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## Can we see pain?\*

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### ABSTRACT

Pain is a highly subjective experience that is difficult to measure objectively due to its varied expression. It is defined as a complex sensory-emotional experience; it is modulated by cognitive factors and involves a broad neural system. Functional neuroimaging has helped to define that neural circuit involved in the perception, modulation and response to painful experience, both in healthy controls and in patients with acute and chronic pain disorders. However, functional activation of the so-called "pain matrix" may also be differentially modulated by sensory and emotional processing components. The latter, for example, can influence the intensity to which a stimulus is perceived as painful. Such a threshold seems to be lower in patients with clinical diagnosis of fibromyalgia (FM) and has been linked to an abnormal pattern of activation of the "pain matrix" when assessed with functional magnetic resonance imaging (fMRI), considering a "syndrome of central susceptibility." Supporting an etiological explanation for FM, studies have noted that a significant proportion of patients with FM demonstrate this abnormal pattern of activation to stimuli of low intensity. Additionally, there is an important and significant temporal dimension to this activation pattern observed in FM patients, where areas commonly associated with the emotional experience of pain show a prolonged response to painful stimuli compared to healthy subjects. Accordingly, fMRI may assist in objectifying the experience of pain in patients with FM in response to nociceptive stimulation.

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### ¿Se puede ver el dolor?

#### RESUMEN

El dolor es una experiencia subjetiva difícilmente evaluable de forma objetiva por su variada expresión. Se define como una compleja experiencia sensorioemocional, modulada por factores cognitivos y que involucra un amplio sistema neural. La neuroimagen funcional ha contribuido a definir este circuito neural en controles sanos y en pacientes con un síndrome de dolor agudo o crónico implicado en la modulación, la percepción y la respuesta de una experiencia dolorosa. Sin embargo, la activación funcional de la "matriz neural" del dolor puede modularse, bien por un componente sensorial bien por un componente emocional. Este último podría mediatizar la intensidad apartir de la que un estímulo se percibe como doloroso. Este umbral parece ser menor en pacientes con diagnóstico clínico de fibromialgia (FM), pacientes que generan una anormal activación funcional del circuito neural del dolor, evaluada mediante resonancia magnética funcional (RMF), lo que se considera un síndrome de susceptibilidad central. En apoyo a esta explicación etiológica, los estudios de RMF constatan que una proporción significativa de pacientes con FM presenta una consistente y anormal activación de la "matriz neural" del dolor a estímulos de baja intensidad. Adicionalmente, se constata una importante y una significativa activación funcional con una duración temporal de activación cerebral superior a la del estímulo nociceptivo aplicado y, específicamente, en las áreas neuroanatómicas implicadas en la dimensión emocional del dolor. En consecuencia, la RMF permite observar, de manera incruenta, la anormal respuesta funcional cerebral a un estímulo nociceptivo en pacientes con diagnóstico clínico de FM.

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Currently, pain is defined as a complex sensory-motor-emotional experience, modulated by cognitive factors that involve an ample neural nociceptive and antinociceptive neural system.<sup>1,2</sup> The functional neuroimaging studies, be it a positron emission tomography (PET) or a functional magnetic resonance image (fMR), have contributed to revealing and defining, along with clinical and experimental pain studies, the neural circuitry involved in the modulation, the perception, and the response to a painful experience.<sup>3,4</sup> In addition, functional neuroimaging techniques are helping unveil the neurobiological secrets of the sensory, emotional, and cognitive aspects of pain.<sup>5</sup>

### Functional magnetic resonance

One of the most important contributions of magnetic resonance (MR) to neurosciences and therefore to the clinical context, has been fMR.<sup>6</sup> This technique detects and localizes in a non-invasive manner, focal brain activation as well as the neural circuit involved while performing a cognitive or sensory-motor task.<sup>7</sup>

In general, fMR studies are based on the acquisition of images during the same sequence while the patient is resting and while they are performing a determined task. Then, both phases are statistically compared (rest and activation), ideally representing metabolic and vascular focal changes in the cerebral cortex that occur during the execution of the task<sup>6</sup> under study, through an event-related block design paradigm.<sup>7</sup> However, fMR currently permits and has become interesting, in certain clinical studies, because of the possibility to evaluate the metabolic and vascular status during resting and the real duration of the pattern of functional activation of the brain by performing a determined study technique.

Different methods have been proposed to determine brain activity with fMR. However, the most sensitive procedure, and the one through which more experience has been obtained<sup>6,7</sup> is the BOLD method (blood oxygen level dependent). In this procedure, the resonance signal depends of the concentrations of blood oxygen, especially the amount of hemoglobin-bound oxygen (oxyhemoglobin) in venous blood.<sup>8</sup> In addition, this method avoids the need to inject a bolus of contrast for the study of brain activity.

It is known that when a subject performs a cognitive, emotional or sensory-motor specific task, an increase in the regional brain blood flow occurs (RCBF) implicated in the task undertaken and, in consequence, an increase in the supply of oxygen.<sup>9</sup> It seems that the increase in RCBF can reach up to 50% as a response to the increase in neuronal activity.<sup>7</sup> However, the increase in the consumption of oxygen is much less than the increase in arterial blood flow.<sup>9</sup> This leads to a higher than normal content of oxyhemoglobin on the venous phase (venous capillaries, venules, and veins) and with respect to deoxyhemoglobin, producing a venous blood arterializations effect.<sup>6,8</sup> This variation in the relationship between the concentrations of oxyhemoglobin (diamagnetic component) and deoxyhemoglobin (paramagnetic component) in the venous phase when the neural tissue is resting and when it is activated defines BOLD contrast.<sup>7</sup>

### Neural pain circuits

Different clinical studies using functional neuroimaging, through either PET or fMR, have evaluated functional changes occurring in the central nervous system when faced with a painful experience, in healthy subjects,<sup>2,4</sup> in patients with neuropathic pain,<sup>3</sup> phantom limb pain,<sup>10</sup> postherpetic neuralgia,<sup>11</sup> chronic back pain,<sup>12</sup> headache,<sup>1</sup> fibromyalgia (FM),<sup>13,14,15,16</sup> irritable bowel syndrome,<sup>17</sup> and complex regional pain disorder.<sup>18</sup> The results obtained have revolutionized the comprehension of the physiologic response to pain and opened new perspectives for a better appraisal of the pathophysiology of the so-called chronic pain syndromes.<sup>12</sup> Therefore, current data on functional neuroimaging show that pain is not a static problem with

a single pathophysiology located to a peripheral muscle or tendon system, but a highly plastic clinical entity affecting multiple central neural systems<sup>1</sup> which defines what is known as the "neural matrix" of pain or the network of cortico-subcortical areas involved in the processing of pain (Figure 1).

The "neural matrix" modulating perception and response to pain seems to mainly involve, both in healthy volunteers as in patients with acute or chronic pain in response to internally or externally generated stimuli, the secondary somatosensory cortex (SII) in a bilateral manner, the insular cortex (IC) and the anterior cingulate cortex (ACC).<sup>2,19,20</sup> In addition, other studies refer to functional activation of the primary somatosensory cortex (SI) contralateral to the stimulated side of the body, the cerebellum, the thalamus, the operculum, the prefrontal cortex (PFC), the supplemental motor area (SMA), the basal ganglia, and the posterior parietal cortex.<sup>1,21</sup>

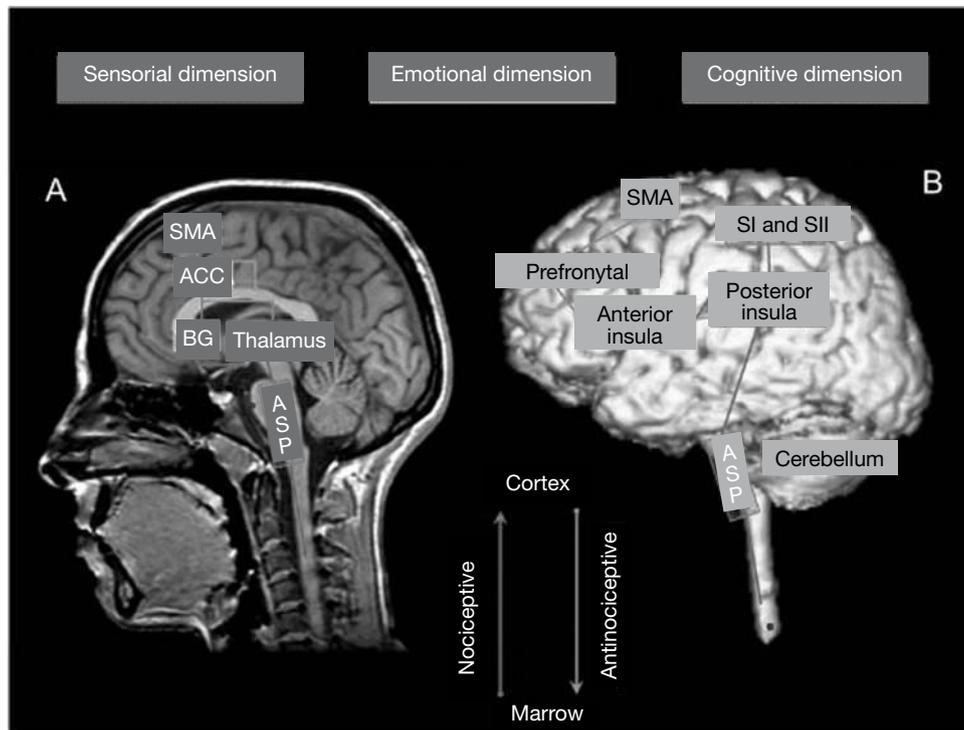
Recent functional neuroimaging studies have allowed for the neuroanatomical differentiation of the classic pain processing dimensions. Sensitive and cognitive dimensions have been located to the superior and dorsal cerebral portion (contralateral SI, bilateral SII, posterior IC, opercular zone, thalamus, SMA, and frontoparietal neocortex).<sup>19,20</sup> The emotional dimension involves the IC in its ventral and anterior portion, the ACC, the basal ganglia, and the PFC.<sup>13,15</sup> As a consequence, functional activation of the neural pain circuit can be modulated either by a sensory component or an emotional one,<sup>21</sup> without forgetting the implication of the cognitive component. The emotional component can mediate the intensity threshold with which a stimulus is perceived as painful.<sup>14,15,21</sup> In fact, this threshold seems to be much higher in patients with chronic functional pain (such as FM)<sup>13</sup> with respect to healthy controls and generate a normal activation of the neural pain circuit.<sup>22,23,24</sup> This has motivated this syndrome to be collectively named, central susceptibility syndrome.<sup>22</sup>

### Functional magnetic resonance and fibromyalgia

FM is one of the most prevalent rheumatic diseases<sup>23</sup> and is very representative of chronic functional pain<sup>24</sup> even if it is one that generates a lot of diagnostic controversy.<sup>25</sup> It is defined as a clinical syndrome characterized by non-articular pain of at least 3 months duration (which predominantly affects muscles and the spine) and hypersensitivity to digital pressure with 4 kg/cm<sup>2</sup>, in at least 11 of 18 predefined sensitive trigger points. In addition and typically it is accompanied by other clinical syndromes, which are not necessary for its diagnosis, such as important emotional stress, fatigue, sleep disturbances, and generalized stiffness.<sup>26</sup>

The etiology of FM remains elusive and is considered as multifactorial and idiopathic, leading to the proposal of 2 possible models that may explain its pathogenesis.<sup>25,27</sup> The first etiological model defends a primary peripheral physiological model which could be due to endogenous or exogenous factors; psychopathological alterations are considered among these.<sup>28</sup> The second model proposes an alteration of the nervous system for the processing of pain signals<sup>15,22</sup> and is based on the existence of an excessive response either to painful stimuli and a reduction in the threshold for pain (hyperalgesia), or to non-painful stimuli (allodynia).<sup>13</sup> Finally, some studies have proposed a mixed etiological model. These demonstrate that the combination of the peripheral sensibilization models and the alteration of the central mechanisms for pain processing could explain the chronic etiology of FM by establishing a positive feedback circuit between them that contributes to the perpetuation of this clinical syndrome.<sup>27</sup>

Recently, support for the etiological model contemplating a central nervous system alteration has seen that these patients have an abnormal pattern of functional brain activation (studied using fMR)<sup>13,14,15,16</sup> as a cerebral response to mechanical or thermal stimuli of different intensities as well as non-painful ones.<sup>13,14,15</sup> The fMR that characterize this brain response pattern shows an increase in



**Figure 1.** Representation of the “neural matrix” of pain and the classic pain-processing classic dimensions in relation to the neuroanatomical areas involved, seen in a sagittal medial cut (A) and sagittal lateral cut (B). Representation of the nociceptive neural system (red arrow) and the antinociceptive neural system (green arrow). ACC indicates anterior cingulate cortex; ASP, ascending spinal pathway; BG, basal ganglia; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; SMA, supplemental motor area.

the sensibility as well as the brain response to pain when faced with low intensity nociceptive stimuli which are subjectively perceived as moderately painful by the patient with FM in terms of extension and magnitude of the activation and in the brain regions that form the “neural matrix” of pain.<sup>13</sup> Deus et al (2006) proposed a fMR study in patients with a clinical FM diagnosis and with an eminently clinical focus. In this, the patients were applied 4 kg/cm<sup>2</sup> of mechanical pressure during the fMR, in a manner similar to what is recommended during the examination of patients with FM. The results helped prove that a significant proportion of patients diagnosed with FM, with a low pain threshold, presented consistent activation of the “neural matrix” of pain to low intensity mechanical stimuli<sup>16</sup> (Figure 2). These results demonstrate central susceptibility for pain responses<sup>22</sup> and the possibility of using fMR as a diagnostic method complementary to the conventional methods.<sup>16</sup>

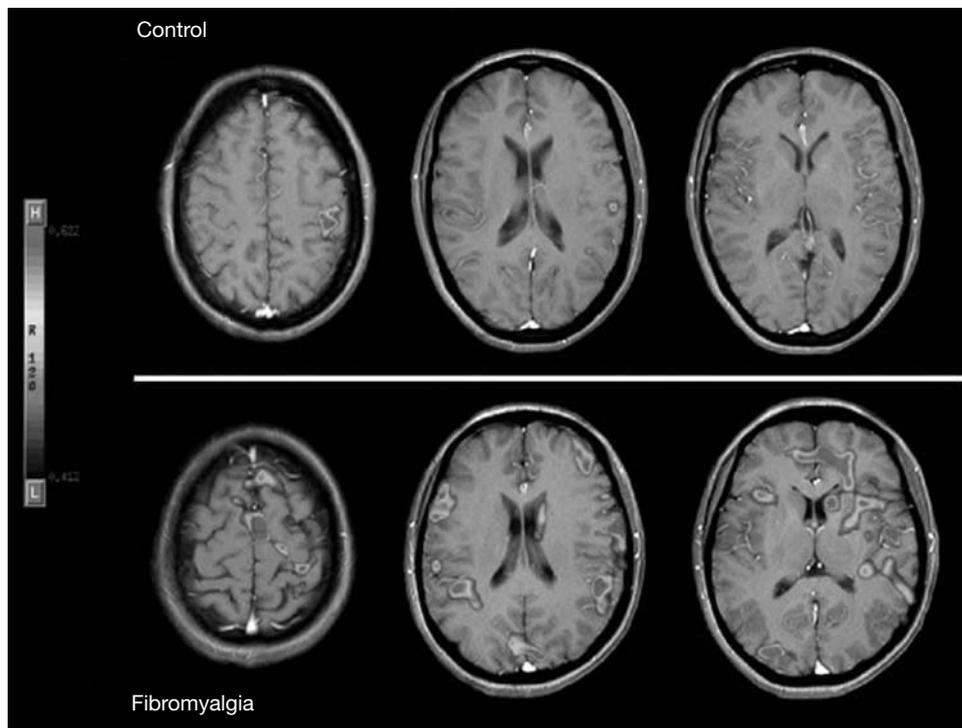
Other authors have proposed that the emotional-affective dimension of pain processing can modulate or explain normal functional activation of the “neural matrix” of pain in patients with FM. In fact, the chronicity of FM seems to be favored by the high prevalence of emotional problems that could modify the experience of pain.<sup>28</sup> In this way, Gracely et al (2004) have evaluated how the degree of catastrophic perception can affect the brain's functional response to pain in patients with the diagnosis of FM.<sup>14</sup> Other psychological studies show that the patients with a diagnosis of FM need more time to recuperate from an adverse painful sensation after receiving nociceptive stimulation.<sup>27</sup> This can demonstrate a temporal perception distortion in patients with FM with respect to healthy subjects, between the application of a painful stimuli and the corresponding functional brain response of the “neural matrix” of pain and, especially, in those brain regions that process the affective or emotional components of the response to an exogenous or endogenous painful stimuli. As a consequence, it would be expected that there is not always a perfect coincidence between the duration

of the painful stimuli and the duration of the subjective experience of pain in patients with FM.

In agreement to this theoretical proposal, a recent study yet to be published and presented as an oral communication by the research group to which the author of this article belongs, has delineated the “neural matrix” implicated to the response to a mechanical stimuli equivalent to 4 kg/cm<sup>2</sup>, something that does not cause relevant pain in a control group with healthy subjects and does so in concordance to the real-time course of the cerebral response and not the temporal course defined by the application of a nociceptive stimuli. In first place, this matrix implies a greater cerebral blood perfusion to the SI contralateral to the stimulated extremity and the SII. This region is activated both in patients with FM as in healthy controls with an equivalent duration, in both groups, to the duration of the applied nociceptive stimuli. Both cortical regions are considered as involved in the sensory dimension of pain processing.<sup>1,29</sup> In second place, an important and significant functional activation, with duration of activation superior to that of the applied nociceptive stimuli of the anterior portion of the insula, only in patients with FM, can be seen. In addition, the activation of this region, as a consequence of the application of a painful stimuli, was proven to be specific and positively related with the pain experienced with patients with FM (Figure 2). These results are in agreement with the previous studies showing an important role of the operculum-insula region in the affective and motivational component of the painful experience, by relating to the emotional dimension of pain<sup>13,14,15,29</sup> and the degree of anxiety that the patient shows when faced to painful stimuli.<sup>29</sup>

#### Future directions of magnetic resonance in fibromyalgia

The study of functional and anatomical neurobiology of FM, through different study procedures that are currently provided by



**Figure 2.** Axial functional magnetic resonance images. The results of brain functional activation in a healthy volunteer are shown in the superior part of the figure after a pressure of 4 kg of weight is applied. Significant changes can be seen only in the contralateral sensory-motor and area of the thumb under stimulation. The results of functional brain activation in a patient with fibromyalgia can be seen in the lower part of the figure. A pattern of activation of the cerebral of the cerebral regions normally involved in response to pain can be seen. Changes were significant in different areas of the parietal lobe (primary somatosensory cortex and secondary somatosensory cortex) and the frontal lobe, the insula, the operculum and the anterior cingulate region. *t* represents Student *t* test.

MR, can be widened. From a functional standpoint there are 3 specific directions to consider. In first place, be it through fMR or perfusion MR, the metabolic and vascular state that occurs during resting-state can be evaluated, as occurs in PET studies. In second place, the analysis of functional activation with fMR could be widened with data-driven procedures. These would complement the data obtained with the conventional analysis of fMR to characterize the brain response to pain with regard to the real-time duration of functional activation of the “neural matrix” of pain. In third place, spectroscopic MR allows the study of brain metabolism *in vivo* and therefore, provides non-invasive biochemical information of anatomical regions of the “neural matrix” of pain.

From the neuroanatomical standpoint, 2 future lines of research can be specified. First, tract studies with MR (diffusion tensor images) would enable the non-invasive evaluation of waters’ molecular diffusion reflecting the configuration of the microscopic tissue of the white substance. This would allow the study of the fascicles or tracts involved in the processing of pain. In second place, it would allow the study of cerebral morphology of certain anatomical areas of interest and involved in the dimensions of pain processing through volumetric or 3D analysis techniques.

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