Chapter 21

Brain Function in Fibromyalgia: Altered Pain Processing and Cognitive Dysfunction

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1. Introduction

Since several decades ago chronic pain understanding has become in one of the most intriguing challenges for health professionals (rheumatologists, psychologists, physiotherapists, anaesthesiologists, pharmacologists, etc). Different reasons are behind that traditionally poor knowledge about the etiology, mechanisms and treatment of chronic pain. Pain has been very often considered as a peripheral entity in which peripheral causes, such as inflammation and structural joint damage, have been only explored. Thus, difficulties to explain painful symptomatology associated to chronic pain patients, such as the great discordance between pain complaints or severity and their supposed peripheral causes, have lead to the development of investigations to advance in the knowledge of pain mechanisms in chronic pain diseases (p.e., non-inflammatory conditions), such as it occurs in fibromyalgia (Buskila, 2009). These studies have highlighted both the important role of central pain-processing mechanisms and its evidently multifactorial status (Lee et al., 2011; Schweinhardt et al., 2008).

Fibromyalgia (FM) constitutes a chronic syndrome mainly characterized by the presence of widespread and diffuse pain (Fan, 2004). Traditionally, FM diagnosis has been only established by the presence of widespread pain during at least three months and tenderness to palpation at specific locations (the so-called 'tender points') following the American College of Rheumatology criteria (ACR, Wolfe et al., 1990). refer to 18 places symmetrically distributed at both sides of the body where patients feel pain when a weak pressure is applied on them with the thumb of the examiner (lower than 4kg/cm2, see Figure 1). Currently, this syndrome is affecting between 2-4% of population (between 80 and 90 percent of patients diagnosed with FM are

women) being one of the most common causes of pain and disability. However, the biological bases for the clinical characteristics of FM remain elusive (Martínez-Lavin, 2004; Montoya et al., 2005; Vierck, 2006). Studies have focused particularly on the mechanisms underlying pain perception, and central signals processing. FM patients refer two kinds of somatic sensations: a) enhanced pain sensitivity to painful stimulation (hyperalgesia) and b) a painful response to a normally innocuous stimulus (allodynia). Central augmentation mechanisms underlying this amplified pain perception have been investigated using advanced imaging techniques that aim to localize and describe alterations in specific areas of the brain. Indeed, scientific evidence suggests that central abnormalities in the processing of pain signals seem to be responsible of such altered pain manifestations (diffuse hyperalgesia and allodynia) in FM (Staud et al., 2004; Thieme et al., 2005).

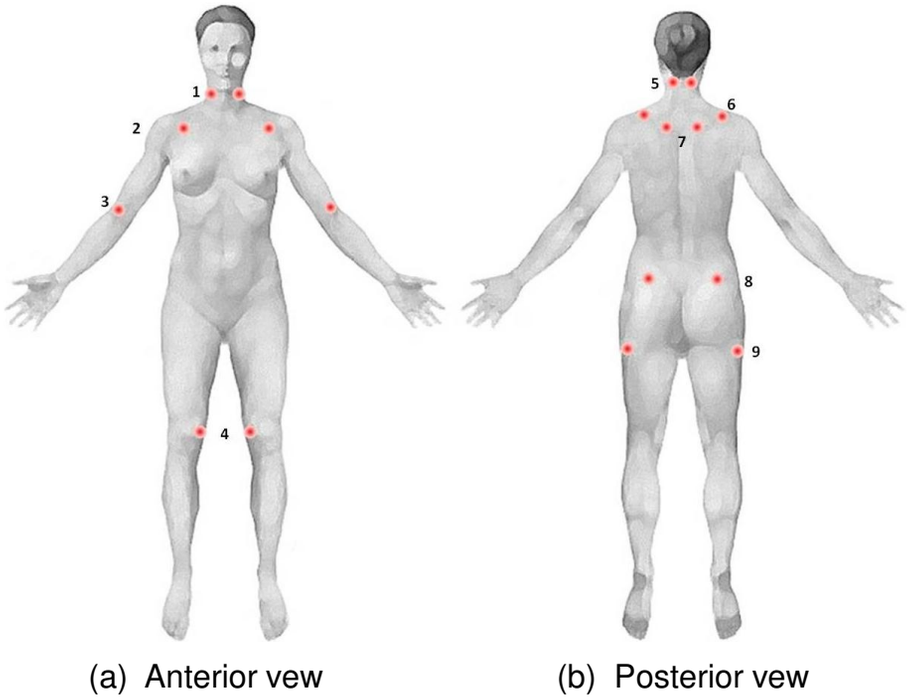

Figure 1. Bilateral tender point locations for the traditional ACR diagnosis criteria for Fibromyalgia (adapted from Wolfe et al., 1990). (a) ANTERIOR VIEW: 1. *Low cervical*: the anterior aspects of the intertransverse spaces at C5-C7, 2. *Second rib*: the second costochondral junctions, lateral to the junctions on upper surfaces, 3. *Lateral epicondyle*: 2cm distal to the epicondyles, 4. *Knee*: the medial fat pad proximal to the joint line. (b) POSTERIOR VIEW: 5. *Occiput*: the suboccipital muscle insertions, 6. *Trapezius*: the midpoint of the upper border, 7. *Supraspinatus*: above the scapula spine near the medial border, 8. *Gluteal*: upper outer quadrants of buttocks in anterior fold of muscle, 9. *Greater trochanter*: posterior to the trochanteric prominence.

Additionally, people with FM frequently experience a great amount of other accompanying symptoms apart from pain, such as physical complaints (stiffness, fatigue, sleep problems), affective disorders (anxiety or depression) and cognitive dysfunctions (failures in memory, attention and concentration). In fact, cognitive failures represent one of the most important complaints of these patients, recently denominated as *fibrofog* (Glass, 2010), leading to produce even greater functional impact than pain itself (Glass, 2009). Based on growing evidence from

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neuropsychological and neuroimaging studies, ACR criteria have been recently modified including the cognitive dysfunction and affective disturbances, among other symptoms, as key factors for FM diagnosis (Wolfe et al., 2010). These findings, along with the lack of peripheral signs of inflammation to account for pain, support the hypothesis that FM is a syndrome characterized by an abnormal processing of information at the level of central nervous system. Therefore, psychoneurobiologic dysfunctions seem to be crucial for trying to explain this multifactorial and still not fully understood clinical condition (Lee et al., 2011; Schweinhardt et al., 2008), but also to give response, at least partially, to the appearance and maintenance of both pain-related and cognitive symptomatology. In the following review, we will try to describe what is currently known about the cerebral mechanisms in pain processing, the neural correlates of cognitive dysfunction and the pathogenesis of FM, with special attention to the genetic basis.

2. Cerebral pain processing in fibromyalgia

Fibromyalgia is considered a chronic pain syndrome which cause (still remain elusive) does not have been found in localized lesions, inflammatory processes or damage to the joints, muscles or other tissues. Experimental evidence indicates that pain processing abnormalities leading to maintenance of pain showed by these patients (e.g., hyperalgesic states) could be due to both central sensitization mechanisms and specific defects in central pain processing related to the loss of normal activity of descending pain-inhibitory (e.g., serotonin-norephinephrine-opioidergic) pathways (Ceko et al., 2012; Lee et al., 2011). Central sensitization related to diffuse hyperalgesia and allodynia is functionally linked to central nervous changes caused by the release of different excitatory neurotransmitters such as serotonin, substance P or glutamate, among others. Through their action on specific receptors (e.g., NMDA) those neurotransmitters might produce enhanced and amplified responses at central nervous level (Woolf, 2004). Specifically, central sensitization can also produce an augmentation of receptive fields in neurons belonging to spinal cord and peripheral fibers. Other neurophysiological indices found in FM patients have involved elevated levels of substance P and serotonin metabolites in cerebrospinal fluid compared with healthy people (Russell et al., 1994; Russell et al., 1992), along with a diminished level of neurotransmitters, which dampen pain sensitivity response (e.g., norepinephrine) suggesting again defects in central pain processing (Russell et al., 1992). Behaviourally, the phenomenon of central sensitization is characterized by lower thresholds in pain perception, pain tolerance and by an enhancement of noxious sensations as a consequence of repeated stimulation, as it occurs in temporal summation (Staud et al., 2003). Additionally, whereas the activation of NMDA receptor channels produces central sensitization, the administration of NMDA receptor antagonists such as ketamine reduces significantly pain perception and facilitates the inhibition of hyperalgesia indices (i.e., temporal summation) in FM patients (Price et al., 2002; Graven-Nielsen et al., 2000). Neuroimaging studies have demonstrated the presence of an augmented activation pattern of pain processing involving several cortical and subcortical regions in FM (Gracely et al., 2002). This

augmented pain processing pattern resulted in response to the same perceived intensity of painful stimulation compared to control participants (Gracely et al., 2002; Cook et al., 2004).

Pain descending inhibitory pathways start from different cerebral levels localized on the brainstem, bulbar region, diencephalic structures and cortical areas. These pathways constitute one of the most important mechanisms involved in the pain perception modulation of sensory information in the dorsal horn of spinal cord. Experimental evidence has described defects in those pain inhibitory pathways leading to a loss of descending endogenous analgesia and the maintenance and enhancement of painful sensations in patients with FM (Julien et al., 2005). These results have been found using different types of acute noxious stimulation. Staud and colleagues (2003) highlighted the presence of diminished pain inhibitory mechanisms in response to hot water in a sample of women with and without FM. Previous studies applying tonic thermal stimulation and by using a tourniquet to produce ischemic pain showed evidence for the defects in descending inhibitory pain activity in FM (Lautenbacher et al., 1997; Kosek et al., 1997). In the same line, diminished periaqueductal gray responses to heat stimulation have been reported in these patients when it was compared with the activity of healthy participants (Cook et al., 2004). Periaqueductal gray region (PGR) has been described as an important structure involved in both ascending and descending pain processing signals (Stahl, 2009). Descending projections from PGR to dorsolateral pontine structures act inhibiting pain signals from peripheral afferent neurons in the dorsal horn of the spinal cord through the release of noradrenaline and serotonin neurotransmitters. Thus, the observed lack of activation within PGR in FM could lead to a loss of descending analgesia enhancing chronic responses of hyperalgesia in these patients (Herrero et al., 2000). Exposed findings demonstrate the main role of abnormalities in central mechanisms as an important key to understand chronic pain in the FM syndrome (Abeles et al., 2007; Bennett, 2005; Lee et al., 2011).

2.1. Morphological brain changes associated with abnormal pain processing in fibromyalgia

Experimental evidence focused on the study of brain areas involved in the processing of painful stimulation has revealed that chronic pain patients show an abnormal activation pattern at specified brain regions (e.g., Kwiatek et al., 2000). Neuroimaging research and its application to the study of pain, has facilitated the identification of a brain network involved in pain processing that has been denominated as 'pain matrix', comprised, among others, by different cortical and subcortical regions: for example, somatosensory regions, insular areas and anterior cingulated cortices (ACC) (Bushnell et al., 2005; Tracey &Mantyh, 2007). Although recently the referred pain matrix has been functionally redefined not only as a pain processing network but also as salience detection system (Iannetti et al., 2010; Legrain et al., 2011; Tracey & Johns, 2010), the role played by somatosensory cortices and other cortical regions, such as posterior parietal cortex or prefrontal areas in the processing of nociceptive signals and in the affective/cognitive modulation processes of pain perception, has been extensively documented (Lorenz et al., 2003; Peyron et al., 2000; Rolls et al., 2003; Sawamoto et al., 2000; Singer et al., 2004; Wiech et al., 2008). For instance, attentional modulations on pain perception have been seen in the increase and/or decrease of activations within insula and ACC (Valet et al., 2004; Wiech et al., 2005).

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Chronic pain diseases are commonly characterized by an abnormal functioning when painful events are processed and as a consequence of it, chronic pain has been understood as an altered perceptual state (Apkarian et al., 2005). Nevertheless, chronic pain is also defined as a dysfunctional condition derived from the appearance of structural brain changes that become more generalized as a function of the years suffering from pain (Baliki et al., 2011). Such changes could cause a dysfunctional neural reorganization affecting brain dynamics (Baliki et al., 2008; Tagliazucchi et al., 2010). Evidence accumulated from the last years through the use of different brain imaging methodologies supports the presence of changes in the brain of FM patients (i.e., structural and functional changes) (García-Campayo et al., 2010; Gracely et al., 2011), although such changes are heterogeneous and a unique interpretation about its clinical meaning remains still unclear. Altered brain morphology was reported by voxel-based morphometry (VBM) studies showing that FM patients had less grey matter density than healthy subjects in several brain regions including insula and ACC (Kuchinad et al., 2007). However, grey matter increase in other cerebral areas belonging to the somatosensory system, such as the Striatum or in those other ones involved in the cognitive modulation of pain (i.e., Orbitofrontal Cortex-OFC) have been seen in patients suffering from FM (Schmidt-Wilcke et al., 2007). Further findings combining diffusion-tensor imaging (DTI) and VBM methodologies have described not only a reduction in grey matter density in FM but also abnormalities in white matter microstructure within thalamus and insular cortex, being highly correlated with the intensity of main FM symptoms (Lutz et al., 2008). Specifically, patients showing higher pain intensity scores were characterized by DTI measurements indicating changes within superior frontal gyrus (SFG). Moreover, changes in SFG and ACC were positively correlated with increased fatigue and self-perceived physical impairment. Affective symptoms defined by higher scores in posttraumatic stress scales were negatively correlated with microstructural changes represented by values of fractional anisotropy (FA) in FM. In this line, Hsu and colleagues (2009) reported decreased grey matter volume in the left anterior insula for patients with FM compared to healthy control participants. This difference in grey matter volume disappeared when the presence of affective disorders in FM patients was controlled. Thus, grey matter volume within this area was inversely correlated with scores in trait anxiety, highlighting the important role of affective disturbances in the explanation of these morphological brain changes. More recent studies have documented that patients with FM syndrome show grey matter atrophy within ACC, mid-cingulate Cortex (MCC) and insular cortex, but affective symptoms like depression are not related to these grey matter changes (Robinson et al., 2011). Along with emotional symptomatology, cognitive alterations in FM have been correlated with changes in grey matter values (Luerding et al., 2008). They found that working memory performance in FM patients was highly and positively correlated with decreased grey matter values within medial prefrontal cortex (MPFC) and ACC, showing that cognitive deficits in FM are associated with changes in brain morphology.

Therefore, mentioned brain abnormalities in the traditionally denominated pain matrix regions might contribute to the alteration of pain processing in FM patients, but they could also affect other domains such as cognitive and affective symptomatology. In fact, it has been proposed that pain and cognitive impairment in FM may co-occur sharing underlying neural networks (Luerding et al., 2008), and as a consequence of it, performance derived from carrying out a

cognitive task when individual is in pain might decrease due to the availability of neural resources is limited and they are invested in pain processing (Seminowicz and Davis, 2007). Additionally, the presence of chronic pain along the years might contribute to the appearance of changes in the brain leading to abnormal activation of brain regions that could exacerbate pain itself and also disturb cognitive function in FM (Kuchinad et al., 2007). Although structural neuroimaging evidence supports the association of chronic pain in FM with grey matter abnormalities, future investigations should be projected to confirm and extend these findings.

2.2. Functional brain changes associated with abnormal pain processing in fibromyalgia

Beyond morphological brain changes, functional imaging investigations have revealed abnormal activation patterns at specific cerebral regions in FM patients (e.g., Cook et al., 2004), however, these anomalies in pain processing are not always circumscribed to activation of brain areas intimately or traditionally related to pain. It has been observed during different experimental situations: in response to painful stimulation, when somatosensory (not painful) information has to be processed and even during resting-state conditions. One of the first neuroimaging studies conducted to investigate such issues demonstrated enhanced brain activation in many regions (i.e., primary and secondary somatosensory cortex, ACC, insula) for FM patients in response to similar levels of pressure stimulation to that one applied to control subjects (Gracely et al., 2002). Moreover, when subjectively painful conditions were established to be comparable (i.e., intensity of stimulation was significantly greater to healthy people than patients for provoke a similar subjective level of pain perception) similar brain activation patterns were found between both patients and control groups. These results indicate that central sensitization defects could be explaining the presence of such augmented activation pattern for painful signals in FM. More recent studies aimed to test the hypothesis of central augmentation pain processing in FM have confirmed and extended those findings (Maestú et al., 2013). Abnormal brain activation of different regions related to the affective/motivational components of pain processing was found in patients with FM during a pain situation induced by a small incision into the skin (Burgmer et al., 2009). Thus, enhanced activations were observed within frontal and cingulated cortices, along with supplementary motor areas. Such altered responses were especially prominent during the pain anticipation period. Additionally, that altered temporal BOLD-signal pattern was found as specific for FM patients when they were compared to other patients suffering from rheumatoid arthritis (Burgmer et al., 2010). It leads to think that fronto-cingulated regions could play a key role as central mechanisms of pain processing responsible to the maintenance and exacerbation of chronic pain in FM.

Previous investigations had already given data about the role of cognitive, affective and social factors on pain processing in FM. Neural responses to somatosensory stimuli can be modulated by cognitive and emotional factors (Cook et al., 2004). Specifically, the catastrophyzing thinking style has been associated with enhanced cerebral responses to pain. Cortical areas involved in pain expectancy or pain-related attention (ACC, MPFC or dorsolateral prefrontal cortex –DLPFC-) showed more intense activity in FM patients who scored high in catastrophizing (Gracely et al., 2004). Affective conditions such as comorbid depression, seem to have influence in the activation of amygdala, but not of somatosensory brain regions during pain processing information (Giesecke et al., 2005). Event-related potentials (ERP) studies have also

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provided data demonstrating abnormal emotional modulation of brain processing in response to somatosensory/non-painful stimuli (Montoya et al., 2005). Somatosensory components (i.e, P50) displayed largest amplitudes when FM patients were introduced within a negative emotional context created with unpleasant slides. The influence of the emotional context was also described during the processing of painful stimulation (Montoya et al., 2004). At the same time, the presence of significant others during the application of painful stimulation was found as a social factor that diminish magnetic brain responses and subjective pain in FM patients compared to control participants (Montoya et al., 2004). Other works have observed that FM patients show a significant enhancement of brain activation within regions involved in the emotional/cognitive aspects linked to pain processing as compared to control subjects, given a painful stimulation (Burgmer et al., 2009). Indeed, larger activation within CCA and anterior insula along with more persisting responses in insular cortex were found for FM patients as well (Pujol et al., 2009). It supports the hypothesis that both affective/cognitive and social factors may play a very important role for pain processing in patients with FM.

On the other hand, the role played by several neurotransmitters, such as dopamine or glutamate, which exerts their functions at the level of central neural system, has been also highlighted in the pathogenesis of FM and studied through the use of neuroimaging techniques (Harris, 2010; Stahl, 2009). Different genetic polymorphisms associated with the functional activity of those neuromodulators have been documented (Ablin et al., 2008), as it will be extensively described later. Evidence on altered levels of mentioned neurotransmitters within the brain of patients with FM has recently reported (Harris et al., 2008; 2009). Dysregulation in levels of glutamate, an excitatory neurotransmitter, has been found within the posterior insula of FM patients being such altered levels associated with experimental pain (Harris et al., 2010). Higher concentration levels of glutamate and glutamine were also detected within the amygdala (Valdés et al., 2010) and posterior insula (Fayed et al., 2010). Patients group showed diminished pain thresholds and high scores in pain and tenderness suggesting that neuronal hiperexcitability elicited by the presence of glutamate may lead to an augmented central pain processing. With respect to other neurotransmitters, different investigations have indicated an abnormal dopamine response to pain in FM (Wood et al., 2007b; Wood et al., 2009). It is known that dopamine is a neurotransmitter involved in pain modulation, but whereas general population showed an increase of dopamine release when a painful stimulus was perceived FM patients did not (Wood et al., 2007a). Thus, that deficiency in dopaminergic reactivity might have a relevant impact on the development and maintenance of chronic pain in FM. In fact, some studies have shown reduced presynaptic dopaminergic activity suggesting that such disrupted neurotransmission could prevent for natural analgesia in FM (Wood et al., 2007b). More recent findings have associated alterations in dopaminergic neurotransmission with a decrease in grey matter density within posterior cingulated cortex, ACC and parahippocampal gyri (Wood et al., 2009). Therefore, these data suggest that pharmacological approaches targeted to the specific or combinated use of glutamatergic and dopaminergic treatments may be effective and should be explored (for a review see, Smith-Wilcke & Clauw, 2010).

Finally, recent investigations postulate that FM could be characterized by an alteration of brain connectivity among different brain networks (Cifre et al., 2012; Napadow et al., 2010). It has been documented that chronic pain produces a disruption in the default mode network (DMN;

Baliki et al., 2008). Evidence coming from neuroimaging studies reported increased resting state connectivity between insula and other brain networks such as the DMN in FM patients. This connectivity pattern was highly and positively correlated with spontaneous pain (Napadow et al., 2010). In fact, when a sample of patients underwent to an acupuncture treatment aimed to diminish pain perception, the degree of connectivity between insula and DMN was also decreased leading to consider resting state connectivity as an objective marker to assess pain in FM (Napadow et al., 2012). Other studies have confirmed the presence of an altered connectivity pattern among brain regions belonging to pain processing network in FM during rest (Cifre et al., 2012). Indeed, such alteration might be due to slow temporal summation effects evoked by C-fiber pain (Craggs et al., 2012).

3. Neural correlates of cognitive dysfunction in fibromyalgia

3.1. Cognitive complaints in FM

It has been suggested that FM syndrome is characterized by an abnormal processing of information in the central nervous system (Montoya et al., 2005; Okijufi et al., 2002) affecting the response to somatosensory stimulation (e.g., painful signals) but also to information belonging to other modalities (e.g., visual, auditory, etc). Several studies indicate that apart from pain and other physical symptoms, cognitive failures are referred by these patients as one of the most important complaints (recently denominated as *fibrofog*; Glass, 2009; Williams et al., 2011), leading to produce even greater functional impact than pain itself (Arnold et al., 2008; Glass et al., 2005). Thus, the incidence rate for memory and concentration difficulties exceeds 90% in FM, being significantly higher that one ocurred in other chronic pain conditions (Arnold et al., 2008; Mease et al., 2008). Additionally, self-reports of patients support the presence of a higher number of cognitive problems than patients suffering from other chronic pain syndromes (Katz et al., 2004), affecting several cognitive domains (Williams et al., 2011). For example, memory complaints of FM patients were positively correlated with the objective perfomance obtained in tasks which set in motion memory resources (Glass et al., 2005). Moreover, these cognitive difficulties manifest persistently in many of daily activities involving the allocation of attentional control resources such as to remember that they have to call someone the next day or to inhibit thoughts that do not allow them to develop other concurrent daily tasks. Experimental evidence confirms that attention, concentration, episodic memory and verbal fluency are impaired in FM (Glass, 2009) showing that such difficulties in the processing of information constitute a very disruptive symptom for patients who have FM, worsening its quality of life and leading to consider it as an independent symptom (Schmidt-Wilcke *et al*., 2010).

3.2. Neuropsychological and behavioural data on cognitive dysfunction in FM

Since the beginning of the past decade growing objective evidence based mainly on neuropsychological studies has shown real and significant impairments of cognitive functions in FM (Glass & Park, 2001; Park et al., 2001). First attempts to characterize dyscognition in FM

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reported deficits in the two declarative memory systems related to the explicit recall of information, episodic and semantic memory. Experimental data revealed poor performance on both standardized (Grace et al., 1999) and non-standarized episodic memory tests (Landro et al., 1997; Grisart et al., 2002). Semantic memory problems have also been documented. FM group showed lower ability for accessing to stored general knowledge than control group when patients were asked to report as many words as they could say starting with a given letter (for example, 'p') and belonging to a specific category (for example, 'fruits and vegetables') (Landro et al., 1997; Park et al., 2001). Along with verbal fluency difficulties, a decrease in naming speed (Leavitt et al., 2008) and speed processing (Veldhuijzen et al., 2012) was also found in FM patients. However, those results are not unequivocal since some studies failed to find differences in cognitive function between patients and healthy control participants (Suhr, 2003). This variability could be related to the lack of previous systematic and detailed research, suggesting that cognitive impairment in FM patients is not generalized; rather is specific-process dependent.

Recent data have suggested that findings on cognitive dysfunction in FM are particularly solid when patients have to deal with tasks demanding for both executive control and working memory resources (Ambrose et al., 2012; Glass, 2010). Impairments in those domains seem to be the key to explain a great part of the cognitive dysfunction in FM. Executive functions (EF) refer to those mechanisms that allow the regulation of both behaviour and other cognitive processes to achieve a specific objective (Muñoz-Céspedes and Tirapu, 2001). Within this theoretical frame, working memory is defined as the support system of those EF aimed to temporarily hold in mind and manage with a variable amount of information (Baddeley, 2000). Thus, working memory dysfunctions have also been seen in FM (Luerding et al., 2008). It has been also observed that patients perform poorly in a variety of tasks involving the allocation of executive control resources to alternate between cognitive sets (Verdejo-García et al., 2009) and to make emotional decisions (Verdejo-García et al., 2009; Walteros et al., 2011) or to face with a task-switching test (Glass, 2006). Tests commonly used to study those executive function processes are Wisconsin Card Sorting Test (WCST) and the Iowa Gambling Task (IGT). Several studies using the Paced Auditory Serial Attention Test (PASAT) have detected a diminished perfomance in FM individuals compared to controls (Leavitt & Katz, 2006; Munguía-Izquierdo et al., 2008). Other working memory components like response inhibition are also suggested to be impaired in FM (Correa et al., 2011). Very similar results have been found during the performance in those tests with a high degree of ecological validity (Test of Everyday Attention, TEA) that includes everyday attentional tasks (Dick et al., 2008). Working memory components measured by TEA were impaired in FM, especially when stimuli competition had to be solved. In this sense, the fact that attentional control difficulties become more evident during distraction (derived from a situation of stimuli competition) has lead to consider it as a key point to better understand cognitive dysfunction in FM (Leavitt & Katz, 2006). It was proposed that failures to inhibit competing stimulation might be an explanation for this difficulty; due to FM patients show hypersensitivity to process information coming from any sensorial modality (Geisser et al., 2008). Such general distractibility could be translated into an attentional orientation towards any type of task-irrelevant stimuli (González et al., 2010) leading to difficulties to focalize attention on relevant information. However, recent

data derived from the use of cognitive inhibition tests indicate that patients with FM do not show a specific problem in such processes (Veldhuijzen et al., 2012).

Although the body of research on cognitive dysfunction in FM has strongly grown in recent years, there are still several unexplored issues in this field of knowledge that should be investigated such as the delimitation of the specific cognitive mechanisms that are altered in these patients. For instance, it is accepted that working memory abilities are impaired in FM, but are different components (e.g., temporal holding of information, inhibition, manage with two concurrent tasks, etc) characterizing working memory equally affected? Kim and colleagues (2012) have indicated that memory is selectively impaired in FM showing the possible existence of a memory dissociation. Data coming from neuropsychological assessments reveal that whereas visuospatial memory abilities are dysfunctional, verbal memory is quite unaffected. Following a similar reasoning, several studies postulate that cognitive dysfunction in FM is restricted to those cognitive mechanisms based on controlled processes (Grisart et al., 2002). However, the presence of a generalized hypervigilance response in FM (Carrillo de la Peña et al., 2006) seems to be under the control of automatic processes, rather than controlled ones (Crombez et al., 2005). Moreover, recent data have demonstrated a reduced performance of patients with FM during an implicit memory task (Duschek et al., 2013). It is the first direct evidence of cognitive disruption associated with processes non-dependent from conscious and controlled resources in FM. Finally, several comorbid symptoms of FM (e.g., anxiety, depression, sleep disturbances, medication, pain, etc) have been associated with a worsening of cognitive dysfunction. Although the impact of affective symptomatology (anxiety and depression) and sleep problems on the cognitive dysfunction in FM might be important, these variables do not entirely explain it (Park et al., 2001; Dick et al., 2008). However, the negative impact of both chronic and acute pain seems to be very robust. When this variable is controlled FM patients show a marked impairment in tasks involving different cognitive domains (Glass et al., 2011; Reyes del Paso et al., 2012; Verdejo-García et al., 2009). Additionally, level of self-reported pain is correlated with cognitive performance in FM (Glass et al., 2005) and it has been highlighted as a mediating variable to explain deficits in self-regulatory processes in these patients (Solberg et al., 2010). Therefore, the role of pain on cognitive disturbances is considered as quite relevant. Nevertheless, the neurocognitive mechanisms by means pain interferes on patient's cognitive function are still unknown.

3.3. Brain activity related to cognitive dysfunction in FM

As it was previously indicated, accumulated evidence supports the presence of clear objective impairments in cognitive function of patients with FM. Cognitive dysfunctional pattern associated with FM (i.e., executive control deficits, working memory failures and declarative memory difficulties) points out to the existence of an altered neural substrate, presumably at least within prefrontal regions, such as inferior prefrontal cortex (IPC), MPFC or ACC along with their connexions with temporal and parietal regions (Glass, 2010; Glass et al., 2011). Although studies focused on these neural mechanisms underlying dysfunctional cognitive processes in FM are still surprisingly scarce, new findings cast some light on the possible altered neurocognitive mechanisms. In this sense, neuroimaging investigations have repeat-

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edly showed increased haemodynamic activity at prefrontal regions (i.e., dorsolateral prefrontal cortex –DLPFC-, ventromedial prefrontal –VMPFC- cortex and ACC) during tasks involving working memory and executive control processes (Bunge et al., 2000; Dagher et al., 1999). Moreover, Altamura and coworkers (2007) have highlighted that the right allocation of working memory resources to accomplish a given task depends on prefrontal regions.

Specific data related to FM patients, have found that working memory performance in FM patients was highly and positively correlated with grey matter values within MPFC and ACC, showing that a decrease of grey matter volume within those prefrontal regions is associated with working memory deficits in FM (Luerding et al., 2008). Additionally, recent functional neuroimaging investigations have revealed diminished activations in cortical regions belonging to the inhibition network, such as ACC, mid-cingulated cortex (MCC) and motor processing areas in patients with FM during the performance in a simple go/no-go task (Glass et al., 2011). At the same time, inefficient activations were detected within insular cortex and IFG when patients had to perform on the mentioned response motor inhibition task. It has been suggested that such effects might be explained via either a greater brain recruitment of cortical compensatory regions different from those involved in response inhibition network. Extending such findings, our research group has tried to characterize cognitive inhibition mechanisms, as part of the altered working memory functions, in patients with FM. Patients showed both enhanced P450 amplitudes and brain activations within IFG in response to an emotional Stroop task (Mercado et al., in press). More in detail, symptom-related words were the kind of stimulation that elicited both the greater frontal P450 amplitudes and the higher IFG activations as compared to rest of stimuli (i.e., general negative-arousing, positive-arousing and neutral words; see Figures 2 and 3). This abnormally enhanced brain activity suggests the presence of a specific difficulty in cognitive inhibition in FM patients (under conditions intimately linked with the core concerns of their disease). However, such supplementary recruitment of neural resources by means same cortical areas only allow them to achieve a comparable behavioural performance to healthy control group during the cognitive inhibition task. These results are in contradiction with those coming from behavioural studies indicating intact cognitive inhibition abilities in FM (Veldhuijzen et al., 2012). A tentative explanation could be related to the idea that brain activity techniques might be more sensitive to detect subtle dysfunctions than behavioural measures alone such as often occurs in FM patients (Glass et al., 2011). Other functional neuroimaging studies have showed that working memory dysfunction (measured through a n-back task) in FM are related to a reduction of neural activity not only at prefrontal regions but also within inferior parietal cortex (IPC) (Seo et al., 2012). It suggests that a different neural activation pattern of the frontoparietal memory network could be explaining, at least partially, cognitive impairments in FM. Diminished early ERP activity of FM patients during a 2-back task has been also detected at inferior parietal sites, Suggesting that problems associated with the early storage of information might be attributable to analtered functioning of parietal areas (Mercado et al.,in preparation). On the other hand, some investigations have indicated the presence of differences associated with the hippocampus activity between patients and healthy control participants (Emad et al., 2008).

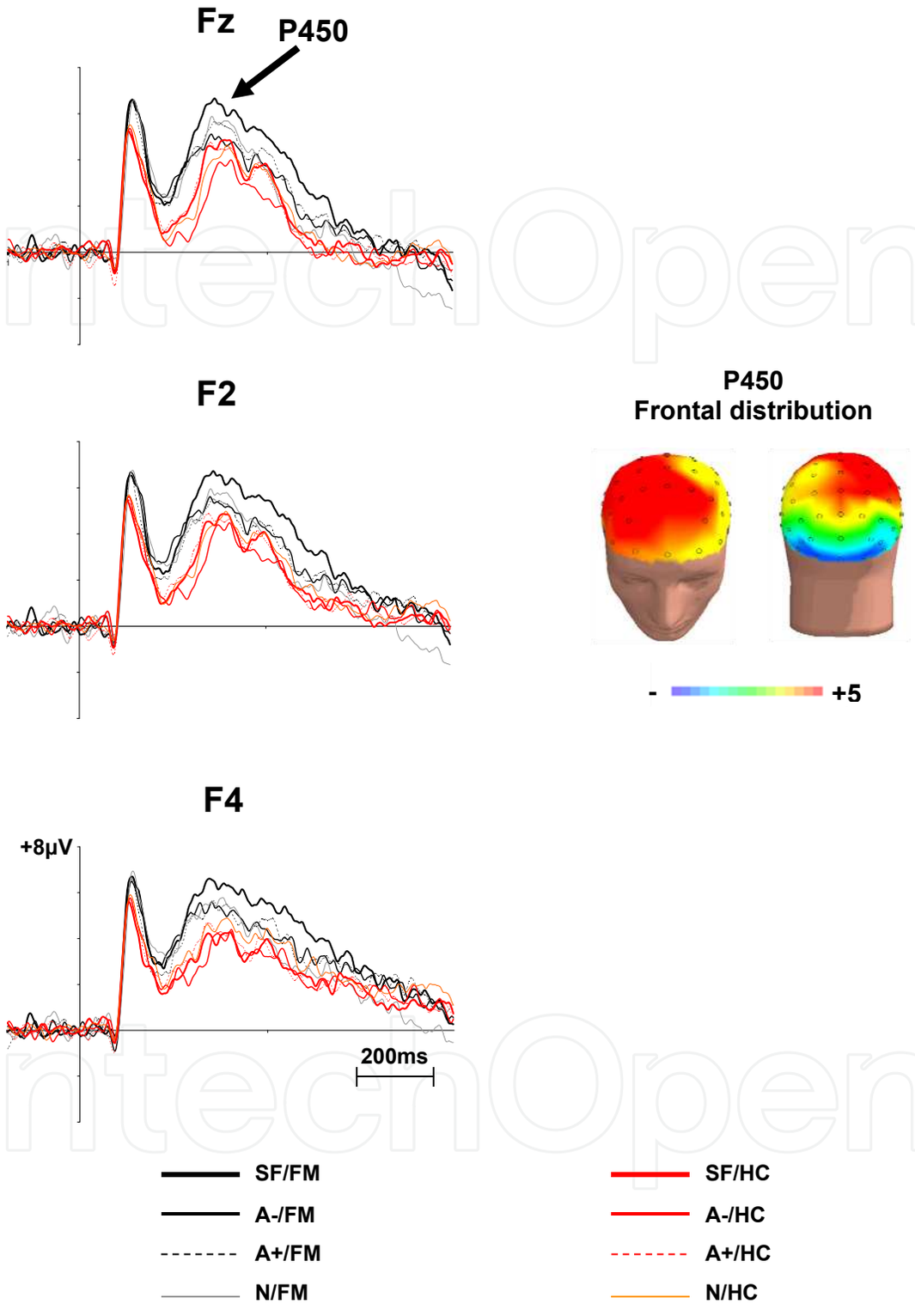

Figure 2. Grand averages of P450 component corresponding to Fibromyalgia (FM) and Healthy control (HC) participants in response to FM symptoms (SF), negative-arousing (A-), positive-arousing (A+) and neutral (N) stimuli. Scales and polarity are shown at F4. 3D maps show topographical distribution of the P450 component. Red areas reflect high activity.

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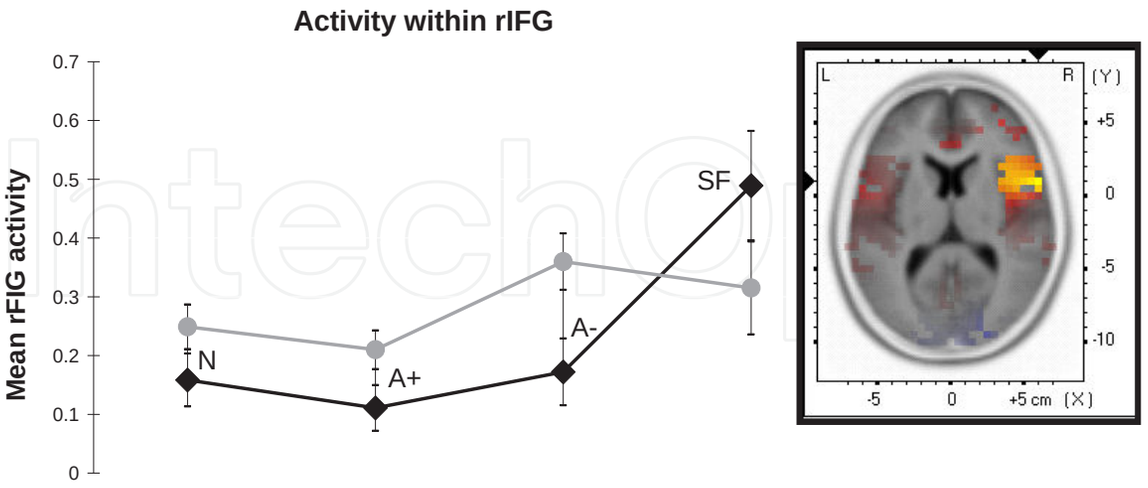

Figure 3. rIFG activity from the emotional Stroop task for patients with fibromyalgia (FM) and healthy control participants (HC). Right side shows sLORETA solutions to non-parametric randomization tests on P450 component. Coronal brain view in MNI305 template, sliced through the region of maximum activity, is illustrated. Left side 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 represent rIFG activity for FM patients and, grey line, for HC participants.

As mentioned before, cognitive dysfunctions and pain processing may rely on partially overlapping regions in FM patients. As a consequence of this, resources taken up by pain processing may not be available for executive functioning (Glass et al., 2011). Pain level of patients might contribute to this effect over cognition. Neuroimaging techiques represent an opportunity to advance in the comprehension of FM and further studies should be done to delimitate deficits in order to develop better diagnostic and classification criteria of FM patients and to better design neuropsychological interventions oriented to increase their quality of life.

4. Genetics in fibromyalgia: Pain and cognition

Genetic predisposition is likely to be an important factor in the development of FM as suggested by several familial studies (Buskila et al., 1996, 2007; Arnold et al., 2004). These studies found that first-degree relatives of patients with FM had lower pain threshold than controls and were 8.5 times more likely to develop FM than relatives of patients with rheumatoid arthritis. The studies also indicated that the relatives of FM patients are more likely to suffer from comorbidities commonly seen in FM, such as mood disorders, irritable bowel syndrome (IBS), temporomandibular disorder (TMD) and headache (Ablin et al., 2008; Buskila et al., 1996, 2007). Identifying the genes responsible for this genetic contribution to risk should provide a better understanding of the complex mechanisms underlying FM and other chronic pain diseases. In recent years, attempts have been made to identify the genes involved in FM

using candidate gene genetic association studies, which look for differences in the frequency of different polymorphisms between cases and controls, or with a quantifiable trait. The majority of such candidates have been genes involved in catecholaminergic or serotonergic neurotransmission, including receptors and transporters for dopamine, serotonin, norepinephrine, and epinephrine, as well as the catabolic enzymes catechol-O-methyltransferase (COMT).

Next we will review, in outline, the main findings made on genes associated with FM. The most widely studied gene to date is **Catechol-O-Methyltransferase (COMT)**, which degrades catecholamines such as dopamine, noradrenaline and adrenalin that are involved in various physiological functions including mood, cognition and stress response (Belfer and Segal, 2011). In particular, a single nucleotide polymorphism (SNP), (rs4680), has received a great deal of attention due its functional implications (Zubieta et al., 2003). This polymorphism causes a substitution from a valina (Val) to a methionine (Met) at amino acid position 158 (*Val158Met*), leading to a three to four fold reduced activity of the COMT enzyme (Lotta et al., 1995). In 2005, Diatchenko and colleagues described three very common haplotypes consisting of four SNPs (rs6269, rs 4633, rs4818 and rs4680-*Val158Met*) accounting for 96% of all haplotypes observed in human populations (Diatchenko et al., 2005). They identified them as low (LPS), average (APS) and high (HPS) pain sensitivity haplotypes, and they found a correlation with much more profound change in COMT activity (up to 20-fold difference).

The *met*/*met* genotype of the COMT *Val158Met* polymorphism has been associated with higher sensitivity in response to pain stimuli and the number of tender points in FM (Cohen et al., 2009) as well as with a high risk for the development of FM (García-Fructuoso et al., 2006; Barbosa et al., 2012). Recently, Martínez-Jauand and colleagues (2013) have shown that the HPS-APS haplotypes are more frequent in FM patients than in healthy controls and that FM patients who possess those genetic combinations displayed an increased sensitivity to experimental pain. These results are in accordance with previous reports showing a strong association between the HPS haplotype and high score on the Fibromyalgia Impact Questionnaire (Vargas-Alarcón et al., 2007). These haplotypes might be associated with increased risk of developing chronic pain disorders (Diatchenko et al., 2005). These data suggest that a decrease of COMT activity might contribute to the maintenance of pain symptoms in FM, and might play a significant role in classifying FM patients (Martínez-Jauand et al., 2013).

COMT variants moderate not only pain but also maladaptive coping processes in patients with FM. Finan and colleagues (2010 and 2011) demonstrated that Met158 allele homozygotes experience more pain in days when pain catastrophizing and pain attention scores were elevated, and a greater decline in positive affect on days when pain was elevated. These findings support the role of COMT and catecholamines in affective reactivity to pain, and in pain-related cognition pathways in patients with FM. A recent study has proposed that the Val158Met can play a relevant role in phenotypic expression of FM. They showed that women with FM and Met/Met genotype had more severe psychological and functional impact scores than those with the Val/Val genotype, although the differences were not significant (Desmeules et al., 2012). More recently, Fernández de las Peñas and colleagues (2012) have shown that FM

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patients with Met/Met genotype exhibit higher disability, anxiety and depression than those with Val/Val and Val/Met genotype.

As indicated above, cognitive dysfunction has been considered as one of the most disturbing symptoms, apart from pain, in patients with FM. Neuropsychological investigations have suggested that executive control and working memory impairments seem to be the key to explain a great part of this cognitive dysfunction in FM (Glass, 2010) and it points out to the existence of an altered neural substrate, presumably within prefrontal regions, such as inferior prefrontal cortex (IPFC), MPFC or ACC (Glass et al., 2011). In this context, it has been shown that more than 60% of released dopamine is metabolized by COMT in the frontal cortex (Karoum et al., 1994), and that the Val158Met polymorphism affects working memory and executive functions in healthy population (Bruder et al., 2005) and some mental disorders such as schizophrenia (Diaz-Asper et al., 2006; Hosak, 2007). Therefore, COMT may be a good candidate for the study of cognitive impairment in patients with FM.

The **endogenous serotonergic system** is comprised of the neurotransmitter serotonin (5-HT), multiple serotonin receptors (5-HT2A, 5-HT3A, 5-HT3B) and the serotonin transporter (5-HTT). This system is a key contributor to both depression and pain in FM. In fact, serotonin is decreased in FM, and selective serotonin reuptake inhibitors have some efficacy in FM (Gupta and Silman, 2004). Despite the complexity of the serotonergic pathway, research has mainly focused on a limited number of genes. Offenbaecher and colleagues (1999) analyzed the genotypes of the promoter region of the serotonin transporter gene (5-HTT) in patients with FM and healthy controls. A significantly higher frequency of the S/S genotype of the serotonin transporter promoter region was found in FM as compared to healthy participants. The S/S subgroup exhibited higher mean levels of depression and psychological distress. It was suggested that these results support the notion of an altered serotonin metabolism in at least a subgroup of patients with FM (Buskila et al., 2007). These findings were subsequently confirmed by a study analyzing Palestinian Arabs and Israeli Jews (Cohen et al., 2002). However, the study in other candidate genes within the serotonergic system failed to demonstrate a significant difference in the frequency of the polymorphism among FM patients and controls (Bondy et al., 1999; Frank et al., 2004; Matsuda et al., 2010).

The **dopaminergic system** has also been the target of extensive study in search of the genetic factors related to FM. Dopamine is a crucial neurotransmitter involved in multiple activities including pain transmission and endogenous analgesia (Wood, 2008). A single nucleotide polymorphism (Ser9Gly) in the dopamine-D3 receptor gene predicts changes in pain threshold in FM patients but not in healthy subjects (Potvin et al., 2009). In the FM group, the Ser9Gly polymorphism was a predictor of decreased thermal pain threshold and diffuse noxious inhibitory control (DNIC) efficacy (Potvin et al., 2009). Polymorphisms in the dopamine receptor 4 (DRD4) gene has also been associated with FM. Buskila and colleagues (2004) reported a significant decrease in the frequency of the 7 repeated allele in exon III of the D4 receptor gene in FM patients, who also demonstrated an association between this polymorphism and the low novelty seeking personality trait. This was considered consistent with the personality profile of FM patients, who scored high on anxiety related personality traits and

low on novelty or sensation seeking. In a study of 384 subjects with DRD4 polymorphism, allele 4 was the most common, occurring in 279 of the 384 subjects (Treister et al., 2009). However, there was no change in cold tolerance, cold perception, cold pain threshold, or heat pain intensity in those subjects compared to subjects with allele 2 or allele 7 (Treister et al., 2009). Dopamine D2 receptor (DRD2) is implicated in different cognitive processes and brain disorder, and polymorphisms in this gene affect gene expression, splicing, and neuronal activity during working memory (Zhang et al., 2007). This has been demonstrated in patients with schizophrenia, whose presence relatively increased density of DRD2 (Laruelle, 1998). Curiously, it has also been observed an increased sensitivity or density of dopamine D2 receptors (DRD2) in FM patients (Malt et al., 2003). Preliminary results in our research group found a significant relationship between promoter SNP (rs12364283) in DRD2 and working memory functioning in FM patients. Specifically, we found significant differences during the performance in both Spatial Span (forward sequence) and n-back tasks. Heterozygotes (TC)-FM patients had a lower performance compared to TC-HC in both Spatial Span and n-back tasks. They also perform worse than homozygotes TT-FM patients but only in the Spatial Span task (Gómez-Esquer et al., 2012). Our results suggest that DRD2 could be playing an important role in working memory functioning in FM patients and support the implication of dopaminergic pathways in the cognitive symptoms of FM.

Another candidate gene is the **β_2-adrenergic receptor** (ADRB2). It mediates physiologic responses such as vasodilation and bronchial smooth-muscle relaxation, and represents a connection between the sympathetic nervous system and the immune system (Small et al., 2003; Catapano & Mangi, 2007). Alterations in the ADRB2 function have been implicated in several psychiatric and psychological disorders, including those associated with chronic pain (Lee et al., 2012). Vargas-Alarcón and colleagues (2009) reported that having the AC haplotype of the two SNPs (rs1042713 and rs1042714) was associated with an increased risk for suffering FM among Mexican and Spanish individuals. Recently, it has been published the first study to demonstrate ADRB2 polymorphism-related differences in intracellular cyclic Adenosine Monophosphate (cAMP) levels in FM Peripheral Blood Mononuclear Cells (PBMC), before and after ADRB2 stimulation. These findings suggest that ADRB2 polymorphisms may influence the response to a variety of β-adrenergic ligands and may help to explain some differences in responsiveness of FM subgroups to the adrenergic agonist medication currently approved for FM treatment (Xiao et al., 2011).

Finally, we will briefly discuss about **SCN9A**, a gene that encodes sodium channel in dorsal root ganglia (DRG). A consistent line of investigation suggests that autonomic nervous system dysfunction may explain the multi-system features of FM. In this context, DRG play a key role in pain perception and sodium channels located in DRG act as molecular gatekeepers of pain detection at peripheral nociceptors. Mutations in this gene have caused severe pain disorders and congenital insensitivity to pain in families, thus demonstrating a critical role in pain processing (Drenth and Waxman, 2007). In FM, Vargas Alarcón and colleagues (2012) demonstrated that, in Mexican women, the frequency of rs6754031 polymorphism of SCN9A was significantly different between FM patients and healthy controls. Interestingly, patients with

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GG genotype had higher Fibromyalgia Impact Questionnaire (FIQ) scores than patients with the GT or TT genotype. These results show that there is an association between the rs6754031 polymorphism and the risk of developing FM as well as the FIQ score. This association raises the possibility that some patients with severe FM may have a DRG sodium channelopathy (Vargas-Alarcón et al., 2012). However, further investigation will be necessary in other ethnic groups with a large sample size to verify this observation.

Despite the large number of studies examining the potential contribution of the candidate gene polymorphism to FM susceptibility, many studies have produced conflicting results (Potvin et al., 2010; Frank et al., 2004; Gursoy, 2002). The explanation for these results could be that individual studies based on small sample sizes have insufficient power to detect positive associations and they are incapable of demonstrating the absence of such association. Recently, Lee and colleagues (2012) have conducted a systematic meta-analysis of seventeen candidate genes and over 35 polymorphisms were identified in studies on FM susceptibility. This meta-analysis demonstrates that the 5-HT2A receptor 102T/C polymorphism confers susceptibility to FM. In contrast, no association was found between the 5-HTTLPR S/L allele, COMT Val158Met, and susceptibility to FM. However, the authors were aware of the limitations of their meta-analysis since both the number of the studies and the number of the subjects included in such studies were too small. This may have not enough power to explore the association between the candidate gene polymorphism and FM. They could not perform the ethnic-specific meta-analysis to detect associations in ethnic groups due to limited data. They have not been able either to examine whether the candidate gene polymorphisms are associated with clinical features of FM (Lee et al., 2012). Therefore, additional research including large numbers of patients and controls is required to conclude the association of the candidate gene polymorphisms with FM. Another approach being made lately to identify genetic factors involved in FM is the use of a large-scale candidate gene approach (Smith et al., 2012). This is the largest candidate genes association study of the FM to date, analyzing 3,295 SNPs corresponding to > 350 genes involved in the biological pathways relevant to nociception, inflammation, and mood. This work observed significant differences in allele frequencies between cases and controls for several novel genes: GABRB3 (in the promoter region of the GABA-A β receptor gene), TAAR1 (trace amine-associated receptor 1), GBP1 (guanylate binding protein 1), RGS4 (regulator of G-protein signaling 4), CNR1 (CB-1 cannabinoid receptor gene), and GRIA4 (AMPA ionotropic glutamate receptor 4 subunit). Three of these genes, TAAR1, RGS4, and CNRI play roles in the modulation of analgesic pathways (Smith et al., 2012). Variation in these 4 replicated genes may serve as a basis for the development of new diagnostic approaches, and the products of these genes may contribute to the pathophysiology of FM and represent potential target for therapeutic actions.

5. Conclusions and future directions

Evidence from FM investigations indicates that psychoneurobiological dysfunctions play a relevant role in the pathophysiology of this multifactorial and still not fully understood syndrome. Specifically, it was suggested that abnormalities in central brain mechanisms are

crucial in the understanding of chronic pain in FM, having little relevance the involvement of peripheral processing systems. Mechanisms of central sensitization and those involving descending inhibitory pathways, along with abnormalities in neurotransmission regulatory processes, seem to underlie patient's manifestations of hyperalgesia and allodynia, among other pain-related symptoms. Experimental findings also have demonstrated that both morphological and functional brain changes are related to widespread and diffuse pain and cognitive symptoms suffered by patients with FM.

On the other hand, patients with FM are characterized by the presence of difficulties in the processing of information reporting that it constitutes a very disruptive symptom in their everyday functioning. Cognitive disturbances are mainly related to both executive functions and working memory processes. Neuroimaging investigations have found abnormal activity within prefrontal and parietal regions when patients had to face a demanding task of executive control resources. However, many researchers are trying to answer an important question in order to advance in the knowledge on FM. Can cognitive dysfunction in FM be considered as a primary symptom like abnormal pain perception or, by contrast, is it a direct consequence of the structural or functional changes produced by pain? Based on present findings, cognitive dysfunctions and pain processing seem to share brain networks (prefrontal, supplementary motor regions and parietal cortices) and as a consequence of this, resources taken up by pain processing may not be available for executive functioning. Thus, performance in those tasks, which need a recruitment of working memory resources from the frontoparietal brain network to be correctly completed, would be very poor in FM. Neuroimaging techniques represent an opportunity to advance in the comprehension of pain and cognition interactions in FM and further studies should be done to explore such deficits and their interrelations.

Current data support the statement that FM constitutes a real syndrome characterized by the existence of multiple changes into the brain. Future investigations should be projected to extend these findings and to establish comprehensive explanations about: 1) cerebral mechanisms that provoke those changes, 2) its consequences on the functional state of patients and, 3) if brain changes constitute a reversible or permanent condition in the brain of FM patients. In this sense, different therapeutic approaches targeted to reverse such changes in the brain (e.g., pharmacological treatments, neuropsychological interventions, transcraneal magnetic stimulation, etc) may be effective and should be explored. The investigation about different genetic polymorphisms is a promising approach that may also help to improve the comprehension of the pathogenesis of this multifactorial and intriguing syndrome.

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