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Neurophysiological and psychosocial mechanisms of fibromyalgia: A comprehensive review and call for an integrative model

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A R T I C L E I N F O

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A B S T R A C T

Research into the neurobiological and psychosocial mechanisms involved in fibromyalgia has progressed remarkably in recent years. Despite this, current accounts of fibromyalgia fail to capture the complex, dynamic,

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and mutual crosstalk between neurophysiological and psychosocial domains. We conducted a comprehensive review of the existing literature in order to: a) synthesize current knowledge on fibromyalgia; b) explore and highlight multi-level links and pathways between different systems; and c) build bridges connecting disparate perspectives. An extensive panel of international experts in neurophysiological and psychosocial aspects of fibromyalgia discussed the collected evidence and progressively refined and conceptualized its interpretation. This work constitutes an essential step towards the development of a model capable of integrating the main factors implicated in fibromyalgia into a single, unified construct which appears indispensable to foster the understanding, assessment, and intervention for fibromyalgia.

1. Introduction

Fibromyalgia (FM) is a complex, often disabling condition. Widespread pain and tenderness have long been recognized as the most distinctive features of FM (Wolfe et al., 1990), although other distressing somatic and cognitive-affective symptoms, including fatigue, sleep disturbance, cognitive impairment, and emotional distress are also frequently present (Wolfe et al., 2016, 2011). This constellation of symptoms imposes, on average, a heavy burden on individuals, families, and society (Arnold et al., 2008; Häuser, Ablin et al., 2015; Schaefer et al., 2016; Sicras-Mainar et al., 2009) and drives major changes in how individuals operate, see, and define themselves (Asbring and Närvänen, 2002; Galvez-Sánchez et al., 2019).

Prevalence estimates of FM have varied largely due to different methodological (e.g., case definitions, assessment tools), sampling (e.g., general vs specific populations) and contextual features (Marques et al., 2017; Queiroz, 2013; Sarzi-Puttini et al., 2020). Meta-analytic and comprehensive reviews on FM morbidity have estimated an overall point-prevalence of 1.8% (Heidari et al., 2017) and a median incidence of 4.3 per 1000 person-years in the general population (Creed, 2020). Research indicates a higher prevalence of FM among women than men (Heidari et al., 2017; Queiroz, 2013), even though diagnostic changes have made the female-to-male ratio more balanced (~1.5:1) than historically reported (9–10:1) (Wolfe et al., 2018).

In recent decades, the conceptualization and definition of FM have changed considerably (Arnold et al., 2018; Wolfe et al., 2016, 2010) from the classification criteria initially proposed (Wolfe et al., 1990). Despite the usefulness of such criteria, they remain, along with the nature of FM more generally, a source of contention (Harth and Nielson, 2009; Häuser and Perrot, 2018; Wolfe, 2009a, 2017). This controversy is fueled by studies documenting the changeable nature of FM symptoms over time, including remission periods, and showing the occurrence of false positive diagnoses in individuals with moderate levels of polysymptomatic distress (Wolfe, 2017). Some authors have proposed that FM is best conceptualized as the extreme point of a polysymptomatic distress or "fibromyalgianess" continuum (Wolfe, 2009b; Wolfe et al., 2013), which seems to be supported by evidence demonstrating that the distribution of FM-like symptoms across the population is continuous (Häuser et al., 2009).

Despite major advances in the understanding of FM (Williams and Clauw, 2009; Haüser et al., 2015), there remain substantial differences in perspectives of its pathophysiology, often between neurophysiological and psychosocial viewpoints. With few exceptions, published reviews on FM tend to be focused on specific aspects of its biology or psychosocial nature, and these reviews both lack detail and bypass the difficult yet urgent task of integrating the ample, complex, and divergent perspectives on FM into an integrative framework. The current narrative review aims at mapping, synthesizing, interpreting, and networking the main biopsychosocial mechanisms at play in FM, acknowledging their deep and intricate interdependence, while exploring their potential for clustering into comprehensive higher-order processes. This narrative review also aims to pinpoint current knowledge gaps, controversies, and inconsistencies within the field of FM, hopefully fostering further lines of inquiry. Several literature searches of published articles focused on specific topics were conducted in different databases (PubMed, Google Scholar) and through reference mining. The guiding hypotheses, associated research questions, and supplementary searches were fine-tuned throughout the search process based on the results obtained and on the continued analysis and debate among the core research group. The broad nature of our questions and the vast landscape of FM research precluded the use of a systematic approach. To minimize the risk of potential reporting bias and to identify possible missing links, we invited a large group of experts in different fields of research in FM to critically review the collected data and its interpretation.

2. Neurobiological and clinical observations on FM

2.1. FM as a primary disorder of central pain processing and modulation

The current dominant paradigm views FM as a disorder of pain processing by the central nervous system (CNS), leading to the core phenomenon of central amplification of pain (Petersel et al., 2011). This concept is supported by significant biological evidence (Harte et al., 2018; Lee et al., 2011; O'Brien et al., 2018; Sluka and Clauw, 2016; Vecchio et al., 2020), which recently culminated in the formal recognition of a third category of pain: nociplastic pain (Kosek, Cohen et al., 2016). Unlike nociceptive and neuropathic pain, the mechanisms underlying nociplastic pain are largely unknown, although central sensitization for somatic and sensory stimuli is thought to play a prominent role (Fitzcharles et al., 2021). Central sensitization refers to the plasticity of spinal mechanisms that increase the ongoing peripheral nociceptive input, leading to neural hyperexcitability and ultimately resulting in a state of pain hypersensitivity, characterized by hyperalgesia, allodynia, and diffuse pain (Latremoliere and Woolf, 2009; Woolf, 2018). This mechanism is not specific to FM but is also found in other central sensitivity syndromes (CSS; Yunus, 2008) and rheumatic diseases (Minhas and Clauw, 2021; Phillips and Clauw, 2013).

2.1.1. Aberrances in pain processing

Neuroimaging studies in FM indicate an abnormally high level of activation of brain regions involved in the anticipation of, attention to, and perceptual/emotional aspects of pain, supporting the notion of a widespread network dysfunction. These brain regions include the medial frontal cortex, the dorsolateral prefrontal cortex (dPFC), the dorsal anterior cingulate cortex (dACC), insula, and subcortical structures such as the amygdala, thalamus, and cerebellum (Burgmer et al., 2009; Gracely et al., 2004; Sawaddiruk et al., 2017).

Abnormalities in the salience network, preferentially referred to as midcingulo-insular network (M-CIN; Uddin et al., 2019), have been found at various levels in FM, including in its activity (Gracely et al., 2002; Harte et al., 2016; Ichesco et al., 2014; Pujol et al., 2009), neurochemistry (Harris et al., 2009), and within- and between-network functional connectivity with other large-scale brain networks (Harris et al., 2013; Ichesco et al., 2014; Kaplan et al., 2019; Napadow et al., 2010; Pujol et al., 2014). Research has shown that chronic pain, including FM, is associated with a failure in the deactivation of nuclear regions of the default mode network (DMN) – one of the prototype resting-state networks (Baliki et al., 2008). Studies agree on the existence of a decreased connectivity of the medial PFC with the posterior components of the DMN and an increased connectivity with the anterior

cingulate and the insular cortex, which seem to be proportional to the intensity of pain (Baliki et al., 2014; Fallon et al., 2016). Neuroimaging results from a large-scale prospective study in children showed that aberrant activity in several brain regions, such as the primary somatosensory cortex and the mPFC, and an augmented functional connectivity between large-scale brain networks (i.e., M-CIN, DMN, and sensorimotor network) predate the onset of multisite pain (Kaplan et al., 2021). Both genes and environmental influences may contribute to this brain function (re)setting (Kaplan et al., 2021). Further prospective studies with control of potential modulators and confounders (e.g., life events, contextual features) are warranted to unravel the specific contribution of different factors and mechanisms.

2.1.2. Impaired descending pain inhibition

Low activity in the lateral PFC, rostral ACC, and brainstem, has been reported and interpreted as reflecting impairment in descending pain inhibition pathways (Jensen et al., 2013; Loggia et al., 2015). Several other observations support the importance of this mechanism, including a diminished connectivity of the periaquectudal grey (PAG; a key hub involved in endogenous pain modulation) at rest and between the PAG and other key pain-processing regions, which has been correlated with clinical symptoms and pain magnification (Coulombe et al., 2017; Truini et al., 2016). This interpretation is reinforced by the lack of a normal resting state association between the PAG and brainstem regions. The PAG is, aside from pain modulation, implicated in affective processing and defensive responding (Buhle et al., 2013). Herein, functionally discrete subregions of the PAG are differentially involved in threat processing and appetitive/aversive motivational states (Silva and McNaughton, 2019; Wang et al., 2022), as well as in the regulation of physiological responses (Buhle et al., 2013; Critchley and Harrison, 2013; Gianaros and Wager, 2015). Many of these functions seem to be disturbed in FM.

2.1.3. Altered sensory processing and integration

Neuroimaging studies have shown "hypotoned" sensory processing and integration in FM, as reflected by: 1) reduced activity and functional connectivity within the cortical sensory system (López-Solà et al., 2014; Kim et al., 2015); 2) attenuated PAG-insula connectivity, resulting in an impaired sensory gating and descending inhibitory regulation; and 3) enhanced secondary somatosensory cortex-DMN connectivity (Pujol et al., 2014). Dysfunctions in sensory integration seem to be related to spontaneous pain, multisensory hypersensitivity, functional impairment, and clinical pain severity (López-Solà et al., 2014; Pujol et al., 2014), whereas abnormal connectivity between the sensory cortex and salience-processing brain regions has been associated with clinical pain, autonomic responding, vigilance towards pain-evoking stimuli, and pain catastrophizing (Kim et al., 2015). Although it has been suggested that widespread pain may be at the root of the observed weakened inter-subregional connectivity of the sensory cortex, further research is needed to understand the direction of this association (Kim et al., 2015). Similarly, the enhanced secondary somatosensory cortex-DMN connectivity has been interpreted as indicating a state of hypervigilance, but this hypothesis needs further testing (Pujol et al., 2014).

2.1.4. Neurochemical disturbances

A dysregulation of neurotransmitters implicated in sleep, mood regulation, pain processing, and physiological stress reactivity has been documented (Becker and Schweinhardt, 2012; Sluka and Clauw, 2016). Specifically, an opioidergic dysfunction in people with FM has been noted (Baraniuk, Whalen, Cunningham, and Clauw, 2004; Harris et al., 2007) and implicated in affective pain dysregulation (Schrepf et al., 2016). It has been argued that there is, in FM, a reduced availability or affinity of mu-opioid receptors, which compromises the engagement of antinociceptive activity in the ACC and PFC, opioid-rich regions that are involved in affective pain processing and modulation (Schrepf et al., 2016). A role for aberrant dopamine signaling in some of the brain network abnormalities reported in FM has also been proposed (Albrecht et al., 2016). Individual variability in neurotransmitter dysregulation may potentially account for the distinct pathophysiological/clinical profiles and treatment response patterns observed in FM (Becker and Schweinhardt, 2012; Sluka and Clauw, 2016).

Collectively, such neurophysiological observations may partly 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" (Woolf and Salter, 2000), an "increased volume control setting" (Clauw et al., 2011), or even an "explosive synchronization" (Lee et al., 2018), meaning that proprioceptive or mildly nociceptive sensorial afferent inputs are augmented, without "brakes," into pain perceptions that promote and amplify suffering (Woolf, 2018). Nociceptive inputs are considered an essential factor in inducing and maintaining central sensitization (Staud, 2010), with pain being its main clinical consequence. Indeed, repeated stimulation of synapses typically leads to structural and functional changes (Luo et al., 2014; Tan et al., 2012) that favor the amplification of the output. This synaptic remodeling after temporal summation of painful stimuli has been demonstrated at multiple levels of the CNS (Bliss et al., 2016; Kim and Nabekura, 2011; Zhang et al., 2015), and implicated in the development of ectopic and aberrant inputs, often found in patients with FM (Lim et al., 2015). Once these pathological alterations have been established in an individual, they will amplify pain by any impending noxious stimulus, regardless of its nature (Woolf, 2018). Such observations represent invaluable progress, but they still do not unveil the origin of the primary causative factor (s).

2.2. Other abnormalities of the central or peripheral nervous system (CNS/PNS)

2.2.1. Peripheral abnormalities

Multiple studies using different neuropsychophysiological methods, such as skin biopsies, evoked potentials, imaging techniques, and somatosensory and autonomous function testing, have reported the existence of small-fiber pathology in FM (Evdokimov et al., 2019; Sommer and Üçeyler, 2019), suggesting its potential role as a source of pain in this condition (Sommer and Üçeyler, 2019). This pathology is observed in about half of the patients with FM (Grayston et al., 2018; Vecchio et al., 2020), but its clinical significance as well as its origin remain controversial (Fasolino et al., 2020; Oaklander, 2016; Sommer and Üçeyler, 2019). At a morphological level, peripheral abnormalities involve decreased density and diameter of nerve fibers in skin and cornea as shown by skin biopsies and corneal confocal microscopy, autonomic denervation, and enhanced innervation of microvascular structures (Caro and Winter, 2014; Doppler et al., 2015; Evdokimov et al., 2019; Kosmidis et al., 2014; Oudejans et al., 2016; Ramírez et al., 2015). Functional changes may also occur leading to altered thermal and mechanical pain thresholds on quantitative sensory testing, and abnormal microcirculation and nerve conduction (Albrecht et al., 2013; Evdokimov et al., 2019; Serra et al., 2014; Sommer and Üçeyler, 2019; Üçeyler et al., 2013). Of note, although some people with FM may describe neuropathic pain features (e.g., Ramírez et al., 2015), the elusive nature of the underlying small-fiber pathology, the specificity of some of the structural and functional peripheral changes reported, and the distinct clinical expression separate this pathology from the typical small fiber neuropathy (Doppler et al., 2015; Üçeyler, 2017). Recent work has added even more complexity to this already puzzling issue, not only by showing that small-fiber involvement occurs in many other pain-related and unrelated disorders beyond FM (Üçeyler, 2016) but also by lending preliminary support to the concept that structural changes in the PNS may actually be driven by biochemical imbalances in specific brain regions, namely the insula (Harte et al., 2017).

Changes can also be observed in muscle fibers of patients with FM,

although with inconsistent results (Borchers and Gershwin, 2015) and contradictory interpretations regarding their potential causative role versus being a byproduct of physical deconditioning, associated symptoms, and/or comorbidities (Gerdle et al., 2020). Examples include atrophy, inflammation, hypoxia, ischemia, and tension in different muscle fibers as well as changes in functional parameters, such as muscle fatigue (Borchers and Gershwin, 2015; Klaver-Krol et al., 2019; Staud, 2011). Such abnormalities have been associated with metabolic and biochemical changes (Gerdle et al., 2020; Olausson et al., 2015), namely reduced levels of phosphates and augmented concentrations of neuromodulators and excitatory neurotransmitters, pro-inflammatory cytokines, and glycolysis products (Andrés-Rodríguez et al., 2020; Borchers and Gershwin, 2015; Ruggiero et al., 2018).

A groundbreaking study showed that the administration of immunoglobulin G (IgG) from patients with FM to mice resulted in sustained and widespread hyperalgesia to pressure and cold, accompanied by diminished muscle function, locomotor activity, and nerve fiber density (Goebel et al., 2021). These manifestations, similar to human FM, were not replicated when IgG-depleted serum from FM patients was injected, or following the administration of IgG from healthy individuals. Of note, the exogenous IgG was especially deposited at dorsal root ganglia (DRG), a site previously advocated to be the prime source of FM (Martínez-Lavín, 2021), with no apparent involvement of CNS structures or other circulating (proinflammatory) mediators. At the DRG, FM IgG binds on satellite glial cells and neurons, altering neuronal activity (Goebel et al., 2021). These findings revisit and extend the perennial debate on peripheral versus central nature of FM. Still, more research on how autoimmunity relates to other FM symptoms and observed neurophysiological patterns, and the mechanisms by which it operates is warranted.

Altogether, these abnormalities are invoked to explain a state of hyperexcitability and sensitization, leading to an augmented tonic nociceptive input from the periphery and even to spontaneous nociceptive neuron firing (Borchers and Gershwin, 2015; Goebel et al., 2021; Staud, 2011). Although some empirical findings support this concept, the nature of such abnormalities remains undetermined (Sommer and Üçeyler, 2019) and their relative contribution to FM a matter of debate (Clauw, 2015b; Oaklander, 2016).

2.2.2. HPA axis and autonomic nervous system (ANS) dysfunction

HPA axis abnormalities characterized by dysregulated cortisol levels at baseline and in response to psychosocial stressors (Coppens et al., 2018; Heim, Ehlert, and Hellhammer, 2000), and altered negative stress feedback sensitivity (Griep et al., 1998; Wingenfeld et al., 2007) have been described in some, but not all studies in FM (McLean et al., 2005). Positive studies reported mixed findings regarding the trajectory of these dysregulations (Catley et al., 2000; Crofford et al., 2004; Gur et al., 2004; Neeck and Crofford, 2000; Riva et al., 2012; Riva et al., 2010). Meta-analytic results suggest that women with FM present significantly lower basal cortisol levels than female controls (Tak et al., 2011). Many reviews, however, underline the non-specific and subset-restricted nature of the observed HPA abnormalities (Borchers and Gershwin, 2015; Harte et al., 2018; Tak and Rosmalen, 2010).

Dysfunctional autonomic functioning has also been documented in FM. Research is contradictory regarding sympathetic abnormalities, with reports of both hypoactivation (Reyes del Paso et al., 2011; Reyes Del Paso et al., 2010) and overactivation of this system (Adler and Geenen, 2005; Eisenlohr-Moul et al., 2015; Meeus et al., 2013; Reyes Del Paso and de la Coba, 2020). An overall dampened sympathetic response to stressors and a deficient baroreflex function have been described (Reyes Del Paso and de la Coba, 2020; Reyes del Paso et al., 2011; 2010). These abnormalities may compromise one's ability to respond effectively to stressors and may negatively influence pain by disrupting baroreflex antinociceptive function (Reyes Del Paso and de la Coba, 2020; Reyes del Paso et al., 2011; Reyes Del Paso et al., 2010; Suarez-Roca et al., 2019). Autonomic dysfunction has been further supported by observations of low cardiac vagal tone as indexed by low heart rate variability (HRV) (Meeus et al., 2013; Staud, Furlan et al., 2008, 2005), which is a putative neurophysiological marker of chronic stress (Brosschot, Verkuil, and Thayer, 2017) and a proposed biomarker for FM (Staud, 2008).

According to the Neurovisceral Integration Model (Thayer et al., 2012; Thayer and Lane, 2009), heart rate variability (HRV) reflects the integrity and effectiveness of the CNS-ANS link, with lower levels of HRV reflecting impaired cortical regulation, and resulting in compromised self-regulation and chronic activation of maladaptive defensive responses (Thayer et al., 2012). Following a polyvagal conceptual approach (Porges, 2007, 2009), a dampened vagal regulation translates an unfolding autonomic resetting in response to a chronic triggering of threat responding. This is attributed to a discrepancy between neuroception (i.e., the automatic and unconscious subjective appraisal of exteroceptive and interoceptive cues as safe, dangerous, or life-threatening) and actual contextual signaling (Kolacz and Porges, 2018). This mismatch may be caused by multiple factors, including early or concurrent adversity, conditioning effects, or symptoms themselves, and seems to be mediated by the insula (Kolacz and Porges, 2018). Abnormalities of insula activity have been consistently described in FM and have been proposed to explain most FM symptoms (De Paepe et al., 2020). Thus, dysfunctions in vagal control and sympatho-vagal balance, as observed in FM, may influence not only affect, stress responses, gastrointestinal and behavioral function, and neurotransmitters modulation (in virtue of vagus nerve regulation of HPA and brain-gut axes), but also impair vagally-mediated immunomodulatory action (Kolacz and Porges, 2018; Martins et al., 2021). Indeed, it has been suggested that FM is primarily a stress-disorder (Lyon et al., 2011; Van Houdenhove and Egle, 2004) and that FM symptoms can be explained by a "sympathetic overdrive" stemming from persistent threat-related activation (Martínez-Lavín, 2004, 2012; Martínez-Lavín and Hermosillo, 2000), which in the long-term, leads to a "wear and tear" of the stress system (Van Houdenhove and Luyten, 2009). At the same time, low vagal tone may also reflect a weaker social engagement system, which is dependent of safety perception (Porges, 2007). One should note, however, that polyvagal theory assumptions have been the object of considerable criticism (Grossman and Taylor, 2007).

Overall, it remains unclear whether the reported HPA/ANS dysregulations are a precursor of FM, a byproduct of persistent pain or functional decline, or a surrogate marker of a co-factor, namely stress (Martínez-Lavín, 2012; Williams and Clauw, 2009). Some studies have suggested that autonomic abnormalities are associated with an increased susceptibility to develop chronic widespread pain (CWP) and FM (Coppens et al., 2018; Heim et al., 2000; Tak and Rosmalen, 2010), particularly in individuals who are psychologically at risk (McBeth et al., 2007). Other studies, however, have failed to find such associations (Generaal et al., 2016). It has been pointed out that many of these abnormalities may be related to a variety of often unaccounted confounding factors, including medication use (Ambrogio et al., 2008), presence of comorbidities (Baumeister, Lightman et al., 2016; Tak et al., 2011; Wingenfeld et al., 2010), and trauma history (Koss and Gunnar, 2018; Weissbecker et al., 2006). For example, depressive or anxiety disorders, common in FM, are typically associated with changes in cortisol levels and ANS function, complicating interpretations (Generaal et al., 2014).

2.2.3. Inflammatory activity

Neuroinflammation has been attributed a role in FM, based on observations of inflammatory signals in the cerebrospinal fluid and the spinal cord (Albrecht et al., 2018; Bäckryd et al., 2017; Kadetoff et al., 2012). In addition, meta-analytic results have indicated that FM is associated with a distinct cytokine profile, characterized by elevated circulating levels of both pro-inflammatory [tumor necrosis factor alpha (TNF-α), interleukin (IL)− 6, IL-8)] and anti-inflammatory (IL-10) cytokines, and eotaxin, although this latter result was based exclusively on

evidence synthesis analysis (O'Mahony et al., 2021). Such results partially concur with previous meta-analytic reviews, which found augmented levels of IL-1 receptor antagonist, IL-8, IL-17A, IL-4, and, inconsistently, IL-6 (Üçeyler, Häuser, and Sommer, 2011). These prior meta-analyses, however, failed to find differences in high-sensitivity C-reactive protein, TNF, IL-10, and other cytokines (Andrés-Rodríguez et al., 2020; Üçeyler et al., 2011).

The release of pro-inflammatory and neuroactive substances leads to the recruitment and activation of local immune cells (Albrecht et al., 2018), and may contribute to sensitization processes and clinical symptoms (Zhang and An, 2007). Collectively, such observations tentatively support suggestions that FM could be seen as an inflammatory disorder of the CNS (Dell'Osso et al., 2015). Similar immune changes in the CNS and peripheral blood, are commonly observed in psychopathological conditions that are often comorbid with FM, such as depression, anxiety disorders, and post-traumatic stress disorder (PTSD) (Michopoulos et al., 2017; Pace and Heim, 2011; Young et al., 2014). Although informative, the nature and methodological limitations (e.g., reporting bias, multiplicity issues, lack of control for confounding factors) of the primary studies included in the reviews advise caution in interpreting results (Andrés-Rodríguez et al., 2020; Üçeyler et al., 2011) and preclude any conclusions on causality (O'Mahony et al., 2021). Further research exploring the roles of neuroinflammation and inflammation in FM is required.

2.2.4. Aberrations in gut-brain axis

The gut-brain axis has been attracting a lot of interest given its bidirectional crosstalk, regulatory effect on body's processes, and involvement in many disorders (Ignatova, 2019; Kim and Shin, 2018; Ma et al., 2019), including some of FM's most common comorbidities. Recent research revealed differences in the gut microbiome of patients with FM when compared to controls, which were associated with symptoms severity (Clos-Garcia et al., 2019; Minerbi and Fitzcharles, 2020; Minerbi et al., 2019). These microbiome alterations showed good discriminative properties in classification analysis (i.e., AUC of 87.8%; Minerbi et al., 2019). There is also some evidence of a beneficial effect of probiotics in chronic widespread pain (CWP), by controlling anxiety and inflammation, although no data is yet available on FM (Roman et al., 2018). Although promising, the study of the microbiome in chronic pain, and particularly in FM, is still in its infancy (Erdrich et al., 2020).

2.3. Genetic predisposition

Approximately 50% of individual variation in the risk of developing CWP/FM has been ascribed to genetic factors (Kato et al., 2006; Markkula et al., 2009), most likely of polygenic inheritance (Buskila and Sarzi-Puttini, 2006). Familial aggregation studies have shown that, compared to controls, first-degree relatives of individuals with FM display lower pressure pain thresholds and greater risk of developing FM (Arnold et al., 2013, 2004; Buskila and Neumann, 1997; Buskila et al., 1996).

Several genetic polymorphisms involving serotoninergic, catecholaminergic, dopaminergic, glutamatergic, canabinoidergic, and adrenergic pathways have been associated with both a higher risk of developing, and of greater severity of, FM (Ablin and Buskila, 2015; Park and Lee, 2017). Similar observations have been made regarding genes involved in the regulation of voltage-gated ion channels, binding proteins, and neuroplastic pathways (Ablin and Buskila, 2015; Kosek, Martinsen et al., 2016; Park and Lee, 2017; Zorina-Lichtenwalter et al., 2016). 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 many of the biological mechanisms described for FM. This also makes them capable of interfering or enhancing psychosocial dimensions and factors. In fact, some of these polymorphisms have also been recognized as risk factors for affective disorders and pain-related disorders other than FM, indicating a shared genetic risk that may, at least partially, account for the high comorbidity between FM and these disorders (Ablin and Buskila, 2015; Park and Lee, 2017). In fact, familial co-aggregation of FM, certain personality traits and affective disorders has been reported (Arnold et al., 2004; Glazer et al., 2010). Moreover, genome-wide cross-trait analyses have unraveled genetic associations among different pain phenotypes as well as among pain phenotypes, depression, and neuroticism, supporting the existence of common genetic factors (Meng et al., 2020). Based on the observation that FM is associated with hypomethylation of genes putatively implicated in autonomic and stress responses and subcortical aberrations, it has been proposed that epigenetic (dys)regulation may also play a role in FM development (D'Agnelli et al., 2019).

2.4. Medical comorbidities

FM often co-occurs with other physical and mental disorders, which complicates clinical decision-making and potentially leads to greater FM severity and burden, negatively impacting clinical outcomes, treatment adherence and response (Hegazi and Micu, 2017; Lichtenstein et al., 2018; Wolfe et al., 2020). FM is comorbid with numerous conditions, including chronic fatigue syndrome, irritable bowel syndrome, headaches, temporomandibular disorder, certain urogynecology and pelvic floor disorders, and regional pain syndromes, suggesting the existence of mutual pathophysiological mechanisms and clinical features (Kindler et al., 2011; Kleykamp et al., 2021; Phillips and Clauw, 2013; Thornton and Robert, 2020). Such comorbidity and shared pathophysiology have led researchers to subsume FM under various umbrella terms, each one emphasizing distinctive aspects, such as CSS (Clauw, 2015a; Yunus, 2008, 2015), functional somatic syndromes/disorders (Barsky and Borus, 1999; Burton et al., 2020), chronic overlapping pain conditions (Veasley, 2015) and more recently, chronic primary pain (International Classification of Diseases-11; Nicholas et al., 2019). A significant overlap between FM and bodily distress syndrome, a new concept comprising the presence of a set of distressing somatic symptoms not explained by well-recognized medical illnesses that persist over a 4-week timeframe, was also reported (Fink and Schröder, 2010; Häuser et al., 2020).

FM co-occurs with immune-mediated and degenerative rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, spondyloarthropathies, osteoarthritis, generalized joint hypermobility-related syndromes (Di Stefano et al., 2016; Hegazi and Micu, 2017; Lichtenstein et al., 2018; Mease, 2017), and neurological diseases such as multiple sclerosis (Marrie et al., 2012), probably due to unfolding central sensitization. The association between FM and immune-mediated diseases, many of which do not have pain as a central symptom, and also allergic diseases and psoriasis, has been attributed to the altered expression of immunoregulatory genes (Jones et al., 2016; Kridin et al., 2020).

Cardiovascular disease and diabetes are also common comorbidities of FM (Hegazi and Micu, 2017; Lichtenstein et al., 2018). Obesity is prevalent among patients with FM and a risk factor for its development (Mork et al., 2010), being associated with more symptoms and greater disability, emotional distress, multimorbidity, medication intake, and lower quality of life (D'Onghia et al., 2021; Gota et al., 2015; Kim et al., 2012; Okifuji et al., 2010). Although the exact nature of the association between obesity and FM is still elusive, the potential pathogenic effect of an inactive lifestyle, sleep disturbances, emotional distress, neuroendocrine dysfunction, and aberrations in endogenous modulatory function, has been underscored (D'Onghia et al., 2021; Ursini et al., 2011).

Apart from awakening unrefreshed, which constitutes a key symptom of FM, sleep disorders, such as restless leg syndrome (Viola-Saltzman et al., 2010), are also observed in FM. Chronic sleep disturbances have been shown to predict CWP/FM (Generaal et al., 2017; Gupta et al., 2007; Mork and Nilsen, 2012), and to negatively influence (and be influenced) by pain, fatigue, and emotional distress through centrally mediated processes (Choy, 2015; Finan et al., 2013; Simpson et al.,

2018).

3. Psychosocial dimensions

3.1. Psychiatric comorbidities

3.1.1. Clinical disorders

Overall, people with FM exhibit greater psychological distress (i.e., depressive and anxiety symptoms) than community and other chronic pain samples (Borchers and Gershwin, 2015). A comprehensive review of FM reported point-prevalence estimates of mood and anxiety disorders varying between 13% and 48% and 27–60%, and lifetime prevalence ranging between 20% and 86% and 16–60%, respectively (Borchers and Gershwin, 2015). A meta-analysis reported that the overall pooled point-prevalence of major depressive disorder in people with FM varied between 25% and 45%, depending on the assessment methods applied, whereas lifetime prevalence reached 65% (Løge-Hagen et al., 2019). Another systematic review found depression to be the most prevalent comorbidity, with a lifetime prevalence of over 52%, followed by panic disorder (33%), bipolar disorder (26%), and PTSD (16%) (Kleykamp et al., 2021). It should be noted that common depression screening tools, particularly those based on self-report, tend to overestimate the prevalence of depression when compared to more in-depth assessment methods.

A relationship between PTSD and FM is also supported by parallel research indicating that both disorders frequently co-occur (Borchers and Gershwin, 2015) and show overlapping symptoms and mechanisms (Häuser et al., 2016); and that their co-occurrence relates to a more severe FM phenotype (Sherman et al., 2000). Similar observations have been made regarding FM and depression (Alciati et al., 2012; Chang et al., 2015; Gracely et al., 2012; Lange and Petermann, 2010). Other anxiety-related disorders (e.g., social phobia, specific phobias) and obsessive-compulsive disorder were found to co-occur less frequently with FM, with current and lifetime prevalence rates ranging between 2% and 18% and 4–14%, respectively (Kleykamp et al., 2021). The presence and severity of medical and/or psychiatric comorbidities, along with the chronic and disruptive nature of FM symptoms and associated stigma, put people with FM at greater risk of developing suicide-related phenomena, although prevalence rates vary depending on the assessment methods and timeframes applied (Levine and Horesh, 2020).

A population study found a minimal overlap of FM and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classification of somatic symptom disorder (SSD), although the authors recognize that design, operationalization, and measurement caveats may have biased prevalence estimates of SSD (Häuser et al., 2020). Such results show that FM does not fulfill DSM-5 classification criteria of SSD (Häuser et al., 2015).

3.1.2. Personality disorders

Personality disorders also seem to be more prevalent among people with FM than among HC (Attademo and Bernardini, 2017). In a recent review, the estimated weighted prevalence of personality disorders in FM was 19% (Kleykamp et al., 2021). Obsessive-compulsive and avoidant personality disorders, previously classified as DSM-IV-TR Cluster C personality disorders (APA, 2000), seem to be the most prevalent in FM, although an increased representation of other personality disorders, such as borderline, histrionic, dependent, and schizoid ones, have also been reported in some studies (Attademo and Bernardini, 2017).

3.2. Psychological vulnerability and resilience factors

Cognitive and affective processes have long been established as relevant modulators of pain perception and processing, beyond the effect of the nociceptive stimulus itself, both in clinical and non-clinical populations (Bushnell et al., 2013; Crofford, 2015; Peters, 2015).

3.2.1. Maladaptive cognitive-affective processes leading to a threat ecology

Much research has focused on the identification of processes that may negatively influence pain experience and hamper adjustment to FM. These processes include, among others, pain-specific cognitions such as pain catastrophizing (Campbell et al., 2012; de Boer et al., 2012; Ellingsen et al., 2021; Ellingson et al., 2018; Feliu-Soler et al., 2017), pain-related fear, and negative expectations and attributions (Cedraschi et al., 2013). These processes are deemed key to pain chronification, as postulated by the fear-avoidance model (Crombez et al., 2012; Leeuw et al., 2007), by fueling interoceptive hypervigilance and avoidance behavior, which ultimately translate into increased levels of pain, distress, physical deconditioning, and functional impairment.

Learning processes play a pivotal role in the acquisition and maintenance of pain-related fear. Several studies indicate that people with FM present deficits in fear inhibition learning in response to safety cues, hyper-conditionability, overgeneralization of fear responses to harmless stimuli, and sustained threat responding to stimuli that are no longer harmful (Jenewein et al., 2013; Meulders et al., 2015; 2017; Sandström et al., 2020). Catastrophizing and contextual features seem to be relevant modulators of pain-related fear acquisition and impaired extinction (Karos et al., 2015; Sandström et al., 2020). By pervading a broad array of otherwise safe contexts and behaviors, threat may become a predominant ecology in FM, leading to greater suffering (Sandström et al., 2020).

These learning impairments are particularly relevant when framed within the Generalized Unsafety Theory of Stress (Brosschot et al., 2018). This theory postulates that a long-lasting heightened stress response can exist above and beyond the actual presence or mental representation of cues signaling threat and be maintained simply by the absence of safety perception. According to this theory, the generalized perception of unsafety may emerge from disturbances in three major domains: 1) the body, in that physical vulnerability or impairment reduces one's ability for adaptive responding; 2) the social context, where different forms of social disconnection constitute a risk factor for a broad array of illnesses; and 3) stress-related contexts, where as a result of conditioning processes, innocuous contexts related to past or current stressors become threat elicitors (Brosschot et al., 2017, 2018). Whereas each one of these aspects in FM is covered throughout this paper, some examples include: a) altered interoception, obesity, and somatic symptoms (for body dysfunction); b) loneliness, invalidation by others, and stigma (for a compromised social context); c) family or work-related environments (for stress-related contexts); and d) multisensory sensitivity to stimuli, indicating a compromised physical environment (Brosschot et al., 2018). The net effect of these learning deficits in FM would likely translate into "…*experiencing facilitators of threat processing but also the lack of inhibitors of threat processing such as access to caring and support from others*" (Gilbert, 2020, p. 11, when referring to anxiety and stress-prone people).

Similar observations apply to general psychological traits and processes that reflect misery and suffering. These include high negative affect and blunted positive affect (Finan et al., 2009; Hassett et al., 2008; Zautra, Fasman et al., 2005), low levels of perceived control and self-efficacy (Cameron et al., 2018), and maladaptive cognitive-emotion regulation strategies (van Middendorp et al., 2008). Indeed, beliefs regarding emotions, difficulties in emotion regulation, and emotion-related goal interference, have been shown to be associated with pain, disability, and greater FM impact (Bowers et al., 2017; Trucharte et al., 2020).

3.2.2. The pain-modulating effect of emotions

It has been demonstrated that positive affect decreases pain perception and increases pain tolerance, whereas negative affect has the opposite effect (Rhudy, 2016; Roy, 2015; Zautra et al., 2005). Emotions can also shape diverse physiological responses to pain, including defensive reflexes, electrodermal activity, and cardiovascular reactivity, and to other salient sensory stimuli (Rhudy et al., 2007; 2005; 2008; van

Middendorp et al., 2013; Gerdes et al., 2014). The nature and magnitude of the modulation is shaped by stimulus valence (i.e., continuum from unpleasant/aversive to pleasant) and by the interaction between valence and arousal, respectively (Rhudy et al., 2008; Rhudy, 2016). Several stimulus modalities, such as odors, images, or music, have been shown to produce this modulatory action (Roy, 2015). Furthermore, the effects of emotions on pain do not depend on them being related to pain itself; emotions can impact pain as long as they are perceived as personally relevant (Rhudy, 2016).

Converging lines of evidence show that emotions influence pain processing both bottom-up (e.g., multisensory integration) and top-down (e.g., descending inhibition) through spinal and supraspinal mechanisms (Roy, 2015). 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 (Bushnell et al., 2013; Wager and Atlas, 2015). Nonetheless, some studies have shown mixed findings concerning emotional modulation in FM. In one study, patients with FM did not display amplified neuro-autonomic responses to viewing negatively-valenced pictures, despite amplified subjective ratings of valence and arousal (Bartley et al., 2009). A study found inhibited rather than enhanced startle response upon exposure to unpleasant pictures (Rhudy, DelVentura et al., 2013), whereas another study did not find a hyporesponsive ANS to elicited emotions in FM (van Middendorp et al., 2013). Regarding the effect of positive stimuli, one study did not find any evidence of disrupted appetitive processing (Bartley et al., 2009), whereas other authors reported findings of diminished appetitive activation and emotional modulation of pain (Kamping et al., 2013; Rhudy, DelVentura et al., 2013). Such inconsistencies across studies may be related to sampling and methodological issues (e.g., patients' characteristics, differences in the nature and duration of stimuli and measurements), (de) sensitization processes, and engagement of different defensive responses (e.g., fear vs anxiety vs "freeze" responding). Nonetheless, future studies are certainly warranted for further clarification.

3.2.3. The role of cognitive (dys)function

'Fibrofog', or dyscognition, constitutes a highly prevalent and disabling symptom of FM which is frequently described in terms of forgetfulness and difficulties concentrating and expressing oneself (Arnold et al., 2008; Glass, 2009; Gelonch et al., 2017). There is substantial evidence of the existence of subjective (Gelonch et al., 2016, 2017; Williams et al., 2011) and objective cognitive impairments in people with FM. Compared to healthy controls, people with FM exhibit difficulties in objective working memory performance, particularly at the executive control level and in encoding, updating, and replacement subprocesses (Glass, 2009; Mercado et al., 2022). Performance-based deficits in implicit, episodic and semantic memory, processing speed, and executive functioning (e.g., attentional and inhibitory control, decision-making) have also been documented (Cherry et al., 2014; Dick et al., 2008; Duschek, Werner, Winkelmann & Wankner, 2013; Duschek, Werner, Limbert et al., 2014; Galvez-Sánchez et al., 2018; Glass, 2009; Leavitt and Katz, 2006; Park et al., 2001; Verdejo-García et al., 2009). One should bear in mind, however, that a mismatch between subjective cognitive complaints and objective cognitive test performance have been reported, suggesting that these measures reflect different phenomena (Estévez-López et al., 2017; Walitt et al., 2016). The literature has shown that objective cognitive dysfunction is especially related to pain severity (Park et al., 2001; Verdejo-García et al., 2009; Dick et al., 2008; Duschek et al., 2014; Reyes del Paso et al., 2012). Sleep, fatigue and cognitive-affective variables, such as mood, alexithymia, and pain catastrophizing have also been associated, although inconsistently, with impairments in both objective and subjective cognitive measures in FM (Galvez-Sánchez et al., 2018; Gelonch et al., 2016, 2017; Glass, 2009; Dick et al., 2008; Miró et al., 2011; Suhr, 2003). Working memory performance in people with fibromyalgia seem to be related to morphological changes in brain regions that subserve both pain and cognitive processing (Luerding et al., 2008), further supporting the cognitive-interfering nature of pain, which in turn, is shaped by pain-related context and features (Eccleston and Crombez, 1999).

There is a growing body of literature showing that people with chronic pain in general, and FM in particular, tend to present attentional biases towards threatening or aversive stimuli, including a heightened attention to symptom-related stimuli (Roelofs et al., 2002; Van Damme et al., 2007; 2004; Duschek et al., 2014; González et al., 2010; Fernandes-Magalhaes et al., 2022; Todd et al., 2018; Schoth et al., 2012). These biases seem to be operative at a preattentive level of processing and in relation to subliminal cues (Mercado et al., 2015; Peláez et al., 2015).

Studies have reported impaired cognitive inhibition (i.e., the ability to suppress or control task-irrelevant stimuli and automatic responding) in people with FM, as evidenced by poor performance in neuropsychological tests and reduced brain activation in areas implicated in cognitive control (Berryman et al., 2014; Cherry et al., 2014; Glass et al., 2011; Martinsen et al., 2014; Mercado et al., 2013). Together, these findings seem to be rooted in an underlying generalized hypervigilance (McDermid et al., 1996; Peters et al., 2000). Contemporary theories of pain and attention posit that such attentional and memory deficits may contribute to the emergence and maintenance of chronic pain (Crombez, van Damme & Crombez, 2005; Eccleston and Crombez, 1999; Eccleston and Crombez, 2007; Todd et al., 2015) through different mechanisms. First, hypervigilance may worsen FM symptoms, by fueling a negative loop of increased threat perception, emotional distress (which shows mutual facilitation effects with pain), and maladaptive behavioral responses (Duschek et al., 2014; Vlaeyen et al., 2016). Second, considering that pain and cognition share common brain networks, there may be a competition for resources that results in mental slowdown and cognitive dysfunction, especially when tasks are cognitively demanding (Glass et al., 2011; Duschek e al, 2014; Park et al., 2001). Engagement of additional cognitive effort and neuroplastic changes might occur as a means to circumvent this cognitive interference and maintain "normal" task performance (Glass et al., 2011; Duschek et al., 2014; Luerding et al., 2008).

The relevance of attentional biases and whether they are causally implicated in chronic pain remains controversial, however, in face of reported null findings, small effect sizes, and similar observations in healthy populations (Sitges et al., 2018; Pidal-Miranda et al., 2019; Crombez et al., 2013). In support of the idea that attentional biases play a role in FM, interventions targeting attentional processes such as traditional cognitive-behavioral approaches and mindfulness have shown promising results (Duschek et al., 2014; Vago and Nakamura, 2011; Pérez-Aranda et al., 2019), despite reported unfavorable findings of attention modification programs for FM (Carleton et al., 2020).

In sum, the nature and role of cognitive impairments in FM emergence and maintenance require further research despite their recognition and reported impact on people's lives. This is particular important considering that this "brain fog" is not specific to FM and also occurs in other non-pain conditions such as post- COVID-19 syndrome (Ceban et al., 2022). Other putative factors implicated in cognitive dysfunction in FM, including neuro-immune-endocrine mechanisms, should be explored in future studies (Lekander et al., 2000; Sephton et al., 2003). Limited integration of cognitive impairments as a relevant outcome in routine assessments and interventions for people with FM is hindering progress in this area.

3.2.4. Positive factors and resilience

Psychological resilience factors have also recently attracted attention (Hemington et al., 2017; Sturgeon and Zautra, 2010). These factors include positive affect, optimism, active pain coping, (self-)compassion, pain acceptance, psychological flexibility, purpose in life, and values-based action (Edwards et al., 2016; Feliu-Soler et al., 2018; Hassett and Finan, 2016; McCracken and Yang, 2006; Purdie and Morley, 2016; Sturgeon and Zautra, 2010, 2013). Studies highlight that the soothing influence of positive affect upon pain perception may operate

through the downregulation of dysfunctional cognitive-affective processes and the promotion of adjustment and resilience by broadening awareness and fostering psychological and behavioral flexibility (Finan and Garland, 2015; Hanssen et al., 2017; Fredrickson, 2001). It is noteworthy that most of the psychological factors that appear to augment pain are commonly reported in high (i.e., disruptive) levels by patients with FM, whereas the opposite is seen regarding resilience factors, such as positive affect (Hassett et al., 2008; Zautra, Fasman et al., 2005).

3.2.5. Heterogeneity of psychosocial patterns

Studies of the psychological profiles of people with FM show substantial heterogeneity, suggesting the possible existence of different FM subgroups [see Pérez-Aranda, Andrés-Rodríguez, Feliu-Soler, Nuñez, et al., 2019 for a brief overview]. One study, guided by operant learning theory, differentiated a 'dysfunctional group' characterized by poor coping strategies, an 'interpersonally distressed group', and a group of 'adaptive copers' (Turk et al., 1998). Another study using subjective and objective measures distinguished five FM subgroups, labelled 'Adapted', 'Fit', 'Positive', 'Poor performer', and 'Maladapted' (Estévez-López et al., 2017). Similar results were found by a recent study, which identified four clusters (i.e., maladaptive, adaptive, vulnerable, and resilient) on the basis of coping strategies, affective load, cytokine profile, and disability levels (Braun et al., 2020). These observations underscore the wide range of coping and personality styles in FM (not all of them being maladaptive; Braun et al., 2020), and the fact that not all patients exhibit psychological problems.

3.2.6. Support from interventions targeting cognitive-affective mechanisms

The key role of cognitive-affective mechanisms in pain perception and modulation is further supported by the effectiveness of interventions targeting self-regulation and psychological processes (Reddan and Wager, 2019). These include neurofeedback, where 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 perception of experimentally-induced pain (deCharms et al., 2005). The same outcome can be achieved through biofeedback by consciously controlling physiological processes involved in pain and emotion, such as HRV and muscle tone (Glombiewski et al., 2013; Hassett et al., 2007).

Other techniques and interventions, such as hypnosis (Dillworth et al., 2012), traditional cognitive-behavioral therapies, and the more recent contextual approaches, including mindfulness-based interventions and Acceptance and Commitment Therapy (Hayes et al., 1999), seem to have an analogous effect, being associated with changes in the activity level (Jensen et al., 2012; Zeidan et al., 2011) and connectivity of certain brain structures (Feliu-Soler et al., 2018; Lazaridou et al., 2017; Shpaner et al., 2014; Yoshino et al., 2018). Cognitive self-regulation strategies, such as reappraisal, have been shown to ameliorate pain ratings as well as cardiovascular and electrodermal indices of pain-related autonomic responding (Matthewson et al., 2019). Changes in the cognitive-evaluative and affective-motivational aspects of pain, including changes in pain valuation (either by modifying its meaning or its salience), pain-associated distress, disruption of perseverative cognitive processes, promotion of perspective-taking, and defusion from pain are suggested to constitute some of the mechanisms by which self-regulation strategies operate to reduce chronic pain impact (Reddan and Wager, 2019). A deeper understanding of the pain-emotion link and the inclusion of "emotional work" in the care of patients seem to be key for a better management of pain in general (Lumley et al., 2011) and for FM in particular (Hsu et al., 2010; Lumley et al., 2008, 2017). Thus, determining which factors predict a good adjustment or confer resilience to FM and under which circumstances seems pivotal and should be further investigated. FM subgrouping may also help to identify group-specific needs and responses to treatment and inform the design of personalized interventions.

3.3. Temperament and personality

Over the years, studies have examined the link between personality and FM in search for a particular profile that would render people more vulnerable or resilient to FM. Published studies have presented inconclusive findings, failing to demonstrate the existence of an "FM personality" capable of discriminating people with FM from others with chronic pain or the general populations (Conversano et al., 2018; Malin and Littlejohn, 2012b; Torres et al., 2013). Understanding the relationship between FM and personality is further complicated by the fact that chronic pain and associated distress may change not only the report of personality traits (Fishbain et al., 2006; Torres et al., 2013), but even personality itself, as suggested by neuroimaging studies (Gustin et al., 2014).

3.3.1. Temperament and the 'Big Five'

Overall, the literature has shown a considerable heterogeneity in the dispositional traits of people with FM, with distinct subgroups being identified based on different personality models and measures (Bucourt et al., 2017; Gonzalez et al., 2020; Torres et al., 2013). Despite this, certain personality traits have been recognized as common in people with chronic pain (Naylor et al., 2017). Depending on the personality profiling tools used, FM has been associated with greater neuroticism/harm-avoidance and reduced extraversion and self-directedness (Bucourt et al., 2017; Malin and Littlejohn, 2012a; Montoro and Reyes del Paso, 2015). Some studies converged in the finding of two main personality-based clusters that are differently correlated with clinical, psychopathological, and functional outcomes (Bucourt et al., 2017; Gonzalez et al., 2020) at short and long-term follow-up (Torres et al., 2013). Of note, high levels of neuroticism were a common feature of the "maladaptive" cluster across studies. Depending on the study, this "maladaptive cluster" was also characterized by low levels of extraversion and conscientiousness. Given that extraversion is generally associated with well-being, positive affect, and social functioning, low levels of this trait may translate into diminished protection against the pernicious effects of neuroticism and psychological distress (Naragon-Gainey and Simms, 2017; Wilt and Revelle, 2017). Contradictory results regarding agreeableness were found across studies (Bucourt et al., 2017; Torres et al., 2013; Garcia-Fontanals et al., 2017).

One study demonstrated that health professionals experienced in managing FM can distinguish patients from controls based on single items of the Revised NEO Personality Inventory (Da Silva et al., 2017). Each health professional, using items of his/her choice, showed in receiver-operating characteristic (ROC) analysis an area under the curve of 0.71–0.81 in predicting the diagnosis. The most predictive items were related with high levels of neuroticism and low levels of trust (Da Silva et al., 2017). Yet these associations do not necessarily demonstrate causality but rather pieces of a very complex puzzle. Remarkably, in a longitudinal study, neuroticism levels were shown to precede and predict the development of joint pain over a follow-up of 23 years (Charles et al., 1999). Similarly, a 25-year longitudinal study found that neuroticism was associated with an increased risk of developing physical diseases, particularly those characterized by chronic systemic pain (Charles et al., 2008).

These observations are relevant in view of the literature linking neuroticism to severe FM symptoms (including pain), pain-related catastrophizing and pain-related anxiety, and worse clinical and health-related outcomes (Bucourt et al., 2017; Kadimpati et al., 2015; Malin and Littlejohn, 2012a; Martínez et al., 2011; Newton-Howes et al., 2015; Seto et al., 2019), although mixed findings have been reported in this regard (Gonzalez et al., 2021). An association of harm-avoidance with deficient pain modulation has also been documented (Nahman-Averbuch et al., 2016).

The pernicious effects of dispositional negativity seem to relate mainly to three mechanisms: 1) an augmented threat reactivity (i.e.,

tendency to magnify and react excessively to mild stressors that are commonly experienced in everyday life), thereby fueling an amplified intensity and time-course of negative affect; 2) a tendency to become easily distressed by novel, ambiguous, or threat-free contexts and for the resulting negative affect to persist and pervade other unrelated contexts; and 3) an increased vulnerability to a multiplicity of stressors due to an individual's dysfunctional expression and behavior (Shackman et al., 2016). Although germane to the comprehension of the psychological factors implicated in FM, neuroticism operates as a risk factor for a wide range of disorders, and therefore lacks specificity and explanatory power when accounting for the etiology of FM (Ormel et al., 2013).

3.3.2. Other personality traits

Other pathological personality traits, such as hypochondriasis, depression, hysteria (e.g., somatization proneness), and schizophrenia-spectrum features (e.g., unusual beliefs) as assessed by the Minnesota Multiphasic Personality Inventory-2 (MMPI-2), have been reported in FM (Gonzalez et al., 2021). It has been argued, however, that higher "schizophrenia" scores in the MMPI-2 in chronic pain populations are more related to the reported clinical manifestations (i.e., somatic and depressive-like symptoms) and disease impact than to the presence of serious mental illness (Moore et al., 1988). Perfectionism, type D personality, and alexithymia also constitute common traits among people with FM (Di Tella and Castelli, 2013; Malin and Littlejohn, 2012b; van Middendorp et al., 2016). These have been associated with lower levels of educational attainment, presence and severity of pain and other somatic symptoms, poor physical health status, negative cognitive processes, low self-esteem, emotional distress, and poor health-related quality of life, although equivocal evidence has been found (Di Tella and Castelli, 2013; Di Tella et al., 2017; Martínez et al., 2015; Montoro et al., 2016; Gocken et al., 2022). Patients with a type D personality, which typically encompasses a proneness towards higher levels of negative affect and a tendency to suppress its expression in social contexts (Denollet, 2005), were 3-fold more likely to have FM, even when accounting for sociodemographic factors (Gocken et al., 2022). A recent meta-analysis showed that alexithymia, that is, a deficit in the ability to understand, identify, and express feelings, is elevated in FM compared not only to healthy controls but also to people with other pain problems, particularly rheumatoid arthritis (Asgarabad et al., 2023). Alexithymia-related deficits may increase vulnerability to pain by favoring misattribution of emotional arousal and somatosensory amplification and by impairing effective emotion regulation (Lumley et al., 2007; Martínez et al., 2015). Some studies have identified potential pathways through which alexithymia, pain, and depression may be linked (Ghiggia et al., 2017), but further research is needed to fully understand the specific role of this trait in FM.

Studies examining the potential protective role of positive dispositional features are rare (Gatchel et al., 2007). Moreover, it remains underexplored whether and how different traits interact with each other to amplify or attenuate FM diathesis. Indeed, particular combinations of dispositional vulnerability and resilience factors may result in greater predictive specificity than each individual trait.

3.4. Life history, (early) adversity, and stress

The complex and multidetermined nature of FM has been underscored recently by a review of longitudinal cohort studies, which identified depression, sleep disturbances, somatic symptoms, and dysfunctional illness behaviors as the strongest predictors of FM (Creed, 2020).

3.4.1. Early adversity

Research has shown that exposure to different types of early life stress (e.g., adverse interpersonal contexts, abuse, loss, or rejection) is commonly reported by individuals with FM (Bohn et al., 2013; Coppens et al., 2017; Davis et al., 2005; Häuser et al., 2011), although studies based on patients' self-report are prone to recall bias, and prospective studies indicate less convincing results (McBeth et al., 2001; Raphael et al., 2001). A meta-analytic study indicated that, overall, exposure to potentially traumatic events increased almost threefold the likelihood of developing functional somatic syndromes (including FM), with the strength of this association being dependent on trauma measurement and features (Afari et al., 2014). Another meta-analysis that focused specifically on different forms of abuse concluded that experiences of physical and sexual abuse, either in childhood or adulthood, were significantly associated with subsequent onset of FM (Häuser, Kosseva et al., 2011). Of note, both publications recognized the methodological limitations of the included studies, such as retrospective or cross-sectional assessment, lack of control for confounding variables, and overall low study quality (Afari et al., 2014; Häuser, Kosseva et al., 2011). Acknowledging these limitations, the link between reports of (early) adverse experiences involving physical and psychological trauma, and FM development later in life has been underscored by many other reviews on the topic (Borsini et al., 2014; Davis et al., 2005; Low and Schweinhardt, 2012; Yavne et al., 2018).

Cross-sectional or retrospective studies are buttressed by longitudinal studies demonstrating that experiences of early adversity are risk factors for developing somatic symptoms, including CWP, later in life (Generaal et al., 2016; Jay et al., 2019; Jones et al., 2009). Still, conflicting findings have been reported, particularly in regard to physical trauma (Jones et al., 2011). A national longitudinal birth cohort study found that financial hardship and low education level (the latter, for men only) in early adulthood were prospectively associated with an increased risk of CWP (Jay et al., 2019). In a study conducted using data from the 1958 British Birth Cohort Study (Jones et al., 2009), the authors found that individuals who had experienced adverse life events in childhood 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 numerous psychosocial variables. In a prospective cohort study, exposure to different types of occupational stressors such as bullying was found to predict the development of FM 2 years later, even when accounting for the effect of sociodemographic, clinical, and lifestyle factors (Kivimäki et al., 2004). Among the musculoskeletal disorders included in this study (i.e., FM, osteoarthritis, and sciatica), only FM was predicted by work-related stressors.

Literature on the impact of early adversity has also indicated that quantity matters. Cumulative adversity, but not trauma type, is linked to a higher risk for chronic pain, when accounting for potential confounders (You et al., 2019). Indeed, even after adjusting for depressive symptoms, healthy individuals with high levels of adversity showed both greater central sensitization and attenuated autonomic pain responses (You and Meagher, 2016). Parallel findings were reported in research conducted in HC and patients with FM, where exposure to psychosocial stress induced allodynia and hyperalgesia in patients with FM (Crettaz et al., 2013). Another study, using ecological momentary assessments, found that stress predicted later pain, even when controlling for potential confounders, whereas the opposite was not seen. Although stress biomarkers did not operate as mediators of the stress-pain link, the authors found that pain intensity was concurrently and positively associated with cortisol levels (Fischer et al., 2016).

The concept that early adversity and/or psychosocial stress may induce enduring states of hyperalgesia and allodynia (Bardin et al., 2009) has been widely reported in preclinical research, using diverse (e.g., types, modalities, and features) psychosocial stressors (Burke et al., 2017; Eller-Smith et al., 2018; Olango and Finn, 2014; Sluka and Clauw, 2016). These observations concur with and are extended by another study showing that mice exposed to repeated psychological stress demonstrated an oxidative lipid dysregulation that affected nociceptive processing and induced a state of hyperalgesia and fatigue-like behaviors (Hung et al., 2020). One should nevertheless bear in mind that the relation between stress and pain is complex, and that contextual, stressor, and individual-related features may account for either pain

facilitatory or pain inhibitory effects of stress (Butler and Finn, 2009; Olango and Finn, 2014).

3.4.2. Mechanisms linking adversity and psychosocial stress to FM

Potential factors linking trauma exposure to pain severity and (dys) function include affective distress, fibromyalgianess, and presence and severity of PTSD symptoms (Coppens et al., 2017). Early adversity may also hinder adaptive socioemotional development and regulation that may drive the body to a "wear and tear" state over time due to stress build-up (allostatic load), which in turn may disrupt the balance between inhibitory-facilitatory processes and favor central sensitization (You et al., 2019; You and Meagher, 2016). There is some evidence that adverse lifetime experiences may be associated with inflammation, life-long aberrations in HPA and ANS function, epigenetic modifications of gene expression, reorganization of neural substrates involved in emotion processing and regulation disruption of sleep patterns and circadian rhythms, and reprogramming of nociceptive and descending inhibitory circuitries (Krugers et al., 2017; Landa et al., 2012; Nelson et al., 2020; VanTieghem and Tottenham, 2018), (Agorastos et al., 2019; Baumeister, Akhtar et al., 2016; Burke et al., 2017; Chen and Lacey, 2018; Low and Schweinhardt, 2012), all of which may contribute to central pain amplification, which is the hallmark of FM. Nonetheless, prospective studies aimed at clarifying these links are still needed.

Early adversity may also profoundly disrupt healthy attachment. One study found that people with FM report more negative rearing experiences, marked by parental overprotection and lack of parental affection, when compared to HC (Romeo et al., 2020). Differences between patients with FM and HC regarding attachment styles have been reported, with the former presenting 2-fold higher levels of insecure adult attachment (Peñacoba et al., 2018), and higher scores on insecure attachment dimensions, namely discomfort with closeness, need for approval, and preoccupation with relationships (Romeo et al., 2020). Moreover, patients with FM scored lower than HC on dimensions related to secure attachment, which points to the existence of negative representations of the self (i.e., as unworthy of care) and/or of others (i.e., as non-responsive and uncaring) (Romeo et al., 2020). A large population study found that insecure adult attachment styles, specifically avoidant attachment, was associated with unexplained chronic pain during the past 12 months, even when controlling for confounders (McWilliams, 2017). Attachment may impact mental and physical health, including the susceptibility to chronic pain, by compromising socio-emotional resources, increasing vulnerability to stress and stress-related somatic symptoms, and impairing effective responding and adaptation to chronic pain (Maunder and Hunter, 2008; Meredith et al., 2008; Mikulincer and Shaver, 2012; West et al., 1986).

3.5. Gender differences

Gender differences in pain are commonplace: many chronic pain conditions, including FM, are more prevalent and often more severe among women than men (Wolfe et al., 2018; Yunus, 2002). Compared to men, women show higher sensitivity to experimentally-induced pain, higher tendency to pain amplification, and less endogenous pain inhibition (Bartley and Fillingim, 2013; Fillingim et al., 2009; Popescu et al., 2010; Racine et al., 2012a). Women also tend to report a greater number, severity, and frequency of symptoms (Barsky et al., 2001) although this may not always be the case in FM (Häuser, Kühn-Becker et al., 2011).

Research on gender-related differences in pain perception and processing has stressed their multifactorial nature, with several biological and psychosocial contributing factors (Mogil, 2012, 2020; Racine et al., 2012b). Among 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 and emotional modulation of pain (Amandusson and Blomqvist, 2013; Bartley and Fillingim, 2013; Martin et al., 2019; Mogil, 2012; Nasser and Afify, 2019; Rhudy, Bartley et al., 2013; Sie et al., 2019). Sex-dependent genetic associations and sex differences in ANS activity and supraspinal connectivity have also been found to affect pain processing and modulation (Bartley and Fillingim, 2013; Dai et al., 2018; Kim et al., 2021; Mogil, 2012).

Psychosocial factors accounting for gender differences in pain include social interaction; gender role expectations regarding pain sensitivity; pain expression, and behavior; distress disclosing; and gender-related personality traits (Barsky et al., 2001; Bernardes et al., 2008; Conversano et al., 2021; Racine et al., 2012b). Additionally, a sex-dependent effect of family history of pain (Fillingim et al., 2000) and adverse experiences in childhood (Fillingim and Edwards, 2005) on pain sensitivity has been demonstrated only for women. Sleep deprivation may also have a stronger and differential impact upon pain and central sensitization in women (Eichhorn et al., 2018; Smith et al., 2019). At the intrapersonal level, variation in psychological distress and psychological processes such as symptoms/illness appraisals, pain catastrophizing, self-efficacy, and coping strategies also seem to contribute to the reported gender differences (Barsky et al., 2001; Bartley and Fillingim, 2013; El-Shormilisy et al., 2015; Racine et al., 2012b).

3.6. Multisensory hypersensitivity

Studies have shown that the hypersensitivity observed in FM is not limited to pain but often extends to other non-nociceptive sensory modalities, with patients showing an augmented discomfort and sensitivity to somatosensory, olfactory, visual, and auditory stimuli (Geisser et al., 2008; Harte et al., 2016; Hollins et al., 2009; Kosek et al., 1996; McDermid et al., 1996; Palmer et al., 2019; Smith et al., 2008; Staud et al., 2021; Suhnan et al., 2017; Wilbarger and Cook, 2011). This multisensory hypersensitivity, which is linked to altered brain activity patterns in sensory processing and integration brain regions such as the insula (Harte et al., 2016; López-Solà et al., 2014), has been found to be the most discriminative neurophysiological feature in FM (López-Solà et al., 2017), and a potential endophenotypic marker of central sensitization (Harte et al., 2018). A link between perceptual amplification and central sensitization has been proposed (Geisser et al., 2008; Hubbard et al., 2020; Suhnan et al., 2017), although the exact mechanisms at play – and whether they are present across sensory modalities or are modality-specific – remain poorly investigated (Staud et al., 2021).

Another potential mechanism that has been advanced to explain this phenomenon is generalized hypervigilance (McDermid et al., 1996; Rollman and Lautenbacher, 1993), although this is still a contentious subject (Tiemann et al., 2012; Van Damme et al., 2015). According to this hypothesis, patients with FM tend to pay excessive attention to bodily perceptions (Borg et al., 2015; Rost et al., 2017) and external cues and to present an exaggerated, sometimes painful, response to somatosensory stimuli, even to those that are innocuous (Carrillo-de-la-Peña et al., 2006; Geisser et al., 2008; Hollins et al., 2009; McDermid et al., 1996). Whereas people with FM tend to consistently report increased subjective hypervigilance and show a stronger orientation towards threats (López-Solà et al., 2014; Rost et al., 2017; Wilbarger and Cook, 2011), results regarding the experimental demonstration of perceptual amplification are less convincing (Borg et al., 2015; Carrillo-de-la-Peña et al., 2015; 2006; Hollins et al., 2009; Peters et al., 2000; Tiemann et al., 2012). Sampling and methodological differences and distinct operational definitions of hypervigilance may be at the core of such marked inconsistency across studies. For example, studies have distinguished two types of heightened body awareness: one maladaptive, related to hypervigilance, where threat-focused monitoring of body sensations predominates; and the other adaptive, characterized by attunement with and through the body, that facilitates the processing and integration of information relevant for self-regulation (Mehling et al., 2009; Valenzuela-Moguillansky et al., 2017). It seems that patients with FM tend to have a predominance of the former, pernicious form of body awareness (Valenzuela-Moguillansky et al., 2017). It is tempting to link

the process of sensory hypervigilance to catastrophizing and rumination and both of them to a hyperactive DMN observed in FM (Ellingsen et al., 2021).

Disturbances in interoception, a construct sometimes used interchangeably with others such as body awareness and defined as the representation of internal bodily states, have also been noted in FM (Duschek et al., 2017; Martínez et al., 2018; Valenzuela-Moguillansky et al., 2017), although disparate findings have been reported (Borg et al., 2018; Rost et al., 2017; Sharp et al., 2021). Research has also shown that people with FM present a distorted body schema; that is, "how the body exists in the mind", characterized by functional and body dissatisfaction, particularly for pain-related body regions (Martínez et al., 2018). Despite showing augmented interoceptive awareness (which correlates with clinical pain levels), patients with FM exhibit an impaired embodiment, comprising a phenomenological disconnection from what is happening in their bodies. This impairment may hinder their ability to change existing negative body representations according to ongoing contextual feedback and impair their ability to rely on bodily cues to help regulate emotions and behavior, thus fueling states of distress and increased pain (Valenzuela-Moguillansky et al., 2017). Disturbances in interoception are particularly relevant considering that it holds an intrinsic survival value (Craig, 2002, 2010), with pain being conceptualized as a homeostatic emotion (Craig, 2003). Interoception involves multiple signals and afferent pathways and provides continuous feedback, helping shape complex mental and behavioral processes, including one's sentience; that is, "the coherent representation of all feelings at one moment" (Craig, 2010; Critchley and Garfinkel, 2017; Critchley and Harrison, 2013).

Finally, a psychological aversion towards salient inputs has also been pointed out as a potential driver of this multisensory hypersensitivity (Perkins et al., 2016). Research has shown that whereas painful and non-painful aversive stimuli may differ in some of the (dedicated) areas they activate and/or in the degree of activation they evoke (depending on stimulus' modality and painfulness), all such stimuli activate common neural networks involved in aversion processing (Hayes and Northoff, 2012). This concurs with the view that the brain activation matrix generated by aversive stimuli is more related to salience processing than to specific features of the stimulus (e.g., being painful or not, being modality-specific). This proposal extends the traditional view of the pain matrix as intrinsically nociceptive to incorporate a broader defensive function (Legrain et al., 2011).

Together, these observations suggest that patients with FM experience a perceived overload of psychological and sensorial inputs that take a predominantly negative valence. It seems plausible that the increased subjective sensitivity to different sources of stimuli coupled with negative cognitive-affective processes evolve into a reverberant source of additional stress, anxiety, and fatigue in FM (Wilbarger and Cook, 2011). As a consequence, maladaptive avoidance and isolation behaviors may ensue (Valenzuela-Moguillansky et al., 2017), in a failed attempt to bypass the (perceived) continuous input storm (Wilbarger and Cook, 2011).

3.7. Social Environment

Pain is a contextual and socially-shaped phenomenon. An increasing body of evidence supports that social determinants and milieu impact health indicators and pain (Che et al., 2018; Krahé et al., 2013).

3.7.1. Social disconnection and social pain

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 (Baumeister and Leary, 1995; Buss, 2019). Potential threats or actual failure to meet this basic interpersonal need increase vulnerability to the detrimental effects of multiple sources of stress (Davis et al., 2001) and translate into an increased likelihood of developing an array of mental and physical symptoms and/or disorders (Hawkley and Cacioppo, 2010; Petitte et al., 2015), including pain. Social disconnection and social distress have been shown to increase pain in patients with FM (Wolf and Davis, 2014) and pain-related responses in healthy subjects (Canaipa et al., 2016; Eisenberger et al., 2006). 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 (Jaremka et al., 2014; Karayannis et al., 2019). The importance of these findings is underscored by repeated observations that patients with FM exhibit greater loneliness, even when compared to patients with other pain disorders, less perceived social support, and increased perceived invalidation from others (Davis et al., 2001; Kool and Geenen, 2012; Kool et al., 2009; Santiago et al., 2017). A study conducted in a chronic pain sample composed mainly of women with FM found that, even when accounting for potential confounders, the perception of others as disregarding, shaming, or judging towards one's pain experience predicted individual pain-related disability (Carvalho et al., 2020). Interpersonal rejection – be it actual, anticipated, or perceived – and other forms of social disconnection affect pain ratings and pain- and emotion-related neural activity, disrupt pain modulation (Karayannis et al., 2019; Landa et al., 2020; Wolf et al., 2015), and enhance inflammatory activity (Eisenberger et al., 2017). Importantly, early experiences with caregivers seem to greatly influence emotional (neuro)development and partly account for individual variability in the extent to which pain-related circuits are modulated by socially distressing experiences (Landa et al., 2020). The negative effects of interpersonal rejection upon central pain modulation seem to persist and extend to future interactions with past rejecters and to be driven by rejection expectations or rejection-related emotional states (Landa et al., 2020). It can also trigger so-called "social pain"; that is, painful feelings ensuing from negative social experiences (Eisenberger and Lieberman, 2004). It has been proposed that social and physical pain have substantial neural overlap (Eisenberger, 2012), with a perceived threat to the (social) self being considered the common denominator to both kinds of pain (Eisenberger and Lieberman, 2004). This concept remains, however, controversial (Cacioppo et al., 2013).

3.7.2. Stigma and invalidation

Illness-related stigma and a sense of invisibility are also prevalent phenomena in FM, fueled largely by the lack of objective markers and by misconceptions surrounding the condition (Sim and Madden, 2008). Two small-scale qualitative studies found that stigmatizing attitudes and lack of understanding from others, along with the nature and severity of symptoms, often give rise to feelings of guilt, shame, burdensomeness, and social isolation (Arnold et al., 2008; Lempp et al., 2009). Invalidation has been previously demonstrated to be associated with threat-related autonomic activity and with poorer prosocial behavior in response to stress-inducing experiments in healthy subjects (Greville-Harris et al., 2016). A study found that invalidation may have different effects upon FM symptoms and quality of life depending on its form and source: discounting by a spouse seems especially pernicious (Ghavidel-Parsa and Bidari, 2021). The existence of prejudice or stereotypical biases and, in some cases, skepticism about FM legitimacy, even within the medical realm, may negatively impact people with FM by disrupting interpersonal relationships and support, compromising care seeking and adherence, hindering early diagnosis, and leading to inadequate or undertreatment (De Ruddere and Craig, 2016; De Ruddere et al., 2016; Sim and Madden, 2008).

3.7.3. Social connection

Just as social disconnection is reliably linked with worse pain-related status, social connection is increasingly recognized as a contributor to mental and physical well-being. It was found that social support has a buffering effect against negative pain-related outcomes, probably through its soothing influence on cognitive-affective processes involved in pain regulation and modulation (Che et al., 2018; Hornstein and

Eisenberger, 2017; Montoya et al., 2004). Recent findings have further proposed that this pain-attenuating effect seems to be dependent on several intra- and interpersonal factors, including attachment styles, participant-partner relationships, and types of interpersonal interactions (Krahé et al., 2013). Also, the perceived quality rather than quantity of social support plays a role when predicting FM-related outcomes (Franks et al., 2004).

4. A call for an integrative model

A central goal of this review has been to synthetize, bridge, and build a comprehensive understanding of the main neurophysiological and psychosocial factors at play in FM. One aspect in particular that we highlight was the dynamic interaction and crosstalk between these apparently independent systems and factors, supported by shared genetic influences, overlapping neural circuits, and systemic and neuroplastic changes induced by certain traumatic events and by pain itself. Although several hypothesis and models have been proposed to account for some of these reported observations, most of them fail to offer a unifying perspective of FM and its complexity.

This review, along with the insights of international experts in the field, served as basis for the development and proposal of a new model of FM – the "Fibromyalgia: Imbalance of Threat and Soothing Systems" (FITSS) model, presented elsewhere (Pinto et al., 2023). According to this model, FM is closely tied to an overly active threat system (responsible for detecting and responding to all types of potential threat) and a blunted soothing system (a system associated with contentment, safeness and affiliation). The imbalance between these systems may stem from multiple factors, including biopsychological, diatheses, and early and current adversity, or may originate in response to illness. The imbalance keeps our central alarm (the salience network) in continuous alert mode. Such dysregulation could account for many of the reported abnormalities in FM. Despite its potential value, this model is not without limitations, including a lack of conclusive evidence, pathophysiological heterogeneity, and vagueness or ambiguity of psychological constructs. It is a heuristic model that is open to critical revision and refinement in the face of new evidence.

5. An agenda for future research and practice in FM

This review highlights a number of potential avenues for research and practice in the field of FM. Future research is needed to establish how and under which circumstances some of the identified mechanisms operate, and whether they are causally implicated in the development and maintenance of FM. Investigations on how adversity/stress may reset or change neural, immune, endocrine and nociceptive systems in the context of FM are required. Studies should be undertaken to explore the operating mechanisms underlying the reported heterogeneity in FM expression, course, and response to treatment.

Studies directed towards a better understanding of the link between psychosocial factors and neurobiological features in FM are warranted. Especially needed are well-designed prospective studies to address the potential relevance of early adversity and psychosocial profiling regarding the "threat ecology", as etiological or maintenance factors of FM. To develop a full picture, additional studies aimed at exploring positive biological and psychosocial assets that may confer resilience seem valuable. There is a need for experimental studies dedicated to study threat processing, safety learning processes, and cognitive biases. New constructs designed to organize different types of emotions according to their functional commonalities around the concepts of threat and soothing may help to foster progress in this complex field.

Longitudinal studies capable of exploring and determining the potential causal pathways and temporal relationships among the many operating mechanisms are warranted. Assessment should be, whenever possible, multimodal and multilevel in nature, covering different biopsychosocial variables and using multi-method approaches, in order to better grasp complex interactions. Emerging methodologies, such as network analysis, machine learning algorithms, and trajectories modelling, that account for the relative contribution of multiple interdependent mechanisms may prove useful.

At the clinical level, this review underscores the potential relevance of a variety of variables that may shape the expression, course, and response to treatment (e.g., presence of neuropathic pain features, trauma history and associated symptoms, comorbidities, current sources of stress). Notwithstanding, the (relative) importance of each variable needs to be established by intervention studies. Although top-down modalities (i.e., from the mind to the body) remain key in the therapeutic armamentarium for FM, future studies should also assess the usefulness and efficacy of complementary bottom-up approaches (i.e., from body to mind, as for example body-focused therapies, polyvagal approach). It might be valuable to investigate whether assessments of the specific clinical outcomes of the diverse mechanisms described in this review might allow for more personalized therapeutic approaches in FM. Last but not least, the efficacy and optimal design of personally tailored mind-body interventions deserve exploration.

6. Conclusion

Despite all advances in research, FM remains a challenging condition not only in how it is operationalized and understood by different researchers and health professionals but also in its treatment. We believe this is in part due to the inherent complexity, multidimensionality, and heterogeneity that characterizes FM and by the lack of a comprehensive framework that integrates current knowledge on the risk and protective factors at play and how they influence FM development, expression, and course. This complexity can be addressed only by adopting a multi-level, out-of-the-box viewpoint, where findings from different disciplines and approaches are brought together and integrated coherently.

This overview of the most relevant observations and their mutual influences in FM indicates how this condition can be generated and maintained by the dynamic interplay between multiple systems and processes (see Fig. 1). We brought together the most relevant and consistent observations from the neurobiological and the psychosocial fields, embracing the inherent complexity and complementarity of these hereunto artificially separated fields. It is crucial to identify and explore the many dynamic interconnections among multiple systems and mechanisms known to be altered in FM and how these same systems are modulated by individuals' genetic makeup, environmental stressors, and individual differences. Only by doing this can we truly gain a more in-depth understanding of FM and foster the development of needed interventions for this disabling condition.

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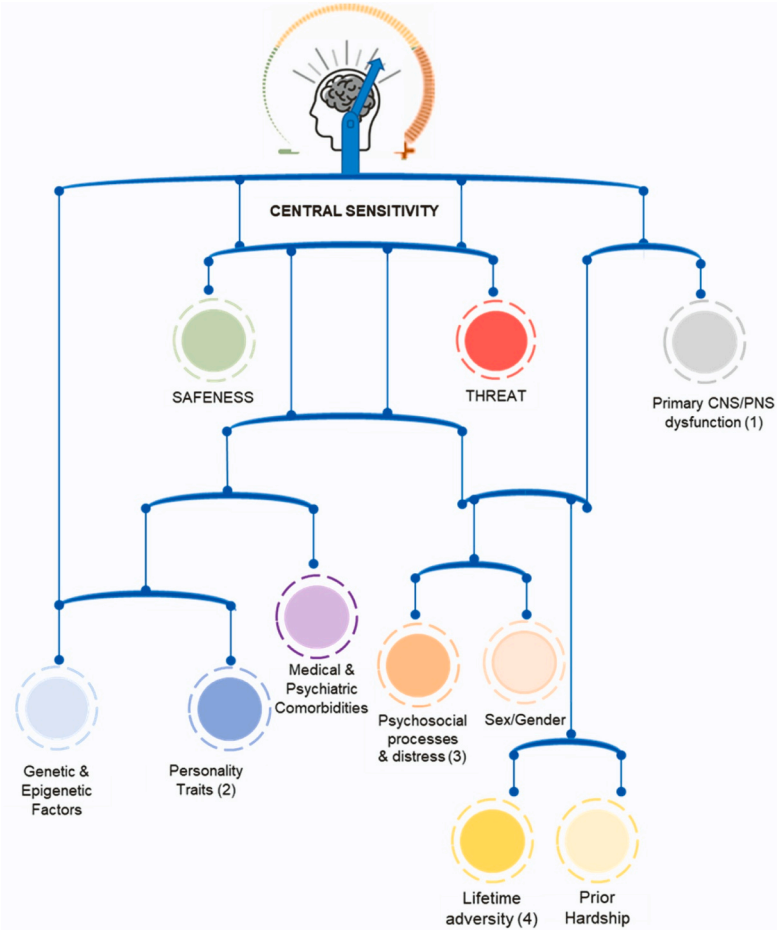

Fig. 1. Summary of the main mechanisms and processes involved in FM. The dynamic and complex interplay among mechanisms of different natures in FM may be compared to a "hanging toy", where all mechanisms are interconnected, and changes in a given mechanism induce a cascade of alterations among all others mechanisms. Note. CNS = central nervous system; PNS = peripheral nervous system; HPA axis = Hypothalamic–pituitary–adrenal axis; ANS = autonomic nervous system.

scope of this work.

Data Availability

No data was used for the research described in the article.

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