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Review Article

The neurological and epigenetic basis of psychosomatic pain: a narrative review.

[1]Dr. Nidhi Vadhavekar, [1]Dr. Manu Pandya, [2]Eisha Naveed, [3]Revan Gunasekaran, [4]Dr. Muskan, [5]Purbali Mitra, [6]Biniam Jemjem, [7]Dr. Muhammad Junaid

[1]Padmashree Dr. D.Y Patil School of Medicine
[2]Liaquat University of Medical and Health Sciences, Jamshoro-Pakistan
[3]K.A.P.V Government medical college, Tamilnadu, India
[4]Kalpana Chawla Government Medical college, Karnal,India
[5]University of Southampton, United Kingdom
[6]Saint Paul Hospital Millennium Medical College, Addis Ababa, Ethiopia
[7]Khyber Medical College, Pakistan

Abstract

Psychosomatic disorders, which are now understood through an integrated biopsychosocial model that bridge the gap between psychological stress and physiological dysfunction of the body. Epidemiological data highlight the widespread prevalence of these disorders globally, particularly in adolescents and high-risk adult populations, who are the ones with significant comorbidities like depression, anxiety, and chronic pain syndromes like fibromyalgia.

The core of this paradigm shift lies in the integration of epigenetics, which demonstrates how chronic stress and trauma can induce stable, long-term changes in gene expression without altering the DNA sequence. Specifically, epigenetic modifications, such as DNA methylation of genes like FKBP5, NR3C1, and BDNF, are shown to dysregulate the hypothalamic-pituitary-adrenal (HPA) axis, heighten inflammatory responses, and impair neuroplasticity, thereby embedding psychological distress into a physical, somatic reality.

Neurological investigations, particularly using functional neuroimaging, reveal that these disorders are not fabricated but are rooted in aberrant neural circuitry. Conditions like functional neurological disorder (FND) are characterized by disrupted connectivity between emotion-processing centers (e.g., the amygdala) and sensorimotor pathways, leading to involuntary physical symptoms. The clinical features of these disorders are multifaceted, marked by a heightened focus on bodily sensations, negative healthcare experiences, and significant functional impairment.

Evolving beyond traditional methods, psychosomatic disorder treatment is now integrative and personalized. New approaches combine CBT with novel therapies like non-invasive brain stimulation, neurofeedback, and pharmacogenomics.

Keywords: Chronic pain, Epigenetics, Functional neurological disorder, Hypothalamic-pituitary-adrenal axis, Psychosomatic disorder.
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Corresponding Author
Name: Dr Nidhi Vadhavekar
Email: **nidhivresearch@gmail.com**

Introduction

Psychosomatic disorders are psychological disorders in which patients experience actual physical pain or sensations that cannot be medically explained. While prevalent in clinical settings, psychosomatic disorders still remain poorly understood, which is partly due to the persistent mind-body dualism embedded in medical thought [1]. But over the years, studies have started to explore how psychological stress, brain-based processes, and even epigenetic changes might all work together to trigger and sustain these disorders [2]. Comprehending these mechanisms is essential to developing personalized and effective interventions.

The psychosomatic model has come a long way from its historical roots in psychodynamic theory and Cartesian dualism. In the past, physical symptoms without clear biomedical explanations were often dismissed as "all in the mind." This not only reinforced stigma but also hid the physical aspects of these conditions [1]. Fibromyalgia,

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Irritable bowel syndrome (IBS), and somatic symptom disorder are now classified under this spectrum, persisting as a diagnostic and therapeutic challenge [3]. Psychological stressors can result in changes to the body's physiology, especially within the neural, endocrine, and immune systems [4]. There is also emerging research suggesting the role of chronic stress in activating epigenetic mechanisms as the psychosocial interface of longstanding psychological stressors and bodily dysfunction [2,5].

Among the most influential contributors to these conditions is psychological stress, which has profound physiological consequences. For example, Kuo et al. conducted a meta-analysis where they found that people with elevated psychosocial stress levels had a 45% higher risk of metabolic syndrome and even higher prevalence of stress syndrome from work-related stress (OR = 1.6971). This connection between emotional stress and metabolic dysfunction is driven by the HPA axis, as well as the production of inflammatory cytokines and autonomic imbalance. These are the same mechanisms that may cause symptom amplification in psychosomatic illnesses.[6]

Beyond external stressors, personality traits and psychological styles significantly influence how distress is interpreted and expressed. Cosci emphasizes the role of alexithymia, Type A behavior, and Type D personality, which is described as negative affectivity and social avoidance, and significantly modulates response to stress and illness behavior and illness response [7]. These traits predispose to the amplification of somatic and chronic symptoms, and the negative coping strategies in the management of chronic illnesses. However, psychological predispositions do not fully explain the onset or persistence of psychosomatic disorders. More and more research is revealing the potential of gene-environment interactions, and in particular epigenetic strategies, to play a role in the biological embedding of chronic stress and emotional trauma.

Epigenetics is essential in the onset and treatment of psychosomatic disorders because it balances the genetic factors and the environment's influence. Specific kinds of epigenetic changes, like Methylation of the DNA and its histones affects the genetic expression associated with the stress response and inflammation, as well as with neuroplasticity, which is critical in disorders such as irritable bowel syndrome, fibromyalgia, and PTSD [2,4]. Psychotherapy is emerging as a possible epigenetic treatment by inducing some positive epigenetic changes which could improve the effectiveness of treatment and help in preventing the disease in future generations [2]. Moreover, the interactions of epigenetic elements in schizophrenia and mood disorders contribute to these disorders. This suggests the need to address genetic and epigenetic factors in the psychosomatic disorders' framework in relation to their clinical features and course [8]. This evidence underscores the need to make strategies for psychosomatic disorders more effective by applying the concepts of epigenetics.

The goal of this study is to bridge the gap between psychological stress and somatic symptoms. This study seeks to unravel the phenomenon of psychological trauma and enduring stress, causing lasting shifts in the expression of certain genes that result in somatic pain and dysfunction, and explores psychological stressors in the context of trauma and chronic stress.

Methodology

This narrative review synthesizes current scientific literature to explore the bio-psychosocial basis of psychosomatic disorders, focusing on the role of psychological stress, epigenetics, and neurobiological mechanisms.

Relevant studies were identified through a comprehensive search of electronic databases, including PubMed, Scopus, and Google Scholar, up to the date of publication. The search strategy employed was a combination of keywords and Medical Subject Headings (MeSH) to identify articles related to the core themes of the review.

The search strategy, which was limited to English-language, peer-reviewed, published literature, key search terms included: "psychosomatic disorders," "psychosomatic pain," "functional neurological disorder," "epigenetics," "hypothalamic-pituitary-adrenal axis," "neuroimaging," "fMRI," and "neurofeedback.

Articles were selected based on their relevance to the review's scope, including original research, meta-analyses, systematic reviews, and scholarly reviews published in peer-reviewed journals. Inclusion criteria prioritized studies that provided direct evidence linking psychological stress to physiological and neurological changes, as well as those discussing novel treatment interventions.

Articles were excluded if they did not directly address the mind-body connection in psychosomatic or functional disorders. The final selection of references was curated to provide a representative overview of the current understanding and emerging trends in the field.

Epidemiology

Psychosomatic disorders represent a multifaceted interface between psychological and physical health, often emerging in response to stressors without identifiable organic

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pathology. Epidemiological studies globally and in diverse populations underscore the significance of these disorders in both developed and developing contexts. In children and adolescents, psychosomatic symptoms such as headaches, abdominal pain, and fatigue are prevalent, with rates ranging between 10–25% [9]. These symptoms frequently reflect stress responses to academic pressure, family discord, and peer challenges. In adolescents, girls show higher susceptibility, particularly during puberty, with notable peaks for stomachaches around age 9 and headaches near age 12[9].

In psychiatric populations in India, the prevalence of psychosomatic disorders was found to be 21.5%. Chronic pain (14.4%) and hypertension (9.9%) were most common, with higher rates among older adults, females, and urban dwellers [10]. The majority of these individuals were also diagnosed with neurotic disorders, suggesting strong links between psychosomatic symptoms and psychiatric conditions such as anxiety and depression. A school-based study in Croatia revealed that 37.4% of secondary school students experienced psychosomatic reactions (e.g., allergies, dysmenorrhea, acne), and 9.06% had established psychosomatic disorders (e.g., asthma, hypertension). Girls were disproportionately affected, and family stressors such as divorce and hereditary predisposition were significant contributing factors. Chronic pain—often considered a somatic manifestation of psychosomatic pathology—is another key aspect of this disorder spectrum. It affects nearly 30% of the global population [11].

In India, a 2018 survey found a chronic pain prevalence of 19.3%, with significantly higher rates in females (25.2%) and older adults [12]. The most affected anatomical sites were the knees and back, and many sufferers reported significant disruption in daily functioning and mental health. Chronic pain is highly comorbid with depression and anxiety. Global studies report comorbidity rates between 13–56% for depression [13]. In India, studies document depression prevalence in chronic pain sufferers ranging from 31% to 88%, with higher rates among women and those with lower socioeconomic status [12, 14].

Common comorbid conditions include fibromyalgia, rheumatoid arthritis, diabetic neuropathy, and cancer pain. Fibromyalgia, as a specific psychosomatic condition, exemplifies these complex comorbid interactions. It is associated with widespread pain, sleep disturbances, cognitive difficulties, and heightened stress response, with depression and anxiety frequently co-occurring [13,15]. Genetic predisposition, neurotransmitter dysregulation, and central sensitization have all been implicated in its pathophysiology. Neurobiological insights suggest that central nervous system dysfunction, immune dysregulation, and stress-related neurochemical changes (e.g., serotonin and norepinephrine imbalance) underpin these disorders [16]. Stress, in particular, has been consistently identified as a precipitating factor, influencing both physical symptoms and mental health outcomes.

The burden of psychosomatic disorders is not uniform. Ecological studies suggest clustering of illness in certain high-risk groups, shaped by sociodemographic, cultural, and psychological variables. Urbanization, modernization, and poor coping strategies compound the risk, making psychosomatic disorders a significant public health issue—especially in rapidly changing societies like India. In conclusion, psychosomatic disorders are widespread, often debilitating, and intricately tied to emotional and environmental stressors. Their comorbid association with Psychiatric illnesses like depression and anxiety further complicate diagnosis and treatment, necessitating integrated and biopsychosocial approaches in clinical practice.

Epigenetic basis

Recent years have witnessed the evolution of the mind-body interface direction towards the effects of chronic stress and trauma and its effect on long-term physiological dysfunction. Epigenetics, which is the science of studying genetic expressions without involving the changing of the DNA sequence, is serving as a lens to examine how stress and trauma impact physiological functioning. Psychological causes in the form of stress and trauma may result in DNA methylation, which may result in long-term physical health consequences. In the presence of long-term persistent symptoms lacking clear fibrotic pathology, the cumulative impact of these somatic symptoms can mark a person as chronically ill in the absence of diagnosable organic disease processes.

The tension of the majority of psychological influences is adequately described by the hypothalamic and pituitary adrenal HPA axis, which induces a hormonal reaction to stress. Traumatic experiences, particularly childhood, have been found to change cortisol response to stress. For instance, methylation of NR3C1, which is a well-known stress receptor, FKBP5, which is known to alter receptor sensitivity, and a number of other genes can contribute towards increasing cortisol levels and lead to the dysregulation of numerous stress response negative feedback loops [17,18]. To make matters worse, these changes appear to extend well into adulthood and have the ability to modify one's physiological response to stress. In animal research, maternal care has been recorded to affect levels of methylation in the NR3C1 gene: offspring nursed by responsive mothers have more regulated HPA activity than those nursed by inattentive ones [19]. This indicates that early life environmental experience becomes biologically embedded through epigenetic change.

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There is also evidence of epigenetic modification associated with trauma to the BDNF gene, which is responsible for supporting and adapting neuronal functions, contributing to epigenetic changes of neuroplasticity. Patients with a history of abuse present with BDNF hypermethylation, which is associated with impaired emotional regulation and heightened pain sensitivity [20]. The same epigenetic patterns have been reported for patients with post-traumatic stress disorder (PTSD), especially in immune and stress pathway regulating genes [21]. These results indicate that trauma may create molecular scars that affect susceptibility to long-term somatic symptoms.

In addition, the immune system plays this role as a significant other intervening factor. Chronic stress is able to upregulate pro-inflammatory cytokines like IL-6 and TNF-α, not only through neuroendocrine mechanisms but also through epigenetic modification of the promoters of these genes [22]. Early adversity has also been linked with enduring changes in inflammatory gene expression, leading to chronic low-grade inflammation [23]. This inflammation frequently accompanies conditions of fatigue, pain, and gastrointestinal dysfunction, even where there are no structural abnormalities. Immune dysregulation such as this could be a molecular bridge between somatic experience and psychological history.

Furthermore, neuroepigenetic variations in genes that govern emotion and pain modulation further complicate matters. For example, the serotonin transporter gene SLC6A4 has been associated with poor control of mood and pain perception due to its active methylation [24]. In the same way, methylation of OXTR (oxytocin receptor gene) has been implicated in reduced emotional resilience and reduced stress-buffering by means of social support [25]. Some neuroimaging studies indicate that these molecular changes may accompany a change in the function of the amygdala and the prefrontal cortex, which have important functions in the pain amplification and emotional salience [26].

The role of epigenetics extends beyond the individual. Research indicates that trauma-induced epigenetic marks, especially in genes such as FKBP5, can be transmitted across generations. For instance, descendants of Holocaust survivors exhibit the same methylation changes as their parents, which suggests defensive biological methylation changes from stress are inherited among the generations [27]. In models studying the effects of stress, some animals exhibit a range of behavioral and hormonal changes that can be passed on to subsequent generations through changes in the methylation of sperm RNA and DNA [28]. Such intergenerational transmission points to how unresolved psychological trauma can perpetuate somatic vulnerability across generations.

Such findings provide promising therapeutic potential. Epigenetic markers like methylation of NR3C1, BDNF, or FKBP5 may potentially be used to identify those at increased risk for somatic disorders precipitated by stress. Some epigenetic alterations have a silver lining: some are reversible. There is evidence that psychosocial treatments like cognitive-behavioral therapy (CBT), mindfulness, and stress reduction programs can influence DNA methylation in genes involved in stress [18]. Research is also in progress for pharmacological therapies, like certain histone deacetylase inhibitors, that may reverse some of the changes in gene expression and the related methylation changes. Targeting the underlying biology of symptoms, rather than just treating, these methods could potentially provide more effective and targeted treatment options.

To summarize, epigenetic factors offer insight into the impact of life events, particularly repeat stress and trauma, in shaping one's biology and health. The modified gene expression in stress, immune, and neurobiological systems determines the chronic somatic responses seen in many complex illnesses. This model moves our understanding beyond a strictly psychosocial framework to a molecular physiology basis and makes possible integrative treatments that address both body and mind.

Clinical features

The Somatic Symptoms Experiences Questionnaire (SSEQ) identifies four major contributors. Individuals often become overly focused on minor bodily sensations, misinterpreting them as signs of serious illness. This can lead to heightened anxiety, increased symptom awareness, and frequent medical consultations [29]. Even without clinical evidence, many patients genuinely feel ill. This internal conviction reinforces their identification with the "sick role," interfering with normal daily functioning. Many patients report feeling unheard or dismissed by healthcare providers. These negative experiences can reduce trust, hinder treatment engagement, and prolong suffering [29]. The emotional toll of ongoing unexplained symptoms often affects work, relationships, and social functioning, which in turn reinforces the perception of physical illness. Together, these factors highlight how emotional and psychological stressors can manifest physically. Addressing these root causes is vital for effective and empathetic management of psychosomatic disorders [29].

Depression and anxiety often present with physical symptoms, especially in primary care. A large study found that depression, anxiety, and somatization frequently co-occur, leading to a complex clinical presentation. Patients with overlapping psychological symptoms reported more severe physical complaints—such as fatigue, pain, and digestive issues—often without a medical cause. Each

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condition affected daily life differently: depression impaired motivation and social engagement, while somatic symptoms increased healthcare use and physical limitations. This evidence underscores the strong link between mental and physical health, calling for integrated care that addresses both together [30].

Emotional distress often manifests as physical symptoms like fatigue, pain, and digestive issues. A large international study found that people with anxiety, depression, or high stress frequently report multiple unexplained bodily complaints. This mind-body connection was consistent across cultures [31]. The study also showed significant overlap between anxiety and depression symptoms, complicating diagnosis based on physical signs alone. These findings stress the importance of a holistic clinical approach that includes mental health evaluation to improve diagnosis and treatment [31].

In primary care settings, distinguishing between emotional distress and physical illness is frequently challenging. Patients with depression, anxiety, or chronic stress frequently present with somatic symptoms like headaches, fatigue, gastrointestinal discomfort, or chest pain—despite no underlying physical pathology [32]. These symptoms often reflect psychological distress and are highly comorbid with somatoform disorders, complicating diagnosis and management. Chronic stress alters physiological responses and heightens bodily awareness, leading to real discomfort that lacks a clear organic basis [32]. This diagnostic

Overlap underscores the need for integrated care models that assess both mental and physical health, especially when patients present with vague or unexplained symptoms.

Emerging evidence also links somatic symptom disorders to underlying personality traits. A 2021 review emphasizes how emotional dysregulation, negative affectivity, and harm avoidance contribute to heightened somatic focus and health anxiety [33]. These individuals tend to internalize stress and express psychological pain physically, not consciously exaggerate symptoms. Recognizing the influence of personality dynamics is critical for accurate diagnosis and comprehensive management [33].

Psychosomatic disorders, mainly those involving functional neurological symptoms, are increasingly understood through advancements in neuroimaging and clinical neuroscience. These disorders often exhibit disruptions in normal neural communication between emotion-processing centers and motor or sensory pathways. Studies associated with functional MRI have identified hypoactivity in motor-related regions and altered connectivity in areas like the anterior cingulate cortex and amygdala, suggesting impaired integration of emotional and sensorimotor processing [34,35]. These findings reflect an underlying neurobiological reasoning that can generate motor or sensory symptoms in the absence of structural brain abnormalities. The frontal and parietal cortices show altered activation in functional neurological disorder (FND). This explains why patients often experience involuntary symptoms despite intact motor circuits [36]. Moreover, limbic dysregulation, particularly due to stress and trauma, seems to play a central role in symptom generation, possibly by influencing downstream somatic responses through hypothalamic and brainstem connections [36]. FND is a psychosomatic dysfunction where neurological symptoms such as paralysis, non-epileptic seizures, or gait disturbances arise without identifiable structural lesions. It is increasingly classified as a "network disorder" rather than one of isolated deficits [37]. Further, altered resting-state connectivity between motor cortices and emotional processing areas like the insula and amygdala supports the hypothesis that FND is rooted in disrupted top-down modulation of bodily functions. This neural dissociation aligns with clinical observations of patients exhibiting clear symptom fluctuations in relation to emotional triggers or psychosocial stressors [38].

Aybek et al.found abnormal activation in the limbic system and prefrontal cortex during the recall of emotionally charged autobiographical memories in patients with conversion disorder. These neural patterns may contribute to the manifestation of motor or sensory symptoms as a form of dissociative coping. Furthermore, the amygdala exhibits hyperactivity during such tasks, possibly leading to autonomic and somatic disturbances. In this light, conversion symptoms can be interpreted as neurologically embedded expressions of unresolved psychological distress, with disruptions in memory recall pathways playing a central role [39].

Treatment interventions

Traditional approaches like psychotropic medications and cognitive-behavioral therapy (CBT) are helpful for some patients, but many continue to suffer without significant improvement. Recent developments in neuroscience and personalized medicine are introducing new, more targeted treatment strategies [40,41]. One area gaining attention is non-invasive brain stimulation (NIBS). Techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) can target specific neural circuits involved in psychosomatic symptoms. TMS directed at the dorsolateral prefrontal cortex (DLPFC) has shown potential in reducing pain and emotional distress in conditions like fibromyalgia and somatic symptom disorder [42]. In patients with FND, reduced activity in motor planning areas and impaired connectivity between the supplementary motor area and limbic circuits suggest a

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disconnect between intention and movement [43]. Likewise, tDCS applied over the motor cortex has demonstrated improvements in mood and pain perception in patients with functional pain syndromes [44].

Another promising approach is neurofeedback, particularly real-time functional MRI (rt-fMRI) neurofeedback, which trains individuals to regulate their own brain activity. A foundational study showed that patients could reduce their perception of pain by learning to control activity in the rostral ACC. More recent trials have explored neurofeedback for FND and chronic somatic pain, with encouraging results [45].

Personalized treatment strategies are also incorporating genetic, imaging, and physiological data. Certain genetic polymorphisms, such as in the serotonin transporter gene (5-HTTLPR) and the catechol-O-methyltransferase (COMT) gene, have been linked to varying responses to antidepressants and CBT in patients with somatoform disorders. Similarly, differences in resting-state brain connectivity and heart rate variability may help predict which patients are likely to benefit from specific treatments [46,47].

There is growing interest in multimodal, integrated treatment approaches. These may combine psychotherapy, neuromodulation, and pharmacogenomic-guided medication choices. For instance, a patient with FND might receive CBT, TMS targeting the DLPFC, and antidepressants selected based on their genetic profile. Mind-body practices such as mindfulness-based stress reduction (MBSR) are also showing benefits in improving autonomic regulation and brain network function in psychosomatic disorders [48,49].

Ongoing research is focused on identifying biological subtypes within these disorders using machine learning on multimodal data. This could allow for truly personalized treatment plans. At the same time, there is a shift toward transdiagnostic models that view psychosomatic disorders as part of broader dysfunctions in brain-body integration, rather than isolated diseases [50].

Conclusion

The comprehensive analysis of psychosomatic disorders reveals a fundamental paradigm shift away from traditional mind-body dualism toward an integrated, biopsychosocial understanding. The evidence presented systematically demonstrates that chronic psychological stress and trauma are not merely triggers but are capable of inducing tangible, long-term physiological changes. These changes are mediated by the dysregulation of key biological systems, including the hypothalamic-pituitary-adrenal (HPA) axis, and are further compounded by epigenetic modifications that alter gene expression related to stress, inflammation, and neuroplasticity.

Epidemiological and clinical data underscore the widespread prevalence of these disorders and their significant comorbidity with psychiatric conditions and chronic pain syndromes. The neurobiological findings, particularly in functional neurological disorders, provide concrete support for a "network disorder" model, where aberrant neural communication, rather than structural pathology, accounts for the physical symptoms.

While this review synthesizes compelling evidence for an integrated model, the field of psychosomatic medicine still faces significant challenges that limit our current understanding and therapeutic efficacy. One primary challenge is the heterogeneity of patient populations. Psychosomatic disorders, including functional neurological disorder (FND) and fibromyalgia, manifest with a wide range of symptoms that vary greatly between individuals. To overcome this, future research must focus on longitudinal, multi-modal studies that track changes in neurobiological, physiological, and psychological markers over time. A second major limitation is the lack of strong, replicable epigenetic research. The development of epigenetic biomarkers for diagnosis and treatment response remains a promising but largely unrealized goal.

Furthermore, current therapeutic interventions are limited by a lack of personalization. Treatment approaches such as cognitive-behavioral therapy (CBT) and non-invasive brain stimulation (NIBS) show promising results; however, their efficacy is not uniform across all patients. This highlights the need for a shift toward personalized medicine that integrates genetic, neuroimaging, and psychological data to tailor interventions. For example, pharmacogenomics could be used to select antidepressants based on a patient's genetic profile, and neurofeedback protocols could be designed to target specific dysfunctional neurological circuits identified through fMRI.

Hence, the future of care necessitates a move beyond monotherapy, combining psychotherapeutic interventions with advanced modalities such as non-invasive brain stimulation, neurofeedback, and pharmacogenomic-guided treatments.

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