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FIBROMYALGIA (MFP PERES, SECTION EDITOR)

Brain Imaging in Fibromyalgia

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Abstract Fibromyalgia is a primary brain disorder or a result of peripheral dysfunctions inducing brain alterations, with underlying mechanisms that partially overlap with other painful conditions. Although there are methodologic variations, neuroimaging studies propose neural correlations to clinical findings of abnormal pain modulation in fibromyalgia. Growing evidences of specific differences of brain activations in resting states and pain-evoked conditions confirm clinical hyperalgesia and impaired inhibitory descending systems, and also demonstrate cognitive-affective influences on painful experiences, leading to augmented pain-processing. Functional data of neural activation abnormalities parallel structural findings of gray matter atrophy, alterations of intrinsic connectivity networks, and variations in metabolites levels along multiple pathways. Data from positron-emission tomography, single-photon-emission-computed tomography, blood-oxygen-level-dependent, voxel-based morphometry, diffusion tensor imaging, default mode network analysis, and spectroscopy enable the understanding of fibromyalgia pathophysiology, and favor the future establishment of more tailored treatments.

Keywords Fibromyalgia · Magnetic resonance imaging · Chronic pain · Postsynaptic potential summation · Pain measurement · Brain mapping · Functional neuroimaging · Tomography · Emission-computed, single-photon · Positron-emission tomography

Introduction

Fibromyalgia (FM) is characterized by chronic widespread allodynia, associated to affective, cognitive, and autonomic dysfunctions. It is frequently accompanied by other functional conditions, suggesting a partial common substrate for these disorders [1].

A composite score for diagnosis is reached by adding the generalized chronic pain from any body site as a main sign, to other symptoms (fatigue, sleep disturbance, headache, depression, and cognitive complaints). Currently, the presence of tenderness in specific points is not mandatory [2].

FM patients have increased sensitivity to several afferences, like intramuscular hypertonic saline injection, auditory/olfactory stimuli, or thermal/electrical pain, leading to the hypothesis of hypervigilance for perceptual modalities, up-regulation of peripheral nociceptive processes, and altered hedonic appreciation. Responses to stimuli are modulated by cognitive and affective influences [3].

There are central nervous system (CNS) abnormalities, including aberrant pain facilitation, generalized decrease in mechanical thresholds, and larger areas of referred pain. Another phenomenon linked to central sensitization is ‘windup’, in which the C-fiber nociceptive input at the spinal cord leads to abnormal temporal summation of pain.

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Windup relies on stimulation frequency, the activation of N-methyl-D-Aspartate (NMDA) receptor, and wide dynamic range spinal neurons [4, 5].

FM also shows decreased central regulation of sensory input. The impairment of spinal cord and supraspinal inhibitory systems, such as the diffuse noxious inhibitory control (DNIC) and the conditioned pain modulation (distraction and habituation effects), lead to altered attentional focusing and hypervigilance to unpleasant stimuli.

Both facilitation increase and inhibition decrease of pain modulation systems could be caused and perpetuated by a tonic activation related to the presence of ongoing widespread pain, so that the saturated systems cannot respond to an external stimulus beyond a ceiling limit.

Moreover, FM is hypothesized as a prolonged stress consequence, affecting modulation of brain circuitry and emotions, via hypothalamic-pituitary-adrenal axis and the sympathetic nervous system [6]. Augmented pain levels are related to an increase in the corticotrophin-releasing hormone, Substance P, and glutamate in cerebrospinal fluid and salivary cortisol; FM patients have hypoactivity of dopaminergic, opioidergic, and serotoninergic systems [7]. The disruption of architecture of sleep in FM is associated with increased pain sensitivity and inhibition of serotonin synthesis [8].

Main Functional Neuroimaging Methods

Pain has been extensively studied with neuroimaging techniques. Despite the variability of equipments and statistics, there is a growing consistency of data regarding the brain regions involved in pain processing. The study of acute experimental painful stimulation in control subjects allowed the definition of the 'pain matrix' areas: primary and secondary somatosensory cortex (SI, SII), thalamus (discrimination); insular cortex (IC), anterior cingulated cortex (ACC), posterior cingulated cortex (PCC), amygdala (affect); dorsolateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex (VPFLC), frontal gyrus, orbitofrontal cortex (OFC) (evaluation); supplementary motor area (SMA), basal ganglia, cerebellum, posterior parietal cortex, PAG, and cuneiformis.

These findings were possible because acute pain studies deliver unbiased stimuli, with rapid onset-offset of relevant evoked pain [9]. Because chronic pain fluctuates and is susceptible to environmental and endogenous influences, neuroimaging designs were adapted to take these covariables into account [10].

Neuroimaging techniques in FM allow the study of abnormal nociceptive processing through quantitative sensory testing, neural networks, neurotransmitters analyses, and changes in anatomical structures (Table 1). They infer neural activity by evaluating the changes of regional cerebral blood flow (rCBF) in response to neuronal metabolic demand within a time interval because there is a coupling between hemodynamic response and underlying neuronal activity duration.

Methods such as the magnetoencephalogram detect brain events from precise acoustic or electrical stimuli with high temporal precision; however, they cannot measure pressure or thermal pain, necessary in study models for FM. The main neuroimaging methods for FM studies are described here: single photon emission computed tomography and positron emission tomography; after injecting radioactive tracers, they measure the increase of regional cerebral blood flow (rCBF), with good spatial resolution.

Functional Magnetic Resonance Imaging

Magnetic proprieties of oxygenated and deoxygenated blood are used as physiological tracers for the blood oxygen level dependent (BOLD) signal, to track changes in rCBF. This data has greater temporal resolution than positron emission tomography (PET) and single photon emission computed tomography (SPECT), but it depends on designs of repeated on–off switching, which hampers the study of long-lasting effects. The functional magnetic resonance imaging (fMRI) analyzes the intrinsic connectivity network (ICN), such as the interaction of multiple brain areas at structural and functional levels. The default mode network (DMN) is the normal activity of self-referential thinking at the resting state. Other ICNs are the executive attention network (EAN) involved in working memory and attention processing, and the medial visual network (MVN). The fMRI also performs a structural analysis of the brain tissue (voxel-based morphometry, [VBM]), and quantifies organizational changes by monitoring the mobility of water molecules in tissues (diffusion tensor imaging, [DTI]). This technique is based on the anisotropic unidirectional movement of water across axons in white matter. The anisotropy increases with myelinization, fiber diameter, and axonal density. Brain degeneration impairs diffusion and increases water motility, expressed as the apparent water diffusion coefficient (ADC), and the reduction in diffusion directionality (fractional anisotropy [FA]). Magnetic resonance spectroscopy (H^1-MRS) permits biochemical analysis, through detection of neurotransmitters, and measures of tissue metabolism. Level changes of substances (such as *N*-acetylaspartate, creatine, choline, and glutamate) and their concentration ratios are associated with brain abnormalities.

PET Studies

Studies that measured resting rCBF in FM using $H_2{}^{15}O$-PET or SPECT preceded the fMRI popularization. They showed

Table 1 Functional neuroimaging studies in fibromyalgia patients

Study	FM patients, *n*	Controls, *n*	Neuroimaging technique	Findings	Conclusions
Kuchinad et al. [58]	10	10 HC	fMRI - VBM	Less total gray matter, mainly in cingulated cortex, IC, medial FC, and parahippocampal gyri. In FM, 3.3 times greater age-associated decrease in gray matter	FM associated with accelerated age-related gray matter loss
Fayed et al. [50•]	10	10 HC	fMRI - H^1-MRS, DTI/DWI	Higher levels of Glx and Glx/Cr ratio in posterior gyrus. Lower level of MI and NAA+NAG in hippocampi	High Glx in posterior gyrus correlated to pain and clinical evaluation, and may be a pathological factor in FM
Valdés et al. [51]	28	24 HC	fMRI - H^1-MRS	Higher levels of Glx and Glx/Cr ratio in right amygdala. Increased inositol levels correlated to more symptomatic FM	Amygdala metabolism in FM suggests possible neural dysfunction in affective processing in FM
Harris et al. [47]	19	14 HC	fMRI - H^1-MRS	Higher levels of Glx and Glu in right posterior insula in FM. Both groups: higher levels of Glu and Glx associated with lower pain thresholds	Higher concentrations of Glu in posterior insula and glutamatergic transmission may play a role in the pathophysiology of FM
Harris et al. [16]	17	17	PET	FM shows reduced MOR binding potential in nucleus accumbens, amygdala, dorsal cingulated cortex. MOR binding negatively correlated with affective pain ratings in these regions of FM	Altered endogenous opioid analgesic activity in FM
Robinson et al. [54•]	14	11 HC	fMRI-VBM	No total gray matter loss detected. In FM, atrophy of mid-cingulate, and mid IC	Accelerated gray matter atrophy
Napadow et al. [66•]	18	18 HC	Resting fMRI for ICN (DMN, EAN)	Greater connectivity within DMN and right EAN, between DMN and IC. Correlation between spontaneous pain and DMN/right EAN/IC	Resting brain activity within networks is associated with spontaneous pain in FM
Giesecke et al. [26]	16	11 HC, 11 CLBP	fMRI - BOLD	Same stimulus: FM and LBP hyperactivated SI/SII, inferior parietal, cerebellum. Same pain: similar activation for three groups	Augmented central pain processing in LBP patients.
Giesecke et al. [34]	7	7 depression, 7 HC	fMRI - BOLD	Clinical pain associated with activation of bilateral insula, contralateral ACC, PFC. Depression – activation of amygdala, contralateral insula. SI/SII not activated	In FM, depression does not modulate discriminative aspects of pain processing, but is associated with activation in brain affective-motivational regions of pain processing
Gracely et al. [35]	15 high catastrophizers	14 low catastrophizers	fMRI - BOLD	Both activated contralateral insula, bilateral SI/SII, inferior parietal lobe, thalamus, cerebellum, posterior cingulate gyrus High: activation in contralateral ACC, lentiform	Catastrophizing influences pain perception through altering attention and anticipation and heightening emotional responses to pain. Activation of motor areas in high catastrophizers reflects greater responses to pain
Adigüzel et al. [72]	14	0	SPECT	Increased rCBF in thalami after amitriptyline; findings correlated to tender points and pain VAS. No improvement of Beck Depression Inventory	Deficits in thalamic CBF in FM improve in parallel to clinical recovery (tender points and VAS) after amitriptyline treatment
Kwiatek et al. [23]	17	22 HC	SPECT	Reduced rCBF in right thalamus/pons. No reduction in left thalamus, caudate. Findings not correlated to symptoms	Reduction in thalamic rCBF was expected; reduced pontine tegmental rCBF must be confirmed in future studies
Wood et al. [14]	11	11 HC	PET	Reduced release of dopamine in basal ganglia during noxious stimulus. Findings do not correlate to symptoms in FM, unlike the HC	FM patients have an abnormal dopamine response to pain
Lutz et al. [68]	30	30 HC	fMRI - DTI, VBM	Lower FA values in FM in the thalami, thalamocortical tracts, and insula. Findings correlated to pain. Increased FA and	DTI might be more sensitive than VBM.

Table 1 (continued)

Study	FM patients, *n*	Controls, *n*	Neuroimaging technique	Findings	Conclusions
				decreases in gray matter volume in postcentral gyri, amygdalae, hippocampi, superior frontal gyri, and anterior cingulate gyri	
Foerster et al. [71]	27	27	fMRI - DSL	Significant correlations between thalamic perfusion and pain-control beliefs of FM. Significantly different distribution pattern of rCBF across several brain regions between the FM and controls. Pattern distribution of rCBF more even in controls	Correlations between thalamic rCBF and pain belief scale. Presumable baseline alterations of brain perfusion in FM patients
Usui et al. [73]	15	0	SPECT	Increased rCBF and pain VAS/ tender points after electroconvulsive therapy	Deficits in thalamic CBF in FM improve in parallel to clinical recovery (tender points and VAS) after electroconvulsive treatment

FM fibromyalgia; *HC* healthy controls; *fMRI* functional magnetic resonance imaging; *VBM* voxel-based morphometry; *IC* insular cortex; *FC* frontal cortex; H^{l}*-MRS* H proton magnetic resonance spectroscopy; *DTI* diffusion tensor imaging; *DWI* diffusion weighted imaging; *Glx* glutamine+glutamate; *Glx/Cr ratio* glutamine+glutamate/creatine ratio; *NAA+NAG* N-acetyl aspartate+N-acetyl aspartyl glutamate; *MI* myoinositol; *Glu* glutamate; *PET* positron emission tomography; *MOR* μ-opioid receptor; *ICN* intrinsic connectivity network; *DMN* default mode network; *EAN* executive attentional network; *CLBP* chronic low back pain; *LBP* low back pain; *SI/SII* primary and secondary somatosensory cortex; *BOLD* blood oxygen level dependent; *ACC* anterior cingulate cortex; *PFC* prefrontal cortex; *SPECT* single photon emission computed tomography; *rCBF* regional cerebral blood flow; *VAS* visual analogue scale; *CBF* cerebral blood flow; *FA* fractional anisotropy; *DSL* dynamic susceptibility contrast imaging

hypoperfusion in several regions, especially in the thalamus. It is speculated that thalamic dysfunction (reduction of gray matter and hypoperfusion) might be a substrate of different types of chronic pain [11].

Consistent with pain modulatory system disturbance in FM, PET results using ligand-binding techniques reveal abnormalities in neurochemical pain control systems such as dopamine (reduced binding of D2D3 receptor) and opioid transmissions (reduced binding potentials for the μ-opioid receptor (MOR) agonist) in several areas, including striatum, ACC, and amygdala [12], inversely correlated to pain ratings. FM patients submitted to a tonic noxious stimulation showed a reduced dopamine release in globus pallidus and striatum [13, 14]. Poor results in cognitive tasks in FM might be related to dopamine dysfunction, since dopamine plays an important role in cognitive abilities and perceptual speed [5]. Low dopamine levels are also implicated in ongoing pain in FM [15].

There is a reduction of mu-opioid receptor (MOR) binding potential in several areas associated with affective modulation of pain (nucleus accumbens, ventral striatum, amygdala, and dorsal cingulated cortex), suggesting compromised opioid activity in FM, but it is not known whether findings refer to augmented opioid levels or reduced receptors availability [16]. This data suggests abnormal activity of opioid-dopamine systems.

^{18}F-fluorodeoxyglucose (FDG)-PET directly assesses glucose metabolism, and it was demonstrated FM show metabolic hypoactivity in the left IC [17]. An rCBF reduction in the retrosplenial cortex, an area of pain-evaluation processing, was also observed [18].

SPECT Studies

Basal hypoactivity of the caudate and thalamus—area of reception of nociceptive inputs and inhibitory pathways—was observed in painful conditions such as traumatic or metastatic neuropathies, spinal cord injury, and restless leg syndrome [19–21]. These findings suggest tonic inhibition after ongoing excitatory inputs and persistent inhibitory activation. They could indicate lack of pain-evoked responsiveness or pain hypersensitivity.

Because researchers focused on different brain areas for rCBF measurements in SPECT for FM, evidences of lower neural activity varied from the bilateral caudate nucleus and thalamus [22], to the right thalamus, inferior pontine tegmentum, and right lentiform, but not in the left thalamus or caudate [23].

The data corroborate the hypothesis of dopaminergic dysfunction in FM because thalamus and caudate are rich in dopamine receptors. Dopamine is involved in motivation mechanisms and motor control; the system deficit could explain the emotional symptoms of FM.

Functional Magnetic Resonance Imaging Evidences

BOLD Studies

Following PET and SPECT, the subsequent studies used fMRI for stimulus-evoked regional brain blood flow. The majority of these fMRI studies used painful blunt pressure applied to the thumb because f its large cortical representation, and value as a surrogate for widespread tenderness.

fMRI studies support clinical findings of augmented sensory processing throughout pain-related cerebral areas. At the same perceived intensity of pain among FM and controls, the same neural matrix was activated and involved discriminative sensory processing (contralateral SI/SII, ACC), association (contralateral superior temporal gyrus [STG], inferior parietal lobe), motor responses (putamen, cerebellum), and affective/cognitive/motivational processing (DLPFC, VMPFC, insula, ACC, caudate, periaqueductal gray matter/PAG). However, at the same painful intensity, there was lower activation of caudate and thalamus in FM, and hyperactivation of pain-related areas. This data demonstrated an alteration in pain processing and central augmented responses of multiple regions involved in somatosensory integration, motricity, and affective-motivational control [24, 25]. The same was observed between FM and LBP patients [26], and using relative/absolute painful and nonpainful heat (anterior IC and thalamus activation) [27].

A study series showed hyperactivation of other brain areas in FM: SSI, SSII, DLPFC, VPFC, inferior parietal cortex, lentiform, cerebellum, IC, mid/ACC, claustrum, and supplementary motor area (SMA) [25, 28–31].

Clinical practice show s that FM sufferers have a lower pain threshold and report higher pain ratings in response to evoked pain stimuli. These are due to altered DNIC (CNS failure of processing afferences), and windup to repetitive stimuli at spinal cord nociceptive neurons [3]. Experimental temporal summation inducing hyperalgesia in FM confirmed the altered pain processing by increased activation of thalami, SI, SII, IC, and rostral and mid-ACC [29, 32].

During an fMRI study with individually calibrated pressure stimulus of the thumbnail, rostral ACC (the primary step of the inhibitory pathway) failed to respond to pain stimulation, suggesting that this is a key region related to FM impairment of pain inhibition [32, 33]. The absence of activity of PAG and ACC thus supports the hypothesis of both pain augmentation and impaired pain inhibitory processes in FM [27].

Pain is a multidimensional experience; affective, environmental, and cognitive factors influence the noxious perception and lead to pain behaviors. Clinical findings suggest depression leads to increased pain perception in FM and is associated with chronic pain. However, fMRI studies show that depression does not influence sensory-discriminative, only affective-motivational, pain aspects (amygdalae, IC, ACC) [34, 35], suggesting higher activation threshold in the former areas because of an affective adaptation following prolonged pain exposure [28, 36].

An individual's perception about his own ability to control adverse events is referred to as locus of control: those with high internal locus believe events are the result of their own actions and are more open to treatment response. Psychophysical experiences show that FM patients presenting an external locus of control are functionally more disabled and have worse outcomes [37], and they show more external locus than those with rheumatic conditions [38]. These findings were confirmed in an fMRI study using pain-evoking pressure: external locus in FM correlated to greater activation of parietal cortex (involved in interpretation and evaluation of sensory input), and lower in SII [28, 36].

Catastrophizing is the behavioral tendency to characterize pain as unbearable, and is an independent predictive of chronicity and poor outcome variable [39]. It can have a broad effect on pain coping, as it worsens pain perception by focusing attention on nociception and increasing emotional and anticipatory responses. An fMRI catastrophizing paradigm showed activation of structures related to anticipation (medial FC, ipsilateral cerebellum), attention (ACC, PFDLC), emotion (ipsilateral claustrum, amygdala), and motricity (lentiform), among catastrophizers [35]. The main aspect of catastrophizing is pain anticipation, with accentuated activation of frontal regions, cingulated, and SMA before and after tonic painful stimulation, with higher levels of reported pain. This effect seems to be a specific pain mechanism of FM, since it was not observed in other rheumatoid conditions [40•, 41].

Cognitive deficits are present in chronic painful conditions [42], and also in FM ('fibrofog'). Although some reports show memory complaints being greater than indicated by objective tests, measured deficits are evident, even after controlling for affect or medications influences.

When performing working memory, attention, speed of information processing, and verbal knowledge tasks, there is similar performance of FM and healthy elderly: both groups, compared with healthy young, have equal grades. However, FM uses relatively more cognitive resources and needs greater neural activation [28, 43]. This was confirmed in a working memory fMRI paradigm, with increased activation of parietal and frontal areas. Poor performance in attention and memory tasks in FM is independent of mood or sleep disturbances [44, 45].

Spectroscopic Evidences

Magnetic resonance (H^1-MRS) spectroscopy can study spontaneous pain and describes biochemical alterations that could precede structural changes. When compared, studies

demonstrate glutamate elevation in different regions in multiple chosen volumes-of-interest (VOIs). However, current data cannot conclude the precise elevated glutamate levels corresponding to hyperexcitability because of intrinsic H^1-MRS technical limitation. Also, the molecular action of glutamate in the brain is not fully understood [46].

Glutamate is a major excitatory neurotransmitter and is highly concentrated in regions involved in somatosensory pain processing and emotional regulation. One might suggest that individuals with high levels of glutamate are prone to present chronic pain sensitization and lower pain thresholds.

In FM, an increase of glutamate and glutamate+glutamine (Glx) in the right posterior insula was associated with low pain threshold [47]. Aiming to establish a cause–effect relationship, the dynamics of metabolite relations were studied by the same group. They observed pain threshold improvement after nonpharmacologic treatment, associated to changes in glutamate level in insula and BOLD response [48].

Another study used H^1-MRS, DWI and DTI in a motor-task paradigm of fMRI. Data revealed high levels of Glx at PCC, which correlated inversely to pain threshold and directly to function and pain scales [49•]. Yet another group demonstrated greater levels of Glx and high glutamate:creatine ratios at the right amygdala, an important region for emotional pain-processing [50].

The hippocampus seems to be an area susceptible for metabolic changes in FM. Reduction of choline and NAA [49•] or myoinositol [51] were detected, suggesting axonal metabolic dysfunction, similar to bipolar disorder and depression [50]. These changes in myoinositol and choline in the hippocampus could explain part of the cognitive complaints in FM.

Activation of glial cells has been considered relevant to the induction and maintenance of chronic pain [5], since astrocytes participate in glutamate recycling. Among depressives and bipolar subjects, there is an increase in absolute levels of Glx and glutamate following astrocytic deficit [52]. This deficit stems from stress, altered gene expression, and changes in extracellular neurotransmitters levels. Augmented glutamine in astrocytes could also precipitate a metabolic cascade, leading to neuronal dysfunction and astrocytic edema. There is a compensatory myoinositol and choline influx to extracellular space, leading to a reduction in their concentration [53]. Therefore, astrocytic deficit might be responsible for alterations in glutamate/gamma-aminobutyric acid (GABA) transmissions in FM.

Voxel-Based Morphometry Studies

Growing VBM evidences indicates structural alterations in chronic pain conditions, like fatigue syndrome, headache, phantom pain, irritable bowel syndrome, headache, and CLBP [54•] , with overlapping results [55, 56]: decrease in regional gray matter density in spinal dorsal horn [56] and in several brain regions (thalamus, FC, ACC, IC, and parahippocampal gyrus) [15, 24, 54•, 57].

Reports of gray matter changes in FM are contradictory, varying according to functional differences among subjects and techniques. Initial VBM studies had shown gray matter decline in PFC, ACC, IC, thalamus, and basal ganglia. Since neither pain duration nor functional disability correlate to gray matter volumes, tissue reductions might be a precondition for central sensitization in FM [58]. Conversely, 1 study showed an increase of gray matter volumes in left OFC, left cerebellum, and bilateral striatum, and reduction in right STG and left posterior thalamus [59]—areas belonging to the somatosensory system, motor functioning, and tonic pain perception. Such increases could be explained by a dopamine regional lack, leading to secondary pallidus-striatal hypertrophy.

However, a recent VBM study investigated gray matter of volumes-of-interest (VOIs) related to pain in FM, previously identified by a temporal summation fMRI paradigm [54•]. Authors observed that 3 VOIs presented gray matter atrophy (left mid-IC, left rostral ACC, and left mid-ACC), and these reductions could not be attributed to influences of negative affect [54•]. Besides, no global gray matter atrophy was seen [57], and no regional gray matter changes were detected in other expected VOIs (left parahippocampal gyrus, bilateral mid-PCC, and medial FC [57, 59].

It is speculated that gray matter reduction and cognitive deficits in FM are related, similar to structural changes and reduced cognitive performance observed in the elderly. VBM verified that FM had a significantly lower global volume of gray matter and 3.3 times greater age-associated decline in gray matter than controls. The longer they had FM, the greater the gray matter loss, especially in the thalamus, mid-PCC, insular and medial FC, parahippocampal gyrus, and ACC. These results support the theory of premature aging of brain nuclei as a cause for FM [57]. Worth noting that parahippocampal gyrus and amygdala atrophy occur following elevated glucocorticoid levels released during sustained stress, supporting the stress-induced theory for FM [58].

The association between poor performance in memory tests, high pain scores, and morphologic brain alterations (Prefrontal Dorsolateral Cortex (PFDLC), supplementary motor area, temporal cortex, medial FC, and ACC) indicates the functional significance of gray matter atrophy in FM, and a structural basis of pain-cognition interaction [60]. Gray matter reduction in those areas may be implicated in emotional and decision-making impairments, since memory tasks and psychomotor speed rely upon mesolimbic pathways [12] Gray matter atrophy in FC and impaired performance on a frontal cognitive task was observed in CLBP [61].

Volumetric brain reduction in depression occurs in frontal, limbic and thalamic regions [62•]. Since a VBM study

revealed no volume difference between right anterior IC of FM without depression and controls [63], it is possible that gray matter atrophy observed in FM is in fact a superposition of other putative causes.

The mechanisms of gray matter decline are not clear, but might involve neuronal apoptosis, decreased dendritic arborization, excitotoxicity, or glial activation abnormalities [12]. Increased free radical activity and brain homocysteine, a typical neurodegeneration biomarker, are found in FM [64]. One cannot know at this juncture whether the findings are a consequence of nociceptive input or a part of FM pathogenesis.

Intrinsic Connectivity Network Functional Imaging

The ICN refers to the magnitude of synaptic activity and neural transmission among brain regions networks. The fMRI signals of ICN follow known synaptic pathways, are consistent with relevant neurophysiological activity, and are used to study spontaneous pain. For instance, in diabetic neuropathy, connectivity is altered in attentional networks, including dorsal ACC and frontal/parietal areas, which are activated for the stimulus salience control [65].

Aiming to investigate the connectivity between networks in FM and the correlation between networks and spontaneous pain, a recent work used resting-state MRI to evaluate 3 brain networks: DMN, EAN, and MVN. Results show greater connectivity in DMN and right EAN, and DMN-insula [66•], and reduction of PAG-rEAN, which are associated with spontaneous clinical pain. Cognitive deficits of FM have a significant neural correlate in the intrinsic connectivity disturbance: upon evoked-pain increase, insula enhances connection to rEAN, hampering normal function of working memory. MVN is not affected in FM [66•].

Insula is a key area in experimental pain and is associated with perceptual function, since it coordinates internal and external inputs, and participates in cortical homeostatic integration, evoked-intensity processing, affective subjective awareness, and anticipation [24, 67]. These recent ICN findings provide a further role for the insula, linking its intrinsic connectivity to spontaneous pain.

Diffusion Tensor Imaging

When studying pain networks, DTI could detect volumetric and microstructural changes in a more sensitive way than VBM because functional and clinical data in FM correspond only to DTI-detected alterations [68]. Subsequently, the superiority of DTI sensitivity was not replicated [49•].

However, an FA increase was seen in the same areas of gray matter loss (postcentral gyrus, amygdalae, hippocampi, ACC, and frontal gyri), which indicates tissue complexity and neuronal disorganization increase [68]. This finding is parallel to a thalamic FA decrease and normal ADC in FM with poor coping profile [69].

Arterial Spin Labeling and Dynamic Susceptibility Contrast Imaging

Other methods of measuring blood perfusion using fMRI are DSC and ASL, which allow the study of task-induced activations and spontaneous pain. ASL uses magnetized blood as contrast; it is relatively invulnerable to artifacts and stable over time, and is able to evaluate long-duration interventions over neural activity. Using heat-evoked pain, ASL studies could find brain activation areas, similar to BOLD [70]. DSC-MRI uses injected gadolinium contrast, and can evaluate spontaneous pain in non-task studies. Recently, DSC showed differences of brain activation patterns between FM and controls, similar to BOLD findings [23, 71].

Functional Imaging Evaluating FM Treatment

Neuroimaging studies can be used to monitor treatment effects in FM. Patients treated with amitriptyline showed an increase of rCBF in thalami and basal ganglia [72]. There was also an improvement of thalamic rCBF and pain ratings in FM submitted to electroconvulsive therapy [73]. The same group verified rCBF reduction in frontal/temporal gyrus, postcentral gyrus, ACC, and occipital gyrus in those who responded poorly to gabapentin [74•]. Treatment with serotonin and noradrenaline reuptake inhibitor (milnacipran) is associated with reduction of pain sensitivity and increased activity in regions implicated in the descending inhibitory system, PCC, and precuneus [36, 75].

An ongoing fMRI study proposes to measure clinical improvement in pain catastrophizing in FM patients submitted to a protocol of repeated exposure to exercise activities images. In this sense, neuroimaging is both an investigation for neural correlates of symptoms, and a therapeutic instrument of virtual reality, for potential improvement of exercise-related catastrophizing in FM [76]. Following this tendency, real-time fMRI has been used to guide the training of FM patients to 'control' rostral ACC, with real-time success feedback. After a training protocol for attention and painful experience control, patients reported pain decrease [77].

Also, FDG-PET tracked patients' clinical improvement after multidisciplinary rehabilitation and modulation of brain metabolism in several limbic structures [78].

Conclusions

In recent decades, neuroimaging has been applied to the study of FM, especially PET, SPECT, and fMRI. This

review briefly reported the main findings that help the determination of objective neural biomarkers for evidences from psychophysical studies (Fig. 1). SPECT and PET data indicate decreased rCBF in the thalamus and caudate, and an absence in the PAG. They also show reduction of dopamine and opioid receptor levels in basal ganglia, amygdala and insula. BOLD-fMRI demonstrates augmented responses, explaining tenderness and allodynia. Windup and behavioral mechanisms such as external locus of control and catastrophizing are linked to enhanced brain activation in pain-evoked studies. Depression is likely an independent factor in the pain sensory-discriminatory dimension. Moreover, FM uses a wider neural network to perform cognitive tasks.

Recently, other techniques have attempted to explore the study of FM etiology. Most VBM studies support the gray matter atrophy hypothesis in the thalami, PCC, ACC, FC, and parahippocampus. HMRS studies report alteration in glutamate metabolism in insula, cingulated, and amygdala, suggesting the astrocytic edema as an underlying phenomenon for FM development. The association of cognitive and executive deficits and regional gray matter abnormalities was evidenced by altered intrinsic connectivity.

Neuroimaging studies evaluate treatments effects in FM, and could demonstrate a decrease of hyperactivated brain areas after tricyclics, gabapentin, milnacipran, electroconvulsive therapy, and non-pharmacologic approaches, such as multidisciplinary rehabilitation programs.

Although controlled, the FM studies use small samples are exploratory, and present methodological variations (management of multiple comparisons/covariates), preventing an absolute comparison of results. Also, heterogeneity of FM population increases individual data variability. Therefore, conclusions must be drawn carefully. Most studies are cross-sectional, preventing a causal inference. Only long-term prospective research and consistent animal models would allow the full understanding of pathophysiological substrates of FM. Further neuroimaging studies on pharmacological treatments and other approaches are encouraged.

The present literature has identified differences between FM and control individuals. However, structural changes, thalamic activation decrease, altered binding of receptors, increased brain glutamate, or changes in pain processing in several sites of neuroaxis are findings observed in other chronic pain syndromes and, therefore, might be chronic pain epiphenomena. Future neuroimaging studies should be able to verify whether the observed neural abnormalities in FM can be modified after a therapeutic intervention, possibly being able to identify onset risk factors and to help define individualized treatments. The current studies cannot provide this information because diagnostic subgroups of FM patients have not been explored as yet. Novel perspectives in brain studies for FM also include analyses of

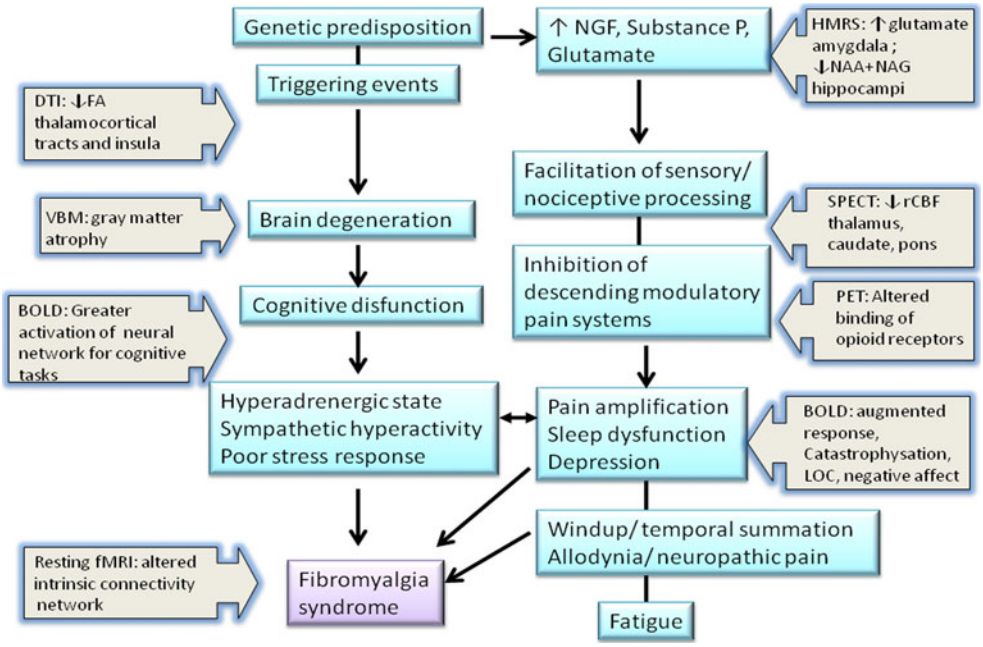

Fig. 1 The use of neuroimaging for the study of different steps of physiopathogenesis of fibromyalgia, according to a theoretical integrated model [1, 79]

sensitivity/specificity of the methods, cost-effectiveness of using neuroimaging in clinical practice as a diagnostic tool or a guide for decision-making when tailoring specific treatments, use of other protons in MRS, placebo response, and use of associated neuroimaging methods.

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