

Functional Neurological Disorder: Historical Trends and Urgent Directions

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Abstract

The objective was to identify the gaps in understanding and management of functional neurological disorders (FNDs) that could be negatively impacting its incidence, prevalence, prognosis, and preventive tools. A narrative review was performed to synthesize evidence from multiple fields including genetic, epidemiological, functional neuroimaging and clinical studies, paying close attention to FND historical trends and recurring themes in nomenclature, classification, epidemiology, therapeutic tools, outcomes, prognosis, and pathophysiology. References included in this review were sourced from PubMed, covering January 1, 2000 to June 30, 2022, and from the references of relevant articles. Multiple problems associated with the current status of approach and management of FNDs were identified, including six major knowledge gaps. To overcome such shortfalls, we recommend the collaborative creation of a multi-network management algorithm that integrates all pathophysiological mechanisms involved in FND onset and perpetuation. It is hoped that an integrative model will facilitate the development of a biographically focused, biopsychosocial-spiritual management and preventive protocol, which incorporates key concepts and skills from the fields of neurology, psychiatry, psychology, and physiotherapy. Such comprehensive and concise protocol could be distributed through upskill programs across several medical specialties. Multidisciplinary collaboration is needed to fill current knowledge gaps, with multispecialty teams helping to overcome the deficits in outcomes and prognosis still affecting FND, one of the commonest and most expensive neurological disorders currently affecting humankind.

Keywords: Functional neurological disorders; Conversion disorder; Functional seizures; Psychotherapy; Pathophysiology

Introduction

Functional neurological disorder (FND) is caused by dysfunc-

tional structures, and networks within the nervous system, in the presence of normal anatomy and tissue structure, what experts convey as “normal hardware but dysfunctional software”. FND is associated with a large number of neurological symptoms and manifestations, presenting to multiple specialists. Despite clear findings steaming from epidemiological, functional imaging, and clinical studies, FND outcomes and prognosis remain suboptimal. In this manuscript, we review FND historical trends and current epidemiological, pathophysiological, therapeutic, and clinical data. Each section presents scientific evidence, highlighting knowledge gaps and emphasizing current approaches to management of FND, which will be of greatest interests to clinicians encountering FND.

Search Strategy and Selection Criteria

References included in this review were identified by searches of PubMed between January 1, 2000 and June 30, 2022, and from the references of relevant articles. The following search terms were used: “hysteria”, “functional”, “functional symptom”, “functional neurological disorder”, “FND”, “conversion disorder”, “somatoform”, “psychogenic”, “psychosomatic”, “medically unexplained”, “functional motor”, “functional weakness”, “functional movement”, “functional seizures”, “functional cognitive”, “PNES”, “nonepileptic seizure”, “functional neurological”, and “children”. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this review.

Historical Trends of FND Classification

Nomenclature throughout history

FND denotes a condition first described in 1900 B.C. in Egypt, characterized by behavioral abnormalities among women who experienced impediments in marriage and childbirth [1, 2]. By 400 B.C., the condition was named “hysteria”, derived from the Latin word “*hystericus*”, meaning uterus or womb [3]. During the 19th century, Sigmund Freud introduced the term “conversion”, describing it as physical symptoms resulting from childhood trauma and unconscious conflicts, which were converted to neurological symptoms [4].

In 1968, the International Classification of Diseases (ICD)-6, and Diagnostic and Statistical Manual of Mental Dis-

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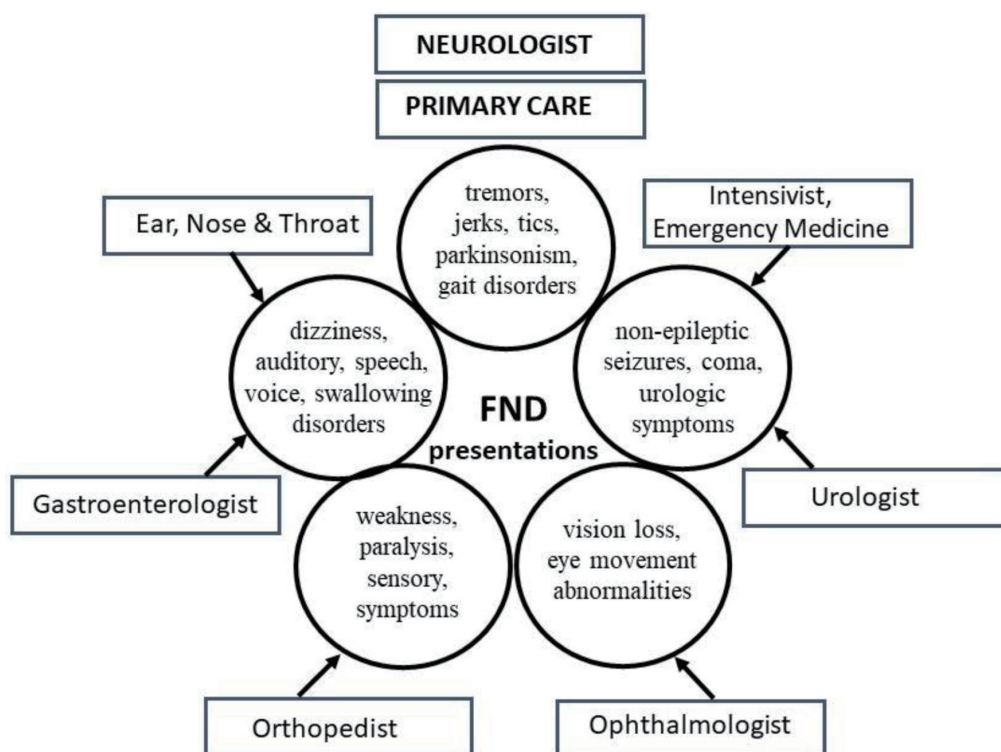


Figure 1. Common functional neurological disorder (FND) presentations and specialists involved in their care. Multiple symptoms grouped together depict the complex FND presentations encountered by various physicians simultaneously. Neurologists and primary care physicians (PCPs) evaluate most symptoms.

orders (DSM)-II [5] classified hysteria as “psychoneurosis”, or of psychogenic origin. In the DSM-III and ICD-9 of 1980, conversion disorder was categorized under “somatoform disorders”, conjoined with hypochondriasis, and somatization [6]. Past and current nomenclature and classification consistently link subconscious psychological processes to functional physical ailments. The importance of this association is further explored in the pathophysiology section.

In 1994, the DSM-IV noted that conversion disorder had multiple subtypes, encompassing motor, sensory, seizures, and mixed [7]. The DSM-V of 2013 [8] introduced the term functional neurological symptom disorder, between parentheses, representing a pathophysiological understanding extending beyond the psychological theory of conversion. In 2022, the DSM-V-TR (text revision) [9] updated the nomenclature by simply moving “conversion disorder” between parentheses. Thus, “conversion” remains part of the latest classification, despite its affiliation to Sigmund Freud’s pathophysiology, rooted in purely psychological mechanisms of disease production, accompanied by associated stigma.

The official term for FND is “functional neurological symptom disorder”, which is rarely used by scientists, clinicians, or patients. Instead, the term FND, without the word symptom is the most often used by patients and the medical community. In fact, patients with FND rarely present with a single symptom, but rather a multitude of symptoms, spanning diverse organs and systems, frequently simultaneously, changing over time, and oftentimes disabling. This disparity

between the DSM’s official nomenclature used in healthcare records, patients’ and clinicians’ experiences, is problematic. The official name “functional neurological symptom disorder”, inadequately encapsulates its clinical presentations. Members of the DSM workgroup should consider adjusting the name of the condition to “functional neurological disorders”, eliminating the word “symptom” and the term “conversion”.

FND will be the terminology utilized throughout this manuscript to align with the predominant body of evidence. Terminologies such as “conversion”, “somatoform”, “psychogenic” and “psychosomatic” will be avoided and substituted with “functional”. For example, “functional seizures” will be used instead of “psychogenic non-epileptic seizures”. We extend this recommendation to all healthcare professionals and patients.

Functional disorders (FD) and FND: current classification considerations

FND refers to a neurological disorder arising from dysfunctional structures and pathways within the nervous system, categorically in the presence of normal anatomy and structure. As the nervous system participates in the functioning of all organs and systems of the human body, its dysfunction can manifest with a multitude of clinical presentations. As a result, patients present to various medical specialists [10] outside the boundaries of neurology (Fig. 1). However, the commonalities under-

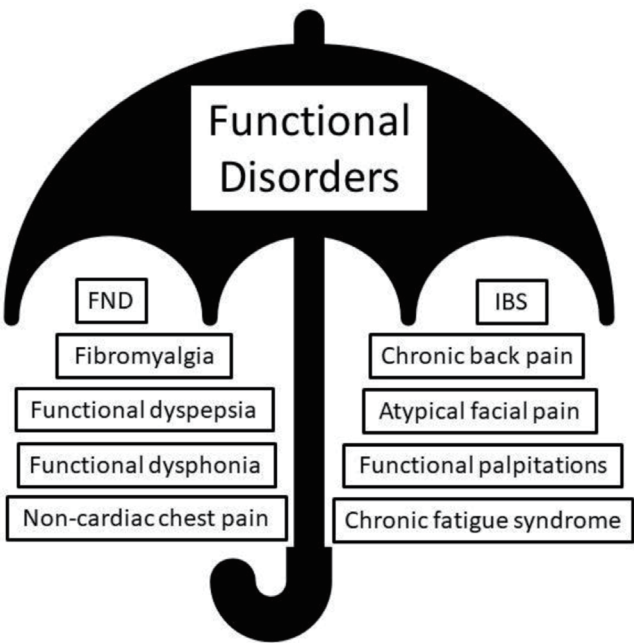


Figure 2. The umbrella of functional disorder (FD), containing functional neurological disorder (FND) and other extra-neurological functional diagnosis.

lying the many functional symptoms encountered in medical practices are frequently overlooked, with patients frequently referred to multiple consultants, and often sub-optimally managed.

An expanding umbrella of FD is being increasingly recognized, under which multiple symptoms and conditions affecting various organs and systems are identified. For years, FND experts have understood that some of the commonest extra-neurological presentations of FD include fibromyalgia,

chronic fatigue syndrome, and irritable bowel syndrome [10] (Fig. 2). Recent evidence suggests shared risk factors and pathophysiological mechanisms underlying many of these conditions [11].

Common dysfunctional cortical and subcortical regions and pathways, involving brain structures mediating emotional, autonomic, and sensorimotor (somatic) functions, such as the thalamocortical pathways, the somatosensory cortex, the insula, and the amygdala, are shared between several FDs, such as FND, pain disorders [12] and migraine [13, 14]. Studies report overlapping dysfunction across four major FND phenotypes: movement disorder, seizures, cognitive and dizziness, without significant pathophysiological differences, for example defective sensory processing, limbic-motor, cognitive-emotional networks, attention and interoception [11, 15] have been noted across subtypes. Patients with functional motor disorders often reveal similar clinical manifestations, such as depression, anxiety, pain, fatigue, and sensory symptoms [16, 17]. This evidence favors the presence of a complex and large, shared, series of pathophysiological mechanisms interlinking various FND subtypes.

Despite this pathophysiological overlap, in clinical practice, the FND diagnosis is quite reductionist, and typically assigned according to the predominant symptomatology or phenotype observed during the encounter, such as FND with mixed symptoms, abnormal movements, or weakness (Fig. 3). This approach may lead providers to infer that each FND subtype represents a distinctive etiology and pathophysiology, characterized only by the clinically manifested defective neural network. For example, while managing a patient with functional motor disorder, the physician recognizes the dysfunctional motor pathways, but may overlook the abnormal limbic, sensory, and attentional processes often present and in need of treatment. The noteworthy overlap in pathophysiology across FND subtypes should be considered when designing universal management protocols. Equally, individualized management

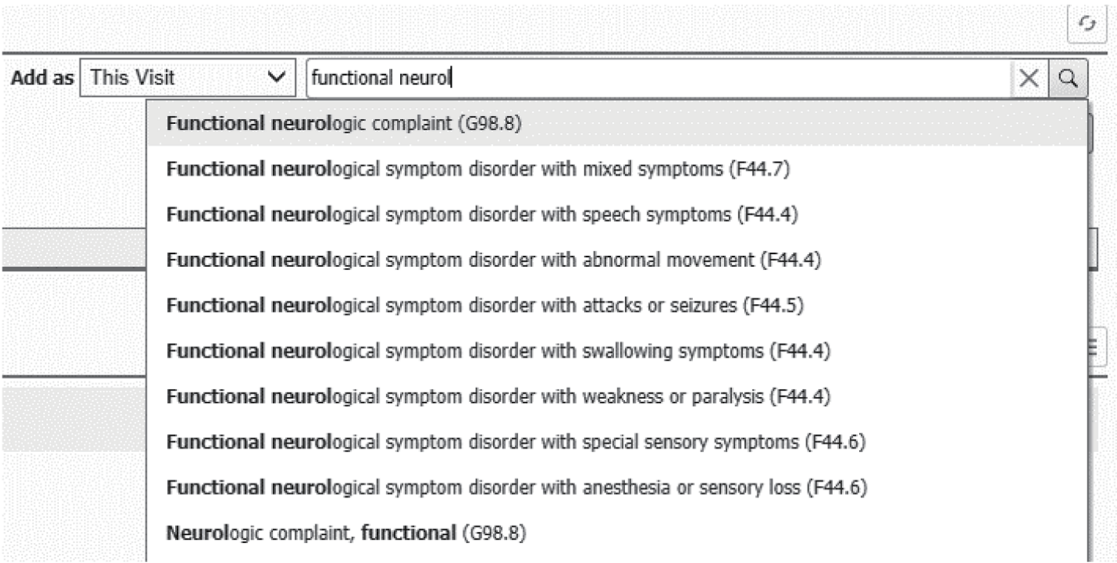


Figure 3. Electronic healthcare record screenshot demonstrating functional neurological disorder (FND) sub-diagnostic categories.

Table 1. Factors Concerning FND and FD Classification and Management

1. FND patients present to multiple specialties.
2. A large umbrella of FD is increasingly recognized.
3. Shared dysfunctional structures, pathways, risk factors and pathophysiological mechanisms underly various FD.
4. Patients with FND commonly have psychological and functional physical symptoms.
5. FND’s reductionist healthcare record classification may overlook the shared pathophysiology across subtypes.
6. There are no generally available management protocols to guide the specialists who evaluate functional symptoms, including PCP, to help them target the common pathophysiological processes and provide individualized FND treatment based on phenotype.

FND: functional neurological disorder; FD: functional disorder; PCP: primary care physician.

contemplating all the functional manifestations of each individual’s presentations is needed.

FND patients frequently have multiple psychological and functional physical symptoms, from various organs and systems simultaneously [18-21], such as anxiety, dissociation, fatigue, cognitive, sensorimotor (somatic) disturbances, more frequently than patients with organic neurological problems [22, 23], often associated with lower quality of life (QOL) [24-26], and poor outcomes [27, 28]. Avoiding mind-body dualism [29] and addressing psychological factors even when they are not easily apparent [8], have been emphasized. However, there are no guidelines about the extent and scope of the psychological assessment to orient the various specialists involved in FD care, including the primary care physician (PCP), who is often responsible for initial management.

This briefly analyzed classification consideration about FD and FND identifies the following remarks (Table 1).

Multidisciplinary collaboration in classification and management

Given the many symptoms individuals with FD present, it would be advantageous for neurologists to collaborate with other specialists, including rheumatologists, pain management, gastroenterologists, as well as members of the DSM workgroup, to create a more accurate and comprehensive mind-body classification system, clarifying that what is being increasingly recognized is an umbrella of FD. Individuals with FD present with conditions such as fibromyalgia, chronic fatigue syndrome, functional dyspepsia, irritable bowel syndrome (IBS), functional palpitations, and non-cardiac chest pain [10]. In alignment with this, experts in medical nomenclature and classification should consider updating the terminology permeating FD. For instance, 1) a grouping of functional rheumatological disorders (FRDs), including conditions such as fibromyalgia, and chronic fatigue syndrome, 2) functional gastrointestinal disorders (FGIDs) embracing functional dyspepsia and IBS, and 3) functional cardiovascular disease (FCVD), comprising functional palpitations and non-cardiac chest pain. This updated classification system, grouping functional diagnostic entities according to organs and systems, will allow for a more thorough study of the dysfunctional processes taking place in the sensory-motor structures of each system in connection with the abnormal central nervous system networks. Such an approach would strengthen collaboration between neurologists and clinicians from different spe-

cialists, allowing them to obtain a deeper understanding of the pathophysiological mechanisms affecting the organs and systems, ultimately improving management algorithm and patient outcomes.

From such a functional understanding, a comprehensive management protocol capable of targeting the shared pathophysiological mechanisms across FD will be more easily developed.

Epidemiological and Social Trends

Older and modern risk factors

Risk factors for FND follow a biopsychosocial model, and include adverse physical, emotional, mental, and environmental circumstances that can occur at early ages (Fig. 4) [30-34]. Although this review focuses on adult FND, it is necessary to provide key data on pediatric FND to demonstrate the relationship between life stages and the childhood-adulthood functional continuum, as characteristics of FND in childhood will inform adult management and disease prevention.

Adult FND patients tend to have a history of traumatic childhood experiences [35, 36], such as sexual [35], physical, or emotional abuse [31, 37-39]. Most adverse life events described in the adult FND population are rooted in childhood [40].

The most studied pediatric FND subpopulation, functional seizures (FS), have a high frequency of preexisting and newly diagnosed psychiatric disorders [41], such as emotional, adjustment, attachment disorders and post-traumatic stress disorder (PTSD) [42]. Adults with FND also have rates of depression between 20% and 40% [43, 44], anxiety approximately 38% [45], and Axis I emotional disorder between 66% and 75% [46]. Both children and adults have high rates of psychological manifestations.

Increasing incidence

The worldwide distribution of FND has been rapidly increasing. The incidence rate of FND between 1976 and 2010 was 4 to 12 per 100,000 patients per year [21, 47-49] and the prevalence was 50 per 100,000 population [50]. In 2010, FND was found to be the second most common reason for new outpatient neurological evaluation [51]. In 2020, FND

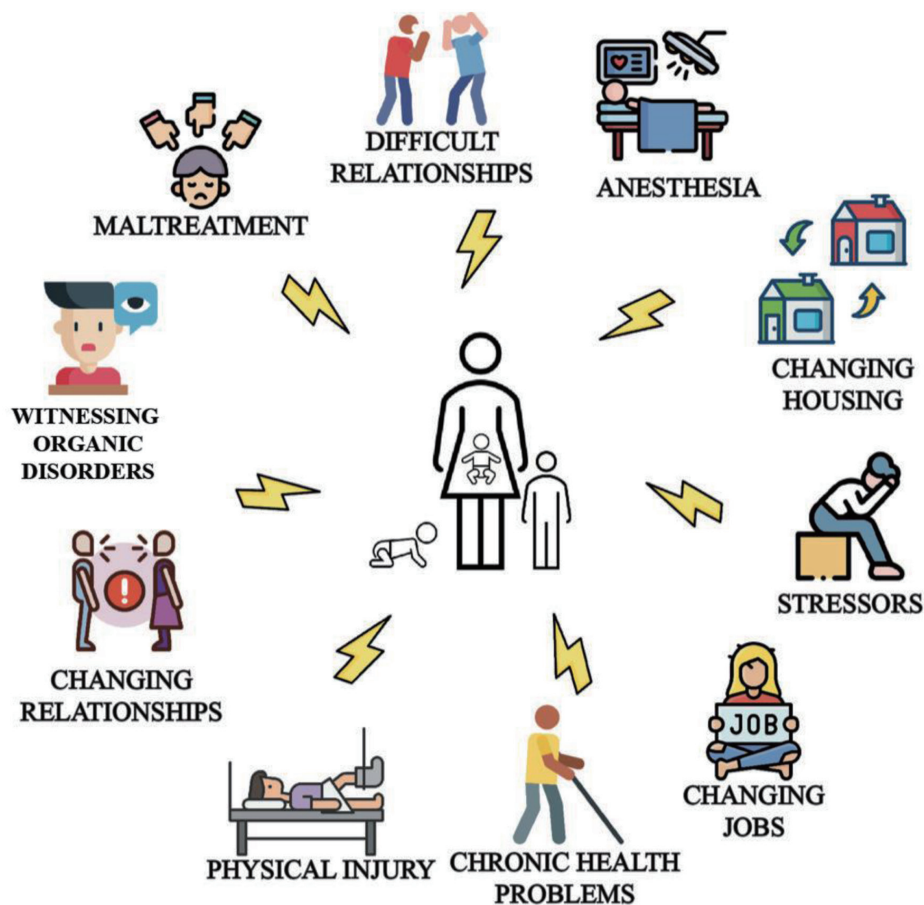


Figure 4. Common triggers and risk factors for pediatric and adult functional neurological disorder (FND) that characterize the biopsychosocial model: emotional antecedents, work problems, accidents, family difficulties [30], change in relationship, housing, employment status [31-33], and witnessing functional or organic movement disorders [34].

was recognized as frequently co-occurring with migraine, another common neurological disorder [52]. In 2021, FND started to be diagnosed after COVID-19 vaccination [53, 54], despite it lacking neurotoxic effects, leading to vaccination hesitancy [54-56]. In 2021, a study suggested that TikTok and social media could be contributing to the spread of FND [57].

FND is also increasing in children and adolescents. In a Danish nationwide study, the overall incidence rate increased from 2.4 per 100,000 population between 1996 and 2014, the full study period, to 7.4 per 100,000 between 2005 and 2014, with its peak in 2014 [58]. Up to 23% of children with FND retain the diagnosis or demonstrate recurrence during adulthood [59].

Little research has been conducted to understand the rising rates of FND. Factors contributing to this surge likely include an increased interest in FND, scientific advancements in the field, the educational work performed by the Functional Neurological Disorder Society, and the improvement and dissemination of diagnostic criteria, all likely promoting FND recognition. The biopsychosocial model stimulates reflections about modern society's stressors influencing FND's incidence, and the role of the educational system and fami-

lies in teaching individuals to effectively deal with adverse circumstances. Regardless of the factors, FND is a global problem, and the field is in need of more epidemiological research.

Mortality

Patients with FS and functional epilepsy (FE) have an increased risk of death [60-62]. One study found that patients with FE younger than 30 years old have up to eight-fold higher risk of death compared to the general population, and that 20% of those younger than 50 years old committed suicide [60]. Suicide is also high in patients with functional motor disorder [62].

Having a psychiatric comorbid condition has been reported to be associated with higher mortality rates [63, 64], and 49% to 100% of patients with FS and FE have a concomitant psychiatric diagnosis [65, 66]. It is reasonable to assume that psychological wellbeing influences FND clinical outcomes.

The brain networks involved in human psychology start developing during the prenatal period, with vital moments during childhood and adolescence; addressing how those years

Table 2. Considerations Regarding FND Epidemiology and Socioeconomic Burden

1. FND incidence is increasing in both children and adults.
2. The childhood-adulthood continuum permeates risk factors and psychological well-being.
3. FND patients frequently have psychological comorbidities that influence clinical outcome.
4. FND carries significant mortality, social, and financial impacts.
5. FND patients frequently change healthcare providers.
6. FND has gained media platform interest over the past decade, although insufficient considering its considerable incidence.
7. The significance of the childhood-adulthood functional continuum has not been systematically integrated into adult early assessment and management protocols.
8. Lacking are standardized psychological assessments to use with a suspected or confirmed FND patient.
9. Globally agreed and adopted FND prevention tools do not exist.
10. Deficient are social educational campaigns discussing risk factors, mechanisms of disease production, and prevention.

FND: functional neurological disorder.

impacted the nervous system of those with FND, must be considered in all management protocols.

Financial and social impacts

Research on FS, one of the most studied subtypes of FND, indicates considerable financial strain on healthcare systems. In Australia, a person with FS utilizes healthcare services at a median of \$26,468 Australian dollars [67]. In the USA, the lifetime cost is around \$100,000, an expenditure similar to treating intractable epilepsy [68].

The FND population incurs high inpatient and outpatient healthcare expenditures, due to frequent primary care, specialty, emergency room evaluations, and hospital admissions [69]. FND patients frequently change PCPs and undergo multiple referrals [70], with the rarely discussed emotional, mental, and financial consequences triggered by such frequent switches in physician-patient relationships. The field is in need of studies seeking to identify preventive measures for such common phenomenon.

Adults with FS and their partners also generate significant social impact due to socioeconomic deprivation and lower employment rate [71]. In Denmark, direct and indirect annual costs of sick pay, disability pension, and home care services approximate €33,697 for patients and €15,121 for their partners [72]. Caregivers experience social stigma [73], psychosocial adversities, and reduced QOL [74]. The literature describing the socioeconomic impact of FND consistently finds a high financial cost [62, 72, 75-77].

FND has triggered BBC, CNN, and other media platforms' interest. Thirteen news stories were shared between 2012 and 2017 portraying patients with complex symptoms being misdiagnosed or presented as medical mysteries [78], advertising the deficits that still exist in FND management.

FND prevention

As previously noted, there is little data to guide the prevention

of FND. As primary prevention aims to reduce disease incidence, the absence of such information delays our ability to stop, or at least slow, the increasing incidence and prevalence of FND.

A review of FND risk factors, incidence, financial, social impacts, and mortality, suggests the need to consider many factors to optimize FND management (Table 2).

FND management focused on biopsychosocial-spiritual assessment

Considering the biopsychosocial triggers, risk factors, and the childhood-adulthood continuum, a comprehensive FND assessment and management protocol would benefit from adopting a biopsychosocial-spiritual model of disease [79, 80], with a biographically focused approach considering how the patient's experiences since the prenatal period and across time, have contributed to the patient's current presentation.

Given the rapidly increasing incidence of FND and its presentation to multiple specialties, we are of the opinion that a biographically focused biopsychosocial-spiritual model is needed across medical practices. Such approach can bring to the patient's awareness the significance of past adverse events, enhancing the patients and families' understanding of FND, promoting enrollment and adherence to therapy. For example, systematic discussions with adult FND patients about how their past experiences have impacted them physically and psychologically, could increase their capacity to overcome challenges, build resilience, influencing clinical outcomes and informing preventive tools.

In sum, guideline recommendations addressing the providers' approach to the patient-physician relationship should consider the biographical and epidemiological data pertaining to the FND population, characterized by adverse events and traumatic experiences. Concepts derived from attunement, attachment theories, defense mechanisms, the functioning of the limbic system, social, and cultural understanding, should be considered when creating such guidelines. Across time, partnerships between the medical community, media outlets,

social media platforms, and policymakers could serve as effective means to transfer knowledge to members of the public.

Outcomes and Prognosis

Therapeutic modalities for FND

A review of 24 studies performed between 1940 and 2013 involving functional tremor, dystonia, parkinsonism, weakness and FND with mixed symptoms, described complete remission in only 20% of the patients, with 40% staying the same or becoming worse over a 7.4 years follow-up period [27]. Outcome studies performed between 1957 and 2006 in patients with functional tremor also reported poor prognosis, with 44% to 90% of patients doing the same or worse upon follow-up [81-84]. Other studies between 2003 and 2010 find that most patients with FND with mixed symptoms have a poor outcome [85, 86].

A similar pattern of outcomes is observed across the world. A study conducted in Sweden in the late 1990s found that 43% to 89% of the patients with functional motor symptoms were out of work [87]. Studies conducted in Canada and the United Kingdom the early 2000s found that 38% to 58% of patients develop other functional symptoms at follow-up, especially weakness [45, 88]. By 2011, less than 30% to 40% of the patients with FS demonstrated remission [89]. Given the disappointing outcomes and prognosis, neurologists have focused on improving the treatments provided to the FND population, including physical therapy (PT) and psychotherapy.

First-line body-oriented modality: PT

PT is an integral part of the treatment of many FND subtypes. PT is used to retrain movement, redirect attention, positively influence illness beliefs [90], trigger plastic adaptation by repetition and task-oriented exercises [91]. In this manner, out of all psychotherapeutic modalities, PT often incorporates principles from cognitive behavioral therapy (CBT). Symptom retraining appears more effective when directed to the underlying mechanisms driving the functional symptoms [92], suggesting the importance of pathophysiology even during PT sessions.

Various PT techniques have demonstrated benefits, such as movement retraining for functional motor symptoms [93], and walking for functional movement disorder [94]. Bicycling, canoeing, and indoor climbing [95], studied in functional gait disorder, resulted in improvements lasting greater than 12 months. Group exercise showed benefits in those with mild to moderate functional symptoms [94]. A review of 33 studies [96] utilizing interventions lasting from 5 to 100 days, revealed significant improvement in over 48% of patients, although complete symptom resolution was low.

Physiotherapy for FND continues to be investigated. A 2016 randomized feasibility study of PT for FND with motor symptoms [97] followed 29 patients who received eight 45 - 90 min therapy sessions over 5 days, mainly utilizing educa-

tion, movement retraining, attention redirection, investigating triggering events, comorbidities, psychological factors, features of self-focused attention, and unhelpful reinforcements. The program promoted daily reflections and the development of a strategic and individualized symptom formulation and management plan. At 6 months, 72% of the individuals receiving the interventions rated their functional motor symptoms improved or much improved in the Clinical Global Impression Scale. Randomized controlled trials (RCTs) are needed to determine if outcome can be further improved via utilizing additional techniques and modalities capable of targeting the patient's underlying pathophysiological mechanisms.

Comprehensive physiotherapy consensus recommendations for functional speech, swallowing [98] and occupational therapy [99] have been published. However, it is unclear how applicable these are to daily clinical assessment and management, outside a physiotherapy session. Most of the assessment and therapeutic interventions recommended are CBT-derived.

First-line psychotherapy: CBT

CBT is a top-down psychotherapeutic modality that works under the premise that a person's thoughts and beliefs affect feelings and behaviors. During CBT sessions, patients are assisted in the identification of cognitive misrepresentations and dysfunctional beliefs, to disrupt coupled cognitive, emotional and behavioral responses to stressors [100].

The evidence supporting the use of CBT in FND goes back to the last century. Kroenke and colleagues found CBT treatment for somatoform disorders effective in 11 out of 13 studies performed between 1966 and 2006 [101]. In 2004, a small open-label study utilizing a 12-session CBT intervention suggested that CBT could aid in the reduction of FS frequency [102]. In 2014, two pilot RCTs using CBT with or without standardized medical care (SMC) were conducted. One suggested efficacy of CBT alone in patients with FS, reducing seizure frequency during the treatment period in 51.4% of patients [103]. This study, however, was insufficiently powered to allow comparisons between treatment arms. The other study, through an intention-to-treat analysis, demonstrated a greater reduction of seizure frequency in the CBT plus SMC. However, 6 months after the end of treatment, the difference between the groups was no longer significant [104].

Trauma-based CBT has demonstrated benefits in the FND population with associated PTSD [105]. A study using CBT or acceptance and commitment therapy achieved and maintained improvement in FS frequency and healthcare costs at 2 years [106]. CBT-informed psychotherapy (CBT-ip) for functional tremor resulted in a significant reduction ($78.7 \pm 33.8\%$) on the psychogenic movement disorders rating scale 12 weeks after completing CBT [107].

The first RCT involving CBT for FS patients was conducted in 2015, assessing the effect of adding CBT to SMC and psychiatric care in 368 patients [108]. The Cognitive Behavioral Therapy vs. Standardized Medical Care for Adults with Dissociative Non-Epileptic Seizures (CODES) trial included a care pathway involving neurology and psychiatry. The CBT interventions taught distraction and refocusing techniques to

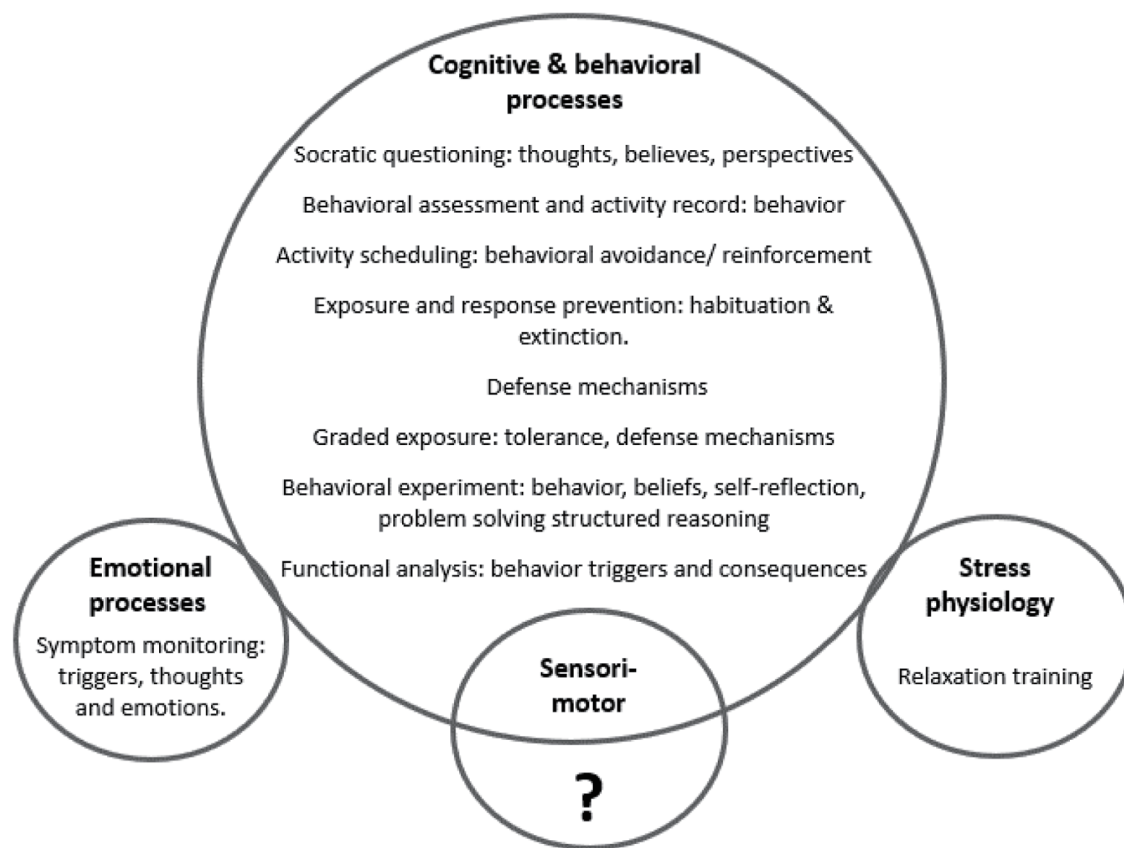


Figure 5. Frequently used cognitive behavioral therapy (CBT) techniques, demonstrating a greater influence in cognitive and behavioral processes, with unclear impact on the sensorimotor (somatic) system, and less impact in the biological (stress physiology) and emotional domains of the nervous system.

interrupt seizures, addressed avoidance behaviors, unhelpful beliefs, trauma processing, and stress management. The primary outcome measure, reduction in FS frequency in the previous 4 weeks, assessed at 12 months, was not met. There was no significant difference in FS frequency between the groups, which demonstrated, in the previous 4 weeks, a median of four seizures in the CBT plus SMC group, and seven seizures the SMC group. The authors proposed various explanations for the findings, such as the limited trauma-focused interventions in a population with significant traumatic history, the possibility that only certain patients might be appropriate for CBT-based treatment, whereas others may benefit from other psychotherapeutic modalities. More recently, the authors suggested that perhaps the impact, or lack thereof, of specific CBT interventions, in certain pathophysiological networks, such as physiological, emotional, spiritual, and social aspects permeating FND production and maintenance could have played a role in the failure to significantly reduce FS frequency [108, 109].

Similar deficits in treatment are found in the clinical trial results in pediatric populations, with low rates of early and sustained remission, high rates of symptom persistence [110] and recurrence, even after multidisciplinary treatment [111, 112]. The Retraining and Control Therapy (ReACT) trial, an RCT utilizing CBT principles to target sense of control and symptom expectations [113], demonstrated symptom recurrence in

two (18%) of the participants after 60 days of treatment completion. Mental health services at 1 month were associated with remission at 12 months, again suggesting the importance of addressing psychological health early. Psychosocial stressors have also been associated with unfavorable outcomes in pediatric populations [114], suggesting the importance of a prompt focus on stress management.

Due to the foundational principles of CBT, its most frequently utilized techniques focus on the cognitive and behavioral mechanisms of FND production and maintenance [115]. CBT is characterized by fewer interventions in the emotional, biological, autonomic, and sensorimotor (somatic) domains of the human nervous system (Fig. 5). A focus on these latter areas may be required to address the unconscious dynamics associated with FND.

Evidence for other therapeutic approaches

Carlson and colleagues conducted a meta-analysis with data extracted from 13 studies involving 228 participants with FS who received various psychotherapeutic modalities, including psychodynamic therapy, paradoxical intention therapy, mindfulness, psychoeducation, and eclectic interventions [116]. Results showed that 47% of patients became seizure-free upon comple-

tion of any psychological intervention, suggesting that various modalities are helpful in FND. The study did not compare or demonstrate superiority of one intervention over the other.

Principles from psychodynamic therapy have been effectively utilized to reduce functional movement disorder [117] and other types of FND [118-120]. It has been suggested that interventions from psychodynamic therapy may effectively address vulnerability factors involved in FE [121]. The need for psychotherapeutic modalities that target emotional and attachment dynamics is increasingly recognized [121-123].

Two prospective uncontrolled studies of mindfulness-based psychotherapeutic approaches conducted in FS patients to improve awareness and acceptance of internal states demonstrated improvement in FS intensity and worry [124, 125]. In one of the studies, some outcomes were maintained 6 months post-treatment [124].

Other treatment modalities showing some evidence for children and adults with FS are education [126], biofeedback [127-129], family therapy [130], group therapy [120], multidisciplinary care [114, 131] and inpatient treatment programs [127]. Recommendations for treating adults and children with FS specify that mood and trauma should be targeted [103, 127].

Multidisciplinary programs

Multidisciplinary or multimodal care for FND involving family medicine, neurological, psychiatric, psychological care, and if needed physiotherapy, are being used in clinical practice [132-135], although they are not widely available, and often require patients to access care at far away hospitals and academic centers. The first published proposal of a multidisciplinary clinical care pathway for FND was performed in children with FS. This care pathway utilized information from a retrospective study that characterized this population from epidemiological and clinical perspectives, paying attention to psychiatric comorbidities and psychological assessment. The authors considered the interventions used, mainly education and CBT, and their outcomes [133]. This multidisciplinary clinical care pathway was then prospectively validated [136] by providing specialized neurological and psychological care to 43 children with suspected FS over a 5-year period. Length of treatment went from 1 to 24 months, and CBT was utilized for most patients ($n = 31$, 72%). Patient education, group therapy, family therapy, biofeedback, and trauma-based CBT were also used.

As part of the pathway's protocol, psychophysiological assessment, biofeedback training and strategies to avoid hyperventilation were implemented following the notions that emotional and autonomic abnormalities underlie the pathophysiology of FE. Some patients were referred to somatization clinics, inpatient or intensive outpatient mental health, and/or rehabilitation programs. Continued outpatient follow-up was encouraged. Dissociation, characterized by depersonalization, and derealization was managed according to published recommendations [137]. Retrospective chart review demonstrated that standardized combined care led to self-reported full or partial remission at discharge in 27 (63%) and 12 (28%) children, respectively. The only statistically significant factors associated with incomplete response were the presence of de-

layed diagnosis, and duration of FE greater than 12 months. The authors recognized as a limitation of the study the absence of random assignment to treatment.

Other models for clinical care pathway formation in the adult FS population have been reported [138], and a multidisciplinary approach to FS treatment is recommended [132]. An expert consensus board review determined that FS management for both children and adults should be multidisciplinary and should include CBT [139]. In functional movement disorder, 1-week multidisciplinary rehabilitation program resulted in an 86.7% symptom improvement upon treatment completion, which decreased to 69.2% at 6-month follow-up [140].

Multiple interpretations can be derived from these data. Complete and sustained remission is a goal that is not yet consistently attained, even with multimodal or multidisciplinary care. This is perhaps due to the predominant utilization of CBT modalities, the lack of easily accessible services, the high number of providers involved in care, and the need to utilize outside referrals, with its financial, and logistic implications. Psychiatric, psychological, psychophysiological assessment, somatization management, and education appear valuable, supporting the need to comprehensively address all systems involved in the production and maintenance of FND.

Current outcomes and unanswered questions

Across studies examining the effectiveness of different treatments for FND - PT, CBT, and multidisciplinary approaches - complete symptomatic remissions in FND are rare, with many patients remaining refractory to the currently available therapies [141]. Unfavorable prognosis, with many patients having persistent symptoms after years of follow-up, is common [27]. A 14-year follow-up of patients with functional limb weakness found ongoing symptoms in most, with greater than expected mortality [142]. Inpatient programs show that, whereas improvements in functional motor symptoms and QOL are probable, disabled patients often do not return to work [140, 143, 144]. The prognosis of FND remains poor, with disability persisting or worsening over time, and with many patients experiencing severe symptoms despite treatment [145].

Regarding psychotherapy duration and healthcare delivery methods, one study demonstrated greater efficacy of CBT-ip for FS, if at least seven sessions were administered over more than 3 months, versus within 3 months [146], suggesting that prolonged engagement in treatment, or a personalized treatment duration, may be more beneficial than shorter standardized therapeutic protocols. The ideal psychotherapy duration has not been clearly determined by RCTs.

Telehealth has been proposed as an appropriate way of delivering psychotherapy [147] and PT [148]. Telehealth could facilitate the care of patients with mobility and financial difficulties, although the efficacy of this approach has not been sufficiently studied. Research in this area is of interest.

There is also a need for better outcome measures for FND. None of the current well-validated outcome evaluations consider all the core features of FND, such as symptom heterogeneity, variability, illness beliefs, social support, comorbid psychological and medical problems, and the role of the clinician collecting

Table 3. Findings From FND Treatment Studies

1. FND is still characterized by suboptimal outcomes despite the utilization of PT, CBT, and multidisciplinary care.
2. Physical, psychiatric, psychological, psychophysiological assessment and care, somatization management, education, and continued follow-up, characterizing multidisciplinary programs, appear to be valuable.
3. CBT possesses fewer interventions in the emotional, autonomic, sensorimotor (somatic), and unconscious nervous system networks.
4. PT, multimodal and multidisciplinary care mainly utilize CBT principles, as opposed to techniques from other psychotherapeutic schools.
5. Other psychotherapeutic modalities have not been thoroughly evaluated through RCTs.
6. Multimodal and multidisciplinary care are difficult to access and involve multiple care providers, complicating the physician-patient relationship.
7. Head-to-head trials comparing the outcomes between various psychotherapies and clinical studies combining skills from various psychotherapies have not been performed.
8. Easy to adopt management protocols that could be universally utilized are lacking.
9. The ideal psychotherapy duration and delivery method has not been sufficiently determined by clinical trials.
10. Well-validated outcome measures considering FND-specific characteristics and pathophysiology are lacking.
11. Therapeutic modalities have not been thoroughly scrutinized against FND pathophysiology.

FND: functional neurological disorder; RCTs: randomized controlled trials; CBT: cognitive behavioral therapy; PT: physical therapy.

a great deal of subjective data such as pain or fatigue [149, 150]. In addition, the percentage of patients who progress to chronicity despite utilizing the best possible treatments, remains unidentified. Therapeutic approaches should be scrutinized against FND pathophysiology to determine if the most favorable therapeutic modalities are currently being delivered.

Key findings from the analysis of outcomes, prognosis, and FND therapeutic modalities are summarized in Table 3.

Therapy and Management for FND

Pathophysiological mechanisms of FND

The pathophysiological mechanisms of FND may include

the following: 1) Childhood trauma and epigenetics [151]; 2) Psychological model and the limbic system [115]; 3) Defense mechanisms [152]; 4) Cognitive and learning theories [151]; 5) Hypnosis model [153]; and 6) Stress and neurobiological theories [153].

Summarizing in a single model, all the pathophysiological evidence described in the above theories, can deepen our understanding of the dysfunctional processes taking place within the nervous system, and affecting the physical body, while avoiding mind-body dualism. All the functional networks that play a role in FND origin and maintenance are biologically interlinked. Thus, theoretically assembling them offers a foundation to develop an integrative treatment algorithm.

The pathophysiological processes affected in the above etiological models can be grouped into four functional networks (Table 4) [116, 151-154]: 1) Neo-cortex; 2) Limbic; 3)

Table 4. Summary of FND Pathophysiological Theories With Supporting Dysfunctional Networks Demonstrating Near-Constant Impairment of Multiple Processes Within Four Major Functional Areas: Limbic System, Neo-Cortex, ANS, and Somatic (Sensorimotor)

Pathophysiological theories	Associated dysfunctional areas, networks, and processes
Psychological [116]	Neo-cortex and sensorimotor networks: Hypo-activation of cortical and subcortical motor pathways. Limbic system: Abnormal emotional regulation. ANS: Hyperarousal. Sensorimotor: Stereotyped motor behaviors.
Neurobiological [153]	Limbic and sensorimotor: Altered conductivity between the amygdala and motor areas. ANS: Lower heart rate variability, hyperarousal.
Childhood trauma, cognitive and learning theories [151]	Neo-cortex: Increased self-focused attention, impaired voluntary attention. ANS: Abnormal functioning of the hypothalamic-pituitary-adrenal (HPA) axis. Sensorimotor and limbic connectivity: somatosensory experiences linked to affective states.
Defense mechanisms [152]	Neo-cortex: Increased vigilant attention. Limbic: Inhibited emotional processing. ANS linked to impaired cognition (neo-cortex): Dissociative response to autonomic arousal.
Hypnosis [154]	Neo-cortex and sensorimotor: Increased connectivity between the motor cortex and the precuneus. Neo-cortex: Increased hypnotic suggestibility.
(Epi)genetic [151]	Neo-cortex: Affected left hippocampal volume, increased dissociation. Limbic: Reduced emotional responsiveness. ANS: Inability to shut down stress responses.

Various networks are simultaneously dysfunctional. ANS: autonomic nervous system; FND: functional neurological disorder.

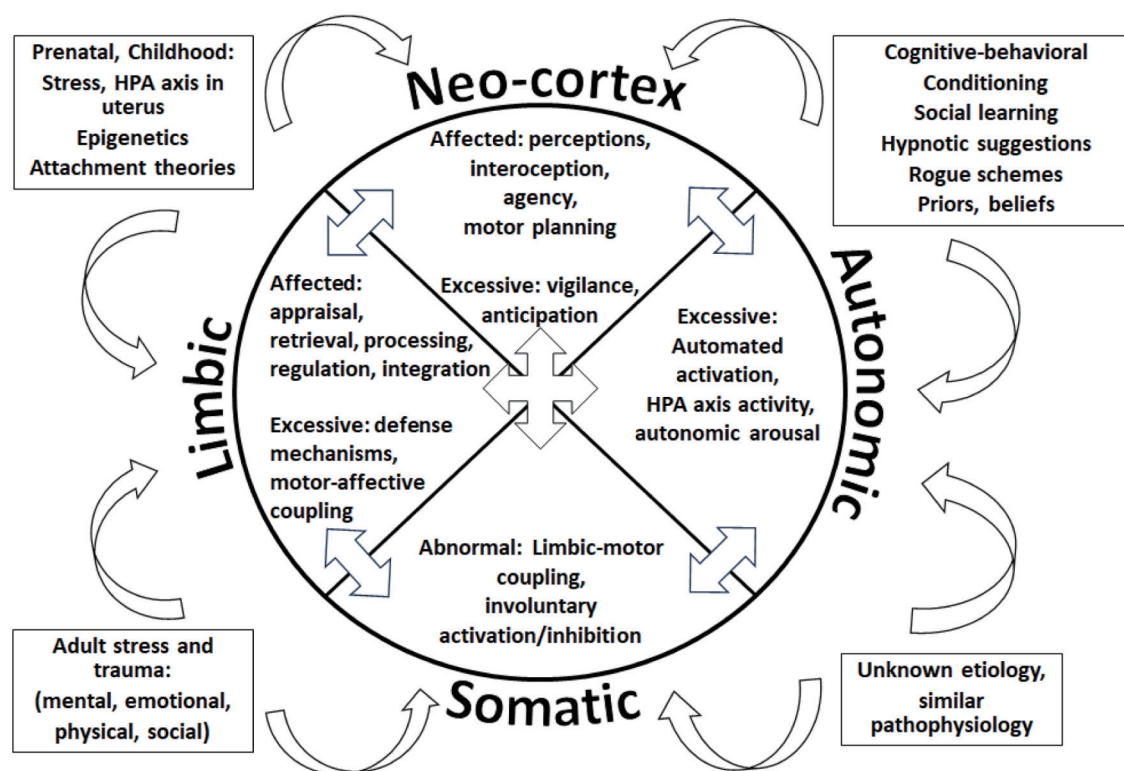


Figure 6. The integrative functional neurological disorder (FND) pathophysiological model representing dysfunctional processes in the cognitive neo-cortex, the limbic system, the autonomic nervous system (ANS), and the sensorimotor (somatic) processes.

Autonomic nervous system (ANS); and 4) Sensorimotor (somatic) processes extending from the nervous system to the interconnected physical regions.

The involvement of these four functional regions, limbic system, neo-cortex, ANS, sensorimotor processes, in the pathophysiology of FND has been demonstrated in the studies cited in the previous sections. For example, when discussing therapies targeting cognition and behavior such as CBT, the presence of somatic complaints, the involvement of the limbic system manifested through associated mood disorders and psychological co-morbidities, and the ANS influenced by traumatic and stressful risk factors are all of note.

Common pathophysiological processes across various FND subtypes have been demonstrated in clinical trials [155, 156], and the need for a transdiagnostic approach capable of therapeutically targeting shared dysfunctional cognitive, emotional, autonomic, behavioral, and social dynamics, has been proposed [157, 158].

The inter-relatedness between these four functional networks and the importance of comprehensively and systematically targeting them all is manifested, for example, when hyperarousal (autonomic), anxiety (mood, emotional), readiness for change (cognitive) and symptom count (somatic) were noted in functional movement disorder patients during triage to therapy [159]. Other studies have found that hypo/hypervigilant states, sleep disturbance, motivation, mood disturbances, anxiety disorders, alexithymia, trauma, chronic fatigue, and chronic pain [160, 161], representing autonomic, cognitive,

limbic, and sensorimotor processes respectively, were involved in the neurocognitive dysfunction of patients with FE.

Multiple studies have demonstrated abnormalities permeating the limbic-motor systems [162, 163], limbic-sensory processes [164], and cognitive-unconscious dynamics [165], some of them in relationship to the motor system [166-168], others associated to the limbic system [169], the sensorimotor pathways [170, 171] and the social network [172]. A large body of evidence speaks about the involvement of the ANS [169, 170, 173-176].

The frequent dysfunction in these four networks: limbic, cognitive, autonomic, and sensorimotor (somatic), has not been systematically assembled into educational and management models.

We introduce an example of how assembling all pathophysiological theories and mechanisms described to cause FND in a single model would look: the integrative FND pathophysiological model (Fig. 6). Our example contains four outer boxes summarizing the theories explaining FND production, in both adult and pediatric populations: 1) Left upper box: During the prenatal period, stress in mothers can affect fetal brain development and later functioning as the mother and fetus share the hypothalamic-pituitary-adrenal (HPA) axis. Throughout this period, stress and trauma can alter a person's genes and their expression, leading to dysfunction in certain nervous system networks. The type of attachment or emotional bond between individuals can impact the operations of nervous system pathways, especially the limbic (emotional)

system. 2) Left lower box: Multiple mental, emotional, physical, and social adverse and traumatic events can impact the performance of neuronal networks. 3) Right upper box: During a person's life, cognitive, learning, conditioning factors, beliefs, and suggestions can determine the brain's software. "Rogue schemes" and "priors" refer to mental representations and predictions that influence the nervous system's processes. Therefore, numerous situations can result in FND. Fortunately, we understand what brain pathways and networks can become dysfunctional due to the above situations, even when the specific etiology seems unclear (right lower box).

All the etiological processes represented inside the boxes, independently or in combination, can influence the nervous system, ultimately affecting one or more of its four large functional regions, denoted by each quadrant of the center pie: the cognitive neo-cortex, the limbic system, the ANS, and the sensorimotor (somatic) processes. Inside each quadrant or functional region, some of the dysfunctional processes described in the literature are represented: 1) In the limbic system, a person's emotional appraisal [168, 177], retrieval [166], processing, regulation [167], and integration [165] could be affected. Excessive defense mechanisms may be present [165], and sometimes motor functions can be abnormally linked to emotional processes [164]. 2) In the neo-cortex, the individual's perceptions [178], interoception [179], agency [180], motor planning [181] could be defective, while vigilance [182], and anticipation [183] may be excessive. 3) The patient's somatic (sensorimotor) networks could demonstrate abnormally tight connections to emotional processes (limbic-motor coupling) [163, 181], sometimes getting automatically activated or inhibited [170, 184]. 4) The person's ANS may show excessive activation [174], HPA axis activity [185, 186], and autonomic arousal [174].

The arrows located between the pies indicate that the abnormal functions inside a quadrant could affect the operations of other functional regions.

The reader must consider the separating lines between functional quadrants and the grouping of the procedures inside each quadrant, as purely symbolic. Human experience is dependent on this intricate web of functional operations, working interdependently, and largely subconsciously.

The distribution of a thoroughly designed integrative pathophysiological model could help healthcare professionals understand the processes originating and maintaining FND, with its many possible presentations. It could also facilitate the recognition of the many emotional, autonomic, somatic, and cognitive manifestations of FND, helping to validate the patient's experience, preventing their dismissal, discharge, and transfers of care, leading to better management, proper allocation of services, and improved healthcare utilization. An integrative pathophysiological model could be utilized at first encounter with all suspected and confirmed FD patients, improving a patients' understanding of their condition and their engagement in therapies. Such a model could also be used to teach trainees and healthcare professionals about FND production and maintenance.

An integrative pathophysiological model could prompt physicians to investigate with patients, in a biographically and biopsychosocial-spiritual manner, how their risk factors,

represented by the outer boxes, could have given origin to dysfunctional limbic, autonomic, sensorimotor (somatic), and cognitive processes.

Of course, the integrative FND pathophysiological model presented here is just an example, describing some of the pathophysiological processes described in the literature, and created to demonstrate the usefulness of an integrative approach. An in-depth literature review designed to identify, analyze, and describe all pathophysiological processes that have been proposed in the literature to affect the limbic system, neo-cortex, ANS and sensorimotor networks - while considering their interrelatedness, clinical manifestations, relevance, assessment, and optimal targeting modalities - should be undertaken.

Multi-network management algorithm for FND

A multi-network treatment algorithm is founded in an all-inclusive pathophysiological model and targets all the dysfunctional processes within the limbic, autonomic, sensorimotor (somatic) and cognitive networks, regardless of the patient's identified etiology or lack of thereof, as some patients describe not having been exposed to the most common risk factors [31].

All functional processes known to be affected in the FND population should be assessed in all patients, and therapeutically targeted when necessary. Such a thorough approach will be similar to giving broad-spectrum antibiotic coverage for an infection caused by a yet unknown pathogen; the chance of a cure despite an unidentified cause is much higher. This strategy is particularly necessary now that the availability of diagnostic tools such as functional neuroimaging, capable of identifying dysfunctional networks, is mostly restricted to academic centers. And, even if the widespread availability of imaging technology capable of detecting dysfunctional networks was to occur, it is unlikely that such a diagnostic instrument would identify the subtle dysfunctional processes (e.g., emotional dysregulation, hypervigilance, lack of interoception, etc.) that are fairly easily found via a comprehensive clinical interview. An integrative, pathophysiological focused assessment and management tool can be made available to rural areas, private practices, and smaller community hospitals.

Although recent reviews advocate for the creation of individualized treatment protocols [11], the methodology to deliver such care is not clear. Current FND treatments vary tremendously, from focusing on the psychophysiological mechanisms behind functional seizures to, in functional motor disorders, noticing the differences between voluntary and automatic movements, using focusing techniques on some cases, while in others, utilizing distraction. The heterogeneity in FND clinical manifestations, severity of illness, the individual's biology, life experiences, socio-spiritual dynamics, and psychological well-being may appear too varied to standardize treatment. FND management must be simplified and systematized, by focusing on the individual's pathophysiological manifestations, which are limited in number, well described in the literature, and often overlap across the umbrella of FD. From a well-known pathophysiological foundation, patient and clinician can become active participants in the design of a path towards

Table 5. Examples of Pathophysiologically Oriented, Intuitive Interventions, and Their Management Impact, Performed During Clinical Interview and Physical Examination

Physical examination feature	Pathophysiological process assessed by the physician	Physiological function	Physician's intuitive intervention and management impact
Patient demonstrates apprehension about FND recovery	Emotional appraisal	Cognition influences emotional responses	"What past events have shaped this emotional response?" Increases patient's awareness about emotional appraisal.
	Emotional retrieval	Recollection of emotionally charged memories	"Tell me about other moments when you have felt that way." Biographical assessment, practices emotional retrieval, allows the exploration of further networks as stated below.
Patient becomes restless and fidgety	Sensorimotor-affective coupling	Physical sensations linked to emotional states	"As you recall those memories and emotions, what are you noticing in your body?" Creates awareness about the link between sensations and emotions, practices interoception, allows exploration of further networks.
	Interoception	Noticing internal sensations	
Patient's movements continue, tapping the right leg, rubbing the hands together. There is mild facial flushing and sweating.	Autonomic activation	Activation of the ANS	"I notice that your energy level and movements have increased, are you sensing that too?" Practices interoception, brings awareness to emotional-motor connections, involuntary motor activation linked to emotions and memories, creates opportunity for autonomic self-assessment and regulation.
	Limbic-motor coupling	Linking emotions to motor functions	
	Involuntary activation of motor pathways	Survival responses to protect against adverse, stressful situations	
The patient states "I am feeling strange right now"	Defense mechanisms	Reduce uncomfortable internal experiences.	"Tell me more about this strange feeling? How does it feel? Where is it? What is it telling you?" Practices interoception, explores defense mechanisms, making sense of the patient's experience, uniting mind-body.

ANS: autonomic nervous system; FND: functional neurological disorder.

functional rehabilitation [187].

To our mind, individualized treatments should consist of having, and delivering to patients, predetermined tools capable of addressing the dysfunctional processes that could be taking place inside each of the four described networks. The pathophysiological processes can be detected through physical examination and then targeted through clinical intuition, following the physiological function of the processes noted to be abnormal. This approach could leave physicians well-equipped for early FND management during their limited initial consultation and follow-up time (Table 5).

Multi-specialty expertise and future recommendations

A multi-network approach must tend to pathways within the brain and between the brain and body, addressing their interconnectedness [188], a concept highlighted since the times of Erasmus, Darwin, and Rene Descartes [189]. An ideal treatment

protocol must also combine skills from the fields of neurology, psychiatry and psychology [190], an efficacious confluence, witnessed when studying the work of physicians specializing in neurology and psychiatry, such as Sigmund Freud, Stanley Cobb, or Mathew J Burke [191].

Neurologists, psychiatrists, psychologists, and physiotherapists following a comprehensive and integrative FND pathophysiological model, should jointly review multiple therapeutic modalities. These include physiotherapies, CBT, psychodynamic, paradoxical intention, mindfulness-based, psychoeducation, eclectic interventions, biofeedback, family, group therapy, hypnosis, dream work, emotionally focused, somatic, and psychedelic therapies. From these, experts must choose the most appropriate techniques to target the pathophysiological processes and subconscious dynamics permeating the cognitive, limbic, autonomic, and sensorimotor networks, causing FND - and perhaps even the umbrella of FDs. This approach could also overcome the management uncertainties derived from the arguments of lumping versus splitting FND subtypes

[192], potentially offering a comprehensive, pathophysiologically targeted treatment for all FD.

The creation of a comprehensive, pathologically focused, multi-network treatment algorithm is not a simple task and must be designed through multidisciplinary collaborative efforts, overcoming the detrimental effects of medical specialists' separateness in FND management.

In summary, the phases to achieve the design of a multi-network FND management algorithm are: 1) To compile all pathophysiological mechanisms and dysfunctional FND networks in a single model; 2) To determine the best assessment procedures; 3) To choose the best techniques from the fields of neurology, psychiatry, psychology, and physiotherapy, capable of targeting limbic, cognitive, autonomic, and somatic subconscious dynamics; and 4) To design in-office interventions and homework exercises for patients.

Multi-specialty training for FND identification and management

Most specialists, especially PCP as the gateway to the healthcare system, are left uninformed as to how to help the FND population at first encounter. Authors [193-198] speak about the iatrogenic harm, unnecessary, costly evaluations, and unwarranted pharmacotherapies impacting the FND population, suggesting that early and appropriate interventions are needed.

Research has shown that an interdisciplinary approach providing early mental health services to families is beneficial [199, 200], and that standardized FND treatment reduces hospital length of stay, subspecialist consultations, and overall health care costs [201]. Programs utilizing multidisciplinary interventions for FND have demonstrated positive results [130, 202-204], although such treatment is most often available only to the minority of patients capable of reaching academic healthcare settings.

A comprehensive management, preventive and educational tool, capable of presenting multi-network interventions to professionals, patients, and family members is supported by FND pathophysiology. A unified assessment, treatment and educational algorithm could also serve as systematic training for the upcoming generations of healthcare professionals.

In summary, major knowledge gaps identified in this review include: 1) The official FND nomenclature contains the word "symptom" and the term "conversion". 2) The absence of a pathophysiologically focused classification system for the umbrella of FD. 3) A biographically focused, biopsychosocial-spiritual assessment and management for FND, that investigates pertinent history from the prenatal period to the moment of each evaluation, has not been developed. 4) All the pathophysiological mechanisms involved in FND production and maintenance have not been reviewed, nor summarized in a single model. 5) A practical multi-network FND assessment and management algorithm capable of targeting subconscious dynamics in the neo-cortex, limbic, autonomic, and sensorimotor networks is missing. 6) An integrative FND pathophysiological assessment, management, and preventive multi-network management protocol is not available across medical specialties.

Conclusions

There are hundreds of epidemiological, genetic, clinical, and functional imaging studies demonstrating the dysfunctional neural regions and pathways associated with FND and other FD. Now is the time to design a biographically focused multi-network assessment, treatment, and prevention algorithm capable of targeting the pathophysiological mechanisms associated with FND. Treatment must go beyond CBT and CBT-predominant physiotherapies to comprehensively address and target the many networks participating in the production and maintenance of FND. Such an endeavor will allow us to make progress treating, as well as hopefully preventing, this increasingly frequent, expensive, and sometimes fatal neurological disorder.

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Conflict of Interest

None to declare.

Author Contributions

Yadira Velazquez-Rodriguez conceived, designed, researched the data, and drafted the article. Yadira Velazquez-Rodriguez and Brooke Fehily analyzed and interpreted the data. Both authors gave final approval of the version to be published.

Data Availability

There are no other related research objects (data, methods, protocols, software, hardware) to publish alongside this review article.

Abbreviations

FND: functional neurological disorder; ICD: International Classification of Diseases; DSM: Diagnostic and Statistical Manual of Mental Disorders; QOL: quality of life; FDs: functional disorders; FRDs: functional rheumatological dis-

orders; FGIDs: functional gastrointestinal disorders; FCVD: functional cardiovascular disease; PTSD: post-traumatic stress disorder; FS: functional seizures; FE: functional epilepsy; PT: physical therapy; CBT: cognitive behavioral therapy; RCTs: randomized controlled trials; SMC: standardized medical care; CBT-ip: CBT-informed psychotherapy; CODES: Cognitive Behavioral Therapy vs. Standardized Medical Care for Adults with Dissociative Non-Epileptic Seizures; ReACT: retraining and control therapy; HPA: hypothalamic-pituitary-adrenal; ANS: autonomic nervous system; PCP: primary care physician

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