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Perspective

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# Emotion regulation and the salience network: a hypothetical integrative model of fibromyalgia

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## Abstract

Fibromyalgia is characterized by widespread pain, fatigue, sleep disturbances and other symptoms, and has a substantial socioeconomic impact. Current biomedical and psychosocial treatments are unsatisfactory for many patients, and treatment progress has been hindered by the lack of a clear understanding of the pathogenesis of fibromyalgia. We present here a model of fibromyalgia that integrates current psychosocial and neurophysiological observations. We propose that an imbalance in emotion regulation, reflected by an overactive 'threat' system and underactive 'soothing' system, might keep the 'salience network' (also known as the midcingulo-insular network) in continuous alert mode, and this hyperactivation, in conjunction with other mechanisms, contributes to fibromyalgia. This proposed integrative model, which we term the Fibromyalgia: Imbalance of Threat and Soothing Systems (FITSS) model, should be viewed as a working hypothesis with limited supporting evidence available. We hope, however, that this model will shed new light on existing psychosocial and biological observations, and inspire future research to address the many gaps in our knowledge about fibromyalgia, ultimately stimulating the development of novel therapeutic interventions.

## Sections



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## Introduction

Fibromyalgia remains a challenging condition from both the clinical and basic science perspectives. Neurocentric and mechanistic approaches to the study of fibromyalgia have focused on central sensitization and have made considerable progress in explaining some of the features of fibromyalgia[1]. Research on the psychosocial aspects of fibromyalgia, however, have followed an independent path. Both the neurophysiological and psychosocial fields have been authoritatively reviewed[2–4], but the potential complementarity and integration of these paradigms have rarely been explored. No biomarker has yet been adopted as a diagnostic criterion, and the origins and significance of the observed biological alterations remain mostly unknown, except for the potential roles of genetic predisposition and environmental influences[5,6]. At the same time, psychosocial research generally lacks specificity for fibromyalgia, and the associations between psychological factors and the neurophysiological abnormalities found in fibromyalgia are often unclear. Thus, there is currently no robust integrative model of fibromyalgia, which hampers basic research, the development of effective interventions, and the ability of health professionals to understand and manage this complex condition. As a consequence, health professionals and patients might rely too heavily on pharmacological approaches, which are only modestly effective, having small-to-moderate effect sizes[7,8].

The goal of this article is to review and integrate the predominant observations in the different fields of research regarding the pathogenesis of fibromyalgia. Our proposed model should be viewed as exploratory and hypothetical, given the gaps in current knowledge and limitations of available research. Nonetheless, we hope that this model will prompt and illuminate future research, thereby generating useful hypotheses and explanations by the scientific community. We start by summarizing an extensive review of the current pathophysiological perspectives on fibromyalgia conducted as a basis for this work. We then propose a novel model that integrates psychosocial and neurophysiological observations, capturing the dynamic interplay and mutual influences between these two domains of inquiry in fibromyalgia. We hypothesize that fibromyalgia is the reflection of a hyperactive 'salience network', a network involved in the detection of relevant and/or salient stimuli, resulting from an imbalance between an overactive threat-handling system and a deficient soothing-affiliative system. The word 'threat' is used to refer to contexts or cues, which can be social or non-social and internal or external, that are perceived as potentially dangerous, harmful, or barriers to desired goals, and that motivate defensive action[9,10]. The opposite applies to 'soothing', by which the individual experiences a state of contentment and safeness that favours engagement in resting, affiliative, or explorative behaviours[10]. This emotion-regulation imbalance might work as a priming factor — a favourable terrain for the development of fibromyalgia — or could be a consequence of pre-existing pain-regulation disturbances, prior experience of chronic pain, inflammatory conditions, or sleep disturbances, among other causes. Whatever the origins of affect and pain dysregulation, this interplay between psychological factors and the brain's salience network seems to provide a suitable explanation for many biological, psycho-social and clinical features of fibromyalgia and related syndromes. Furthermore, we explore the possibility that similar mechanisms are shared by the many central sensitivity syndromes, which have a wide variety of phenotypes.

The hypothesized model, which we term the Fibromyalgia: Imbalance of Threat and Soothing Systems model, has many clinical and research implications. By embracing this complexity and integration, we aim to provide a framework that helps clinicians to better understand and empathize with their patients, while inspiring researchers to embrace deeper explorations of the mechanisms underlying fibromyalgia. We hope that this model eventually leads to advances in current treatment strategies and the development of novel ones.

## A leading model of fibromyalgia

Before presenting our hypothesized integrative model, we provide here an overview of the processes widely recognized and accepted to be factors in the pathogenesis of fibromyalgia. The current perspective is depicted in Fig. 1 (adapted from Häuser et al.[3] and briefly summarized in this section); more information on the processes involved can be found in wide-scope reviews[3,4,11–13] and in a comprehensive review we performed as the first step in the development of the integrative model presented herein[14].

A widely accepted model of the various pathophysiological processes in fibromyalgia views fibromyalgia as a nociplastic pain condition with many features of central sensitization, in which innocuous stimuli or normally painful stimuli are perceived as (more) painful, and in which various factors have a modulatory role, including peripheral (inflammatory) and central (cognitive–emotional) mechanisms[4]. Some symptoms, such as fatigue or sleep impairment, that are common in fibromyalgia, can also reflect central sensitization[13].

Genetic predisposition is recognized to have a role in fibromyalgia, accounting for 48–54% of the individual variation in the likelihood of developing chronic widespread pain[15]. Most of the identified polymorphisms are related to the various neurotransmitters and receptors of the central nervous system (CNS) and can influence a variety of the mechanisms involved in fibromyalgia, including but not limited to emotion and pain regulation (reviewed elsewhere[16,17]). Within the past few years, a potential role for epigenetic dysregulation in fibromyalgia has also been proposed[18].

It has been proposed that fibromyalgia should be considered as part of the spectrum of 'chronic overlapping pain conditions' (COPCs), a term that brings together numerous painful conditions characterized by the absence of known peripheral lesions that could explain the symptoms and by high levels of co-occurrence[19–21]. Many, but not all, people with fibromyalgia have or develop other COPCs[22]. Likewise, 2% to 80% of patients with other COPCs present fibromyalgia[22]. The International Classification of Diseases-11 now classifies most of these conditions as 'chronic primary pain', a new major category comprising five subtypes that reflect the distinct anatomical sites or body systems affected by pain[23]. Fibromyalgia belongs to the 'chronic widespread pain' subtype; the other four are complex regional pain syndrome, chronic primary headache or orofacial pain, chronic primary visceral pain, and chronic primary musculoskeletal pain.

An even wider scope emerges when the broader overarching concept of central sensitivity syndromes is considered[24]. Central sensitivity syndromes comprise most COPCs as well as conditions not primarily typified by pain, such as periodic limb movement in sleep, multiple chemical sensitivity, female urethral syndrome and post-traumatic stress disorder[24] (see Fig. 2). All these conditions share evidence of central sensitivity and, to a lesser extent, similar neurotransmitter imbalance. They all show small-to-moderate response to serotonin-norepinephrine reuptake inhibitors and other centrally acting agents (for example, gabapentinoids) and little to no response to NSAIDs and opioids. These central sensitivity syndromes are frequently comorbid, are more common in women than in men, have a high prevalence of stress-related manifestations and psychopathology, and are associated with high sensitivity to daily and chronic stressors and increased sensitivity to everyday environmental sensory stimuli[24].

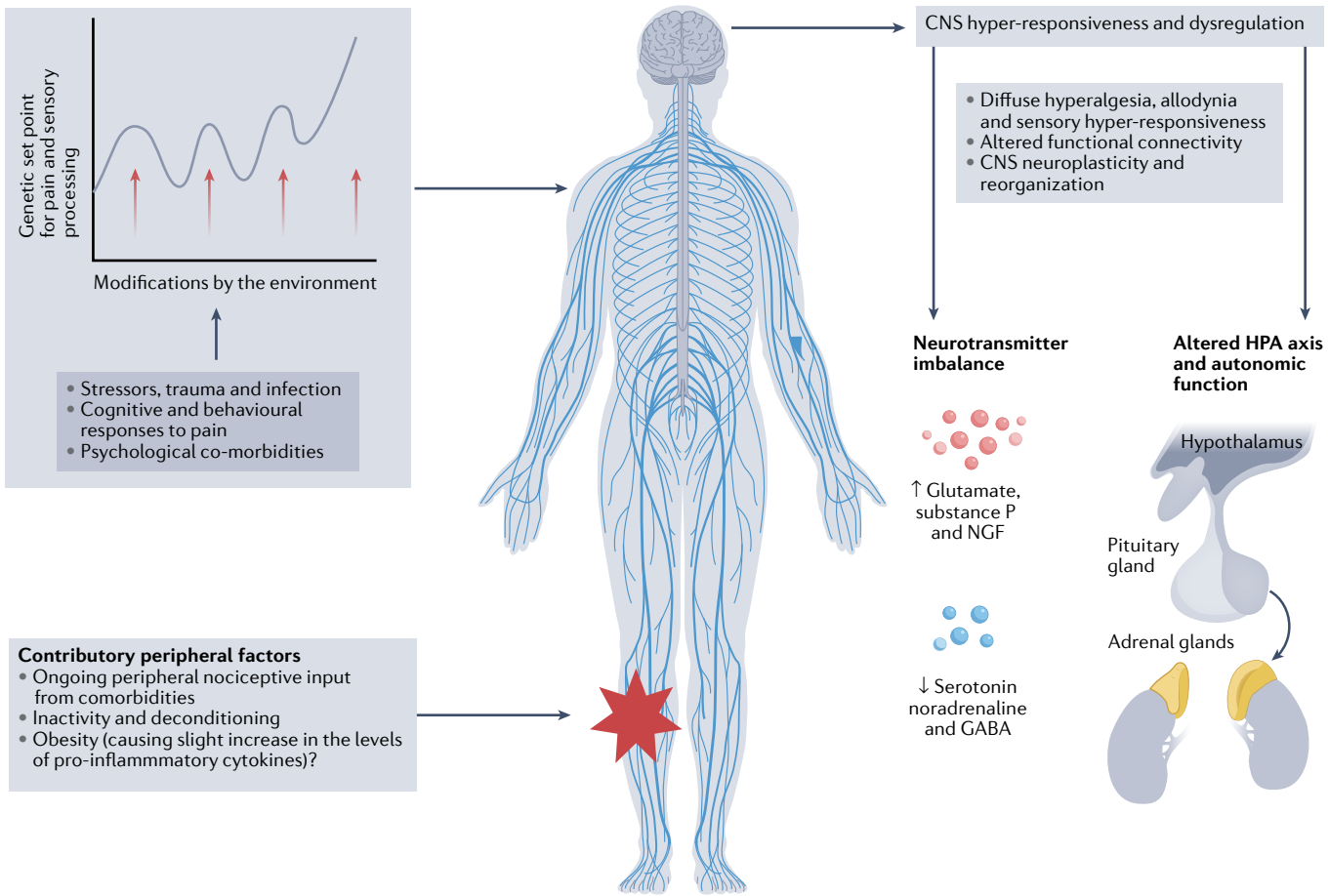


**Fig. 1 | Potential pathophysiological processes in fibromyalgia.** Sensitization of the central nervous system (CNS) has been suggested as one of the main pathophysiological changes underlying fibromyalgia[11]. The genetic set point for sensory (including pain) regulation can be modified by psychological factors, such as anxiety, depression and catastrophizing, as well as biopsychosocial stress (for example, trauma, childhood adversities, major life events or infections). Peripheral factors, such as ongoing nociceptive input produced by co-morbidities, can also affect pathogenesis. In the CNS, several changes can be noted, including neurotransmitter imbalances, altered functional connectivity and changes in the hypothalamic–pituitary–adrenal (HPA) axis, which influence the autonomic system. Red arrows represent stressors. GABA, γ-aminobutyric acid; NGF, nerve growth factor. Adapted from ref.[3], Springer Nature Limited.

According to Yunus[24], a sensitized brain is the common foundation of fibromyalgia and related central sensitivity syndromes (Fig. 2). Among many other experts, Melzack[25,26] and Apkarian et al.[27] note that the perception of painful stimuli does not result solely from the brain's passive registration of tissue trauma but also from its active generation of subjective experience through a widely distributed neural network that subserves the sensory-discriminative, affective-motivational, and evaluative-cognitive dimensions of pain.

## Development of a new model

Guided by an original clinical hypothesis generated by author J.A.P.S., which highlighted the perception and cross-amplification of threat in fibromyalgia, we drafted a conceptual map to identify intermediate questions, of a narrower scope, suitable to guide focused literature searches in PubMed and Google Scholar. The hypothesis, conceptual map and guiding questions were repeatedly refined on the basis of the results obtained and recurrent discussions among the core research group (A.M.P., J.A.P.S., R.G. and J.W.G.J.). These discussions coalesced into an integrated comprehensive model, which was further fine-tuned by continued searches of the literature and repeated rounds of consultation with distinguished experts in the field, who became co-authors. We included experts from both the psychosocial and the neurobiological fields of fibromyalgia research. The final document and hypothetical model resulted from several rounds of consensus among all authors. The FITSS model is built upon three major pillars: first, heightened threat is a predominant feature of fibromyalgia; second, the soothing-affiliative system is hypoactive in fibromyalgia; and third, this imbalance persistently activates the brain's salience network, with consequent cross-amplification of negative input, including, but not limited to, pain. Evidence supporting these pillars and their interplay is presented in the following sections.

## Pillar 1: heightened threat

Numerous lines of evidence support the concept that people with fibromyalgia endure increased levels of distress in daily living and have been more frequently exposed to stressful life events in the past than

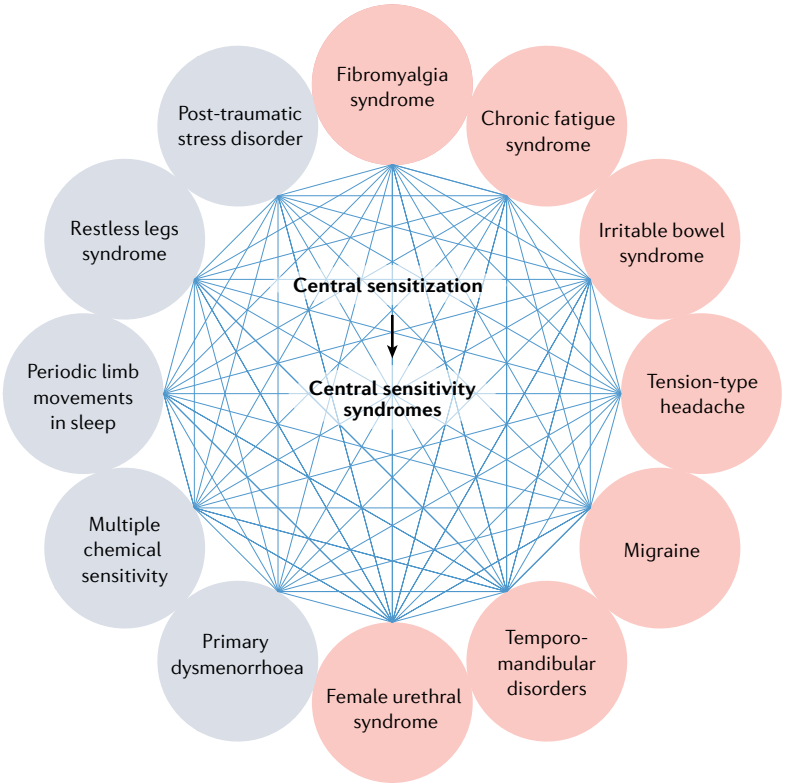


**Fig. 2 | Central sensitivity syndromes and chronic overlapping pain conditions.** Diagram of the conditions belonging to central sensitivity syndromes according to Yunus[24] and conditions classified as chronic overlapping pain conditions by Veasley[22] (shaded in pink). The diagram is aimed at illustrating the overlapping nature of many central sensitivity syndromes and chronic overlapping pain conditions and the putative role of central sensitization as the common underlying pathophysiological mechanism.

have healthy individuals. The Generalized Unsafety Theory of Stress postulates that the interaction of three domains — bodily state, social context and stress-related contexts — could lead to a generalized perception of unsafety, which activates the default stress response[28,29]. All three of these domains are operative in fibromyalgia.

## Compromised domains, unsafety and stress

The body of people with fibromyalgia provides numerous signals that could be perceived as threatening (for example, widespread pain, fatigue or multisensory hypersensitivity) and that could explain the aberrant autonomic functioning reported in fibromyalgia[30]. Of note, findings regarding the nature of this autonomic dysregulation are contradictory, with some studies showing a reduction of sympathetic activity[31,32] but others pointing to a sympathetic overdrive[30,33,34]. Studies have also found reduced parasympathetic tone (with a disrupted sympathovagal balance that compromises the flexibility of the autonomic response to stressors), blunted sympathetic reactivity to stressors, and impaired baroreflex function (which impairs baroreflex antinociceptive action)[31,32,35].

Acute or chronic stress might augment and fuel these threat signals, as suggested by preclinical and observational studies[36–38], resulting in a vicious circle. It should be noted, however, that longitudinal studies addressing the dynamic interactions within a threat network of somatic symptoms, sympathetic nervous system activity, and stress in fibromyalgia are lacking. According to the Generalized Unsafety Theory of Stress[29], physical vulnerability, such as that associated with ageing, obesity, or pain, might contribute to a generalized, although frequently unconscious, sense of unsafety. Pre-morbid or concomitant diseases, such as chronic systemic inflammatory conditions or other forms of chronic pain, can be expected to have similar effects.

Aberrant interoception — the representation of internal bodily states — might have a role in perceiving the body as threatening. Interoception and external sensory information are integrated and modulated at the insula by top-down processes[39,40]. Despite inconsistent findings[41,42], some studies point to disturbed interoception in people with fibromyalgia[43,44].

The social context of people with fibromyalgia has been characterized by high levels of loneliness[45], perceived invalidation (that is, dismissal of endured suffering) and lack of understanding from others[46–48], which elicit both threat and anger. Interpersonal rejection — whether actual, anticipated or only perceived — and other forms of social disconnection have been shown to increase pain[49–51] and can enhance inflammatory activity[52]. Early experiences with caregivers might account in part for individual variability in the extent to which pain-related circuits are modulated by socially distressing experiences[51]. A similar mechanism has been demonstrated in a study showing that differences in experimentally induced pain across ethnic groups were related to racial discrimination; such negative social experiences were associated with greater activation of brain regions implicated in pain valuation and modulation[53]. The origins and importance of these socially driven biases probably vary widely among people with fibromyalgia but, when present, they can elicit and maintain threat perception and minimize potentially buffering factors. Stigmatization and invalidation from others, including health-care providers, can contribute to strained interpersonal relationships, social exclusion and withdrawal, and constitute a barrier to adequate treatment-seeking and care[54–56].

The third domain relevant to the Generalized Unsafety Theory of Stress, stress-related contexts, refers to contexts that have become

associated with past or current stressors, such as the workplace or home environment. Associations between self-reported life adversity (for example, abuse, traumatic accidents, prolonged illness or combat) and fibromyalgia have long been recognized[57,58]. A 2-year prospective cohort study found that exposure to work-related stressors, including marked workload, low decision latitude and workplace bullying, increased the risk (twofold to fourfold) of later reporting new-onset fibromyalgia, even after adjustment for various sociodemographic, clinical and lifestyle factors[59]. No association was found between occupational stress and other musculoskeletal disorders (such as osteoarthritis and sciatica), suggesting that such work-related stress could be specific to the development of fibromyalgia[59].

In stress-related contexts, the perception of threat can be fed by an unremitting flow of daily concerns, worries and hassles[60–62], derived from the person's inner and outer world. Other personality, cognitive-affective and social factors, such as neuroticism[63], perseverative thinking[60,61], pain catastrophizing[64], unbalanced affect and limited adaptive resources[65–70], as well as unsupportive social environments[46,47], can contribute to minimizing safeness and augment perceptions of threat. A qualitative study of a small group of women with fibromyalgia reported that participants exhibited "signs of a threatening world of experiences"[71]. In an exploratory study of autonomous nervous system (ANS) regulation, patients with temporomandibular joint disorder and fibromyalgia displayed a defensive response pattern when faced with a safe context, as opposed to the engaged pattern observed in healthy individuals[72]. However, the level of distress varies among persons with fibromyalgia and different phases of their lives, as it does in the general population. It is tempting to explore a parallel with the concept of 'fibromyalgianess'; that is, the existence of a degree of fibromyalgia-like symptoms continuously distributed in the general population, which defines fibromyalgia as a condition when it becomes clinically relevant[73–75].

### Perception of threat

The observations reviewed above suggest that many people with fibromyalgia have a hyperactive threat and self-protection system, which is a crucial component of the model of affect regulation systems proposed by Paul Gilbert[10,76]. This tripartite model, comprising threat, drive and soothing systems, builds upon sources ranging from affective neuroscience to evolutionary psychology, and brings together relevant contributions from numerous scholars[76]. Although we, in accordance with Gilbert, refer to a 'threat system', it should be acknowledged that such a system involves a complex network of neuroanatomical structures involved in affect regulation and threat-related processes. The same is true for the other two systems in Gilbert's model, which are subserved by both shared and dedicated biological mechanisms as well as drive and soothing-related variables.

The threat system, which is omnipresent across species, is programmed to detect and evaluate impending threats and promote defensive actions, rapidly and effectively[10,76]. The neurophysiological basis of this system includes limbic structures (amygdala and hypothalamus), the insular cortex and the hypothalamic–pituitary–adrenal axis[77–79]. The perception of threat elicits responses that can be activating (for example, fight, flight or avoidance) or inhibitory (for example, freeze or submission), which are selected and used in a context-dependent manner[9,10]. The threat system is commonly associated with sympathetic activity[80], which is implicated in the fight-or-flight response, although other responses to threat can also engage the parasympathetic nervous system (for example, freeze-or-faint response)[81]. Persistent perceptions of threat might maintain the threat system in a state of (hyper)activation[76]. The role of Pillar 1 is further discussed later in the context of the complex interplays taking place in fibromyalgia.

Of note, the threat system is often deeply and intricately associated with what Gilbert[10,76] refers to as the drive-excitement (or incentive- and resource-seeking) system. This positive affect regulation system incorporates the desire and pursuit of survival-relevant needs, rewards and resources (such as material and financial resources or social status)[82]. The drive system is mediated by neurophysiological structures of the 'reward system', including the nucleus accumbens, sympathetic activity, and multiple neuromodulators that influence pleasure and motivation[10,82], such as dopamine, opioids and cannabinoids[83,84]. The potential role of the drive system in people with fibromyalgia is less clear than the roles of the threat and soothing systems and, therefore, is in need of further study.

## Pillar 2: hypoactive soothing

The soothing, contentment and safeness (or affiliative-focused) system, as conceptualized by Gilbert, is considered an endogenous regulator of threat-related neurophysiological and emotional arousal[10,76,85,86]. The soothing-affiliative system is responsive to caring and affiliative cues[82], and is associated with positive affect states such as equanimity, warmth, kindness, compassion and social connectedness[76]. These systems are also associated with safeness, which is more than just safety. Safety can be seen as the containment of threat, whereas safeness reflects a state of contentment and proneness to exploration-oriented action that ensues when contexts are perceived as safe[10].

The regulatory properties of the soothing-affiliative system are associated with the inhibitory action that neural circuits involving prefrontal regions exert upon subcortical areas[87,88]. Soothing and affiliation also engage neurophysiological mediators such as the parasympathetic nervous system and its 'rest and digest' functions[89], along with neuromodulators such as endorphins and oxytocin[76,82,90]. Oxytocin is implicated in 'tend and befriend' coping responses[91] and in reducing the activation of the amygdala and its coupling to brainstem regions that are implicated in fear response[92]. These soothing-related processes also seem to have a role in pain modulation in a variety of contexts[93,94], including pain downregulation by means of social affective touch[95]. Interestingly, many studies have documented an attenuated parasympathetic cardiac control in patients with fibromyalgia, as indexed by low heart rate variability[33,96].

In contrast to threat recognition, soothing and safeness are not inborn, but rather are learned through the recognition of safety cues, usually during childhood. Some people with fibromyalgia exhibit safety learning deficits, sustained and elevated responses to pain-related threats, overgeneralized pain-related fear and impaired extinction of fear generalization[97–100]. Adverse early-life experiences, especially when recurrent, can hamper safety learning, thus fostering a threat bias[101–103]. Later in life, the presence of actual threat will no longer be required — the mere lack of an effective safety system suffices to trigger threat perception and prompt the associated responses[9,28,29]. This activation can be unconscious, invoking a chronic activation of the stress response even when people are unable to identify a specific stressor[29,104].

Attachment theory[105] is a valuable framework for understanding both normative and individual aspects of the process of affect regulation[106]. Attachment influences brain maturation, has deep connections to the limbic system and ANS, and facilitates the expansion of a child's coping repertoire[107]. Social bonds constitute an important survival

resource and a primary source of both safety and threat signals[29]. Multiple studies offer accounts of the buffering effects of social connection on fear-learning processes[108], threat signalling[109], (dis)stress regulation[110,111] and modulation of subjective and neural responses to pain[112,113]. Stressful early-life experiences are frequently reported by people with fibromyalgia[58,114], as is insecure attachment (for example, avoidant or anxious-ambivalent attachment styles)[115–117]. People with fibromyalgia also frequently report invalidation by others and low social support[45,46,48].

Although causality cannot be established and conflicting findings have been reported[118], some studies have demonstrated an association between early adversity and the development of generalized pain later in life[119–121]. Despite noting caveats such as the lack of control for confounding effects, a 2021 meta-analysis concluded that self-reported exposure to stressful or traumatic events in childhood and adulthood is associated with an increased likelihood of having fibromyalgia later in life[122]. This study also showed that of all types of stressors (including medical trauma), different types of abuse and other lifetime stressors were positively associated with fibromyalgia, and physical abuse was the strongest predictor, increasing the risk of having fibromyalgia by more than threefold[122]. Such clinical studies are buttressed by basic research. For example, healthy college students in the top 5% of self-reported childhood adversity showed elevated levels of central sensitization as measured by quantitative sensory testing[123]. Similar findings were observed in a study involving a large community sample of Native American and non-Hispanic white individuals: lifetime adversity (that is, number of traumatic events) showed a dose-dependent relationship with a neurophysiological marker of central sensitization, even after controlling for demographics, mood and psychological symptoms[124]. Subsequent analyses on the same cohort showed that exposure to adversity was also associated with an impaired neurophysiological marker of descending inhibition of spinal nociception[125].

Research has consistently shown that, in addition to elevated levels of negative affect, fibromyalgia is characterized by low levels of positive emotions[65,67,68], which could be linked to a lack of soothing. Individuals with fibromyalgia also classify positive stimuli as less arousing and as less pleasant and intense during experimentally induced pain[126,127] compared with patients with RA and with healthy individuals, which seems to indicate a disruption of the reward system[128] and potentially of the soothing-affiliative system.

Of course, some people with fibromyalgia have secure attachments and some have not experienced early-life adversity or stressful social environments. However, insecure attachments or adversity, if present, can have long-term detrimental effects and constitute one of many potential vulnerability factors. Once established, the imbalance between threat and soothing might feed hypervigilance to, and amplification of, other potential alarm signals, as well as ruminative and anticipatory processes, thus 'refuelling' the system and increasing the perception of threat and unsafety[29,104] (Fig. 3).

Different neurodevelopmental trajectories can result in variations in the pattern of activation and co-regulation of the three affect regulation systems described earlier, namely threat, drive and soothing. Genetic predisposition, contextual variability and early life experiences are just some of the factors deemed capable of determining the intrinsic details and dynamic nature of the balance in affect regulation[10,101,129,130]. The range of their combinations reflects the heterogeneity among people with fibromyalgia and influences the relevance of elevated threat and poor soothing in any individual person.

## Pillar 3: the salience network

The brain's salience network identifies and manages salience — a general concept that encompasses prominent, striking or unusual features in both the internal and external environments. Of particular relevance to the FITSS model is that the salience network also gauges the potential threat-value of any neural input, whatever its nature: painful, tactile, auditory, visual, olfactory, proprioceptive, biochemical, cognitive or emotional[131,132]. This network is sensitive to brain changes induced by real or imagined threats[133]. It also seems to have a role in pain processing, being part of the neurological signature of physical pain[134]. The salience network thus operates as a multimodal 'central alarm', a concept that makes sense from an evolutionary point of view, as it serves the crucial objective of survival. This network is also responsible for filtering signals and bringing them to awareness in the neocortex[132,135], triggering a cascade of cognitive relays that affect how the signals are appraised and consciously perceived, interpreted and managed[136]. The salience network has also been implicated in responses to disease states; for example, cytokines derived from inflammation decrease motivation and motor activity (sickness behaviour), whereas activation of the midcingulo-insular pathways induces a hyper-alert status. Both of these responses subserve survival[137].

### Salience network architecture

The insula, together with the anterior cingulate cortex (ACC), the prefrontal cortex and the periaqueductal grey, is a core structure of the salience network[131,138,139]. A universal taxonomy of large-scale brain networks proposed in 2019 suggests that the salience network should preferably be designated as the midcingulo-insular network (M-CIN)[139]. These structures are also central to the neurophysiological signature of fibromyalgia[140].

Multiple studies across laboratories have shown that fibromyalgia is associated with abnormalities involving the salience network/M-CIN and its relationship with other primary and secondary sensory areas and regions of the default mode network (DMN; involved in basic brain activity in resting mode, which has been associated with mind-wandering and self-referential processes)[141]. These studies report the following: responses to pain in the salience network are augmented and longer-lasting in people with fibromyalgia[142–144]; responses to other sensory and emotional stimuli are greater in parts of the network such as the insula/operculum and posterior cingulate (compared with age- and sex-matched healthy controls)[140,145,146]; excitatory glutamatergic activity is augmented in the insula of patients with fibromyalgia[147,148]; activity in the salience network in response to non-painful multisensory stimuli is augmented in fibromyalgia[145,146,149], even when responses in primary sensory cortices are attenuated[145]; and connectivity within and between the salience network/M-CIN and the DMN is augmented in fibromyalgia[149–154]. These findings indicate that the mutual influence between this multimodal central alarm system and a system more traditionally associated with processing of self-referential, social cues and assigning value to emotional stimuli is increased in the context of fibromyalgia.

A neurophysiological pattern of CNS activation consisting of neural hypoactivity in regions associated with sensory processing (primary and secondary sensory cortices, basal ganglia and cerebellum) and hyperactivity of regions involved in multimodal integration (insula, operculum and posterior cingulate cortex) and self-referential processes (medial prefrontal region) was found to discriminate people with fibromyalgia from matched healthy individuals (sensitivity 84%, specificity 94%)[140].

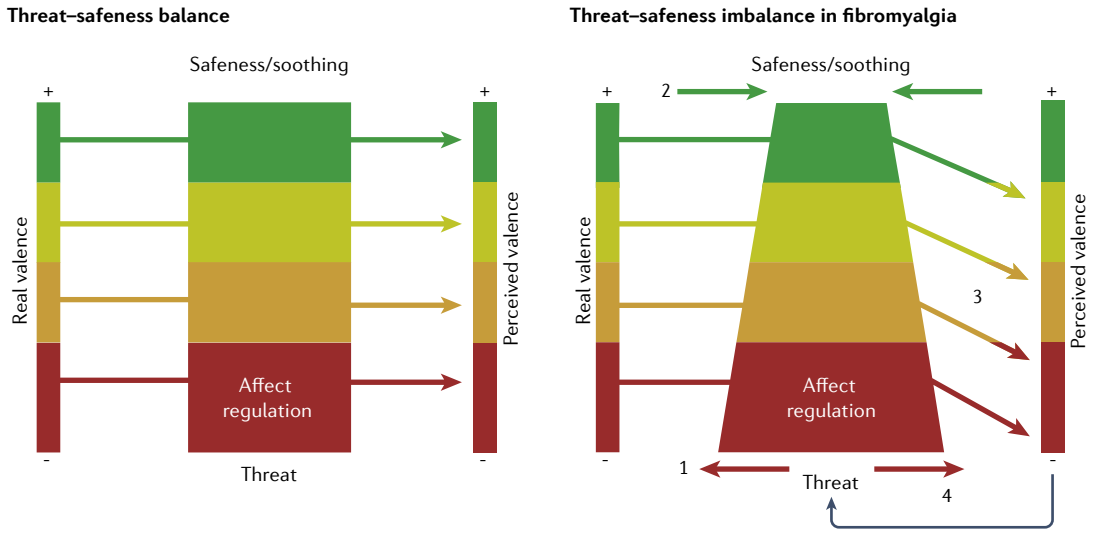


**Fig. 3 | The threat–safeness (im)balance model of fibromyalgia. a**, In the normal situation, the threat–safeness perception is in balance. The systems can be viewed as working like a glass filter between reality (left side) and its perception by the individual (right side). **b**, Imbalance of the threat–safeness perception. We propose that in fibromyalgia, once the imbalance is crystalized, threat becomes overactive (1), whereas the effectiveness of safeness and soothing mechanisms decreases (2). The imbalanced systems work like a prism, deviating the signals to a more negative tone (3). This mechanism will affect all signals, irrespective of their nature: pain is amplified, moderately pleasant noises become unpleasant, soothing attempts by others may be interpreted as aversive and negative events may be sensed as catastrophic. The negative experienced signals will shape the tone of the salience network into a more threat-focused mode, thus reinforcing the paradigm of a threatening world and feeding a vicious self-perpetuating circle of general alarm status and distress (4).

The anatomical overlap with the structures proposed in Gilbert's model to serve the threat system is not surprising. The insula is an important contributor to the management of executive function and decision-making tasks[155], whereas the ACC is a network convergence zone that is critical for decision-making, based on the integration of the diverse relevant parameters and error estimation[156–158]. A meta-analysis identified amygdalar and insular hyperactivation as neural correlates of an exaggerated fear response, a feature shared among different anxiety disorders, which can also be found in fear-conditioning studies with healthy people[159].

The core structures of the salience network have rich interconnections throughout the CNS, ANS and peripheral nervous system, enabling their participation in complex neural and biological functions, from emotion processing and memory to cardiac, digestive and immunological functions[160,161]. Information from the external milieu (for example, sensory data) enters the insula through direct thalamic and neocortical afferents, where interoceptive (biological and visceral) information, conveyed through the ANS, also reaches the cortex. This process facilitates multimodal integration, enabling the perception of a stimulus to be construed and modified by information from different sources and natures (varying from purely sensorial to cognitive and emotional) and conveyed through different afferents[162]. The functional modulation of this region enables weighting of information stemming from the salience network/M-CIN, shifts the focus of attention, holds pain information in working memory and allows access to the motor system if escape or defence seems important[163]. Perceived social rejection, which is a prototype of social pain, incites the salience network/M-CIN to respond to self-relevant and highly salient cognitive stimuli that are not nociceptive in nature[164]. Again, the insular and cingulate cortices seem to be the most relevant structures[164–166], suggesting that they probably influence behavioural choices.

The salience network/M-CIN is also implicated in the central control of autonomic processing and activity, particularly sympathetic regulation[167]. A series of studies demonstrated the involvement of the salience network/M-CIN in autonomic responses to social threats, via a cortical-subcortical pathway comprising the pregenual ACC and the thalamus[168,169]. Besides interfering with the regulation of internal responses, (social) threats also interfere with the perception of viscerosensory information, which contribute to the maintenance or generation of further threat signals and appraisals[170]. The concept of an integrated neurovisceral system overlapping with cognition and emotion regulation circuits has been outlined by previous frameworks such as the Neurovisceral Integration Model[171,172]. This model conceives heart rate variability as an indicator of central–peripheral neural network interactions and integration of the CNS and ANS[171]. According to this model, higher levels of heart rate variability reflect an effective top-down cortical control of sympathoexcitatory subcortical circuits and consequent modulation of cardiac activity, and are associated with positive self-regulation. Low heart rate variability, by contrast, reflects blunted prefrontal cortical regulation, resulting in overactivation of sympathoexcitatory subcortical circuits that tends to translate into protracted defensive responses, including increased threat processing (for example, hypervigilance) and dysfunctional (self)-regulation (for example, perseverative thinking)[171–173].

The profuse cross-modal interconnection of the structures involved in the brain salience network provides the grounds for one of our main hypotheses: afferent signals – either sensory or emotional – if perceived as potential threats, will amplify each other in the salience network/M-CIN, augmenting the sense of threat and fostering an early response as well as increasing the probability of survival.

It has been recognized that most brain responses to noxious stimuli result from multimodal neural activity[174], irrespective of the sensory

modality involved, rather than from a specific response of structures exclusively dedicated to nociception. This multimodality probably becomes more relevant as pain evolves from acute to chronic, and the process of pain modulation progressively engages the limbic-cortical circuitry involved in emotional memory formation, motivation and distortion of perception[175]. Multisensory amplification has recently been proposed as a potential endophenotypic feature of conditions characterized by top-down central sensitization, of which fibromyalgia is a prime example[13]. The neural populations representing pain and emotion in salience network regions such as the anterior midcingulate cortex, probably communicate with each other but are not identical[176]. The anterior midcingulate cortex seems to operate as a motivational and autonomic hub in which pain and emotion systems converge and interact, allowing for cross-sensitization[176–178].

### Other neurobiological correlates

The dorsal anterior insula acts as a coordinator of brain networks regulated by the salience network/M-CIN, including the DMN, which is involved in self-related and social cognitive functions[179], and the central executive network (CEN), which is involved in the maintenance and manipulation of information as well as decision-making[155,180,181]. Such coordination is critical because the DMN and CEN support contrasting internally directed and externally directed modes of cognition, respectively. These processes could explain why abnormal salience detection can concomitantly affect attentional and internal affective processing. A hyperactive salience network/M-CIN is expected to enhance the activity of the DMN and often activate the CEN[150]. Metaphorically speaking, in the context of ongoing threat, sentinels cannot fall asleep, and alarms must be kept operative and answered. Enhanced connectivity among the DMN, CEN and insula has been demonstrated in fibromyalgia[150,154]. The ventromedial prefrontal cortex, one of the hubs of the DMN, has been associated with parasympathetic activity[173] and safety signals in threat-conditioning studies[182], generally attenuating the experience of pain in healthy people[183]. Interestingly, however, ventromedial prefrontal cortex activity is associated with more pain in fibromyalgia[140], as well as in other chronic pain conditions[184,185]. Changes in these large-scale brain networks might help to explain spontaneous chronic pain[150,186,187], cognitive impairment[150], sleep disturbances[188,189], repetitive negative thinking (such as rumination)[190,191], neuroticism[192] and emotional disorders[132], which are symptoms and processes frequently observed in fibromyalgia.

In addition, dysfunction of the opioid system has been proposed to be important in the pathophysiology of fibromyalgia[193] and could explain the mechanisms underlying several aspects of the integrative model presented here. First, opioids have a role in the regulation of the salience network[194]; second, the anxiolytic and sedative effects of opioids would have threat-reducing effects; third, opioids enhance hedonistic feelings and mediate adaptive responses to social disruption[195], which would enhance the soothing-affiliative system; and fourth, opioids are well-known to have analgesic effects. Following exposure to painful stimuli, patients with fibromyalgia fail to activate the rostral ACC (rACC), a primary link in the descending pain regulatory system and a region rich in μ-opioid receptors (MORs)[196]. Furthermore, a reduced pain-related functional connectivity between the rACC and other parts of the descending pain inhibitory system, including the periaqueductal grey, has been reported in fibromyalgia[197]. The weaker pain-related activation of rACC in people with fibromyalgia was associated with a lower MOR binding potential and with higher ratings of pain affect[193]. Furthermore, individuals with fibromyalgia with a longer disease duration exhibited more pronounced functional and structural rACC aberrations, suggesting a role for the rACC in the development of fibromyalgia symptoms[198]. Schrepf et al.[193] suggested a model of affective pain dysregulation in fibromyalgia whereby initially high levels of tonic endogenous opioids[199] lead to downregulation of MORs, resulting in dysfunctional descending pain inhibition. Given that the pain and the reward and salience systems are closely integrated and both are involved in the regulation of stress[195], an analogous mechanism could also be envisioned for stress-induced conditions. Hypothetically, various psychosocial stressors would initially trigger an elevated endogenous opioid tone, as an attempt to restore homeostasis[195], with prolonged stress leading to a downregulation of MORs and dysfunctional endogenous opioid signalling. Therefore, hypothetically, the dysregulation of endogenous opioid systems in fibromyalgia could be regarded as a common pathway for the development of pain and/or stress-induced cerebral aberrations that is important for maintaining fibromyalgia symptoms. These mechanisms would also explain the lack of efficacy of opioids in the treatment of fibromyalgia[200].

Small nerve fibre pathology has been pointed out as a potential source of peripheral nociceptive input in patients with fibromyalgia, challenging the primary role of central sensitization. This phenomenon is observed in approximately 50% of people with fibromyalgia according to a 2018 meta-analysis[201]. However, the results of a preclinical study suggested that small-fibre pathology can be driven by a top-down mechanism, induced by increased glutamate transmission (activation) in the posterior insula[202].

## Integration of the three pillars

In this section, we discuss the integration of the three pillars and mechanisms into a bridging model of fibromyalgia (Fig. 4).

### The vicious circle maintaining fibromyalgia

Integrating the observations discussed earlier, we hypothesize that the imbalance between augmented threat-perception and blunted soothing-affiliative systems could have a role in the processes leading to the development or maintenance of fibromyalgia in a considerable proportion of individuals. We acknowledge that this hypothesis is not completely novel, given that stress has long been suggested as a driver of fibromyalgia[33,203–205]. Similar hypotheses have been put forth regarding central sensitization[206], chronic pain[207–210] and some COPCs, including fibromyalgia[211]. The idea that a (neurochemical) dysregulation at the insula might be implicated in many fibromyalgia symptoms beyond pain has also been recently proposed[212].

What is novel, however, is our proposal that the imbalance in the affect-regulation systems, which results in an emotional 'negative filter', might operate as a persistent activator of the salience network/M-CIN, and this activation could mediate many of the manifestations and putative pathogenic mechanisms observed in fibromyalgia, with an emphasis on the central amplification of pain. The salience network/M-CIN is in a strategic position to embody the 'defective volume control setting' proposed by Clauw et al.[5] as the source of pain amplification in fibromyalgia and perhaps also in other COPCs and central sensitivity syndromes.

This emotional negative filter might be a primary triggering factor in some people with fibromyalgia, or in others it might emerge as a consequence of primary pain disturbances or other chronic conditions. In either case, once established, this threat-focused processing is hypothesized to provide a continuous influx of negative valence, keeping the salience network in overdrive and promoting central sensitization of all sorts of threatening inputs — foremost pain and potentially painful

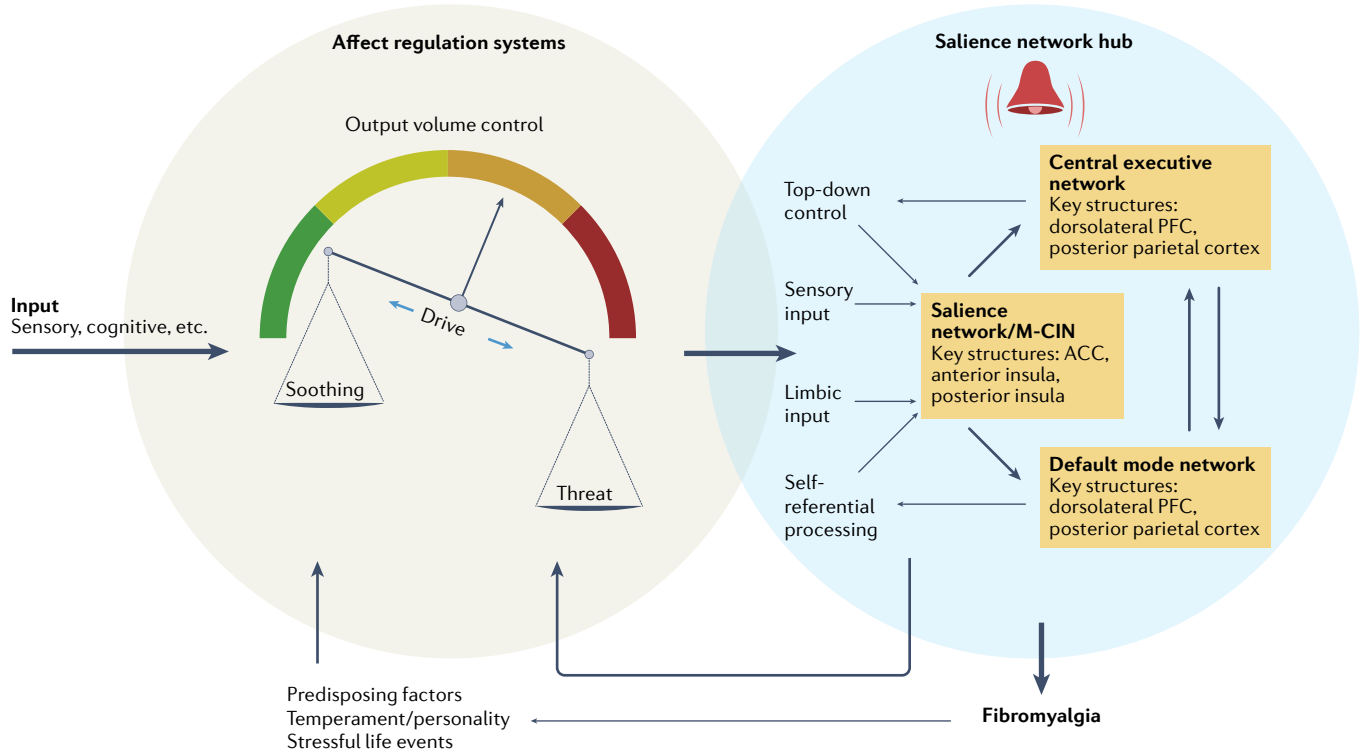


**Fig. 4 | An integrative model of fibromyalgia.** We suggest that fibromyalgia is influenced by an imbalance of the affect regulation systems – hyperactive threat and hypoactive soothing systems – and propose the Fibromyalgia: Imbalance of Threat and Soothing Systems (FITSS) model. This imbalance can be driven by biological predisposing factors, concomitant pain conditions, stressful and/or traumatic experiences and conditioning (learning) patterns. The imbalance imprints a negative bias to incoming stimuli, cross-amplifies different types of adverse cues and provides a continuous source of potentially threatening signals to the salience network/midcingulo-insular network (M-CIN), which acts as a multimodal 'central alarm' system, resulting in persistent activation of the fight-or-flight response. This over-activation is proposed to elicit the biological responses underlying fibromyalgia symptoms and feeds back into the negative imbalance of emotion regulation. Most neuroanatomical structures depicted as part of the salience network/M-CIN hub in this figure have been described as affected in the neurophysiological signature of fibromyalgia[140]. Numerous neurophysiological observations, including the reduced integration of non-painful stimuli and their inhibitory effects on the salience network[151] and the dysregulation of the opioid system[193], might have a role in the processes leading to pain amplification. ACC, anterior cingulate cortex; PFC, pre-frontal cortex.

stimuli but also other sensory signals as well as bodily and emotional cues, thereby boosting and expanding the negative vicious circle[13,132,135]. Post-traumatic stress disorder is the prototypical condition associated with hyperactivity of the salience network/M-CIN[213]. It is frequently comorbid with fibromyalgia and the two conditions share a variety of common clinical and neurobiological features[214,215]. This lends support to our proposal. In fact, chronic stress and other negative emotional states have been shown to increase pain sensitivity[38,216] and the perception of smells as unpleasant[217], again underscoring the potential for cross-amplification. In fibromyalgia, pain has been shown to be influenced by complex cognitive processes, including the perception of pain-related threat[97–99]. An experimental functional MRI study found that healthy individuals had diminished activation of the anterior insula when pain stimuli were less intense than expected, whereas people with fibromyalgia maintained activation and displayed increased responses to pain-related threats. This activation was associated with higher ratings of pain catastrophizing, indicative of a 'better-safe-than-sorry' strategy in response to pain[100].

Chronic pain has been described by Vachon-Presseau et al. as "a complex web of sensory and emotional experiences, coupled with behavioural adaptations", with pain and affective states being controlled by largely overlapping brain circuitries[185]. These researchers also noted that an increase in the nociceptive value attributed to afferent information is established and maintained by emotional memories elaborated in the corticolimbic circuitry. This augmented valuation drives cortical reorganization, given that pain becomes more emotional, resulting in distorted perception and decision making. Although the work of this research group has been focused on chronic pain conditions other than fibromyalgia, their insights seem to align harmoniously with the observations described above and with the model proposed.

The output of the hyperactive salience network/M-CIN can be quite varied, given its many connections. The output could result in one of the diverse phenotypes seen within fibromyalgia, COPCs, or the central sensitivity syndrome spectrum. We hypothesize that hyperactivation of the salience network/M-CIN, whatever its biological or psychosocial origin, might be the common root – the 'matrix' bringing together these clinically diverse phenotypes. This common mechanism would explain why these conditions share a high level of co-occurrence and clinical overlap, despite differing in their systemic nature and the

presence, distribution and centrality of pain. This mechanism might also explain other features shared by many of these conditions: the predominant negative affect tone, the tendency towards anxiety and depression, and the favourable response to some antidepressants as opposed to opioids.

### Integrating paradigms

The model proposed here brings together and integrates harmoniously the main paradigms previously proposed. The models that envisage stress as the primary cause of fibromyalgia, championed by van Houdenhove and Egle[203], Martinez-Lavin[204] and Lyon et al.[205], are represented in our proposed model by the importance given to the threat–soothing imbalance. The involvement of the ANS, highlighted in some paradigms[33,211,218], is considered in our model as both a cause and a consequence of salience network/M-CIN hyperactivation. The paradigms that place central sensitization in the driving seat of fibromyalgia are reconciled in the role attributed, in our model, to the core hubs of the salience network/M-CIN: the insula and the ACC, sites of the most compelling neurobiological evidence of central sensory amplification[13,146]. Alterations in these structures, namely the insula, may also explain the changes observed in the peripheral nervous system[173]. The observations regarding neuroinflammation[219,220] are integrated into the view that chronic stress conditions are accompanied by similar changes[221–223].

## Limitations of the proposed model

### Multidirectionality and the causality conundrum

Hyperactivation of the salience network/M-CIN might be the end result of widely diverse combinations of vulnerability factors and starting points, such as predisposing genotypes, primary neurological abnormalities that lead to pain amplification, early and later stressful life events, premorbid or comorbid diseases, with an emphasis on chronic localized pain or inflammatory pain conditions, and continued distress fuelled by inner or external sources, including pain and fatigue themselves. The disequilibrium between the threat and soothing systems highlighted in our model is not meant to represent the sole cause of salience network/M-CIN hyperactivation in fibromyalgia but more likely is one of its many potential sources and players.

We recognize that there is, to date, no convincing evidence that affective processes, whether originating from inner or external sources, precede and cause fibromyalgia. However, the evidence for a disproportionate frequency of early adverse experiences among people with fibromyalgia suggests that this factor could be important. The same interpretation can be applied to observations that depression[224,225] and chronic occupational stress[59] predict generalized pain. However, longitudinal studies using biological markers of distress have presented contradictory results, with some being positive[226] and some negative[227,228].

An interesting contribution to this debate is provided by a recent experimental study in mice that demonstrated that exposure to a repeated and intermittent psychological stressor, consisting of a modified sound-stress paradigm, induced long-lasting hyperalgesia (a marker of central sensitization) as well as fatigue-like behaviors[229]. This finding expands on previous observations that animals can develop central sensitization when exposed to subchronic swim stress[230] and even to early-life stressful events, such as separation from their mother in the neonatal period[231]. Despite the need for further research and replication of these findings in humans, these studies provide support for the proposal that psychosocial stress might be causally implicated in chronic hyperalgesia.

Sandström et al.[100] found that pain-related cues were important for exacerbating pain in people with fibromyalgia compared with healthy individuals, but it is not known whether this heightened valuation of pain-related threat precedes or is a consequence of chronic pain, or both.

In 2021 a large-scale prospective study in children aged 9–10 years[232] demonstrated that many of the typical neurophysiological changes associated with multisite pain actually precede its development. Although the exact cause of these functional abnormalities remains undetermined, the authors who reported the findings suggested that "it is possible that brain circuits have been primed by innate (genetic) or acquired (early life stress or environmental exposure) factors". We suggest that chronic stress, of whatever origin, deserves consideration as one of the potential causative factors of these premorbid observations. In fact, many of the sites reported as hyperactivated and/or hyperconnected in this study are critically involved in the evaluation and response to stress and/or threat, namely in children and adolescents[233–235].

The ability of chronic stress to upregulate the salience network has been clearly demonstrated both in healthy individuals[236] and in clinical populations[237]. This evidence does not mean that all cases of fibromyalgia start with emotional imbalance. Stress and depression can also be initiated or aggravated by chronic pain[238], as in inflammatory rheumatic diseases[239]. Similarly, sleep deprivation or disturbance has been shown to exacerbate pain and cause fibromyalgia-like symptoms[240]. The aetiological interactions among stress, sleep disturbances and pain are multidirectional.

A 2020 review of longitudinal cohort studies of the risk factors associated with the development of fibromyalgia and chronic widespread pain identified a number of predictors, supporting the view that "there are many aetiological routes into fibromyalgia"[241]. Depression, sleep disorders, somatic symptoms and dysfunctional illness behaviours were the strongest predictors. Other risk factors included early-life adversity, demographic variables (female sex, middle age and older), lifestyle factors and premorbid illnesses[241].

The interrelationships among all these factors highlight the difficulty in disentangling them. The neurophysiological and psychosocial factors involved in fibromyalgia are strongly and intricately interconnected. It is difficult, and probably impossible, to clarify the conundrum of causality. Some factors are both cause and consequence of fibromyalgia, with each reciprocally influencing the other. In fact, the simplistic notion of linear cause and effect seems outdated and unhelpful. Perhaps it should be replaced by the overwhelming evidence that mutual and powerful dynamic influences exist among all these different manifestations and mechanisms, operating before, during and after fibromyalgia onset.

### Phenotypic heterogeneity

Fibromyalgia is a clinical condition with extensive heterogeneity in its phenotypic manifestations. As a result, most studies tend to find that only some people with fibromyalgia present with the identified correlates. This heterogeneity is probably a reflection of the variable blend of the underlying resilience and vulnerability factors, as well as pathophysiological mechanisms. Similar phenotypes might emerge from different drivers and, conversely, apparently diverse phenotypes could reflect common mechanisms. It is broadly accepted that central pain sensitization is fundamental to fibromyalgia. However, none of the many peripheral, neuroimmune, endocrine or autonomic mechanisms described in fibromyalgia has been demonstrated to be either

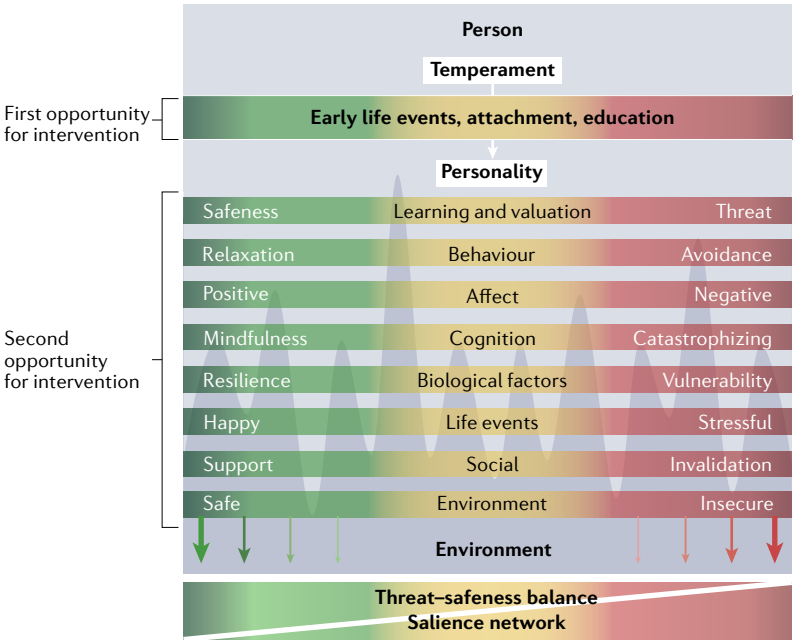


**Fig. 5 | Development of threat–safeness (im)balance and opportunities for intervention.** The figure depicts psychological domains of the Fibromyalgia: Imbalance of Threat and Soothing Systems (FITSS) model in interaction with biological factors, life events and social context. During individual development (in this figure following a trajectory from top to bottom), a number of variables contribute to the continuum of threat–safeness balance. Biological factors determine temperament, which is shaped by early life (including attachment experiences) into the more stable personality. Personality integrates a large number of dimensions in individually differing proportions, some of which enhance hyperevaluation of threat whereas others have a soothing effect. Early learning and valuation focused on threat or safeness and a variety of behavioural, affective and cognitive processes will provide impulses in one and/or the other direction. Life events and the current environmental and social context, in interaction with personality, may provide decisive triggers and powerful maintenance forces towards a predominance of threat or safeness perception. Biological factors may favour either resilience or vulnerability in all instances. The dynamic balance between these and other threat-versus-safeness forces will shape the tone of the salience network. There are several opportunities for intervention aimed at reinforcing safeness and decreasing threat perceptions. The first opportunity entails educating and protecting children from hardship and adverse early-life experiences that hinder the learning of safeness. The second opportunity comprises identifying, preventively addressing and/or intervening in stressors as well as relevant personality, cognitive-affective and social factors that can contribute to minimizing safeness and augment perceptions of threat. Note: the colour codes represent the expected contribution of the variable to the continuum of the threat–safeness balance, with red representing a tendency towards a more threat-focused mode. Examples of each factor are shown at either end.

necessary or sufficient to cause or maintain fibromyalgia symptoms, nor is any of them universally observed in all people with fibromyalgia. In some individuals, the major determinant might lie in genetic factors, whereas in others physical injuries, infections, prior pain disorders (such as rheumatoid arthritis), psychosocial trauma or psychological mechanisms are, in some combination, the main triggers and drivers of fibromyalgia. We recognize this heterogeneity but believe that there is a need to explore and summarize shared characteristics, pathophysiological mechanisms and higher-order processes that could have an important role in the development and maintenance of fibromyalgia, at least for a substantial portion of people.

### Competing views, quality of evidence and unanswered questions

In trying to bring together psychosocial and neurophysiological constructs, our model risks opposition by scholars from both camps. The conceptual overlap, ill-definition, and circularity of psychological domains render much of the available evidence equivocal and open to several interpretations. Neurophysiological constructs are snapshots of more complex processes and usually only correlate with criterion measures rather than causal. However, neither side should doubt that psychosocial and neurophysiological processes are connected or fail to recognize that, as proposed in our model, we need to embrace the challenges of understanding their crosstalk if we are to make real progress in recognizing and treating chronic complex conditions like fibromyalgia.

Surely, many pieces of the puzzles are missing. Methodological caveats such as cross-sectional designs, small samples, response bias, lack of prospective and experimental studies, lack of control over potential confounders and small effect sizes limit interpretation of the literature. We highlight some of these unanswered questions below in the hope that our hypothetical model is inspirational enough to guide future research.

## Potential implications of the model

### Future research directions

We believe that the FITSS model provides a useful roadmap for several lines of research that could, in the future, provide insights that call for revision and refinement of the model. Longitudinal studies using observations from early and later life stages, and potential moderators and mediators (for example, personality traits such as alexithymia

(difficulty in identifying and describing feelings), attachment styles, psychological flexibility, physical and psychosocial stressors, in addition to social support) are needed to evaluate our assumption that hyperactivation of the threat system could promote and maintain fibromyalgia. Research should explore how these factors relate to emotion regulation, pain and the risk of developing fibromyalgia or other central sensitivity syndromes, as well as to potential buffering factors. Large-scale prospective studies that follow children into young adulthood, such as the Adolescent Brain Cognitive Development study[242], are expected to provide valuable insights regarding causal factors in the development of fibromyalgia, the validity of our model and differences in the trajectories of different subgroups of patients. The use of experience sampling methodology and dynamic symptom networks in prospective studies[243] deserves consideration with respect to addressing individual variability in the underlying mechanisms and outcomes associated with fibromyalgia. Research addressing the mechanisms underlying the increased prevalence of fibromyalgia among patients with autoimmune disease, including diseases for which pain is generally not the cardinal symptom (for example, systemic lupus erythematosus), is also warranted.

Cross-sectional and experimental designs that specifically address the relevance and interplay of threat, soothing and drive in fibromyalgia would yield information that could be useful in the design of personalized interventions. Neuroimaging and psychophysiological research could clarify the biological and behavioural aspects of affect regulation systems and their relationships with pain amplification in fibromyalgia, and test the concept of cross-amplification between salient inputs of different natures and whether those inputs engage the salience network/M-CIN. Dynamic network modelling tools could take individual differences into account. We should also widen our view and make use of innovative approaches designed to bring together the dynamic interactions between psychology and neurophysiology (for example, see the work by Vachon-Presseau et al.[244]).

### The FITSS model and (future) therapeutic strategies

Further research is warranted to determine for whom and by what means existing and novel interventions and strategies for fibromyalgia might be most effective, as well as their neurobiological correlates (especially when considering the evidence regarding their effect on physiological, immune[245–250] and neural markers[251–257]).

For now, the FITSS model highlights several opportunities for intervention at different stages in the development and maintenance of fibromyalgia (Fig. 5). The first opportunity entails protecting children from adverse early life experiences that hinder the learning of safeness. The second opportunity comprises identifying and preventively addressing relevant personality traits and life events and providing personalized interventions that assist people with fibromyalgia in mitigating dysfunctional processes and enhancing those that provide resilience, such as acceptance, psychological flexibility[258], optimism[259], self-compassion[260], (self-)forgiveness[261], mindfulness[262] and social connectedness[263]. Our model suggests that addressing pain and stress and strengthening these resilience factors could help to reset the 'volume control' (Fig. 4 and Box 1) and alleviate dysfunctions associated with fibromyalgia. Clinicians are already advised to use psychological interventions in people with fibromyalgia who have high levels of psychological distress or maladaptive coping strategies[200], as these interventions have shown effect sizes similar to, and sometimes superior to, those of mainstream medications[8,264]. Classic cognitive-behavioural therapies are considered the gold-standard but other interventions such as mindfulness[262], acceptance[265,266], compassion-based strategies[243,267,268] and interventions targeting trauma, adversity, intrapersonal and interpersonal conflicts (such as emotional awareness and expression therapy) have been showing promising results[269]. Compassion-based approaches, such as compassion-focused therapy[76], or hybrid interventions combining mindfulness and acceptance with compassion (similar to what is being done for the treatment of cancer[270] or chronic pain[271]) might be of particular relevance to fibromyalgia because, unlike other classic therapies targeting the threat system, these therapies also focus on the development and cultivation of soothing-related processes.

Yet, the overall modest effect sizes of any current therapy in fibromyalgia underscores the need to develop novel therapeutic strategies, with effect-evaluation studies that have greater statistical power, methodological rigour and longer follow-up periods than current ones.

In daily practice, costs, accessibility and negative beliefs about the legitimacy of fibromyalgia are major obstacles to disseminating

## Box 1

## Building blocks of the FITSS model

- The Fibromyalgia: Imbalance of Threat and Soothing Systems (FITSS) model is based on the concept of a hyperactive salience network (also known as the midcingulo-insular network), primarily or secondarily driven by a sensitized and hyperactive threat system and a hypoactive soothing-affiliative system.
- This imbalance of threat and soothing systems:
  - can be triggered or enhanced by a variety of biological and psychological predisposing factors, and by stressful physical or psychological events throughout the life course; and
  - favours threat-focused processing that provides a continuous source of negative affective perceptions, thus reconfirming and reinforcing the imbalance (see Fig. 3).
- The unremitting influx of threat forces the salience network to function in a near-continuous alert mode, which might help to explain the amplified perception of a variety of stimuli as unpleasant or threatening, including pain as well as the sensory-neurophysiological abnormalities associated with fibromyalgia.
- The final phenotypical expression of these processes depends on the interplay of an individual's specific vulnerability and resilience factors, including biological, psychological and social resources (see Fig. 4).
- This model suggests that fibromyalgia can be alleviated by strategies that:
  - reduce the perception of threat, such as trauma processing, exposure techniques, emotional awareness and expression, behavioural engagement and approach-oriented coping; and/or
  - reinforce soothing abilities, safeness perception and affiliative behaviours, including optimism, acceptance, compassion, forgiveness, self-care, mindfulness, valued living, social support and connectedness, affective touch, all of which might be improved by psychosocial intervention (see Fig. 4 and Fig. 5).

psychosocial interventions. Overcoming these barriers requires insurance coverage, different delivery formats and education of primary care physicians and the general public. Information and communication technology-based approaches also show promising results in producing short-term improvements in negative mood and disability in fibromyalgia, although their effectiveness compared with face-to-face strategies has yet to be established[272]. Research on pharmacological and neurophysiological treatments should be continued as well, guided by the integrative mechanisms described above.

## Conclusions

The FITSS model proposed herein integrates psychosocial and neurophysiological observations in fibromyalgia, identifying the midcingulo-insular salience network and the management of threat and soothing processes as the core underlying processes. This model highlights the powerful interactions among these domains and the potential of this interplay to generate diverse phenotypes from an essentially common pathophysiology. This multilevel framework is not intended to dispute or replace any of the mechanisms proposed so far but rather to harmonize and integrate existing observations and models into a coherent biopsychosocial framework incorporating data from various fields of research, including neurobiology, genetics and psycho-sociology.

We hope that this model will inspire the design and testing of novel studies and interventions, respectively, integrating psychosocial and neuroscientific approaches that take advantage of the individual's neural plasticity and ability to re-establish a neuropsychological balance and promote lasting well-being. Practising clinicians will, we hope, find here novel perspectives capable of fostering their understanding of people with fibromyalgia and promoting empathy and efficacy in clinical interactions.

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## Author contributions
A.M.P., F.P., M.L. and R.G. researched data for the article. J.A.P.S., A.M.P., R.G., E.K. and M.L. wrote the article. J.A.P.S., A.M.P., R.G., T.D.W., M.A.L., W.H., E.K., M.L.-S., J.L.R. and J.W.G.J. made a substantial contribution to discussion of the content. All authors reviewed and/or edited the manuscript before submission.

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