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RESEARCH ARTICLE

Chasing the Perplexing Purple Butterfly through Biopsychosocial Model-based Precision Medicine: The Enigma of Fibromyalgia Unraveled

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ABSTRACT

A purple butterfly symbolizes the heightened sensitivity to even a gentle touch in fibromyalgia, which is a common syndrome with persistent widespread pain and tenderness. The biopsychosocial model is currently the main framework used to appreciate different factors contributing to chronic pain in fibromyalgia. Widespread pain in fibromyalgia is affected by multiple biopsychosocial factors (cognitive ability, depression, somatization, psychological trauma, anxiety, and social deprivation/isolation), which interact and contribute to chronic persistent pain. Interaction of influences such as gender, neuroendocrine milieu, and the hypothalamo–pituitary–adrenal axis also affects fibromyalgia susceptibility and its clinical expression. Multiple neuroanatomic and neurochemical systems with many autonomic, cognitive & affective processes manifest as multisymptom illness in fibromyalgia. While the etiology of fibromyalgia is elusive, the associated symptoms indicate the role of autonomic dysfunction in its pathophysiology. Fatigue and widespread pain characterizing fibromyalgia may be consequent to peripheral tissue ischemia caused by sympathetically mediated vasoconstriction. In light of some common denominators among fibromyalgia patients, which include genetic variation, sympathetic hyper-activation, maladaptive thoughts, ineffective coping strategies, and nonrestorative sleep, an individualized care approach can help subgroup and phenotype these patients for specific diagnosis and management. A multidisciplinary approach involving person-centered approaches to biopsychosocial concepts in fibromyalgia, incorporating relaxation therapy, physical activity, and psychotherapy targeting negative emotions that amplify pain, maladaptive coping strategies, and environmental stressors, can help manage fibromyalgia 's course, outcomes, and treatment.

Introduction

Fibromyalgia (FM) is one of the most common chronic pain conditions where widespread pain coexists with multiple symptoms such as fatigue, insomnia, cognitive dysfunction, sensory hypersensitivities (mechanical, thermal, visual, auditory), etc.[1-3]. Fibromyalgia is diagnosed in the primary care setting as a clinical diagnosis based on the patient's self-report of widespread Pain and the American College of Rheumatology (ACR 2010/ 2016) diagnostic criteria as a polysymptomatic pain disorder[4,5].

Fibromyalgia patients complain of hyperalgesia and allodynia and describe the pain using descriptors like a tingling sensation or pins-and-needles, which indicate similarity to neuropathic pain[6,7]. Fibromyalgia patients also complain of coexisting focal painful disorders, e.g., localized muscle pains from myofascial trigger points (TrPs) and joint pains from micro-traumas/osteoarthritis. Nociceptive inputs from such comorbidities substantially contribute to the specific FM complaints. However, very few systematic clinical studies corroborate the effects of comorbidities and local treatment on FM symptoms in standardized conditions[8]. Fibromyalgia pain differs from classical rheumatic disorder pain as FM pain cannot be correlated or defined according to the extent of the tissue inflammation or damage[6,9]. Mounting evidence suggests that complaints of paresthesias in FM patients manifest in a non-dermatomal pattern and are categorically different from the specific neuroanatomic distribution of nerve entrapment disorders[10].

The etiology of FM is still elusive, with evidence pointing towards a multifactorial causation as genetic predisposition, endocrine factors, stressful life events, physical trauma, sleep problems, and emotional and cognitive disturbances have been implicated in its pathogenesis. Yet, no single objective clinical test is available to confirm its diagnosis[11]. There is a considerable presence of autonomic symptoms in FM patients, e.g. dizziness and orthostatic intolerance, dry mouth and eyes, urine incontinence and bladder discomfort, constipation, dyspnoea, palpitations, sexual dysfunction, difficulty swallowing, decreased sweating, skin discoloration, etc.)[12].

Variation in FM pain also depends on the season, comorbidities, and physical activities. Physical inactivity augments pain intensity, forming a vicious cycle due to deconditioning[13,14]. Moreover, physical or mental stress is also a known factor associated with worsening of pain[7]. Temporal fluctuations in FM pain with variability in pain intensity over variable time periods are observed, affecting and determining treatment responsiveness[15].

Available management strategies are limited to generic treatment modules, which have shown benefit in a few small-scale studies. Therefore, precision medicine comprising a healthcare framework for managing chronic pain and associated symptoms in different FM phenotypes may hold promise in its diagnosis and management[16]. The emerging precision pain medicine model focuses on managing each patient by identifying their risk profiles for disproportionate pain and developing and optimizing treatment plans [17].

The literature review suggests neuroplasticity, both central and peripheral sensitization, dietary deficiencies, epigenetic loci, and genome-wide tendencies, and subsequently, proposes a separate set of considerations for patients with fibromyalgia to ensure individualized medicine. Evidence from clinical, preclinical, and genetic studies supports the existence of some shared factors in FM and comorbid gastrointestinal and psychiatric conditions. A treatment plan based on a biopsychosocial model seems better than the strategy based on the reductionistic single-mechanism targeted treatment approaches. Henceforth, precision medicine is consistent with personalized, multidisciplinary approaches involving behavioral, dietary, and pharmacological interventions for FM management[18,19].

This perspective discussion aims to present a precision approach to pain management in fibromyalgia on a biopsychosocial model, which we argue, can offer a higher quality of life while limiting drug use. We succinctly review important neuropsychological constructs with autonomic dysfunction as a prime illness, core brain networks, and alterations in stress physiology implicated in fibromyalgia.

Methods

Our work takes the form of a narrative review which was conducted on the basis of a comprehensive literature search to find relevant

articles. This study was not registered in any international protocols registry, such as Prospero, because it is a narrative review. We searched 3 databases from inception to October 2023 (PubMed/MEDLINE, Scopus, and Google Scholar) encompassing publications reporting quantitative and qualitative research. We limited our search to peer-reviewed publications in English. We used the following search terms in combination with Boolean search modifiers (AND, NOT and OR): fibromyalgia, pain, musculoskeletal pain, chronic pain, sympathetic pain, widespread generalized pain, neuropsychological factors, coping, contextual factors, conceptual models, pain matrix, biopsychosocial, autonomic function, disability.

Consistent with our study objectives, we selected only publications that primarily addressed fibromyalgia-related neuropsychological factors or relevant conceptual models involved in fibromyalgia outcomes, within the biopsychosocial perspectives. Ethical considerations, including guidelines for publication with respect to plagiarism, have been completely complied with by all authors of this manuscript.

PAIN HYPERSENSITIVITY: FUNDAMENTAL MECHANISMS AT A GLANCE

Comprehensive pain management in FM patients should include evaluation and search for central and peripheral pain generators as both central sensitization and increased pain response to peripheral nociceptive and non-nociceptive stimuli characterize fibromyalgia[10]. Each of these processes, either separately or in combination, contributes to FM symptomatology but does not adequately explain the chronic pain insurgence and persistence. A better grasp of the underlying neurobiological mechanisms would allow the development of successful targeted diagnostic techniques and therapeutics [20].

The absence of a structural lesion in the somatosensory system in FM has resulted in its exclusion from the category of neuropathic pain disorders. The placement of fibromyalgia in the nociceptive pain category is also partly accurate. Following its exclusion from the existing nociceptive/neuropathic dichotomy, "nociplastic pain" as a pain-generating mechanism has been proposed for this disorder[21]. The mechanistic basis of nociplastic pain, another pain descriptor commonly used to describe the nature of pain in FM patients, lies in the increased neural processing of and/or decreased inhibition of pain stimuli[21,22]. Such pain phenotyping is very important because it promotes the application of multidisciplinary health care within the biopsychosocial perspectives [23].

Nociplastic pain may be caused due to supraspinal, spinal, and peripheral mechanisms comprising sympathetic-afferent coupling[24]. Supraspinal mechanisms include specific characteristics such as hyperresponsiveness to pain stimuli, hyperactivity and altered functional connectivity between areas responsible for pain perception and inhibition, increased substance P and glutamine levels in cerebrospinal fluid, and inhibition of GABAergic transmission[25]. Apart from structural and neurochemical alteration, changes in the size and shape of gray and white matter in areas related to pain are also present[26]. In structural brain imaging, fibromyalgia patients have lesser total gray matter volume & density in regions associated with pain modulation or stress, such as the cingulate, insular and medial frontal cortex, the parahippocampal gyri, thalamus, and amygdala. Atrophy in some crucial brain areas indicates the plausibility of premature aging in fibromyalgia patients[4].

Spinal mechanisms involve clustering and convergence of signals from different loci of pain, amplified spinal reflex transmission, reduced spinal inhibition, winding-up, temporal summation, and immune system activation among other glial cells [27,28].

Peripheral mechanisms include increased neuronal expression of voltage-gated sodium channels, decreased potassium channel expression, and increased sympathetic activity 18,24. Dysfunctional pain processing present in fibromyalgia, as well as in disorders such as irritable bowel syndrome (IBS), migraine, etc., is accompanied by an augmented peripheral nociceptive processing and the central nervous system (CNS)- mediated somatic symptoms (e.g. fatigue, sleep, memory, and mood disorders)[29]. Coexisting conditions, such as autoimmune disorders, sickle cell disease, or osteoarthritis, can augment the ongoing nociceptive input in FM. In contrast, the CNS changes, including the gray matter reduction, improve after removing the peripheral nociceptive input[29,30]. Sympatho-sensory coupling is proved by intradermal injection of norepinephrine, which decreases

thermal pain threshold even in normal subjects [31].

Hyperalgesia, allodynia, temporal summation, and hypersensitivity to various external stimuli, such as sounds or lights, indicate central sensitization (CS) or hyperactivation [7]. Central or spinal sensitization (secondary hyperalgesia) consists of a more robust response of neurons to stimuli from diseased and adjacent, non-diseased areas[32]. Central sensitization to pain implies hyperexcitability, increased synaptic efficacy of sensory and nociceptive neurons, hyperexcitability of ascending nociceptive pathways, and inhibition of the descending antinociceptive pathways[11]. The phenomenon of CS is characterized by neuroplasticity caused by phenotypic reorganization of sensory neurons, alteration of spontaneous firing activity, lowered activation threshold, prolonged activation after a nociceptive stimulus, and termination of sensory neurons in the superficial laminae of the dorsal horn normally occupied by nociceptive neurons and receptive field expansion [33]. Therefore, non-painful stimuli such as light touch and pressure evoke painful sensations (allodynia)[18]. Persistent peripheral pain signal transmission may trigger CS as the interaction of excitatory neuropeptides (e.g., substance P) with neuronal G protein-coupled membrane receptors lowers action potential thresholds in 2nd-order neurons in the dorsal horn.

Furthermore, a reduction in descending GABA and glycine-mediated inhibition further augments ascending neuron excitability. Apart from both the ascending and descending pain pathways operating abnormally and causing central amplification of pain signals, FM patients exhibit changes in the levels of neurotransmitters that alter pain processing[4]. The release of sensory neuropeptides from presynaptic neurons plays a central sensitization role, e.g., Substance P by lowering the threshold of synaptic excitability, sensitizing dorsal horn neurons at relatively long distances from the original input location, causing increased internalization of substance P receptors, increased expression of c-Fos, and persistent structural changes, can contribute to central sensitization[27].

Fatiguing muscle contraction, measured by pressure pain threshold (PPT), induces generalized descending facilitation in FM patients, indicating a shift of descending pain modulation from inhibition towards facilitation in fibromyalgia[34]. Cortical hyperexcitability is another characteristic feature of the transition from episodic to chronic pain as evident in migraine headaches[27]. Using cortical excitability parameters assessed by transcranial magnetic stimulation (TMS) [viz. motor evoked potential (MEP), cortical silent period (CSP), short intracortical inhibition (SICI), and short intracortical facilitation (SICF)], greater disinhibition in the motor cortex and the descending inhibitory pain modulation system in FM and MPS is found to exist. There is also a higher inter-hemispheric disinhibition and dysfunctional descending pain modulatory system in chronic pain without any tissue injury compared to a structural lesion[35]. However, another study reported no difference in corticomotor excitability parameters (resting motor threshold and motor evoked potential amplitude) between FM patients and healthy controls, and probably such discrepancies can be attributed to pain chronicity duration[36.] Reduced activity of endogenous analgesia during pain chronification may contribute to establishing and maintaining chronic pain states as seen in other pain states also[37].

Temporal summation, different adaptation, or habituation to painful stimuli indicate CS in FM patients. The sensitization following the temporal summation is a "spinal-up" process in which the dorsal horn neurons respond to repetitive C-fiber stimulation[38]. Temporal summation of pain reflects the progressive enhancement of C-fiber evoked responses of dorsal horn neurons (wind up), which is dependent on N-methyl-D-aspartate (NMDA) receptor mechanisms and shares common features with those of early phases of Long Term Potentiation (LTP) in the hippocampus[39,40]. The details of temporal summation, wind-up, homosynaptic, and heterosynaptic potentiation are beyond the scope of this paper[40]. Chronic constriction injury in rats and exposure of a defined medium organotypic culture of rat spinal cord to Brain-derived Neurotrophic Factor (BDNF) increase dorsal horn neuronal excitability (increase in amplitude and frequency of spontaneous excitatory postsynaptic currents EPSC) and contribute to central sensitization[41].

A new concept of a tetrapartite synapse consisting of an astrocyte, microglial cell, and pre and postsynaptic neuronal terminals has been

proposed where the glial mechanism involving microglia and astrocytes and their effect on calcium mobilization and subsequent production of pro-inflammatory cytokines and reactive oxygen species that promote neurogenic inflammation on activation, contribute to persistent pain[42]. Naltrexone decreases the pro-inflammatory cytokines and reactive oxygen species production by suppressing microglial signaling. Thus, a low dose of naltrexone reduces fibromyalgia symptoms, as measured by improved pain threshold testing and self-reported symptoms[4].

Despite more substantial evidence for CS and its role in nociceptive processing, considerable studies report that the peripheral components also generate widespread pain in FM patients 29. Peripheral pain generators consist of nociceptive input from a localized musculoskeletal or visceral pathology area (skin, muscle, tendon, and joints), and the impulses originating from them constitute nociceptive stimuli that travel in peripheral nerves to form synapses in the spinal cord's dorsal horn[10].

In fibromyalgia, post-herpetic neuralgia (PHN), and painful diabetic neuropathy (DN), the epidermal innervation density is reduced. The remaining peripheral sensory nerves show sensitization (increased spontaneous activity, hyper-responsivity to noxious stimuli, and heightened responsiveness to non-noxious stimuli)[43].

Peripheral sensitization (primary hyperalgesia) deals with sensitized nociceptors with a low excitation threshold, so non-toxic stimuli can trigger action potentials and produce a more robust response to supra-threshold stimuli[32]. Synaptic transfer of information about the intensity, duration, and location of the peripheral noxious stimuli occurs from nociceptors to dorsal motor neurons[44]. An initial noxious stimulus that causes tissue damage and results in the release of bradykinin and prostaglandins that sensitize or activate nociceptors, which in turn release substance P and calcitonin gene-related peptide (CGRP)[45,46]. Peripheral release of Substance P enhances neurogenic inflammatory response and causes vascular permeability, edema, warmth, redness, vasodilatation, and protein extravasation via neurokinin 1 (NK1) receptor activation. Facilitation of sensitization of second-order spinal neurons via activation of the NK1 receptors on ascending spinal neurons results in spontaneous pain and hyperalgesia. Trauma-induced facilitated SP signaling has been found to stimulate TNF overexpression, resulting in periarticular bone loss, joint tenderness, and the development of chronic pain in complex regional pain syndrome (CRPS)[47]. Resultant vasodilatation, capillary permeability, hyperplasia of nerves, and the upregulation of receptors for noxious stimuli are observed in injured nociceptors and uninjured nociceptors [48].

Repeated stimulation increases nociceptor excitability despite their high thresholds for activation brought out by a range of cytokines released from the site of tissue injury and surrounding cells and also the acquisition of mechanosensitivity by silent nociceptors[45]. Repeated stimulation also upregulates excitatory receptors, such as transient receptor potential V1 (TRPV1) channels, leading to an increased sensitivity to pain (hyperalgesia). Increased neuronal expression of voltage-gated sodium channels and decreased expression of potassium channels facilitate peripheral sensitization in chronic pain syndromes[18,40].

Lidocaine injections in tender points increase local pain thresholds and decrease secondary heat hyperalgesia in a remote site in FM patients[39]. In FM patients, local treatment of coexisting pain disorders produces symptom relief, as seen by either a conventional dose reduction or better symptom control at the same doses[8]. Laser Doppler flowmetry studies have documented a blood flux reduction primarily over the tender points in patients with fibromyalgia, concluding that excessive fatigue could be caused by peripheral tissue ischemia and hyperactivation of deep tissue nociceptors by anaerobic metabolites and inflammatory cytokines[49].

AUTONOMIC DYSFUNCTION IN FIBROMYALGIA: THE KEY PLAYER

Peripheral sympathetic-afferent coupling forms the basis for sympathetically maintained pain, which cannot be explained based on spinal and supraspinal mechanisms[50]. A vicious cycle results from increased sympathetic efferent activity due to increased nociceptive input. The number of alpha-adrenoceptors in the epidermis is higher in the hyperalgesic skin of patients with reflex sympathetic dystrophy[51]. In sympathetically mediated pain disorders, alpha1 adrenore-

ceptors are expressed on primary afferent nociceptors (C- and A-δ nociceptive afferents), so norepinephrine released by the postganglionic sympathetic terminals activates them. Heightened activity in nociceptive fibers leads to up-regulation of alpha (α)1 adrenoceptors in the cell body[52-54]. The activity of α1-adrenoceptors sensitizes nociceptive neurotransmission, and their subtypes are differentially expressed in response to painful nerve damage. Variation in the gene encoding the β2-adrenoceptor is associated with vulnerability to develop persistent pain, as seen after motor vehicle collision[55]. Norepinephrine injection into the human skin potentiates capsaicin-induced heat hyperalgesia by activating α1-adrenoceptors. In contrast, sympathectomy and α1-adrenoceptor blockade inhibits capsaicin-induced c-fos expression in dorsal horn neurons and hyperalgesia induced by intradermal capsaicin respectively 56. Sympathetic blocks eliminate the sympathetically mediated activation of the nociceptive fibers and down-regulate the production of α1 receptors[52]. Genes that modulate -adrenergic receptor-mediated signaling, such as catechol-O-methyltransferase (COMT), affect pain sensitivity[57]. Conversely, deleting genes that encode adenylyl cyclase, PKA (cAMP-dependent protein kinase), and PKC (Ca2+/phospholipid-dependent protein kinase) impair the development of pain sensitivity[40].

During disinhibition of SNS outflow and diminished descending inhibition, the SNS effect on primary afferents is amplified, and stress-induced hyperalgesia is unmasked. This unmasking enhances pain sensation through sensitizing and nociceptive stimuli via a positive feedback loop [31].

Thus, while the etiology of FM is not fully understood, available information suggests that FM may stem from autonomic nervous system dysfunction that has been reported at rest and after a physiological stressor such as exercise[58]. However, symptom severity may not be congruent with the grade of autonomic dysfunction in patients with fibromyalgia. FM patients with widespread subjective impairment of function may only present with modest objective measures of autonomic dysfunction [59]. On the contrary, a recent study reporting cardiovascular hyporeactivity in response to stress also infers that the magnitude of the autonomic adjustments to postural changes with a second-to-second basis resolution is inversely associated with the severity of clinical pain[60]. The reduced reactivity observed in FM sufferers during standing may lead to suboptimal cerebral blood perfusion, thereby promoting the greater orthostatic intolerance observed in the disease. However, we previously reported that the cardiac autonomic reflex arc is intact in fibromyalgia patients despite autonomic symptoms[14]. The absence of altered reactivity in our FM patients can result from baseline overactivity in some parameters, creating a ceiling effect. Cardiac abnormalities may occur during and after exercise, even when physical fitness is considered[61]. We hypothesized that possible impaired neuro-effector mechanisms (vascular end-organ dysfunction) initiate and perpetuate pain and result in physical deconditioning and disordered autonomic function in FM patients 62. Decreased cardiovascular reactivity may also promote pain as phasic increases in cardiovascular parameters such as blood pressure (BP) via baroreceptor afferents are known to produce antinociceptive effects[60]. Reports are present in literature about small distal fiber (intra-epidermal unmyelinated nerve fibers) neuropathy, presenting a reduction in both bundles and the diameter of dermal unmyelinated nerve fiber in fibromyalgia. Such a picture of neuropathy in FM matches the neurologic and autonomic nervous system (ANS) symptoms, including alterations in heat and cold thresholds, tingling, numbness, etc. Thus, FM can be placed on a continuum between purely peripherally induced (including small fiber neuropathy) and centrally induced pain [12].

Reduced respiratory sinus arrhythmia (RSA) in FM patients indicates malfunctioning of the polyvagal pathways and reduced high-frequency (HF) HRV may mean a diffuse recalibration and reorganization of ANS regulation along with altered pain signaling[63]. The Polyvagal Theory provides a theoretical framework whereby dysregulation of the autonomic and immune systems can benefit by non-invasive transcutaneous vagal nerve stimulation (tVNS) to improve fibromyalgia symptoms[64].

Low autonomic reactivity is also linked to decreased immune functioning, orthostatic intolerance, and negative affective states (i.e., depression and chronic stress) in FM patients [60]. Quantitative Sensory Testing (QST) shows that FM patients have lowered tolerance thresholds

and an altered sensation perception, indicating generalized sensitization. Fibromyalgia patients tend to use more pain-related descriptors for describing the quality of the nociceptive stimulus. These responses are consistent with fundamental psychophysiological theories on the dysregulation and impaired processing of somatosensory (tendency to react; meant for quantification of sensations) and affective stimuli (tendency to ascribe a specific quality to a stimulus) in fibromyalgia[65].

BIOPSYCHOSOCIAL MODEL FOR PAIN IN FIBROMYALGIA (FM) AND CENTRAL AUTONOMIC NETWORK (CAN)

Stress is an integral part of the chronic pain syndrome as FM patients exhibit heightened stress and arousal, and also causes exacerbations of symptomatology in fibromyalgia [66]. Stress is a strong candidate for cross-reactivity with pain mechanisms with a similar neuroanatomical substrate[67]. Based on a biopsychosocial perspective, several neuronal processes are involved in the stress response. Brain–heart interactions, commonly called the central autonomic network (CAN), link the periphery with the immune system, the hypothalamic-pituitary-adrenal (HPA) axis, and the ANS[68]. Reduced heart rate variability (HRV) signifies high sympathetic activation, disturbed regulation of the ANS, and inadequate adaptation of the cardiovascular system and is also a sign of chronic stress[69]. A general arousal model put forward to explain abnormal psycho-physiological features associated with chronic pain links arousal of the ANS and sustained muscle activity and generates and perpetuates pain. Another specificity model connects the development of pain to environmental stressors, genetic predisposition, previous experiences, and personality types[70].

The stress response begins following a response generated by the stressor in the amygdala, which activates the hypothalamus, thereby setting forth an autonomic nervous system (ANS) and endocrine response. Sympathetic activation raises heart rate (HR) but decreases heart rate variability (HRV). The hypothalamus releases corticotropin-releasing hormone (CRH), which signals adrenocorticotropic hormone (ACTH) release in the pituitary gland, mediating cortisol release from the adrenal cortex [71].

Stress-induced prolonged and enhanced mechanical hyperalgesia is mediated by glucocorticoids and catecholamines, which affect signaling pathways in primary afferent nociceptors. Such phenomenon underlies pain in FM, irritable bowel syndrome, posttraumatic stress disorder, and depression. Interactions between glucocorticoid and adrenergic receptor signaling pathways within the primary afferent nociceptor contribute to hyperalgesia[57]. Adrenergic pathways implicated in the stress response mechanisms and pain processing mechanisms interact and affect pain sensitivity and vulnerability, leading to its persistence[51]. Activation of glucocorticoid receptors found in the brain reduces systemic mechanical pain thresholds. In contrast, the glucocorticoid receptors in the dorsal horn respond to peripheral nociceptive stimulation and can induce antinociception[55]. Corticotrophin-releasing hormone also stimulates raphe nuclei, and the activation of serotonin pathways is part of the acute stress response. Serotonergic projections to the spinal cord can enhance/prolong, or extinguish acute pain and act by influencing the antinociceptive effects of opioids at the spinal cord level. Low levels of serotonin availability due to a genetic variation in the serotonin transporter are associated with fibromyalgia[55].

Effects of chronic stress on the immune system have been well studied and affect the immune system directly via effects on the HPA axis and sympathetic nervous system. Stress also indirectly affects immune function by promoting poor sleep, depressed mood, and adverse health behaviors (e.g., poor diet/sedentary behavior)[72]. Immune system activation modulates nociceptive pathway excitability, and the silent nociceptors may be activated in states of immune or endocrine challenge and chronic pain conditions[43]. The presence of pro-inflammatory mediators and organ-specific & non-specific autoantibodies in the serum of FM patients supports the immune system's role in its pathogenesis. Infections (hepatitis C virus, HIV, or Borrelia burgdorferi) may also trigger fibromyalgia in vulnerable individuals[7].

The cause-and-effect relationship between the altered emotional states and the development of pain is yet to be established. The locus coeruleus (LC)-noradrenergic system is a hub for arousal, stress, cognition, and pain. It is a constituent of

many neuronal networks concerning different behavioral and sensory processing, including pain[73]. Activation of the locus coeruleus-norepinephrine (LC-NE) system results in a stress response associated with anxiety, depression, posttraumatic stress disorder, and other affective or mental disorders. Stress activates noradrenergic neurons in the LC, spreading adrenergic transmission in the hypothalamus, prefrontal cortex, brainstem, cerebellum, and amygdala[74]. Long-term exposure to maternal stress during early infancy results in continuous hyper-reactivity of the LC-NE and HPA axes and higher salivary cortisol levels. On the other hand, adequate maternal responsiveness enables sufficient LC-NE and HPA axes dampening, leading to a higher stress threshold, cognitive control, and affective stress coping. Thus, traumatic stress in early life modifies the stress-response setpoint, and such individuals are prone to stress-related disorders during later life [66].

Different areas of the brain that are involved in processing the nociception and perception of pain constitute the pain matrix (PNM) and consist of the anterior cingulate cortex, medial cingulate cortex, insula, prefrontal cortex, and primary and secondary somatosensory cortex[75]. Functional magnetic resonance imaging (fMRI) analysis of hyperalgesic nocebo responses shows increased activity in some areas related to pain and emotional processing, including CAN. Functional connectivity analysis of spontaneous resting state shows a correlation between the hippocampus and pain network, suggesting a significant role of an affective-cognitive-pain pathway in nocebo hyperalgesia[76]. Functional brain imaging studies show differential responses in PNM to controlled stimuli in related syndromes presenting with CS. The highly interacting subnetworks regions of the pain matrix can be subdivided into sensorimotor areas, salience areas, emotional arousal areas, descending pain modulation, central autonomic network, and central executive network. This distributed network interacts with the default-mode network (DMN), whose activity shifts towards the central executive network when pain stimuli are processed in the sensorimotor network. Increasing nociception also activates the salience network, which involves emotional-arousal and the central autonomic network (CAN), resulting in pain and associated responses [77].

Autonomic dysfunction is linked to chronic pain status and may manifest as anxiety in fibromyalgia. The anterior insula, a part of PNM, has been implicated in modulating anxiety responses[78]. Negative emotions like anger or fear are associated with increased activation in the amygdala, anterior cingulate cortex, and anterior insula, further regulating attention towards pain and exaggerating pain repulsiveness associated with pain[79]. Fibromyalgia is associated with sensitization to cold stimulation rather than habituation, and higher mean differences for cold pain thresholds may be due to hypervigilance effects 38. Fibromyalgia patients are selectively attentive to pain-related cues from the body and the environment consisting of family and other social groups. A feed-forward effect occurs when an overindulgence of family members results in more anxiety and an increased perception of pain [80].

CONNECTING LINK: PAIN CONNECTOME AND FUNCTIONAL NETWORKS

Pathophysiology of persistent pain involves local and central sensitization mechanisms[40]. As discussed earlier in this text, sensitization due to bottom-up and top-down processes maintains the persistent pain cycle and affects the sympathetic nervous system[81]. Central sensitization extends beyond the somatosensory system and spreads out further by causing an appropriate sensitization of spinal sympathetic reflexes in response to diminished descending neural transmission. This reorganization of sympathetic circuitry might also explain sympathetic over-activity in fibromyalgia[78]. Central sensitization development and maintenance also attributed to a functional impairment of the autonomic and immune systems, may manifest as a referred pain[82]. Prolonged sustained inflammatory states cause the reorganization of ascending neural networks, producing sensitization to noxious input and sympathetic reflexes. The activation of glial cells and the neuro-glial interactions are new mechanisms associated with chronic pain[75].

Altered "neuromatrix" is characterized by increased activity in brain areas not generally related to acute pain signal processing[30]. The increased PNM-CAN overlap and connectivity after spinal cord injury (SCI) results in dysregulated pain and autonomic processing, manifesting as chronic post-SCI persistent pain

[78]. In spinal cord injury patients, analgesia is produced during neuromodulation (by transcranial direct current stimulation interventions) targeted at descending pain pathways at the level of the anterior cingulate cortex (ACC)[78].

Central Sensitization and exhaustion of endogenous pain and inhibitory mechanisms cause greater activation of the PNM in fibromyalgia[11,83]. Functional brain-imaging (fMRI) studies have also shown activations at a much lower intensity PNM during nociceptive stimulus in FM patients. MR spectroscopy shows abnormal signaling in areas, including the amygdala, and increased glutamate and glutamine activity. Reduced mu-opioid receptor binding in pain modulatory regions inferring an altered endogenous opioid analgesic activity in fibromyalgia may describe little efficacy of therapeutic opioids [4].

A study in our laboratory on FM patients assessed central sensitization by functional near-infrared spectroscopy performed to evaluate cortical oxygenation in the prefrontal cortical areas. Autonomic activity by heart rate variability, electrodermal activity, and deep breathing test in three physiological states, viz. rest, sympathetic stress (cold pressor test), and deep breathing, were also measured. Fibromyalgia patients have central sensitization with equivocal sympathetic hyper-reactivity, a blunted response to stress, and an intact parasympathetic system on the basis of which FM patients can be subgrouped for diagnosis and management. Thus, central nervous system alterations may amplify pain differentially, which causes hypersensitivity to pain in FM patients [84].

BIOPSYCHOSOCIAL CONTRIBUTION TO PAIN OUTCOMES

The biopsychosocial model can help understand the mechanisms of pain chronification based on neuroplasticity, pain modulation, central sensitization, and the pain neuromatrix (PNM). The biopsychosocial model of pain provides essential cues for a better interpretation of the chronification of pain in vulnerable patients and is incorporated into patient education programs to assist them in avoiding emotional responses that may worsen pain[27,85]. The complex interaction of external and internal factors determines an individual's susceptibility to developing a chronic pain condition [86]. Clinical heterogeneity in the form of subgroups with different pathophysiology and with dissimilar treatment responses exists. Altered pain processing in FM may be due to differential neuroendocrine, neurotransmitter, and neurosensory disturbance[4].

Fibromyalgia pain represents a multidimensional confluence of affective, autonomic, cognitive, and behavioral factors whose interplay influences the pathogenesis of this disease. Fatigue and mood disorders are commonly found in fibromyalgia and may alter the pain experience[87]. Based on the sensitization model, the patient education strategy in FM adopts a biopsychosocial approach in which appropriate physical, psychological, behavioral, and environmental factors are used to explain the maintenance of pain. Such a strategy helps identify the subgroups of patients vulnerable to sensitization [88]. Such a management approach is also utilized to formulate clinical yellow flags for chronic musculoskeletal pain[89]. Chronic widespread pain has complex biopsychosocial underpinnings. Biomarkers for diagnosis, management, and development of new therapeutics should be widely tested in various cultural contexts[90]. In line with this model, genetic and environmental factors such as early life experiences, infections, trauma, stress, cultural background, perceived social support, and personality traits could determine coping strategies, which may be the harbinger of fibromyalgia[19,91,92]. Physical or psychosocial burden increases susceptibility to emotional vulnerability in later life through sensitization or failed inhibition of the HPA-axis by glucocorticoid-related hippocampal damage [66].

Psychosocial factors influencing the development and course of pain progression include depression and catastrophizing, further augmenting pain and disability [93,94]. Catastrophizing behavior is reflected in the disability to carry out routine tasks and low quality of life and determines the cognitive response style in a chronic pain state. High catastrophizing subjects are more aroused, aware, and vigilant of Pain[87]. Catastrophizing also augments autonomic parameters, muscle stress, and pain response by interfering with the effective functioning of the endogenous opioid system, as seen in rheumatoid arthritis patients. Reductions in catastrophizing provide additional

analgesic benefits in many treatment modalities[95].

Fear of movement and self-efficacy are other variables that affect physical activity levels in FM patients[96]. The chronic debilitating pain in FM may be similar to incapacitating reflex sympathetic dystrophy (RSD) symptoms. The symptomatology of RSD fosters helplessness and thus perpetuates passive coping and sympathetic overactivity. Passive coping instills fear of movement and leads to muscle deconditioning. Such maladaptive behavioral patterns are reinforced via operant conditioning, forming a vicious cycle[14,97]. The fear-avoidance model of pain exerts a nocebo-like effect, whereby the fear of pain may worsen pain (nocebo hyperalgesia)[76].

Genetic and epigenetic factors also affect pain development and persistence in FM patients. However, environmental factors also influence gene expression and produce behavioral changes. The psychological processes related to chronic pain also manifest as dysregulation of cognitive, neuromuscular, and autonomic systems and the endogenous opioid system[33]. Thus, an entanglement of biological (sensory-motor, inflammatory, and immune systems), psychological, and social factors yields the most promising explanations for the pathogenesis of fibromyalgia [70,98].

CHRONICLES OF CHRONIC PAIN IN FIBROMYALGIA

Despite clinical recognition of fibromyalgia as a chronic pain disorder, there is no set of criteria based on controlled studies involving FM patients, carried over substantial lengths of time, that deals distinctly with how to approach fibromyalgia that remits or appears from time to time[99]. The Ising model from physics has been utilized to enlighten on acute pain distributed chronification when minor variations lead to sizeable and neural networks undergo synchronization and desynchronization. The shaping and reshaping of neural networks induced by multifaceted pain-modulating, pain experience-regulating mechanisms reset and lock the homeostat at a higher level, which leads to a continued persistent pain experience [30,100].

A review of the literature also supports a robust bidirectional link between persistent pain and psychosocial variables such as mood disorders, depression, anxiety, and distress associated with the transition from acute to chronic pain[19]. In response to peripheral inputs, neuroplasticity develops, and CS is exacerbated, evolves & progresses further. The stages of its development are activation (transient, activity-dependent), modulation (slower but functional changes occur), and modification (chronic, irreversible structural and architectural alterations) [27]. The transition from peripheral to central sensitization is a form of pain chronification [32]. Central sensitization may also occur without peripheral sensitization, as in fibromyalgia-associated hyperalgesia, which arises spontaneously without tissue damage[27]. This increase in central sensitization across time also helps explain how autonomic dysregulation manifests chronically in painful disorders[78]. Understanding the time-dependent changes in mechanisms resulting in pain chronification and time-varying responses to cytokines will enable us to stage chronic pain and provide tailored interventions to FM patients[45].

BRIDGING ETIOLOGY AND PATHOPHYSIOLOGY IN FIBROMYALGIA

While the above sections highlight the emerging neurocircuitry and mechanisms associated with chronic widespread pain and neuroendocrine & autonomic signatures in FM, more work remains. Efforts are needed to contextualize the pathophysiology of FM within a biopsychosocial framework and associated autonomic dysfunction. The understanding of FM heterogeneity will help highlight the importance of individual differences and the need for precision medicine for various FM subtypes [92]. Few studies have reported traumatic life events, and understanding the impact of these experiences on FM pathophysiology can provide essential insights [71]. Certain novel findings have also been reported that may supplement the treatment options in fibromyalgia, such as the transfer of neutrophils from primed mice and patients with FM confers mechanical pain to recipient naïve mice, sensitizes evoked action potential firing of spinal cord neurons, and causes neutrophil infiltration into the dorsal root ganglia. Further investigations focussing on the neutrophil phenotype in FM to shed light on mediators of the cross- talk between these neutrophils and sensory neurons are necessitated to develop therapeutic targets for pain control [101].

GAPS IN FIBROMYALGIA CARE:

Pathogenesis of fibromyalgia pain is complex, and apparent gaps in etiology and diagnosis result in insufficient and ineffective management.

These gaps include a knowledge deficit regarding the mechanisms underlying chronic pain in fibromyalgia, the debatable status of nociplastic pain terminology, and drug overdependence. Doubtful recognition of nociplastic pain in fibromyalgia is one fundamental issue that has been a matter of discussion over recent years since a group of experts from the International Association for the Study of Pain explains the pathogenesis of fibromyalgia as "nociplastic pain" instead of nociceptive or neuropathic pain. The nociplastic pain concept mechanistically describes central sensitization in fibromyalgia instead of the available evidence advocating fibromyalgia as neuropathic pain syndrome[102]. Similarly, the chicken-egg analogy can be applied to overlapping similar pain disorders like fibromyalgia and myofascial pain syndrome (MPS). Whether chronic pain is related to long-term activation of peripheral pain pathways causing central sensitization leading to the development of FM or primary FM disorder culminates into MPS is unknown [80].

Similarly, the cause and effect of autonomic dysfunction and chronic widespread pain in fibromyalgia remains unknown. The cause of pain vulnerability in some populations is unknown [103]. However, the literature mentions the need for further research on why pain in some conditions is localized, whereas in other states, pain is diffuse. Unraveling the actual role of nociplastic pain in all chronic pain conditions is paramount in precision medicine and may provide an alternative model of care[21]. The trigger for phenotype switch in DRG neurons after peripheral inflammation, infection, or nerve injury or spontaneously in fibromyalgia, which induces central sensitization only in some individuals, is yet to be wholly understood [40]. Various clinical, psychosocial, neurophysiological, and pharmacological components form the basis of the large inter-individual variability of pain and treatment response [104]. We have reported a significant yet unmet need for including personality biomarkers and patient characteristics to guide personalized pain treatment [92].

BIOPSYCHOSOCIAL INTERVENTIONS FOR FIBROMYALGIA PAIN

A cornerstone of the biopsychosocial model is the emphasis on examining the psychological and social components, in addition to the physical features of an FM patient. Here, we outline the elements of a comprehensive biopsychosocial approach for increased pain perception in FM in light of the autonomic dysfunction, which we consider to hold the center stage in the pathophysiology of fibromyalgia (figure 1). The importance of an interdisciplinary team management strategy in this model seems unarguable. Different team members, including physicians, and psychologists, nurses, can screen the FM patients and assess biopsychosocial factors. Appropriate pain treatment for FM patients should be tailored to the pain phenotype and FM subtype. Fibromyalgia patients' current rehabilitation programs focus on pharmacological management only. In synergy with drug therapy, recognizing the biopsychosocial factors can steer clinicians toward additional treatment approaches, such as pain neuroscience education, cognitive behavioral techniques (CBT), or self-regulation/mindfulness strategies. CBT plus pain neurophysiology education with therapeutic exercises is more effective than applying only a drug regimen. Accordingly, multimodal/ multifactorial treatment approaches using a biopsychosocial model, which addresses relevant comorbidities and lifestyle factors for each patient, might amplify the rehabilitation effects for FM patients and produce the most successful treatment outcomes.

Whatever the mechanism, the aim of psychophysiologically based interventions such as relaxation techniques are also advised and designed to reduce levels of muscle activity and autonomic arousal, thereby decreasing pain[70].

Table 1- Biopsychosocial Interventions Modalities for Fibromyalgia Pain

Modalities	Operating Strategies
Psychological Means	· Education & reassurance: stress management, Cognitive psychotherapy, management of dysfunctional behavior, Sleep hygiene training, caffeine reduction
Social means	· Increasing social networks, Family psychotherapy
Biological Means	· Biofeedback, relaxation training, Exercise, endurance, flexibility and strength exercises
Autonomic	
Neuromodulation	· TENS (transcutaneous electric nerve stimulation)
Pharmacological means	· Antidepressants (duloxetine, milnacipran) and anticonvulsant (pregabalin).
	· Medication that targets key symptoms (i.e., fatigue, sleep, depression) of FM should also be considered as adjuncts to exercise and CBT

Conclusion

A mechanistic explanation for pain chronification may not be sufficient to address and manage chronic pain in FM patients. A lacuna in understanding the pathophysiology of chronic pain and biomarker-driven assessments for fibromyalgia needs to be filled. Biopsychosocial factors contribute to pain modulation and may serve as a tool for better phenotyping that will lead us towards improved quality of life for FM patients. Chronic pain in FM has several psychosocial and functional consequences in the domains of cognition, emotion, and behavior. As the tenets of the biopsychosocial model suggest, chronic pain is a multifactorial phenomenon with many physiological and psychosocial components. The array of biopsychosocial factors in FM patients should be identified and treated as potential risk factors, to improve our ability to predict pain and treatment response, paving the way for personalized pain treatment.

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Figure 1:

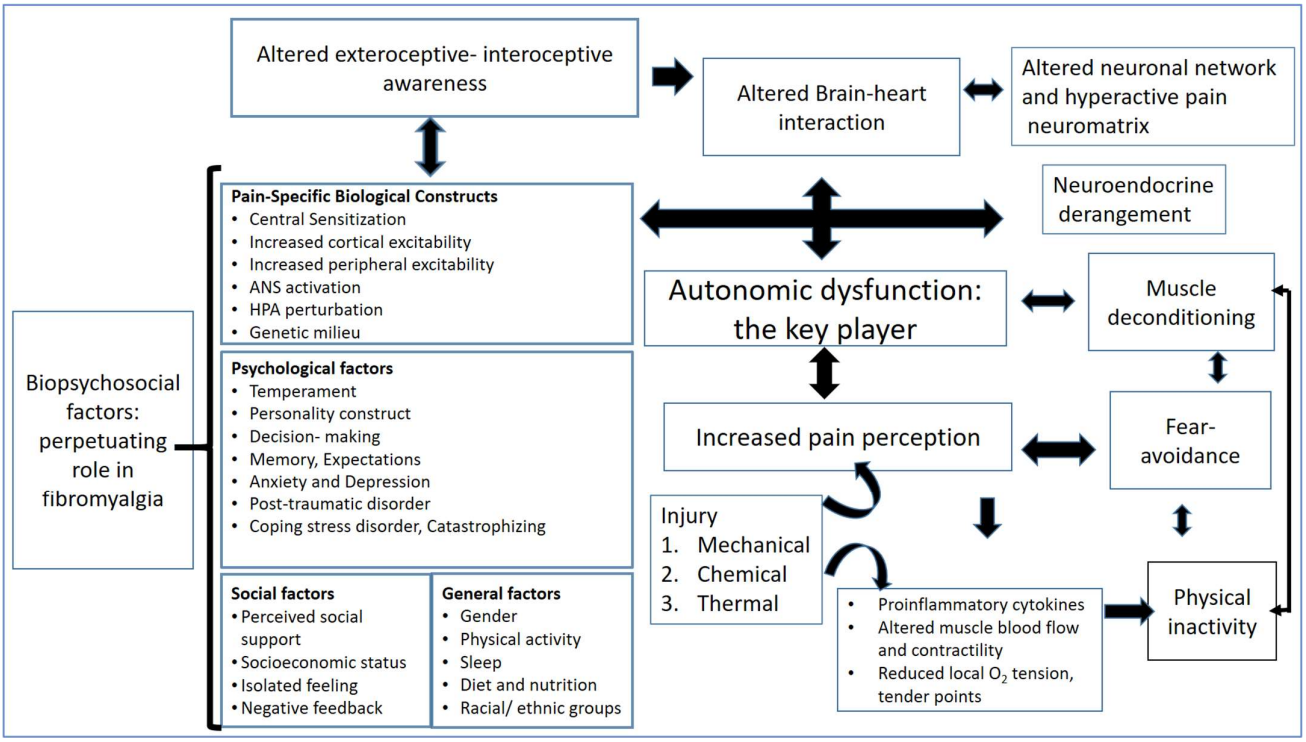

Figure 1 legend: Addressing biopsychosocial factors that are involved in persistent and widespread pain in fibromyalgia should be the focal point of all management strategies. Autonomic dysfunction, which manifests as an increased resting sympathetic activity and decreased stress reactivity seems to be the key player in the fibromyalgia pathophysiology.