related stimuli were processed as compared to the rest of stimuli. Beyond ERP activity, the activation detected within right inferior frontal gyrus (rIFG) was also strongest for FM symptom-related words. Despite task performance between patients and healthy participants showed a clear trend to be different, however it was not statistically significant. A careful functional interpretation of the present data in relation to clinical variables (anxiety, pain, etc.) is given as follows.

Previous studies have demonstrated that ERP modulations peaking between 400 and 550 ms post stimulus (component usually called as N450) are involved in elaborative cognitive processes, such as conflict detection, attentional control or cognitive inhibitory mechanisms (van



**Fig. 4.** rIFG activity from the emotional Stroop task for patients with fibromyalgia (FM) and healthy control participants (HC). A) Shows sLORETA solutions to non-parametric randomization tests on P450 temporal factor scores. Voxels where the group  $\times$  stimuli contrast reached statistical significance are represented ( $p < 0.001$ ). Three orthogonal brain views in MNI305 template, sliced through the region of maximum activity, are illustrated. B) Shows mean rIFG activity for FM patients and HC participants across the four word categories: FM symptoms (SF), negative-arousing (A-), positive-arousing (A+) and neutral (N) stimuli Error bars reflect standard errors. Black line represents rIFG activity for FM patients and, gray line, for HC participants.

Hooff et al., 2008; Badzakova-Trajkov et al., 2009). Specifically, during classical Stroop tasks, the amplitude of N450 is modulated by the congruence between the word and the ink color, being larger when incongruent trials appear (Markela-Lerenc et al., 2004) as a reflect of higher allocation of cognitive inhibition resources to reduce interference (Lansbergen et al., 2007; Langenecker et al., 2004). Several studies have also found this attentional control effect in emotional Stroop experiments (Taake et al., 2009). McNeely et al. (2008) found a higher processing of negative and/or positive words reflected by the amplitude of N450 over left frontal scalp regions, suggesting the set in motion of an underlying interference process mainly triggered by events capable of automatically capture attention, such as those conveying affective meaning (van Hooff et al., 2008).

Although identification of present component with those obtained from previous ERP studies may be not direct due to differences in polarity, P450 here detected could be assimilated to the Stroop interference components. Requirements linked to the emotional Stroop task, inhibiting a cognitive learned routine (accessing to the meaning of a read word) and focusing on ink color, lead us to consider that the type of attentional control process reflected by P450 is mainly associated with cognitive inhibition. Thus, the largest amplitude of P450 elicited by FM symptom-related words is in line with previous emotional Stroop studies where N450 amplitude is also modulated by words with emotional valence (McNeely et al., 2008; Thomas et al., 2007), reflecting capture of attention by these words and reinforcing the idea that cognitive inhibitory anomalies are reflected by this component. Additionally, others investigations have involved enhanced amplitudes of both N450 and P450 in stroop interference processes. However, whereas N450 is prominent at frontocentral and parietal sites, P450 shows greatest positivities at lateral frontal sites (Lansbergen et al., 2007) as it has been here described. Moreover, P450 component originated within the IFG which has been related to the allocation of cognitive inhibition resources (Aron et al., 2004; Aron, 2007). Consequently, current P450 could be defined as ERP wave related to cognitive inhibition and it would share similar functional meaning as N450. Therefore, taking these assumptions into account, prominent P450 amplitudes in response to symptom-related stimuli in FM lead us to think that this interference effect would be reflecting difficulties in stopping an unwanted cognitive process (i.e., investing a greater effort to avoid attentional capture and interference: accessing the meaning of the word) due to the special relevance of stimuli (i.e., symptom-related information).

Another relevant issue to be debated is the nature of the attentional mechanisms underlying cognitive inhibition difficulties in FM. It has been proposed that FM patients are characterized by hypervigilance towards pain-related information (Gonzalez et al., 2010; Carrillo-de-la-Pena et al., 2006; Rollman, 2009). Such attentional mechanisms have been applied to explain the cognitive dysfunction often displayed by chronic pain patients during tasks demanding executive control processes (Crombez et al., 2005). Recent neurocognitive models based on mentioned constructs could help us to explain stroop interference effects taking into account interactive influences of bottom-up and top down attentional mechanisms (Legrain et al., 2009). Thus, pain and other FM symptoms represent relevant signals that could have a privileged access to attentional resources in order to select actions aimed to face them. Hence bottom-up driven resources might be quite automatically directed towards such stimulation, due to its special salience. However, when the individual priority is assigned onto the processing of cognitive tasks, top-down selection can modulate bottom-up influences (Bar, 2003). Given this, the fact that P450 amplitudes are enhanced when FM individuals process symptom-related information might be reflecting a supplementary allocation of top-down resources trying to maintain goal-relevant priorities in order to perform in the cognitive task. Interestingly, the specialized prefrontal network including Dorsolateral prefrontal cortex (DLPFC), ACC and IFG, has been shown to recruit top-down resources (Duncan and Owen, 2000) modulating both

attention towards nociceptive stimuli (Tracey and Mantyh, 2007) and maintaining cognitively-relevant priorities (Lavie and Fockert, 2006).

According to our results, rIFG recruited the greatest neural activation in FM individuals when symptom-related stimuli were displayed. This brain region has been identified as one of the key structures implicated in control interference and cognitive inhibition, along with ACC (Markela-Lerenc et al., 2004; Aron, 2007). The role played by IFG in inhibition is further supported by neuroimaging studies where the speed and efficiency of action stopping were predicted by the extent of activation within the rIFG (Aron, 2007, 2008) as well as during performance in Stroop tasks (Langenecker et al., 2004). Additionally, some investigations have detected significant activation within inferior frontal cortices during the inhibition of unwanted memories (Anderson et al., 2004) and the retrieval of a specific painful experience among other competing targets (Kelly et al., 2007).

Despite that important differences were found in cerebral activity between FM patients and HC participants, behavioral results have showed no group differences in RTs and accuracy. Lack of empirical data combining behavioral and neural indices in response to cognitive tasks in FM made hypothesizing tentative explanations difficult. A possible explanation for these unexpected behavioral results can be found in the attentional control theory proposed by Eysenck et al. (2007). Following their theoretical view, anxiety is considered as an important factor that can negatively affect the efficient neural functioning of attentional control processes (Fales et al., 2008). As mentioned before, FM patients showed a higher level of anxiety (trait and state) compared to HC participants. Given this context, FM would impair efficiency (e.g., increased use of processing resources) in performance but not effectiveness (i.e., accuracy and TR) promoting the use of compensatory attentional control resources (i.e., cognitive inhibition) to achieve only a HC comparable performance. Although results from studies using modified Stroop tasks have generated mixed evidence (Roelofs et al., 2002; Crombez et al., 2000) on behavioral performance when chronic pain patients and healthy participants were compared, our results are similar to previous ERP and neuroimaging studies focused on either cognitive inhibition using emotional Stroop task (McNeely et al., 2008) or motor inhibition in FM using Go-Nogo task (Glass et al., 2011). Another plausible explanation could be associated with the idea that very simple experimental tasks (as the one was used in the present study: naming of the ink color of words) do not allow to emerge deficits in the performance of individuals with FM (Glass, 2009; Glass et al., 2011), because such alterations are frequently only described when tasks with high cognitive load are used (Leavitt and Katz, 2006). Further studies taking into account this point are needed to solve such limitation.

Therefore, we suggest that enhancement of both P450 amplitudes and the activity detected within IFG in patients with FM could be reflecting the activation of a compensatory mechanism to keep behavioral performance in an acceptable level through an extra recruitment of top-down attentional control resources. These effects lead to think that brain activity techniques might be more sensitive to detect subtle dysfunctions than behavioral measures alone such as often occurs in FM patients (Glass et al., 2011).

Finally, different aspects associated with pharmacological treatments of patients should be considered as a possible limitation, since it has been proposed as a source of potential influence over cognitive performance. Some patients in our study were taking benzodiazepines and antidepressants. Although benzodiazepines and antidepressants have been reported as substances affecting cognition in different degrees, two facts lead us to think that our patients kept free from such influence. Evidence has mainly related benzodiazepine influence over temporal lobe functions, mainly memory processes (Ghoneim, 2004; Puga et al., 2005), but not over processes directly linked to prefrontal regions. On the other hand, several studies have showed that low antidepressant doses (like those being taken by our patients) are unlikely to affect cognition (Grisart et al., 2002) and it could even produce an improvement in cognitive efficacy

(Wroolie et al., 2006). In addition, in light of results obtained in our study, cognitive inhibition functions in concrete do not seem affected by potentially psychoactive drugs. Nevertheless, a more efficient control of medication in FM would contribute an improvement for future studies (Roldán-Tapia et al., 2007). Finally, the influence of other potentially important symptoms in FM, such as depression, catastrophism or sleep disturbances (Reyes del Paso et al., 2012) would be interesting to analyze in future studies.

In summary, our findings indicate greater prefrontal neural activity (i.e., P450 amplitudes and activity detected within rIFG) in FM patients relative to HC participants during a cognitive inhibition task, mainly when FM symptom-related information is processed. However, this interference effect was not found at the behavioral level. We hypothesize that enhanced rIFG activity and P450 amplitude could be reflecting the activation of a compensatory mechanism to maintain the performance in the cognitive task through a supplementary recruitment of top-down cognitive inhibitory resources. Dysfunctional consequences for patients who commonly undergo stressful conditions (i.e., chronic pain and fatigue) could be derived from this over-effort. Although further studies should be done to delimitate attentional control deficits in FM, current data suggest some relevant implications to better understand cognitive dysfunction in these patients in order to develop neuropsychological rehabilitation programs aimed to improve self-regulation abilities such as the capability to inhibit thoughts or change feelings (Solberg Nes et al., 2009) reducing the functional impact of the disease.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijpsycho.2013.03.017>.

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