Temporal preparation and inhibitory deficit in fibromyalgia syndrome

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RUNNING HEAD: Fibromyalgia and temporal orienting

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Abstract
Cognitive deficits in fibromyalgia may be specifically related to controlled processes, such as those measured by working memory or executive function tasks. This hypothesis was tested here by measuring controlled temporal preparation (temporal orienting) during a response inhibition (go no-go) task. Temporal orienting effects (faster reaction times for targets appearing at temporally attended vs. unattended moments) and response inhibition were impaired in fibromyalgia compared to the control group. It is concluded that frontal networks underlying attentional control (temporal orienting and response inhibition) can be a dysfunctional neurocognitive mechanism in fibromyalgia.

Keywords: attention; temporal orienting; response inhibition; go no-go task; controlled processing; fibromyalgia.
INTRODUCTION

The ability to anticipate and prepare efficient responses to forthcoming events, temporal preparation, is important for many tasks including attention, learning, language and motor control (Nobre, Correa, & Coull, 2007). However, temporal preparation has rarely been evaluated in clinical settings, probably because this function and the cognitive tasks to measure it are not well known so far. The aim of the present research was to test temporal preparation in patients diagnosed of fibromyalgia.

Fibromyalgia is a chronic pain syndrome of unknown cause characterized by widespread musculoskeletal pain for a minimum of 3 months and pain elicited by digital palpation of at least 11 out of 18 specified bilateral tender points (Wolfe et al., 1990). The prevalence of fibromyalgia is estimated to appear in 2-5% of the population, and it predominantly affects women who are typically diagnosed during their working years, which leads to substantial social and economic costs (White et al., 2008). Pain is considered the core feature of fibromyalgia, but patients may also suffer from many other symptoms such as fatigue, poor sleep quality, depressive and anxious symptoms, stiffness, numbness, cold sensitivity, irritable bowel syndrome, headaches, or cognitive dysfunction (Spaeth & Briley, 2009). Patients with fibromyalgia frequently have subjective cognitive complaints that contribute to the overall disability of the syndrome. However, only a few studies have investigated whether such cognitive complaints are objectively present.

Research on cognitive functioning has reported main impairments in working memory
in patients with fibromyalgia versus healthy controls (see Glass, 2009; Glass & Park, 2001, for reviews). Recently, there is an increasing number of studies also reporting cognitive deficits in tasks demanding attention and executive control, such as the Paced Auditory Serial Additions Test (Grace, Nielson, Hopkins, & Berg, 1999, Mungia-Izquierdo, Legaz-Arrese, Moliner-Urdiales, & Reverter-Masía, 2008), Test of Everyday Attention (Dick, Eccleston, & Crombez, 2002, Dick, Verrier, Harker, & Rasquiq, 2008), Trail Making Test (Mungia-Izquierdo et al., 2008), Wisconsin Card Sorting Task and Iowa Gambling Task (Verdejo-García, López-Torrecillas, Pita Calandre, Delgado-Rodriguez, & Bechara, 2009). However, no such deficits have been found when attention was measured through less demanding tasks, such as the Attention/Concentration Index of the Wechsler Memory Scale (Grace et al., 1999).

These divergent results suggest that attention deficits might be mainly observed on tasks demanding controlled attention to select relevant from distracting information rather than on tasks not involving distraction (e.g., digit span, digit symbol).

Although a precise aetiology of these cognitive deficits remains unknown, current research is establishing clear links between fibromyalgia symptoms (i.e., pain, fatigue and sleepiness), neurophysiology of frontal brain networks and deficits in controlled attention. Anatomical studies have found reduced gray matter volume in the cingulo-frontal cortex and amygdala in patients with fibromyalgia (Burgmer et al., 2009; Kuchinad et al., 2007). Moreover, neurocognitive deficits linked to fibromyalgia show significant correlations with local brain morphology changes in the frontal lobe and anterior cingulated gyrus (Luerding, Weigand, Bogdahn, & Schmidt-Wilcke, 2008). These areas are typically involved in both executive functions (Pardo, Pardo, Janer, & Raichle, 1990) and pain processing, since their
metabolic activity increases during painful stimulation in fibromyalgia patients (Gracely et al., 2004). This neural overlapping between pain and executive function is also evident behaviourally, since pain processing can compete for attention resources and therefore impair controlled processing (see Solberg Nes, Roach, & Segerstrom, 2009, for a review). Likewise, research on sleep and fatigue has shown clear associations with executive dysfunction (e.g., Altena et al., 2008).

The above studies hence suggest that behavioural impairments in executive control may be mediated by those fibromyalgia symptoms (pain, sleep, fatigue) that typically produce malfunctioning of frontal networks. Therefore, it may be hypothesised that attention deficits in fibromyalgia would be mainly observed in tasks demanding controlled attention. The present study measured controlled temporal preparation and response inhibition during a go no-go task in fibromyalgia and control participants to test this hypothesis.

Temporal preparation is generally measured by presenting a warning signal, a preparatory interval and a target stimulus to which participants have to respond as quickly as possible. Recently, it has been demonstrated that preparation can be intentionally controlled by providing explicit and predictive temporal information to the warning signal. This type of temporal preparation was termed 'temporal orienting of attention' by Coull and Nobre (1998), in analogy to the orienting of attention in the spatial rather than the temporal dimension (Posner, 1980). In temporal orienting studies, the warning signal acts as temporal cue indicating with high probability (e.g., p = 0.75) whether the target will appear early (e.g., at the short 400-ms interval) or late (e.g., at
the long 1400-ms interval). Temporal orienting effects are indexed by faster RTs for targets appearing at validly cued intervals (e.g., early cue – short interval) as compared to invalidly cued intervals (e.g., late cue – short interval, leading to an earlier than expected target).

Temporal orienting involves controlled temporal preparation (see Correa, 2010, for a review), since it relies on predictive endogenous cueing, it involves the prefrontal cortex (Triviño, Correa, Arnedo, & Lupiáñez, 2010) and is interfered by a concurrent working memory task in a dual-task procedure (Capizzi, Sanabria, & Correa, 2009). Therefore, if fibromyalgia involved a selective deficit in controlled attention, and given that temporal orienting relies on controlled attentional preparation, we should find impaired temporal orienting in fibromyalgia patients in relation to the control group. Furthermore, the use of a response inhibition go no-go task should also reveal impaired performance in fibromyalgia as compared to the control group, since response inhibition tasks are known to demand controlled attention (Norman & Shallice, 1986).

METHODS

Participants

Thirty-seven female volunteers participated in the experiment. The fibromyalgia group included 18 patients (mean age: 48 years, SD: 6.5), who were referred from the Service of Rheumatology and Pain Unit of the Hospital Virgen de las Nieves (Granada, Spain) to a cognitive-behavioural program carried out in the Psychology Clinic Unit of the Faculty of Psychology. All patients met the diagnostic criteria for fibromyalgia as
defined by the American College of Rheumatology (Wolfe et al., 1990). Data from one patient could not be analysed because she did not complete the experiment. The control group included 19 participants (mean age: 42 years, SD: 8.9), who were recruited from the community and intended to match fibromyalgia patients in age and education.

Exclusion criteria for all participants included pregnancy, having a medical history of significant head injury, neurological disorder, concomitant major medical conditions (e.g., inflammatory arthritis, untreated thyroid disease, malignancy, etc.), or any serious major axis I diagnoses of the DSM-IV-TR (APA, 2000). In addition, the control group was free of pain and sleep disorders, and of any relevant depressive or anxiety symptoms at the moment of the study.

All participants in the fibromyalgia group were on stable doses of medication. Almost all subjects (72.2%) were receiving pharmacological treatment at the moment of test, mainly antidepressants (64.3%, tricyclic, selective serotonin reuptake inhibitors or other type), anxiolytics (63.2%, benzodiazepines), non-steroidal anti-inflammatory (57.1%), analgesics as tramadol (50%), and other drugs (35.7%). Subjects taking narcotics were excluded from the study. None of the control subjects were taking psychoactive medication. The experiment was conducted according to the ethical standards of the 1964 Declaration of Helsinki.

**Apparatus and stimulus**

*Tests*

The McGill Pain Questionnaire (MPQ, abbreviated version; Melzack, 1987) in its Spanish version (Lázaro et al., 2001) assessed several dimensions of the pain experience
using 15 verbal pain descriptors (sensorial and affective), a current pain index, and a visual analogue scale ranging from 1 to 10 (“no pain” to “extreme pain”, respectively) to assess pain intensity in the last week. The Hospital Anxiety and Depression Scale (HAD; Zigmond & Snaith, 1983) in its Spanish version (Herrero et al., 2003) assessed anxiety and depression symptoms through 14 items that were scored on a scale from 0 to 3. The Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupher, 1989) in its Spanish version (Royuela & Macías, 1997) includes 19 items to explore seven dimensions of sleep quality: Subjective Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbances, Use of Sleeping Medication, and Daytime Dysfunction.

**Behavioural task**

The E-prime software was used to control the experiment (Schneider, Eschman, & Zuccolotto, 2002). The task stimuli and procedure were very similar to those used in our previous experiments (Correa, Lupiáñez, & Tudela, 2006; Correa, Sanabria, Spence, Tudela, & Lupiáñez, 2006). All the stimuli were presented at the centre of the computer screen over a black background. The fixation point consisted of a black plus sign (0.38° x 0.76° of visual angle at a viewing distance of 60 cm). The temporal cue was either a short bar (0.38° x 0.95°) or a long bar (0.38° x 2.1°). The short bar indicated that the target would probably appear early (after 400 ms), and the long bar indicated that the target would probably appear late (after 1400 ms). The go target (0.38° x 0.76°) was either the letter ‘O’, or the letter ‘X’, whereas the no-go target was the digit ‘8’. The trial proportion was of .20 for the no-go target and of .4 for each of the go targets. In the go condition, participants pressed the ‘B’ key whenever an ‘O’ or an ‘X’ appeared. In the no-go condition, participants should inhibit responding; otherwise they were
provided with feedback showing the Spanish word for ‘incorrect’ for 500 ms and a 2000-Hz auditory tone for 50 ms.

**Procedure**

Participants from the fibromyalgia group received two individual assessment sessions. The first session consisted of a 1 to 2 hours semi-structured interview focusing on the onset and course of symptoms, life history, lifestyle, work, personal relations, family and woman’s attitudes upon her illness, and psychological status. After the interview they were given a set of questionnaires to be completed at home. Control participants received one session of semi-structured interview focusing on her medical and psychological status, but they did not complete the questionnaires.

The second session was scheduled to collect the questionnaires from the fibromyalgia group, and to apply the behavioural task with similar testing conditions for all subjects. Participants were seated at a viewing distance of about 60 cm and performed a go no-go task. They were instructed to respond as quickly as possible only to the go targets, and to avoid responding to the no-go target. Each trial began with the fixation point presented for 1000 ms. The temporal cue was then presented in red for 50 ms. Next, the screen remained blank for a variable delay of 350 or 1350 ms depending on the interval for that trial (Figure 1). The target was displayed for 100 ms and was then replaced by a blank screen until the participant made a response or for a maximum duration of 2000 ms. A final pause of 500 ms, which was used to present feedback on incorrect trials, preceded the next trial.
The experiment included one practice block and four experimental blocks. The practice block included 16 consecutive trials with early cues followed by 16 consecutive trials with late cues. The experimental blocks were divided into 2 ‘early’ blocks, in which the cue indicated that the target would probably appear after 400 ms, and 2 ‘late’ blocks, in which the cue indicated that the target would probably appear after 1400 ms (cue validity: 75%). Thus, temporal expectancy was manipulated between blocks to optimise temporal orienting effects (Correa et al., 2006). Blocks of early and late cues were presented in alternating runs, and the order of presentation was counterbalanced across participants. Each experimental block included 120 trials that were randomly presented. They were divided according to cue validity (90 valid and 30 invalid). In the valid early cue condition, the cue was early and the target appeared after an interval of 400 ms. In the invalid condition, the cue was early and the target appeared after an interval of 1400 ms. Likewise, the late cue was paired with the 1400-ms interval in valid trials, whereas it was paired with the 400-ms interval in invalid trials. Twenty-four out of 120 trials
were no-go trials (holding the same trial proportion of valid-invalid and SOA conditions), in which the digit “8” was presented, so that the participant had to withhold responding (20% of no-go trials). Participants had an optional break in the middle and the end of each block.

**Design and data analysis**

Practice trials and trials with anticipatory responses before target onset were not analysed. The RT analysis computed mean RTs between 100 and 1500 ms (0.16% of trials rejected) from correct responses. The error analysis computed mean error percentages from responses in the no-go condition (i.e., false alarms). Both RTs and false alarm percentages were submitted to separate 2 (group: control, fibromyalgia) x 2 (validity: valid, invalid) analyses of variance (ANOVA), with group as a between-subjects factor and validity as a within-subject factor. These analyses were designed to test whether temporal orienting, as indexed by validity effects, differed between fibromyalgia and control groups.

**RESULTS**

**Demographic results**

Fibromyalgia and control groups showed no significant differences on either age ($t = 1.82, p = 0.08$) or educational level ($U = 124.50, p = 0.91$). Most of the subjects from the fibromyalgia group were married (76.9%), and had elementary education (23.5%), secondary education (47.1%) or university studies (29.4%). Some of them were either retired (7.7%), unemployed (15.4%) or on sick leave (15.4%). Mean duration of disease was 4 years ($SD = 2.48; \text{range} = 0.2 - 8$). The mean score in Pain-MPQ of the fibromyalgia group was 7.61 ($SD = 1.73$), which indicates relatively high levels of pain.
The mean score in Sleep Quality-PSQI (M = 16.08, SD = 2.53) was about 4 SD above the cut-off for poor sleepers (scores higher than 5; Buysse et al., 1989). The mean score of the fibromyalgia group in Anxiety-HAD (M = 10.62, SD = 5.34) and Depression-HAD (M = 8.69, SD = 4.88) was close to clinical levels (greater than or equal to 11; Zigmond & Snaith, 1983).

**Behavioural results**

The RT analysis showed a significant main effect of validity, $F(1, 34) = 18.9, p < .001, \eta^2 = .36$, leading to faster RTs for valid (mean: 451 ms) compared to invalid trials (462 ms). The interaction between group and validity was significant, $F(1, 34) = 4.37, p = .04, \eta^2 = .11$. This interaction is displayed in Figure 2 (left), which clearly shows that validity effects were only significant in the control group (RT-invalid minus RT-valid: 16 ms; $F(1, 34) = 21.94, p < .001, \eta^2 = .63$), but not in the fibromyalgia group (validity effect: 6 ms; $F(1, 34) = 2.41, p = .13$). The figure also shows that overall RTs were slower for fibromyalgia than for control group, although this difference was only marginally significant, $F(1, 34) = 3.64, p = .07, \eta^2 = .097$.

![Figure 2. Left: Mean RTs as a function of validity in control and fibromyalgia groups. Right: Mean false alarms (percentage of responses to the no-go condition) as a function of validity in control and fibromyalgia groups. Vertical bars represent standard errors of the mean. Note that only the control group showed temporal orienting effects in RTs, while the fibromyalgia group showed reversed temporal orienting in false alarms.](image-url)
The group x validity ANOVA on false alarm percentages revealed a main effect of validity, $F(1, 34) = 8.4, p < .01, \eta^2 = .2$, leading to higher false alarms for valid (14%) vs. invalid trials (10%). This validity effect was driven by the fibromyalgia group, $F(1, 34) = 9.36, p < .01, \eta^2 = .37$, rather than the control group, $F < 1$ (group x validity: $F(1, 34) = 2.39, p = .13$). Remarkably, the temporal orienting effect in the fibromyalgia group impaired performance, leading to higher false alarms on valid vs. invalid trials (Figure 2, right).

**DISCUSSION**

Research on fibromyalgia has reported impairments in both working memory and executive control (Glass, 2009), which are cognitive functions closely related to controlled attention. However, the ability to control the deployment of attentional resources over time ('controlled temporal preparation' or 'temporal orienting') had remained to be investigated. Our main hypothesis was that fibromyalgia patients would show a deficit in the temporal orienting of attention. We tested this hypothesis by comparing the performances between fibromyalgia and control groups through a temporal orienting procedure. Additionally, the use of a go no-go task afforded the novel study of response inhibition in fibromyalgia. The results showed a deficit in temporal orienting and response inhibition related to fibromyalgia.

The main finding of this study was that the fibromyalgia group did not show temporal orienting effects on RT measures. This result fits well with research linking temporal orienting with neurocognitive mechanisms involved in the control of attention over time. Specifically, neuroimaging studies have revealed activation of prefrontal areas
associated to temporal orienting (Coull, Frith, Buchel, & Nobre, 2000; Coull & Nobre, 1998), a neuropsychological study has shown altered temporal orienting in patients with right prefrontal lesions (Triviño et al., 2010; see also Vallesi et al., 2007), and a behavioural study has found that a concurrent working memory task abolished temporal orienting in healthy participants (Capizzi et al., 2009). These studies suggest that the prefrontal cortex controls the deployment of attention over time according to temporal expectations induced by the predictive cue. Hence, fibromyalgia deficits in temporal orienting may be related to dysfunction in this frontal brain network.

We additionally found that overall RT performance tended to be slower in fibromyalgia as compared to the control group. This slowing might be interpreted as a general deficit in vigilance according to findings of impairments either in speed of processing (Cote & Moldofsky, 1997), in sustained attention (Dick et al., 2002; 2008) or in the alerting system (Miró et al., in press) in fibromyalgia patients. Alternatively, it could be argued that this RT slowing may be rather reflecting a difficulty for response inhibition in the go no-go task. Although patients showed similar performance to controls as measured by false alarms, it was at the cost of responding more slowly. The ability to inhibit inappropriate responses has been traditionally considered as an executive function (e.g., Norman & Shallice, 1986; Schneider & Shiffrin, 1977), which might be altered in fibromyalgia.

The hypothesis of impaired response inhibition in fibromyalgia was further supported by the finding that fibromyalgia patients failed more frequently to inhibit responses to no-go targets appearing at expected vs. unexpected moments in time. This result fits
well with a recent study using this same task (Correa, Triviño, Pérez-Dueñas, Acosta and Lupiánez, 2010), which suggested that temporal preparation interfered response inhibition selectively in participants with high non-clinical trait impulsivity. Thus, response inhibition in our ‘valid’ condition could have become harder due to an over-activation of the response enhanced by temporal orienting. The extra demands for inhibiting a strong over-activated response may have exacerbated the deficit for response inhibition in fibromyalgia.

These data are convergent with the idea that both temporal orienting of attention and response inhibition involve controlled processing and are effortful, and that the costs of this effort may be exaggerated under the conditions of fatigue, sleep deprivation, or chronic pain that typically co-exist in fibromyalgia. This explanation is in line with previous reports of deficits in executive control in fibromyalgia, especially when distracting information needs to be filtered out for adequate task performance. This is the case of tasks such as Trail Making Test (Munguía-Izquierdo et al., 2008), Paced Auditory Serial Additions Test (Grace et al., 1999; Munguía-Izquierdo et al., 2008), Wisconsin Card Sorting Task and Iowa Gambling Task (Verdejo-García et al., 2009), or flanker task (Miró et al., in press). As mentioned above for temporal orienting, a frontal network is typically involved in such executive functions (Posner & Digirolamo, 1998; Shallice & Burgess, 1996; Stuss et al., 2005).

To conclude, the common involvement of frontal brain areas in both temporal orienting and response inhibition suggests that a frontal dysfunction may underlie the behavioural deficits on these two functions observed in our fibromyalgia group. This hypothesis is
supported by the finding of altered morphology in frontal areas of the brain, which correlates with the cognitive deficits observed in fibromyalgia (Burgmer et al., 2009; Kuchinad et al., 2007; Luerding, Weigand, Bogdahn, & Schmidt-Wilcke, 2008). Nevertheless, further research is yet needed to understand the neurocognitive mechanisms associated to cognitive dysfunction, as biological and psychological correlates of the illness may underlie the cognitive deficits. For example, poor sleep typically present in fibromyalgia may contribute to hypo-functioning of the frontal cortex (Lineberger, Means, & Edinger, 2007; Moldofsky, 2008). Moreover, although pain is considered the core feature of fibromyalgia, patients frequently suffer from fatigue and poor sleep quality, which can affect up to 99% of fibromyalgia patients (Hamilton et al., 2008; Theadom & Cropley, 2008). Negative consequences of sleep disturbance as insomnia and chronic sleep loss on cognitive functioning are well known (Elmenhorst et al., 2009).

It is also probable that concomitant disorders (pain, depression or anxiety) are mediating the cognitive dysfunctions observed here, since chronic pain consumes the limited attentional resources necessary for controlled processes (Grisart, Van der Linden, & Masquelier, 2002). So far, it is under open debate whether these subtle deficits can be mainly attributed either to neurological dysfunction (e.g., altered neuroendocrine stress response, Sephton et al., 2003) or to the influence of psychological variables such as depression, anxiety, pain or poor sleep (Suhr, 2003; Sephton et al., 2003; Grace et al., 1999; Glass & Park, 2001; Dick et al., 2008; Munguía-Izquierdo et al., 2008; Verdejo-Garcia et al., 2009). The combined study of cognitive, psychological and neurobiological variables should improve our current scientific knowledge of the
fibromyalgia syndrome.
NOTES

1. In order to clarify the role of sleepiness in our findings we computed correlations between the behavioural validity effect and the PSQI scores (total scores and its seven dimensions) in the fibromyalgia group. The lack of significant correlations (all ps > .18) suggests that our main behavioural findings cannot be only accounted for differences in sleep quality. Similar null findings were obtained in relation to the role of pain as measured by the MPQ (r = -0.15, p = 0.635). In order to test the role of fatigue in our findings, we tested whether the fibromyalgia group showed greater fatigue over the session as compared to the control group. That is, we compared the effect of experimental block (i.e., time on task) between both groups. The analysis showed similar block effects on both groups (block x group: F(3, 102) < 1), suggesting a rather weak contribution of fatigue in our main finding. The mild involvement of these psychological variables in the behavioural effects, although surprising, has been previously reported in the literature (e.g., Verdejo-Garcia et al, 2009).
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