BRAIN DYNAMIC OF COGNITIVE AND AFFECTIVE PROCESSING IN PATIENTS WITH FIBROMYALGIA

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Duration: 3 years
1. Summary of the project

1. Objectives. The current research project was driven by the idea that fibromyalgia (FM), like other chronic pain conditions, could be characterized by an abnormal activation of the pain network (a complex system of brain regions involved in pain processing which includes somatosensory and motor cortices, thalamic nuclei, insula, anterior cingulate cortex, prefrontal and posterior parietal cortices, periaqueductal gray matter). In particular, we have examined the hypothesis that persistent pain in FM patients would lead to altered emotional/cognitive processing, which would be also associated with an abnormal activation of anterior brain regions (prefrontal cortex, anterior cingulate cortex, and insula) of the pain network. The proposed experiments were focused on the following specific aims:

   a) Aim I: to examine the dynamic properties of brain network and spontaneous pain fluctuations in patients with fibromyalgia (FM). For this purpose, theoretical tools and extensive software were developed to unveil the topological, functional and scaling properties of the pain network in FM patients, and to compare them with other brain networks.

   b) Aim II: to investigate the dynamic properties of brain networks involved in the processing of emotional information in FM patients and healthy controls. It was hypothesized that FM patients would display an abnormal processing of affective information and an abnormal activation of those limbic (anterior cingulate cortex, insula) and frontal regions (orbitofrontal, medial and dorsolateral prefrontal cortices) involved in healthy processing of emotions.

   c) Aim III: to study the dynamic properties of brain networks involved in attention-demanding and working-memory tasks in FM patients and healthy controls. It was hypothesized that given that frontal cortices are involved in pain processing and they play an important role in attention and memory functions, FM patients would exhibit a poor performance in cognitive tasks as compared
with healthy controls, together with an abnormal activation of anterior brain regions.

2. Methods. Basically, the project proposed to compare brain activity of patients with fibromyalgia and pain-free controls by using fMRI, when subjects were either performing an experimental task or at rest. In addition, we have included the assessment of pain sensitivity, the determination of several genetic polymorphisms, and the recording of EEG as additional experimental techniques to explore pain in fibromyalgia patients.

3. Work plan. The proposal was developed during 3 years by conducting several experiments related to the 3 aims of the proposal. Thus, the first aim (analysis of brain networks and pain characteristics) was basically achieved during the first year of the project; the second aim (study of brain networks involved in affective processing) was achieved during the second year, and the third aim (study of cognitive processing) was achieved during the third year. An extension of the project deadline until 31/03/2012 was approved by La Marató TV3 Foundation on 25/01/2011.

2. Results

The major research achievements of the present project were:

- Patients with fibromyalgia display significant reductions in gray matter density and alterations of functional brain connectivity, which are related to clinical pain characteristics

Previous studies have shown that chronic pain might be associated with morphological changes in brain regions involved in pain processing, such as cingulate cortex,
somatosensory cortices, thalamus, insula and medial prefrontal cortex (the so-called pain network). Nevertheless, there was no information about how abnormal changes in pain-related brain structures were associated with clinical pain characteristics (e.g. pain duration, pain intensity and affective distress elicited by chronic pain) and functional brain connectivity. In one study we observed that fibromyalgia patients displayed significant reductions in gray matter density (using voxel-based morphometry) in anterior cingulate cortex, supplementary motor area and right angular gyrus (Figure 1). Moreover, it was observed that gray matter density in anterior cingulate cortex was negatively associated with pain duration and pain intensity (Figure 2). Analyses of resting-state functional connectivities of brain regions with reduced gray matter density further revealed that fibromyalgia patients showed an enhanced functional connectivity of anterior cingulate cortex with primary and secondary somatosensory cortices compared with healthy controls, as well as reduced functional connectivity of supplementary motor area with thalamus, and angular gyrus with periaqueductal gray matter (Figure 3). These findings suggest that structural and functional changes in these pain-related brain areas are present in fibromyalgia.

Figure 2. Relationships of gray matter density in cingulate cortex (ACC), primary somatosensory cortex (SI) and insula (IC) with pain duration, pain intensity, depression (BDI) and pain-related affective distress.

Figure 3. Analysis of functional connectivity from resting-state BOLD time series in three brain areas with gray matter reductions (cingulate cortex [ACC], supplementary motor area [SMA] and angular gyrus [ANG]) in fibromyalgia (FM). Red lines show augmented connectivity in FM patients, whereas blue lines indicate reduced connectivity in FM patients as compared with healthy controls.
Moreover, our results further support the idea that the conjoint analysis of morphological changes and resting-state functional connectivity might help to a better understanding of fibromyalgia.

A further study was aimed to apply a new fMRI technique based on non-linear connectivity estimation (Resting Bold Event Triggered Averages – rBeta) to analyze alterations of resting state activity in fibromyalgia, with an emphasis on examining these alterations at a single subject level. Significant differences were observed in thalamic and insular functional connectivity with frontal, parietal and other regions belonging to the default mode network (a functional network that increases brain activation at rest). Connectivity strengths were correlated in fibromyalgia patients with measures of depression (thalamic connectivity) and anxiety (insular connectivity) (Figure 4). These differences allowed a clear discrimination between both groups at a single subject level. Similar findings were obtained for the connectivity of insula with supramarginal and angular cortices, which were significantly correlated with anxiety variables. In addition, the intensity of spontaneous activations of anterior cingulate cortex acts as a predictor of pain interference in daily activities.

- Psychophysiological empathic responses to the view of others’ pain and anger faces are altered in fibromyalgia patients

Facial expression is one of the most relevant non-verbal behaviors in the communication of pain, providing
information to the onlookers for an accurate estimation of others’ pain. However, little was known about brain processing of pain expressions in comparison with other affective facial expressions in fibromyalgia patients. We designed a preliminary experiment to examine the effects of pain expression intensity on affective ratings and brain dynamics by recording EEG in healthy volunteers. Participants were asked to rate the affective characteristics of 144 stimuli depicting facial expressions of pain and anger with three levels of expression intensity (high, mild, low), as well as neutral faces (Figure 5). Results indicated that pain faces were judged as more unpleasant and arousing than anger and neutral faces for all intensity levels. Moreover, facial expressions of pain elicited more enhanced amplitudes of the visual-evoked potentials (VEPs) than anger and neutral faces in the latency between 350 and 550 ms after stimulus onset (Figure 6); whereas anger faces elicited greater P200 amplitudes than pain and neutral faces. These findings indicated that brain activity elicited by affective faces was modulated by the intensity of facial expressions and suggested the involvement of different brain mechanisms during the processing and recognition of facial expressions of pain and anger in healthy volunteers.

In a second experiment, we recorded VEPs and brain oscillations, corrugator activity, and heart rate to the presentation of pain, anger, happy and neutral faces in fibromyalgia patients and pain-free controls. Although pain and anger faces elicited greater unpleasantness, arousal and corrugator activity than happy and neutral faces in all participants, fibromyalgia patients displayed enhanced ERP amplitudes, increased theta power and reduced alpha power to pain and anger faces as well as a more prominent cardiac deceleration to anger faces than to either happy or neutral faces. By contrast, pain-free controls showed larger ERP amplitudes to happy faces than to negative faces. These findings suggested
that information processing in fibromyalgia should be characterized by enhanced defensive reactions and an increased mobilization of attention resources to pain and anger faces as well as by a reduced allocation of attention resources to happy faces.

A third study was aimed to explore affective and emphatic responses to facial expressions of anger, happiness and pain in fibromyalgia patients by using fMRI. Abnormal activity was found in several brain regions involved in processing of facial expressions in fibromyalgia patients compared with healthy controls. In particular, increased hemodynamic responses and increased connectivities to the rest of the brain were observed in frontal brain regions associated with emotion regulation and cognitive control (frontal pole and superior, middle and inferior frontal gyrus) when viewing pain faces as compared to healthy controls (Figure 7). Moreover, reduced activations in orbitofrontal cortex, temporal fusiform gyrus, inferior temporal gyrus and occipital fusiform gyrus were observed in fibromyalgia patients when viewing happy and anger faces. These results indicated that fibromyalgia patients activate different strategies to cope with facial expressions of pain in others. Moreover, it suggests that fibromyalgia patients may display significant deficits in evaluating facial expressions of happiness and anger and in selecting a suitable response to these emotions.

*Figure 7. Activation maps elicited by the presentation of happy, anger and pain faces. Fibromyalgia patients elicited greater activation than healthy controls in several regions of the frontal lobe (red spots), particularly, when viewing pain faces.*
- Brain networks involved in attention and memory for pain- and emotion-related information in fibromyalgia patients

Studies on the effects of chronic pain on cognitive functions were further conducted by using different experimental tasks. In a first study, patients with fibromyalgia (FM) and healthy controls (HC) participated in both an emotional gambling and an associative learning task. The aim of the study was to examine whether fibromyalgia could be associated with deficits in cognitive functions related to associative learning and executive functions (decision making). Results indicated that fibromyalgia patients had poorer performance than healthy controls in both tasks (Figure 9), showing more perseveration errors in the learning task, and more disadvantageous decisions, as well as a more random behavior in the gambling task. These findings indicated that chronic pain imposes a high cost on executive control, undermining mainly affective processes involved in cognitive functions such as learning, memory, attention and decision-making.

A second experiment was aimed to examine the effects of emotion on working memory load in patients with fibromyalgia by using a variant of the so-called n-back task with facial expressions of pain and happiness. The task was conducted in the fMRI scan and consisted of three conditions (Figure 9). In the 0-back condition (low load), participants had to decide whether the current face presented on the screen was also presented in the first trial of the run. In the 1-back condition (mild load), target faces were defined as those that appeared one trial before. In the 2-back condition...
(high load), target faces were defined as those that appeared two trials before. fMRI volumes were recorded during task performance and at rest following the different loads of the working memory task. Results during task performance indicated that encoding of faces elicited significant activations of brain areas related to self-awareness (superior frontal gyrus, precuneus cortex), processing of face stimuli (fusiform gyrus), visuospatial

**Figure 10.** Activation maps elicited by the n-back working memory task comparing fibromyalgia patients (FM) and healthy controls (HC). FM patients showed greater activation in frontal structures than HC when performing the task with pain faces (upper panel) and high load (below panel).

**Figure 11.** Group differences on the activation of the default-mode network (DMN) during the rest periods after the n-back working memory task. Fibromyalgia patients (FM) elicited greater activation than healthy controls (HC) in 4 regions of the DMN when happy (left panel) and pain (right panel) faces were used in the cognitive load of the preceding memory task.

imagery (precuneus cortex), and emotion regulation (insula) in both fibromyalgia and pain-free controls. Nevertheless, fibromyalgia patients displayed increased activations of the frontal lobe during the high-demanding condition (2-back) and the encoding task using pain faces as compared to controls (Figure 10).

To analyze the influence of the cognitive load of a preceding working memory task on brain activity at rest, the activation of the default-mode network (DMN) was also compared for the two different face stimuli. As has already been mentioned, the DMN is a functional network characterized by increased activation at rest and decreased activation during task performance. The degree of DMN activation after performance on a working memory task seems to be influenced by the cognitive challenge required by the task and to reflect the recovery of brain resources from high cognitive
demands. In this sense, our findings that pain and happy faces elicited a greater activation of the DMN in fibromyalgia patients than in healthy controls (Figure 11) suggest that the cognitive challenge of the working memory task was greater for fibromyalgia patients than for healthy controls.

- **Enhanced pain sensitivity in fibromyalgia is modulated by genetic markers**

An additional result of the project, which was not originally expected, was related to the characterization of fibromyalgia patients on the basis of genetic markers. In this sense, we were able to determine four functional polymorphisms of the catechol-O-methyltransferase (COMT) gene in fibromyalgia patients and to examine differences in pain sensitivity related to the activity level of this gene. Our results indicated that patients with a genotype leading to low COMT activity were more sensitive to pain than patients with high COMT activity. Our research plan for the forthcoming years includes the assessment of the effects of this genetic marker on affective and cognitive brain processing in fibromyalgia.

3. **Relevance and possible clinical applicability of the final results**

The major results of the present project indicate that brain processing of information is significantly altered in fibromyalgia patients. In particular, our data have shown that fibromyalgia patients are characterized by morphological brain changes in relevant regions for the processing of pain and emotions, an altered functional connectivity of these regions with the rest of the brain, abnormal brain responses to affective stimuli and to high-demanding cognitive tasks, and by an enhanced pain sensitivity which is probably mediated by genetic factors. All these features should be integrated in a multidisciplinary assessment of the fibromyalgia syndrome to a better understanding of the impact of chronic pain in patients’ lives. Furthermore, our findings provide support for the utility of those therapeutic strategies centered on behavioral and cognitive changes of the patients. Thus, together with a biopsychosocial approach to understand the
multiple factors involved in the maintenance of the fibromyalgia syndrome, new techniques and tools that facilitate the training of the self-regulation of brain activity could be helpful to revert the enormous impact of chronic pain on the brain.

4. Publications


