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Functional Neurological Disorder: New Phenotypes, Common Mechanisms

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Abstract

People with functional neurological disorder (FND) are frequent in neurological practice. A new approach to the positive diagnosis of FND focuses on recognisable patterns of genuinely experienced symptoms with signs that show variability within and between tasks over time. Psychological stressors are common risk factors but may be absent. We review four entities,

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Authors' contributions

All authors have contributed equally including conceptualisation, literature review, writing, and revision.

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Jo.S, reports royalties from UpToDate for articles on FND and runs a free self-help website for people with FND. He carries out independent expert medicolegal work including in relation to FND. He is on the medical advisory board for FND Hope and FND Action.

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Search Strategy and Selection Criteria

References for this Review were identified by searches of PubMed between January 2016 to March 2021), and references from relevant articles. The search terms "Functional Neurological Disorder", "Conversion Disorder", "Functional movement disorder", "Psychogenic movement disorder", "(Psychogenic OR Dissociative OR Nonepileptic) AND (Seizure OR attack OR spell)"), ""Persistent Postural Perceptual Dizziness", and "Functional Cognitive Disorder" were used. Reference lists were searched. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this Review.

functional seizures, functional movement disorders, persistent perceptual postural dizziness, and functional cognitive disorder, outlining similarities and arguing they are variants of a disorder at the interface between neurology and psychiatry. All four have distinctive features and are increasingly possible to diagnose with the support of clinical neurophysiology and other biomarkers. Current understanding of FND pathophysiology includes overactivity of the limbic system, symptom modelling as part of a predictive coding framework, and dysfunction of brain networks that gives movement the sense of voluntariness. Evidence increasingly supports tailored multidisciplinary treatment that may involve physical and psychological therapy approaches.

Keywords

Functional Neurological Disorder; Conversion Disorder; Psychogenic; Functional movement disorder; Dissociative seizure; Psychogenic non-epileptic seizure; Persistent Postural Perceptual Dizziness; Functional Cognitive Disorder

Introduction

The name “functional neurological disorder” (FND) conveys the idea of a condition in which the primary pathophysiologic processes are alterations in functioning of brain networks rather than abnormalities of brain structures. Functional disorders though long recognized, were largely neglected in mid-20th century, and given various diagnostic labels including conversion, psychogenic, and dissociative disorders. There are psychiatric diagnostic criteria in DSM-5 where it is called "Conversion disorder (Functional Neurological Symptom Disorder)" but also diagnostic criteria created by neurologists, psychiatrists, and other healthcare professionals in partnership[1,2-4]. Here we define the term FND to denote clinical syndromes consisting of symptoms and signs of genuinely experienced alterations in motor, sensory, or cognitive performance that are distressing or impairing and manifest: 1) one or more patterns of deficits consistent predominantly with dysfunction of the nervous system and 2) variability in performance within and between tasks.

The most common presentations of FND are functional seizures (also called dissociative or psychogenic non-epileptic seizures) and functional movement disorders including paresis. Other common manifestations are somatosensory or visual symptoms, and speech disorders, which we exclude here due to space constraints. Chronic dizziness and cognitive dysfunction as part of a functional disorder have occupied an uncertain place in relation to FND, and we review them below. We discuss possible shared mechanisms and distinguishing processes as well as the observation that persons with FND may present more than one phenotype and/or alternate from one to another over time. We include evidence from neuroimaging, neurophysiologic, and genetic studies and new concepts of voluntary motor and sensory control to explain the unique alterations in neurological functioning that identify FND as a bona fide disorder. We also provide a review of improved practical diagnostic techniques, potential biomarkers, and emerging evidence for improved treatments based on a better understanding of mechanisms.

Epidemiology

FND has been reported from age 4-94 years.[5,6] There is a striking female preponderance of 60-80%, although the gender gap is narrower in early and late life.[7,8] Functional movement disorders have a lower female predominance than functional seizures, which may relate in part to their later median onset (late 30s for movement disorders,[7] late 20s for seizures[8]).

Global and historical data, though of limited quality, suggest that FND occurs at similar rates across geographical regions[9] and eras[10]. The spectrum of symptoms is similar in North America, Europe, Korea, India, and Brazil. FND is one of the commonest reasons for new outpatient neurological consultations, comprising 1 in 6 referrals[11]. Population studies suggest an incidence of 10-15/100,000[12,14], translating to an estimated prevalence of 250,000-300,000 people in the USA alone. Levels of disability[11], caregiver burden, and adverse effects on quality of life [15] are similar to other neurological conditions. Healthcare costs for inpatient treatment of adults with FND in the US exceed $1 billion annually[16]. Access to accurate diagnosis and treatment is problematic worldwide,[17] and the evaluation process is often stigmatizing[18].

Predisposition, precipitants, perpetuants, and outcomes

FND is multifactorial. Risk factors for FND in adults include exposure to recent psychological stressors and histories of childhood adversity, particularly neglect[19], with odds ratios centred about 3-4. Such events were *not* reported in over 50% of people with FND in most published studies (Fig. 1). Female preponderance in FND is likely to be partly attributable to their higher frequency of childhood adversity[20], although other disorders such as multiple sclerosis are more common in women, and women are more likely to present to health services generally. Risk factors in children include family dysfunction, bullying, and perceived peer pressure, less often abuse[21]. FND frequently co-exists with depression, anxiety, and traumatic stress disorders, and cluster B personality traits[22,23]. FND also co-exists with other functional somatic disorders including chronic pain and irritable bowel syndrome suggesting common risk factors or mechanisms[242526]. Fatigue and pain may have more effect on quality of life than FND symptoms themselves[27,15]. Psychiatric comorbidities are not unique to FND and are also common in structural neurologic disorders.

Predisposition may include genetic factors. In a study of 18 single-nucleotide polymorphisms from 14 candidate genes among 69 patients with functional movement disorder[28], the G703T polymorphism of the tryptophan hydroxylase 2 gene significantly predicted clinical manifestations and alterations in neurocircuitry. Compared with GG homozygotes, carriers of a T allele had earlier age at symptom onset, an interactive effect with childhood trauma in predicting symptom severity, and decreased connectivity between right amygdala and middle frontal gyrus. Epigenetic processes such as methylation may underlie relationships among genes, physiologic reactivity, and environmental exposures, including childhood adversity. Patients with FND may have less resilient responses to stress as indicated by decreased 24-hour heart rate variability[29]. A pilot study of 15 patients with

FND found increased methylation of the oxytocin receptor gene, which plays a role in regulating responsivity to stress[30].

Many clinicians associate FND exclusively with psychiatric morbidity, but observations beginning in the 19th century found that structural illnesses and injuries may predispose or precipitate FND, as in epilepsy predating functional seizures[31] or migraine preceding functional limb weakness[25]. Physical injury, acute illness, and drug side effects may precipitate FND by causing novel nociceptive or unexpected sensory experience[25]. Certain neurologic disorders are more likely than others to trigger comorbid FND. For example, Parkinson disease is a likelier precipitant than Alzheimer disease[32], perhaps due to specific effects on motor-linked networks.

Clinicians often fear making diagnostic errors in patients who present with FND, but misdiagnosis of FND in neurologic clinics is no more common than misdiagnosis of other neurological and psychiatric disorders[33]. In fact, erroneous diagnosis of FND as epilepsy[34] or multiple sclerosis[35] may be more frequent than the other way round.

The prognosis of FND is poorer than most clinicians expect. In one study, 40% of patients were unchanged or worse after a mean of 7 years. Only 20% achieved remission[36]. Remission rates of functional seizures may be higher (40-50%) than other FND symptoms, but considerable variability exists among studies[36]. Mortality also may be higher (e.g., 2-3 fold increase in patients with functional seizures), although the causes are unclear[37].

Seizures

Functional seizure(s), also known as psychogenic nonepileptic seizures (PNES) and dissociative seizures, manifest episodes that resemble epilepsy or syncope. Accurate diagnosis can be challenging and often delayed because symptoms are transient and complete histories may be available only from witnesses (Tables 1 and 2).

No single symptom is pathognomonic of functional seizures. Studies have highlighted an overlap between pre-ictal panic-like symptoms and functional seizures[51], in which dissociation may occur in response to autonomic arousal and be perpetuated by classical and operant conditioning. Qualitative conversational analysis of seizure descriptions distinguished functional seizures from epilepsy with surprisingly high sensitivity and specificity[47]. A machine learning algorithm processing clusters of patient/observer responses to questionnaires showed promise in distinguishing epilepsy from syncope, but this is not yet ready for diagnosing individual patients[52].

The “gold standard” for diagnosis is recording patients’ typical episodes consistent with functional seizures on video EEG (vEEG)[53]. Events occur spontaneously within 2 days of monitoring in 81% of those receiving a definitive diagnosis [54]. Signs with high sensitivity or specificity for functional seizures are long duration of events, fluctuating asynchronous limb or side to side head movements, pelvic thrusting, ictal eye closure, ictal crying, post-ictal memory recall,[53] and peri-ictal responsiveness[55]. vEEG results require experienced interpretation because they may be normal with certain focal types of epilepsy, e.g., hypermotor frontal lobe seizures. In addition, interictal non-epileptiform abnormalities in

functional seizures are still commonly misinterpreted by non-experts[56]. Many patients lack access to specialized monitoring units or have "indeterminate" diagnosis due to equivocal or uneventful monitoring. They can be managed successfully using published minimum criteria from the International League Against Epilepsy (ILAE) for less than certain diagnosis[1]. Video only recordings interpreted by experts, including videos captured by smartphone[48], appear acceptably reliable compared to vEEG[57]. Ambulatory EEG can be useful when routine EEG is equivocal or when medication withdrawal is not needed[58].

Suggestive seizure induction, using transparent and consented procedures, avoided expensive vEEG in 21% of patients with functional seizures and decreased indeterminate testing by 13% in one study[46].

Research on biomarkers to differentiate epileptic from functional seizures is ongoing, but history, risk factors, and ictal data currently are more reliable. Prolactin and lactate levels may be elevated after epileptic convulsions but need to be drawn within 1-2 hours of events, can be normal after focal seizures and sometimes abnormal after functional seizures[59]. A study of four plasma proteins sampled within 24 hours in 137 patients showed promise[50]. Wrist-worn accelerometers distinguished convulsive epileptic seizures from functional seizures with 70% sensitivity and 86% specificity[49] Neuropsychological assessment did not distinguish functional seizure(s) from epilepsy but may be helpful with other aspects of assessment and formulation[53].

Movement disorders including limb weakness

Functional movement disorders (FMD) may manifest with any type of abnormal movement[38]. Most series found that tremor is most common, followed by dystonia[24], myoclonus[43], and gait disorders[41]. Less common are parkinsonism[32], tic[60], stereotypy[61], facial movements like hemifacial spasm[40], and chorea. In a multicentre study of 410 patients with FMD, the most common clinical presentation was a 'mixed' phenotype (46% of patients)[26]. Paresis and paralysis merit inclusion among manifestations of FMD because they commonly overlap with hyperkinetic movements and may share similar pathophysiologic alterations of higher control of voluntary movement. In FMD, disruptions of voluntary movement contrast with preserved habitual or reflexive movements of the same body part, which is helpful in distinguishing FMD from isolated dystonia.

Other common features of FMD included sudden onset of symptoms (70%) and high rates of comorbidity with anxiety (52%), fatigue (45%), and pain (42%)[26]. The sudden onset of FMD with weakness makes it a common mimicker of stroke, after migraine and seizure, especially in patients being considered for thrombolysis or needing hospitalization. Among 1165 people in one study admitted for acute stroke-like presentations, 8.4% had FMD, 14% other medical conditions, and 78% stroke[14].

Diagnosis of FMD rests on key elements of clinical history and characteristic signs on examination (Tables 1 and 2). Although emphasis has been placed on examination, historical features can provide guidance for differential diagnosis. In a study of 874 patients with hyperkinetic movement disorders, 91% were correctly identified using an algorithm of

historical features[62]. Those suggesting FMD included early age and abrupt onset, more than one movement type, fluctuations during the day, waxing and waning longitudinal course, presence of pain or fatigue, positive psychiatric features, and family history. In 99 patients with functional dystonia, an algorithm of similar historical features had good specificity/sensitivity against other types of dystonia[63].

In FMD, there are movement patterns that can be diagnostic (Table 1) [38]. Variability may be detected by comparing movements initiated with patients' full attention, movements performed with distraction, habitual movements (e.g., shifting position in a chair), and movements induced by tendon reflexes. Various tests may demonstrate these differences including Hoover's sign or the hip abductor sign of functional leg weakness and the tremor entrainment test.[38] Techniques of suggestibility and deception run counter to principles of patient autonomy unless undertaken after informed consent and may add little to well-gathered histories and transparent examinations.

Clinical neurophysiological tests may aid diagnosis. Specific tests are phenotype specific and can be found in reviews and in Table 1[38,42]. New methods may prove useful if validated (Table 1). Functional and structural neuroimaging studies have identified group differences between patients with FMD and comparison groups but cannot be used diagnostically for individual patients[42].

Persistent Postural-Perceptual Dizziness (PPPD)

The Bárány Society defined the functional vestibular disorder of persistent postural-perceptual dizziness (PPPD) for the International Classification of Vestibular Disorders (Box 1)[2]. Key symptoms of PPPD are chronic dizziness, unsteadiness, and swaying or rocking (non-spinning) vertigo exacerbated by patients' own movements and exposure to visually complex or motion-rich environments (Case 1) (Table 3). Earlier descriptions of phobic postural vertigo, space motion discomfort, visual vertigo, and chronic subjective dizziness, informed the definition of PPPD[2].

Studies from hospital and university-based neurology clinics found the prevalence of PPPD to be 20% among all patients with vestibular symptoms rising to 40% in a dedicated dizziness centre making PPPD the most common cause of chronic dizziness in those settings[64]. The median patient age was mid-50s with a 2:1 female predominance. Illnesses precipitating PPPD are similar to its predecessors and include structural vestibular conditions such as benign paroxysmal positional vertigo and unilateral peripheral vestibulopathies (23-25% of cases), vestibular migraine (11-20%), panic and generalized anxiety disorders (15% each), mild traumatic brain injuries (3-15%), stroke (2%), dysautonomias (1-7%), and other medical conditions (3-6%)[64]. Neuroticism may predispose to PPPD and high levels of body vigilance and aberrant illness-related beliefs at the time of precipitating events may predict persistent dizziness[64].

Physiologic investigations of patients with PPPD and its predecessors have identified stiffened postural control sometimes accompanied by excessive upper body sway[65]. Gait changes include widened base of support, shorter stride length, and momentary two-footed

stance mid-stride[65]. Patients with PPPD also showed overreliance on visual versus vestibular and somatosensory inputs (i.e., visual dependence), making them susceptible to degradation of dynamic visual acuity on exposure to moving visual stimuli[65]. Spatial navigation may be impaired.

Functional cognitive disorder

Cognitive symptoms traditionally have been excluded from definitions of FND, but recent work highlighted how similar principles of 'ruling in' positively identifiable symptoms and signs can be applied to this area (Case 2) (Table 3). Recent consortium diagnostic criteria defined functional cognitive disorder as a condition of cognitive symptoms with clear evidence of internal inconsistency, not better explained by another disorder, and causing distress or impairment or warranting medical evaluation[4]. Similar to other FND, "internal inconsistency" referred to differences between occupational functioning and observed performance during interview, and variable patterns within cognitive tests. Analysis of behaviour and language during consultation helps discriminate functional from neurodegenerative disorders. Patients with functional cognitive symptoms give detailed and specific descriptions of episodes of memory failure, are more likely to attend alone, and are more concerned about their symptoms than others around them[66,67]. Validity tests on cognitive batteries may not be helpful as often thought. Single tests are commonly positive in conditions like epilepsy, and mild cognitive impairment.[68]

Functional cognitive disorder may account for symptoms in a proportion of patients with subjective cognitive decline or mild cognitive impairment who do not 'convert' to dementia. A recent meta-analysis of patients attending memory clinics found that 24% received descriptive diagnoses consistent with functional cognitive disorder[69].

Functional cognitive disorder may also coexist with structural and metabolic causes of cognitive decline. The relationship may be comorbid, with both disorders contributing to disability or change over time with anxiety-related prodromal functional symptoms predating onset of dementia. In some cases, a disease biomarker such as an amyloid PET scan may prove to be a false positive, never progressing to degenerative illness.

Abnormal metacognition is prominent in functional cognitive disorder[70]. Individuals with functional cognitive disorder describe cognitive failures experienced by healthy people in everyday life[71]. They may perceive severe impairment despite good performance on tests or in occupational settings. A bias toward 'good old days' has been noted, although it remains unclear whether this is a risk factor or consequence.

Phenotypes of functional cognitive disorder have been proposed[69] including isolated cognitive symptoms, illness anxiety about dementia, cognitive symptoms in mixed FND[72], and dissociative amnesia. A subtype for cognitive symptoms caused by anxiety or depressive disorders was suggested, but anxiety and depression may also be viewed as comorbidities that exacerbate cognitive symptoms[73].

Distinguishing FND from factitious disorder and malingering

Unfortunately, many patients with FND are still commonly subject to suspicion that they may feigning symptoms[74] and this is the source of significant stigma[18]. Actually, there is no more reason for this concern with FND than for many other neurological complaints such as pain or fatigue[75].

Feigning is often divided into factitious disorder (wilfully simulating symptoms for medical care) or malingering (simulating symptoms for other gain). Both require evidence of conscious deceptions and actions[75], primarily a major discrepancy between reported and observed function - for example someone claiming persistent leg paralysis whose family member provides a video clip of them dancing. Discrepancy between reported symptoms and day to day activity, or variability in performance that the patient does report, do *not* provide evidence of feigning.

An expanding range of evidence supports FND as a genuinely experienced disorder. Its semiologic manifestations, aetiological risk factors, and co-existence with other medical and psychiatric conditions are similar around the world and throughout history, allowing for cultural differences in attributions of illness. Neurophysiological studies including those looking at event related potentials and sensory attenuation[76 77] as well as functional neuroimaging studies[78 79 80 81]have identified differences between FND and feigning. Differential positive treatment responses obtained in randomized controlled trials of therapeutic interventions designed specifically for patients with FND[8283] are hard to explain if such studies were contaminated by inclusion of individuals feigning illness by unknowing investigators.

Pathophysiology

The fundamental pathophysiology of all the entities reviewed here can be considered in a similar way, a dysfunction of sensory processing, motor or thought output, or both. FMD, functional seizures, and functional cognitive disorder have prominent output abnormalities, whereas PPPD has both sensory and motor dysfunction. Our understanding of the model is best explained in terms of movement and will be described that way.

A key element of FND is a partial loss of voluntary control over the body: patients do not feel they are the agents of their abnormal movements. This can be understood in the frame of predictive coding models on how the brain generates the sense that we are the agent of what happens in our body, in particular generating movements (Figure 2). When a movement is planned, a motor command is sent to the motor cortex which will execute the movement. In parallel, a feedforward signal goes to the so-called agency network (an important hub being the right temporo-parietal junction). Once the movement is executed, feedback information goes to the agency network and a comparison between the feedforward and feedback data occurs; when there is a good match, the sense of agency arises[38]. A similar model has been developed to explain functional seizures and functional somatic symptoms in general[84,85]. Many recent studies converge to a mechanism of abnormal sense of agency, with neuroimaging studies pointing to abnormal activation of the right temporo-parietal

junction[38,42] A pilot uncontrolled study found clinical improvement after non-invasive stimulation of this area in seven patients with functional seizures[86].

In FND, evidence points to overweighting the feedforward message under the influence of prior expectations, attention, and emotion (Figure 2). A cognitive bias -"jumping to conclusion" - found in FND patients supports this hypothesis: patients tend to favour their prior hypothesis/expectation of an outcome over objective data regarding the future outcome[87]. A recent electrophysiological experiment confirmed slow sensory information processing in FND patients suggesting a reduced attention allocation to objective body signals[88] and this could explain this shift toward too much emphasis on the feedforward signal. In chronic functional dystonia, increased pain tolerance has been found, despite normal pain threshold indicating a dissociation between the discriminative and affective components of pain[89]. It can be postulated that here also attention plays a role in "filtering" the feedback signal during multimodal integration including emotional salience. Abnormal increased attention to the symptom found in FND also explains why explicit/deliberate movements (lifting the leg during examination) are harder to execute in FND patients than implicit/automatic movements: a different motor program is involved[38].

Increased activity in the limbic system found in neuroimaging (fMRI) during motor and emotional tasks[90], increased cortisol levels, and abnormal heart rate variability[91] all point to abnormal stress reactivity and emotion regulation in FND[90]. Such abnormalities can be important precipitating and perpetuating factors.

Findings in functional seizures and PPPD, although less extensively studied, suggest similar abnormalities in agency and emotional networks as seen in FMD. Functional neuroimaging studies in people with functional seizures highlight increased connectivity between the insula, motor, and parietal areas[92]. Small studies of ictal SPECT in functional seizures highlighted abnormalities of agency and limbic networks[93]. Changes in PPPD were more nuanced. Connectivity in parietal areas was increased on resting state fMRI in proportion to symptom severity,[94] but cortical folding was decreased in right temporal- parietal regions which showed reduced activity and connectivity in response to vestibular stimulation.[95]

Several studies have demonstrated brain anatomical differences (grey matter and basal ganglia volumes) in FND[96]. Recent machine-learning classifying paradigms have been able to correctly identify FND patients and healthy controls with good accuracies, both with resting state functional and structural brain images[78]. Correlation between structural changes and clinical data (symptom severity, emotion/mood, dissociation, gender, childhood trauma[78]) strongly suggest a link between symptoms of FND and brain anatomical difference but longitudinal studies are needed to address the question of causality.

Treatment

Effective treatment for all types of FND begins with establishing therapeutic two-way communication to understand and engage patients in their own recovery process (Table 2). Neurologists have traditionally avoided taking responsibility for people with FND, although are often most appropriate to engage patients in treatment. Explaining the diagnosis with

clarity, confidence, using the principles of a 'rule in' process, is a key step in treatment[97] Patients should be provided written information, although a randomised trial showed that this alone is insufficient to improve outcome[98].

Multidisciplinary treatment which individualises the patient's problems has gained more support than a purely psychological approach[3399]. A common theme of such approaches is treatment based on a new understanding of FND symptoms, and not just the individual's aetiological risk factors. For example, therapy for functional seizures now commonly focuses on psychophysiological mechanism of the events. Therapy for FMD builds on the differences between automatic and voluntary movement that form the diagnosis and use these in physical therapy. Clinical experience suggests that treatment for co-existing conditions such as migraine, orthostatic intolerance, and anxiety or depression is also important.

New approaches to physiotherapy for FMD have some of the strongest evidence for treatment[33]. Whereas someone with stroke may be encouraged to focus on their affected limb, in FMD physiotherapy, explicit use of distraction and preserved automatic movements are used to 'retrain' aberrant motor function. A randomized study compared 29 patients with physical therapy to 28 controls with similar amount of conventional physiotherapy[82]. At 6 months, 72% of the physical therapy group rated their symptoms as improved compared with 18% in the controls. A physical therapy program can be managed by telemedicine and still be successful[100] . In PPPD, studies of vestibular rehabilitation [101] reported reductions in sensitivity to motion and dizziness. Occupational therapy also has an important role in FND, and consensus recommendations have been published[102], but has generally only been tested as part of multidisciplinary treatment.

Psychological therapy has been tested in many forms of FND[103] and is the treatment of choice for functional seizures. Controlled studies and case series found that 82% of patients had 50% reduction in seizure frequency immediately following treatment[104]. In the past decade, f a limited number of randomized controlled trials (RCT) showed benefit of cognitive behavioral therapy (CBT) informed psychotherapy over standard medical treatment for seizure frequency over periods up to 6 months[103]. In a RCT of 368 patients with functional seizures both groups improved but there was no difference in seizure frequency from adding CBT to standardised therapy. CBT did however lead to improvement in 8 out of 13 secondary outcomes such as general functioning, distress, somatic symptoms, and duration of seizure freedom[83]. Other types of therapy such as mindfulness-based psychotherapy, psychodynamic psychotherapy, and prolonged exposure therapy for those with PTSD show promising outcomes[105]. Self-help treatments for stress reduction[106] have been shown to be safe and acceptable to patients and may be helpful for patients with limited access to treatment. There is less evidence for psychological therapies for functional movement disorder,[103] and there is only one such study for functional cognitive disorder[107]. For PPPD, CBT enhanced response to sertraline[108] and acceptance and commitment therapy produced significant benefits when combined with vestibular rehabilitation.[109]

Trials of psychopharmacologic treatments have been small and inconclusive for FND seizure and motor symptoms, although treatment of comorbidity is less controversial[110]. In PPPD,

eight uncontrolled trials, totalling >300 patients, found that selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors reduced mean severity of PPPD or previous syndromes of persistent dizziness by 50% in 6-12 weeks[65]. For functional seizures, removing any anti-seizure medications that are not treating common comorbidities such as anxiety or depression (or epilepsy) has been shown to be helpful and safe[111].

Repetitive transcranial magnetic stimulation has had mixed results in FMD[112] . A large placebo controlled trial of botulinum toxin therapy for tremulous and jerky FMD showed no benefit[113]. Treatments such as hypnotherapy, therapeutic sedation and intensive inpatient treatment may help some patients[114].

Future Directions and Conclusions

For decades, FND has been a disorder restricted strictly to conditions involving the voluntary motor and sensory nervous system. We have not had space here to discuss sensory disorders, such as functional anaesthesia or blindness or other motor disorders such as speech and swallowing symptoms, which all have their own diagnostic features based on similar principles. Functional seizures are paroxysmal motor events, one strong reason to keep them in the same category, along with the fact they commonly co-occur with other FNDs [26]. We have included two other common FND subtypes involving dizziness and cognition to explore their overlap (Figure 1)

A striking feature of many functional disorders is their triggering by and co-existence with recognised pathophysiological events. FMD and functional seizures are often triggered by injury or other neurological disease. For PPPD, an initial, usually vestibular event is part of the definition. Functional cognitive disorder commonly follows mild traumatic brain injury after the point when natural recovery might have been expected to occur. Psychological factors, such as adversity, personality traits, or psychiatric disorder may be relevant as predisposing, precipitating, and perpetuating factors at all stages of FND but contrary to previous conversion disorder models, are not a prerequisite. The strength of these triggering pathophysiological events, which themselves often shape the symptom of the subsequent functional disorder, may partly explain why there is such heterogeneity in background risk.

Figure 2 illustrates overlapping physiological processes. In all entities reviewed here, the person with FND develops an abnormal model of the way his or her brain and body function. The model confirms and reinforces the abnormal function. The underlying push toward the abnormal model comes from a physical or emotional experience that cannot be subsumed into normal function. FND is arguably what might be expected to happen when “predictive processing” in the brain goes awry.

There are also commonalities in our best therapeutic approaches to all these disorders. Physical therapy in FMD promotes automatic movements over abnormal overlearnt impaired voluntary ones. In PPPD habituation exercises aim to ‘desensitise’ a similarly aberrant sensory and motor system where there is an overlearnt abnormal “attentional spotlight” on the symptom of dizziness. Similarly, psychotherapies like CBT for FND, aim to modify, among many targets, the various inputs in Figures 1 and 2 that may contribute to the

disorder, including interoception, attentional style, cognitions, emotions, and psychological comorbidities.

Clearly there are important differences between these diverse symptoms. Seizures are paroxysmal, PPPD and FMD are typically continuous and are arguably as different as panic disorder and depression. As with panic and depression, they co-exist more often than by chance and treatment typically improves with an understanding of their overlap.

The new principles of making a 'rule in' diagnosis based on clinical signs map on to a new understanding of pathophysiology and treatment and allow diagnosis in people with other neurological conditions. Establishing reliability in positive diagnosis of PPPD and functional cognitive disorder will be especially important in evaluating their relevance to controversial syndromes such as those arising in Havana and after Covid-19 infection. With increasing evidence-based treatment, the diagnosis of FND should be seen as a process of looking for potentially reversible cause of disability and distress whether or not an individual has abnormalities on conventional laboratory or radiological testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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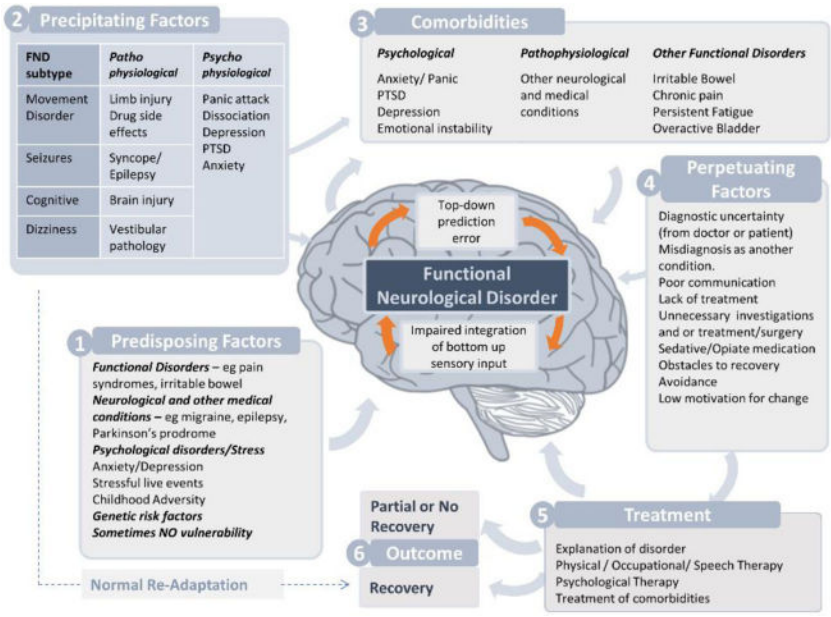

Figure 1.

Functional Neurological Disorder can be triggered by pathophysiological and/or psychophysiological events. Acknowledgements to Stoyan Popkirov for the graphic concept.

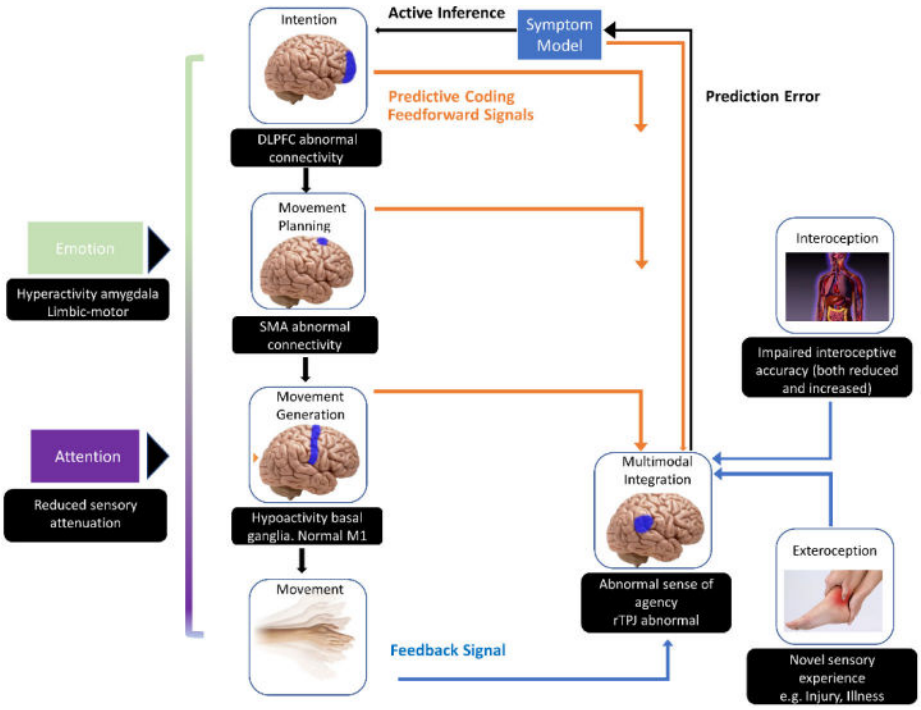

Figure 2. Neural mechanisms of FND.

This scheme relates to FMD but its principles are applicable to all FNDs. Movements are generated by motor cortex after planning/preparation in SMA. This produces feedforward signals to be compared to feedback from interoceptive and external signals after action. If signals don't match, movement will not be appreciated as voluntary. The brain has a model of the body and world which adds predictive coding to this multimodal integration. Feedback signals that don't match predictive coding create prediction error, which modifies the model so that predictive coding matches subsequent feedback. In FND, it is hypothesized that prediction error is not accurately updated, perpetuating dysfunction.

FMD = functional movement disorder; DLPFC=Dorsolateral Prefrontal Cortex; SMA=Supplementary Motor Area; M1= Primary Motor Area; rTPJ=Right Temporoparietal Junction

Table 1.

Positive Diagnostic Features and Biomarkers of Functional Movement Disorder and Functional Seizures.

Functional Movement Disorders	
Commonly used	**Newer diagnostic tools and research biomarkers**
Tremor	
Tremor entrainment or cessation to externally cued rhythm	Whack-a-mole sign: holding down a tremulous body part[38]
Variability of frequency and amplitude	Coherence between antagonist muscles measured with standard coherence or wavelets [39]
Dystonia	
Fixed inverted and/or plantarflexed ankle	Dystonia of the face: downward lip pulling, orbicularis oculi spasm, platysma spasm[40]
Fixed clenched fist	Sustained facial movement to evoke a spasm[40]
	Functional hemifacial spasm lacks the "Other Babinski sign" (raising of eyebrow on affected side)
Gait and Balance	
Variability of gait performance	Classification of gait types into 7 types: ataxic, spastic, weak gait, antalgic, parkinsonian, hemiparetic, dystonic[41]
Gait performance shows excellent balance	"Huffing and Puffing" sign: huffing, grunting, grimacing, and breath holding after small amounts of exercise[38]
'Walking on ice gait', Dragging monoplegic gait, or knee-buckling gait	Posturographic improvement with distraction (guessing numbers written on back or cognitive task)[42]
Jerks/Myoclonus	
Truncal jerking – especially with facial movement *	Increased startle[43]
Positive Bereitschaftspotential (BP) before movement using back-averaging	Event related desynchronization (ERD) using back averaging[42]
Limb Weakness and generic motor	
Hoover's sign	Absence of amplitude suppression of median nerve somatosensory evoked potential[42]
Hip Abductor Sign	Decreased prepulse inhibition of the blink reflex by stimulation of the index finger[44]
Drift without pronation	Absence of contingent negative variation in reaction time task[45]
Seizures	
Eyes closed	Transparent suggestive seizure induction[46]
Prolonged attacks	Qualitative conversation analysis[47]
Hyperventilation	Use of smartphone video[48]
Awareness during generalised shaking	Wrist-worn accelerometers[49]
Ictal or post-ictal weeping	Post-ictal plasma proteins[50]

* the diagnosis of functional jerks can be difficult, but 58% of 179 patients with truncal myoclonus had FND in one series[43].

Table 2.

Diagnostic and Treatment Pitfalls in FND.

Diagnostic Pitfalls in FND	
Pitfalls that can lead to a wrong FND Diagnosis	**Pitfalls that can lead to failure to make a correct FND diagnosis**
Jumping to conclusions based on psychological history/stress	Absence of psychological risk factors/stress
Failure to consider an additional medical/neurological cause	Failure to consider FND in presence of additional medical/neurological condition
Not basing diagnosis on presence of positive diagnosis signs	Lack of awareness of positive features of FND
Diagnosis based on 'bizarre' presentation alone	Male, older patient
Reliance on normal investigations	Placing too much weight on incidental imaging findings (e.g., white matter lesions)
Treatment Pitfalls in FND	
Do's	**Don'ts**
Explain the diagnosis on the basis of positive clinical features of FND	Only describe normal investigations or frame as a medical mystery
Where possible demonstrate positive clinical signs supporting the diagnosis. Explain to family and friends as well.	Jump straight to risk factors ('stress', 'psychological') when discussing possible causes of symptoms
Check and consolidate understanding of the diagnosis. Consider copying correspondence to patients. Provide written information. Signpost to online information and support organizations.	*Only* provide written/online information without also providing or referring on for treatment
Encourage early and active goal-directed rehabilitation. Engage family and friends with that process.	Encourage unrealistic expectations. Improvement is a gradual active process, and many patients do not improve.
Refer for appropriate therapies (physiotherapy, psychology, speech-language therapy, occupational therapy)	Discharge without any plan for follow-up or further treatment while patient remains significantly symptomatic and/or disabled by symptoms
Treat comorbidities - e.g., depression, anxiety disorders (including PTSD), sleep disorders. Refer to psychiatry if necessary.	Neglect to treat comorbid psychiatric disorders
Address unhelpful medication regimes; opiates, benzodiazepines, and other sedative medications can worsen symptoms of FND	Suddenly withdraw medications without warning
Connect with other professionals to prevent unnecessary and potentially harmful investigations or treatments. Support with training.	Assume that all new symptoms are FND; FND may be comorbid with or precede other neurological disorders. Assess new symptoms on their own merits.

Table 3.

Diagnostic criteria for Persistent Postural Perceptual Dizziness (PPPD) and Functional Cognitive Disorder

Persistent Postural Perceptual Dizziness **Bárány Society diagnostic criteria**	**Functional Cognitive Disorder** **proposed diagnostic criteria**[4]
A. One or more symptoms of dizziness, unsteadiness or nonspinning vertigo on most days for at least 3 months. **a.** Symptoms last for prolonged (hours-long) periods of time but may wax and wane in severity. **b.** Symptoms need not be present continuously throughout the entire day. **B.** Persistent symptoms occur without specific provocation, but are exacerbated by three factors: upright posture, active or passive motion without regard to direction or position, and exposure to moving visual stimuli or complex visual patterns. **C.** The disorder is triggered by events that cause vertigo, unsteadiness, dizziness, or problems with balance, including acute, episodic or chronic vestibular syndromes, other neurological or medical illnesses, and psychological distress. **a.** When triggered by an acute or episodic precipitant, symptoms settle into the pattern of criterion A as the precipitant resolves, but may occur intermittently at first, and then consolidate into a persistent course. **b.** When triggered by a chronic precipitant, symptoms may develop slowly at first and worsen gradually. **D.** Symptoms cause significant distress or functional impairment. **E.** Symptoms are not better accounted for by another disease or disorder.	**A.** One or more symptoms of impaired cognitive function. **B.** Clinical evidence of internal inconsistency **a.** The ability to perform a task well in a particular cognitive domain at certain times, but with significantly impaired ability demonstrated in the same domain, particularly when the task is the focus of attention. **b.** Not simply fluctuation over time. **c.** Consider red flags for other cognitive disorders which may present with features of inconsistency or fluctuation * **C.** Symptoms or deficit that are not better explained by another medical or psychiatric disorder, although comorbid disorders allowed. **D.** Symptoms or deficit that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, or warrants medical evaluation

*"Red Flags" discussed in the source document[4] included: 1) Inconsistency between cognitive domains – e.g. impaired single word vs sentence comprehension in semantic dementia, difficulties relating to visual comprehension (such as posterior cortical atrophy) that can produce effects similar to internal inconsistency, e.g. the reverse size effect, effects of apathy or low mood, intact implicit memory with defective conscious memory (e.g. Korsakoff's); 2) Variability over time can occur in other disorders such as Lewy Body Dementia, delirium and obstructive sleep apnoea.