

Review

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Review

Biomarkers and Rehabilitation for Functional Neurological Disorder

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Abstract: Functional neurological disorder, or FND, is widely misunderstood, particularly when considering recent research that suggests that the illness has a biological rather than a psychiatric basis. Nonetheless, the long-held view that FND is a purely psychiatric disorder without biological basis, or even a contrived (malingered) illness, remains pervasive both in modern medical care and general society. This is because FND involves an intermittent course of involuntary disability that rapidly alternates with improved neurological control. This has in turn caused shaming, low self-efficacy, and social isolation of the patients. Little research has examined the numerous biomarkers that are shared between FND and canonical neurological disorders and the encouraging outcomes that can follow conventional neurological rehabilitation, modified for this disorder. This review summarizes current research on FND biomarkers and physical rehabilitation results. General healthcare providers would benefit their care for their patients through their improved understanding the illness and recourses for support and treatment that are provided in this review.

Keywords: functional neurological disorder; MRI; rehabilitation

1. Introduction

Functional neurological disorder (FND) involves involuntary, intermittent neurological symptoms or signs that vary in relation to the extent of the patient's self-attention to the symptoms or emotional excitation. Although "FND" is the term that was most recently professionally adopted for this illness, for centuries it was addressed by many other names (hysteria, conversion disorder, psychogenic disorder, among them [1]). The recent name change was recommended in 2014 by specialists who treat FND to allay patients' concerns for their being inappropriately diagnosed with mental disease [2]. ("Functional neurological symptom disorder" is a widely used but much less frequent synonym.)

This review will show that FND can share characteristics with canonical neurological disorders. As a result, FND itself should be considered as a neurological disorder as well. Although some reviews have stated that FND has a poor prognosis, recent rehabilitation trials have shown more favorable outcomes, which will be reviewed here. The author, a practicing and investigational neurologist, has been the medical director for the FND Clinic at the University of Alabama at Birmingham, Spain Rehabilitation Center, Birmingham, USA, for the past 7 years, having evaluated and treated more than 400 individuals with FND. This review, drawn from the author's clinical experiences as well as current literature review, may revise the public and professional views of FND and thus help to demystify this vexing disabling illness.

2. Clinical Characteristics of FND

Although FND has been noted to have a peak age of onset at about 40 years [3,4], it can begin anytime between childhood all the way to geriatric age [5–9]. Any voluntary activity can be affected

by FND, including limb or facial movement, speech, cutaneous or muscular perception, and vision. The patients' self-attention to their symptoms or emotional excitement can aggravate them, while distraction from them may reduce their severity [10]. FND symptoms can be provoked by direct medical examination and subside when the patient believes not to be observed or undergoing formal evaluation [11–13]. The intermittent dysfunction is not apparently caused by epileptic brain discharges, transient cerebral ischemia, medication side effects, intoxication, metabolic or endocrinological diseases, systemic infection, or fatigue. As many as 18% of patients who are seen on neurological hospital wards can have FND [14].

FND has a high incidence of comorbid mood disorder, though this does not occur with all patients [9,15–18]. The disturbances are frequently considered to “mimic” canonical neurological disorders [19–22], which may lead to falsely infer that the patients contrive their symptoms. FND lacks characteristic abnormalities on clinical structural brain or spinal imaging [23,24]. Psychological care, particularly Cognitive Behavioral Therapy (CBT), can attenuate the symptoms [25]. The “conversion disorder” hypothesis for FND was postulated by the noted Austrian psychiatrist Sigmund Freud (1856-1939), in which early life trauma becomes unintentionally mentally repressed and resurfaces later as involuntary somatic complaints [26]. This perspective remains widely accepted by clinicians [27], even though the hypothesis is untestable and unproven [28]. There is consequent common stigmatization and social isolation for persons with FND [29,30]. For these reasons, FND has long been viewed by the public and clinicians as a psychiatric illness in which the patients' mood disorder is at the root of the disturbance [31], or the symptoms are intentionally produced (malingering) [32], and it lacks a biological cause.

As far back as the 1880s, the eminent French neurologist Jean-Martin Charcot (1825-1893) considered FND (then termed hysteria) as a neurological disorder [33]. Because the fluctuating manifestation of FND led Charcot to consider that a structural brain lesion could not be responsible, the view that FND was a neurological disorder fell by the wayside for most of the 20th century because of Freud's demonstration that FND can improve with psychoanalysis or hypnosis. However, starting nearly 30 years ago, the findings of distinct regional cerebral metabolic changes in physiological brain imaging studies in persons with FND, not found in neurologically healthy individuals [34,35], invigorated neuroscientific investigations in FND. These continue at an accelerating pace, as shown by the annual rate of publications for FND that are listed in the public registry of medical research publications, PubMed (<https://pubmed.ncbi.nlm.nih.gov>; Figure 1). These studies as well as those that tested other biomarkers imply, instead, that FND has a biological basis. As will be shown here, many of these biomarkers are in common with canonical neurological disorders. Moreover, rehabilitative techniques that are commonly practiced with canonical neurological disorders (e.g., stroke, spinal cord injury, traumatic brain injury) have been shown similarly to benefit FND and are detailed later.

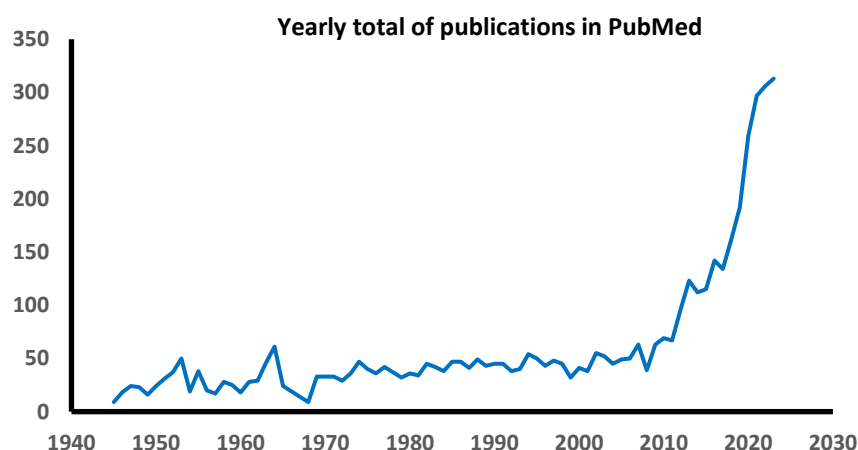


Figure 1. Yearly total of publications appearing in PubMed that included the terms “functional neurological disorder,” “functional neurological symptom disorder,” or “conversion disorder.” The

alternate terms “hysteria” and “psychogenic disorder” are not included in this graph because they include other disorders that are not FND in addition to FND.

3. Biomarkers for FND

3.1. Advanced Structural Brain Imaging Findings in FND

Structural brain MRI analysis, primarily using voxel-based morphometry, has indicated significant structural changes in brain grey areas. These findings are evident only with advanced statistical processing of brain MRI data at the patient group level and not in individuals with standard clinical brain MRI. As of now, 21 studies have evaluated morphological brain abnormalities in persons with FND (Table 1). The preponderance of volumetric brain studies in FND found reduced focal cortical or subcortical grey tissue areas when compared to individuals without FND. There was no pattern of volume loss that characterized FND.

Table 1. Summary of volumetric grey area changes on structural brain imaging in FND.

Volume findings	Number of studies	References
Focal decrease	11	[36–46]
Focal decrease and increase in different areas	4	[47–50]
Focal increase	3	[51–53]
No difference compared to non-FND subjects	3	[54–56]

Similarly, there has been no characteristic volume loss pattern in patients with Parkinson disease, a common neurodegenerative disease [57], even though numerous voxelwise brain grey matter analyses consistently have shown cortical atrophy [58].

As shown by Table 1, alternative, less frequent patterns also occurred: (1) both volumetric focal decrease and increase in the same study group, (2) only focal volume increase, and finally (3) no difference in brain regional volume compared to non-FND participants. Of note also is that for dystonia, for which there is evidence that it is a neurodegenerative disease [59], and Alzheimer disease, a leading neurodegenerative disease [60], quantitative brain morphological assessment has shown both focal decreased and increased volumes in the same populations [61,62]. Thus, strictly focal brain regional volume decrease is not characteristic of canonical neurodegenerative illness.

3.2. Genetic Analyses

Genetic bases for several neurodegenerative disorders have been identified, although these diseases more often are sporadic than familial. In Parkinson disease 90 genetic risk factors have been identified [63]. Heritability for multiple sclerosis has been well described [64]; the HLA DRB1*1501 haplotype has been most significantly associated with increased risk for the disease, among more than 200 other genes [65]. The finding of numerous genetic mutations in forms of dystonia in the later 20th century changed the neuroscientific view of dystonia from earlier decades that it had a psychiatric etiology to being a neurological disorder [66,67].

In contrast to this considerable body of study, research for specific genotypes in FND has markedly lagged. A tryptophan hydroxylase 2 gene polymorphism—*G703T*—has been shown to predict early age onset of FND [68]. Functional seizures, also called paroxysmal or psychogenic nonepileptic seizures, are generally considered to be a kind of FND. Such seizures are associated with polymorphisms of the *FKBP5* gene, but only when co-occurring with depression [69].

3.3. Low-Grade Inflammatory Biomarkers

Inflammatory biomarkers have been identified in diverse neurodegenerative disorders. Recurrent inflammation of the central nervous system is well known to be a major determinant of disability in multiple sclerosis [65]. Chronic inflammation in the central nervous system in this disease contributes to neurodegeneration through impairing remyelination [70]. Evidence of low-

grade nervous system inflammation has been recently found in other neurodegenerative diseases, including Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis, based on either measuring serum pro-inflammatory cytokines or identifying increased microglial activation in the brain on positron emission tomography [71,72].

Recent research has identified elevated serum cytokines as well in persons with FND, in particular, IL6, IL12, IL17A, IFN γ , TNF α and VEGF-a [73]. Elevated serum C-reactive protein levels have been identified in children and adolescents with FND [74]. These findings thus far have not led to successful pharmacological trials for inflammatory modifiable agents for FND.

3.3. *Autonomic Disturbance in Canonical Neurological Disease and FND*

In some canonical neurological disorders, specific autonomic disturbances have been found that are shared with FND, which are discussed here.

3.3.1. Increased Cardiac Contraction Rate

Tachycardia has been rarely characteristic in specific canonical neurological disorders. Mitochondrial membrane-associated neurodegeneration (MPAN) is a rare disorder that has been described only in the 21st century. It is typified by iron accumulation in the basal ganglia, progressive cognitive decline, spasticity, dysarthria, dystonia, and optic atrophy [75]. Mean onset is at age 10 years. Cerebral atrophy has been described in a subset of the patients. About 30% of MPAN patients have cardiac disease, including cardiomyopathy, arrhythmia, and sustained tachycardia [76]. Orthostatic tachycardia has been found in patients with multiple system atrophy, another neurodegenerative disorder (described further below) [77]. A subset of patients with functional movement disorder are found also to have elevated heart rate at rest, including the Postural Orthostatic Tachycardia Syndrome (POTS), compared to neurologically healthy control subjects [78–80]. Several patients in the present author's FND clinic have been diagnosed with POTS by their cardiologists.

3.3.2. Superficial Tissue Blood Flow and Temperature Changes

Cool and dusky appearance of the distal limbs (the “cold hand sign”) is a characteristic of multiple system atrophy and less often in other neurodegenerative disorders [81–85]. On clinical examination, multiple system atrophy is diagnosed by combined limb rigidity, bradykinesia, postural instability, ataxia, and autonomic nervous system disturbance. Average age of onset is 53 years. Longitudinal structural MRI studies of patients with multiple system atrophy demonstrate progressive degeneration in the putamen or the pons [86]. Longitudinal follow-up on clinical examination demonstrates progression on the Unified Multiple System Atrophy Rating Scale; mean interval between diagnosis and death is 69 months [87].

FND has been reported not to occur in multiple system atrophy [88]. However, in his FND clinic, in recent years patients have brought to this author's attention of acute, intermittent distal limb dusky discoloration. The author began prospectively to evaluate the color of the patients' limbs in the clinic with photography. In a preliminary report at the 2022 meeting of the Functional Neurological Disorder Society in Boston, the author observed “purple feet” in 17% of 89 consecutive patients diagnosed with FND [89]. Since that time, the author has observed the phenomenon to be even more frequent, and it is under further study.

The phenomenon resembles closely the “cold hand sign” of multiple system atrophy, as vividly illustrated by Klein et al [83]. The disturbance in the author's FND patients is more evident in the feet than in the hands; it can be recognized in some cases at the forearms and the knees as well. The patients seldom volunteer the notice of this disturbance and usually are not bothered by it. The discoloration increases after a few minutes at repose with the lower extremities in a dependent position. There is usually no edema and only rarely somatosensory discomfort. In functional hemiparesis the disturbance is unilateral and ipsilateral to the paretic limbs. Often the distal limbs are cool to touch, and in some cases, they have hyperhidrosis. After mild manual compression of the

dorsal surfaces of the hands or the feet, the blanching may require as much as 10 seconds to return to baseline. The phenomenon suggests delayed capillary refilling, which also was observed in multiple system atrophy [90]. There is no age dependency for the phenomenon in the author's FND clinic.

Figure 2 shows purple feet in a young patient seen in the author's FND clinic. The 18-year-old woman had been followed in the clinic since the prior year. She and her father reported frequent episodic loss of consciousness and staring, with unremarkable EEG; also episodes of poor concentration, partial ptosis of the right eye, and sense of ocular vibration. Her 40-year-old mother had been followed in the same clinic for two years, for the 12-year-history of episodic sense of head vibrating, visual loss, limb paresthesias, bilateral ankle intorsion, and diplopia, with on examination episodic facial flushing, leg tremor only during examination, and prolonged capillary refilling in the feet after light digital compression.



Figure 2. The examiner leaves blanched "fingerprints" after gentle digital compression on both feet of an 18-year-old woman in the author's FND clinic with eight years of FND. Note also the purple discoloration of her feet, compared to the areas with delayed capillary refilling immediately after compression.

There have been no published instances of this phenomenon in FND. Of note, the distinguished British neurologist Samuel Alexander Kinnier Wilson (1878-1937), who rejected the psychiatric basis for FND, described a patient with functional paraplegia and lower extremity analgesia [91]. Not only did the patient fail to sense the pushing of a needle through the calf, but also no bleeding followed. But when the patient regained skin sensation after the examiner applied a wire brush to the leg, bleeding followed from pin prick. This phenomenon has not been replicated.

Rarely the phenomenon is painful. Figure 3 shows self-taken photographs by a second patient from the author's FND clinic. The 20-year-old woman had been followed in the FND clinic for the prior year for the four-year complaint of episodic loss of consciousness of uncertain etiology, induced by emotional upset and variable paraparesis. The brain MRI scan was unremarkable. After a year of follow-up, she urgently notified the author of the acute painful and stiff left hand, along with discoloration (Figure 3A). The phenomenon was self-photographed and forwarded to the author. The author urged that the patient to be seen by her local emergency department to rule-out peripheral vascular insufficiency. Work-up in the emergency department demonstrated normal peripheral arterial flow as evaluated by ultrasonic evaluation, and the patient was advised to return to home. The disturbance subsided after a day without specific treatment.

The patient subsequently e-mailed to the author of complaint of another peculiar finding that co-occurred with the hand complaint, which was an elongated roughly linear area of depigmentation that was vertically oriented along her abdomen and not painful (Figure 3B). This also dissipated after a day. The author forwarded the images to the chairman of the section of rheumatology at his

university for an opinion, who could not recognize the etiology. The patient continues to be followed for variable paraparesis and sustained delayed pedal capillary refilling after manual compression.

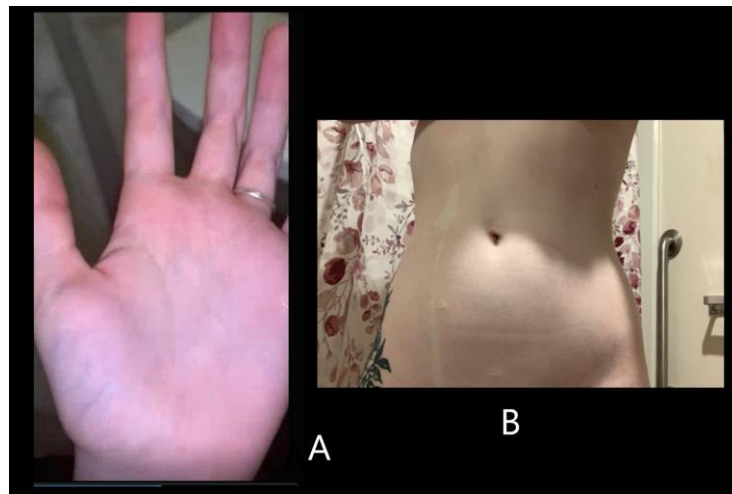


Figure 3. Self-photographed acute dermal changes in a 20-year-old woman with FND. **(A)** Erythema of fingertips and cyanosis of the thenar eminence, diffuse hand pain and stiffness. **(B)** Painless right paramedian linear depigmentation of the abdomen.

3.3.3. Gastrointestinal Motility Disturbances

Irritable bowel syndrome (IBS) refers to motility difficulties that can include irregular defecation and abdominal pain, without finding structural tissue abnormalities on standard imaging or scoping procedures after excluding inflammatory bowel disease [92]. IBS is common in FND [93,94]. Many patients in the author's practice complain of reduced ease of esophageal passage of food or pills, which is termed "globus pharyngeus," formerly called "globus hystericus" [95]. Similarly, various forms of functional (physiological) gastrointestinal motility impairments occur commonly in Parkinson disease, as much as 65% of patients, and the symptoms often long precede the onset of limb motor disturbances [96]. A similar proportion occurs in multiple sclerosis [97].

3.3.4. Joint Hypermobility Disturbances

In recent years this author has noted that many clinic patients diagnosed with FND have hypermobile upper extremity joints (Figure 4), and less often in the hips and distal lower extremity limbs. In the upper limbs, these findings have not disturbed their activities in the patients encountered in this clinic. When these patients were referred for formal orthopedic or rheumatologic evaluation for possible Ehlers-Danlos syndrome, a multiple organ disorder that includes excess joint laxity, these were generally ruled out.



Figure 4. Hypermobility at the metacarpal joints in an FND clinic patient from the author's practice.

Concurrent with these observations, an unusually high prevalence (55%) of joint hypermobility was reported in a sample of 20 FND patients in a separate investigation [98].

The association between joint hypermobility and other neurological disorders has not been comprehensively examined, most likely in part because joint hypermobility is given little attention in formal medical training, and the finding is widely regarded as benign [99]. This latter view may overlook multiple organ dysfunction that frequently accompanies joint hypermobility, including gastrointestinal motility and cardiovascular autonomic disturbances.

Although general laxity of connective tissues could mechanically contribute to neurological disturbances due to compression of central nervous tissue, including from low-lying cerebellar tonsils in the type I Chiari malformation [100] and spinal instability [101], as have been identified, other neurological disturbances have no clear relationship to mechanical tissue disturbances. A case report of Ehlers-Danlos syndrome identified co-existing limb myopathy on electromyography and ophthalmoplegia [102]. A sample of 90 individuals who scored abnormally high on a joint mobility assessment were found to have significantly reduced visual-evoked potentials latencies and amplitudes compared to individuals without excess hypermobility [103]. Joint hypermobility therefore can be a biomarker for extensive multiple organ dysfunctions.

3.3.5. Behavioral Biomarkers of FND Shared With Canonical Neurodegenerative Disorders

Clinical Blending between FND and Canonical Neurological Disease

Compelling research suggests that functional movement disorder can often evolve to canonical neurodegenerative disease. In medical chart review, 26% of patients who were diagnosed with Parkinson disease ($n = 53$ total) had earlier developed FND [104]. An additional 8% of Parkinson disease patients had concurrent FND, and most of the Parkinson disease patients (57%) later developed FND. Similarly, Onofrij et al as well as Pareés et al in many instances observed FND to progress to either Parkinson disease or dementia with Lewy bodies [88,105,106]. Elsewhere, three cases of Creutzfeldt-Jakob disease were reported to have initially presented with functional movement disorder [107]. The present author had observed this as well in a 62-year-old man in his clinic, diagnosed initially with functional movement disorder, and then Creutzfeldt-Jakob disease was diagnosed a few months later. He succumbed to the disease two months after the latter diagnosis was made, following rapid neurological decline. In another patient from the clinic, an 18-year-old woman diagnosed with FND has shown in serial photography over 12 months progression to fixed

unilateral intorsion ankle dystonia (Figure 4). When most recently seen, the patient wanted to defer a trial of botulinum toxin administration, pending evaluation by her orthopedic surgeon.



Figure 4. Progressive dystonia resulting in involuntary, fixed ankle intorsion of the right foot. Note also rubor of the same extremity, unlike the other foot. Bandage was worn because dystonia induced chafing with her customary footwear.

Emotional Upset Effects on Symptoms

Emotional upset often provokes symptoms in FND [108]. Similarly, motor symptoms in Parkinson disease can be aggravated by anxiety or other emotional upset [109,110]. Anxiety or depression have been associated with worse performance on a standard test of visual information processing speed among persons with multiple sclerosis [111–115]. Fear of falling can aggravate postural control and gait control among persons with multiple sclerosis [116,117]. High anxiety is a risk factor for dystonic progression that starts with blepharospasm (involuntary contraction of eyelids) to other parts of the body [118].

Exaggeration of Symptoms

In a study by Pareés et al, persons with FND ($n = 8$) were noted to self-report limb tremor more often than was captured by objective recordings of wrist-worn accelerometers worn in the home [119]. This finding suggests that persons with FND are prone to accentuated self-attention to their bodies, leading to their increased somatic complaints. This mismatch was greater than in a group of patients with “organic” tremor (not otherwise specified; $n = 8$) who wore the same instruments. Nonetheless, the latter group also exaggerated their time with tremor when compared to the accelerometry data, thus showing that there is not an absolute difference between persons with FND compared to those with “organic” tremor with regard to symptom reporting.

A subsequent, slightly larger study by Kramer et al, using similar methods, found that while persons with FND reported more tremor disturbance than did persons with “organic” tremor, the self-reported “symptom burden” between persons with FND ($n = 14$) and those specifically with Parkinson disease ($n = 6$) did not differ [120]. The persons with “organic” tremor (including those with essential tremor, Parkinson disease, and other forms) were objectively recorded to have spent more time in tremor than in those with FND, but the differences were slight. Though the findings did not support symptom exaggeration differences between persons with FND and those with other forms of tremor, it should be noted that the study was based on a small subject sample. These results,

however, suggest that the differences between persons with FND vs those with Parkinson disease are minimal with respect to subjective motor symptom impact.

Expectation Effects on Symptoms

The research literature on FND extensively suggests that it is sensitive to suggestibility, i.e., placebo effects, though the studies appear to have had poor experimental design [121]. As far back as 1880, Charcot applied hypnotic suggestion to modify symptoms in persons with FND [122]. Nonetheless, such suggestibility effects are by no means restricted to FND. Placebo effects (expectation to improve) and the obverse, nocebo effects (expectation to worsen), are widely demonstrated in persons with Parkinson disease in reaction to treatments [123]. Low expectation can deter persons with Parkinson disease from pursuing physical exercise [124]. Similar effects are noted in many other involuntary movement disorders, including restless legs syndrome, Huntington disease, tics, amyotrophic lateral sclerosis, and multiple system atrophy [125–127].

Context-Specific Changes on Walking Ability

Patients with FND can improve their mobility during their formal rehabilitation by changing the method of locomotion. For example, an FND patient with impaired walking can improve by gliding the feet across the floor instead of lifting, as if moving across a slippery surface [128]. Starting with a more stable form of locomotion, more complex activities can be gradually introduced as part of rehabilitation, which is described further below. Persons with Parkinson disease likewise can change their ability of locomotion by adopting different movement approaches or patterns. Walking backwards or running can improve motor control in Parkinson disease, Huntington disease, or dystonia [129]. Freezing of gait in Parkinson disease can be improved with shoes that project laser points of light in front of the wearer or crawling on all four limbs [130,131]. Rhythmic auditory cues can improve voluntary movement in both Parkinson disease and FND [132,133]. Parkinson disease patients with freezing of gait may easily locomote by pedaling a bicycle on a street [134].

Competing Voluntary Activities that Can Reduce Symptoms

As noted under section 2, Clinical characteristics of FND above, redirecting attention in persons with FND can ameliorate their symptoms [10]. Similar effects may occur with canonical neurological disorders. Classically, dystonia includes brief amelioration of the motor symptom through a self-initiated voluntary action by the patient, most often, touching a specific part of the body. This behavior is commonly referred to as a “sensory trick” or “*geste antagoniste*” [135]. Although most often such *gestes* are simple, an inventory of such *gestes* shows that they can involve a wide variety of actions, including bending forward, yawning, wearing a scarf, cap, turban, or tight goggles, leaning on one’s elbows, picking at one’s teeth, singing, humming, drinking, kissing, whistling, chewing gum, laughing, piano playing, thinking about talking, running in a counterclockwise direction, listening to a loud radio, mirror viewing, or voluntary eye closure [136]. Such diversity raises consideration that these ameliorative actions may reflect the beneficial effect of redirecting attention from the predominant symptom, as suggested in the overviews of FND and Parkinson disease above.

Cognitive Impairments

Cognitive impairments are common following canonical brain disease, as can be expected. These can also occur with FND. Among them are impaired memory [137], reduced processing speed [138–141], abnormal executive function [141–145], and impaired Theory of Mind (social cognition) [146,147].

Positive Response to Psychotherapy on Motor Symptoms

CBT, a form of psychotherapy, is a leading treatment for FND [148]. The treatment identifies events that trigger symptoms, diminishes attention to the impairment, redirects attention to better retained voluntary activities, cultivates self-efficacy, reduces emotional upset, and develops

mindfulness (concentrating on current emotions and not focusing on events in the past or the future) [108]. The approach can reduce tremor severity and other motor symptoms in FND [149,150]. Although CBT is provided to persons with Parkinson disease mainly to control their mood disorders, preliminary findings indicate that the approach can also improve their walking [151].

Lower Extremity Dysesthesia and Compulsion To Move The Limbs

Restless legs syndrome involves annoying leg sensations (pain, tightness), most often while the patient is recumbent, and the compulsion to move the legs for relief. Increased leg movements also can occur in restless legs syndrome without leg discomfort, particularly during sleep. The worldwide prevalence is about 3% [152]. In a minority of patients with restless legs syndrome (10%), symptoms worsen over 5 years [153]. Restless legs syndrome considerably occurs in canonical neurological movement disorders, including Parkinson disease, multiple system atrophy, and multiple sclerosis [154,155]. Recent quantitative brain MRI studies of restless legs syndrome have shown significant thinning of the cerebral cortex and regional white matter atrophy [156,157], suggesting that it is a neurodegenerative disorder.

Until the quantitative neuroimaging studies referred to above were published, restless legs syndrome was regarded primarily to be a “functional” (that is, physiological) disorder [158]. In a recent study of 96 individuals with functional movement disorder, the incidence of restless legs syndrome according to formal screening criteria was 44%, compared to 8% in neurologically healthy controls [159]. The complaint of restless legs (either nocturnal dysesthesia or the urge to move the legs, confirmed by overnight sleep study) is common in the patients who are seen in the present author’s FND clinic.

4. Rehabilitation for FND

Until recent years, the long-term prognosis for FND was considered to be dismal [160–162]. Although numerous biomarkers for FND have been identified, these findings have not thus far indicated a consistently efficacious medical treatment for its impaired voluntary activities.

However, neurological rehabilitation has shown promise for controlling the symptoms of FND. In recent years there has been increasing interest, developing, and testing neurological rehabilitation for FND, and moving from case series reports to larger clinical trials.

The greatest advances have been in applying neurological rehabilitation toward controlling motor symptoms. Table 2 summarizes trials in chronological order up to the present that applied physical rehabilitation techniques for >5 patients with functional movement disorders. This summary encompasses more than 1300 individuals (mostly adults, but also children) who were treated and followed for the durations of the trials.

Table 2. Summary of physical therapies for FND.

Study [reference]	N *	Diagnostic method**	Intervention†	Dose (months)	Settin g††	Motor symptoms targeted‡
Weiser, 1976 [163]	7	MD referral	PT, counseling	0.25-2	Out	paresis
Delargy, 1988 [164]	6	MD referral	PT	0.36-2.5	In	walking
Leslie, 1988 [165]	20	MD referral	PT	1-3	In or Out	walking, paresis
Speed, 1996 [166]	10	MD referral	PT	0.14-0.8	In	walking
Heruti, 2002 [24]	30	MD referral	PT	Not stated	In	paresis

Moene, 2002 [167]	45	DSM-III	PT + hypnosis vs PT	3	In	dystonia, walking, tremor, paresis
Schrag, 2004 [162]	26	Fahn-Williams	PT + CBT	Not stated	Not stated	dystonia, tremor
Schwingenschuh, 2008 [168]	12	Fahn-Williams	PT + CBT	Not stated	Out	dystonia, walking, tremor
Dallochio, 2010 [169]	16	Fahn-Williams	Walking therapy	3	Out	dystonia, walking, tremor
Czarnecki, 2012 [170]	80	Fahn-Williams	PT vs TAU	0.25	Out	walking, tremor, paresis
Saifee, 2012 [171]	26	MD referral	PT + CBT	0.75	In	dystonia, tremor, paresis
Demartini, 2014 [172]	36	MD referral	Multidisciplinary rehab	1	In	dystonia, walking, tremor, paresis
Espay, 2014 [173]	10	MD referral	Entrainment with biofeedback device	0.03	Out	tremor
Jordbru, 2014 [174]	40	MD referral	PT + CBT vs waitlist	0.75	In	walking
Nielsen, 2015 [175]	47	Gupta-Lang	PT	0.25	Out	dystonia, walking, tremor, paresis
Dallochio, 2016 [176]	29	Fahn-Williams	CBT vs CBT + PT vs TAU	3	Out	dystonia, walking, tremor
Matthews, 2016 [177]	35	MD referral	PT	≤ 2	In	walking
Nielsen, 2017 [178]	57	Fahn-Williams	PT vs nonspecific PT	0.25	Out	dystonia, walking, tremor
Jacob, 2018 [179]	32	Fahn-Williams	PT	0.25	In	dystonia, walking, tremor
Jimenez, 2019 [180]	49	DSM-5	Pain multidisciplinary rehab	0.25	Out	FMD
Bullock, 2020 [181]	12	DSM-5	VR motor rehab + mirror feedback	2	Out	FMD or sensory symptoms
Demartini, 2020 [182]	18	Gupta-Lang	PT	5.25	Home	dystonia, walking, tremor, paresis
Maggio, 2020 [183]	50	DSM-5	PT, CBT, goal setting	1.5-3	Out	dystonia, walking, tremor, paresis
Petrochilos, 2020 [184]	78	MD referral	PT, Multidisciplinary rehab, CBT	1.4	Out	dystonia, walking, tremor, paresis

Gandolfi 2021 [185]	33	Gupta-Lang	PT	0.25	Home	dystonia, walking, tremor, paresis
Hebert, 2021 [186]	13	Fahn-Williams	PT	0.25-0.5	In	dystonia, walking, tremor, paresis
Callister, 2023 [187]	201	Gupta-Lang	PT	0.25	In	walking, tremor, paresis
Guy, 2024 [188]	31	DSM-5	PT + CBT	2	Out	dystonia, tremor, paresis
McCombs, 2024 [189]	77	MD referral	Sensory-oriented OT	4	Out	dystonia, walking, tremor, paresis
Nielsen, 2024 [190]	241	Gupta-Lang	PT vs TAU	0.75	Out	dystonia, walking, tremor, paresis
Polich, 2024 [191]	22	MD referral	PT	0.5	In	walking, paresis

Table 2. Summary of physical therapies for FND (continuation).

Study	Outcome measure††	Immediate results	Follo w-up (mont hs) ¶	Results¶¶
Weiser, 1976 [163]	Neurol exam	100% improved	1-96	86% retained gains
Delargy, 1988 [164]	Neurol exam	100% improved	8-14	100% retained gains
Leslie, 1988 [165]	Neurol exam	85% improved	NA	
Speed, 1996 [166]	FIM	100% improved	7-36	78% retained gains
Heruti, 2002 [24]	Neurol exam	55% improved	NA	
Moene, 2002 [167]	Neurol exam	65% improved; no difference between groups	6	84% retained gains; no difference between groups
Schrag, 2004 [162]	Neurol exam	33% improved	NA	
Schwingenschuh, 2008 [168]	Neurol exam	80% improved	NA	
Dallochio, 2010 [169]	PMDRS	70% improved	NA	
Czarnecki, 2012 [170]	Neurol exam	73% improved	25-33	Experimental group 60% self-rated improved vs 22% control treatment

Saifee, 2012 [171]	Nonspecific self-assessment	58% improved	NA	
Demartini, 2014 [172]	COPM, CGI	67% improved	12	COPM: 100% retained gains; CGI: 33% retained gains
Espay, 2014 [173]	PMDRS	100% improved	3-6	50% retained gains, the other measures declined
Jordbru, 2014 [174]	Functional Mobility Scale, FIM	Experimental group generally improved	12	100% gains retained
Nielsen, 2015 [175]	CGI	96% improved	3	85% retained gains
Dallochio, 2016 [176]	PMDRS	Experimental groups improved, unlike TAU	NA	
Matthews, 2016 [177]	Modified Rivermead Mobility Index	Generally improved	NA	
Nielsen, 2017 [178]	CGI	Assessment delayed until 6 m	6	Experimental group > control group gains
Jacob, 2018 [179]	CGI, PMDRS	87% improved	6	67% retained (only CGI assessed)
Jimenez, 2019 [180]	In-lab movement measures	Generally improved	NA	
Bullock, 2020 [181]	Oxford Handicap Scale	Improved experimental group only	NA	
Demartini, 2020 [182]	PMDRS, CGI	Improved (67%)	6	72% retained gains
Maggio, 2020 [183]	Subjective change	Improved (34%)	NA	
Petrochilos, 2020 [184]	CGI, COPM	Generally improved	6	100% retained gains
Gandolfi 2021 [185]	S-FMDRS, other in- lab measures	Generally improved	3	Gains lost
Hebert, 2021 [186]	CGI	93% improved	12	77% retained gains on CGI
Callister, 2023 [187]		84% improved	NA	

COPM ability subscale				
Guy, 2024 [188]	Lab assessments	Generally improved	3	100% retained gains
McCombs, 2024 [189]	Clinician judgement	62% improved	NA	
				No difference between groups on SF-36;
Nielsen, 2024 [190]	SF-36; CGI	Not reported	12	results favored CGI, but statistics not stated
PT, OT judgement (ordinal scales)				
Polich, 2024 [191]	Berg Balance Scale	95% improved	NA	

*N, number of patients who remained to the conclusion of the study. **Diagnostic method: DSM, Diagnostic and Statistical Manual of Mental Disorders (various editions); Fahn-Williams [192]; Gupta-Lang [193]; MD referral, clinician referral. †Intervention: CBT, Cognitive Behavioral Therapy; OT, occupational therapy; PT, physical therapy; TAU, treatment as usual; VR, virtual reality. ††Setting: In, inpatient; Out, outpatient; Home, home-based therapy. ‡Motor symptoms targeted: FMD, functional movement disorder not otherwise specified. ‡‡Outcome measure: CGI, Clinical Global Impression self-rated scale; COPM, Canadian Occupational Performance Measure; FIM, Functional Independence Measure; Neurol exam, neurological examination; PMDRS, Psychogenic Movement Disorder Rating Scale; S-FMDRS, Simplified Functional Movement Disorder Rating Scale. ¶ Follow-up: NA, not reported. ¶¶ Results: SF-36, 36-item Short Form Health Survey.

The published studies generally had favorable outcomes, and in many cases, gains retained over months or years. A considerable limitation among the studies has been the common lack of comparing one treatment to another in groups that were matched for the degree of disability. In addition, in most reports patient groups had diverse symptoms that were targeted for treatment, leaving unclear whether treatment outcomes depended on the individual symptoms treated.

Although the approaches somewhat differed from each other, a common approach was to start with having patients practice voluntary movements that can be performed with little difficulty, and then advance gradually through more complicated movements, with praise at every stage of accomplishment [194]. This is subsumed under the term “shaping” [170,187,195–197], which has been used in specific forms of physical rehabilitation (e.g., Constraint-Induced Movement therapy) for canonical neurological disorders, including stroke, cerebral palsy, traumatic brain injury, and multiple sclerosis [198–201]. In addition, because FND symptoms are affected by self-attention to the deficits, the rehabilitation techniques emphasized increasing general physical activity without drawing attention to the particular part of the body or context, which could aggravate the symptoms. An example for the effect of attention on an FND deficit is the Hoover sign [202]. This involves the inability to extend a hemiparetic leg following direct command while supine or seated, but can occur when the patient is asked to redirect self-attention to the opposite leg and elevate it. In that case, the affected leg’s extension is necessary to stabilize the pelvis during the maneuver. Such a demonstration of retained movement capability when self-attention is redirected can serve as a foundation for rehabilitation.

5. Other Treatments

To a lesser extent, other treatments for FND have been investigated. Because these methods are early in their development, the treatment results are not provided here. The methods have included CBT alone [149], hypnosis [203], and transcranial magnetic stimulation [204]. Although various psychotropic medications have been tried for FND and can help to manage mood disorder, there is

thus far no leading efficacious pharmacological treatment for the FND symptoms themselves [205,206].

6. Discussion

The purpose of this review is to amply demonstrate that FND, a much misunderstood illness, shares many objective laboratory and clinical characteristics with canonical neurological disease. Moreover, conventional neurological rehabilitation techniques can ameliorate FND symptoms. This review thus intends to demystify the illness and encourage clinical practitioners to approach FND patients empathetically and supportively. This evidentiary foundation allows practitioners to indicate to their patients that (1) the illness is not a psychiatric disorder, and thus to discard the unsupported implication that it can corrupt reality testing, and (2) the illness can respond positively to rehabilitation techniques that are similarly applied to other neurological disorders. In doing so, this review aims to bring FND into mainstream neurological care, to regard it as a neurological disease, and not to treat it as a fringe, exotic, or mysterious illness.

Even more important, the many biomarkers that FND shares with multiple other neurological disorders should prompt clinicians who evaluate and treat FND to be aware of and routinely evaluate for its multiple organ comorbidities. The constellation of autonomic, cardiovascular, immunological, gastroenterological, and orthopedic disturbances are not unique to FND. In recent research, this pattern also was found to be common in patients who presented with gastrointestinal motility disturbances that lacked observable tissue pathology, who were not noted to have FND [207]. Consequently, treating an FND patient warrants investigating these possible other disturbances and consult specialists in these areas as needed. The diverse biomarkers also suggest that FND may not strictly be a neurological disorder. As yet, although there is no clear physiological or developmental process in common with these disturbances that may also underlie FND, these findings should encourage further hypothesis development and clinical investigation to clarify the pathological process that is involved with FND.

Evaluating and directing treatment for FND requires the expertise of a neurologist, owing to the complexity of the symptoms [208–211]. The optimal management of FND would start with accurate diagnosis. However, there are many difficulties with doing so:

1. There is no gold standard for diagnosing FND. In our review of studies of FND biomarkers [212], we found that there are three main rival methods: the Fahn-Williams method and its variants [192], the method outlined in the various editions of the Diagnostic and Statistical Manual of Mental Disorders [213], and the referring physician's personal judgement. Without a consensus diagnostic method for FND, rapid progress in research for treatment will likely be hindered.
2. Seldom considered has been the extensive list of alternate paroxysmal neurological disorders that are not known to be affected by self-attention or emotional excitation, and which lack distinctive features on conventional clinical neuroimaging. These include frontal lobe epilepsy, paroxysmal dyskinesia, and autoimmune encephalitis [214]. This list obliges the involvement of a neurologist who is highly experienced with assessing FND (indicated above) vs. the alternate neurological disorders, thus to direct the patient to appropriate management.
3. Even when a neurologist with expertise in FND may be involved, current clinical practice often limits the time to evaluate new patients to 30 minutes, due to economic pressures and meeting the demands of a large practice [214]. In contrast, as much as an hour is necessary to conduct a thorough historical intake and comprehensive neurological evaluation, and provide empathetic patient and family education and care planning. Furthermore, the patient's concurrent cognitive limitations (described in section 3.3.5.7) can limit or slow these steps. As a result, the modern medical practice milieu may prolong evaluating and ultimately arranging care for persons who may have FND or other paroxysmal disorders.
4. Even with involving a neurologist who is expert with FND, optimal care, including treatment by a neuropsychologist and rehabilitative physical therapists, occupational therapists, or speech-language pathologists, can be limited because of the relatively few medical centers that can provide these services with commensurate expertise with FND. Consequently, there can be a

considerable waitlist for patients to be seen, along with the hardship for arranging travel to such places.

To assist the management by the clinician who initially sees persons who may have FND, the web site FND Hope - FND Hope International (<https://fndhope.org>) lists such centers that have the available expertise. In addition, referring the patient and family to the web site <https://neurosymbols.org/en/> can acquaint them with the diverse appearances and complexities of FND. Doing so can equip them with the knowledge to better understand the illness, which in turn could help to reduce the time for evaluation and allay concerns that the illness is not a mental disorder or a different neurological disorder with episodic symptoms, such as multiple sclerosis [215,216].

7. Conclusion

This overview of the biomarkers and responses to conventional neurological rehabilitation for FND demonstrates that it is a neurological disorder. Consequently, the patient should be approached with this in mind, following appropriate diagnosis. Becoming familiar with the content of this review can prepare the clinician to approach the patient with confidence that FND is not an unknowable, enigmatic disorder, and that optimism should be conveyed to guide patients to improved self-control of their symptoms with competent rehabilitation.

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