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An updated overview of the neurophysiological and psychosocial dimensions of fibromyalgia – a call for an integrative model

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Abstract:
Research into the neurobiological and psychosocial mechanisms involved in fibromyalgia (FM) has progressed remarkably in recent years. Despite this, current accounts of FM fail to capture the complex, dynamic and mutual crosstalk between neurophysiological and psychosocial domains.

We conducted a comprehensive review of the existing literature in order to synthesise current knowledge on FM, explore and highlight multi-level links and pathways among different systems and build bridges between existing approaches. An extensive panel of international experts in neurophysiology and psychosocial aspects of FM discussed the collected evidence and progressively refined and conceptualized its interpretation.

Fibromyalgia is a complex condition resulting from the dynamic interplay between multiple systems and processes. We provided an updated overview of the most relevant observations in FM to date as well as the potential pathways by which they exert they are related and exert their mutual influence, to produce the manifestations commonly associated with FM.

This review constituted the first step towards and supported the development of a much needed model capable of integrating the main factors implicated in FM into a single, unified model that may prove valuable in understanding and managing FM.

Keywords: Fibromyalgia, comprehensive review, neurophysiological abnormalities, psychosocial processes, integration
Introduction

Fibromyalgia (FM) is a complex and disabling condition that affects 2-5% of the general adult population, \(^1,2\) with a higher prevalence among women, \(^3\) and imposes a heavy burden on individuals, families and society. \(^4-7\) Generalised musculoskeletal pain and tenderness have long been recognised as the most distinctive features of FM \(^8\) although many other (equally) distressing somatic, cognitive and affective symptoms such as fatigue, sleep disturbance, cognitive impairment and emotional distress are also often present. \(^9,10\) Over the last decades the concept and clinical operationalization of FM has change considerably, with several modifications \(^9-11\) to the classification criteria initially proposed \(^8\). Notwithstanding relevant advances on FM research \(^12\) there is still the need for an integrative model capable of bridging the gap between different current perspectives of FM.

Here, we provide the main findings of a literature review we conducted on the pathophysiology and psychosocial dimensions of fibromyalgia (FM) as well as their interpretation. This review along with the insights of international experts in the field served as a basis for the development of an integrative model of FM. \(^13\)

Published Observations on FM Pathophysiology and their interpretation

Abnormalities of the nervous system: FM as a primary disorder of pain modulation

The predominant current paradigm describes FM as a disorder of pain processing by the central nervous system (CNS) leading to the core phenomenon of central amplification of pain. \(^14\) This concept is supported by significant biological evidence. \(^15-18\) Repeated stimulation of synapses typically leads to structural and functional changes \(^19,20\) that favour the amplification of the output. This synaptic remodelling after temporal summation of painful stimuli has been demonstrated at multiple levels of the CNS, including the spine, the insular and the anterior cingulate cortices, the primary somatosensory cortex and the medial prefrontal cortex. \(^21-23\) This mechanism has been implicated in the development of ectopic and aberrant inputs and in the disinhibition of the primary somatosensory cortex, which seems to occur in patients with FM. \(^24\) In addition to these subcellular and cellular processes and to other morphological alterations involving for example grey matter volume and density \(^25\), a higher level of neurobiological dysfunction has been extensively characterised in FM. Many neuroimaging studies indicate an abnormally high level of activation in brain areas involved in the anticipation of (medial frontal cortex), attention to (dorsolateral prefrontal cortex, dorsal anterior cingulate cortex) and perceptual/emotional aspects of pain (insula and subcortical structures such as the amygdala, thalamus, and cerebellum), supporting the notion of a widespread network dysfunction in this clinical condition. \(^26-28\) Conversely, low activity is typically described in the prefrontal cortex (namely on its lateral aspect), anterior cingulate cortex and the brainstem, which has been interpreted to reflect impairment in descending pain inhibition pathways. \(^29,30\) Interestingly, studies have shown that chronic pain, including FM, is associated with hyperactivation (actually, a failure in the deactivation of nuclear regions) of the default mode network (DMN), one of the prototypes of the functional magnetic resonance imaging (fMRI) resting-state networks. \(^31\) Studies also concur in the existence of a decreased connectivity of the medial prefrontal cortex with the posterior components of
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the DMN and an increased connectivity with the anterior cingulate and the insular cortex, which seem to be proportional to the intensity of pain. These neurophysiological observations may also account for clinical correlates: they corroborate a certain level of tonic pain processing activation and support the increased emotional and attentional exacerbation of pain stimuli, as observed in FM.

Some authors have referred to these changes as a “gain in pain” or an “increased volume control setting”, meaning that proprioceptive or mildly nociceptive sensorial afferents are augmented, without “brakes”, into (highly) nociceptive perceptions that promote and amplify suffering. Central sensitisation is also presumed to be at the root of the multisensory hypersensitivity commonly reported by patients with FM, although further studies are needed to understand the operating mechanisms. Such observations represent invaluable progress, but they still do not unveil the origin of the primary causative factor(s). As described below, genetic vulnerability and epigenetic changes have been suggested as a potential source of central sensitisation. Also, nociceptive inputs are considered an essential factor in inducing and maintaining central sensitisation, with pain being its main clinical consequence.

Once the pathological alterations described above have been established in an individual, they will be activated and amplify pain by any impending noxious stimulus, independently of its nature.

Other abnormalities of the central or peripheral nervous system

A potential source of primary pain in FM is suggested by studies that indicate the (co-)existence of a small-fibre pathology, characterized by structural and functional changes in the peripheral nervous system of these patients. According to a meta-analysis, small-fibre pathology seems to be a prevalent phenomenon, affecting nearly half of the patients with FM. At a morphological level, peripheral abnormalities may encompass decreased thickness of nerve fibres in skin and cornea, autonomic denervation, and enhanced innervation of microvascular structures. Functional changes, in turn, may occur along the somatosensory pathway, resulting in altered pain thresholds as well as altered microcirculation and nerve conduction. Changes can also be observed in muscle fibres of patients with FM, although conflicting results have been reported. Examples include atrophy, inflammation, hypoxia, ischemia and tension in different muscle fibres as well as changes in functional parameters such as muscle fatigue. Such abnormalities seem to be associated with metabolic and biochemical changes. Research has shown reduced levels of high-energy phosphates (and respective metabolites) and other phosphates essential to muscle activity as well as augmented concentrations of neuromodulators and excitatory neurotransmitters, pro-inflammatory cytokines and glycolysis products. Collectively, these abnormalities could explain a state of hyperexcitability and sensitisation, leading to an augmented tonic nociceptive input from the periphery and even to spontaneous nociceptive firing. Despite some empirical findings supporting this concept, the nature of such abnormalities remains undetermined and its relative contribution to FM a matter of debate. Recent work has added even more complexity to this already puzzling issue, not only by showing that small-fibre involvement occurs in many other pain–related and unrelated disorders beyond FM but also by lending preliminary support to the concept that structural changes in the peripheral nervous
system may be driven by biochemical imbalances in specific brain regions (e.g., the insula).\textsuperscript{45}

An autonomic dysfunction characterised by tonic sympathetic hyperactivity and parasympathetic hypoactivity (particularly during night time) along with an overall blunted sympathetic response to stress has been indicated in FM.\textsuperscript{46,47} This has been further supported by observations of abnormalities in heart rate variability (HRV) of patients with FM,\textsuperscript{47,48} including low vagal tone, which is considered to be a putative biomarker of chronic stress.\textsuperscript{49}

Although some studies have pointed out that aberrations in the hypothalamus-pituitary-adrenal (HPA) axis and in the autonomic nervous system (ANS) are associated with an increased susceptibility to develop chronic widespread pain (CWP),\textsuperscript{50,51} it remains unclear whether these dysregulations are a precursor of FM, a byproduct of the functional decline associated with this condition, or a surrogate marker of a co-factor, namely stress.\textsuperscript{12,52}

In fact, these abnormalities may stem from many other confounding factors, including medication use,\textsuperscript{53} presence of comorbidities\textsuperscript{54} or trauma history,\textsuperscript{55} that are not always accounted for in studies investigating the association between HPA/ANS abnormalities and FM. Moreover, depressive or anxiety disorders that are typically related to hypercortisolemia may mask hypocortisolemia in FM.\textsuperscript{56} Overall, a meta-analysis and meta-regression did not find diminished levels of cortisol in FM.\textsuperscript{57} Confounding factors may partially explain not only the conflicting findings, with different HPA activity patterns being reported across studies, but also the fact that these abnormalities are non-specific and circumscribed only to a subset of patients with FM.\textsuperscript{17,39} It is also important to note that different designs, methods and measurements may also underlie and help explain apparently divergent findings.

Future longitudinal and methodological sound studies not limited to both cortisol levels and HPA axis responsiveness may provide better insight into HPA axis functioning and the nature of a possible link between these abnormalities and FM.

Chronic stress may lead to dysregulation of the HPA axis that in turn will result in abnormalities in the regulatory function of neuroendocrine mechanisms which may favour a chronic pro-inflammatory status.\textsuperscript{58} In line with this, (neuro)inflammation has also been advocated to play a role in FM based on observations of inflammatory signals in the cerebrospinal fluid, the spinal cord, and peripheral nerve endings.\textsuperscript{59-61} The release of pro-inflammatory and neuroactive substances that lead to the recruitment and activation of local immune cells,\textsuperscript{62} may contribute to sensitisation processes and clinical symptoms.\textsuperscript{59,61} Such observations tentatively supported suggestions that FM should be seen as an inflammatory disease of the CNS,\textsuperscript{63} equivalent to the labelling of a sister condition, chronic fatigue syndrome, as “myalgic encephalomyelitis”. Noteworthy, similar immune changes in the CNS, and even in the peripheral blood, are commonly observed in psychopathological conditions that are often comorbid with FM and chronic fatigue syndrome, such as depression, anxiety disorders, and post-traumatic stress disorder (PTSD).\textsuperscript{64-66} Despite this, the nature and exact role of inflammation in FM development need to be further clarified by future studies.\textsuperscript{59}

Given its bidirectional crosstalk with the brain and regulatory influence upon multiple body functions\textsuperscript{67} as well as its involvement in various psychiatric, centrally-driven, and immune-mediated disorders,\textsuperscript{68,69} some of which recognized comorbidities of FM, the microbiome-gut-brain axis has received increased attention in recent years.
A recent study revealed significant differences in the gut microbiome of patients with FM when compared to healthy controls, with the former displaying an altered faecal microbiome profile characterised by an altered abundance of several bacterial taxa. This variance in the microbiome composition of patients with FM was uniquely associated with FM symptoms severity and, most importantly, it demonstrated good discriminative properties in classification analysis, with an area under the receiver operating characteristic (ROC) curve of 87.2%. Even though promising, the study of the microbiome in chronic pain, and particularly in FM, is still in its infancy. Future studies aimed at clarifying the exact nature of these microbiome alterations as well as their (specific) role in FM development and pathophysiology are necessary.

Genetic predisposition

There is data to support a genetic predisposition to CWP and FM: nearly 50% of the variance in CWP/FM symptoms has been ascribed to polygenic inheritance. Familial aggregation studies have shown that first-degree relatives of individuals with FM (e.g., siblings, offspring) present, compared to controls, lower pressure pain thresholds and a significantly greater risk of developing FM. This familial aggregation occurs not only for FM, but also for certain personality traits (e.g., harm-avoidance) and affective disorders associated with FM. Studies that have attempted to distinguish between genetic and environmental influences found familial aggregation of FM and increased vulnerability to CWP to be largely attributable to genetic influences, with shared environment playing a minor role. Several genetic polymorphisms involving serotonergic, catecholaminergic, dopaminergic, glutamatergic, canabinoidergic, and adrenergic systems have been associated with both a higher risk of developing FM, and clinically more severe FM. Similar observations have been made regarding genes encoding voltage-gated ion channels and regulating binding proteins, and in neuroplastic pathways. Although results are frequently inconclusive or contradictory, almost all genes proposed as risk factors for FM are related to neurotransmitters and their receptors, which makes them liable to play a part in each of the biological mechanisms described previously. This also makes them capable of interfering or enhancing psychosocial dimensions and factors. In fact, some of these polymorphisms have also been recognised as risk factors for other affective and pain-related disorders, indicating a shared genetic risk that may, at least partially, account for the high comorbidity between FM and these disorders. Based on the observation that FM is associated with hypomethylation of genes putatively implicated in autonomic and stress responses and subcortical aberrations, it has recently been proposed that epigenetic (dys)regulation may play a role in FM development.

Medical comorbidities

FM often co-occurs, in a lesser or greater degree, with other physical disorders, potentially leading to greater disease burden and negatively impacting clinical outcomes, response to treatment and clinical decision making. Specifically, FM has been associated with chronic fatigue syndrome, irritable bowel syndrome, headaches, dysmenorrhea, temporomandibular disorder, interstitial cystitis/painful bladder syndrome and regional pain syndromes, suggesting the existence of mutual pathophysiological mechanisms and clinical aspects. Such comorbidity and shared pathophysiology have led researchers to subsume FM under varying umbrella...
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terms, each one emphasizing distinctive features, such as central sensitivity syndromes, functional somatic syndromes, or chronic overlapping pain conditions. FM is also found to occur in immune-mediated and degenerative rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome, spondyloarthopathies, and osteoarthritis and neurological diseases such as multiple sclerosis, probably due to unfolding central sensitisation. This mechanism is also postulated to underlie the association between FM and some generalised joint hypermobility-related syndromes. Similarly, an association between FM and allergic diseases has been reported, potentially driven by an altered expression of immunoregulatory genes. Cardiovascular disease and diabetes are also comorbidities of FM.

Psychosocial dimensions

A) Psychiatric comorbidities

In a comprehensive review of fibromyalgia, it is reported that mood and anxiety disorders are common among patients with FM, with point-prevalence values varying between 13-48% and 27-60% and lifetime prevalence ranging between 20-86% and 16-60%, respectively. Another systematic review with meta-analysis reported that the overall pooled point-prevalence of major depressive disorder in patients with FM varied between 25% and 45%, depending on the assessment methods applied, while lifetime prevalence reached 65%. Authors also draw attention to the tendency of screening tools, particularly those based on self-report, to overestimate the prevalence of depression in FM when compared to more in-depth methods such as clinical interviews. Overall, depressive and anxiety symptoms scores are significantly greater than those reported in community samples and other pain-related disorders. Also, PTSD and FM show considerable similarities and frequent co-existence. Sleep disturbances have been shown to predict CWP/FM, and to negatively influence pain (and be influenced by it), fatigue and emotional distress levels, with authors suggesting that it may constitute a transdiagnostic factor across affective disorders and FM. Findings suggest that the relationship between sleep and pain may be centrally mediated. Apart from awaking unrefreshed, which constitutes a key symptom of FM, sleep disorders such as restless leg syndrome are also common in FM. A brief review concluded that when compared to healthy controls, patients with FM tend to present a higher prevalence of personality disorders. In a community sample, 13.3% of the participants met the diagnosis for at least one personality disorder, whereas in patients with FM the prevalence reached 31.1%. Avoidant, Dependent, and Obsessive-Compulsive Personality disorders, commonly referred as Cluster C Personality disorders (which have marked fear and anxiety as hallmark), seem to be the most prevalent personality disorders in FM. The rate of reported comorbidity between FM and
personality disorders is extremely variable and may depend on the setting in which it is taken (clinical or research) and the kind of assessment performed (self-report or diagnostic interview).

B) Psychological vulnerability and resilience factors

Cognitive and affective processes have long been established as relevant modulators of pain perception and processing, above and beyond the effect of the nociceptive stimulus itself, both in clinical and non-clinical populations. Over time, research has mainly focused on the identification of processes that may negatively influence pain experience and hamper adjustment to FM. These include, among others, pain-specific cognitions (such as pain catastrophizing, negative expectations, and attributions), specific ways of emotion processing such as alexithymia, and vulnerability to invalidation by others. Remarkably, the same observations apply to general psychological traits and processes that reflect misery and suffering. These include disordered affect characterised by high negative affect and blunted positive affect, low levels of perceived control and self-efficacy, and maladaptive cognitive-emotion regulation strategies.

More recently, psychological resilience factors have attracted attention. They include factors such as positive affect, pain acceptance, optimism, active-pain coping, psychological flexibility, purpose in life, and values-based action. Studies highlight that the soothing influence of positive affect upon pain perception operates through the downregulation of dysfunctional cognitive-affective processes and the promotion of adjustment and resilience by broadening awareness and fostering psychological and behavioral flexibility.

It is noteworthy that most of the psychological factors with aggravating impact upon pain are commonly expressed in high (i.e., disruptive) levels by patients with FM whereas the opposite is seen regarding resilience factors, such as positive affect. Nevertheless, psychological profiles of people with FM differ. One study guided by operant learning theory could differentiate a ‘dysfunctional group’ characterised by poor coping strategies, an ‘interpersonally distressed group’ characterised by interpersonal difficulties, and ‘adaptive copers’ characterised by adequate coping strategies. Another study using subjective and objective measures distinguished five FM subgroups, labelled ‘Adapted’, ‘Fit’, ‘Positive’, ‘Poor performer’, and ‘Maladapted’. These studies suggest that there is a wide range of coping and personality styles in FM and that not all of them are maladaptive nor do all patients report high levels of distress. Regarding affective factors, a large body of evidence has systematically demonstrated, with few exceptions, that positive affect decreases pain perception and increases pain tolerance, whereas negative affect has the opposite effects. Emotions have also been shown to shape, to a greater or lesser degree, diverse physiological responses to pain, including defensive reflexes, electrodermal activity, heart rate, and blood pressure as well as to salient sensory stimuli other than pain, as for example sound. While valence (i.e., the experienced "goodness" (positive valence) or "badness" (negative valence) of an event, object, or situation) determinates the nature of the modulation (e.g., facilitation vs inhibition), the strength of the modulatory effects seems to be determined by the interaction between valence and arousal. Several stimulus modalities (i.e., odours, pictures, music), have been shown capable of producing this modulatory action. Furthermore, the effects of emotions upon pain do not depend on them being...
related to pain itself or not: they will be operative as long as they are perceived as personally relevant. Converging lines of evidence have shown that emotions influence the processing of pain both bottom-up (e.g., multisensory integration) and top-down (e.g., descending inhibition) through spinal and supraspinal mechanisms. Placebo and nocebo effects are clear examples of these phenomena and they seem to produce hypoalgesia or hyperalgesia through the same modulatory systems engaged by emotions. Nonetheless, some studies have shown mixed findings regarding emotional modulation in patients with FM. Specifically, in a study, patients with FM did not have amplified neuroautonomic responses to negatively charged pictures, despite describing amplified subjective ratings on valence and arousal. A study found startle response to be inhibited rather than enhanced in response to unpleasant pictures, while in another study, a hyporesponsive ANS to elicited emotions in FM was not observed. Regarding the effect of positive stimuli, a study did not find any evidence of disrupted appetitive processing, while two other studies reported a diminished appetitive activation and emotional modulation of pain. Such inconsistency across studies may be related to sampling (patients’ characteristics) and methodological issues (differences in stimuli and measurements), (des)sensitisation processes, the engagement of different defensive responses (e.g., fear vs anxiety responding, the inhibitory “freeze” response), and blunted autonomic responses to acute stressors, which is typical of chronic stress conditions, including FM. Nonetheless, future studies are certainly warranted for further clarification.

One thing is clear: a deeper understanding of the close link between emotion and pain (and underlying mechanisms) and the inclusion of “emotional work” in the care of patients seem to be key for a better management of pain in general and of FM in particular. The key role of cognitive-affective mechanisms in the perception and modulation of pain is further supported by the effectiveness of interventions targeting self-regulation and psychological processes. Additional support comes from studies using biofeedback, which have shown that, following a period of training using real-time neuroimaging, individuals can become proficient in reducing the activation of brain regions involved in pain processing, thus reducing the concurrent perception of experimentally-induced pain. The same can be achieved by consciously controlling apparently autonomous physiological processes involved in pain and emotion, such as HRV and muscle tone. Other techniques and interventions as for example hypnosis and cognitive-behavioral therapies, including the more recent contextual approaches such as mindfulness and acceptance and commitment therapy, seem to have an analogous effect, being associated with changes in the activity level and connectivity of certain brain structures.

C) Temperament and personality

Several studies examined the link between personality characteristics and FM. Such work has looked for a particular personality profile that renders people more vulnerable or resilient to the development of FM. Published studies have presented inconclusive findings, failing to demonstrate the existence of a specific personality profile capable of discriminating patients with FM from healthy controls at the individual level. Understanding the relationship between FM and personality is further complicated by the fact that chronic pain and its associated emotional states may change not only the report
of personality traits, but even personality itself, as suggested by neuroimaging studies. Despite these limitations, certain personality traits have been identified as common in chronic pain and FM. Depending on the personality profiling tools used, FM has been associated with greater expression of neuroticism/harm-avoidance and reduced levels of extraversion and self-directedness. Harm-avoidance in particular may be relevant given its reported association with deficient pain modulation and with affective symptoms. Perfectionism, type D personality, and alexithymia have also been associated with pain and other bodily symptoms as well as emotional distress and negative cognitive processes. In a study, members of our group have demonstrated that health professionals experienced in managing FM can distinguish patients from controls, as a group, based on single items of a personality profiling tool (NEO-PI-R). Each individual health professional, using items of his/her choice, showed in ROC analyses an AUC of 0.71–0.81 in predicting the diagnosis, with no relevant differences between rheumatologists and psychologists. The most predominant items indicated high levels of neuroticism and low levels of trust. Yet, these associations do not necessarily demonstrate causality, but constitute small pieces of a very complex puzzle. Remarkably, however, in a longitudinal study, a high level of neuroticism has been shown to precede and predict joint pain over a follow-up of 23-years. Similarly, a 25-year longitudinal study, showed that neuroticism was associated with an increased risk of developing physical diseases, in particular, those characterised by chronic systemic pain (e.g., odds ratio= 1.37, 95% CI = [1.28–1.47] for CWP). Studies examining the potential protective role of positive dispositional features are scarce. Moreover, it remains underexplored whether and how different traits interact with each other to amplify or attenuate FM diathesis. In fact, it may be hypothesized that peculiar combinations of dispositional vulnerability and resilience factors may result in greater predictive specificity than individual traits themselves.

**D) Traumatic life events**

Research has consistently shown that recall of exposure to different types of early life stress (e.g., adverse interpersonal contexts, abuse and neglect, loss or rejection), is a common experience among many individuals with FM, although studies based on patients’ self-report are prone to recall bias. Nevertheless, recall should be taken seriously, because the memory of past stressors may give a better reflection of one’s current reality than the actual events in the past. While recognizing methodological limitations in the available evidence, a study concluded that early experiences of physical and sexual abuse were significantly associated with subsequent onset of FM. This link between adverse experiences involving physical and psychological trauma and FM development has been confirmed by many other reviews on the topic. The importance of such findings is underlined by longitudinal studies demonstrating that experiences of adverse early life events represent an important risk factor for developing somatic symptoms, including CWP, later in life. Using a representative sample from the UK, it was found that financial hardship and low education level (this one only for men) in early adulthood were prospectively associated with an increased risk of CWP. In a study conducted using data from the prospective 1958 British Birth Cohort Study, the authors found that individuals who had experienced adverse life events in childhood
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such as socioeconomic disadvantage, maternal death, and living in institutional care, were at higher risk of developing CWP later in life, even after controlling for psychosocial variables.

Studies on the impact of early adversity have also shown that quantity matters. The number of adverse events (and corresponding cumulative effect) is more likely to contribute, in a dose-dependent manner, to the development of chronic pain than the particular type of event individuals have been exposed to, even when controlling for potential sociodemographic, affective, and clinical confounders. One possible pathway through which traumatic events, such as abuse, impact on pain severity and (dys)function is via affective distress and fibromyalgia-ness (also referred to as polysymptomatic distress, representing the distribution of FM symptoms along a continuum).

Other explanation for the pernicious effect of early adversity is that by hinder effective socioemotional development and regulation, it drives the body to a “wear and tear” state due to stress buildup (allostatic load), which in turn may disrupt the balance between inhibitory-facilitatory processes and favour central sensitisation. Indeed, even after adjusting for depressive symptoms, healthy individuals with high levels of adversity showed both greater central sensitisation and attenuated autonomic pain responses. Interestingly, there is some evidence that adverse early experiences may be associated with inflammation, life-long aberrations in the HPA and ANS function, epigenetic modifications in the regulation of gene expression for neurotransmitters (e.g., serotonin and dopamine) and other endogenous proteins, and reprogramming of the nociceptive and descending inhibitory circuitries, all of which may directly or indirectly contribute to central amplification, the hallmark of FM. Nonetheless, prospective studies aimed at clarifying this link are warranted.

E) Social Environment

An increasing body of evidence supports the role that social determinants (e.g., social connectedness, social support) and milieu may have on health indicators, including pain and psychopathological symptoms. Humans depend on others – on their protection, caring and cooperation – to thrive and reproduce and are thus fundamentally predisposed to connect and form social bonds. So, potential threats or actual failure to meet this basic interpersonal need may translate into an increased likelihood of developing an array of mental and physical symptoms and disorders, including pain. For example, social disconnection and social distress have been shown to negatively influence pain ratings in patients with FM and pain-related responses in healthy subjects. Longitudinal studies have found an association between social isolation/loneliness and worse functional status, greater levels of pain interference, depression and fatigue in clinical and non-clinical samples. Vice versa, social connection has been increasingly recognized as a contributor to mental and physical well-being. It was found that social support has a buffering effect upon pain, although recent findings have further proposed that this pain-attenuating effect seems to be dependent on several intrapersonal and interpersonal factors, including attachment styles, participant-partner relationship, and type of interpersonal interaction. Also, the perceived quality of social support (rather than quantity) plays a role when predicting FM-related outcomes. Also, research indicates that social support has a buffering effect against negative pain-related outcomes, probably through its soothing influence on cognitive and affective processes involved in pain processing and modulation.
The importance of these findings is underscored by repeated observations that patients with FM exhibit greater social isolation/loneliness (even when compared to patients with other pain disorders), less perceived social support, and increased perception of invalidation from others. Interpersonal difficulties are thought to make patients with FM more vulnerable to the negative effects of multiple sources of stress.

**F) Multisensory hypersensitivity**

Studies have shown that the hypersensitivity observed in FM is not limited to pain but that it often extends to other non-nociceptive sensory modalities, with patients showing an augmented sensitivity to tactile, olfactory and auditory stimuli. This multisensory hypersensitivity, which is linked to altered brain activity patterns in sensory areas and areas implicated in sensory integration, has been found to be a distinctive neurophysiological feature in FM, and a potential endophenotypic marker of central sensitisation. In fact, this link between perceptual amplification and central sensitisation had already been proposed by previous studies.

Another potential mechanism that has been advocated to explain this phenomenon is generalised hypervigilance, although this hypothesis remains controversial. According to this hypothesis, patients with FM tend to pay excessive attention to internal (i.e., bodily perceptions) and external cues and to present an exaggerated, sometimes painful, response to somatosensory stimuli, even those otherwise innocuous or insignificant.

While patients tend to consistently report increased subjective hypervigilance and show on average a stronger orientation towards threats, results regarding the experimental demonstration of perceptual amplification are less convincing. Sampling and methodological differences as well as distinct operational definitions of the concept of hypervigilance may be at the core of such marked inconsistency across studies. For example, a study distinguished two types of heightened body awareness: one maladaptive related to hypervigilance, where a threat-focused monitoring of body sensations predominates; and the other adaptive, characterised by an attunement with and through the body, that facilitates the processing and integration of information relevant for self-regulation. It seems that patients with FM tend to present this former, pernicious form of body awareness.

Future studies should take both types of body awareness into consideration, which may establish and further clarify the role of hypervigilance in FM. Also the hypothesis of affiliating the process of sensory hypervigilance to catastrophizing and rumination and both of them to a hyperactive DMN observed in FM is tempting. Altogether, these observations suggest that patients with FM seem to be subjected to a (perceived) overload of psychological and sensorial input that tends to take a predominantly negative valence. Whatever their origins, it seems plausible that the increased subjective sensitivity to different sources of stimuli coupled with negative cognitive-affective states and processes evolve into a reverberant source of additional stress, anxiety and fatigue in FM.

As a consequence, maladaptive avoidance and isolation behaviours may ensue, in a failed attempt to bypass the (perceived) continuous input storm.

**Gender differences**

Gender differences in pain are a relevant topic, considering that many chronic pain conditions, including FM, are more prevalent and severe among women. Research has
demonstrated that, compared to males, females have, overall, higher sensitivity to experimental-induced pain, higher tendency to pain amplification, and lower endogenous pain inhibition.\textsuperscript{226-228} Research on the mechanisms underlying this gender-related variability in pain perception and processing has stressed their multifactorial nature, with biological and psychosocial factors contributing to the phenomenon.\textsuperscript{229,230} Among the biological factors, both sex hormones (hormone levels, interaction with the opioidergic system, anti or pronociceptive action) and menstrual cycle have been shown to influence responses to experimentally-induced pain as well as emotional modulation of pain.\textsuperscript{228,229,231} While sex-dependent genetic associations have been shown to affect pain perception, also sex-differences in other systems implicated in pain modulation, such as autonomic nervous system activity and supraspinal connectivity, have been noted.\textsuperscript{228,229}

Psychosocial factors accounting for gender-differences in pain include social interaction, gender role expectations regarding pain sensitivity and pain expression and gender-related personality traits, such as masculinity/femininity.\textsuperscript{230,232} Additionally, a sex-dependent effect of past pain experiences\textsuperscript{233} and adverse experiences in childhood\textsuperscript{234} on pain sensitivity has been demonstrated, with this association being significant only for females. At a more intrapersonal level, variation in psychological distress and psychological processes such as pain catastrophizing, self-efficacy, and coping strategies also seems to contribute to the reported gender-differences.\textsuperscript{228,230}

\textbf{Conclusion}

Despite all advances, fibromyalgia remains a challenging condition not only in terms of how it is operationalized and understood by different health professionals but also in terms of its clinical management. We believe this is in part driven by the inherent complexity and multidimensionality that characterizes fibromyalgia and by the lack of a comprehensive framework that integrates current knowledge on the risk and protective factors at play and how they influence the development, expression and course of the disease.

This complexity can only be addressed by adopting a multi-level viewpoint where findings from different disciplines and approaches are brought together and integrated in a coherent way. It is therefore crucial to identify and explore the many interconnections between multiple systems and mechanism known to be altered in FM and how these same dynamic systems come to be modulated by people’s genetic makeup, environmental stressors and individual differences.

Only by doing this can we truly gain an in-depth understanding of what fibromyalgia is and how best to treat it.
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